Doctoral Thesis

Virtual reality rehabilitation in spinal cord injury patients

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Virtual reality rehabilitation in spinal cord injury patients

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Presented by

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Summary

Patients with an incomplete spinal cord injury (iSCI) are limited in their lower limb motor function and are also associated with a wide range of physical and psychosocial problems, including in particular neuropathic pain. The consequences of spinal cord injury are challenging to treat and the potential for recovery is still very limited. Although recent training-based neurorehabilitation approaches using virtual reality (VR) show some promise, the methods employed to date address only patient motivation issues and thus do not tap into the potential of VR. In particular, they do not directly promote activation of the underlying sensorimotor network to (re)activate cortical structures involved in control of the lower limbs.

This thesis makes a contribution to the understanding of the brain processing involved in lower limb movements mediated by VR, and its application to the treatment of iSCI patients. It is known that observing, imagining, and even understanding motor actions activate the neural networks involved in motor execution. Using VR training to activate this supraspinal network projecting to surviving parts of the spinal tract may thus promote rearrangement of the network and bring substantial locomotion benefits and pain reduction to iSCI patients. To test this principle, a new VR neurorehabilitation system was developed to provide task-specific VR training of isolated movements. The system displayed life-sized virtual lower limbs on a large screen, controlled by the user via size-adjustable shoes with integrated orientation sensors.

This thesis contains four studies, all based on the combination of observation and motor imagery, i.e. online motor imagination, a cognitive process in which a subject imagines himself/herself in the displayed movement situation. The first study using fMRSI shows that it is possible to extensively activate the neural correlates of the lower limb motor execution network using online imagination, even in the absence of overt movement. The first ever VR training system for lower limbs combining action observation, imagination and execution was developed, with four training applications for different lower limb muscles and functions. In
the *second study*, a first investigation of the system in a pilot single-case study on iSCI patients showed that the training was well accepted by the patients and seemed to be enjoyable even if they were not familiar with VR. The motivation was high, which is promising for simple training of repetitive movements. The VR rehabilitation system required active patient effort at all times and the results demonstrated improvement of lower limb motor functions and reduction of pain intensity. The *third study*, a training study on iSCI patients with motor dysfunction and neuropathic pain, revealed positive effects on a short-term and longitudinal development. In the *fourth study*, the findings were extended for a VR lower limb training scenario called “footbag”, showing that motor online imagination and imitation for the VR “footbag” game and those of playing the game without or with reward revealed similarly activated brain regions. Furthermore, the results suggested that playing a game and being in control of the VR lower limbs is a rewarding activity per se.

The findings of this thesis extend previous results promoting the use of pure motor imagery, or of action imitation, as therapeutic approaches in lower limb neurorehabilitation. The use of VR techniques in neurorehabilitation may have profound implications on the facilitation of post-injury retraining of function and potentially promote reparative plasticity and functional recovery. It has been shown that the VR system improves motor function and reduces neuropathic pain in iSCI patients. A further advantage of the system is its low cost compared to other training technologies, e.g. robotics. Essentially, the patients were able to generalize the training of individual movements to achieve functional improvements on their own with no task-specific training. An open question for future investigation is the extent to which these results can be generalized to other neurological patient groups, e.g. stroke.
Zusammenfassung


Diese Arbeit enthält vier Studien, welche alle auf der Kombination von Beobachten und motorischem Vorstellen beruht - ein kognitiver Prozess, in welchem sich die Person in die dargestellte Bewegungssituation hineinversetzt. Die erste Studie mit fMRT zeigt, dass es mit dieser Kombination möglich ist, das neuronale Netzwerk für die motorische Ausführung der

1. General Introduction

1.1 Spinal cord injury

1.1.1 General information

The central nervous system consists of the brain and the spinal cord. The function of the spinal cord is primarily the conveyance of information between brain and body and can be divided in the following major functions: conveying motor information, which travels down the spinal cord, conveying sensory information in the reverse direction, and operating as a center for the coordination of reflexes. The consequences of an injury of central cord reflect this organization.

A spinal cord injury (SCI) results in an impairment of sensorimotor and/or autonomic function, e.g. dysfunction of the bowel and bladder or sexual dysfunction. The symptoms can diversify depending on the density, location and completeness of the lesion of the spinal cord. Lesions in the thoracic and lumbar regions lead to paraplegia and lesions of the cervical region of the cord can impact all four limbs, i.e. tetraplegia. The incidence of SCI in Switzerland lies between 300-400 cases per year (Eberhard, 2004), world-wide between 10.4 and 83 per million inhabitants and in about 50% of the cases, motor and/or sensory function is preserved below the lesion level (Wyndaele & Wyndaele, 2006). SCI patients with preserved motor and/or sensory function are called incomplete (iSCI) whereas complete SCI patients have no sensory and motor function below the lesion. Restoration of motor function is of high priority for SCI patients (Ditunno et al., 2008). Besides impaired ambulatory functions, neuropathic pain is additionally a common issue among SCI patients. In average, 40-60% following SCI are affected by neuropathic pain which is caused by immediate or remote damage within the spinal and/or peripheral nervous system (Siddall et al., 2003; Soler et al., 2007).
1.1.2 Classification of spinal cord injury

An SCI is generally classified by the completeness and the neurological level of lesion. The “International Standards for Neurological and Functional Classification of SCI” was designed by the American Spinal Injury Association (ASIA) for standardising assessments of spinal cord functions (Marino et al., 2003). The ASIA Impairment Scale (AIS) is a multi-dimensional approach to categorize motor and sensory impairment in individuals with SCI. It identifies motor and sensory levels indicative of the most top spinal level demonstrating “unimpaired” functions. The motor level of the lesion assesses ten key muscles bilaterally with manual muscle testing (0 for total paralysis to 5 for active movement, full range of motion against gravity and normal resistance). The sensory level of the lesion in 28 dermatomes are assessed bilaterally using pinprick and light touch sensation, scored as 0 (absent), 1 (impaired) or 2 (normal). The results are summed up to produce overall motor and sensory scores. Furthermore, the evaluation of motor and (anal) sensory function is used as a basis for the determination of the AIS classification. The different injury levels are graded from A to E (Table 1.1).

<table>
<thead>
<tr>
<th>Classification (AIS)</th>
<th>Functional impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = complete</td>
<td>No sensory or motor function is preserved in the sacral segments S4-S5.</td>
</tr>
<tr>
<td>B = incomplete</td>
<td>Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.</td>
</tr>
<tr>
<td>C = incomplete</td>
<td>Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3 (Grades 0-2).</td>
</tr>
<tr>
<td>D = incomplete</td>
<td>Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade greater than or equal to 3.</td>
</tr>
<tr>
<td>E = normal</td>
<td>Motor and sensory function is normal.</td>
</tr>
</tbody>
</table>

Table 1.1: Classification of SCI according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS) (Marino et al., 2003).

1.1.3 Assessment of motor function after spinal cord injury

Besides complete SCI patients who have no preserved motor function below the injured level, iSCI patients might have residual motor and sensory function. This offers the possibility to retain, regain or improve their ability to walk. Major deficits are muscle weakness and
1. General Introduction

reduced walking speed associated with angular displacements (Pepin et al., 2003; Shin et al., 2011; Gil-Agudo et al., 2011). Mobility and making improvement of remaining locomotor function are reported as one of the most important activities for people with neurological disorders (Chiou & Burnett, 1985; Ditunno et al., 2008).

Well established assessments of locomotor function are the 10 Meter Walking Test (10MWT) (van Hedel et al., 2005, 2006), Spinal Cord Independence Measure (SCIM, mobility part) (Catz et al., 2007) and the Walking Index for Spinal Cord Injury II (WISCI II) (Dittuno et al., 2001). The Berg Balance Scale (BBS) assesses balance during functional activities (Berg et al., 1995) and the ASIA motor score of the lower (LEMS) and upper (UEMS) extremities assesses muscle strength which has been shown to correlate with walking speed (Marino et al., 2003; Kim et al., 2004). In addition, video and locomotion analysis are used to quantify gait patterns, motor evoked potentials (MEPs) to assess corticospinal tract function (Zorner et al., 2010) and functional magnetic resonance imaging (fMRI) to reveal brain activation patterns.

1.1.4 Assessment of pain after spinal cord injury

Beside the apparent consequences after SCI as loss of motor, sensory and autonomic functions, pain is often rated by patients as an important issue. After SCI, a person commonly experiences several types of pain that can be classified as nociceptive or neuropathic pain based on the three-tier taxonomy from the International Association for the Study of Pain (IASP) (Bryce et al., 2011).

Nociceptive pain can be further divided into musculoskeletal or visceral subtypes, while neuropathic pain can be divided into “at level” or “below level”. Musculoskeletal pain is described as dull, aching, worse with movement or exercise and appeared to be arising from musculoskeletal structures. The pain is generally located in the region of preserved sensation close to the site of spinal injury although it may radiate. However, chronic musculoskeletal pain may occur with overuse of structures such as the arm and shoulder.
Visceral pain is perceived as abdominal pain described as spontaneous, dull, poorly localized or cramping, and appears to be related to abdominal pathology. The classification of neuropathic pain was based on the location in a region of sensory disturbance with neuropathic features (burning, stabbing, electric, shooting). These symptoms experienced in the dermatomes at or just above the level of injury were defined as neuropathic at-level pain. An important variant of at-level neuropathic pain is seen after injury to the cauda equina. Pain located diffusely below the level of the spinal cord lesion was defined as below-level neuropathic pain (Bryce et al., 2012).

Musculoskeletal pain is the most common but least severe type of pain. Its prevalence decreases at approximately six months after initial injury, only to reappear some years later due to overuse syndromes. In contrast, neuropathic pain is severe and persistent. At 5 years following injury, its prevalence is 41% for at-level neuropathic pain and 34% for below-level neuropathic pain (Siddall et al., 2003). These different types of pain demonstrate specific characteristics that reflect different underlying mechanisms. Unfortunately, only a minority of SCI patients profit from conventional pain treatment. It seems that once pain problems emerge in the first months or years after a SCI, the prevalence or intensity of pain do not appear to increase or decrease over time. If a patient has developed neuropathic pain, it is unlikely that the symptoms will resolve on their own (Störmer et al., 1997; for review Siddall et al., 2009).

Clinically relevant pain information can be assessed using a structured interview (van Hedel et al., 2011). This interview collected pain related variables during the last 7 days in accordance to the recently developed pain data core set (Widerström-Noga et al., 2008). The interview contained items on the clinical presentation of pain (neuropathic or musculoskeletal, at- or below-level), various pain related features as intensity, onset of pain, frequency, course of pain, alleviating and aggravating factors and information regarding medication. The pain intensity was rated on an 11-point Numerical Rating Scale (NRS, from 0 (no pain) to 10 (worst pain imaginable)) computed as a mean of the NRS scores at time of
the examination, average and maximum pain intensity during the last week. In addition, pain related symptoms such as allodynia and paresthesia were reported as present or absent. Taking medical data prior neurological assessments into consideration, pain can then be classified into nociceptive pain (i.e. musculoskeletal and visceral) and neuropathic pain (at-level and below-level) according to the IASP taxonomy described above. To assess neuropathic pain levels, usually subjective pain questionnaires are used such as the Neuropathic Pain Scale (NPS) (Galer & Jensen, 1997). The NPS investigates distinct pain qualities frequently associated with neuropathic pain. The questionnaire rates ten different aspects of pain on a NRS. In general, intensity and unpleasantness of pain are asked and additionally, intensity of sharpness, hotness, dullness, coldness, itching and skin sensitivity; intensity of surface and deep pain and a temporal pattern item (intermittent, variable, or stable). Patients have to rate the different pain items as an average of the pain experienced in the last 7 days.

1.2 Virtual reality rehabilitation for motor dysfunction and neuropathic pain

Despite evidence that sensorimotor dysfunction and associated neuropathic pain may share some underlying mechanisms, they are currently treated very differently. Pharmacological interventions are typically used for neuropathic pain while physical therapy and exercise are used to treat motor dysfunction, a common therapeutic approach considered as “bottom-up”. The exercises activate the neuromuscular system and enhance coordination and muscle force from the “bottom”. However, the sensorimotor system and neuropathic pain can be instead generated by changes in cortical activity initiated by a cognitive task, i.e. “top-down” process. Such rehabilitation interventions which promote cortical plasticity are considered to rearrange brain areas and the underlying neural networks. In iSCI patients the supraspinal input projecting to surviving parts of the spinal tract will subsequently be improved and may thus bring substantial locomotion benefits and pain reduction. A possible intervention proposes the use of virtual reality (VR)-mediated movement training programs challenging task-specific trainings with isolated limb movements.
The use of VR is currently exploding in all fields of rehabilitation (Adamovich et al., 2009; Bohil et al., 2011). VR is defined as the use of computer-based technologies to interactively simulate environments (Holden, 2005). Information can be provided with the same senses existing in the real world to obtain information about the virtual world. The basic components for VR systems are a computer and the VR presented on a monitor. Typically used devices include besides the visual displays, also auditory output and haptic devices to provide physical limb support. Below, we focus on the neural correlates of virtual reality and motor modalities and the application of VR technology in therapy to assist locomotion and pain therapy.

1.2.1 Virtual reality and motor modalities
Observation, motor imagery and execution activate overlapping cortical networks which increases in intensity when objects are engaged (Rizzolatti & Cragheiro, 2004; Buccino et al., 2006; Caspers et al., 2010). Motor imagery is thought to be able to additionally modify and improve motor performance (Gandevia, 1999). Two fMRI studies on SCI patients have demonstrated the preservation of motor system activation during motor imagery, although adaptive changes in activation have been built up over time in chronic SCI patients (Cramer et al., 2005; Hotz Boendermaker et al., 2008). It is thought that, due to modified cortical function, chronic SCI patients require considerably more cognitive effort to perform motor imagery than healthy persons (Hotz Boendermaker et al., 2008). It thus seems to be particularly important to provide motivational and visual aids to SCI patients performing motor imagery. In VR interactions the user is required to combine observation with execution and also with motor imagination, i.e. online motor imagination - a cognitive process in which a subject imagines himself/herself in the displayed movement situation. Besides online motor imagination, it is also important for therapeutic contributions in what extent observation and observational aspects combined with imitation and playing for lower limbs differ.
1.2.2 Virtual reality and motor dysfunction

Systems implementing automation of locomotion therapy using VR usually provide at least one of two key features: physical therapy assistance by haptic support of leg motion, and enhance the patients’ motivation to participate actively in therapy through the use of gaming scenarios. Currently, a multitude of VR systems are addressing improvements of ambulatory functions. A locomotion interface based on two movable footpads using a forced-trajectory method without feedback or audio-visual inputs, improved locomotion in hemiplegic patients in a single-case series (Yano et al., 2003). Similarly, a robot-assisted gait training (RAGT), also providing forced-trajectory haptic support, increased ground walking speed in chronic iSCI patients (Wirz et al., 2005). A 2D VR-based gaming system which provided visual feedback of patients’ posture via a video camera enhanced locomotor abilities and improved lateralization of motor cortical activation in chronic stroke patients (You et al., 2005). A system known as the “Rutgers Ankle” combined an ankle haptic interface with audio-visual feedback in gaming scenarios, which in a single-case study on a stroke patient enforced the muscle for ankle movements, endurance and walking ability (Deutsch et al., 2001). To address the lack of need for active participation and decay of cortical motor plans by patients in forced-trajectory walking, VR was combined with patient-exerted forces using RAGT on children with various neurological disorders (Koenig et al., 2008). However, it is extremely difficult to provide active haptic feedback with accurate movement kinetics due to their inertial properties. One promising method to circumvent these problems is to provide virtual representations of the leg mapped directly to patient leg movements that can be supported according to each patient’s current abilities. Compared to the studies using VR, the scenarios are advantageously supported by the virtual presentation of the limbs by strongly activating the above mentioned cortical network. Furthermore, key concepts relevant for motor learning can be strongly supported by the use of VR, i.e. repetitive practice, motivation to endure practice and in particular the directly mapped representation of the leg to provide patients with feedback about their performance (Holden, 2005).
1.2.3 Virtual reality and pain

Neuropathic pain in the absence of afferent somatosensory input has been shown to correlate with primary somatosensory cortex reorganization in amputees (Flor et al., 1995) and SCI patients (Wrigley et al., 2009). Although there are possible explanations as pain may relate to inappropriate cortical representations of proprioceptive signals, induced by a mismatch between intended movements and movement feedback (Harris, 1999), the basic model underlying chronic neuropathic pain is still unclear. The sensorimotor cortex can be activated by off-line modalities such as observation and imagination of an action. In different patient groups suffering from neuropathic pain, there is anecdotal evidence that these networks can be induced by using visual aids to replace the abolished sensory feedback. Mirrors placed along the midline of the body have been used with amputees to reduce phantom arm limb pain (Ramachandran & Hirstein, 1998). The same method has also been tested successfully on the legs of patients with complex regional pain syndrome (McCabe et al., 2003). A “virtual walking” illusion tested on SCI patients aimed to reduce the neuropathic pain. Video of the top half of patients’ bodies were matched to video of walking legs and shown on a screen in front of them. The SCI patients in the study by Moseley (2007) performed 10-minutes of virtual walking on 15 consecutive weekdays and in the study by Soler et al. (2010) each patient received 10 times a 20-minutes treatment sessions over 2 weeks. The treatment reduced neuropathic pain leading the authors to conclude that virtual walking may be a viable treatment for pain after spinal cord injury. While this illusion is more entertaining than pure motor imagery, interactive therapy modes involving goal-directed tasks would be highly desirable to maintain patient motivation and participation.

Previous efforts to use VR in pain therapy do not explicitly activate the above mentioned mechanisms. Beneficial effects have been seen with VR-based pain distraction in burns patients (Hoffman et al., 2000) and children undergoing surgical procedures (Gold et al., 2006), suggesting that temporary analgesia is achievable. These systems are unlikely to be useful for treating chronic neuropathic pain, as they are based on temporarily shifting attention away from pain in the body rather than on inducing long-term effects, such as in the
1. General Introduction

study by Moseley (2007). Thus, there is no evidence for an interactive VR therapy for neuropathic pain yet.

1.3 Aim of the thesis

The aim of this thesis is to elucidate the brain activation background of VR and playing a game with presented lower limb movements and to develop and test the effect of an interactive VR-mediated lower limb rehabilitation system. The system combines action observation, motor imagery and execution, on motor dysfunction and neuropathic pain in iSCI patients. In order to fully exploit the potential of VR for motor therapy and neuropathic pain reduction, scenarios are required that combine visual aids with interactive gaming activities. The use of gaming in VR should provide for much higher training intensity and motivation, by providing patients with immediate task feedback and by experiencing themselves successfully performing a given task.

The specific issues addressed in this thesis are the following:

The first study shows a neuroimaging investigation of real lower limb movements on the basis of the combination of observation and motor imagery, i.e. "observation with online motor imagination" - a cognitive process in which a subject imagines himself/herself in the displayed movement situation, as induced in many VR applications, in particular playing a game. The following studies show a newly developed technology in form of an interactive computer-based therapy system for the lower limbs combining action observation, imagination and execution, i.e. game scenarios and interaction devices. In the second study, the developed VR neurorehabilitation system is investigated in a pilot single-case clinical study with iSCI patients. The third study investigates the short-term and longitudinal development of intensive VR training of motor dysfunction and neuropathic pain in iSCI patients. In the fourth study, the findings are extended with a neuroimaging investigation for a VR lower limb training scenario in healthy subject.
2. Neural correlates of observation combined with imagination of lower limb movements

2.1 Abstract

The combination of observation and motor imagery, i.e. “observation with online motor imagination” - a cognitive process in which a subject imagines himself/herself in the displayed movement situation, is induced in many virtual reality (VR) applications, in particular gaming. In the present study we show activation resulting from observation coupled with online imagination and with online imitation of a goal-directed lower limb movement using functional MRI (fMRI) in a mixed block/event-related design. Volunteer healthy subjects viewed a video (1st-person perspective) of a foot kicking a ball. They were instructed to observe-only the action (O), observe and simultaneously imagine performing the action (O-MI) or imitate the action (O-IMIT). We found that when O-MI was compared to O, activation was enhanced in the pre-supplementary motor area, ventral premotor cortex and inferior parietal lobule. The O-MI and O-IMIT conditions share many activation foci in motor relevant areas as confirmed by a conjunction analysis. These results show that it is possible to extensively activate the lower limb motor execution network using O-MI, even in the absence of overt movement. Our results may have additional implications for the development of novel interventions in neurorehabilitation.
2.2 Introduction

In recent years there has been a steady increase in the number of people engaging in virtual reality (VR) interactions, in particular in gaming. Moreover, VR is being increasingly used in neurorehabilitation (for a review see Adamovich et al., 2009 and Bohil et al., 2011). In many of these interactions the user is required to combine observation with motor imagination, i.e., a cognitive process in which a subject imagines himself/herself in the displayed movement situation. Some games on the market, in particular so-called 1st-person shooter games, automatically induce observation and imagination. With respect to neurorehabilitation, games are used to (re)activate cortical structures (e.g. Gaggioli et al., 2006; Eng et al., 2007; Villiger et al., 2011b) that have been damaged by injury. The hypothesis underlying this approach is that, in the gaming situation, motor imagination coupled with observation should optimally activate neural structures involved in movement control. However, to date such an effect has not yet been demonstrated.

Over the last two decades several research groups have published data, which give strong support to the simulation or resonance theory of action formulated by Jeannerod (2001). According to this theory, observing, imagining, and even understanding motor actions activate the neural network involved in motor execution. Most experiments have focused on the upper limbs and investigated either observation or motor imagery, but not the simultaneous combination of both (Munzert et al., 2009). Furthermore, investigations of observation or motor imagery of lower limb movements is quite sparse. Table 2.1 summarizes the results for toe/foot movement experiments that focused on at least one of the above-mentioned activities.

During observation of simple goal-directed foot movements, the first fMRI study revealed activation in the ventral premotor cortex (PMv) and in additional foci of the posterior parietal cortex (Buccino et al., 2001). Similar activation patterns during observation of goal-directed foot movements were subsequently reported by other groups (e.g. Aziz-Zadeh et al., 2006; Orr et al., 2008). In these experiments the observed stimuli were never presented from the
1st-person perspective. Only one investigation systematically compared 1st- versus 3rd-person perspective for observation and imitation of hand and foot movements and revealed that the 1st-person (kinesthetic) perspective recruited the motor execution network more extensively than the 3rd-person (visual) view (Jackson et al., 2006). Hence, stored motor programs might be more easily activated when stimuli are presented in the 1st-person perspective. With respect to motor imagination, similar findings have also been reported (Solodkin et al., 2004) and most investigations on motor imagery of foot movements have supported this concept (Lafleur et al., 2002; Stippich et al., 2002; Ehrsson et al., 2003; Roux et al., 2003; Alkadhi et al., 2005; Enzinger et al., 2008; Hotz-Boendermaker et al., 2008; 2011). Thus, during motor imagery, brain areas in the neural motor network involving (pre)supplementary motor area, premotor cortex and parietal cortical lobules (e.g. Alkadhi et al., 2005; Hotz-Boendermaker et al., 2008) are engaged. In addition some studies reported M1/S1 activation (Ehrsson et al., 2003; Orr et al., 2008). To date, however, investigations on brain activity elicited by observation with simultaneous, i.e. “online”, motor imagery of foot movements have not been reported.

In the present investigation, we apply the combination of observation and motor imagery, which we call “observation with online motor imagination”, for a simple transitive foot movement as a tool for future assessment of lower limb motor neurorehabilitation. To control the neural activation specific to online motor imagination, an online imitation condition, as in Jackson et al. (2006), was used in this study. Thus, the present fMRI study investigated brain activity during goal-directed lower limb movements, presented from the 1st-person perspective, during observation-only (O), online motor imagination (O-MI) and online imitation (O-IMIT). We predicted that observation combined with the instruction to imagine the displayed movements (O-MI) would potentiate the activation of areas responsive to motor observation and thus induce broader and greater activation than observation-only (O). This would make this approach a potentially useful surrogate for motor execution and provide a means to activate the relevant lower limb cortical networks in stroke or incomplete spinal cord injury (SCI) patients.
## 2. Online motor imagination of lower limbs

<table>
<thead>
<tr>
<th>Paper</th>
<th>Action</th>
<th>Observation</th>
<th>Imagination</th>
<th>Imitation / Execution</th>
<th>Stimulus</th>
<th>Mode</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkadhi et al., 2005</td>
<td>no goal-directed</td>
<td>no</td>
<td>yes (1st)</td>
<td>no / yes</td>
<td>Foot movements</td>
<td>fMRI</td>
<td>8 SCIs / 8 Controls</td>
</tr>
<tr>
<td>Aziz-Zadeh et al., 2006</td>
<td>goal-directed</td>
<td>yes (3rd)</td>
<td>no</td>
<td>no / no</td>
<td>Foot pressing on objects</td>
<td>fMRI</td>
<td>12</td>
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<tr>
<td>Buccino et al., 2001</td>
<td>goal-directed</td>
<td>yes (3rd)</td>
<td>no</td>
<td>no / no</td>
<td>Foot pressing on objects / kicking a ball</td>
<td>fMRI</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>no goal-directed</td>
<td>yes (3rd)</td>
<td>no</td>
<td>no / no</td>
<td>Foot mimicking object actions</td>
<td>fMRI</td>
<td>12</td>
</tr>
<tr>
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<td>yes (3rd- sagittal)</td>
<td>no</td>
<td>no / yes</td>
<td>Foot movements</td>
<td>fMRI</td>
<td>20</td>
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<td>no goal-directed</td>
<td>no</td>
<td>no</td>
<td>yes, online (1st) / no</td>
<td>Foot movements</td>
<td>fMRI</td>
<td>12</td>
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<td>yes (3rd)</td>
<td>no / no</td>
<td>Foot pressing on objects</td>
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<td>11 SCIs / 12 Controls</td>
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<td>no / no</td>
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<td>no</td>
<td>yes (1st)</td>
<td>no / yes</td>
<td>Toe movements</td>
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<td>yes (1st)</td>
<td>no / yes (also passive)</td>
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<td>yes (1st)</td>
<td>no / no</td>
<td>Foot pressing on car accelerator</td>
<td>fMRI</td>
<td>11 SCIs / 19 Controls</td>
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<td>not goal-directed</td>
<td>no</td>
<td>yes (1st)</td>
<td>no / yes</td>
<td>Foot movements</td>
<td>fMRI</td>
<td>9 SCIs / 12 Controls</td>
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<tr>
<td>Hotz-Boendermaker et al., 2011</td>
<td>not goal-directed</td>
<td>no</td>
<td>yes (1st)</td>
<td>no / yes</td>
<td>Foot movements</td>
<td>fMRI</td>
<td>9 SCIs / 12 Controls</td>
</tr>
<tr>
<td>Jackson et al., 2006</td>
<td>no goal-directed</td>
<td>yes (1st / 3rd)</td>
<td>no</td>
<td>yes, online (1st / 3rd) / no</td>
<td>Foot movements</td>
<td>fMRI</td>
<td>16</td>
</tr>
<tr>
<td>Jastorff et al., 2010</td>
<td>goal-directed</td>
<td>yes (3rd)</td>
<td>no</td>
<td>no / no</td>
<td>Foot dragging, dropping, grasping, pushing objects</td>
<td>fMRI</td>
<td>18</td>
</tr>
<tr>
<td>Lafleur et al., 2002</td>
<td>not goal-directed</td>
<td>no</td>
<td>yes (1st)</td>
<td>no / yes</td>
<td>Foot movements</td>
<td>PET</td>
<td>9</td>
</tr>
<tr>
<td>Lee et al., 2009</td>
<td>not goal-directed</td>
<td>no</td>
<td>yes (1st)</td>
<td>no / no</td>
<td>Toe movements</td>
<td>fMRI</td>
<td>5</td>
</tr>
<tr>
<td>Orr et al., 2008</td>
<td>goal-directed</td>
<td>yes (3rd- sagittal)</td>
<td>yes (3rd- sagittal)</td>
<td>no / yes</td>
<td>Foot pressing on objects</td>
<td>fMRI</td>
<td>10</td>
</tr>
<tr>
<td>Rocca and Filippi, 2010</td>
<td>not goal-directed</td>
<td>yes (3rd)</td>
<td>no</td>
<td>no / yes</td>
<td>Foot movements</td>
<td>fMRI</td>
<td>21</td>
</tr>
<tr>
<td>Roux et al., 2003</td>
<td>not goal-directed</td>
<td>no</td>
<td>yes (1st)</td>
<td>no / yes</td>
<td>Toe movements</td>
<td>fMRI / PET</td>
<td>10 Amputees / 10 Controls</td>
</tr>
<tr>
<td>Sahyoun et al., 2004</td>
<td>not goal-directed</td>
<td>no</td>
<td>yes, preparation (1st)</td>
<td>no / yes (also passive)</td>
<td>Foot movements</td>
<td>fMRI</td>
<td>12</td>
</tr>
<tr>
<td>Sakreida et al., 2005</td>
<td>not goal-directed</td>
<td>yes (3rd- sagittal)</td>
<td>no</td>
<td>no / no</td>
<td>Foot movements</td>
<td>fMRI</td>
<td>19</td>
</tr>
<tr>
<td>Stippich et al., 2002</td>
<td>not goal-directed</td>
<td>no</td>
<td>yes (1st)</td>
<td>no / yes</td>
<td>Toe movements</td>
<td>fMRI</td>
<td>14</td>
</tr>
<tr>
<td>Wheaton et al., 2007</td>
<td>not goal-directed</td>
<td>yes (3rd)</td>
<td>no</td>
<td>no / no</td>
<td>Foot / leg movements</td>
<td>fMRI</td>
<td>12</td>
</tr>
<tr>
<td>Yuan et al., 2010</td>
<td>not goal-directed</td>
<td>no</td>
<td>yes (1st)</td>
<td>no / yes</td>
<td>Foot movements</td>
<td>fMRI</td>
<td>13</td>
</tr>
<tr>
<td>Villiger et al.</td>
<td>goal-directed</td>
<td>yes (1st)</td>
<td>yes, online (1st)</td>
<td>yes, online (1st) / no</td>
<td>Foot kicking a ball</td>
<td>fMRI</td>
<td>12</td>
</tr>
</tbody>
</table>

**Table 2.1:** fMRI / PET papers with (not) goal-directed toe / foot movements during observation, imagination and imitation. Papers only with pure execution are not listed and the viewpoint (1st- or 3rd-person) is labeled in brackets.
2.3 Methods

2.3.1 Participants
Twelve healthy volunteers participated (mean age 25 years, range 18 - 29 years, 5 females). They had normal or corrected-to-normal visual acuity, no history of psychiatric or neurological disorder and were right-footed (preferred kicking foot). Informed consent was obtained from all subjects and the experimental protocol was in accordance with the Declaration of Helsinki and performed with the approval of the local Ethics Committee.

2.3.2 Stimuli and task
The stimulus was a 5 s video clip showing a 1st-person perspective view (i.e. looking down on the feet) of a right foot kicking a ball towards a wooden goal (Fig. 2.1). At the start of the video clip both feet were together on the ground. After 0.75 s the right foot lifted and moved forwards towards the ball, kicked it sideways into the goal, and returned to the starting position. The movement phase lasted about 3.5 s. A scrambled version of the video clip (Fig. 2.1) was used as a control (baseline) for low-level visual perception (Iseki et al., 2008). The following four conditions were investigated:

1) Observation-only (O): the subjects had to carefully observe the video clip showing the goal-directed foot movement. The instruction used was: ‘Please look carefully at the video’.

2) Online motor imagination (O-MI): the subjects observed the video displaying the goal-directed foot movement and had to imagine themselves performing the movement at the same time, i.e. online). The instruction was: ‘When you see the foot moving in the video, start immediately to imagine that the presented moving foot is yours and try to control the movement in your mind by continuously watching the video’.

3) Online imitation (O-IMIT): the subjects executed a right-foot dorsiflexion, followed by a movement like a ‘windshield wiper’ going from the right to the left and back to the starting position. The instruction was: ‘When you see the foot moving on the video,
2. Online motor imagination of lower limbs

start immediately to perform the presented movement with your own foot and keep watching the video’.

4) Scrambled video clip as baseline (SCR): the subjects had to carefully observe the scrambled video clip after receiving the same instruction as in the O condition.

The subjects’ behavior was monitored with a video camera and controlled for immobility in the O, O-MI and SCR conditions and for appropriate movements during O-IMIT.

2.3.3 Neuroimaging and behavior

Before the scanning session, subjects received verbal and written information about the experiment and practiced the approach. Both the 5 s video clip and its scrambled version were presented outside the scanner. Without mentioning the O-MI task, the O and SCR conditions were presented. The instruction was given for the O-IMIT task and the required movement was performed online until it was correct.

The fMRI session consisted of 2 runs, each containing 7 blocks of 6 trials of the same condition. Each block was preceded by 1.5 s written instruction (“observe”, “observe and imagine”, “observe and imitate”). The blocks were presented within the run in pseudo-random order (Fig. 2.1). One trial consisted of a 5 s video clip followed by an inter-stimulus interval (ISI) of a duration jittered between 3.5 and 6.5 s. The ISI was a grey screen with a fixation cross.

In the first run only O and SCR were included, to avoid that the two active conditions (O-MI and O-IMIT) interfere with O. This run lasted 10 min 15 s and was followed by a rest period during which the subjects received verbal information for the tasks presented in the second run. This information was as follows: ‘While the video clip is presented, there are two new tasks, one is to imitate the movement online (“observe and imitate”) and the other to imagine the movement online (“observe and imagine”). Before the task, you will get a written instruction on the task you have to perform. After the instruction ‘observe and imagine’ you have to imagine that the presented foot is yours and you have to try to perform the
movement in your mind, while watching the video. And during the task ‘observe and imitate’ you have to make the foot movement you exercised before, while watching the video’. This second run included pseudo-randomly interleaved blocks of O-MI, O-IMIT and SCR and lasted 18 min 27 s (Fig. 2.1).

This protocol was designed to yield the same number of trials (42) in each condition. For the SCR condition, this number was achieved by cumulating the blocks of the first and second runs. The video was presented on a rear-projected screen located inside the scanner room, approximately level with the subject’s feet. The participants could see the screen via a mirror attached to the head coil, and the legs and head were stabilized to minimize movement artefacts.

![Figure 2.1: fMRI design. The session consisted of 2 runs containing a total of 7 blocks of each of the 4 conditions. Each block contained 6 trials of the same condition. Each block was preceded by the presentation (1.5 s) of an instruction. Within a run the blocks were presented in pseudo-random order. Each trial consisted of a 5 s video clip followed by an inter-stimulus interval (ISI) with a duration jittered between 3.5 and 6.5 s. In the first run only the O and SCR conditions were included. The second run included blocks of O-MI, O-IMIT and SCR. The protocol was conceived to yield the same number of trials in each condition (42).](image)

After the scanning session, participants completed the kinesthetic part of the Vividness of Motor Imagery Questionnaire (VMIQ) (Isaac et al., 1986). In addition, they rated their subjective ability to mentally perform the foot movement using a 5-point rating scale from 1 (best) to 5 (worst).
Electromyographic (EMG) activity was recorded in four subjects after the scanning outside the scanner, using dual surface electrodes (Noraxon, Cologne, Germany) placed on the anterior tibialis muscle of the right leg. The EMG signals were amplified, band-pass filtered (10-500 Hz) and rectified. All signals were sampled at 1500 Hz and the muscle activity during the four conditions was analyzed by calculating the root mean square (RMS). The RMS values of the EMG responses of the conditions were compared to each other.

2.3.4 Neuroimaging data acquisition

The functional images were measured with T2*-weighted echo-planar images (EPIs) with blood-oxygenation-level-dependent (BOLD) contrast on a 3-T, whole-body, MRI scanner (Philips Medical Systems, Eindhoven, The Netherlands) equipped with an 8 channel SENSE™ head coil. The stimulus presentation was controlled and synchronized with the fMRI scanning using Presentation (Neurobehavioral Systems Inc., Albany, CA, USA).

The image acquisition parameters were as follows: repetition time (TR) = 3 s, echo time (TE) = 35 ms, flip angle (FA) = 82°, field of view (FOV) = 220 mm, matrix = 80 x 80 mm, 45 slices with 3 mm thickness without gap, voxel size = 2.75 x 2.75 x 3 mm. The first five images were discarded to allow for signal stabilization, the following 610 volumes were collected and stored.

2.3.5 Neuroimaging data analysis

All fMRI analyses were performed using SPM5 (Welcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). Functional images from each subject were realigned, spatially normalized into the Montreal Neurological Institute (MNI) space with a resolution of 2 x 2 x 2 mm and then smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel. For removing the low frequency noise, a high-pass filter with a cut-off of 128 s was used. Data were analyzed using a random-effect model to allow for population inferences (Friston et al., 1999). The general linear model (GLM) was fitted for each subject by a design matrix comprising the onsets and durations of each condition.
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(video) and convolved with the standard canonical hemodynamic response function. The four conditions described previously were included in the model. Six regressors (of no interest) were incorporated to account for rigid-body movement effects. Respective parameter estimates (beta) and contrast images (cons) were computed by voxelwise comparisons.

To determine the group activation in the three conditions (O, O-MI and O-IMIT) and for the baseline (SCR), the single-subjects contrasts were entered into a second-level analysis for each of the contrasts (t-tests and a flexible full factorial ANOVA completed with post-hoc t-tests). The designed neuroimaging analyses were used to achieve three objectives. First, we wanted to determine the neural regions which were activated during O, O-MI and O-IMIT. Therefore, main effects of O, O-MI and O-IMIT conditions were contrasted with the baseline (SCR) condition using a one-sample t-test. Second, six contrasts were defined using paired t-test for O vs O-MI and vice-versa, O vs O-IMIT and vice-versa, and O-MI vs O-IMIT and vice-versa. Finally, to determine areas of overlapping brain regions a conjunction analysis was conducted (conjunction null method) (Nichols et al., 2005). The resulting SPM(T) maps were thresholded at p < 0.05 (cluster-level false discovery rate [FDR] corrected, cluster extent threshold > 10 voxels) (Worsley et al., 1996). For completeness but not further discussed, voxels showing task-related differences that did not survive correction for multiple comparisons but showed a p-value of < 0.001 are reported as statistical trends in the results section. Percent signal changes of the BOLD responses (± standard error of the mean [SEM] across subjects) were computed for the group local maxima in selected conjunction activated regions for each condition (O, O-MI and O-IMIT).

All imaging results were displayed on either rendered cortical surface or on slices of a high-resolution structural MRI scan of a standard brain from the MNI. Anatomical identification was performed with the WFU PickAtlas (Wake Forest University, Winston-Salem, NC, v2.4) and the included Anatomic Automatic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003). The cortical identified regions included the paracentral lobule (M1/S1), the pre- and supplementary motor area (preSMA, SMA), cingulate gyrus (CG), precentral
gyrus and frontal operculum (PMd and PMv), superior parietal lobule (SPL), inferior parietal lobule (IPL) and precuneus (PCu), prefrontal cortex (PFC), insula (INS), hippocampus (HC), and occipitotemporal cortex (OTC). And subcortically, the thalamus (THAL), putamen (PUT), caudate nucleus (CN), and cerebellum (CB–peak location based on Schmahmann et al., 1999) were selected.

2.4 Results

2.4.1 Imaging results

2.4.1.1 Effects of the conditions

To obtain the activation patterns specific to the O, O-MI and O-IMIT conditions, each condition was first contrasted with the SCR condition (baseline). The group results are summarized in Table 2.2. Overall, the distribution and strength of the activations increased from O to O-MI to O-IMIT.

The O condition activated a region in the medial wall of the parietal lobe, identified as the posterior PCu, a multimodal sensory input integration area. Additional foci were found in the left posterior THAL. Low-level visual activations were excluded by the scrambled baseline, i.e. no V1 activation, but the observation of the foot movements still activated bilaterally the OTC. Voxel showing task-related differences that did not survive correction for multiple comparisons across the whole brain, but showed a p-value of < 0.001, are the left IPL (-56, -30, 24), the right posterior THAL (20, -30, 4) and the CB (Crus I; 40, -60, -32). These regions are not listed in Table 2.2.

During the O-MI condition all the cortical areas detected in the O condition, i.e. PCu, IPL and OTC, were also activated. In addition to the O condition, PM areas involved in motor imagery were also activated and an important new focus was located in the left anterior INS. Subcortically, foci were found in the left PUT and anterior THAL and in the right CB (Crus I). Additionally, subthreshold activations (p < 0.001, not listed in Table 2.2) were observed in the
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left inferior PFC (-46, 12, 8), preSMA (-6, 14, 43), the right PUT (21, -2, 10), bilateral CN (left: -18, -10, 19; right: 10, 7, 2), and the left CB (Cr us I: -38, -56, -32).

As expected, the O-IMIT condition activated an extensive motor cortical network including the foot representation in the left M1/S1 cortex and SMA. These regions were activated neither in the O nor in the O-MI conditions. In addition, O-IMIT activated more strongly almost all areas found in the O-MI condition, i.e. preSMA, bilateral PMv, IPL and OTC, PCu and, subcortically, left anterior THAL and bilateral CB. Two small foci (p < 0.001, not listed in Table 2.2) were additionally detected in the right HC (16, -8, -12) and the left mediolateral PFC (-32, 34, 34).

<table>
<thead>
<tr>
<th>Region</th>
<th>Left/Right</th>
<th>O &gt; SCR</th>
<th>O-MI &gt; SCR</th>
<th>O-IMIT &gt; SCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracentral lobule (M1/S1)</td>
<td>L</td>
<td></td>
<td>-4 -36 72</td>
<td>6.18 75</td>
</tr>
<tr>
<td>Supplementary motor area (SMA)</td>
<td>L/R</td>
<td></td>
<td>-6 -12 64</td>
<td>10.74 1284</td>
</tr>
<tr>
<td>Presupplementary motor area (preSMA)</td>
<td>L/R</td>
<td></td>
<td>6 4 46 10</td>
<td>20 1084</td>
</tr>
<tr>
<td>Ventral premotor cortex (PMv)</td>
<td>L</td>
<td>-52 6 2</td>
<td>6.49 83 56</td>
<td>8 2 5.64 54</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>56 8 2</td>
<td>5.64 54</td>
<td>50 5 0 7.35 74</td>
</tr>
<tr>
<td>Precuneus (PCu)</td>
<td>L/R</td>
<td>6 -66 32</td>
<td>7.66 606</td>
<td>50 6 -64 63</td>
</tr>
<tr>
<td>Inferior parietal lobule (IPL)</td>
<td>L</td>
<td>-50 -46 24</td>
<td>5.74 46</td>
<td>60 -34 28 4.99 55</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td></td>
<td>-54 -68 2</td>
<td>8.49 241</td>
</tr>
<tr>
<td>Occipitotemporal cortex (OTC)</td>
<td>L</td>
<td>-52 -70 4</td>
<td>6.52 271</td>
<td>42 -74 2 7.32 292</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>46 -60 18</td>
<td>8.49 305</td>
<td></td>
</tr>
<tr>
<td>Insula (INS)</td>
<td>L</td>
<td>-32 8 10</td>
<td>5.38 48</td>
<td>-40 -14 -6 6.99 111</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus (THAL)</td>
<td>L</td>
<td>-22 -26 6</td>
<td>6.10 58</td>
<td>-14 -6 4 5.48 54</td>
</tr>
<tr>
<td>Putamen (PUT)</td>
<td>L</td>
<td>-22 0 12</td>
<td>6.96 56</td>
<td></td>
</tr>
<tr>
<td>Cerebellum (CB) Lobule VI</td>
<td>L</td>
<td></td>
<td>-18 -72 24</td>
<td>7.03 60</td>
</tr>
<tr>
<td>Cerebellum (CB) Crus I</td>
<td>L</td>
<td></td>
<td>-38 -54 34</td>
<td>7.40 79</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>40 -62 30</td>
<td>9.47 137</td>
<td>40 -58 30 10.24 300</td>
</tr>
</tbody>
</table>

Table 2.2: MNI coordinates for group activations for observation-only (O), online motor imagination (O-MI) and online imitation (O-IMIT) versus the baseline (SCR) condition. A threshold of p < 0.05 was applied after correction for multiple comparisons using the FDR method (cluster extent threshold k > 10 voxels).
2. Online motor imagination of lower limbs

2.4.1.2 Interaction effects

Contrasts between O, O-MI and O-IMIT

In the second level analysis, the conditions were contrasted with each other to reveal the activations specific to each condition (Table 2.3). The contrasts between the O condition and the other conditions (O > O-MI and O > O-IMIT) did not reveal any significant differences in activation.

<table>
<thead>
<tr>
<th>Region</th>
<th>Left/Right</th>
<th>O-MI &gt; O</th>
<th>O-IMIT &gt; O</th>
<th>O-IMIT &gt; O-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracentral lobule (M1/S1)</td>
<td>L</td>
<td>x -4, y 38, z 72, t 5.93, Vol 102</td>
<td>x -4, y 6, z 70, t 9.67, Vol 1265</td>
<td>4, y -6, z 46, t 13.82, Vol 1910</td>
</tr>
<tr>
<td>Supplementary motor area (SMA)</td>
<td>L/R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presupplementary motor area (preSMA)</td>
<td>L/R</td>
<td>4, x 20, y 46, t 6.85, Vol 48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate gyrus (CG)</td>
<td>L/R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventral premotor cortex (PMv)</td>
<td>L</td>
<td>-52, x 2, y 0, z 7.67, t 297</td>
<td>-56, x 6, y 2, z 9.55, t 1613</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>54, x 4, y 0, z 7.22, t 184</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus (PCu)</td>
<td>L</td>
<td>-8, x 52, y 72, z 10.59, Vol 856</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior parietal lobule (IPL)</td>
<td>L</td>
<td>-42, x 56, y 50, z 5.72, t 55</td>
<td>-62, x 22, y 14, z 10.03, t 495</td>
<td>52, x 38, y 34, z 6.52, t 292</td>
</tr>
<tr>
<td>R</td>
<td>58, x 22, y 30, z 4.92, t 43</td>
<td>-62, x 22, y 36, z 11.17, t 950</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula (INS)</td>
<td>L</td>
<td>-32, x 12, y 6, z 5.46, t 47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen (PUT)</td>
<td>L</td>
<td>-24, x 12, y 0, z 10.73, t 102</td>
<td>-22, x 8, y 6, z 11.78, t 936</td>
<td>34, x 0, y 4, z 8.63, t 521</td>
</tr>
<tr>
<td>R</td>
<td>-20, x 28, y 5, z 43, t 51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum (CB)</td>
<td>Lobule VI</td>
<td>L</td>
<td>-22, x 70, y 22, z 6.81, t 212</td>
<td>-30, x 50, y 32, z 10.86, t 500</td>
</tr>
<tr>
<td>R</td>
<td>28, x 56, y 28, z 5.14, t 71</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.3: MNI coordinates of contrasts for O-MI > O, O-IMIT > O and O-IMIT > O-MI (observation-only (O), online motor imagination (O-MI) and online imitation (O-IMIT). A threshold of p < 0.05 was applied after correction for multiple comparisons using the FDR method (cluster extent threshold k > 10 voxels).

The most prominent contrast was between O-MI and O which revealed a strong increase in activation in preSMA, in PMv and IPL bilaterally, and in the left INS and PUT (Fig. 2.2). PMv had the broadest and strongest activation. Most regions are involved in both kinesthetic motor imagery and movement execution.

The O-IMIT > O contrast revealed regions specific to motor execution, such as M1/S1, SMA, PMv and PUT in the left hemisphere contralateral to the moving right foot. The activation patterns also included foci in the anterior CG, bilateral IPL and in both lobules VI of the CB.
 Compared to the O condition, a more anterior part of the PCu was activated. This region has been shown to be functionally more connected to the motor cortex (Margulies et al., 2009).

The contrast O-IMIT > O-MI revealed enhanced activation in the right SMA and IPL, but not in M1/S1. Additional activations were found in the right PUT and in the left CB (lobules VI). The inverse contrast O-MI > O-IMIT did not reveal any significant activation changes in cortical and subcortical regions.

![Activation patterns during right foot movements in healthy subjects from the contrast O-MI > O are displayed. The significant regions are listed in Table III. Results are superimposed on the MNI template. Numbers in the color bar correspond to t-values. Abbreviations: preSMA: presupplementary motor area; PMv: ventral premotor cortex; IPL: inferior parietal lobe; INS: insula; PUT: putamen.](image)

**Figure 2.2:** Activation patterns during right foot movements in healthy subjects from the contrast O-MI > O are displayed. The significant regions are listed in Table III. Results are superimposed on the MNI template. Numbers in the color bar correspond to t-values. Abbreviations: preSMA: presupplementary motor area; PMv: ventral premotor cortex; IPL: inferior parietal lobe; INS: insula; PUT: putamen.

**Conjunction**

The conjunction analysis of the three conditions taken together (O + O-MI + O-IMIT) revealed strong common bilateral activation in the OTC (left: -52, -70, 4; right: 44, -72, 0) and subthreshold activation (p < 0.001) in left SPL (-36, -46, 68), PCu (-6, -60, 52) and right CB (Crus I: 40, -60, -28).
Of greater interest were the shared regions in the pair-wise conjunctions of O and O-MI, of O and O-IMIT and of O-MI and O-IMIT. In the conjunctions of O and O-MI and of O and O-IMIT the same clusters as in the conjunction of all three conditions taken together were activated. In contrast, the interesting conjunction of O-MI and O-IMIT revealed shared activation in additional regions, i.e. in left PMv, in IPL bilaterally and in left INS (Fig. 2.3 and Table 2.4). In addition, subthreshold activations (p < 0.001, not listed in Table 2.4) were shown in the right PMv (54, 4, 4) and INS (32, 18, 8) and subcortically, shared activations were found in left THAL (-8, -22, 4) and PUT (-28, -2, 16).

Figure 2.3: Conjunction (shared activations) of O-MI and O-IMIT are displayed in the left two columns. Significant regions are listed in Table IV. The results are superimposed on the MNI template and numbers in the color bar on the left side correspond to t-values. In the right column, percent signal changes of the BOLD responses (± SEM across subjects) for the group local maximum in left PMv, right IPL, right OTC, and left INS are shown in each condition (O, O-MI and O-IMIT). Abbreviations: same as Fig. 2; OTC: occipitotemporal cortex.
Table 2.4: Conjunction (shared activations) of O-MI and O-IMIT. A threshold of p < 0.05 was applied after correction for multiple comparisons using the FDR method (cluster extent threshold k > 10 voxels). Underlined peak coordinates are given in Fig. 2.3.

2.4.2 Behavioral assessment

The mean rating of the kinesthetic part of VMIQ from 1 (image as vivid as normal vision) to 5 (no image at all) (Isaac et al., 1986) was 2.1 (SD = 0.7). Hence, the imagined movements were on average very clear and vivid. Additionally, the subjects had to rate their subjective ability to imagine themselves simultaneously performing the observed foot movement with a scale from 1 (best) to 5 (worst). All reported that they had no difficulty to imagine themselves in the position of the acting person displayed in the videos and controlling the foot movement. The mean rating was 1.7 (SD = 0.7). The correlation between the two ratings was highly significant (Pearson R = 0.696, p < 0.05). No activity was found in the right anterior tibialis muscle during O and O-MI. In contrast, the EMG activity significantly increased during O-IMIT when compared to the O and O-MI recordings (p < 0.05).

2.5. Discussion

Our aim was to compare the neuronal activation pattern revealed by observation of a goal-directed action (O) with that evoked when the subject imagines him/herself performing the action simultaneously (O-MI). The control condition of O-MI was observation with online imitation (O-IMIT). The results confirmed our prediction that O-MI compared to O induced broader and stronger activations in the foot motor network. In addition O-MI activated regions
similar to those involved in O-IMIT. These results confirm our expectations that O-MI can be as effective as motor execution in order to activate the motor control system.

2.5.1 Online motor imagination (O-MI) compared to passive observation (O)

In humans the action observation network is activated by the observation of bodily movements and consists of a broad network of brain regions involved in visual analysis of action and visuomotor performance (Cross et al., 2009). In our investigation, the simple observation (O) of a goal-directed foot movement yielded the weakest and most restricted activation pattern. Strong activations were mostly found in the visually processing posterior part of the PCu (Margulies et al., 2009) and OTC regions, which transmit information from earlier visual areas (Jastorff & Orban, 2009) to the parietal and PM components of the action observation network (Cross et al., 2009).

In our study, the observed signal change in the IPL and PM during observation did not reach the statistical threshold. Investigations of observation of goal-directed hand movements, also did not consistently find PM activation (Van Overwalle & Baetens, 2009). Other studies on observation of transitive or intransitive foot movements reported only weak activations in these regions (Orr et al., 2008; Hotz-Boendermaker et al., 2011). However, activation in the parietal and PM regions during observation of intransitive foot movements was present when attention was required in a forced-choice paradigm (Sakreida et al., 2005).

In contrast to the O condition, O-MI consistently activates regions in IPL and PMv. In addition, neural correlates of motor imagery, such as in preSMA and basal ganglia, were detected when the two conditions were contrasted (see for review Table 2.1 and Munzert et al., 2009). Up to now, only one investigation has combined observation and imagination of dance sequences (Cross et al., 2006). It revealed activation patterns similar to those of our present study, though with small additional activation foci in M1 and S1.

In our experiment, all participants reported that they were able to perform 1st-person kinesthetic motor imagery while simultaneously observing the video clip displaying the goal-
directed foot movement. This was supported by the strong significant correlation between the general ability to perform kinesthetic motor imagery, as assessed by the VMIQ, and the participants’ subjective rating of their ability to perform the task. In our previous studies on kinesthetic motor imagery of lower limb movements, activation patterns similar to those in the present study had been reported (Alkadhi et al., 2005; Hotz-Boendermaker et al., 2008).

Most investigations on motor imagery of foot movements have given support to the concept that the motor network is more activated when stimuli are presented in the 1st-person perspective (Lafleur et al., 2002; Stippich et al., 2002; Ehrsson et al., 2003; Roux et al., 2003; Alkadhi et al., 2005; Enzinger et al., 2008; Hotz-Boendermaker et al., 2008; Yuan et al., 2010; Hotz-Boendermaker et al., 2011).

In the present O-MI condition, activation foci were also disclosed in PCu and INS. Such activation of PCu has been elicited by the 1st-person motor imagery of walking in a virtual environment (Iseki et al., 2008). The PCu is located in the mesial posterior cortex and has been shown to be activated by self-related stimuli and engaged in self-related mental representations and visual-spatial imagination tasks (Cavanna & Trimble, 2006; Northoff et al., 2006). With respect to the anterior INS, activation has been reported for cognitive processes, such as attention and control of goal-directed tasks (Dosenbach et al., 2008; Nelson et al., 2010). Furthermore, Farrer & Frith (2002) also suggested that this region is linked to the awareness of causing an action, i.e. sense of agency.

### 2.5.2 Control condition: online imitation (O-IMIT) of a transitive foot movement

The functional network activated during observation with synchronous imitation (O-IMIT) of transitive movements of the lower extremity has not yet been reported. In the present study this condition was used as a control, to test the role of execution in the activation patterns under the same conditions as O-MI. When contrasting O-IMIT with O, activations were found similar to those reported for execution, i.e. M1/S1, SMA, PUT and CB as expected (Dobkin et al., 2004; Sahyoun et al., 2004; Hotz-Boendermaker et al., 2008).
To our knowledge, the only investigations comparable to ours are those of Chaminade et al. (2005) and Jackson et al. (2006). Both studies included 5 s video clips of single hand or foot movements presented in 1st-person perspective. In the study by Chaminade et al. (2005), the subjects were required to perform the presented hand or foot gestures or to execute another gesture, either with the same or the other limb (hand or foot). They proposed that increased bilateral occipitotemporal activity was associated with increased visual attention and that visuospatial description of the body was mainly sustained by the IPL. Jackson et al. (2006) addressed the question of perspective. The video clips were presented either in the 1st- or 3rd-person perspective and the subjects either watched (observation) or imitated the actions in synchrony (imitation). They clearly showed that imitation during observation in the 1st-person perspective preferentially recruits motor regions while activation is shifted towards visual areas in the 3rd-person perspective. The activation patterns found in our present O-IMIT condition in the 1st-person perspective were comparable to the findings of this latter study, especially in M1/S1, PMv, IPL, PCu and CB. Therefore, the 1st-person perspective during O-IMIT may facilitate the integration of kinesthetic information and improve the reproduction of the action (Jackson et al., 2006).

In both studies mentioned above the movements were intransitive. To our knowledge, only two studies have compared imitation of goal-directed and not goal-directed hand and finger movements (Koski et al., 2002; Grezes et al., 2003). For foot movements, this issue needs to be systematically tested in future experiments.

### 2.5.3 What is common to O-MI and O-IMIT?

We showed in previous publications that kinesthetic motor imagery and execution of foot movements are closely related and may even be one and the same phenomenon with just quantitative variations of the same continuum (Hotz-Boendermaker et al., 2008). This finding is validated in the present study by the contrasts between the conditions and their conjunctions.
The contrast between O-IMIT and O-MI revealed enhanced activation in SMA and right IPL, but not in M1/S1. This last finding could indicate that O-MI also activated the primary motor representation, although at a sub-threshold level, as has been previously suggested for motor imagery of hand movements (Porro et al., 1996). Studies on motor imagery of lower limbs have reported either M1/S1 activation (Ehrsson et al., 2003; Orr et al., 2008) or no activation (Enzinger et al., 2008; Hotz-Boendermaker et al., 2008).

The conjunction of the O-MI and the O-IMIT conditions revealed a large number of shared regions, several of them belonging to the execution network, such as parietal and PM regions and ipsilateral CB (Sahyoun et al., 2004; Jackson et al., 2006; Orr et al., 2008). Together with the lack of findings in the contrast between O-MI and O-IMIT, this conjunction strongly suggests that the motor execution network can be engaged when the observation of an action is combined with simultaneous motor imagery, i.e. by the imagination that the action is performed by the subject. This conjunction also revealed activations in other interesting regions related to the perception or feeling of the self, such as in the anterior INS and the part of the IPL expanding in this study to the temporal-parietal junction. This region has been shown to be involved in the perception of the self and of its interactions with the external world and therefore to be a neural correlate of body ownership (Tanaka et al., 2001; Blanke et al., 2002; Farrer & Frith, 2002; Blanke et al., 2004; Arzy et al., 2006; Ionta et al., 2011).

2.5.4 Implications for motor learning and rehabilitation

In conclusion, the results of this study extend previous findings promoting the use of motor imagery, or of imitation, as therapeutic approaches in lower limb neurorehabilitation (Buccino et al., 2006; Dickstein & Deutsch, 2007; Garrison et al., 2010; Malouin & Richards, 2010). The recruitment of similar neuronal populations during O-MI or O-IMIT should facilitate post-injury retaining of function and potentially promote functional recovery. These findings may thus have a clinical value for neurorehabilitation when motor programs are still at least partly present, as it is often the case in stroke (Dobkin et al., 2004) or spinal cord injury patients.
2. Online motor imagination of lower limbs

(Hotz-Boendermaker et al., 2008). An open and important question is how the activation patterns will change after long-term training in the condition O-MI and how their shaping over time will correlate with improved motor performance.

2.6 Acknowledgment

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3. Virtual reality rehabilitation system for neuropathic pain and motor dysfunction in spinal cord injury patients

3.1 Abstract

Spinal cord injury (SCI) causes both lower limb motor dysfunction and associated neuropathic pain. Although these two conditions share related cortical mechanisms, different interventions are currently used to treat each condition. With intensive training using entertaining virtual reality (VR) scenarios, it may be possible to reshape cortical networks thereby reducing neuropathic pain and improving motor function. We have created the first VR training system combining action observation and execution addressing lower limb function in incomplete SCI (iSCI) patients. A particular feature of the system is the use of size-adjustable shoes with integrated motion sensors. A pilot single-case clinical study is currently being conducted on iSCI patients. Two patients tested to date were highly motivated to perform and reported improved physical well-being. They improved in playing skill and in controlling the virtual lower limbs. There were post-intervention indications of neuropathic pain decrease, muscle strength increase, faster walking speed and improved performance on items relevant for ambulation. In addition functional MRI before and after treatment revealed a decreased activation pattern. We interpret this result as an improvement of neuronal synergies for this task. These results suggest that our VR system may be beneficial for both reducing neuropathic pain and improving motor function in iSCI patients.

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2This manuscript is published in Proceedings of the International Conference on Virtual Rehabilitation, 2011, doi: 10.1109/ICVR.2011.5971865. The authors are Michael Villiger, Marie-Claude Hepp-Reymond, Pawel Pyk, Daniel Kiper, Jeremy Spillmann, Bruno Meilick, Natalia Estévez, Spyros S. Kollias, Armin Curt, Sabina Hotz-Boendermaker and Kynan Eng. Data were assessed and analysed by Michael Villiger. The manuscript was written by Michael Villiger and revised by the co-authors.
3.2 Introduction

Injury of the spinal cord often leads to long lasting lower limb motor dysfunction and associated neuropathic pain. These problems are challenging to treat and new approaches are needed to relieve chronic pain. Over the past two decades it has been established that observation of goal-directed actions, motor imagery and action execution activate overlapping cortical networks (for reviews see Rizzolatti & Craighero, 2004; Buccino et al., 2006; Caspers et al., 2010). Hotz-Boendermaker et al. (2008) showed that it was possible to activate these networks even in complete SCI patients during attempted, imagined and observed foot movements. These findings suggest that it may also be possible to activate cortical motor networks in iSCI patients that still project through non-injured parts of the spinal cord onto muscle effectors. In addition, there is evidence that neuropathic pain in SCI patients may be caused by a mismatch between motor output and sensory feedback, which may be reduced by employing motor imagery combined with visual illusions of virtual limbs (Moseley, 2007). Hence, neuropathic pain and motor dysfunction might share related cortical mechanisms, and interventions which directly address these mechanisms might bring substantial benefits to iSCI patients.

We believe that the best way to activate cortical areas related to both action observation and execution is using a VR-based interactive visuo-motor intervention. Due to technological progress the use of VR is currently expanding. VR systems are attractive for various research fields and applications in rehabilitation. Most lower limb rehabilitation systems using VR focused on posture, balance and walking and were used in a variety of populations, but less was done regarding goal-directed movements (Holden, 2005; Deutsch et al., 2007; Adamovich et al., 2009).

Here, we focus on goal-directed movements and the application of VR technology in therapy to assist users with distraction from pain and automation of motor therapy by physical support of constricted movements and enhancement of patient motivation (Eng et al., 2007). Clinical assessments before and after treatment aimed to test the hypothesis that training
with the VR rehabilitation system reduces pain and improves lower limb motor function in iSCI patients.

3.3 Methods

3.3.1 Study design

The study was designed as a single-case series. The main inclusion criteria were:

- Incomplete SCI (AIS C or D) with preserved motor function below the lesion level.
- Normal or corrected-to-normal visual acuity.
- No history of psychiatric or other neurological disorders.
- Right handed (test applied according to the Edinburgh Inventory) (Oldfield, 1971) and footed (preferred kicking foot).

All patients were aware of the purpose of the study. Informed consent was obtained from the patients and the experimental protocol was in accordance with the Declaration of Helsinki and performed with the approval of the local Ethics Committee.

3.3.2 VR rehabilitation system (intervention)

The participants were trained 16-20 times during a period of 4 weeks (4-5 x 45-minutes per week). The VR rehabilitation system consists of a PC and a large-screen display (132 cm diagonal) showing life-size virtual representations of the feet and legs. Adjustable shoes incorporate inclination angle sensors (accelerometers) in the foot and lower leg. Due to elastic components built into the shoes, it can be quickly fitted to patients with different-sized feet (Fig. 3.1).

A menu system based on a virtual assistant was developed to make the system as easy to use as possible for therapists. In consultation with physical therapists, motivating VR scenarios were created to provide clinically relevant interactions for training foot and leg movements in a sitting or standing position. The existing scenarios are (Fig. 3.2):
1) Footbag: A simple exercise in which the patient juggles a bag between the left and right foot, using dorsal ankle flexion movements (tibialis anterior [TA] contraction), a necessary exercise to prevent foot dragging. The trajectory of the bag is pre-set so that it always moves correctly through the air between the left and right feet.

2) Hamster splash: Hamsters run up to the patient’s toes. The patient’s task is to perform a dorsal flexion of the ankle to launch each hamster into a swimming pool. The reward for launching the hamsters higher (faster ankle movement) is a higher score and more elaborate hamster movements (somersaults, swimming patterns).

3) Star kick: The patient performs a knee extension by kicking a ball towards the displayed stars. For every hit, the patient receives a reward.

4) Planet drive: Cars are moving on a planet highway towards the virtual feet. The patient’s task is to avoid touching the cars by displacing the foot and legs sideways.

In each session, scenario acceptance level, performance and pain level were collected. Additionally, patients filled in a questionnaire after the session to measure how well they could immerse in the tasks, whether they had the feeling that the presented virtual feet and legs were theirs and how well they could control them as previously showed (Tsakiris et al., 2010).

Figure 3.1: Overview of VR rehabilitation system.
3.3.3 Clinical assessments

Besides the training program, both pain and motor function were investigated to test for possible transfer effects between the two. Data on pain were collected using a structured interview called the Pain Protocol which was developed at Balgrist University Hospital and is currently being evaluated in a multicenter study within the EM-SCI framework (European Multicenter Study about Spinal Cord Injury, www.emsci.org) and the Neuropathic Pain Scale (NPS) assessing distinct pain qualities associated with neuropathic pain (Galer & Jensen, 1997). The following measurements were performed to quantify motor function:

- **American Spinal Cord Injury Association Impairment Scale (AIS)** - classification of individuals with SCI (A-E): information about the motor level of the lesion determining effort from 0 (total paralysis) to 5 (active movement, full range of motion, against gravity and provides normal resistance) of key muscles (for lower limb: hip flexors, knee extensors, ankle dorsiflexors, long toe extensors and ankle plantar flexors) and information on the sensory levels of the lesion tested with light touch and pin prick (Marino et al., 2003; Labruyere et al., 2010).

- **Spinal Cord Independence Measure (SCIM)** - assessing activities of daily life and independence in subjects with spinal cord lesion (Catz et al., 2007).
3. Virtual reality rehabilitation system

- Walking Index for Spinal Cord Injury II (WISCI II) - assessing the need to rely on walking aids and/or personal assistance (Dittuno & Ditunno, 2001).
- Berg Balance Scale (BBS) - assessing balance during functional activities (Berg et al., 1995).
- 10 Meter Walking Test (10MWT) - examining gait speed over 10 m (van Hedel et al., 2005; 2006).
- Transcranial Magnetic Stimulation-Motor Evoked Potential (TMS-MEP) - noninvasive method to excite cortical neurons and measure changes in corticospinal tract function (Thomas & Gorassini, 2005; Villiger et al., 2011a).
- Video analysis (VA) - assessing locomotion.

In addition, to gain insight into possible cortical reorganizational processes before and after the intervention, each patient was asked to play the “footbag” scenario in a 1.5T Magnetic Resonance Imaging (MRI) scanner. These fMRI data were analyzed using SPM 5.

3.4 Results

To date, the training sessions have been completed by two chronic iSCI patients (AIS D) with preserved motor function below the lesion level and at least half of the key muscles below the level of lesion have the full range of motion against gravity (Table 3.1). In addition, Patient 2 complained about neuropathic pain below the lesion level.

3.4.1 VR rehabilitation system (intervention)

The patients tested so far enjoyed the scenarios, were highly motivated to perform the VR tasks and reported improvements in their physical well-being. Fig. 3.3 displays the performance of the patients during the “footbag” scenario (game time = 120 s); the patients also improved similarly in the other scenarios. Over time, the patients reported better identification with the presented virtual feet and legs as demonstrated by the results of the questionnaires regarding control and feelings for the VR lower limbs. In parallel, enhanced ability to play the scenarios resulted in stronger feelings of controlling the virtual limbs. In
addition, Patient 2 was also distracted from pain while playing and reported a decreased sense of pain after playing.

<table>
<thead>
<tr>
<th>Pat</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Age at injury (years)</th>
<th>Lesion level</th>
<th>AIS</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>70</td>
<td>68</td>
<td>C8</td>
<td>D</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>60</td>
<td>58</td>
<td>T4</td>
<td>D</td>
<td>yes</td>
</tr>
</tbody>
</table>

**Table 3.1:** Clinical data of the iSCI patients

3.4.2 Clinical assessments

Table 3.2 shows the key clinical results of the pain and motor function assessments. Patient 2 reported a slightly decreased pain sensation after the intervention on the Numerical Rating Scale (NRS). Overall, the muscle strength (ASIA lower limb motor score - LEMS) increased, especially for the TA muscle. Hence, foot lifting was easier to perform, a finding also reflected in better locomotion (WISCI II, VA) and walking speed (10MWT) in both patients. They also improved in balance tasks (BBS, e.g. standing on one leg) which is important for ambulation and in daily life activities (SCIM). Interestingly, the relative MEP latency of the TA muscle improved significantly in patient 2 (Latency MEP/height). The fMRI measurements showed a similar but weaker activation pattern after intervention (Fig. 3.4, FWE correction, p < 0.05, extent threshold k = 10).
3. Virtual reality rehabilitation system

<table>
<thead>
<tr>
<th></th>
<th><strong>Patient 1</strong></th>
<th><strong>Patient 2</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before intervention</td>
<td>After intervention</td>
</tr>
<tr>
<td>Pain intensity on a NRS (0-10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LEMS (points)</td>
<td>47 / 50</td>
<td>49 / 50</td>
</tr>
<tr>
<td>10MWT (s)</td>
<td>12.9</td>
<td>10.8</td>
</tr>
<tr>
<td>WISCI II (points)</td>
<td>16 / 20</td>
<td>19 / 20</td>
</tr>
<tr>
<td>BBS (points)</td>
<td>50 / 56</td>
<td>54 / 56</td>
</tr>
<tr>
<td>SCIM (points)</td>
<td>33 / 40</td>
<td>34 / 40</td>
</tr>
</tbody>
</table>

Table 3.2: Clinical assessments before and after interventions

Figure 3.4: Activation pattern while playing “footbag” scenario in a 1.5T MRI-Scanner - 1a) Patient 1 before intervention, 1b) Patient 1 after intervention, 2a) Patient 2 before intervention, 2b) Patient 2 after intervention.

3.5 Discussion

The testing of the VR rehabilitation method combining action observation with execution showed promising results. The new training system was well accepted by the patients and seemed to be enjoyable even when they were not familiar with VR. The motivational aspect is high, which is promising for simple training of repetitive movements. In addition, goal-oriented scenarios (rather than just locomotion) and adaptable difficulty levels in the VR system might improve patient concentration and the efficacy of the rehabilitation. The VR rehabilitation system requires active patient effort at all times and the results demonstrated improvement of lower limb motor functions that are relevant in ambulatory functions and a small reduction of pain intensity. The similar but weaker activation pattern after intervention measured with fMRI revealed a direct effect of treatment as an improvement of neuronal synergies on cortical activity.
As the single cases showed promising results, further randomized controlled trials will be conducted to gain evidence for future therapeutic applications of this system in iSCI patients. Furthermore, testing of the efficacy of the transfer effects between motor functioning and neuropathic pain evaluation will be extended. The optimization of the training will maximize the potential benefits of the VR system for neurorehabilitation.
4. Virtual reality-augmented neurorehabilitation improves motor function and reduces neuropathic pain in incomplete spinal cord injury patients

4.1 Abstract

To assess the effectiveness of virtual reality (VR)-augmented neurorehabilitation in improving lower limb function and neuropathic pain in chronic, incomplete spinal cord injury (iSCI) patients. It was hypothesized that intense training of observed and executed leg movements in VR would have beneficial effects on limb function and neuropathic pain. Patients used a VR system with a 1st-person view of virtual lower limbs, controlled via movement sensors fitted to the patient’s own shoes to provide vivid feedback between real and virtual limb movements. Four tasks were used to deliver intensive training of individual muscles (tibialis anterior, quadriceps, leg ab-/adductors. The tasks were designed to engage the patients’ motivation through feedback of task success. 14 chronic iSCI patients were treated over 4 weeks in 16-20 sessions of 45-minutes. The training was accepted by all patients with high enjoyment, motivation and attention. Besides subjective positive changes expressed by the patients (PGIC), objective measures of walking capacity, balance and strength (10MWT, SCIM, WISCI II, BBS, LEMS, locomotion) revealed significant improvements in lower limb function. In addition, intensity and unpleasantness of neuropathic pain were reduced. The overall findings remained stable 12-16 weeks after termination of the training. VR-augmented training can provide beneficial effects for motor function and neuropathic pain in chronic iSCI patients. These results suggest that the intervention has equivalent to even superior effects than traditional task-specific therapies.

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3This manuscript is under review in the journal Neurorehabilitation and Neural Repair. The authors are Michael Villiger, Dominik Bohli, Daniel Kiper, Pawel Pyk, Jeremy Spillmann, Bruno Meilick, Armin Curt, Marie-Claude Hepp-Reymond, Sabina Hotz-Boendermaker and Kynan Eng. Data were assessed and analysed by Michael Villiger and Dominik Bohli. The manuscript was written by Michael Villiger and revised by the co-authors.
4. Virtual reality-augmented neurorehabilitation in SCI

4.2 Introduction

Injury of the spinal cord (SCI) does not always result in life-long complete wheelchair dependency, but is often influenced by the preservation of supraspinal neural transmission bypassing the zone of injury. Indeed in about 50% of patients, motor and/or sensory function is preserved below the lesion level resulting in an incomplete SCI (iSCI) (Wyndaele & Wyndaele, 2006). However, iSCI often leads to long lasting lower limb motor dysfunction associated with a wide range of physical and psychosocial problems, including pain, which are all challenging to treat. Motor dysfunction and associated neuropathic pain may share some underlying cortical mechanisms which are currently treated very differently. Conceptually, the promotion of cortical plasticity based on rehabilitation interventions is considered to rearrange neural networks in the brain to improve the supraspinal inputs onto the damaged spinal cord. As a result, outcomes in the domains of both locomotion and pain may benefit from such interventions. The present investigation proposes the use of virtual reality (VR)-augmented training programs of movements. VR provides interactive, multimodal sensory stimuli and biofeedback that can be provided as representations of the world and also as abstract scores that additionally motivate the patient. Furthermore, timely and constant adjustment of presented motor tasks is targeted to prevent or reduce the exhaustion or demotivation of a patient (Holden, 2005; Adamovich et al., 2009; Bohil et al., 2011). Important variables in learning and relearning of motor skills and the concomitant changing neural organization are quantity, duration and intensity of training sessions (see for a review Adamovich et al., 2009). Such a requirement can be specifically addressed using VR environments. Besides the external stimulation, the rehabilitation results in internal activation of higher motor cortical areas and might induce plastic changes due to intensive task repetition. The expected VR-augmented neurorehabilitation exploits the idea that action observation and processing system in turn activates downstream cortical areas involved in movement execution (Eng et al., 2007).

Observation, motor imagery and execution induce activation in overlapping cortical networks which increases in intensity when objects are engaged (for reviews Rizzolatti & Craighero,
This system can still be activated in chronic complete SCI patients using motor imagery, attempted movements and observation of foot movements (Hotz-Boendermaker et al., 2008; 2011). The recruitment of functionally interconnected brain areas coupling observation, motor imagery and execution can be engaged by VR movement tasks (Eng et al., 2007).

Some iSCI patients have enough residual sensory and motor function to retain, regain or improve their ability to walk. Nevertheless, walking speed is usually strongly reduced (Shin et al., 2011) and muscle weakness is one of the major deficits observed in iSCI subjects (Pepin et al., 2003; Shin et al., 2011). These impairments are associated with changes in hip, knee and ankle angular displacements (Gil-Agudo et al., 2011) and the weakness of the ankle plantar flexors results in a lack of foot clearance during swing phases resulting in foot drag (Patrick, 2003). Mobility is rated one of the most important activities of daily living for people with neurological disorders (Chiou & Burnett, 1985), making improvement of remaining locomotor function one of the primary aims (Ditunno et al., 2008).

Besides motor impairments, neuropathic pain affects about 40-60% of patients following SCI caused by immediate or remote damage within the spinal and/or peripheral nerve system (Siddall et al., 2003; Soler et al., 2007). Long-term prognosis for the management of neuropathic pain following SCI is rather poor (Siddall, 2009) and in many instances the pain continues or even worsens over time (Jensen et al., 2007). It has been demonstrated in several neurological disorders that the perturbation of the somatosensory system could be reversed or modulated by employing motor imagery and execution combined with visual illusions. The ‘virtual walking’ illusion studies by Moseley (2007) and Soler et al. (2010) used a mirror for the upper body and a video screen showing a video clip of walking legs. SCI subjects were given the illusion that they were watching themselves walking. This illusion induced an analgesic effect.
Based on the findings in these studies, we hypothesized that iSCI patients using VR-augmented movement tasks should show improvements in motor function and reduction in neuropathic pain that could outlast the training sessions and be transferred into daily life.

4.3 Methods

4.3.1 Patients

Incomplete SCI outpatients (age 28-71 years) from the University Hospital Balgrist (Zurich, Switzerland) were included in the study between August 2010 and March 2012 (Table 4.1). Inclusion criteria were: clinically incomplete, chronic SCI (time since injury > 1 year), motor level of lesion below C4, able to sit in a chair without assistance and support systems (e.g. securing belt), preserved motor functions below the level of lesion corresponding to ASIA (American Spinal Cord Injury Association) impairment scale (AIS) C or D at time of inclusion (C = sensorimotor incomplete, with an average strength of the muscles below the level of lesion < 3; D = sensorimotor incomplete, but with average muscle strength ≥ 3) (Marino et al., 2003). Several patients were experiencing neuropathic pain which was assessed using a structured interview (van Hedel et al., 2011). Neuropathic pain according to the IASP (International Association for the Study of Pain) is experienced in an area of sensory abnormality corresponding to the spinal cord lesion. The pain was required to be not primarily related to spasms or any other movement and must had started after the SCI. Exclusion criteria were psychiatric or other neurological disorders, head injuries causing cognitive or visual impairment, spasticity limiting performance of lower limb movements, and medication influencing ability to attend to therapy for 45-minutes. Furthermore, patients with depressive symptoms (score > 14 in the Beck Depression Inventory, BDI) were excluded (Hassanpour et al., 2011).

All patients were aware of the purpose of the study and informed consent was obtained from them. The experimental protocol was in accordance with the Declaration of Helsinki and performed with the approval of the local Ethics Committee.
Table 4.1: Clinical and demographical characteristics of SCI patients. Sex: M = male; F = female. Aetiology: T = trauma; ME = medical aetiology. Level of lesion: C = cervical; T = thoracic. AIS classification: C = sensory-motor incomplete, with the average strength of the muscles below the level of lesion < 3 (i.e. movement over the full range of motion against gravity); D = sensory-motor incomplete, but with the average muscle strength ≥ 3. Level of pain: at-level of pain - defined as pain located within the dermatome and three dermatomes below the lesion level; below-level of pain - defined as pain present more than three dermatomes below the lesion level; below-level of pain extending to the at-level area is classified as below-level of pain if the patient is unable to distinguish two separate pain problems.

<table>
<thead>
<tr>
<th>Pat</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Aetiology</th>
<th>Level of lesion</th>
<th>AIS</th>
<th>Years since injury</th>
<th>Level of pain</th>
<th>Localization of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>70</td>
<td>M</td>
<td>ME</td>
<td>C8</td>
<td>D</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>60</td>
<td>F</td>
<td>ME</td>
<td>T4</td>
<td>D</td>
<td>2</td>
<td>Below</td>
<td>Genital area, lower limb</td>
</tr>
<tr>
<td>P3</td>
<td>28</td>
<td>M</td>
<td>T</td>
<td>C6</td>
<td>D</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P4</td>
<td>71</td>
<td>F</td>
<td>ME</td>
<td>T12</td>
<td>D</td>
<td>3</td>
<td>At</td>
<td>Abdomen</td>
</tr>
<tr>
<td>P5</td>
<td>54</td>
<td>M</td>
<td>ME</td>
<td>C5</td>
<td>D</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P6</td>
<td>61</td>
<td>M</td>
<td>T</td>
<td>C4</td>
<td>D</td>
<td>4</td>
<td>At and below</td>
<td>Thoracic, Arms, lower limb</td>
</tr>
<tr>
<td>P7</td>
<td>30</td>
<td>M</td>
<td>ME</td>
<td>C5</td>
<td>D</td>
<td>3</td>
<td>Below</td>
<td>Lower limb</td>
</tr>
<tr>
<td>P8</td>
<td>59</td>
<td>F</td>
<td>T</td>
<td>T12</td>
<td>D</td>
<td>11</td>
<td>At and below</td>
<td>Abdomen, lower limbs</td>
</tr>
<tr>
<td>P9</td>
<td>30</td>
<td>M</td>
<td>T</td>
<td>C5</td>
<td>C</td>
<td>8</td>
<td>Below</td>
<td>Lower limbs</td>
</tr>
<tr>
<td>P10</td>
<td>62</td>
<td>M</td>
<td>ME</td>
<td>T9</td>
<td>D</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P11</td>
<td>67</td>
<td>F</td>
<td>T</td>
<td>T12</td>
<td>D</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P12</td>
<td>43</td>
<td>M</td>
<td>T</td>
<td>T11</td>
<td>D</td>
<td>20</td>
<td>At</td>
<td>Genital area</td>
</tr>
<tr>
<td>P13</td>
<td>56</td>
<td>M</td>
<td>T</td>
<td>T12</td>
<td>C</td>
<td>6</td>
<td>Below</td>
<td>Lower limb</td>
</tr>
<tr>
<td>P14</td>
<td>47</td>
<td>F</td>
<td>ME</td>
<td>C7</td>
<td>D</td>
<td>4</td>
<td>Below</td>
<td>Lower limbs</td>
</tr>
</tbody>
</table>

4.3.2 Virtual reality-augmented training

The training study used a VR-augmented therapy system for lower limbs combining action observation and execution (Fig. 4.1). The system and the motivating training tasks are described in more details in Villiger et al. (2011b). The movements of the patient’s real lower limbs are transferred to virtual lower limbs in real time using sensory modules with accelerometers, adjustable to the patients’ shoes. The virtual lower limbs are presented in a 1st-person perspective on a large monitor (132 cm diagonal). Clinically relevant interactions for training foot and leg movements in a sitting or standing position were developed. These were:

1) Footbag: A simple exercise in which the patient juggles a ball between the left and right foot, using dorsal ankle flexion movements (approx. 60/min), a necessary exercise to prevent foot dragging. The trajectory of the ball is pre-set so that it always moves correctly through the air between the left and right feet.
2) **Hamster splash:** Hamsters run up to the patient’s toes. The patient’s task is to perform a dorsal flexion of the ankle (approx. 25/min) to launch each hamster into a swimming pool. The reward for launching the hamsters higher (faster ankle movement) gives a better score and triggers more elaborate hamster movements (somersaults, swimming patterns).

3) **Star kick:** The patient performs a knee extension (approx. 25/min) by kicking a ball towards the displayed stars. For every hit, the patient receives a score reward.

4) **Planet drive:** Cars are moving on a highway towards the virtual feet. The patient’s task is to avoid touching the cars by displacing feet and legs sideways.

During a training session, each interaction was presented 3 times for 2 min. On average, within one training session around 300 repetitions of ankle and 75 knee movements were performed (per leg).

![Figure 4.1: Overview of the virtual reality (VR) training setup (left) and the different interactions for training the various lower limb muscles and functions (right). Ankle flexion: footbag - juggling a ball (1), hamster splash - launching hamsters into a swimming pool (2). Knee flexion: star kick - kicking balls towards stars (3). Leg adductors/abductors: planet drive - (avoiding) touching oncoming cars (4).](image)
4.3.3 Clinical study design

The iSCI patients were trained with the 4 VR tasks during a period of 4 weeks in 16-20 sessions of 45-minutes (4-5 per week). At entry to the study, general patient information was collected: age, gender, height, weight, aetiology and level of lesion, AIS, time since injury, medication, pain presence, pain intensity and pain location. After each training session, patients rated their enjoyment, motivation and attention level on a 11-point Numeric Rating Scale (NRS) from 0 (worst) to 10 (best), as well as their mood and pain level before and after each session.

4.3.3.1 Primary outcomes

To control for possible transfer effects, primary outcomes for both motor functions and pain were assessed at 4 different time points: Pre-baseline assessments 4-6 weeks before treatment, baseline assessments immediately before starting the treatment, post-assessments after completing the training program and follow-up assessments 12-16 weeks after treatment (Table 4.2). The primary outcome measures were as follows:

* Walking speed: 10 Meter Walking Test (10MWT) assessing gait speed (van Hedel et al., 2005; 2006).
* Balance: Berg Balance Scale (BBS) which assesses balance during functional activities with 14 balance items from 0 (no balance) to 4 (good balance) (Berg et al., 1995).
* Muscle strength: Lower extremity motor score (LEMS) from 0 (complete paralysis) to 50 (normal strength) (Marino et al., 2003).
* Mobility: The transfer, indoors and outdoors mobility parts of the Spinal Cord Independence Measure (SCIM - hereinafter referred to as ‘SCIM mobility’) from 0 (no mobility) to 40 (normal mobility) were assessed together with the Walking Index for Spinal Cord Injury II (WISCI II) from 0 (unable to walk) to 20 (able to walk without assistive devices) (Dittuno & Ditunno, 2001; Catz et al., 2007).
Neuropathic Pain: The items ‘intensity’ and ‘unpleasantness’ were measured on a NRS from 0 (no pain) to 10 (worst pain imaginable) from the Neuropathic Pain Scale (NPS) (Galer & Jensen, 1997).

Self-reported relieving effect: At the end of the treatment (post-assessment), the Patients’ Global Impression of Change (PGIC) was evaluated according to the method of Farrar et al. (2001) for both motor and pain with no change (score 0-1), minimally improved (score 2-3), much improved (score 4-5) and very much improved (score 6-7) (Farrar et al., 2001). The patients answered the following question: ‘since beginning treatment at this program, how would you describe the change (if any) in activity limitations, symptoms, emotions and overall quality of life related to your condition?’

4.3.3.2 Data analysis

For statistical analysis (PASW 19.0 software, SPSS, Chicago, USA), variables were represented as mean ± standard error of the mean (SEM). The differences between the time points (within-group differences) were analyzed using Friedman’s test and pair-wise comparisons were performed with the Wilcoxon signed-rank test to assess significant differences in the group for two time points. The significance of percentage changes at each assessment time point compared to the baseline was also performed by pair-wise comparisons. Significance was set at $p \leq 0.05$.

4.3.3.3 Locomotion

To control for transfer effects, locomotion was assessed at baseline and at post-assessment. Gait patterns were recorded and quantified with a 3-dimensional motion analysis system (Vicon MX, Oxford, UK). Patients walked with their preferred speed on a treadmill and a sufficient number of gait cycles was recorded. Statistical analysis for locomotion was performed individually. Gait parameters obtained from 15 gait cycles were presented as mean ± standard deviation (SD). The Plug-in gait model was used to calculate angular displacements of hip, knee and ankle joints. All signals were analyzed off-line using Matlab.
(Matlab 7.10 R2010a, Mathworks Inc., Natick, USA) which calculated the kinematic parameters. For each patient, the 15 consecutive walking cycles were normalized to the actual gait cycle duration (heel strike to next heel strike of same foot = 100%). The time-normalized gait cycles were then used to average the mean angular displacement profiles of the lower limb joints. To check whether the data were comparable to that of healthy subjects, a control group was incorporated. Baseline and post-assessment angular values at specific points of the gait cycle were compared using t-tests.

4.4 Results

4.4.1 Patient characteristics and motivational factors

All 14 patients completed the training (mean age 52.7 ± 14.9 years). The clinical characteristics are summarized in Table 4.1. Two of the patients were AIS C and 12 AIS D. Nine of the patients reported neuropathic pain. The patients were quickly familiarized with the VR system. The patients reported high enjoyment (9.6 ± 0.7), motivation (8.8 ± 0.3) and attention (8.7 ± 1.2) levels during training. Seven of them reported a better mood after the training in more than 50% of the sessions. One patient (P8) mentioned a transient occurrence of musculoskeletal pain in the right leg due to its increased use during the sessions. Four patients reported less pain sensation in at least 50% of all training sessions, combined with sensations of lightness or positive tingling in the legs.

4.4.2 Primary outcomes

Table 4.2 summarizes the primary outcome measures across the various assessment time points (pre-baseline, baseline, post- and follow-up). No significant differences between pre-baseline and baseline measurement were found, indicating stability of all the measured variables. With respect to the assessment of motor functions, only one patient was unable to perform the walking tests (P9). For the other patients, walking speed was significantly increased in comparison to the baseline assessment for both post- and follow-up assessments (post \( p \leq 0.001 \), follow-up \( p \leq 0.003 \)). Similar statistically significant increases
were found for all patients in BBS score \( p \leq 0.001 \), muscle strength \( p \leq 0.001 \) and mobility \( p \leq 0.004 \) at both post- and follow-up assessments. With respect to pain, in the post- and follow-up assessments significant decreases were found in intensity \( p \leq 0.004 \) and unpleasantness \( p \leq 0.016 \).

<table>
<thead>
<tr>
<th>Assessment time points</th>
<th>Pre-Baseline(^a)</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Post(^a)</th>
<th>Follow-up(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks</td>
<td>-4</td>
<td>0</td>
<td>1 - 4</td>
<td>5</td>
<td>12 - 16</td>
</tr>
<tr>
<td>10MWT</td>
<td>13.4 ± 4.1</td>
<td>12.9 ± 3.6</td>
<td>11.6 ± 3.4**</td>
<td>12.3 ± 3.4*</td>
<td></td>
</tr>
<tr>
<td>(n = 13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBS</td>
<td>40.2 ± 18.5</td>
<td>41.4 ± 16.7</td>
<td>44.9 ± 14.5**</td>
<td>45.4 ± 13.4**</td>
<td></td>
</tr>
<tr>
<td>(n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEMS</td>
<td>40.5 ± 9.2</td>
<td>40.4 ± 7.9</td>
<td>43.1 ± 7.8**</td>
<td>42.4 ± 8.2**</td>
<td></td>
</tr>
<tr>
<td>(n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCIM mobility</td>
<td>30 ± 8.1</td>
<td>29.8 ± 8.1</td>
<td>31.7 ± 7.3**</td>
<td>31.8 ± 7.4**</td>
<td></td>
</tr>
<tr>
<td>(n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WISCI II</td>
<td>14.5 ± 4.8</td>
<td>14.5 ± 4.8</td>
<td>15.6 ± 5.2**</td>
<td>15.6 ± 5.2*</td>
<td></td>
</tr>
<tr>
<td>(n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIC motor</td>
<td></td>
<td></td>
<td></td>
<td>5.4 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Pain intensity</td>
<td>6.3 ± 1.7</td>
<td>6.6 ± 1.2</td>
<td>3.9 ± 1.8*</td>
<td>4.6 ± 2.0*</td>
<td></td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain unpleasantness</td>
<td>7.6 ± 1.5</td>
<td>8.0 ± 1.1</td>
<td>4.7 ± 1.8*</td>
<td>5.9 ± 1.9*</td>
<td></td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIC pain</td>
<td></td>
<td></td>
<td></td>
<td>4 ± 1.6</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Comparison with respect to baseline values in each group with Wilcoxon signed rank test.

The percentage changes after treatment compared to baseline are displayed in Fig. 4.2 for the post- and follow-up assessments. Significant increases were found in walking speed with 11.9% and 9.8% \( p \leq 0.001 \), balance with 16.5% and 13% \( p \leq 0.021 \) resp. 0.002, muscle strength with 7.3% and 6.6% \( p \leq 0.002 \) and mobility with 8.5% and 9.6% \( p \leq 0.001 \) resp. 0.004. Significant NRS decreases were also found in pain intensity with 38.9% and 36.3% \( p \leq 0.008 \) and unpleasantness with 37.9% and 29.6% \( p \leq 0.016 \). When considering a 30% improvement as a categorical effect size for patients with neuropathic pain \( (\text{Farrar et al., } 2001; \text{Dworkin et al., } 2005; \text{Dworkin et al., } 2008) \), 4 out of 9 (44.4%) patients reached this level.
All patients rated the motor and pain relieving effects of the treatment using the PGIC after the last day of treatment (Fig. 4.2). For the PGIC motor, 13 out of 14 patients rated motor function as markedly improved (much improved or very much improved). For PGIC pain, 4 of the 9 patients rated their pain as markedly reduced, 4 as minimally and only 1 reported no change.

Figure 4.2: Above: percent changes in primary outcome measures in post- and follow-up assessments versus baseline. Data are shown as mean ± SEM. *p ≤ .05 and **p ≤ .001 (Wilcoxon signed-rank test). Below: patients’ global impression of change (PGIC) of motor function and pain after the last day of intervention, rated on a seven-point scale. Abbreviations see Table 4.2.

4.4.3 Locomotion

Seven of the patients (mean age 48.3 ± 14.7 years, range 28-62 years) with a mean height of 1.73 ± 0.10 m were able to participate in the locomotion assessment (P3, P5-P8, P10, P12). For the control group, seven healthy subjects were recruited (mean age 31.9 ± 6.2 years, range 24-42 years) with a mean height of 1.71 ± 0.08 m. Due to the variability in the patients’ individual response patterns no group analysis was performed. Every iSCI patient
was compared individually with the whole control group. The range of ankle dorsiflexion increased at least unilaterally in 6 of 7 patients (P3, P5-P8, P10) after treatment. As an example, P3 increased ankle dorsiflexion during swing after treatment around 90% of the gait cycle: \( p < 0.01 \) (Fig. 4.3). Additionally, an increased knee flexion during early stance at baseline due to knee extensor weakness which was additionally evident in 4 subjects (P3, P5, P6, P7), was improved after treatment in P3 and P5. Knee extensor weakness was also compensated in 2 subjects (P10, P12) with a hyper-extended knee joint during weight bearing. Slight reduction in hyperextension was evident at post-assessment suggesting an increased reliance on their knee extensors.

**Figure 4.3:** Angular displacement profiles of left ankle dorsi-plantar flexion (red: baseline, blue: post) of patient 3 compared with the control group (black dashed line). X-axis: percentage of the gait cycle, 0% = heel strike, toe-off indicated by a vertical line. Y-axis: joint angle.

**4.5 Discussion**

The study aimed to assess the effectiveness of using 1st-person VR to provide intensive training of lower limb movements in chronic iSCI patients. The VR-augmented training program combined action observation and execution in a playful manner. The VR conditions were very well accepted and the patients remained motivated throughout the program. The comparison between before and after training periods revealed that: (1) iSCI patients performed significantly better in several motor tasks (walking speed, balance, mobility,
locomotion) with increased lower limb muscle strength, and (2) almost half of the iSCI patients experiencing neuropathic pain, reported significant short and long term decrease in pain intensity and pain unpleasantness.

4.5.1 Motor outcomes

Patients' walking capacity improved significantly after the training sessions with respect to gait patterns, speed, muscle strength and balance. Striking improvements were found in ankle dorsiflexion, reducing foot drag that is considered a main problem for walking in iSCI patients. Functional gait analyses revealed an increase on ankle dorsiflexion, obvious from the first gait cycle on in 6 out of 7 tested patients. In combination with stronger knee extensor or general improvements in muscle strength, this increase probably enabled the patients to walk faster and more stably (improvement in 10MWT and BBS). Indeed Kim et al. (2004) showed that muscle strength was correlated with walking speed. The BBS has been shown to relate well with other mobility measures and muscle strength (Wirz et al., 2010) and is important for postural control (Deliagina et al., 2008). The functional assessments also confirmed the improvements in ambulatory functions after treatment. The SCIM mobility (indoors and outdoors) significantly increased as well as the WISCI II. Five patients improved over several WISCI II levels; an improvement of one level is already clinically relevant (Burns et al., 2011). The subjective reports of the patients matched the objective assessments, as 93% of the patients rated their motor functions as markedly improved. This result is in contrast with a recent study stating that the measured improvements after treatment were not similarly perceived in patients (van Hedel et al., 2011). Overall, the significantly improved walking capacity after the intervention demonstrates that this therapy can be beneficial for all chronic iSCI patients who are functional walkers (Daverat et al., 1988). The expression “functional” refers to the walking ability necessary to perform some tasks of everyday life, e.g. crossing a street with a walking speed of at least 0.6 m/s (Zorner et al., 2010).

Most interestingly, although the present investigation did not apply task-specific training (e.g. actual training of walking) as has been done in several previous studies in chronic iSCI
patients, it achieved effects that were comparable or even better. A study of robot-assisted gait training (RAGT) 3-5 times a week over 8 weeks showed increased gait speed in nearly all subjects although only 2 of the 20 iSCI patients showed improvements in walking ability as determined by the WISCI II (Wirz et al., 2005). Additionally, the RAGT compared with over-ground walking training did not improve gait more (Vaney et al., 2012). Another study using lower extremity strength training (12 weeks, 30 sessions) was able to attenuate neuromuscular impairments and to improve gait speed in 3 tested iSCI patients (Gregory et al., 2007). Finally, in accordance with our findings, a recent study showed that unspecific strength training of the lower extremities led to better results in walking measures, compared to task-specific RAGT, in iSCI patients with limited ambulatory function (Labruyere, 2011).

Repetitive practice, motivation to endure practice and feedback about performance are key concepts relevant for motor learning (Holden, 2005); using our VR-augmented system patients performed over 5000 ankle movements per leg during a month of training, while maintaining high ratings for enjoyment, motivation and attention. This number is higher than that reported in a previous study (Gregory et al., 2007). The high number of repetitions, leading to high stimulation of motor brain areas, may have also induced plastic cortical and subcortical changes. In a recent study with stroke patients, effective cortical reorganisation could be achieved with a mirror therapy setup (Michielsen et al., 2011). Unlike what occurs in locomotion task-specific training, the visual feedback in the VR tasks might activate top-down processes in overlapping sensorimotor networks of observation, motor imagery and execution supporting functional recovery. However, further studies are needed to shed light on the underlying mechanisms involved in the top-down process and to what extent they play a role in inducing cortical plasticity.

4.5.2 Pain outcomes

Besides the improvement of motor function, the self-reported measurements indicated that the training substantially reduced neuropathic pain intensity as well as the unpleasant experience of pain. These effects were found both immediately after the treatment and also
up to 12-16 weeks after treatment. Explaining these findings is difficult as the neuropathic pain underlying mechanisms are still not well documented. However, 2 recent investigations have reported beneficial effects of visual illusions on pain (Moseley, 2007; Soler et al., 2010). In the study by Moseley (2007), SCI patients performed 10 min of virtual walking on 15 consecutive weekdays and in Soler et al. (2010), each SCI patient received 10 x 20-minutes sessions over 2 weeks. In line with these studies, our prolonged, repetitive and extensive training, i.e. 4 weeks with 45-minutes sessions, is most probably one of the reasons for the positive long-lasting effects of the treatment, as pain relief seemed to increase with the training. However, important differences to their and our studies were that their patients suffered from complete motor SCI and the presentation of the virtual limbs was not from a 1st-person perspective. The advantage of the 1st-person perspective of the lower limbs is the kinesthetic matching which gives support to the illusional effect, i.e. moving avatars as in our setting, compared to a 3rd-person only visual perspective (Jackson et al., 2006; Kobashi et al., 2012). In this context it is also noteworthy that pathological pain is associated with organisation changes in the somatosensory cortex of SCI patients (Wrigley et al., 2009; Henderson et al., 2011). Motor imagery and execution in a VR-augmented situation may be able to reverse or modulate these changes and therefore reduce pain with an effect outlasting the training period.

4.5.3 Conclusion and implications
Using VR-augmented training in chronic iSCI patients undergoing no other therapy revealed benefits in motor function and pain reduction that outlasted the training period, with effects that were overall as good or better than almost all other known training-based intervention studies. These effects may have been due to the customizable dosage and intensity of VR-augmented training, the activation of top-down cortical process via simultaneous action observation, motor imagery and execution, or the combination of both. Larger trials including control groups will be required to better determine the true efficacy of the intervention and the
relative contributions of dosage, training intensity and top-down cortical activation to reach the overall clinical effect.

The positive effects seen in this study challenge traditional task-specific therapeutic approaches that are thought to work by a bottom-up strategy. Essentially, our patients were able to generalize the training of individual movements to achieve functional improvements such as locomotion on their own. Further studies on different patient groups with SCI and other conditions will be required to determine to what extent this finding applies to motor rehabilitation in general.

The playful VR-augmented approach used in this study enhances the motivation of the patients to perform the repetitive movements required for therapeutic success. In contrast to conventional therapies, VR-augmented training can provide an unlimited amount of scenarios and difficulty levels to achieve a desired training dosage and a desired functional outcome, while keeping motivation and attention at a high level. The VR-augmented neurorehabilitation may be applicable to any kind of patients suffering from sensory or motor impairment.

4.6. Acknowledgments

Thanks goes to Rob Labruyère for assisting in patient recruitment and Michael Brogioli for developing tests. This research was supported by the International Foundation for Research in Paraplegia (IRP) and the Neuroscience Center Zurich (ZNZ).
5. Brain activation patterns during lower limb gaming in a virtual reality environment

5.1 Abstract

Virtual reality (VR) is used in many fields of neurorehabilitation scenarios involving not only motor execution but also to imagined and observed actions. Using functional MRI, we show neural correlates of these three modalities for a VR game named “footbag” and compare them with those of playing the game without or with an additional reward. Volunteer healthy subjects viewed a game video presented in the 1st-person perspective consisting of two feet juggling a ball, i.e. “footbag”. They were instructed to either passively observe the action (O), to observe and simultaneously imagine performing the action (O-MI), or simultaneously imitate the action (O-IMIT). Two play game conditions were added without (PLAY) or with reward displayed as medals (REWARD). In this VR environment, O-MI, O-IMIT, PLAY and REWARD activated similar motor regions, especially the fronto-parietal network and the insula. PLAY contrasted to the O-IMIT condition showed additional activation in brain areas related to reward (medial prefrontal cortex and striatum). Interestingly, the activation pattern in the REWARD condition did not differ from the PLAY, thus suggesting that playing a VR game is a rewarding activity per se. These results may have strong implications for the development of novel interventions in neurorehabilitation.

This manuscript is in preparation. The authors are Michael Villiger, Marie-Claude Hepp-Reymond, Daniel Kiper, Jeremy Spillmann, Natalia Estévez, Spyros S. Kollias, Kynan Eng and Sabina Hotz-Boendermaker. Data were assessed and analysed by Michael Villiger. The manuscript was written by Michael Villiger and revised by the co-authors.
5.2 Introduction

In virtual reality (VR) a computer-simulated real or imaginary world is experienced by the user through a human–machine interface (Holden, 2005). VR can provide similar sensory input as in the real world and has the potential to add, augment or decrease feedback and requirements. In addition, VR can induce subjects to perceive the environment as real and vivid. The use of VR systems has been expanded in daily life, work and training settings such as the simulation of realistic situation, but it is currently exploding in all fields of physical rehabilitation and neurorehabilitation (Bohil et al., 2011). In rehabilitation, the most important variables in learning and relearning of motor skills are quantity, duration and intensity of training sessions (for review see Adamovich et al., 2009), requirements that can be optimally addressed by playing games in a VR environment. The repetitive application of VR improves the appropriate coordination patterns as a result of the strengthening of motor programs in the cortex, thus priming the corresponding motoneurons of the muscles necessary to execute a motor task (Page et al., 2001).

Multisensory integration of visual, tactile and proprioceptive information can be created in interactive VR systems providing body awareness and activating motor representations beneficial for learning and recovery (Blanke et al., 2002; 2004; Holden, 2005; Deutsch et al., 2007; Adamovich et al., 2009; Bohil et al., 2011). The application of VR systems is not restricted to execution, and can also be used in motor imagery and action observation which are conceived as offline operations of physically performed actions and activate overlapping cortical networks (for reviews see Rizzolatti & Craighero, 2004; Buccino et al., 2006; Caspers et al., 2010).

However, the neural correlates of a gaming scenario in a VR environment that involves action observation, motor imagery and imitation have not been investigated so far. Passively observed actions performed by conspecifics and robots (Gazzola et al., 2007) activated brain regions on real human limbs, while observing virtual hands revealed weaker activation patterns than real ones (Perani et al., 2001). Observation of real-time virtual hand avatar
movements from a 1st-person perspective with the intention to imitate them activated networks similar to that recruited for the executed movements, and the real-time control of the virtual hands was associated with the sense of an embodied “extension” of the subject’s own hand (Adamovich et al., 2009).

In the present study, we aim to extend these findings in a VR game scenario for lower limbs, i.e. “footbag”. In particular we investigate neural activation patterns under various conditions: passive observation (O), online motor imagination (O-MI), online imitation (O-IMIT) and directly playing the game without (PLAY) and with an additional reward (REWARD). Our main expectations are:

1) In all active conditions, compared to passive observation, similar brain regions will be activated, probably to different degrees.
2) Playing a game in a VR environment will activate special brain regions related to self-awareness or to reward.
3) Playing with additional reward should activate additional brain areas than playing without reward.

5.3 Methods

5.3.1 Participants

Twelve healthy volunteers (mean age 41.4 years, range 26 - 61 years, 6 females) participated in this study. They had normal or corrected-to-normal visual acuity, no history of psychiatric or neurological disorders and were right-footed (preferred kicking foot). Informed consent was obtained from all subjects. The experimental protocol was in accordance with the Declaration of Helsinki and had the approval of the local Ethics Committee.

5.3.2 Stimuli and task

Thanks to technology advances, a VR-based interactive visuo-motor intervention system for the lower limbs has been developed (Villiger et al., 2011b). Virtual legs and feet are
presented in the 1st-person perspective and goal-directed movements can be performed by the patients in various scenarios. The intervention is based on the idea that stimulation of the action processing system in turn activates downstream cortical areas involved in movement execution (Eng et al., 2007).

To investigate the underlying role of the VR-based interactive intervention, we chose the “footbag” scenario for use in the MR environment. The VR system is based on the Unity 3D game development tool (Unity Technology, San Francisco, USA). For the present experiment, we used sensory modules with accelerometers fixed on the top of the left and right foot. The movements of the subject’s real feet are transferred to the virtual feet in real-time and the presented “footbag” scenario showed the two virtual feet juggling a ball from a 1st-person perspective, i.e. looking down on the feet (Fig. 5.1). The life-size virtual lower limbs are presented on a rear-projected screen located inside the scanner room at the approximate level of the subject’s feet and have the same orientation as the real ones. The participants could see the screen via a mirror attached to the head coil, and legs and head were stabilized to minimize movement artefacts. The stimulus was presented either as a video clip showing the virtual feet juggling a ball, or as a video game in which the subjects had to juggle the ball displayed on the screen. The videos in both conditions started with both feet motionless on the ground and as soon as the ball appeared the juggling started. The following five tasks were investigated:

1) Observation-only (O): the subjects had to carefully observe the video clip showing the “footbag” scenario. The instruction used was: ‘Please look carefully at the video’.

2) Online motor imagination (O-MI): the subjects observed the video displaying the “footbag” scenario and had to imagine themselves performing the movement at the same time, i.e. online). The instruction was: ‘When you see the feet moving in the video, start immediately to imagine that the presented moving feet are yours and try to control the movement in your mind while continuously watching the video’.
3) Online imitation (O-IMIT): the subjects executed left- and right-foot dorsiflexions while watching the “footbag” scenario. The instruction was: ‘When you see the feet moving on the video, start immediately to perform the presented movements with your own feet and keep watching the video’.

4) Playing (PLAY): the subjects executed left- and right-foot dorsiflexions as in the O-IMIT condition but now the subjects controlled the ball juggling themselves. The instruction was: ‘When you see the ball, immediately start to juggle’.

5) Rewarded playing (REWARD): the instruction was the same as for the PLAY condition. However, the participants received a reward after each fifth juggle while playing. The reward was displayed on the screen as a bronze, silver or gold medal depending on the performance.

Subjects’ behavior was monitored with a video camera and controlled for immobility during the baseline, O and O-MI conditions, and for appropriate movements during O-IMIT, PLAY and REWARD conditions.

5.3.3 Neuroimaging and behavior

We used a scrambled version (SCR) of the ball juggling as baseline (Fig. 5.1) (Iseki et al., 2008). Before the scanning session, subjects received verbal and written information about the experiment, and practiced the task outside of the scanner with both video stimuli and baseline. Without mentioning the O-MI condition, to avoid contamination of O, instructions were given for the O-IMIT and PLAY conditions and the required movements trained until they were correct. The subjects ignored at the time that the second gaming condition would include a reward.

The fMRI session consisted of 5 runs, each containing 5 blocks of the same condition intermingled with the baseline. Each run started with a 30 s baseline. The time duration of each block and scrambled baseline was 30 s (Fig. 5.1). Each run lasted 5 min and was followed by a rest period during which the subjects had to rate how strongly the VR
environment and movements were perceived as real and vivid, and afterward received information on the tasks presented in the next run.

Each session started with the O task, to avoid outcome of O being influenced by the other conditions, and ended with the REWARD task, to avoid PLAY being contaminated. The other three conditions were presented in a pseudorandom order. After the scanning session, participants completed the Vividness of Motor Imagery Questionnaire (VMIQ) (Isaac et al., 1986).

Figure 5.1: The fMRI session consisted of 5 runs of 5 min, each containing 5 blocks of the same condition intermingled with the scrambled baseline presented between the condition blocks. The time duration of each block and baseline was 30 s.

5.3.4 Neuroimaging data acquisition

The functional images were measured with T2*-weighted echo-planar images (EPIs) with blood-oxygenation-level-dependent (BOLD) contrast on a 1.5-T, whole-body, MRI scanner (Philips Medical Systems, Eindhoven, The Netherlands) equipped with an 8 channel SENSE™ head coil. The stimulus presentation was controlled and synchronized with the fMRI scanning. The image acquisition parameters were as follows: repetition time (TR) = 3 s, echo time (TE) = 50 ms, field of view (FOV) = 220 mm, matrix = 80 x 80 mm, 33 slices with 4 mm thickness without gap, voxel size = 2.75 x 2.75 x 4 mm. The first five images were discarded to allow for signal stabilization, the following 100 volumes per task were collected and stored.
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5.3.5 Neuroimaging data analysis

All fMRI analyses were performed using SPM5 (Welcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). Functional images from each subject were realigned, spatially normalized into the Montreal Neurological Institute (MNI) space with a resolution of 2 x 2 x 2 mm and then smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel. For removing the low frequency noise, a high-pass filter with a cut-off of 128 s was used. Data were analyzed using a random-effect model to account for population inferences (Friston et al., 1999). The general linear model (GLM) was fitted for each subject by a design matrix comprising the onsets and durations of each condition and convolved with the standard canonical hemodynamic response function. The four conditions described previously were included in the model. Six regressors were incorporated to account for rigid-body movement effects. Respective parameter estimates (beta) and contrast images (cons) were computed by voxelwise comparisons.

To determine the group activations in the five conditions (O, O-MI, O-IMIT, PLAY and REWARD), the single-subjects contrasts were entered into a second-level analysis for each of the contrasts (t-tests and a flexible full factorial ANOVA completed with post-hoc t-tests). The designed neuroimaging analyses were used to achieve the following objectives. First, we wanted to determine the neural regions which were activated during the various conditions. Therefore, main effects of the conditions were contrasted with the baseline (SCR) using a one-sample t-test. Second, to determine areas of overlapping brain regions a conjunction analysis was conducted (conjunction null method) (Nichols et al., 2005). Finally, contrasts were defined between the conditions. The resulting SPM(T) maps were thresholded at p < 0.05 (cluster-level false discovery rate [FDR] corrected, cluster extent threshold > 10 voxels, (Worsley et al., 1996). All imaging results were displayed either on rendered cortical surface or on slices of a high-resolution structural MRI scan of a standard brain from the MNI. Anatomical identification was performed with the help of the WFU PickAtlas (Wake Forest University, Winston-Salem, NC, v2.4) and the included Anatomic Automatic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003). The
identified cortical regions included the paracentral lobule (M1/S1 primary foot representation), the pre- and supplementary motor area (preSMA, SMA), cingulate gyrus (CG), precentral gyrus/frontal operculum/inferior frontal gyrus (PMv/IFG), middle frontal gyrus (MFG), superior frontal gyrus (SFG), superior parietal lobule (SPL), inferior parietal lobule (IPL), precuneus (PCu), insula (INS) and occipitotemporal cortex (OTC). Subcortically, the thalamus (THAL), putamen (PUT), caudate nucleus (CN), and cerebellum (CB–peak location based on Schmahmann et al., 1999) were selected.

For the specific contrast between the PLAY and REWARD conditions, an anatomical region of interest (ROI) analysis was additionally performed. Based on the known functional neuroanatomy of the human reward system (for review see Haber & Knutson, 2010), following ROIs were defined for both hemispheres: prefrontal cortex (orbital, ventromedial and dorsal), anterior CG, striatum, amygdala and hippocampus.

5.3.6 Behavioral assessment

Using the kinesthetic part of the VMIQ, the subjects rated their subjective ability to mentally perform movements using a 5-point rating scale from 1 (image as vivid as normal vision) to 5 (no image at all) after the scanning session (Isaac et al., 1986). Furthermore, after each run, the subjects had to report how strongly the VR environment was perceived and whether the movements were felt as real and vivid, using a numeric rating scale from 0 (not at all) to 10 (best). Three questions adapted from the study by Tsakiris et al. (2010) had to be answered. These questions were: “During the run there were times when... 1.) …it felt like the feet I was looking at were my own feet”, 2.) …it felt like I was in control of the feet I was looking at”, and 3.) …I was immersed into the presented video”. The scores of the three questions were subsequently averaged.
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5.4 Results

5.4.1 Imaging results

5.4.1.1 Activation in the various conditions

To obtain the activation patterns specific to the O, O-MI, O-IMIT resp. PLAY and REWARD conditions, each condition was contrasted with the scrambled baseline (SCR). The group results are listed in Table 5.1. Overall, the extent and strength of the activations increased from O to the other conditions (O-MI, O-IMIT, PLAY and REWARD). Fig. 5.2 displays the activation patterns when subjects imagined (O-MI) and imitated (O-IMIT) the presented foot movements (top) and below, played without (PLAY) and with reward (REWARD).

<table>
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<th>O &gt; SCR</th>
<th>x y z</th>
<th>t value</th>
<th>Vol.</th>
<th>O-MI &gt; SCR</th>
<th>x y z</th>
<th>t value</th>
<th>Vol.</th>
<th>O-IMIT &gt; SCR</th>
<th>x y z</th>
<th>t value</th>
<th>Vol.</th>
<th>PLAY &gt; SCR</th>
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<th>x y z</th>
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Table 5.1: MNI coordinates for group activations for observation-only (O), online motor imagination (O-MI), online imitation (O-IMIT), playing (PLAY) and playing with reward (REWARD) versus baseline (SCR). A threshold of \( p < 0.05 \) was applied after correction for multiple comparisons using the FDR method (cluster extent threshold \( k > 10 \) voxels).
The **O condition** of the virtual feet playing “footbag” activated a region in the medial wall of the parietal lobe, identified as the posterior PCu. Additional foci were found in the left posterior THAL. Low-level visual activations were excluded by the scrambled baseline, i.e. no V1 activation, but the observation of the foot movements still activated bilaterally the OTC.

During the **O-MI condition** the three cortical areas detected in the O condition were also activated. In addition, the PM areas involved in motor imagery were also activated (preSMA, SMA and PMv). Furthermore, foci were found in the CG, right SPL, SFG and left anterior INS and subcortically, in the left PUT, posterior THAL and bilateral CB (Crus I/Crus II). As expected, the **O-IMIT condition** activated an extensive motor cortical network including the foot representation in the M1/S1 region and almost all areas found in the O-MI condition, i.e. SMA, bilateral PMv/IFG, IPL and OTC, right SFG and subcortically, left THAL and CB. In addition, left SPL activation was detected. The **PLAY and REWARD conditions** activated an extensive motor cortical network including the foot representation in M1/S1, and all the regions found in O-IMIT and, as in the O-MI condition, the left INS and right SPL. The only new regions were the left MFG in both conditions and the PUT in the REWARD condition.

**Figure 5.2:** Activation patterns during the VR “footbag” in healthy subjects on rendered brains. Above: O-MI > SCR (red); O-IMIT > SCR (blue); overlap of both (purple). Below: PLAY > SCR (purple); REWARD > SCR (yellow); overlap of both (orange-brown). The significant regions are listed in Table 1. Abbreviations: M1/S1: paracentral lobule; preSMA/SMA: pre-supplementary motor area; PMv/IFG: ventral premotor cortex/inferior frontal gyrus; MFG: middle frontal gyrus; PCu: precuneus; SPL: superior parietal lobule; IPL: inferior parietal lobule; OTC: occipitotemporal cortex.
5. Brain activation during lower limb gaming

5.4.1.2 Common activations

To investigate the common underlying mechanism of the four active conditions (O-MI, O-IMIT, PLAY and REWARD) during the “footbag” game, conjunctions were computed. Table 5.2 shows the outcome of the conjunction of O-MI, O-IMIT, PLAY and REWARD with shared cortical brain region activation in SMA, right SFG, PMv/IFG, PCu, SPL, IPL and OTC, and subcortically in the left CB (Crus I).

<table>
<thead>
<tr>
<th>Region</th>
<th>Left/Right</th>
<th>Conjunction O-MI, O-IMIT, PLAY and REWARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementary motor area (SMA)</td>
<td>L/R</td>
<td>x  -6 y  -6 z  72 t-value 3.76 Vol. 15</td>
</tr>
<tr>
<td>Superior frontal gyrus (SFG)</td>
<td>R</td>
<td>x  38 y  -2 z  60 t-value 4.08 Vol. 37</td>
</tr>
<tr>
<td>Ventral premotor cortex/inferior frontal gyrus (PMv/IFG)</td>
<td>R</td>
<td>x  54 y  16 z  -10 t-value 4.11 Vol. 36</td>
</tr>
<tr>
<td>Precuneus (PCu)</td>
<td>R</td>
<td>x  20 y  -70 z  62 t-value 3.79 Vol. 53</td>
</tr>
<tr>
<td>Superior parietal lobule (SPL)</td>
<td>R</td>
<td>x  36 y  -54 z  62 t-value 5.72 Vol. 265</td>
</tr>
<tr>
<td>Inferior parietal lobule (IPL)</td>
<td>R</td>
<td>x  68 y  -28 z  26 t-value 3.55 Vol. 11</td>
</tr>
<tr>
<td>Occipitotemporal cortex (OTC)</td>
<td>L/R</td>
<td>x  -54 y  -74 z  -4 t-value 6.66 Vol. 633</td>
</tr>
<tr>
<td>Cerebellum (CB) – Crus I</td>
<td>L</td>
<td>x  -44 y  -62 z  -24 t-value 4.79 Vol. 56</td>
</tr>
</tbody>
</table>

Table 5.2: Conjunction (shared activations) of O-MI, O-IMIT, PLAY and REWARD. A threshold of p < 0.05 was applied after correction for multiple comparisons using the FDR method (cluster extent threshold k > 10 voxels).

5.4.1.3 Contrasted condition effects

The following conditions were contrasted with each other to reveal specific activations (Table 5.3). **O-MI > O** revealed an increase in activation in preSMA and CG, in PMv/IFG, SFG, IPL, INS and CB bilaterally (Fig. 5.3). Most regions are known to be involved in both kinesthetic motor imagery and movement execution. The contrast **O-IMIT > O-MI** only revealed enhanced activation in SMA, in the right anterior THAL and in the left lobule IV/V of the CB. No significant activation was found in M1/S1. The **PLAY > O-MI** contrast revealed regions specific to motor execution, such as M1/S1 and SMA, and foci in the left THAL and right CB lobule IV. The most prominent contrast was between **PLAY and O-IMIT** which showed strong activation in the prefrontal cortex (MFG) and the striatum (CN, Fig. 5.3). No significant activation changes in cortical and subcortical regions were found in all inverse contrasts. Finally, the contrasts between **PLAY and REWARD** did not reveal any BOLD signal changes.
5. Brain activation during lower limb gaming

for whole brain and as well as in the ROI analyses. Finally, in the contrast REWARD > PLAY no specialized regions were uncovered.

<table>
<thead>
<tr>
<th>Region</th>
<th>L/R</th>
<th>O-MI &gt; O</th>
<th>O-IMIT &gt; O-MI</th>
<th>PLAY &gt; O-MI</th>
<th>PLAY &gt; O-IMIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracentral lobule (M1/S1)</td>
<td>L/R</td>
<td>x y z t</td>
<td>x y z t</td>
<td>x y z t</td>
<td>x y z t</td>
</tr>
<tr>
<td>Supplementary motor area (SMA)</td>
<td>L/R</td>
<td>4 -2 68 5.38 49</td>
<td>-2 -4 50 12.42 580</td>
<td></td>
<td></td>
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<tr>
<td>Presupplementary motor area (preSMA)</td>
<td>L/R</td>
<td>8 16 64 5.78 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingulate gyrus (CG)</td>
<td>L/R</td>
<td>16 -2 44 6.80 48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventral premotor cortex/inferior frontal gyrus (PMv/IFG)</td>
<td>L</td>
<td>-56 18 2 6.40 48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>60 22 6 6.44 80</td>
<td></td>
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<tr>
<td>Middle frontal gyrus (MFG)</td>
<td>R</td>
<td>8 58 4 4.96 45</td>
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<td></td>
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<tr>
<td>Superior frontal gyrus (SFG)</td>
<td>L</td>
<td>-14 8 58 6.10 67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>14 28 52 8.76 48</td>
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<td></td>
</tr>
<tr>
<td>Inferior parietal lobule (IPL)</td>
<td>L</td>
<td>-64 -36 28 5.75 101</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>50 -40 52 5.31 39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula (INS)</td>
<td>L</td>
<td>-40 22 2 5.43 56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>36 12 -4 4.93 46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus (THAL)</td>
<td>L</td>
<td>-4 -18 6 5.95 67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>-4 -16 8 9.14 364</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus (CN)</td>
<td>R</td>
<td>12 22124 4.49 42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum (CB) lobule IV/V</td>
<td>L</td>
<td>-2 -48 -2 5.64 55</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cerebellum (CB)</td>
<td>L</td>
<td>-2 -46 -36 5.88 45</td>
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<tr>
<td>Crus VI</td>
<td>R</td>
<td>24 -60 -26 5.98 47</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>34 -74 -20 8.86 161</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 5.3: MNI coordinates for group activations for O-MI versus O, O-IMIT versus O-MI, PLAY versus O-MI and PLAY versus O-IMIT. A threshold of p < 0.05 was applied after correction for multiple comparisons using the FDR method (cluster extent threshold k > 10 voxels).

Figure 5.3: Specific activation patterns during the VR “footbag” game in healthy subjects from the contrasts O-MI > O (left) and PLAY > O-IMIT (right). The significant regions are listed in Table 5.3. Numbers in the color bar: t-values. Abbreviations: see Fig. 5.2; INS: insula; CB: cerebellum; CN: caudate nucleus.
5. Brain activation during lower limb gaming

5.4.2 Behavioral assessment

The mean rating of the kinesthetic part of the VMIQ from 1 (image vivid as normal) to 5 (no image at all) was 2.3 (SD = 0.9). Hence, the imagined movements were on average very clear and vivid. Additionally, subjects had to rate, after each run, their subjective impression on how strong the VR environment and the movements were perceived as real and vivid from 0 (not at all) to 10 (best). All subjects reported high ratings except in the O condition (4.2, SD = 2.5). The other mean ratings were for O-MI 7.9 (SD = 1.8) and for O-IMIT 7.1 (SD = 1.7); the highest ratings were given for PLAY 8.7 (SD = 1.2) and for REWARD 9.1 (SD = 1.0).

5.5 Discussion

The goal of this study was to investigate the neural correlates of the VR scenario “footbag” under different experimental conditions. According to our expectations, the results confirmed that observation alone did not produce much activation. In contrast, during O-MI, O-IMIT, PLAY and REWARD many similar regions were activated, primarily in the fronto-parietal network and the INS as well as in motor regions. We also found that playing a game in a VR environment did activate two special brain regions, but that no new regions were revealed by playing with additional reward.

5.5.1 The core-network of playing virtual “footbag”

Gaming in a VR environment is not restricted to execution but is thought to be composed of various modalities, such as motor imagery and observation. Passive observation (O) of virtually lower limbs in action did not elicit resonance in sensorimotor areas but mainly in the visually processing posterior part of the PCu (Margulies et al., 2009) and in the OTC regions (Downing et al., 2001; Peelen & Downing, 2005). These two activated regions were also significantly activated in the conjunction analysis of the four motor tasks, i.e. O-MI, O-IMIT, PLAY and REWARD. The PCu may act as a relay station between the visual perception of movements and actual performance of an action. Parts of the OTC, such as the extrastriate
5. Brain activation during lower limb gaming

body area, are reported to be important for identifying a moving agent or specific movement (David et al., 2007).

In contrast to the passive observation (O), imagined and actual performance combined with the visual input of the lower limbs induced a strong sense of being part of the VR environment. This finding supports earlier reports that the visual display of virtual hands can be perceived as one’s own if the task has an active basis (Adamovich et al., 2009). The conjunction analyses with the four tasks further confirmed the existence of a strong core-network that encompasses a fronto-parietal circuit including SMA, PMv/IFG, SPL and IPL. These regions are well known to support internal simulation and preparation of movements and to be active during intentional action observation (Rizzolatti & Luppino, 2001; Gallese et al., 2004; Kilner et al., 2004; Adamovich et al., 2009). Activations within these regions have also been reported to play a central role in the successful induction of illusions (Tsakiris et al., 2010; Bekrater-Bodmann et al., 2012). In addition, IPL activation expands to some extent to the temporal-parietal junction, a region involved in the perception of the self (Tanaka et al., 2001; Blanke et al., 2002; Farrer & Frith, 2002; Blanke et al., 2004; Arzy et al., 2006; Lewis, 2006; Ionta et al., 2011). The core-network is not only dependent on direct self-control of the virtual feet such as in the playing conditions but also in the O-MI and O-IMIT conditions when the virtual feet are animated on the video clips.

5.5.2 Online motor imagination and imitation of virtual “footbag”

In addition to the core-network, the mentally performed O-MI condition revealed a foci of activation in the anterior INS, a region involved in cognitive processes such as attention and control of goal-directed tasks (Dosenbach et al., 2008; Nelson et al., 2010). Studies reported that increased activation of the INS was detected when the subjects became increasingly aware of being in control of an action (Farrer & Frith, 2002; Corradi-Dell’acqua et al., 2008). Furthermore, the anterior part of the PCu has been shown to be engaged in mental representations during 1st-person motor imagery walking in a virtual environment (Cavanna & Trimble, 2006; Northoff et al., 2006; Iseki et al., 2008). In our study the behavioral outcome
in the VMIQ and the subjective feeling of being part of the VR environment and the foot movements were quite strong when mentally playing footbag while observing this action on the video. Compared to an earlier experiment with real foot movements (Villiger et al. submitted), the present O-MI condition contrasted to baseline showed a broader activation pattern, i.e. preSMA, SMA, SFG and SPL. Tsakiris et al. (2010) had shown that preSMA was clearly linked to the feeling that one controls one’s own bodily actions. A further fMRI experiment, Goldberg et al. (2006) provided evidence that the SFG is also involved in self-awareness. Thus, virtually presented foot movements seem to be more effective than real foot movements in giving subjects the illusion of responsible for the presented foot movements.

Furthermore, in the O-MI condition with virtually presented feet compared to the O-IMIT task, our subjects were able to immerse in the VR environment slightly better. Interestingly, the O-IMIT condition did not show activation in the anterior INS what could be shown in the other above study with real feet and less preSMA and SMA activation. But SPL was more strongly activated. We conclude that the movements required by the present task with virtual foot movements were easier to perform than the previous one. Furthermore, the functional network activated during O-IMIT of playing virtual “footbag” reveals many shared regions compared to the O-MI condition. In line with these findings, the contrast between O-IMIT and O-MI revealed only three small areas related to motor execution. Hence, the findings, that physical movements are not mandatory for the sense of being part of the VR environment and the virtual foot movements and the activation of the core-network, may have far-reaching relevance for therapeutic neurorehabilitation approaches of VR systems. This is most important in patients that cannot perform physical movements or realize instructions.

5.5.3 The effect of playing a game

Playing virtual “footbag” revealed similar activation patterns as the conditions without direct control of the virtual legs, i.e. O-MI and O-IMIT. Adamovich et al. (2009) investigated 13 healthy subjects while playing different hand game scenarios in a 1st-person perspective.
Similarly to our playing conditions, they detected activation in the INS, parietal cortex and the OTC, identified as extrastriate body area. These regions may integrate the visual feedback of the VR display together with concurrent proprioceptive feedback and efferent copy of motor commands and, as mentioned in the previous section, reflect improved ability to embody the VR limbs and consolidate self-awareness.

The direct control of the virtual legs, i.e. the contrast between PLAY and O-IMIT, revealed activation in the medial MFG and in the CN. These regions may preferentially respond to rewarding outcomes (Knutson et al., 2003; Daw et al., 2006) and reward-based learning (Haber & Knutson, 2010). Signals from the INS or the temporal-parietal junction can be received to support the perception and control of the self, and to operate in a motivational top-down manner.

5.5.4 Rewarded game playing

Interestingly, playing “footbag” with the additional reward did not activate many additional brain regions. The only region which was exclusively activated in the REWARD condition when PLAY and REWARD were contrasted to the baseline was the MFG known to respond to more abstract rewards (Haber & Knutson, 2010). This prefrontal region appears to have a pivotal role in our VR game and indicates that the direct self-control of the virtual feet induces a strong motivational effect and does not require further reward. Thus, these results suggest that playing a game and being in control of the lower limbs in a VR environment is a rewarding activity per se. This strongly indicates that such well-designed games in a VR environment are best suitable for neurorehabilitation.

5.5.5 Conclusion

During virtual lower limb observation with online imagination and imitation, and in particular during playing, a shared activated core-network relevant for motor functions and self-awareness is recruited. This network is not exclusively dependent on the direct self-control of the virtual feet. Yet, effective playing of the virtual “footbag” has a strong influence of the
subjects’ motivation. Our findings may have profound implications for the use of VR games in neurorehabilitation and potentially promote reparative plasticity and functional recovery.

5.6 Acknowledgment

We thank Dr. Lars Michels for his assistance in analyzing the data. This research was supported by the International Foundation for Research in Paraplegia (IRP) and the Swiss National Science Foundation (SNF), grant number PMPDP3-124282/1. The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
6. **General Discussion**

The aim of this thesis was to investigate the neural correlates of lower limb movement observation, imagination, imitation and goal-directed execution and the efficacy of VR with patients. A novel aspect was the combined application of imagination and imitation while observing a goal-directed movement of the lower limbs in a 1st-person perspective, a very common paradigm for virtual reality (VR) interaction. Furthermore, the thesis investigated outcomes of a newly created VR-augmented neurorehabilitation system for chronic incomplete spinal cord injury (iSCI) patients.

A total of 4 studies were conducted. The *first study* analysed neural correlates of the combination of observation and motor imagery, i.e. “online motor imagination” with pre-recorded video of real foot movements. The *second study*, conducted on iSCI patients, was a pilot single-case study investigating the first VR training system combining lower limb action observation, imagination and execution. The *third study* investigated the short- and long-term effects of intense VR training on motor function and neuropathic pain in iSCI patients. Finally, the *fourth study* investigated brain activation patterns during lower limb 1st-person VR interaction with a training scenario called “footbag”.

The findings of each individual study have been discussed in the specific discussion sections. In the following, the findings are discussed in relation to each other and are briefly summarized in the context of the research questions stated in the general introduction of the thesis.

### 6.1 Motor modalities of virtual reality interaction

Relevant studies of toe/foot movement experiments that focused on observing, imagining, imitating and/or executing actions, or a combination of these, are listed in Table 2.1. The neural correlates of lower limb movements have been only sparsely investigated compared to the upper limbs, and no study to date has examined the combination of observation and
motor imagery. The fMRI results in the first study confirmed that a combination of motor imagery and observation can extensively activate the motor execution network of the lower limb, even in the absence of overt movement. It is known that SCI patients require more cognitive effort to perform motor imagery than healthy persons. Hence, it seems to be particularly important to provide motivational and visual guidance to SCI patients performing motor imagery. Online motor imagination might promote post-injury retraining of function and functional recovery.

These results are in line with the second fMRI study. Online motor imagination of an interactive VR “footbag” scenario with virtually presented lower limbs was investigated, revealing that during online motor imagination, imitation and playing “footbag” without or with reward many similar regions were activated, primarily in brain area regions relevant for motor functions and self-awareness. Yet, effective playing of the virtual “footbag” has a strong influence of the subjects’ motivation, and playing the VR game is a rewarding activity per se.

Thus, the findings indicate strong additional implications of novel interventions in neurorehabilitation for iSCI patients. This was researched by the development and testing of a VR-augmented neurorehabilitation system. Instead of the common therapeutic setting that uses a “bottom-up” approach, the VR system induces the opportunity of using “top-down” processes.

### 6.2 Virtual reality neurorehabilitation

As stated in the previous section, playing a game with goal-directed virtually presented lower limbs in a 1st-person perspective enhances activation of sensorimotor networks and self-awareness. However, also important is the fact that VR provides a rewarding and motivating environment which supports high-intensity training. Although playing per se is a rewarding task, feedback of the performed movements, e.g. number of achieved juggles, is fundamental for the patients. It helps the patients to rank their performance and gives additional input for further training sessions.
The four playing scenarios of the VR system for the isolated movements of the different muscles tibialis anterior, quadriceps and leg ad-/abductors were chosen in collaboration with physiotherapists. The core muscles of locomotion were all well addressed and trained. Nevertheless, more gaming scenarios for other lower limb muscles and functions may additionally amplify the improvements of motor dysfunction and the reduction of neuropathic pain. Although the training with the four VR scenarios was motivating and the patients were able to generalize the training of individual movements to achieve functional improvements such as locomotion, further work is needed to clarify the challenging outcome compared to task-specific locomotion trainings. Especially the underlying brain mechanisms of motor function improvements and neuropathic pain reduction with the VR-augmented neurorehabilitation system need further investigation. To address this issue, a further fMRI study with iSCI patients is in preparation. Brain activation of the iSCI patients are measured to determine whether the playing condition of the “footbag” scenario produce different activation patterns before and after the training period and also compared to a healthy control group. The activation patterns of the patients, tested to date, were generally reduced in magnitude after the training suggesting improved efficiency in recruiting cortical areas to control lower limb movements.

The simple usage of the shoe device and the low costs of the equipment predestinates the system not only for clinical- but also for home-use. VR-augmented neurorehabilitation may not be limited to SCI patients. Other patient groups, e.g. stroke patients, would benefit by such an intervention due to the strongly involved cortical sensorimotor network. Furthermore, it might be worth to incorporate such a system as a preventive approach against chronic pain.

6.3 The addressed issues

The thesis extends our understanding of brain activation during VR-augmented neurorehabilitation. The online motor imagination of goal-directed lower limb movements in a
1st-person perspective can extensively activate the neural correlates of the lower limb motor execution network and thus be used for therapeutic approaches. Our VR neurorehabilitation training system for lower limbs combining action observation, imagination and execution in iSCI patients required active patient effort at all times, was usable, well accepted and the motivation was high. In the pilot single-case and training studies, positive effects on a short-term and longitudinal development in iSCI patients with motor dysfunction and neuropathic pain were shown. In addition, playing a “footbag” game with virtually presented lower limbs in a 1st-person perspective activates brain areas involved in sensorimotor actions and self-awareness, and is a rewarding activity per se which strongly influences subjects’ motivation.

To evaluate the effectiveness of VR-augmented neurorehabilitation therapies, it is crucial to further improve our knowledge of the underlying mechanisms and their outcomes, such as presented in this thesis.
7. References


## 8. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10MWT</td>
<td>10 Meter Walk Test</td>
</tr>
<tr>
<td>AAL</td>
<td>Anatomic Automatic Labeling</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>AIS</td>
<td>ASIA Impairment Scale</td>
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<td>ASIA</td>
<td>American Spinal Injury Association</td>
</tr>
<tr>
<td>BBS</td>
<td>Berg Balance Scale</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
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<tr>
<td>BOLD</td>
<td>Blood Oxygenation Level Dependent</td>
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<td>Cingulate Gyrus</td>
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<td>Caudate Nucleus</td>
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<td>Electromyography</td>
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<td>EM-SCI</td>
<td>European Multicenter Study about SCI</td>
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<tr>
<td>EPI</td>
<td>Echo-Planar Image</td>
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<tr>
<td>FA</td>
<td>Flip Angle</td>
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<td>FDR</td>
<td>False Discovery Rate</td>
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<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<tr>
<td>FOV</td>
<td>Field of View</td>
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<tr>
<td>FWHM</td>
<td>Full-Width at Half-Maximum</td>
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<td>Family-Wise Error</td>
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<td>GLM</td>
<td>General Linear Model</td>
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<td>HC</td>
<td>Hippocampus</td>
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<tr>
<td>IASP</td>
<td>International Association for the Study of Pain</td>
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<td>IFG</td>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>INS</td>
<td>Insula</td>
</tr>
<tr>
<td>IPL</td>
<td>Inferior Parietal Lobule</td>
</tr>
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<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>IRP</td>
<td>International Foundation for Research in Paraplegia</td>
</tr>
<tr>
<td>iSCI</td>
<td>Incomplete Spinal Cord Injury</td>
</tr>
<tr>
<td>ISI</td>
<td>Inter-Stimulus Interval</td>
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<td>LEMS</td>
<td>Lower Extremity Motor Score</td>
</tr>
<tr>
<td>m</td>
<td>Meter</td>
</tr>
<tr>
<td>M1/S1</td>
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<tr>
<td>MEP</td>
<td>Motor Evoked Potential</td>
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</tr>
<tr>
<td>min</td>
<td>Minutes</td>
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<tr>
<td>mm</td>
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<td>ms</td>
<td>Milliseconds</td>
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<td>NPS</td>
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<td>NRS</td>
<td>Numeric Rating Scale</td>
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<td>O</td>
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<td>O-MI</td>
<td>Online Motor Imagination</td>
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<td>Precuneus</td>
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<td>PGIC</td>
<td>Patients’ Global Impression of Change</td>
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<td>PMv/PMd</td>
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<td>Robot-Assisted Gait Training</td>
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<td>RMS</td>
<td>Root Mean Square</td>
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<td>Abbreviation</td>
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<td>s</td>
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<td>Spinal Cord Injury</td>
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<td>SCIM</td>
<td>Spinal Cord Independence Measure</td>
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<td>SCR</td>
<td>Scrambled Video Clip as Baseline</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>SEM</td>
<td>Standard Error of the Mean</td>
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<td>SFG</td>
<td>Superior Frontal Gyrus</td>
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<td>Swiss National Science Foundation</td>
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<td>SPL</td>
<td>Superior Parietal Lobule</td>
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<td>Statistical Parametric Mapping</td>
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<td>TE</td>
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<td>Thalamus</td>
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<td>UEMS</td>
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<td>ZNZ</td>
<td>Neuroscience Center Zurich</td>
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</table>
Curriculum Vitae

Name
Villiger Michael

Date of Birth
8th of March 1981

Citizenship
Erstfeld (UR) / Sins (AG), Switzerland

Education
2009 - 2012 PhD at ETH Zurich, Switzerland
Research conducted at the Spinal Cord Injury Centre, University Hospital Balgrist, Zurich

2007 - 2008 Bachelor of Science in Human Movement Sciences and Sport at ETH Zurich, Switzerland

2001 - 2007 Diploma / Master of Science in Biology - Neuroscience at ETH Zurich, Switzerland

1999 - 2004 Degreed Tennis Instructor, Swiss office for sport

1994 - 2001 High School, Schweizerische Alpine Mittelschule Davos, Switzerland

Working Experience
2008 Research Assistant, Human Performance Lab, Calgary, Canada

2008 - present Sport- / Tennisexpert, Swiss office for sport / Tennisassociation Grison, Switzerland

2006 Teaching neuronal basics at Kantonsschule Enge, Rämibühl Zurich, SAMD Davos, Switzerland
**Selected Presentations**

**Oral Presentations**


ENRC European Neurorehabilitation Congress, Merano (I), 2011. ‘Virtual reality training for the rehabilitation of lower limb motor dysfunction and neuropathic pain after spinal cord injury’.

International Conference on Virtual Rehabilitation, Zurich (CH), 2011. ‘Virtual reality rehabilitation system for neuropathic pain and motor dysfunction in spinal cord injury patients’.

**Poster Presentations**

ZNZ Neuroscience Centre Zurich Symposium, Zurich (CH), 2011. ‘Virtual reality rehabilitation training system for motor dysfunction and neuropathic pain after spinal cord injury’.


FENS Federation of European Neuroscience Societies Forum, Amsterdam (NL), 2009. ‘Neural correlates of observation, imagination and imitation of goal-directed foot movement: an fMRI study’.

Publications


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