A novel fMRI-compatible robotic device to assess brain activity during lower limb movements

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A NOVEL fMRI-COMPATIBLE ROBOTIC DEVICE TO ASSESS BRAIN ACTIVITY DURING LOWER LIMB MOVEMENTS

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presented by

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II. Summary

The role of the central nervous system in human locomotion and in the control of lower limb movements is still not well known. However, such knowledge is desired to map the brain function in healthy people and derive new therapy approaches for patients suffering from damage to the central nervous system, such as following stroke or spinal cord injury.

Brain function is preferably measured by functional magnetic resonance imaging, because this method delivers high resolution mapping, monitors activity in the whole brain, and does not harm the human by ionizing radiation or a radioactive contrast medium. To guarantee controlled and, thus, repeatable and comparable movements, a robotic device is needed that cannot only track the movements of subjects during subject-active movements, but also allows the generation of repetitive movements and forces during subject-passive movements.

Within the scope of this thesis, the requirements of such a device were determined and a pneumatically driven Magnetic Resonance Compatible Stepper (MARCOS) was designed and constructed. MARCOS allows gait-like movements with the corresponding ground reaction forces inside an MR scanner. In addition, different modes also allow several variations of these movements such as only single leg movements, parallel movements of the leg, and different force profiles at the feet. Furthermore, completely different movements like fine motor tasks and motor learning are assessable. During all of these
movements, the corresponding brain activity can be recorded by the MR scanner.

The device was designed in such a way that the scanner does not affect its function and the device does not affect the functioning of the scanner. The influence of MARCOS on the scanner was assessed and found to be negligible.

The control of MARCOS was subject to non-linearities and latencies introduced by the pneumatic components such as tubes, valves, and cylinders with large friction. In addition, biomechanical differences between subjects such as different limb lengths and masses as well as differences in the attachment of the subject to MARCOS introduce uncertainties and further non-linearities. An easy to use control-strategy was found by implementing a self-adapting iterative learning controller that not only adapts for all recurring non-linearities, but also to different subjects.

Head motion was limited by a newly developed fixation system, including shoulder belts, a vacuum pillow, a special hip fixation, and a newly designed head bowl. This fixation reduced the head motion to less than 1.5 mm, even though alternating foot forces of up to 300 N were applied.

Studies with healthy subjects demonstrated that measurements with MARCOS are possible and result in activation of expected brain areas. A single subject study with nine different stepping movements was performed. Here, single and alternating leg movements were analyzed as well as active and passive
movements, and movements with and without a simulated ground reaction force. In general, active movements induced more brain activity and more active clusters than passive movements and the application of force also increased the brain activity.

Based on this study, the conditions alternating active and passive, with and without a simulated ground reaction force were chosen to be assessed on 14 healthy subjects. The results showed that brain activity evoked by MARCOS is stable and repeatable.

In addition, a fine motor task was implemented, allowing a subject to balance a virtual ball on a virtual mechanical bar. MARCOS was used to display the gravitational forces of the ball and the bar. Visual feedback was provided to the subject into the scanner room via a projector and a silver screen.

In conclusion, MARCOS now allows the assessment of different kinds of lower limb movements in the fMRI. MARCOS is the only known device that can also provide significant forces to the foot. It can now be used in further studies with healthy subjects, e.g. for motor learning tasks or fine motor tasks, but also for studies with patients, to assess the effect, success and progress of different rehabilitation strategies.
III. Zusammenfassung

Bis heute ist nicht bekannt, welche Teile des zentralen Nervensystems die Kontrolle der unteren Extremitäten des Menschen übernehmen. Besonders die Rolle, die das zentrale Nervensystem bei der menschlichen Fortbewegung spielt, ist bis heute sehr wenig erforscht. Therapien nach einem Schlaganfall oder einer Wirbelsäulenverletzung können aber von solch einem Wissen profitieren. Um dieses Wissen zu gewinnen, muss die Gehirnaktivität während der Fortbewegung gemessen werden.


Ebenso sind feinmotorische Bewegungen möglich. Während jeder diese Bewegungen kann der Scanner die Aktivierungen im Gehirn aufzeichnen.

Der Einfluss des Gerätes auf die Magnetfelder des Scanners wurde gemessen und durch entsprechende Material-, Sensor- und Aktuatorwahl so klein gehalten, dass die Messungen nicht von dem Gerät beeinflusst werden. Andersherum stören auch die Magnetfelder des Scanners nicht die Funktion von MARCOS.


Die Kopfbewegungen während der Messungen in MARCOS konnte mit Hilfe einer neu entwickelten Fixierung auf 1.5 mm bei bis zu 300 N Fußkraft reduziert werden. Diese Fixierung besteht aus einer Hüftorthese, die den Körper gegen ein Vakuumkissen verspannt, aus Schultergurten und aus einer neu designten Kopfschale in Kombination mit der Crania-
Fixierung von Pearltec, ein aufblasbarer Ring, der um den Kopf gelegt wird.


Diese Studie wurde als Basis genommen, um Bewegungen für eine Studie an 14 gesunden Probanden auszuwählen. Aktive und passive alternierende Beinbewegungen mit und ohne Fußkraft wurden ausgewählt. Die Studie konnte bestätigen, dass der Bewegung entsprechende Gehirnaktivierungen reproduzierbar mit MARCOS erzeugt werden.

Zusätzlich wurde eine fein-motorische Aufgabe implementiert, in der ein Proband einen virtuellen Ball auf einem virtuellen Balken balanciert. Die Gravitationskraft des Balls wurde von MARCOS auf die Füße des Probanden übertragen, eine visuelle Darstellung der Szene auf eine Leinwand in den Scannerraum projiziert.

IV. Preamble

Chapters 2, 3 and 4.1 are based on the following manuscripts:

1 Introduction
1.1 Motivation

A dysfunction of neuronal circuits relevant for locomotion develops if spinal cord injured subjects remain immobile after an injury [5]. Gait training with robotic gait orthoses like the LOKOMAT (Hocoma AG, Switzerland, [5]) has been proposed to prevent such a neuronal dysfunction.

Currently, neither the underlying mechanism of dysfunction, nor the therapeutic effects of gait training on spinal and supraspinal neuronal circuits are completely understood. Knowledge about these mechanisms would help to improve the therapeutic efficacy of gait training. While training effects on spinal neuronal centers have been described [6], training effects on supraspinal centers are almost unknown. A better insight might be achieved by the assessment of brain activity during gait or lower limb movements. This can help to recognize the significance of specific brain regions in the recovery of function and the effects of specific training regimes on brain centers in CNS injured subjects.

An established method to assess brain activity is functional magnetic resonance imaging (fMRI). It is a non-invasive technique featuring high spatial resolution of brain activity without any serious contraindication. In combination with an MR-compatible robotic device enabling gait-like movements in a repetitive and controlled manner, fMRI can measure brain activity during gait-like movements.
To run fMRI measurements of a patient performing gait-like movements a new device is recommended that can produce periodical, reproducible, and smooth gait patterns of the lower extremities of a patient lying supine in the MR scanner. The device must be MR safe and MR compatible, and must not cause artefacts due to the movements and electromagnetic effects. In addition, head motion must be limited in order to allow standard image analysis.

Using such an “MR-compatible stepper” will induce neural activities in cortical and subcortical structures, in the cerebellum and in the spine, which will be recorded by an fMRI protocol. The result can be used to investigate brain activity during gait related movements and to assess different therapy strategies.
1.2 State of the art: MR compatible robotics

Applications for MR compatible robots (reviews: [7, 8]) can be found in surgery [9-13] and needle biopsies [14, 15] (Figure 1), e.g. prostate interventions [16] (Figure 4). Applications also exist in neuroscience [17-24] (Figure 2) to map brain functions of controlled and repeated movements, and in the field of rehabilitation [8, 25, 26] (Figure 3).

Figure 1: Robot assisted needle placement for prostate biopsy in an open MR scanner [14]. The inset shows an optical tracking marker.

However, placing a robotic device into the magnetic resonance scanner environment raises several challenges and constraints to its design:

- It should not harm or endanger the subject, e.g. by parts that might be attracted by the magnet.
The magnetic field of the scanner should also not affect the functionality of the device.

The device should not disturb the imaging process by magnetic interference or radio frequencies.

The device should not disturb the imaging process by introducing head motion or vibrations to the scanner.

The restricted space inside the scanner bore must be taken into account.

These challenges complicate the choice and application of actuators and sensors.

The challenge of an appropriate actuation has been solved by different researchers in different ways. Thereby, actuation principles as pneumatic cylinders or stepper motors were used [27-29] (Figure 3) as well as hydraulic cylinders in master-slave configuration [22, 30] (Figure 2, right) or with long tubes [23, 31] (Figure 2, left). In addition, forces and movements were transmitted via cables [32] or produced by ultrasonic motors [9, 33], electro-rheological fluids [25, 34, 35] and special electromagnetic principles [36].
Introduction

**Figure 2:** Hydraulic robots for functional brain imaging of arm (left, [24]) and wrist movements (right, [22]). The robot in the left image is actuated via valves and long tubes. The robot depicted in the right image uses the master-slave principle.

As sensors, optical principles optical encoders such in [37] or camera-based measurements were used as well as resistive strain gauges [38].

**Figure 3:** MR_CHIROD v.3: A device for brain imaging during handgrip rehabilitation [25]. It uses electro-rheological fluids.

The choice of materials for these devices is mostly restricted by the magnetic susceptibility [39]. Common plastic materials like PET and Ertalyte have a very small influence on the magnetic fields of the scanner. If the design avoids large movements of specific parts and if placed outside of the scanner bore, also
metals with low magnetic susceptibility, like aluminum and brass, can be used inside a scanner [39, 40]. Otherwise, eddy currents would be induced in these materials, which lead to a disturbance of the magnetic fields of the scanner and, thus, to image artefacts.

Figure 4: The robot “MrBot” for prostate interventions [16] in an MR scanner. Also this robot uses pneumatic stepper motors.
1.3 State of the art: brain activity assessment during gait and gait-related movements

1.3.1 Analysis of brain activity during natural gait
The assessment of brain activity during natural gait is challenging, as most brain assessment methods as functional magnetic resonance imaging (fMRI), Electroencephalography (EEG), positron emission tomography (PET), and single photon emission computed tomography (SPECT) needs a stabilized head. Today, brain activity during natural gait has only been studied with PET and SPECT [41-43]. However, walking on a treadmill and acquiring brain activity was not concurrently but consecutively performed. Furthermore, assessments of brain activity by PET and SPECT require administration of a contrast medium, which can be harmful.

Also near-infrared spectroscopy (NIRS) has been applied to assess brain activity during natural gait [44, 45]. In contrast to PET and SPECT, this method allows concurrent acquisition of brain activity during gait without contrast medium, and thus, is a very promising method. However, it has a rather poor spatial resolution [46]. Electroencephalography (EEG) suffers from artefacts due to movements of the electrodes and muscle activity. In addition, EEG only allows measuring the brain activity close to the skull.
1.3.2 Analysis of brain activity during multi-joint leg movements

As the high resolution acquisition of brain activity during natural gait is – today - not possible without application of harmful contrast mediums, researchers focused on simplified movements of the lower limbs involved in human locomotion that can be analyzed with alternative high resolution methods as fMRI.

Promising, because similar to gait, is the assessment of brain activity during cycling movements. Cycling movements can also be performed in a supine position of the subject. Thus, they were investigated with fMRI [47, 48] and SPECT [49] with the help of an MR-compatible device. However, in lack of an appropriate fixation, these approaches suffered from excessive head motion. Furthermore, they did not consider appropriate foot loading, although foot loading is an important facet of gait.
1.3.3 Analysis of brain activity during gait-related single joint movements and imagined walking

Several research groups investigated brain activity during simplified gait-related movements. They concentrated on isolated joint movements, like ankle or knee flexion / extension [19, 20, 50-53], However, a coordinated movement of several joints is important to obtain a realistic gait pattern and activate gait-like muscle activity in the legs [54, 55], with the associated nervous representations in the brain.

Brain activity during imagery of walking was also measured [52, 56-60], because motor imagination is easy to apply and does not induce head motion. A similar strategy was pursued with EEG.
EEG allows measurements in an upright position with a high temporal resolution, e.g. measurements of brain activity during the phase of gait initiation [59, 60]. Measurements during natural gait are difficult with EEG, again due to artefacts induced by disturbing signals from muscle activity (e.g. from the eyes) and movements of the electrodes.

The approaches of measuring brain activity during motor imagination or during the gait initiation phase, however, does not evoke the same brain activity as the real execution of motor tasks, as shown e.g. for hand movements [61].

1.3.4 State of the art: Conclusion
In conclusion, today no device exists that enables brain activity assessment of gait or gait-like movements during an fMRI session. Measurements with SPECT and PET should not be performed, as these methods are invasive and go with adverse reactions.
1.4 Goal of this thesis

The goal of this thesis is to develop and evaluate a MR-compatible stepping device that generates periodic leg movements and that does not affect MR image quality. This device should be used in fMRI studies to comprehensively investigate the neuronal activity in the brain of healthy subjects during gait-like movements. These measurements can serve as a database to compare brain activity of healthy subjects to patients suffering from stroke or a chronic spinal cord injury.

Thereby, not only the challenges of devices used inside the MR scanner (interactions between device and the scanner) must be taken into account, but also the possibility that leg movements cause head motion and, thus, motion artefacts on the MR images. Furthermore, space inside the scanner bore is limited, which limits the movement range of the subject as well as the application of bulky technical components.
1.5 Overview

In Chapter 2, the development of the magnetic resonance compatible stepper MARCOS is described. At the beginning, the requirements are derived. The description of the realization follows. The chapter continues with an optimization of the biomechanics, to achieve angle trajectories close to these during gait. In the next section, measurements to determine the influence to the magnetic fields of the scanner are presented. The last section presents a study about fixations to minimize head motion.

Chapter 3 describes the control of MARCOS. It starts with the challenges and requirements and continues with the basic feedback controllers. Afterwards, an iterative learning controller is presented that enables an adaptation to different subjects and accounts for non-linearities in the system.

In Chapter 4, three different experimental fMRI studies are described. At first, a single subject study applying nine different movement conditions is presented, followed by the presentation of a study on 14 healthy subjects tested in four movement condition. Both studies proofed the feasibility of brain activity measurements with MARCOS. A further study reveals the applicability of MARCOS in the field of fine motor tasks and motor learning.
2 Design of the Magnetic Resonance Compatible Stepper MARCOS
2.1 Requirements for the Magnetic Resonance Compatible Stepper MARCOS

2.1.1 Biomechanical requirements
The basic requirement was the assessment of brain activity by fMRI during lower limb movements. The evoked brain activity should be as closely as possible related to that during gait. To assess brain activity, fMRI was preferred, as it is an established, non-invasive method without side effects.

Measurements inside the MR environment require not only special robotic devices, but also enforce the subject to lie in a supine position having the upper body inside a small scanner tube. Therefore, only simplified gait movements can be realized. In the following, literature was reviewed related to possible modifications of gait characteristics that may not substantially affect the general characteristics of brain activity during gait.

Movement range
The movement ranges of the hip, knee and ankle joint should be close to those during natural gait. During gait, the hip angle varies between 15° extension and 20° flexion [62]) the knee flexion ranges from 0° to 60° flexion, and the ankle joint varies between -20° extension and 10° flexion (Figure 6). In the scanner, these movement ranges are not possible, due to the supine posture leading to unnatural gravitational effects (swing phase not supported by gravity) and additional body contact at
the trunk from the bench to the back, leading to a smaller workspace. Also, reaching negative hip angles is hindered by the supine position. Still, the pattern must remain similar in several key characteristics in order to lead to a locomotor pattern in the relevant leg muscles [6]. These key characteristics concern the temporally coordinated movements of ankle, knee, and hip joints in the sagittal plane [63, 64].

![Diagram of hip, knee, and ankle joints](image)

**Figure 6: Hip, knee and ankle joint of the human leg.**

The EMG patterns during slow walking do not change qualitatively compared to walking with normal speed, but the movement ranges become smaller [65]. Therefore, for the planned device, it will not be necessary to reproduce the exact joint angle ranges, but it should include as many joints as possible. Even if not the full range and the correct temporal coordination is reached, a device that moves the hip, the knee, and the ankle joint will allow significant insights into human locomotor control. Researchers claimed to be able to evoke gait-
like brain activity patterns during much simpler or even single joint movements (foot: [47, 48, 52], knee [51], arm swing [45]). Thus, simplified movements can also be an option.

In addition, leg muscle EMG activity is amplified if both legs move in an alternating manner [55]. Accordingly, the device should enable alternating movements of both legs.

**Movement speed**

A faster movement speed leads to greater acceleration of the legs and to larger forces. This results in a greater head motion. Therefore, the lowest movement speed is desired, that does not change the characteristics of natural gait with a speed of approximately 1.3 m/s [66, 67] and a movement frequency of approximately 1 Hz. In Suzuki 2004, it was shown with NIRS that faster movement speeds evoke stronger activity in the bilateral prefrontal cortex and the premotor cortex [68]. However, the qualitative changes were small. As these data do not provide a high resolution insight, it cannot be derived if the speed changes brain activity qualitatively. The minimum speed was found by looking at the muscle activity during different gait speeds measured by Ivanenko in 2002 [54]. Thereby, stronger muscle activity can be found during fast movement speeds, but the electromyogram trajectories of the most important muscles (gluteus maximus, vastus lateralis, rectus femoris, biceps femoris, tibialis anterior, lateral gastrocnemius) does not change their shape due to different speeds – only the amplitude [69].
Hence, for the design of the MR compatible stepper, the movement speed can be chosen freely but should be as fast as possible without causing too much head motion.

Foot loading

Studies about body weight supported treadmill walking showed that electromyographic activity of leg muscles and angular trajectories at the hip and knee remain physiological as long as they incorporate ground reaction forces at least in the magnitude of half the body weight [54, 70] (approximately 400 N) and sufficient hip joint excursions [6]. A NIRS study showed in five subjects that body weight support even increases the brain activity without modifying gait parameters [44]. Accordingly, the device should be able to move the legs in an alternating manner and to generate forces of up to 400 N at the foot sole.

2.1.2 Technical requirements

The most important technical requirements are:

- Safety
- MR-compatibility
- Account for the limited space
- Do not induce head motion larger than 2 mm, or limit head motion with a fixation
- Perform the movements defined in chapter 2.1.1

In terms of safety, it should be considered that stroke and spinal cord injured patients are in the future focus.
The need for MR compatibility requires a careful choice of materials, actuators, and sensor technology. The device must not disturb the imaging process of the scanner and the scanner neither must disturb the functioning of the device. Further, the device must fit into the scanner and enable the forces, movement ranges and speeds defined in the movement requirements.

Movements of the leg and forces at the feet must not induce head motion larger than 2 mm (the used voxel size in this direction is 3 mm). Head motion larger than 2 mm would not allow standard image analysis. Movements up to this value can be corrected by the motion correction algorithm of the MATLAB toolbox statistical parametric mapping (SPM).

2.1.3 Summary

Based on this literature review, the requirements were defined. Accordingly, the robot should:

- Guarantee safety
- Follow the restrictions and needs of the MR environment such as MR-compatibility, accounting for the limited space
- Perform simplified gait movements including the hip, knee and ankle joint
- Achieve movement ranges as during natural gait
- Move both legs with a frequency equivalent to 2-5 km/h in an alternating manner
- Apply ground reaction forces of up to 400 N
- Limit head motion to below 2 mm
2.2 Realization

Based on the requirements defined in the literature review, a pneumatically driven MR-compatible stepper (MARCOS, Figure 7, Figure 9) was designed and built.

Pneumatic actuation was chosen, because it allows an MR-compatible design while featuring high maximum forces and good control performance [40]. Furthermore, pneumatic actuators are compliant and can easily be switched to a force-free state by connecting both cylinder chambers to the atmosphere, which is important to guarantee safety. All ferromagnetic parts in the piston were replaced by custom-made pieces manufactured from aluminum and brass.

Figure 7: Principle sketch of MARCOS
Each knee and foot of the subject is strapped to a modified pneumatic cylinder (DNC 40-320-P-K10-S11 (Knee), DNC 32-350-P-K10-S11 (Foot) Festo, Esslingen am Neckar, Germany). The vertical cylinder at the knee induces forces that move the knee up and down. At each leg, these forces are guided through two orthopedic cuffs (altered commercial K1 orthoses from Fior & Gentz GmbH, Lüneburg, Germany, Figure 8), one proximally and one distally, placed around the knee and connected by a hinge joint.

Figure 8: The altered K1 knee orthosis, to fix the subjects knee in MARCOS

These cuffs are used in order to optimally distribute the force to a large contact surface, thus reducing contact pressure. The axis of the hinge joint is roughly aligned with the anatomical axis of the knee. The pneumatic cylinder at the foot induces a force in
such a way that the foot moves along the linear guide. This force is guided through the foot sole in order to generate the appropriate afferent input (Figure 7, Figure 9).

Figure 9: MARCOS in the fMRI scanner

The position and orientation of the linear guide at each foot can be adjusted to vary hip and knee joint trajectories. At the hip, flexion between 0° and 40° is possible (during gait it varies between 15° extension and 20° flexion [62]). At the knee, flexion can range from 0° to 60° at the knee (during gait between 0° and 60° flexion). The foot orientation is fixed so that the angular displacements at the ankle range between 45° and 90° (during
gait between -20° and 10°) (Figure 7). The desired input signal is always sinusoidal, to reduce jerk and, thus, head motion.

The cylinders connected to the knees are controlled by proportional flow valves, while the cylinders connected to the feet are controlled by pressure-control valves and a proportional multi-way valve (Figure 11). For safety reasons, the proportional way valve is always set to a position that produces forces that press against the foot only (no pulling in negative x-direction, see also Figure 7).

Resistive strain gauges on aluminum substrate serve to record forces. They are fixed between each piston and the corresponding orthopedic cuff. The position of each cylinder is measured redundantly by optical encoders (Type MS20, RSF Elektronik AG, Schwerzenbach, Switzerland) with a ceramic scale and a foil potentiometer (MTP L22, Resenso, Ins, Switzerland).
Two personal computers are used for signal analysis and control: The sensor evaluation PC runs Linux, and processes data from the data acquisition boards (Beckhoff Automation GmbH, Verl, Germany). It communicates via Ethernet with the control PC, which runs Matlab xPC real-time target (Mathworks Inc., Natick, MA, USA) and executes low-level pneumatic control and high-level gait pattern control. Based on the signals received from the sensor evaluation PC, new control signals are calculated and sent back to the sensor evaluation PC that feeds them through to the output board. The output board generates the analog control voltage for direct use in the control and safety valves (Figure 10).
As soon as the model is loaded from the XPc host to the target, the host is only used to present the graphical user interface to control MARCOS. The user can choose the kind of movements and also give the control to the scanner control computer, running the software Presentation (Neurobehavioral Systems, Inc, Albany). In this mode, the Presentation software can trigger the start of movements, the kind of movements and the breaks, while logging this data together with the scanning progress. The communication is realized through the serial port.

**Figure 11: Pneumatic control layout of MARCOS. In the normal state, the safety valves connect the cylinder chambers to the atmosphere.**

Several redundant mechanisms are incorporated in order to ensure safety for the subjects:

1. Mechanical stops on each cylinder restrict anatomically inappropriate positions.
2. The position of each cylinder is redundantly measured by two position sensors. Divergent values are detected.
by the control software, which would launch an emergency stop.

3. Sensors and communication between the sensor evaluation CPU and the control CPU are supervised by the control software. In case of an error, an emergency stop is launched.

4. Watchdog circuits supervise the computers and communication.

5. The software supervises the forces and launches an emergency stop if a threshold is reached

6. Emergency stops can be launched by the operator by pressing an emergency switch.

7. In case of an emergency stop (launched by software or manually), all cylinder chambers are connected to the atmosphere by closing the safety valves (Figure 11). Then, the cylinders can be moved freely and the subject can easily be released from MARCOS.

To prove stability and safety, relevant parts for safety or with high mechanical stress were analyzed with a finite element method in respect to tension and displacement. If needed, they were adapted to guarantee stability. The calculation for the finite element method was executed with Pro/Engineer Wildfire2 (PTC, the product development company, Needham, USA).
2.3 Optimization of the kinematics

MARCOS features one degree of freedom at each leg enabling a movement pattern that is comparable to stepping on the spot.

A change of the height and slope of the linear guide changes also the characteristics of the angular displacement at knee and hip. Accordingly, the trajectory of the knee angle is determined as soon as a hip angle trajectory and a linear guide position are given. Thus, a change of the position of the linear guide changes this relation.

2.3.1 Methods: the discrete optimization algorithm

To achieve movements of the legs as close as possible to the movement during natural human gait, the slope and position of the linear guide were optimized. The reference trajectories of natural gait were based on measurements performed by the Institute for Biomechanics (ETH Zurich, Zurich, Switzerland).

A discrete optimization algorithm was programmed in MATLAB (The MathWorks). The algorithm allows setting boundary conditions to account for hardware limitations of the device and weightings for the hip and the knee angle. The knee angle trajectory was weighted with the same value as the hip angle trajectory. The algorithm calculated the slope and position for which the error between the optimized hip and knee angle trajectories are minimal compared to the angle trajectories during walking. The hip and knee angle amplitudes were normalized. The algorithm calculated the error for each discrete
time step of all possible linear guide parameters. After that, a
discrete minimum search of the sum of the error over all time
steps was applied to find the optimal position for the slope.

2.3.2 Results and discussion
The optimized trajectories for the knee and the hip angle
resemble those of the trajectories recorded during physiological
gait (Figure 12, reference). In particular, the swing phase at the
knee (60-100% of gait cycle) is almost simultaneously initiated
and the maxima/minima of the optimized trajectory are at
similar times as the extremes of the physiological trajectories
(Figure 12, green lines). The optimized knee trajectory covers the
whole range of motion. The hip trajectory does not cover the
entire natural range of motion, but still some negative angles
(corresponding to hip extension) are achieved (Figure 12, red
lines). The extremes of the hip trajectory do not resemble the
original data as well as those of the knee and can only be
reached if the back of the subject is elevated and tilted.
Figure 12: Optimization results - The dashed vertical line indicates the start of the swing phase. The reference trajectories were measured during natural gait. The optimized trajectories are theoretically achievable with a one degree of freedom stepping movement. The realized trajectories could be realized in the setup with the scanner.

Such an optimization could be used to find the optimal setting for each individual subject. However, new calculations for each subject would be needed, taking different body sizes into account. In addition, a constant setup would have to be guaranteed. In practical use, such a precise setup is not possible:

- The individual and for each subject changing cushioning leads to different hip heights and angulation
- The fixation in the knee and foot orthoses differs from setup to setup
• Changes in the distance and position of MARCOS changes the height of the linear guide and therefore the characteristics between hip and knee angle.

In addition, some other practical reasons contradict the direct use of the optimized trajectories:

• Sinusoidal movements are preferred, because they are less jerky and, thus, induce less head motion.
• The negative hip angle was not realizable in the practical use, because the elevation of the back resulted in an increased blood flow to the head. This was perceived as uncomfortable and not practical for the duration of fMRI measurements (about one hour).

Therefore, the result was taken as an approximate value and was preset once and for all subjects.

With the current setup, hip angles ranging from 0° to 40° flexion (during gait it varies between 15° extension and 20° flexion) and knee angles from 0° to 60° (the same as during gait) are possible. During the experiments presented in the later chapters of this thesis, the hip angle ranged between 0° and 25°, the knee angle between 0° and 48° (Figure 12).
2.4 Influence on the MR-Environment

To minimize interference with the MR scanner, MARCOS only consists of PVC, Ertalyte, aluminum, and brass, as these materials are characterized by a low magnetic susceptibility. The region of interest, i.e. the human brain, is more than one meter away from the nearest metallic part of MARCOS. Movements of metallic parts with relevant electrical conductivity were avoided as much as possible to limit the generation of eddy currents.

All sensor signals are collected inside the scanner room, and transferred to the control computer via fibreoptic cables. The only metallic cable leading into the scanner room is a shielded DC cable for the sensor power supply. To avoid artefacts, the shield of the cable is connected to the shielding of the scanner room, and the DC current is low-pass-filtered.

2.4.1 Methods: Measurements and the temporal signal to noise ratio

The influence on the MR environment was measured by calculating the change of the temporal signal-to-noise ratio of 49 points in the center of a measured slide (fMRI sequence) of a phantom (bottle of water). The following conditions were tested as suggested in the literature [71]:

I. baseline: MARCOS was outside the scanner room,
II. connected: MARCOS was mounted on the bench (cables connected)
III. moving: while mounted on the bench, MARCOS was powered and the actuators moved

IV. 2nd baseline: the first condition was repeated

The measurements were performed inside a 3.0 T MR system (Philips Medical Systems, Eindhoven, The Netherlands) combined with an 8-channel SENSE™ head coil at the university hospital Zurich. For functional acquisition, a T2*weighted, single-shot, field echo, EPI sequence of the whole brain with a SENSE factor of 2 was applied to collect signals from 39 contiguous slices (TR = 2 sec, TE = 40 ms, flip angle = 82°, FOV = 220 mm × 220 mm, acquisition matrix = 128 × 128, in-plane resolution = 1.7 × 1.7 mm^2, slice thickness = 3 mm).

To calculate the temporal signal-to-noise ratio tSNR, the values of 49 voxel in the middle of the phantom were measured 20 times. The mean value for each voxel time series was divided by its standard deviation [39].

\[
tSNR = \frac{\text{mean}(\text{voxel}(1..20))}{\text{sdev}(\text{voxel}(1-20))}
\]

The results were analyzed with a Kruskalwallis statistical test in Matlab (Mathworks Inc., Natiek, MA, USA).

2.4.2 Results of the tSNR measurements

The Kruskallwallis test showed a significant difference (chi-sq=9.62, p=0.022) for the conditions “moving device” and “2nd baseline” (Figure 13). All other conditions were not significantly different.
Figure 13: Temporal signal-to-noise ratio (tSNR) of $T2^*$-weighted measurements with MARCOS: No device (1\textsuperscript{st} baseline), Cables connected, moving device, No device (2\textsuperscript{nd} baseline). The star (*) marks the statistical difference of the condition “Moving” and “2\textsuperscript{nd} baseline”.

2.4.3 Discussion: Does MARCOS disturb the magnetic fields of the scanner?

The temporal signal to noise ratio was significantly different only in the condition in which the device moved compared to the second base line scan. However, it was not possible to define a threshold for an acceptable difference. As the difference was quite small, and no difference to the first baseline scan was encountered, MARCOS was used in a pilot study (see chapter 4.1). During the evaluation of this study, standard evaluation methods could be applied and the expected brain activity was
found. Thus it can be assumed that the device had no considerable impact on image quality.
2.5 Head movement reduction

Too much head motion can disturb the imaging process. The movements of the legs and the forces at the foot sole induce head motion especially in the cranial-caudal direction. Therefore, head motion in this direction was investigated during different movement conditions. In this direction, head motion has to be limited to a range of 2 mm over a period of three seconds, i.e. over a period required for a complete functional scan of the head. In the experiments a voxel size of 3 mm was used. Head motion up to 2 mm can be corrected by the motion correction algorithm of the Matlab toolbox SPM (statistical parametric mapping).

In several pre-studies, different versions of fixations were tested with respect to comfort, ease of use and effectiveness of head motion suppression. Shoulder belts, a vacuum pillow placed at the back, a custom-made rigid hip fixation (Figure 14, Figure 17), and a custom-made head bowl (Figure 15) was tested in particular in a setup outside of the MR scanner.
2.5.1 Methods: Measurements outside of the scanner

Table 1: The eight tested conditions in the head motion analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder belts</td>
<td>On</td>
<td>On</td>
<td>On</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Air in vacuum pillow</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Force at the feet</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

To measure the impact of different fixation techniques and how they can avoid head motion while a force is acting on the feet, the conditions shown in Table 1 were tested with four subjects (Table 2).
Table 2: The four tested subjects

<table>
<thead>
<tr>
<th></th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>25</td>
<td>33</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>88</td>
<td>72</td>
<td>65</td>
<td>74</td>
</tr>
<tr>
<td>Size [m]</td>
<td>1.73</td>
<td>1.8</td>
<td>1.82</td>
<td>1.82</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
</tbody>
</table>

At the same time, as additional conditions, sinusoidal forces between 0 and 300 N were either applied or not applied at the sole of the feet. All conditions were tested with alternating leg movements with a frequency of 0.5 Hz. The resulting head movements were measured with an opto-electronic motion capture system (four Oqus 3 cameras, Qualisys, Gothenburg, Sweden).

An initial head motion step at the beginning of leg movements, has only negligible influence to the fMRI results. Therefore, the evaluation focused on the high frequency movements after the initial step. These movements were caused by the acceleration forces and contact forces during the stepping movements, as well as the alternating foot loading. Of importance is the head motion that occurs during one scan of the head, i.e. within three seconds.
The amplitude for each subject and condition was tested in respect to its normal distribution with a Kolmogorov-Smirnov test and compared to the other conditions with a Friedman test (Bonferroni adjustment). The significance level was set to 5%. Afterwards, the conditions were compared between the subjects with the same Friedman test.

2.5.2 Results: Head motion during movements in MARCOS

For three out of the four tested subjects, head motion was below 1.5 mm for all conditions (Figure 16). The differences between the different conditions were not significant for all subjects. Also differences between the subjects were not significant in most cases. Significant differences were found between Subject 1 and
Subject 2 in the conditions: no shoulder belts, air in the vacuum pillow, no air in the vacuum pillow and force at the foot sole.

Head motion of one of the four subjects was up to 3 mm.

**Figure 16**: Head motion amplitude: mean, minimum and maximum for all conditions: (1) all conditions with shoulder belts on (2) all conditions without shoulder belts (3) all conditions with air in the vacuum pillow (4) all conditions without air in the vacuum pillow (5) all conditions with force at the foot sole (6) all conditions without force at the foot sole. The significantly different conditions are colored in blue.

### 2.5.3 Discussion: What is the best fixation?

As no significant differences between the conditions could be encountered, it is assumed that all fixations are able to fixate the subject sufficiently. As consequence, the fixation method can be chosen according to the comfort of the subject.
Interestingly, in some conditions significant differences of head motion amplitude were found between Subject 1 and Subject 2. Also the visual inspection of the results suggest differences between subjects, but no differences between the conditions (Figure 16). Thus, it seems to be more important to apply the tested fixation methods properly than to apply as many as possible. Further proof supporting this theory is that the subject with the strongest head motion was measured first and not fixated as carefully as the others.

The vacuum pillow with air inside was chosen in combination with the hip fixation and the shoulder belts. This combination was rated as most successful and comfortable and, thus, are recommended to be applied during fMRI measurements (Figure 17).

Figure 17: Fixation methods used in the scanner: Head bowl with the Crania fixation from Pearltec, shoulder belts and a hip fixation in combination with a vacuum pillow.
In all fMRI measurements conducted in the scope of this thesis, these fixation methods were applied. Additionally, the Crania fixation (Pearltec AG, Zurich, Switzerland) was used. This fixation is an inflatable ring that is placed between the head and the head coil. Subjects can regulate the pressure via a small pump, similar to those used for blood pressure measurements. Subjects are asked to use as much pressure as possible without compromising comfort. This fixation was not tested outside of the scanner, but was applied during measurements, as it is easy to use, comfortable, and increases the fixation performance according to visual inspection in the scanner.
3 Control of the non-linear, over-actuated system MARCOS
MARCONS can work in two different modes: Firstly, the subject is passive (“subject-passive mode”) and secondly, the subject is active (“subject-active mode”). Also anything in between is possible. In subject-passive mode, MARCONS imposes the gait-like movement on the subject. In subject-active mode, the subject generates the movement, while the robot follows the movements in such a way that the interaction forces between the legs and the knee orthoses are minimized. In both modes, the force that acts on each foot is controlled independently to impose a specified profile. This is possible due to the redundancy of the system: the kinematic constraints allow movement in only one degree of freedom, so that each leg is over-actuated. This enables the robot to enforce motion of the leg using the knee actuator and to regulate a desired foot force using the foot actuator. As the force profile is independent of subject activity, subject-active and subject-passive modes differ mainly in the way the knee actuator is controlled.
3.1 Challenges and requirements

The robotic system MARCOS comprises non-linearities in all of its pneumatic components:

- The proportional multi-way valves have a non-linear characteristic curve, and produce a flow which is not only depending on the opening, but also depending on the pressure behind the valve.
- The tubes from the valves to the cylinders introduce dead time and low pass filter effects.
- The cylinders themselves require different filling strategies depending on their position. Small cylinder chamber sizes require less air to establish a desired pressure than large chamber sizes.
- Further, the need for MR-compatibility limited the choice of materials in the cylinders. Thus, sub-optimal material pairing at the areas of contact between the piston and cylinder housing increase the friction.

In addition, the mechanical design comprises a large and varying non-linearity: as long as the leg is stretched, a force at the foot sole has no influence on the cylinder at the knee, but in a bent position, the influence is large. Moreover, the orthosis at the knee bears some clearance.

Last but not least, the system properties changes strongly, when different subjects of different heights and weights are attached to MARCOS.
MARCOS was designed to move humans in the scanner. Thus, control performance as good as in modern industry robots is not needed. More important are smooth movements and a sufficient repeatability of the movements during a task. Only if the repeatability of the movements is given, comparable results can be produced. The repeatability of the movements between subjects with different body weights and lengths should be given as well.

The cylinder at the knee can change the height of the knee and thereby the angle of the hip and knee joint. In doing so, 0.01 m change in the position of the cylinder leads to a hip angle change of approximately 1°. Already the orthosis comprises non-controllable clearance of approximately 0.01 m. For this work, this can be neglected, as subjects only perceive angle changes of approximately 1°[72]. Hence, the controller only has to achieve a control performance in the range of this value. The desired performance was set to the half, corresponding to an accuracy of 0.005 m.

Also for the force controller, smooth force profiles and repeatability is more important than the control of an exact value – as long as this value does not change between subjects and trials, the evoked brain activity remains comparable. During walking, forces of up to 100 to 150% of the body weight occur at the feet [73], corresponding to forces of 750 N to 1125 N. The desired force accuracy was set to approximately 2 % of this value, i.e. 20 N.
3.2 Subject-passive mode

A standard method for controlling robotic devices is using PID controllers. However, due to the non-linear and changing properties of the system and over actuation, such a controller is not sufficient to achieve the desired positioning performance of 0.005 m. Still, they are useful for an inner control loop, which accounts for differences and variations of the system that cannot be addressed by feed forward controllers.

Therefore, the subject-passive mode combines feedback position and force controllers with an iterative learning feed forward controller, exploiting the cyclic nature of the task to improve performance.

3.2.1 Feedback force controller

The force control at the foot has a cascaded structure. An inner pressure control loop is realized directly by proportional pressure control valves. The reference pressure $u_{footcyl}$ is calculated using an outer proportional force controller with additional feed-forward terms (Figure 18):

$$ u_{footcyl} = \frac{F_{ref} + P_{foot}(F_{ref} - F_{meas}) + \kappa F_{ref}x}{A} $$

with reference foot force $F_{ref}$, measured force $F_{meas}$, proportional gain $P_{foot}$, piston area $A$, piston displacement $x$, and a manually tuned constant gain $\kappa$. The term $\kappa F_{ref}x$ approximately compensates for the dependency of pressure build-up on
chamber volume, resulting in a simplified version of the control strategy as suggested similarly in [74].

**Figure 18: Schematic of the feedback controllers**

### 3.2.2 Feedback position controller

The position controller enforces the desired knee trajectory by regulating the position of the cylinder that is attached to the knee by the cylinder’s proportional flow valves. The controller output is the valve opening \( \hat{u}_{pos} \). A value of 0.5 corresponds to a standard nominal flow rate of 350 l/min, 0 corresponds to a closed valve, -0.5 to a standard nominal flow rate of 350 l/min in the opposite direction). This output is calculated proportional to the difference between the desired knee position \( y_{ref} \) and the measured position \( y_{meas} \), with a proportional gain \( P_{pos} \) (unit 1/m):

\[
\hat{u}_{pos} = P_{pos}(y_{ref} - y_{meas})
\]

One side effect of proportional valves is their non-linear behavior. To partially compensate this, the approximate inverse...
of the valve’s static response is used to transform controller output $\hat{u}_{pos}$ to actuator input $u_{pos}$. This transformation is simply a linear function with a dead zone, because there is no noticeable flow for input values lower than 0.03:

$$u_{pos} = \begin{cases} 
0, & \hat{u}_{pos} = 0 \\
\hat{u}_{pos} - 0.03, & \hat{u}_{pos} < 0 \\
\hat{u}_{pos} + 0.03, & \hat{u}_{pos} > 0 
\end{cases}$$

This value is converted to a voltage and directly sent to the proportional flow valve (Figure 18).

### 3.2.3 Iterative learning feed forward controller

The standard feedback controllers are not sufficient to achieve the desired control accuracy. Therefore, during the subject passive movements, a self-adapting feed forward term was added. This is possible, because the passive movements are repetitive. This means that non-linearities from the tubes, valves and the mechanics have similar characteristics during each movement cycle and also the subject does not change his properties during the time in MARCOS. Consequently, it suggests itself to measure and compensate these recurring effects. This was done by the implementation of an iterative learning controller (ILC) [75].

The iterative learning controller compensates for all repeating disturbances, e.g. non-linearities at the valves, tubes, cylinders, as well as friction and inertial forces and differences between subjects. The iterative learning controller can exploit the particular characteristics of this task, where repetitive
movements are investigated. This iterative learning controller is implemented for the multi-input multi-output system consisting of the cylinders at the foot and the knee for both legs. For each leg, it delivers a two-dimensional feed-forward control vector \( u_k(t) \) (units \((1, \text{ Pa})^{-1}\)) for the current cycle \( k \) as a function of time \( t \) (At the beginning of each cycle, time \( t \) is reset to zero). The entries of this vector correspond to the knee cylinder (for position control) and the two foot cylinders (for force control) in the system. This control output is re-calculated from cycle to cycle, using the control signal \( u_{k-1}(t) \) that was applied during the preceding cycle \( k-1 \) and the corresponding four-dimensional (two positions, two forces) error trajectory \( e_{k-1} \) (units \((\text{m, N})^{-1}\)). The previous control output \( u_{k-1} \) is pre-multiplied by a two-by-two “forgetting matrix” \( Q \), whereas the corresponding error trajectory \( e_{k-1} \) is shifted in time by \( \Delta t \) and then pre-multiplied by the diagonal two-by-two “learning matrix” \( P_{ILC} \):

\[
 u_k(t) = Qu_{k-1}(t) + P_{ILC}e_{k-1}(t + \Delta t)
\]

The matrix structure of the ILC allows a coupling of the system. However, for these tests the matrices were chosen to be diagonal, and thus the ILC works independently for each cylinder. Still, the cross coupling of the actuation variables is compensated through their time dependency. The diagonal values of the forgetting matrix \( Q \) were chosen to be 0.9. The learning matrix \( P_{ILC} \) is also diagonal, with gains 0.7 for position and 0.2 for force errors. The time shift \( \Delta t \) for the error vector was manually
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adjusted to compensate for the delay in the reaction time of the system (position controller: $\Delta t = 0.15s$; force controller $\Delta t = 0.05s$).

The calculated feed-forward control signal $u_k(t)$ is added to the output of the position and force feedback controllers.

![Control chart of subject-passive mode](image)

**Figure 19: Control chart of subject-passive mode**
3.3 Subject-active mode

In subject-active mode, the robot follows the movements of the subject in such a way that interaction forces between the legs and the knee orthoses are minimal. As a result, the robot is compliant and any physiological knee position $y$ can be achieved by the subject. To this end, the force at each knee $F_{\text{meas,knee}}$ is controlled to be constant, only counteracting the gravitational force $F_w$ (unit N) evoked by the weight of the orthoses (0.8 kg).

This force control thereby has to be realized with the proportional flow valves controlling the knee cylinder. It is implemented as a proportional force feedback with gain $P_1$. Again, the non-linearity resulting from a varying chamber size is taken into account by adding the term $P_2xF_{\text{meas,knee}}$ to the controller, in analogy to the foot cylinder control described above:

$$u_{\text{knee}} = -(P_1 + P_2x)(F_{\text{meas,knee}} - F_w)$$

The force feedback control for the foot cylinder remains unchanged compared to the subject-passive mode. However, no iterative learning scheme is used in the subject-active mode, because the subject controls the movement, such that disturbances are no longer guaranteed to be repetitive (and thereby predictable).
3.4 Evaluation protocol

The controllers for the subject-passive and the subject-active modes were tested outside of the scanner on seven subjects (Table 3).

<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>29</td>
<td>29</td>
<td>25</td>
<td>31</td>
<td>29</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>72</td>
<td>80</td>
<td>74</td>
<td>87</td>
<td>68</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>Size [m]</td>
<td>176</td>
<td>170</td>
<td>182</td>
<td>183</td>
<td>183</td>
<td>182</td>
<td>179</td>
</tr>
<tr>
<td>Gender</td>
<td>male</td>
<td>male</td>
<td>female</td>
<td>male</td>
<td>male</td>
<td>male</td>
<td>female</td>
</tr>
</tbody>
</table>

For subject-passive mode, sinusoidal trajectories at 0.5 Hz were predefined for both the force on the foot sole and the knee position. The ranges of these trajectories were 0 to 200 N for force and 0.01 to 0.18 m for position.

At first, the system performed three movement cycles without the iterative learning controller. Thereafter, iterative learning started and lasted over 30 movement cycles. Then, learning was stopped ($Q$ equal to the identity matrix and $P$ equal to 0), and the final feed forward trajectory continued to be added to the controller signals for ten more cycles. In the end, the feed-forward signals were set to zero and 10 cycles were performed with only the feedback controller active.

To evaluate the benefit in control performance achieved by the iterative learning controller, the phase shift between the upper
peaks of the desired and measured trajectories for position and force were analyzed, as well as the variability of the movement. The learning progress in reducing the time shift was analyzed with a Friedman test followed by a Bonferroni adjustment with posthoc Wilcoxon test. The level of significance was set to 0.05.

The controller performance for the patient-active mode was evaluated by measuring the maximal reaction forces between the cylinder and the knee orthoses. The subjects were asked to move freely with a similar amplitude and frequency as during the passive mode for 15 cycles.
3.5 Results: Control performance of the ILC and the feedback controller

3.5.1 Subject-passive mode
Both the median value and the variability of the phase shift during position control with iterative learning were smaller than during position feedback control only (Figure 20): After 30 learning cycles, the median of the phase shift of one cycle was significantly reduced from 0.283 s (10/90 percentile range: 0.0775 s) to 0.054 s (10/90 percentile range: 0.016 s, Wilcoxon test, \( p = 0.015 \)). From the eighth cycle onwards, the time shift no longer differs significantly from any following time shifts. The maximal variability (10/90 percentile range) of the movement was reduced from 0.0415 m without the iterative learning controller to 0.0065 m with the learning controller.
Figure 20: The position of the knee (y): median and 10/90 percentile of ten cycles from the left leg of seven subjects. 0.2m corresponds to a knee angle of approx. 50°
Figure 21: The time shift and standard deviation of the upper turning point plotted over the learning iterations.

Also the force controller with the iterative learning control reached a smaller maximal variability (maximal 10/90 percentile range: 15 N, without ILC: 44 N) than the feedback-controller alone (Figure 22). The maximal error was reduced from 26.5 N to 20.7 N.
Figure 22: The median and 10/90 percentile of the force at the foot. Displayed are the median of ten cycles before and ten cycles after 30 learning cycles of all seven subjects.
3.5.2 Subject-active mode

Figure 23: Reaction force at the knee for the active mode for the voluntary movement of one subject over ten cycles plotted over the position.

The controller for subject-active mode kept the interaction forces between the knee orthosis and the leg smaller than 20 N (desired: 0 N) (Figure 23) at an operating force range of 0-200 N. For comparison, in the uncontrolled case (valves open), the reaction forces are approximately 100 N.

The force control in subject-active mode had the same performance as during subject-passive mode, as it is independent of the knee movements.
3.6 Discussion: What has been achieved?

The control of MARCOS was subject to non-linearities and uncertainties in the kinematic setup including the human subject and the pneumatic components. The two cylinders at each leg are mechanically coupled through the human leg. Thus, forces from one cylinder have an impact on the performance of the other cylinder. The limb masses and lengths and joint viscoelasticities differ between subjects as well as the attachment of the knee orthoses. For these reasons, the characteristics of the coupling between the two cylinders can change between subjects. Hence, the feedback P-controller was not able to reach a satisfactory control performance, and model-based controllers would need extensive parameter identification. An iterative learning controller was implemented to compensate for these model uncertainties.

This controller needed about eight cycles to learn a feed forward trajectory. This corresponds to 16 s for movements performed with a frequency of 0.5 Hz. Thus, the preparation time prior to the intended fMRI study is not considerably extended while the control performance is significantly improved. The average error in positioning was thereby reduced to 0.0065 m. This error should have no influence on fMRI results, because it is below the clearance in the orthosis and below the threshold of human perception. Additionally, the variability of the movements between subjects was also reduced. The performance of the force controller is already satisfactory with the feedback controller only. This is probably due to the different control strategy that
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aims at controlling the pressure, not the flow as during position control. As the control was already satisfactory without it, force control did not profit very much from the iterative learning controller. The error of the force was reduced from 27 N to 20 N. However, also the variability between subjects could be reduced by it. The error of the force with and without the iterative learning controller will also not have any influence on the fMRI results, as this error is small compared to the forces acting during natural gait, and because the repeatability is given. In consequence, brain activity patterns of the same movement should not vary and can be compared to brain activity of other subjects performing the same movement.

In conclusion, the iterative learning controller enhanced the overall performance of MARCOS so that we can expect comparable fMRI data for a group of subjects performing passive lower limb movements inside the fMRI environment.

In subject-active mode, subjects had to overcome maximal reaction forces of up to 20 N at the knee. This force is low in comparison to the force induced by the weight of the leg (approximately: 150 N) and low compared to the forces acting during natural walking (approximately: 1000 N). The force control at the feet is the same as in passive mode without the iterative learning controller. Accordingly, also this mode will produce reproducible brain activity patterns.
4 Experimental fMRI studies
As described so far, MARCOS is able to move the legs of subjects in an alternating manner, resembling an on-the-spot stepping. Also, the force application at the foot sole works reproducible for different subjects. The magnetic fields of the scanner are not considerably influenced, so that meaningful results can be expected from fMRI measurements.

In the scope of this thesis, three studies were carried out:

- A single subject study to demonstrate the basic possibilities of MARCOS (proof of concept)
- A pilot study with four different movement conditions on 14 healthy subjects, to show that brain activity is reproducible in a larger subject group and to demonstrate that meaningful studies can be carried out. In addition, this study might be used as a database for comparison with brain activity in patients.
- A single subject study, to establish a fine motor fMRI task with MARCOS and to show further possibilities with this device.
4.1 Proof of concept

This study was performed to demonstrate standard movements that are possible with MARCOS. One movement condition takes up to ten minutes time, thus, for larger subject groups the number of the conditions has to be as small as possible to minimize the time in the scanner. The main aim of this study was to compare as many movements as possible to choose the movements applicable for a larger subject group. The larger subject group then can demonstrate the reproducibility of brain activity with MARCOS.

4.1.1 fMRI parameters

The study was carried out on a Philips Achieva 1.5 T MR system with an 8-channel SENSE™ head coil. The functional acquisitions used a T2* weighted, single-shot, field echo, echo-planar-imaging sequence of the whole brain (TR = 3 s, TE = 50 ms, flip angle = 82°, FOV = 220 mm × 220 mm, acquisition matrix = 128 × 128, in-plane resolution = 1.7 mm × 1.7 mm, slice thickness = 3.8 mm, SENSE factor 1.6, resulting in 35 slices). Whole brain anatomical images were acquired using a 3D, T1-weighted, field echo sequence (TR = 20 ms, TE = 4.6 ms, flip angle = 20°, in-plane resolution = 0.9 mm x 0.9 mm, slice thickness = 0.75 mm, 210 slices).

4.1.2 Task parameters

According to the movement conditions allowed by MARCOS, nine different movement paradigms were applied:
1) alternating passive stepping at 0.5 Hz (Alt-pas)
2) alternating active stepping at 0.5 Hz (Alt-act)
3) passive left leg movement at 0.5 Hz (L-pas)
4) passive right leg movement 0.5 Hz (R-pas)
5) active left leg movement at 0.5 Hz (L-act)
6) active right leg movement at 0.5 Hz (R-act)
7) alternating passive stepping at 0.5 Hz with foot loading (0 to 200 N) (Alt-pas-F)
8) alternating active stepping at 0.5 Hz with foot loading (0 to 200 N) (Alt-act-F)
9) alternating passive stepping at 1 Hz without foot loading (Alt-pas-1 Hz)

These movements were applied in one subject (male, 30 years, weight: 72 kg, no neurological or orthopedic problems, signed informed consent) while brain activity was measured. The experiment should serve as a proof of concept, thus, no general conclusions are drawn about brain activity during movements with MARCOS. Ethical approval for this measurement was obtained by the local cantonal ethics committee. Each movement paradigm was executed 30 times for 10 s (five steps for 0.5 Hz), interleaved by a pause of 5 s. The subject was asked to keep the eyes closed and to relax. Before scanning, he got familiar with the movements of the robot and the head and body fixation.

The movement and breaks performed by MARCOS during the block design fMRI measurements were triggered by the software Presentation (Neurobehavioral Systems, Inc, San Francisco Bay Area, USA), that also labeled the scans with the respective condition.
4.1.3 fMRI analysis

Image processing and analysis were performed using SPM8 (Welcome Department of Cognitive Neurology, London) implemented in MATLAB 7.6/R2008a (Mathworks Inc., Natick, MA, USA). All functional images were re-aligned to the mean image followed by normalization into the standard stereotactic space using the Montreal Neurological Institute template. Spatial smoothing was performed applying a Gaussian filter of 8 mm full width half max. A first-level statistical analysis was conducted by modeling each single condition in a general linear model using the canonical hemodynamic response function. This data analysis was performed on a single-subject basis, to identify the activated neuronal network involved in the respective movement tasks.

4.1.4 Brain activity patterns: Hypothesis

As no comparable literature has been published with respect to cortical underpinnings of gait-like movements, the hypothesis was derived from studies that investigated isolated joint movements [51] or imagination of walking (e.g. [43]).

Main brain activity in primary and secondary sensorimotor areas, S1, M1, SMA, was expected. Especially when the subject was actively moving the legs, enhanced brain activity was expected within the sensorimotor areas as compared to the passive movements.
4.1.5 Results: Brain activity during the nine different movement conditions

The amplitude of high-frequent head motion during one scan of the fMRI measurements remained below 2 mm for most conditions (Table 4). In task Alt-pas-F, a strong drift during the first scans was detected. Activity in the primary motor/sensory network (S1/M1, SMA, preSMA) was observed in all conducted tasks.

Leg movements in MARCOS were smooth with a maximum position error of 0.005 mm and a maximal force error of 20 N (Figure 24).
Experimental fMRI studies

Table 4: Mean head motion during fMRI measurements and its standard deviation (std) during different tasks (SPM movement regressors).

<table>
<thead>
<tr>
<th>Task</th>
<th>Lateral mean/std [mm]</th>
<th>Rostrocaudal mean/std [mm]</th>
<th>Dorsoventral mean/std [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alt-pas</td>
<td>0.08/0.07</td>
<td>1.54/0.62</td>
<td>1.25/0.6</td>
</tr>
<tr>
<td>Alt-act</td>
<td>-0.28/0.17</td>
<td>-0.05/0.48</td>
<td>-0.63/0.4</td>
</tr>
<tr>
<td>L-pas</td>
<td>-0.06/0.05</td>
<td>-0.81/0.28</td>
<td>-2.41/0.80</td>
</tr>
<tr>
<td>R-pas</td>
<td>0.06/0.12</td>
<td>0.44/0.79</td>
<td>0.18/0.67</td>
</tr>
<tr>
<td>L-act</td>
<td>0.09/0.06</td>
<td>0.1/0.05</td>
<td>-0.23/0.15</td>
</tr>
<tr>
<td>R-act</td>
<td>-0.01/0.03</td>
<td>0.31/0.23</td>
<td>0.46/0.3</td>
</tr>
<tr>
<td>Alt-pas-F</td>
<td>-1.11/0.3</td>
<td>-1.51/0.78</td>
<td>-8.12/1.81</td>
</tr>
<tr>
<td>Alt-act-F</td>
<td>-0.45/0.21</td>
<td>-0.46/0.25</td>
<td>-2.26/0.86</td>
</tr>
<tr>
<td>Alt-pas-1Hz</td>
<td>-0.09/0.14</td>
<td>0.01/0.53</td>
<td>-1.13/0.56</td>
</tr>
</tbody>
</table>

Figure 24: Desired and measured trajectory of the subject’s knee and forces at subject’s feet during fMRI measurements with MARCOS. This data was recorded during th subject passive condition with force at the foot sole.
Experimental fMRI studies
Figure 25: Brain activity patterns of the single subject during all tasks. Depicted is a section in which the maximal activated voxel has been identified. Activity clusters were projected onto the T1_single_subject template, implemented in SPM8 with a conservative statistical threshold (FWE corrected, $p < 0.05$, 10 extended voxels).
In all conditions, brain activity was observed within a cluster covering post- and pre-central regions in the paracentral lobule (Figure 25, Table 5). The activity was restricted to the upper-leg/knee/lower-leg region within the human homunculus. The condition L-pas induced a large activity cluster covering right precuneus (BA5), postcentral areas (BA3) and primary/supplementary motor areas (BA4/6). Additionally, small clusters within the ipsilateral anterior cerebellar lobe and the right putamen were observed (not shown).

The condition R-pas induced a comparable activity cluster in contralateral hemisphere including the precuneus (BA5), postcentral gyrus (BA3) and primary/supplementary motor areas (BA4/6), whereas no activity was observed in the cerebellum.

L-act and R-act also induced activity within precuneal, postcentral and motor primary/supplementary motor areas. L-act additionally induced activity within ventral portions of the posterior cingulate.

Alt-pas and Alt-act induced activity patterns covering bilateral areas of the precuneus, sensory and motor/premotor regions. In comparison to Alt-pas, Alt-act induced stronger activity, reflected by a larger cluster.

Alt-pas-F and Alt-act-F showed a more heterogeneous picture. Both conditions induced less activity compared to the ones without application of foot sole force (Alt-pas/act).
Alt-pas-1Hz induced again activity within precuneal, sensory and motor/premotor areas.

For detailed results, see also the table in the appendix.

4.1.6 Discussion: Are measurements with MARCOS feasible?

Head motion remained within a range that allowed meaningful data analysis and interpretation in almost all conditions. Only during the first 20 scans of task Alt-pas-F, the head drifted over 10 mm. For the following 140 scans, head motion remained in a range of below 2 mm.

According to the observed brain activity during the various experimental challenges, our hypotheses could be verified on single-subject basis: The more "uncommon" the motor task and the more "active" and "challenged" the subject was, the more activity was elicited within the sensorimotor brain areas. Activity was localized on the "core" centers of the sensorimotor network, specifically Brodman areas (BA3/4/5/6). Only the passive movement of the left leg induced activity within the cerebellum.

In conclusion, the present device can provide insight into human brain activity, while performing different gait-like leg movements in both active and passive modes. A significant foot loading could be applied by MARCOS, providing contact forces at the foot soles during stepping. This is an important facet, as the sensory feedback of this specific force is of high relevance during walking [6]. Thus, MARCOS provides the opportunity to study the effects of essential cues of locomotion in healthy subjects and potentially in patients with movement disorders on brain activity.
activity. Therefore also therapeutic effects might reliably be assessed by this approach.

Based on these measurements, the conditions for a larger study with healthy subjects were chosen to be:

- Alternating active
- Alternating passive
- Alternating active with force
- Alternating passive with force

These movements show strong brain activity and are relevant for the rehabilitation, as they are close to gait and resemble motion of daily live.
4.2 Healthy control group

Fourteen right handed subjects (age 26-38, 4 female, 10 male) with no contraindications participated in the study. The study paradigm was approved by the local ethics committee and was conducted according to the guidelines of the Declaration of Helsinki. Participating subjects were financially compensated.

4.2.1 fMRI parameters

The study was carried out in the MR-Center of the University of Zurich and ETH Zurich, on a Philips Achieva 1.5 T MR system equipped with an 8 channel SENSE™ head coil. The functional acquisitions used a T2* weighted, single-shot, field echo, echo-planar-imaging sequence of the whole brain (TR = 3 s, TE = 50 ms, flip angle = 82°, FOV = 220 mm × 220 mm, acquisition matrix = 128 × 128, in-plane resolution = 1.7 mm × 1.7 mm, slice thickness = 3.8 mm, SENSE factor 1.6, resulting in 35 slices). Whole brain anatomical images were acquired using a 3D, T1-weighted, field echo sequence (TR = 20 ms, TE = 4.6 ms, flip angle = 20°, in-plane resolution = 0.9 mm x 0.9 mm, slice thickness = 0.75 mm, 210 slices).

4.2.2 Task parameters

The single subject study presented in chapter 4.1 showed stable brain activity during all tasks. The following four conditions are assumed to be the ones closest to gait and, thus chosen as conditions in this study:

1) alternating passive stepping at 0.5 Hz
2) alternating active stepping at 0.5 Hz
3) alternating passive stepping with applied foot force at 0.5 Hz
4) alternating active stepping with applied foot force at 0.5 Hz

Subjects were carefully instructed prior to the fMRI measurements. The start and end time of the conditions were communicated auditorily via an MR compatible headset system. All tasks included 30 repetitions of the respective movement tasks (9 s) interrupted by a break (5 s).

After a task, subjects’ comfort was checked and if needed the attachment of MARCOS was corrected to guarantee a good fixation and smooth movements. Especially during the force tasks, the fixations have to be as tight (but still comfortable) as possible.

4.2.3 Data analysis

Image processing and analysis were performed using SPM8 (Welcome Department of Cognitive Neurology, London) implemented in MATLAB 7.6/R2008a (Mathworks Inc., Natiek, MA, USA). All functional images were realigned to the mean image followed by normalization into the standard stereotactic space using the Montreal Neurological Institute template. Spatial smoothing was performed applying a Gaussian filter of 8 mm full width half max. A first level statistical analysis has been conducted by modelling each single condition in a general linear model using the canonical hemodynamic response function. This data analysis was performed on a single subject basis by
Experimental fMRI studies

comparing the active phase of each condition with the rest phase in order to identify the neuronal network involved in the respective movement tasks. In a following step, a group analysis was conducted by running a second level one-way-anova over all four conditions using the contrast images derived from the single-subject analysis. Relative changes in BOLD activity were calculated to disentangle specific supraspinal contribution to each of the conditions. All activity levels are shown on a statistical level of $p<0.001$ uncorrected and an extent threshold of 5 voxels. The results are superimposed onto the MNI single-subject T1 template and illustrated with the viewer program xjView 8.1 (http://www.alivelearn.net/xjview).

4.2.4 Results: Brain activity of the 14 healthy subjects
The study focused on BOLD related alterations of the entire brain during four different gait-like movement tasks in 14 healthy subjects. All four conditions revealed significant brain response.
**Experimental fMRI studies**

*alternating active / passive stepping at 0.5 Hz*

Figure 26: Group Brain activity patterns during passive a) and b) as well as during active c) and d) stepping. Depicted are the sections in which the maximal activated voxel has been identified. Activity clusters were projected onto the T1_single_subject template, implemented in xjView with a statistical threshold of \( p < 0.001 \), uncorrected and 5 extended voxels.

Brain activity of the alternating passive stepping condition revealed a large cluster (1112 voxels) covering bilateral motor (BA4) and supplementary-motor (BA6) areas as well as somatosensory (BA 3) and associative sensory areas (BA5). The activity further extended into predominantly left pre-cuneal divisions (Figure 26 a). A smaller cluster (5 voxels) has been
observed in left lateralized cerebellar culmen (Figure 26 b, see also the appendix for detailed results).

The active condition revealed brain activity within basically the same regions (Figure 26 c), however, the cluster covering areas of the motor/sensory-motor network counts 207 voxels, whereas the cerebellar cluster was slightly larger (21 voxels) compared to the passive condition and extended into bilateral divisions.
alternating passive / active stepping with applied foot force at 0.5 Hz

Figure 27: Group brain activity patterns during passive stepping with applied foot force. Depicted are the sections in which the maximal activated voxel has been identified. Activity clusters were projected onto the T1_single_subject template, implemented in xjView with a statistical threshold of p < 0.001, uncorrected and 5 extended voxels. a) precentral gyrus, b) cerebellum, c) posterior cerebellar lobe
Figure 28: Group Brain activity patterns during active stepping with applied foot force. Depicted are the sections in which the maximal activated voxel has been identified. Activity clusters were projected onto the T1_single_subject template, implemented in xjView with a statistical threshold of $p < 0.001$, uncorrected and 5 extended voxels. d) BA 4 and BA 6, e) BA 10 and BA 47, f) left posterior cerebellar lobe

Brain activity related to active and passive stepping with an applied foot force revealed a much smaller cluster compared with the conditions without foot force. Bilateral clusters were observed (Figure 27 a) encompassing 29 voxels and covering the left sided precentral gyrus including BA 4 and BA 6, respectively, as well as 26 voxels right sided. They also cover the precentral gyrus including mainly BA 6. Further activity was restricted to
the cerebellum with a large cluster shown in Figure 27 b) including 87 voxel within the left posterior cerebellar lobe. This cluster covered additionally some subdivision of the cortex (BA 19). The small clusters in Figure 27 c) covered bilaterally subdivisions of the posterior cerebellar lobe with 11 voxel left sided and 18 voxel right sided, both mainly located within the pyramis and uvula of the cerebellum.

Focusing on brain activity related with active stepping together with an applied foot force, Figure 28 d) shows bilateral clusters within mainly precentral gyri covering predominantly BA 4 and BA6. The right activity cluster in Figure 28 d) encompassed 25 voxel and the left activity cluster encompassed 8 voxel. Another cluster in this condition was observed in right frontal cortical areas, mainly covering BA 10 and BA47 with a total of 43 voxel (Figure 28 e). Finally, the last condition revealed a small cluster in the left posterior cerebellar lobe with 10 voxel (Figure 28 f).

4.2.5 Discussion: Is brain activity in MARCOS reproducible?

In the following, the results major finding of the four gait-like movement tasks in 14 healthy subjects:

- A locomotion network was observable consisting in primarily motor/premotor as well as in somatosensory/multisensory cortical areas and cerebellar subregions.
- An unexpected finding was related with the active stepping condition with applied foot force by revealing
an activity cluster within right frontal cortical areas (BA10/47).

- Both conditions without applied foot force revealed clearly larger clusters within primary motor, premotor, supplementary motor and somatosensory cortical subregions.

The conditions applied in the current study are very simple as it's basically close to natural gait, although in an unusual (supine) position. Therefore, predominantly cortical activity within the locomotion network was expected. This was also described by La Fougère et. al. [43]: They compared real locomotion with imagined locomotion and observed much more activity during imagination of locomotion then during real locomotion.

The smaller activity clusters when applying the ground reaction forces was surprising. More activity was expected during this condition. However, this finding might be in line with the results from La Fougère (they found the lowest activity in the "real" condition compared with the imagined). Transferred to the results gained with MARCOS, it can be hypothesized that the nearer a movement task resembles the real locomotion, the fewer contribution of the brain is required. This could be related with the fact, that the execution of a "simple" locomotion task goes from primary motor subdivisions directly to the spinal central pattern generators without encompassing basal ganglia and brainstem locomotion centers [43].
Visual observation of the subjects in the scanner revealed additional interesting findings that might be important for further studies. The most important finding was that most subjects were not able to keep the frequency during the subject active conditions. Most subjects accelerated the movements especially during the subject-active task with applied foot force. In future studies, this should be taken into account. More detailed instructions should be given to the subjects addressing the movement frequency. For instance, a metronome could be presented during all active conditions to present the desired speed. As well, it is thinkable to implement a controller, allowing movements only in the desired speed. A disadvantage of this approach would be the generation of additional contact forces between the subject and the robot, as long as the subject is not moving with the desired speed. Such a controller would also comprehend the danger that the subject does not move at all and relies on the guidance of the robot. Still, this approach might help patients, who might not be able to move their legs over the full time period.
4.3 Fine motor task: Balancing in the scanner

4.3.1 Motivation
So far, this work has focused on the assessment of brain activity during cyclic active and passive lower limb movements that do not require fine motor skills. However, assessment of brain activity during fine motor skills might also be of interest: In arm rehabilitation, improvements of the function of the whole arm were achieved by training fine motor tasks including hand movements and hand-eye coordination [76, 77]. In future, it might be that also new therapeutic approaches involving fine motor tasks of the lower limbs are applied in rehabilitation. However, knowledge about brain activity during fine motor tasks involving lower limbs is currently limited but may help to develop new therapeutic approaches and even might help to gain a deeper understanding about the control of fine motor task control in healthy subjects.

For being able to draw broad conclusions out of such measurements, a comprehensive fine motor task applicable for such investigations should:

- be coordinatively demanding
- allow adjusting the difficulty level
- include multi-modal feedback (vision and haptics)
- be possible in the MR environment

MARCOS provides a freely programmable platform that also can be used to implement such a task.
4.3.2 Task description

The task to investigate brain activity during fine motor tasks within the scope of this thesis was to balance a virtual bar with the feet while lying on the back. On the virtual bar, a ball was presented that should be moved into the middle of the bar by making small movements with the feet, changing the slope of the virtual bar (Figure 29). The ball obeyed virtual (and adjustable) gravitational forces and friction. The gravitational forces of the ball and the bar were displayed at the feet of the subject. The visual feedback was provided by a silver screen in the scanner room (Figure 29). The haptic feedback was provided by MARCOS.

The difficulty level could be adjusted by changing the friction (damping factor $d$), the gravitation ($g$), starting conditions (velocity and position) and the weight of the ball. Further, the movements of the feet can be scaled or even switched, so that e.g. the real left foot moves the virtual right foot.

![Figure 29: The visual feedback displayed during the fine motor task on the silver screen in the fMRI scanner. It could be seen by the subject via a mirror system mounted at the head coil.](image)
4.3.3 Realization

The implementation of this task was accomplished by Severin Summermatter in the scope of a semester thesis [78].

A physical model was used to calculate the input for the visual and haptic display during the task running on the xPC target computer. Based on the boundary conditions including the starting position \( \eta_0 \) and the starting velocity \( \dot{\eta}_0 \), the velocity and position for the next time step was calculated each time step (0.00025 s) by integrating the current gravitational acceleration \( \ddot{\eta} \) of the ball, given by the angle \( \alpha \) of the bar (\( g \) is representing the adjustable gravitational constant):

\[
\ddot{\eta} = -g \sin \alpha(t)
\]

The new velocity calculates as:

\[
\dot{\eta}(t) = \ddot{\eta}(t)t + (1 - d)\dot{\eta}(t - 1)
\]

And the new position as:

\[
\eta(t) = \frac{1}{2} \dot{\eta}(t)t^2 + \dot{\eta}(t) + \eta(t - 1)
\]

Only gravitational effects were taken into account for the calculation of the forces at the feet. The movements of the feet were quite slow; thus, acceleration forces could be neglected. Therefore, only the position and weight of the ball and the bar, the angle of the bar and the distance between the feet were needed to calculate the forces [78].
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The calculated desired forces $\ddot{F}_{des}$ served as an input for the existing force controller. The position of the ball $\eta$ and the position of the feet ($\bar{x}_{measured}$, measured by the standard MARCOS sensors) were coded into ASCII code and sent via a serial port to the presentation computer (Figure 30). This computer displayed the actual position of the ball and the inclination of the bar (Figure 29).

![Signal flow for the fine motor task](image)

**Figure 30: Signal flow for the fine motor task [78].**

### 4.3.4 Methods: Brain activity assessment during the fine motor task

A single subject fMRI study was performed to show the feasibility of the task. The experimental condition, the task, was based on balancing of the ball. Within ten seconds, the subject was asked
to move the ball into the target position and to keep it there. As in the task condition, the current performance is visually perceived by the subject. Thus, activity also in the visual cortex can be expected. In order to determine the activity only caused by the fine motor task, a control condition was also presented: The same bar with a rolling ball on it was presented. During this condition, the subject did not move and only watched the rolling ball. These two conditions, the task and the control condition, were presented in a random order, each followed by a break condition. This was repeated 30 times. The break condition lasted five seconds in which a cross was presented. The subject was asked to watch the cross.

Three different task conditions were assessed:

1. The ball started at a random position on the bar.
2. The ball started at a random position on the bar. The legs were switched: if the subject moved the right leg, the left virtual leg moved.
3. The ball started at a random position at the bar and additionally had an initial velocity.

It was assumed that the switching of the legs and an initial velocity increases the difficulty level and, thus, the brain activity.
4.3.5 Results: Brain activity during fine motor control of the lower limbs

**Figure 31: Brain activity during the fine motor task vs. rest, balancing of a rolling ball on a bar with a random initial position.**

Significant brain activity was only found in task 1: The balancing task with a random initial position. Brain activity in both sides of the cerebellum, the sensory (S1) and motor (M1) cortex and premotor and supplementary motor area (SMA) were observed during the balancing task (Figure 31). In addition, the superior parietal lobe showed increased activity.
4.3.6 Discussion: Are brain activity assessments during fine motor tasks feasible with MARCOS?

This brain activity of the first task is in agreement with the theory that the sensory and motor cortex always show increased activity during motor tasks. The regions activated in the cerebellum are known for the handling of error corrections. The supplementary motor areas are involved in motor learning and preparation of complex movements, thus, also in fine motor tasks. Finally, also the activity of the superior parietal lobe is explainable as this region is involved in the coordination of visual input and motor execution.

It was surprising, that only the first task evoked a significant brain activity, although the other two seem to be more difficult. It might be explained by the fact, that the subject was a sportive person and got used to the task fast. So, he might have found a strategy to solve the problem regardless of the initial velocity or the switched legs. It also should be considered, that this was a single subject study with only 30 repetitions of the task. More subjects or more repetitions would probably evoke significant brain activity also in task 2 and 3.

In conclusion, this task showed the possibilities of MARCOS to present a fine motor task for the lower limbs inside the fMRI scanner. This might help to develop and investigate new rehabilitation approaches.

In addition, applications in the domain of motor-learning are possible. For this, the task should be difficult, so that the subject needs approximately 20 to 30 trials to figure out a
strategy how to solve that problem. Afterwards, this strategy can be applied in another 20 to 30 trials. Differences in brain activity between these two conditions might be important to understand the learning process. Gained knowledge may also be applied to rehabilitation, as rehabilitation is also a kind of learning.

The difficulty of the task can be adapted by decreasing the friction of the ball, so that the subject would have to develop braking strategies, by increasing the weight of the ball, so that higher forces are acting on the feet of the subject or by adding a scaling factor to the movements of the feet. This would lead to large movements of the virtual ball, although the subject executed only small movements with the feet. Thus, the subject would have to control his/her movements more carefully.
5 Conclusions
In this thesis, a novel pneumatic device, MARCOS, was developed that enables active and passive lower limb movements of a human subject lying supine on the MR bed in the MR bore. MARCOS is the only known device that allows the application of forces at the sole of each foot of the subject. This unique feature can be used, e.g. to simulate ground reaction forces as occurring during walking or stepping. It was shown, that even during conditions with high ground reaction forces under each foot the head and body fixation system reduced head movements to a low range that allowed standard fMRI analysis without movement artefacts.

Accurate position control of pneumatic cylinders is especially challenging in MR-compatible robotics, as the cylinders need long tubes to keep the valves outside the scanner room. Based on tests it can be concluded that purely model based controllers are not feasible for such devices. Model uncertainties due to different biomechanical properties of different subjects as well as tolerances in the attachments and the overactuated design of MARCOS would make an accurate model too complex. Consequently, an easy to use innovative iterative learning controller was implemented. This controller compensates all repetitively occurring non-linear effects and, therefore, facilitates the application of pneumatic robots in the fMRI environment.

MR-compatibility tests with phantoms revealed only little influence of MARCOS on the magnetic fields of the scanner. In pilot fMRI studies with healthy subjects, comprehensive brain activity in the corresponding brain regions was evoked. In
Conclusions

Conclusion, based on the developed device it is now for the first time feasible to assess brain activity during movements of the lower limbs with simulated ground reaction forces. Experiments on patients will help to understand current therapy approaches and to develop new therapy strategies. Experiments on healthy subjects will provide basic insights into the control of gait-like movements.

Additionally, with MARCOS brain activity during any other lower leg movement can be investigated: As an example, an interactive fine motor task for the lower limbs was implemented. In a single subject study, regions responsible for error processing, and leg-eye coordination were activated. It is concluded that further experiments in this unexplored field can reveal new insights into motor learning of fine motor tasks and into fine motor coordination of the lower limbs.
6 Outlook
Outlook

In the scope of this thesis, a robot for fMRI measurements on healthy subjects and patients was developed and proved to evoke the expected and reproducible brain activity. This robot can now be applied for further studies to investigate gait and gait therapy. In addition, applications in the domain of movement learning and Cardio training are possible.
6.1 Studies to investigate brain activity during gait-like movements and to improve therapy

Further studies with healthy subjects are planned to investigate the impact of different foot load and different stepping speeds on brain activity. Moreover, patients suffering from spinal cord and brain injuries should be included to elucidate brain activity due to a passive/active gait-like stepping movement as well as the effects of training on brain activity in order to optimize therapeutic protocols and approaches.

The assessment of patients may help to:

- gain a deeper understanding of therapy approaches
- evaluate therapy success
- establish an objective measurement of therapy success
- find the right therapy approach for patients

To gain a deeper understanding of therapy approaches, brain activity before, during and after different therapies of many patients should be assessed. All therapy strategies should lead to a change in brain activity. Such a change, for example activity in a new region that is taking over the control of the legs, may help to understand the direct effects of therapy.

If, in parallel to the brain activity changes, the Fugl-Meyer score is measured, a database can be established, showing the correlation of brain activity and the Fugl-Meyer score. The Fugl-Meyer assessment is a method to assess recovery of patients.
after stroke. Thereby the patient performs different tasks, while
the evaluator measures the needed time or surveys the range of
motion of the limbs.

If a correlation between the Fugl-Meyer score and brain activity
can be found, more objective measurement for therapy success
might be possible.

Continuous assessments starting directly after the injury and
continuing until the therapeutic success, can establish a huge
database. In the best case, different therapeutic approaches can
be assessed with MARCOS and added to this database. Once
this database is established, it can be used for choosing the right
therapy for new patients. For that purpose, the patient’s brain
activity can be assessed directly after the injury and compared to
the database. If a similar brain activity shift due to the injury
was encountered before and treated with different therapeutic
approaches, the best one can be chosen for the new patient.
6.2 Motor learning

Thanks to the modular concept and separated controllers for the knee and foot unit also complex movements are possible, like a fine motor task. Such tasks can be used to investigate motor learning.

In addition to the fine motor task, Laura Marchal-Crespo started investigating movement learning with a synchronization task. Thereby, one leg is actuated by MARCOS as during the subject-passive task. The other leg should be synchronized by the subject. The movement of the subject can be disturbed by force peaks (disturbance mode), or the movement error can be amplified (error amplification). Both disturbances can help to improve the learning effect.

This task was already implemented and tested in pilot fMRI studies. The assessment of a larger subject group is work in progress.
6.3 Cardio training

Besides an application in rehabilitation and neuroscience, it is also possible to apply MARCOS as an exercise device in the scanner to increase blood pressure and heart rate for MR measurements on the heart. Such an application was proposed by Prof. Kozerke (Institut f. Biomedizinische Technik, ETH Zurich, Zurich). To use MARCOS in this application, only the foot unit with its force control is needed. Thus, it is possible to apply a constant or alternating force when the subject is stepping. The standard force controller can be used, only the reference force has to be adapted.
7 Design recommendations for MR compatible robots
Designing MARCOS has revealed some important recommendations for future designs of MR-compatible robots concerning their geometry, required human body fixations, and pneumatic actuation.
7.1 Simplification of the geometry

Gait is a complex movement involving many degrees of freedom. While designing MARCOS, it became obvious that not all degrees of freedom can be implemented.

The complexity of an MR-compatible device increases with the number of degrees of freedom. In general, each additional degree of freedom requires additional sensors and actuators, which all have to be MR-compatible. Therefore, the first step in designing an MR-compatible device with human-robot interaction should address the number of the required joints and featured displacements at these joints. In the case of MARCOS, the main joints needed during walking (hip, ankle, knee) were chosen. They are moved and controlled in the main direction of locomotion. Special attention should be paid to the number of required passive degrees of freedom to cope with biomechanical constraints.

In a next step, it should be checked how many generalized degrees of freedom are needed to move these joints in the desired movement ranges. For example, in the case of MARCOS, only one generalized degree of freedom is needed to move the hip, ankle and knee joint (see Fig. XX). Such a reduction can help to simplify the geometry and reduce the overall amount of actuators and sensors as it is not always important to move each joint with an independent degree of freedom.
7.2 Pneumatics and control

After defining the desired movement, a proper actuation principle can be chosen. This choice is mainly limited by the desired forces and the movement range. Passive dissipative movements can also be realized by electro-rheological fluids.

The kind of actuation principle can have a large influence on the MR-compatibility of the device. On a first view, pneumatics can easily be designed in such a way that influences to the MR scanner are minimal. But it should be considered that also the valves are needed to actuate the system. Pneumatic valves often use magnetic principles to control the position of the piston and can, therefore, disturb the magnetic fields of the scanner, or get disturbed by it. Thus, it is desirable to keep the valves far away from the scanner. Keeping the valves outside of the scanner room reduces the number of cables leading through the shielding to a minimum. However, it increases the control challenges because of low-pass filter effects and dead times introduced by the transmission effects of the air in the long tubes.

As movements during fMRI measurements are mostly repetitive, an iterative learning controller can ideally cope with these control challenges. An iterative learning controller adapts to all repetitively occurring influences. Such a controller was applied in MARCOS and provided a sufficient accuracy without the need of adapting control settings for each subject.
A safe state of pneumatic devices is crucial in human-robot interaction. In contrast to electromagnetic actuators, pneumatic actuators cannot be switched to a force free state by just disconnecting the electrical power supply. Even disconnecting the pneumatic power is not enough, because most valves have low leakage flows. In combination with the compressibility of air, this leads to a slow pressure loss in the cylinder chambers and, therefore, also to a slow force reduction.

To account for safety issues, safety valves in front of each cylinder chamber, as used in MARCOS, are strongly recommended. The use of 5/3 way valves allow the desired switch to a force free state and, in addition, feature the possibility to detect blocked valves (see Fig. XY). Such a blocked device can be detected with a pneumatic/electric switch that is connected to the pressure supply through all of the safety valves. This kind of detection enhances the safety level of the device according to DIN EN ISO 13849-1.
7.3 Fixation of the human during movements for fMRI measurements

A fixation of the head is crucial to acquire meaningful results of fMRI measurements. Each movement to be guided by the MR-compatible device may result in different head movements and needs an adequate fixation. During the development of MARCOS, a strategy was developed to find the best combination of fixation techniques (Figure 32)

An analysis of the head movements during the desired functional movements can reveal the dominant head movement direction; thus, a major input on the design of fixation techniques.

The next step of designing a fixation should include testing of different fixation techniques. This can be challenging, because the fixation techniques can influence each other. E.g. shoulder belts may have a strong influence to fixations applied to the head of a subject. They can e.g. reduce the contact forces between the head and the fixation and thereby reduce the effects of any of these fixations. On the other hand, a fixation at the head might not be applicable without shoulder belts, as the contact forces might get too high and, therefore, result in discomfort or even pain.

In addition, attention should be paid to long time effects of each fixation technique. A hand grip can be useful for a subject to stabilize the body, but can cause unwanted brain activity due to fatigue - if applied over a long time. As well, a vacuum pillow can be effective right after application – but if it loses its stiffness,
this fixation becomes worse than the same vacuum pillow with the air inside.

Therefore, the testing should not only include a testing of each fixation technique detached from each other, but it should also include as many combinations as possible.

![Flowchart for designing a head fixation](image)

**Figure 32: Flowchart for designing a head fixation**
8 Acknowledgements
During my work at the Sensory-Motor-Systems Lab, I experienced a lot of support and guidance from my advisor Robert Riener whom I would like to thank first. He managed to create a dynamic and constructive working environment and established a lab culture affected from helpfulness from all of the lab members.

From Spyros Kollias and Volker Dietz I could learn many things in the field of neuroscience, which - at the beginning - helped me to fix the requirements for MARCOS, and later to apply the device to real subjects. They both accompanied me the whole way during my thesis, always a motivating word on the lips. I want to thank especially Spyros Kollias also for infrastructural support as e.g. the access to the scanners from the IBT and personal support. The IBT supported my work by providing the fMRI scanners. Related to this, I thank Roger Lüchinger for support and answering all questions related to the technical challenges of scanners.

In the second half of my thesis, Peter Wolf and Heike Vallery accompanied my way through the daily challenges of the life of a doctoral student. Peter not only helped me financing the project by supporting the completion of several grants, he also guided me through several processes of publications, supported me with constructive input and was always available - not only for scientific questions. Heike was a great advisor in every question and discussion related to control and mathematics – and I probably will never understand, how she managed to find the time to always lend a helping hand, although she was involved.
in nearly every project of the lab. Another important person for my thesis was Andreas Brunschweiler, who was a reliable support and practical help in all electronic questions. I also thank him for critically analyzing the safety issues of MARCOS. After Andi left the lab, Michael Herold-Nadig filled the gap of electronic support.

In the beginning of the thesis, Ningbo Yu and Armin Blickenstorfer facilitated my start and shared their huge treasure trove of experience with me. Later, Mike Brügger joined the team. Mike offered his experience in scanning and handling of subjects also on weekends and during Christmas. He also analyzed the required fMRI data and helped me writing the corresponding chapters in the papers and this thesis.

Roger Gassert, a pioneer of MR compatible robotics whom I only knew as an author of important papers before, unexpectedly joined ETH and from there on shared his knowledge with me during discussions on the corridors and talks. I am glad that he agreed to be my co-examiner. The same thank also goes to Lutz Jäncke, who agreed to be my co-examiner.

I thank all the lab members for creating a nice working atmosphere and for their spontaneous help whenever this was necessary. Especially Georg Rauter was cooperative in discussions about technical and software issues. Special thanks also go to Lukas Jäger, Anja Kollmar and Laura Marchal-Crespo, for joining the team around MARCOS, for finding new applications, carrying out some studies, for discussions and help in general.
Acknowledgements

I thank Alessandro Rotta and Pascal Wespe, who manufactured MARCOS in the machine shop and gave me valuable advice for the choice of materials and helped me finding design solutions.

Severin Eisner, Julian Egger, Christoph Ludwig, Rainer Schädler and Severin Summematter contributed as students to the project.

I thank Diana Siedler and Sabina Eipe for administrative support and small talk.
9 References


References


References


References


10 Curriculum Vitae
Curriculum Vitae

CURRICULUM VITAE

PERSONAL DETAILS
Dr. Christoph Hollnagel

Born: 18.03.1981 in Bad Oldesloe, Germany
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          CH-8047 Zurich
Mobile: +41 76 2156129

WORK EXPERIENCE

05/2007 to 03/2012 ETH Zurich, Institute for Robotics and Intelligent Systems
Sensory-Motor Systems Lab; Scientific assistant
Awarded title (November 2011): Dr. sc. ETH
Conception, design, simulation, implementation and control of MR-compatible
pneumatic/hydraulic robots for functional magnetic resonance imaging (fMRI)
investigations
Additional tasks:
• Pro/Engineer System administrator and support
• Grant-writing (4 of 5 successfully)
• Organization of lectures and exercises
• Supervision of master and semester students
• Organization of lab tours, contact person for guests

12/2005 to 07/2006 Research Centre Karlsruhe, Helmholtz-Gesellschaft,
Institute for Applied Computer Science (IAI); Research assistant
• Assembly of a robot arm prototype
• Project start administration

06/2005 to 10/2005 Volkswagen AG, Wolfsburg (Research and Development)
Internship
• Automated the analysis of data from motor test benches
• Programmed an automated plausibility test for data from test benches
• Programmed tools for repetitive tasks with Visual Basic

07/2004 to 09/2004 Institute for Applied Computer Science / Automation (AIA)
University of Karlsruhe (TH); Research assistant
• Simulated a robot with „Workspace“
• Set up exercises for students practical courses
• Tutor for a practical course

08/2001 to 11/2001 D.T.I. Dr. Trippe Ingenieurgesellschaft mbH, Karlsruhe
Internship
• Developed and constructed parts for a drain-robot
• Organized, realized and evaluated experiments
• Redesigned and programmed the company homepage

07/2001 to 08/2001 Institute of process control and robotics (IPR)
University of Karlsruhe (TH); Internship
• Basic internship for the studies
• Learned different metal treatments
EDUCATION

10/2001 to 12/2006  Study of mechanical engineering, University of Karlsruhe (TH)  
Specialization in Mechatronics  
Awarded title: Diplom-Ingenieur (Grade 1.6)

06/2006 to 12/2006  Fraunhofer Institute for Information and Data Processing  
Diploma Thesis (Grade 1.0)  
Title: “Visually controlled grasping with a humanoid robot hand with an integrated camera”  
- Design and implementation of a controller  
- Programming of a camera based position recognition system

10/2004 to 07/2005  Research Centre Karlsruhe, Helmholtz-Gesellschaft,  
Institute for Applied Computer Science (IAI)  
Student Research Project (Grade 1.0)  
Design and construction of a robot arm for a service robot  
- Simulation of the mathematical behavior in Maple  
- Design and construction (CAD) of the robot arm

09/2003  Vordiplom in Mechanical engineering

1991 to 2000  Emil-von-Behring Gymnasium Großhansdorf, Abitur (Grade 1.9)

07/1999  English Study Centre Hilderstone College, Broadstairs, England

06/1998 to 08/1998  High school exchange student in Villa General Belgrano, Argentina

Additional courses  
Computational Intelligence, Adaptive control systems, Biologically inspired robotic systems, Scientific programming, Methodical development of mechatronic Systems

ACTIVITIES

2009-2010  Member of the executive board of Telejob.ch, an academic job platform

2010-2011  Member of the Bio-Robotics Network Zurich (BiRoNZ)

Since 2009  Member of different bands, founder and bandleader of our institute band

04/2002 to 07/2006  Chairman and Trainer of the Hockey teams of the University of Karlsruhe (TH)  
- Organized training locations and timetables  
- Realized trainings and team events  
- Employed additional trainers  
- Coordinated two international tournaments per year and excursions to tournaments  
- Finance coordinator

Referee B-Licence,  
Player for Vilnius (Lithuania) at the European Cup Winners Cup 2003 in Zagreb, Croatia

Hobbies  
Field Hockey, playing guitar, dancing, sailing/windsurfing, snowboarding, model making, design and soldering of guitar effects

FURTHER KNOWLEDGE

Computer  
MS Windows, Linux, Pro/Engineer, C++, HALCON, Java, Visual Basic & VBA, Maple, Adams (basics), MATLAB, Eagle

Languages  
German (native), English (fluent), Spanish (advanced), French (basics)

MILITARY SERVICE

07/2000 to 04/2001  Military Service in Boostedt and Bad Segeberg - Planning and realization of international military competitions and field practices
11 List of publications

11.1 First author papers

11.1.1 Journals
Hollnagel, C, et al., A non-linear iterative learning controller of an over-actuated pneumatic MR-compatible stepper, **Submitted**: Biomedical Engineering online, 2011

11.1.2 Conferences
11.2 Further papers


11.3 Supervised semester theses

The following work was supervised by the author of this thesis

Egger, J., Movement Artifacts Analysis of the head during Gait-like Movements, in D-MAVT. 2008, ETH Zurich: Zurich. [82]

Summermatter, S., C. Hollnagel, and R. Riener, Implementation of a fine motor task in a MR scanner using the magnetic resonance compatible stepper MARCOS. 2011. [78]

Murr, W., Investigation and Suppression of Head Movements during Robot-Guided Motor Tasks in fMRI Studies, in D-MAVT. 2007, ETH Zurich: Zurich. [83]

Ludwig, C., Modeling and Control of an MR-compatible Pneumatic Stepper, in MAVT. 2008, ETH Zurich: Zurich. [84]
12 Appendix
### Table 5: fMRI results of the single subject study

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