Dissertation

CHANGES OF BRAIN STRUCTURE ASSOCIATED WITH AGE-RELATED WHITE MATTER HYPERINTENSITIES AND THEIR RELATIONSHIP TO GAIT DISTURBANCES

submitted by
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under the Supervision of
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Declaration

I hereby declare that this dissertation is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this dissertation. Due acknowledgement has been made in the text to all other material used. Throughout this dissertation and in all related publications I followed the guidelines of „Good Scientific Practice“.

Parts of this dissertation have already been published (own work) and may therefore resemble in content and syntax.

Graz, May 4, 2015

This work is dedicated to myself.
It has been a way.

To my family and friends.
For the company.

And to my mum and dad.
For all foundation.

Acknowledgement

Sometimes less is more.

In first place I want to thank my supervisor Prof. Christian Enzinger, who has been not only a scientifically highly-valued mentor but also companion in PhD and life to me.

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Not least, also other (in-house and external) people have contributed in their own way to this thesis; including the "PhD Crew", "Neuro Crew", family and friends. Mum, Birgit, Tanja, Wolfgang, Martin, Annemarie and Bettina – this work is also your reward.

Thanks to all these special people.

I consider myself lucky.

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Abbreviations and Definitions

ALE	Activation Likelihood Estimation
ARWMC	Age-related White Matter Changes
Bip	Bipedal Movements
BL	Baseline Condition
BOLD	Blood Oxygenation Level Dependent
CLR	Cerebellar Locomotor Region
CPG	Central Pattern Generators
CT	Computed Tomography
DLPFC	Dorsolateral Prefrontal Cortex
DS	Double Support (Time)
GLM	General Linear Model
GM	Brain Grey Matter
EPI	Echo-Planar Imaging
FEAT	fMRI Expert Analysis Tool
fMRI	Functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
Hb	Hemoglobin
LF	Left Foot
LGT	Lern- und Gedächtnistest
ME	Motor Execution
MIQ	Movement Imagery Questionnaire
MI	Motor Imagery

MMSE	Mini-Mental State Examination
MNS	Mirror Neuron System
MRI	Magnetic Resonance Imaging
MLR	Mesencephalic (Midbrain) Locomotor Region
MO	Motor Observation
MRE	Magnetic Resonance Elastography
MTI	Magnetic Transfer Imaging
PMC	Primary Motor Cortex
PMRF	Pontomedullary Reticular Formation
RF	Right Foot
ROI	Region of Interest
SLS	Single Limb Support (Time)
SLST	Single Leg Stance Time
SPPB	Short Physical Performance Battery
SVD	Small Vessel Disease
SMA	Supplementary Motor Area
STN	Subthalamic Nucleus
TFCE	Threshold-Free Cluster-Enhanced (Thresholding)
TMT-B	Trail Making Test- Version B
VBM	Voxel-Based Morphometry
WCST	Wisconsin Card Storting Test
WFQ-R	Waterloo Footedness Questionnaire-Revised
WGE	Waveguide Elastography
WM	Brain White Matter
WMH	White Matter Hyperintensities

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Abstract in German

Das vorliegende PhD Projekt setzt sich aus drei zusammenhängenden Studien unter Stützung auf das zentrale Forschungsinstrument der Magnetresonanztomographie (MRT) zum Einfluss von Alter, zerebralen Marklagerveränderungen (sog. „white matter hyperintensities“, WMH) und Gehen auf die strukturelle und funktionelle Organisation der zerebralen Sensomotorik zusammen. Dabei behandelte die erste Studie die Fragestellung nach dem Effekt des Alters auf die zentrale Steuerung von Sprunggelenksbewegungen als Surrogat-Bewegung für Gehen. Die zweite Untersuchung beschäftigte sich mit allfälligen strukturellen kortikalen Korrelaten von WMH. Die dritte Studie schließlich zielte auf die Entwicklung eines neuen funktionellen MRT (fMRT) Paradigmas zur Untersuchung der Motorik der unteren Extremität ab. Neben dem isolierten Erkenntnisgewinn zu den Teilfragen der einzelnen Substudien, lassen sich in Extrapolation verschiedene Variabilitätsindikatoren für weiterführende Trainingsstudien bei Personen mit WMH und Gangstörungen ableiten.

In der ersten Studie untersuchten wir in einer großen Stichprobe anhand der fMRT potentielle Alterseffekte in der zentralen sensorimotorischen Kontrolle der unteren Extremität, in verschiedenen Hirnregionen und mithilfe von zwei differenten Analysemethoden. Dabei zeigten sich bei gleichbleibender behaviouraler Leistung mit zunehmendem Alter erhöhte Aktivierungen in Bereichen des Precuneus und des Kleinhirns.

In der zweiten Studie wurden signifikante Korrelationen zwischen Veränderungen des Kortex und des Marklagers im Sinne von WMH gefunden. Personen mit ausgeprägten WMH wiesen dabei in Bereichen, die mit Motorik, Kognition und visueller Wahrnehmung assoziiert werden, ein lokoregionär geringeres kortikales Hirnvolumen auf. Als Novum wurde in der Analytik die Läsionstopographie dabei explizit berücksichtigt.

In der dritten Studie schließlich, zeigten sich in einem neuartig konzipierten und implementierten fMRT Paradigma robuste Aktivierungen in sensorimotorischen Netzwerken zur Steuerung, Vorstellung und Beobachtung von Bewegungen der unteren Extremität. Es ergaben sich auch Hinweise auf diesbezügliche Geschlechtsunterschiede: Männer wiesen stärkere Aktivierung in frontalen und parietalen Arealen sowie dem Gyrus praecentralis auf als Frauen.

Die drei Studien liefern folgende neue Einblicke rund um Struktur- und Funktionsänderungen des Gehirns im Kontext von WMH. 1. In gesunden Personen scheinen altersassoziierte Änderungsprozesse in der funktionellen Sprunggelenksantwort kompensatorisch für den Erhalt motorischer Leistung im Gehirn stattzufinden. 2. Die in der strukturellen Studie gefundenen Volumensunterschiede in Abhängigkeit von stärkerer WMH Ausprägung, unterstützen die Annahme einer fronto-kortikalen Diskonnektion der Nervenfasern bei einer Läsionstopographie mit Nähe zum korticospinalen Trakt. Und 3. die funktionellen geschlechtsabhängigen Unterschiede in den Hirnantworten bei motorischer Vorstellung implizieren ein besseres Vorstellungsvermögen von Männern in einem kombinierten fMRT Paradigma zur motorischen Ausführung, Beobachtung und Vorstellung von Sprunggelenksbewegungen.

Schlussfolgernd konnten damit wesentliche neue Einblicke zur Rolle von WMH im alternden Gehirn gewonnen werden. Das neu entwickelte fMRT Paradigma erscheint für zukünftige Studien zur Thematik, insbesondere bei Patienten mit Marklagerveränderungen, sinnvoll anwendbar. Die Ergebnisse deuten zudem darauf hin, dass zukünftige derartige Studien Alterseffekte korrigiert und bei mental-motorischen Trainings potentielle Geschlechtsunterschiede berücksichtigt werden müssen. Mit der Konzeption von Trainings zum Funktionserhalt im Alter im Zusammenhang mit WMH gewinnen derartige Einsichten an Bedeutung.

Abstract in English

The PhD thesis consists of three separate yet interlinking neuroimaging studies dealing with the interplay of age, cerebral white matter hyperintensities (WMH), and gait (i.e. walking). The studies provide fundamentals for subsequent follow-up fMRI training studies in individuals with WMH but also stand for their own. In a consecutive series of investigations, we were first interested in the effects of age on brain response elicited by fMRI ankle movements, second, potential relationships between WMH and cortical microstructural changes and third, the development of a novel fMRI "walking" paradigm.

Based on limited previous research, study 1 investigated potential functional changes in the central motor control of lower limb movements with age, using a big sample approach and two analysis techniques. Two regions turned out to be increasingly activated with higher age, i.e., the cerebellum and the precuneus.

Study 2 then focused on the relationship of WMH and (regional) grey matter volume changes, using voxel based morphometry and a novel lesion masking approach. Apart from previously described behavioural, functional and structural white matter changes in individuals with WMH, WMH were associated with grey matter volume decreases in several brain area associated with motor, cognitive and visual functions.

Finally, in study 3, the development of a novel fMRI "walking" paradigm including motor, cognitive and visual domains in a single experiment was realized. As a corollary (and unexpected) finding, sex influenced the brain's response to motor imagery, with men showing stronger activation in frontal, parietal and premotor regions than women.

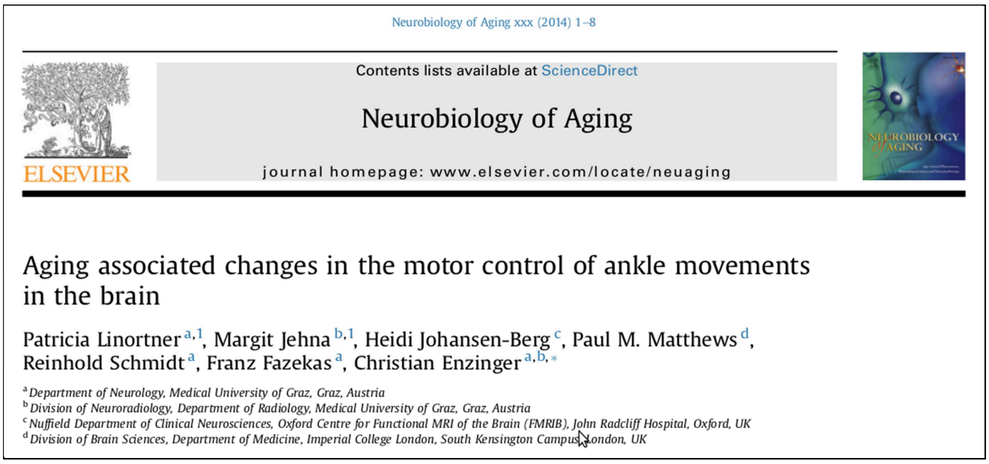
The results yield several new important insights. Given that task performance did not vary with age, study 1 suggests the noted functional changes with age to be at least partially compensatory for other age-related changes in the sensorimotor network responsible for

the control of limb function. The structural volume decreases in people with pronounced WMH in study 2 may be attributed to disconnection of fronto-cortico networks in the context of WMH in proximity to the corticospinal tract. Finally, the sex differences in the motor-imagery condition of the newly developed fMRI paradigm of study 3 suggest a different processing of movement-based mental imagery tasks in men than women.

The current PhD project met the objective of developing and implementing a refined and stable fMRI “walking” paradigm, tested in healthy people, for future use in individuals with WMH. Further, the findings demonstrate the necessity to correct for potential age-effects and sex differences, esp. in mental-based motor trainings in WMH. These observations gain importance in light of future interventional studies (i.e., movement-related training in the motor and cognitive domain) in people with pronounced WMH, aiming to ameliorate existing deficits or even postpone structural changes.

Publication Status

Study 1: **Published** in **Neurobiology of Aging** (Impact Factor: 6.2)



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Aging associated changes in the motor control of ankle movements in the brain

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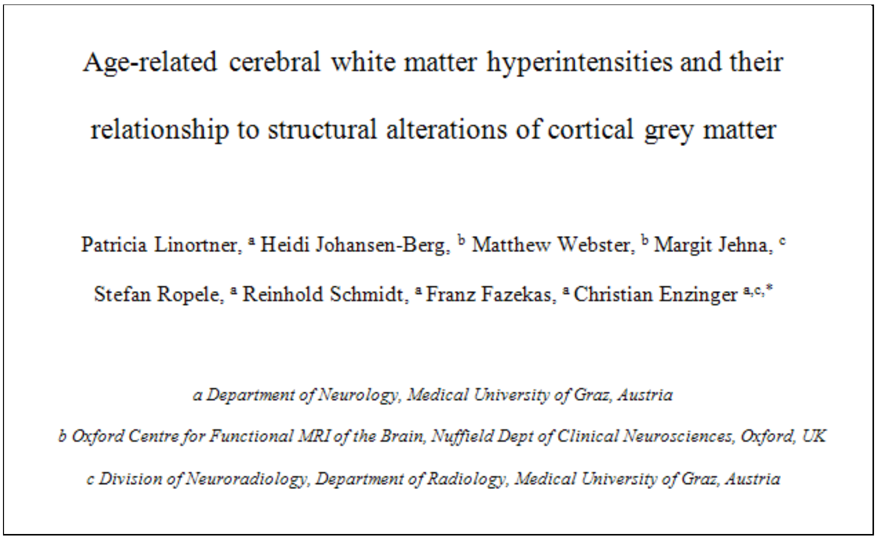
Study 2: **Planned to submit** to **Cerebral Cortex** (Impact Factor: 8.3)



Age-related cerebral white matter hyperintensities and their relationship to structural alterations of cortical grey matter

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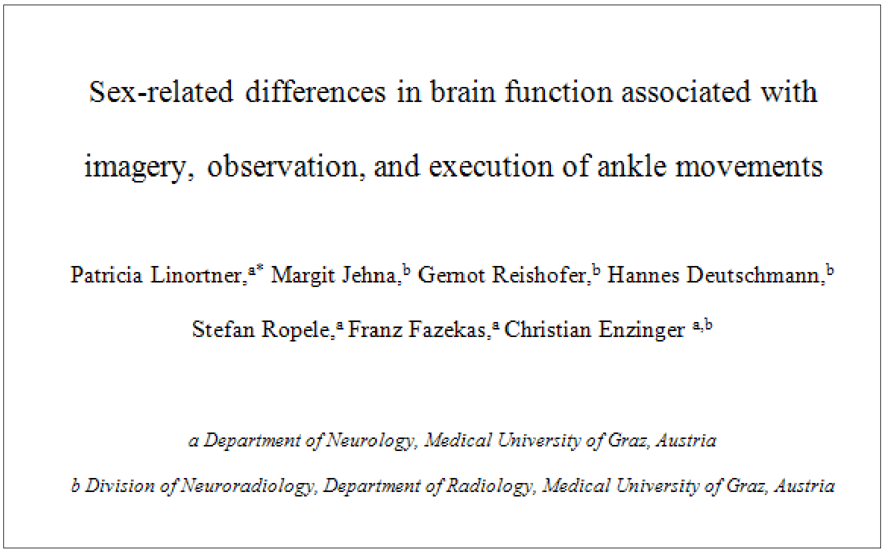
Study 3: **Planned to submit** to **PLOS ONE** (Impact Factor: 3.5)



Sex-related differences in brain function associated with imagery, observation, and execution of ankle movements

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Chapter 1

Introduction

Successful ageing against the background of increasing life expectancy and population growth represents one of modern-day's challenges of the healthcare system. At that point, cognitive and physical well-being are of equal importance, ranging from age-appropriate cognitive function (such as memory, planning, situation awareness) to intact mobility and physical condition (necessary for autonomous performance of activities of daily living) (cf. Bülow & Södergvist, 2014).

Diseases within the geriatric neurological domain opposing this vision include cerebrovascular diseases including stroke, dementia and Parkinson, for instance. However, brain function and morphology changes with ageing can also be a consequence of cerebral white matter hyperintensities (WMH; Hachinski et al., 1987). These microstructural variations (abnormalities) tend to increase with age and amongst others, gait and balance dysfunction may occur if they are more pronounced (Pantoni, 2010; Baezner et al., 2008).

The author's diploma thesis already concentrated on cerebral WMH and their impact on the functional organization of the motor system (Linortner, 2009). The present doctoral thesis extends these investigations within the ageing research domain and explores brain function and structure with relation to age, cerebral WMH and gait (walking).

First and foremost, for a better understanding, the primary subchapter will describe terminology and provides background knowledge on gait, WMH and used neuroimaging methods. Subchapter two will then discuss and relate study-specific literature to the different project parts, including proposed research questions and hypotheses.

1.1 Background and Fundamentals

1.1.1 Gait and Walking

Terminology

Human gait has developed already 3.6 million years ago (Simonsen, 2014). Gait is characterized as any method of locomotion characterized by periods of loading and unloading the limbs. This means running, hopping, cycling and walking belong all to the category “human gait”, whereby “walking” is the most frequently used gait. A reciprocal motion describes a gait form, in which legs are swung forward alternately (Kirtley, 2006).

Gait cycle

A “gait cycle" (one stride) in humans describes the state when two steps have been taken; normally characterized by alternating right and left foot movements. It is divided into stance- and swing phases (40%- and 60% of the gait cycle, respectively). When one side (e.g. right) is at 50% of the cycle, the initial contact of the other side (e.g. left) occurs. The time when both feet are on ground is called double support (DS) time; the time between DS times is called single limb support (SLS).

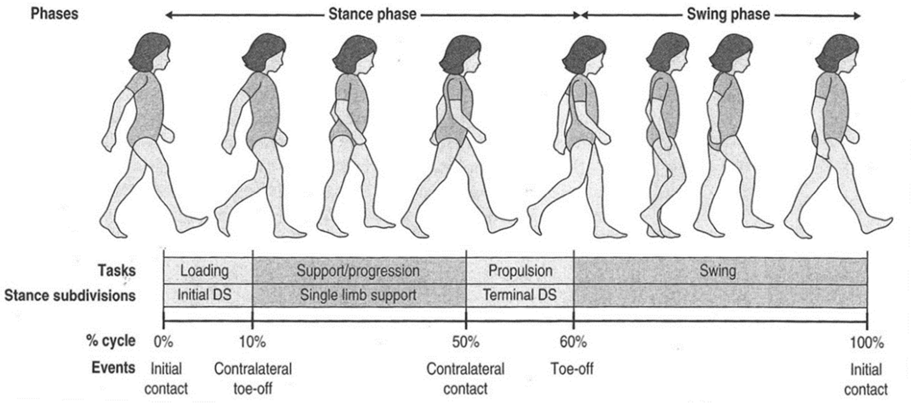

Figure 1. Gait cycle classification. The gait events define the three fundamental functions (loading, support/progression and propulsion/swing). DS stands for double support time (see text for explanation) (Kirtley, 2006; Neptune et al., 2001)

Walking comprises 20% DS time (as 2 x 60% = 120; -100 = 20%); as speed increases, DS time falls and running begins at 0% DS time (Seema & Singh, 2012; Neptune et al., 2001; Kirtley, 2006; Kirtley et al., 1985). Figure 1 describes the gait cycle.

Major bones and joints

The human locomotor system comprises thirty-six bones and three joints that are involved in gait. The major bones (bone groups, respectively) include the pelvis (six-bones), the femur, the patella, tibia and fibula and the foot (consisting of hindfoot, midfoot, forefoot; twenty-six bones). The three joints comprise the hip joint, knee joint and ankle joint (Drake, 2009; Whittle, 2008; Heller, 2005). Since the focus of the PhD project is on ankle dorsiflexion movements (ankle dorsiflexion movement as surrogate for key component of gait; Capaday, 2002), the subsequent and following (anatomical) descriptions will focus on structures involved with this gait-related movement.

The ankle joint connects the foot with the lower leg. It is divided into an upper ankle joint (tibiotarsal articulation), responsible for dorsi- and plantarflexion movements and a lower ankle joint (talotarsal articulation), enabling pro- and supination of the foot (Aumüller, 2010). Starting from plantigrade position (zero-degree-position), the hanging, unloaded foot can be flexed approximately 40-50° to plantar and extended 20-30° to dorsal (Schünke, 2011; Sobotta, 2010). The bones most prominently contributing to dorsi- and plantarflexion movements of the ankle are the tibia and fibula of the lower leg and the talus of the foot (Faller, 2012). See also Figure 2.

Major muscles and ligaments

Once the human body is in motion, it is kept moved by its own kinetic force. The muscles here control and stabilize the progression; as do the ligaments by providing joint stability (Dykyj, 1988).

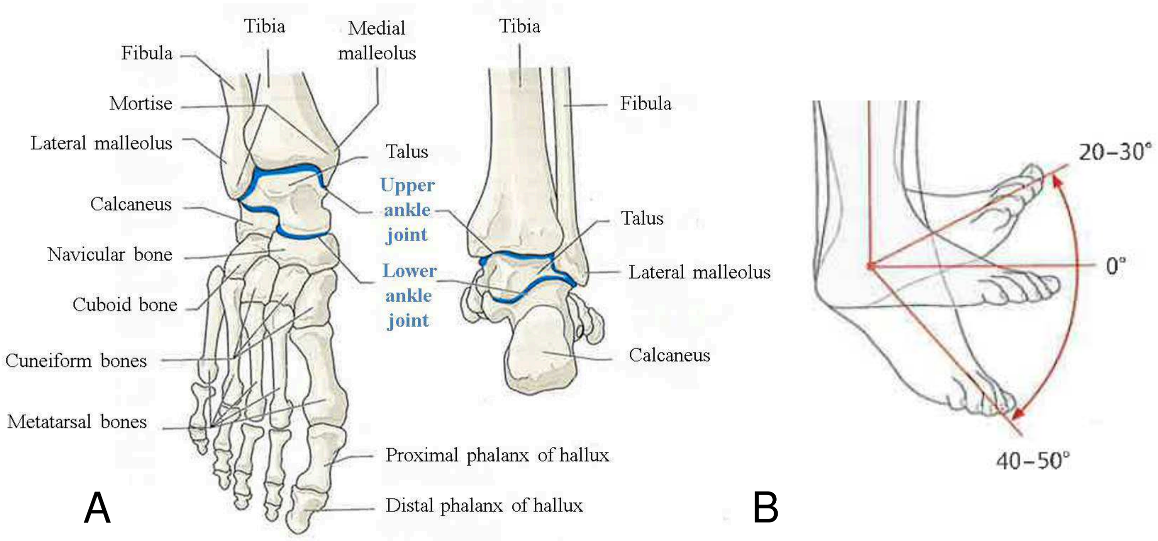

Figure 2. A) Major bones of the lower leg and foot, and ankle joint; view from anterior (left side) and posterior (right side) (Faller, 2012, adapted to English) B) Normal range of motion in the upper ankle joint (Schünke, 2011)

The main muscle groups involved in human gait can be categorized by the joints they are associated with: For the hip joint, in frontal plane: gluteus medius/minimus (abductor), adductor longus/magnus (adductor); in sagittal plane: iliopsoas (flexor), gluteus maximus and hamstrings (extensor). For the knee joint, in sagittal plane: hamstrings (flexor), quadriceps = vasti + rectus femoris (extensor). And as for the ankle joint: in frontal plane: tibialis anterior, tibialis posterior (inverter), peronei (everter); in sagittal plane: triceps surae = gastrocnemius + soleus (plantarflexors) and tibialis anterior (dorsiflexor) (Schiebler, 2007; Kirtley, 2006).

The last muscles (muscle groups) of the ankle joint are the most interesting and important ones for the studies performed as part of this thesis. Innervation of the tibialis anterior muscle is performed by the deep fibular nerve; the gastrocnemius and soleus are supplied by the tibial nerve (Schiebler, 2007). See also Figure 3.

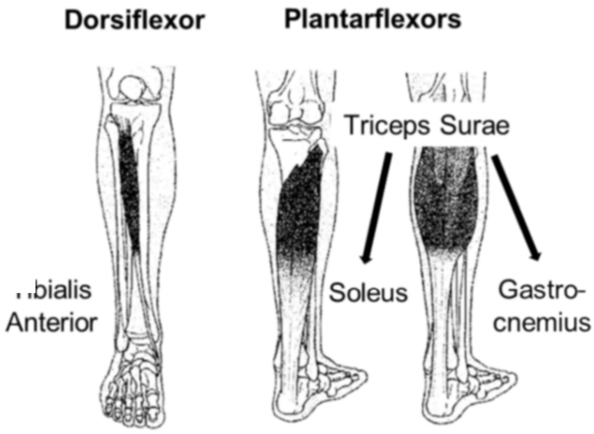

Figure 3. Muscle group(s) involved in ankle movements (adapted from Kirtley, 2006).

The upper ankle joint is stabilized by four strong ligaments: one medial and three lateral ones (Faller, 2012). The medial collateral ligament, also called deltoid ligament, is attached to the medial malleolus, prevents excessive eversion of the ankle joint and consists of four parts: a tibionavicular, tibiocalcaneal, anterior tibiotalar and posterior tibiotalar one, that attach to the navicular bones, calcalneus and talus. The lateral ligaments, as there are the anterior talofibular, the posterior talofibular and calcaneofibular, prevent over-inversion of the ankle joint. They all originate from the lateral malleolus and span to the calcaneus and talus (Platzer, 2013). The ligaments are illustrated in Figure 4.

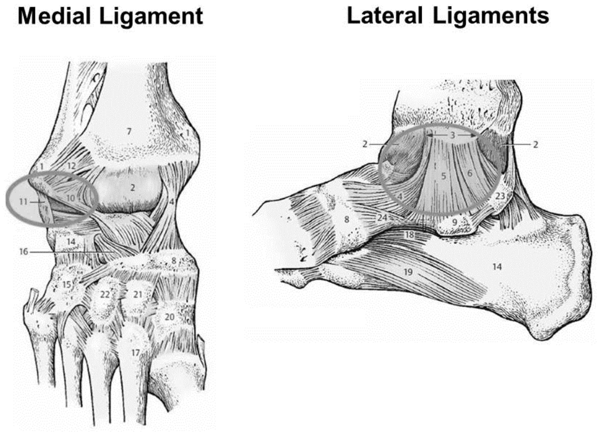

Figure 4. Ligaments of the ankle. Left side: Medial ligament (3) with tibionavicular (4), tibiocalcaneal (5), and tibiotalar (6) parts. Right side: Lateral ligaments: the anterior talofibular (10), the posterior talofibular and the calcaneofibular (11) (adapted from Platzer, 2013).

Spinal locomotion

In humans, an interplay of spinal generators (modulators) and supraspinal controllers is responsible for locomotion (i.e. walking, in particular). Following an initial, as first instance brainstem-originating, supraspinal start impulse, so-called "central pattern generators" (CPGs) in the spinal cord then manage the rhythmic generation of stepping movements (Guertin, 2013; Van Hedel & Dietz, 2010; Dietz, 2003). This pool of nerve cells (specialized groups of interneurons, separately for each limb) receives information of the periphery (i.e. lower limbs) and adapts the movement accordingly. Central motor diseases such as Parkinson's disease and spasticity exhibit a maladaptation (misinterpretation) of these afferent signals. As of today, it still remains unclear how autonomously CPGs control normal human gait (cf. experiments with DOPA injection in decerebrated cats and with spinal cord injury patients) (cf. Guertin, 2013; Jahn & Zwergal, 2010; Jahn et al., 2008; Orlovsky et al, 2003; MacKay-Lyons, 2002; Marder & Bucher, 2001).

Supraspinal gait control

In short, the hierarchical gait control concept encompasses the following structures and paths: Cortical motor- and premotor areas send locomotor commands via projection fibers to the subcortical basal ganglia and onwards to locomotor centers of the brainstem and the cerebellum. They, in turn, control the spinal generators. In more detail, the primary motor cortex (PMC) and supplementary motor area (SMA) are the main controllers of gait, executing and triggering movements. The basal ganglia, such as globus pallidus and subthalamic nucleus (STN, located ventral to the thalamus) are responsible for initiation, termination and regulation of motor commands. The cerebellum modulates the rhythm and speed of gait. In the brain stem (disinhibited by the cortical impulses), the mesencephalic/midbrain locomotor region (MLR) receives input from the cerebellar locomotor region (CLR) to integrate multisensory information (filtering of sensory influx in addition to gait control) and sends this data pool via the pontomedullary reticular formation (PMRF) to the spinal CPGs.

Apart from this efferent pathway, afferent signals from the limbs complete the circuit. Here, the gait pattern is altered by feedback loops passing through spino-cerebello-thalamic connections. The assumption of an indirect pathway of gait modulation rather than execution, of SMA, basal ganglia and brainstem locomotor centers, is still subject of debate. Figure 5 illustrates pathways and interconnections. (Nutt et al., 2011; Jahn & Zwergal, 2010; Jahn et al., 2010; La Fougère et al., 2010; Le Ray et al., 2011; Jahn et al., 2008)

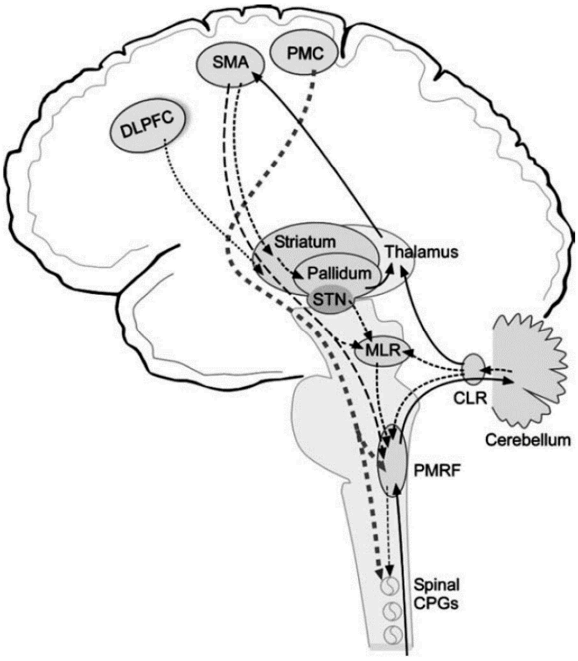

Figure 5. Current concept of supraspinal gait control in humans (Nutt et al., 2011; see text for abbreviations). The dorsolateral prefrontal cortex (DLPFC) is involved in motor planning of complex movements and plays a secondary part in general gait control.

1.1.2 White Matter Hyperintensities

The brain central nervous system consists of two major components: the cell-body-rich grey matter (including glia, neuropil, capillaries) and the conduction-strong white matter (neural pathways, myelinated axons) (cf. Amunts et al., 2014; Amunts et al., 2007; Toga et al., 2006). White matter hyperintensities (WMH) are one form of white matter degeneration, not directly disease-related but still associated with various structural, cognitive and behavioural changes. They will be described in detail in the following.

Terminology

Historically, WMH were first discussed in the late 1980, when they were spotted on Computed Tomography (CT) images. Hachinski et al. (1985) introduced the term “leuko-araiosis”, to separate those signal hypodensities from Biswangers’s disease. They were also called “unidentified bright objects” on MRI for a while, based on their unknown aetiology (Kertesz, et al., 1998). Nowadays several (for the most part) synonymously used terms exist for WMH, ranging from “leukoaraiosis” to “(age-related) white matter hyperintensities” to “white matter changes” (Figure 6; Wardlaw et al., 2013).

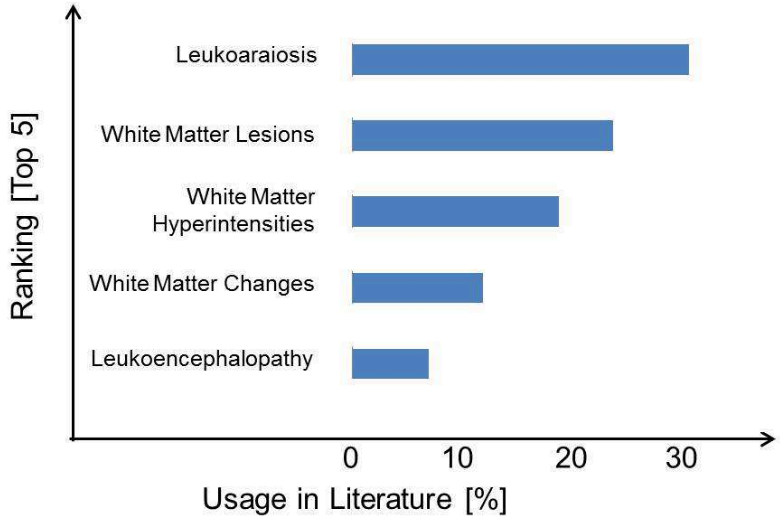

Figure 6. Heterogeneity of WMH terminology and ranking, %-usage in literature (adapted from Gattringer & Fazekas, 2014)

Characterization

Superior to the mentioned CT determination, WMH are better characterized as areas of high signal-intensity on T2- and FLAIR-weighted Magnetic Resonance Imaging (MRI) scans. To separate them from the effects of focal large infarcts on white matter, these lesions should not be adjacent to focal areas of cortical damage or ventricular enlargement. Another hallmark is their bilateral and symmetrical occurrence in the hemispheric white matter (Pantoni, 2010; Hachinski et al., 1987).

Grading and Categorization

Different WMH grading and categorization scales exist, being based on qualitative or semi-quantitative rating (WMH severity and distribution) and quantitative measurements (WMH number and volume) (Kapilamoorthy et al., 2005; Kapeller et al., 2003). As for qualitative rating, we here used the visual Fazekas' scale (cf. Figure 7; Fazekas et al., 1987). This inventory separately rates periventricular and subcortical WMH, and allows categorization into four groups: No WMH (type 0), punctuate WMH (mild degree, type 1), early-confluent WMH (moderate degree, type 2) and confluent WMH (severe form, type 3). Other popular inventories include the ARWMC scale (age-related white matter changes scale, Wahlund et al., 2001) and the Scheltens' scale (Scheltens et al., 1993) (cf. also Xiong and Mok, 2011). For a comparison of rating scales see Kapeller et al. (2003).

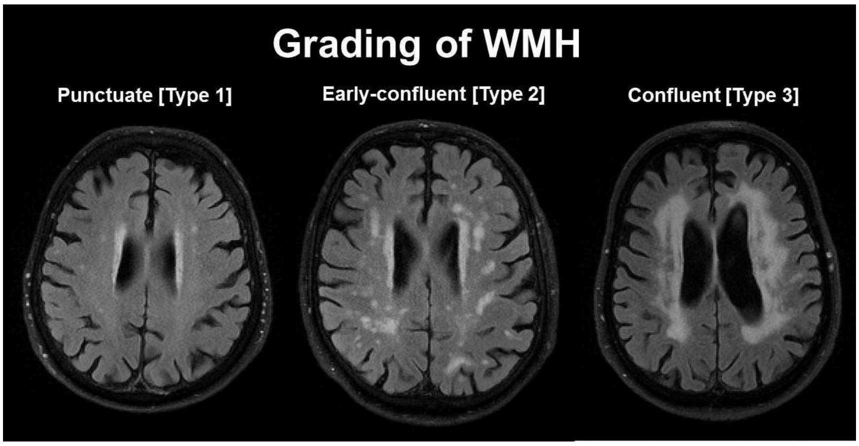

Figure 7. Grading of WMH based on the Fazekas' scale (Fazekas et al., 1987). Illustrative example from study 2 of the PhD project.

Topography and Progression

Punctuate vs. early-confluent and confluent WMH differ in their spatial distribution. While punctuate WMH show a more diffuse distribution pattern, early-confluent and confluent WMH occur more consistently around perfusion "watershed" regions, suggesting an ischemic component (Enzinger et al., 2006). Latter groups also tend to progress with time, making them "more severe" and "malignant" (Enzinger et al., 2007; Schmidt et al., 2003).

Pathogenesis

A model for the pathogenesis of WMH has been introduced by Pantoni (2010), with a connection of genetic- and risk factors leading to cerebral small vessel disease (SVD) and resulting in WMH as one causal outcome consequence. Thereby the path leads from SVD-induced loss of smooth muscle cells, lumen restriction and vessel wall thickening to reduced cerebral blood flow and loss of autoregulation. This in turn provokes chronic, diffuse and subclinical ischemia, which, further, nurtures incomplete infarct(s). The demyelination, loss of oligodendrocytes and axonal damage are then seen as diffuse hyperintensities on the T2-weightes MRI sequences. (Pantoni, 2010)

Risk factors and Correlates

WMH are found in both, patients and healthy subjects. In healthy, asymptomatic older people, about 10% display structural variations of WMH grades 2 and 3 (O'Sullivan, 2008). Since these are associated with advanced age, they are often referred to as age-related WMH (Pantoni et al., 2010; Wahlund et al., 2001). Apart from higher age, increased blood pressure, hypercholesterinaemia, hyperglycaemia, nicotine abuse and female sex are considered major risk factors (Van Dijk et al., 2008; Yamaauchi et al., 2002; Longstreth et al., 1996). Thus, cerebrovascular processes can be seen as markers and/or consequences (Gerdes et al., 2006).

Pronounced types of WMH (types 2 and 3, respectively), are associated with global functional decline in the elderly, including gait and balance dysfunction (Erkjinjuntii et al., 2011; Inzitari et al., 2009; Baezner et al., 2008). Other correlates are increased risk of falling, cognitive dysfunction, depression, urinary problems and neurological signs (independently of other vascular brain lesions) (Poggesi et al., 2013; Firbank et al., 2012; Schmidt et al., 2005; Teodorczuk et al., 2007).

Therapeutic Aspects

Therapeutic approaches vary depending treatment of causes (genetic- and risk factors) vs. symptoms. In a recent multi-ethnic, genome-wide association study (*N* > 20.000), four novel genetic loci that implicate inflammatory and glial proliferative pathways in the development of WMH in addition to proposed ischemic mechanisms could be identified (Verhaaren et al., 2015). An association between levels of structural biomarkers in cerebrospinal fluid (neurofilament light protein, Alzheimer' Disease-independent) and WMH load were also found (Bjerke et al., 2014; Pantoni, 2010). For the control of vascular risk factors, anti-hypertensive drugs, cholesterol-lowering drugs and anti-diabetic drugs are of potential interest; Vitamin B12 might have a preventive effect (Godin et al., 2011; Pantoni, 2010; Pieters et al., 2009). Behavioural consequences such as gait disturbances and cognition may be counteracted by training with respective inventories; mood disturbances can be ameliorated using anti-depressants (neurotransmitter-level rising; Herrmann et al., 2008).

1.1.3 Neuroimaging [1]

There are different neuroimaging techniques that allow to obtain objective information on brain structure (e.g. MRI, CT) and brain function (e.g. Functional Magnetic Resonance Imaging [fMRI], MEG, EEG, PET and NIRS[2]). These techniques differ in terms of invasiveness and spatio-temporal resolution (Camprodon & Stern, 2013; Bourne 2010; Jezzard et al., 2001, see also Figure 8); for the purpose of this study we used the non-invasive (f)MRI, providing a relatively high spatial resolution.

Recently, the use of hybrid imaging (such as MRI/PET, CT/PET) and multi-parametric-imaging (such as MRI, DTI, MRS[2], resting state, optical imaging) has increased with the goal to get coherent information on brain structure, function and metabolism (Townsend et al., 2013; Beyer and Moser, 2013; Mantini et al., 2010). Also, these more elaborated connectivity measures promise a better understanding of activation pattern (connectivity) (Smith, 2012).

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[1] „MRI“ and „fMRI“: Resembling Chapter 2 – Material & Methods of Linortner (2009).

[2] MEG, EEG, PET, NIRS, MRS: Not inlcuded in list of abbreviations.

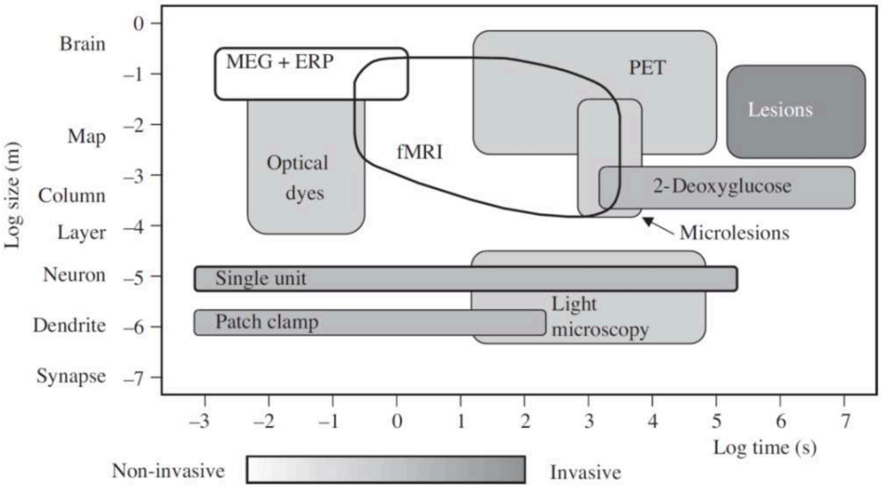

Figure 8. FMRI as a technique comprising relatively high spatial- and temporal resolution (Jezzard et al, 2001).

Magnetic Resonance Imaging (MRI)

MRI provides information on brain structure, allowing WMH detection and grading. The technique is based upon a strong magnetic field, nuclear spins and powerful radio frequency pulses. In short, there is the magnetic field and the spinning-charged hydrogen atoms (with special interest on their magnetic nature). Based on the angular momentum of protons and electrons, they naturally spin around their axes, in random directions (not aligned). As soon as an external magnetic field is present (MRI scanner), more spins align parallel to the magnetic field. Resonance is then reached with transmission of powerful radio frequency pulses. In the moment the radio frequency field is switched off, the spins return to their original equilibrium. In the process, they lose part of the energy they gained before. This energy is measured with surface coils and its location can be traced back; this information is then used to generate the images. (cf. Bushong & Clarke, 2014; Reiser et al., 2008; Weishaupt et al., 2006; Liney, 2006; Jezzard & Clare, 2001)

Voxel-Based Morphometry (VBM) analysis requires structural MRI, for instance. This neuroimaging technique explores differences in grey and white matter volume at a microstructural level, by comparing (focal) tissue concentration voxel-wise, i.e. voxel-by-voxel, within a group or across groups (Whitwell, 2009; Good et al., 2001; Ashburner & Friston, 2000).

Functional Magnetic Resonance Imaging (fMRI)

FMRI provides information on brain function, allowing the study of the functional brain response in response to a given paradigm, e.g. ankle movements, which are considered a key component of walking. FMRI measures brain activity indirectly, based upon blood oxygenation changes (BOLD effect, blood oxygenation level dependent; Logothetis & Pfeuffer, 2004; Ogawa et al., 1990). Another approach is the measurement of blood flow changes (cf. Kwong & Chesler, 2000).

Using blood itself as endogenous contrast medium for fMRI, the BOLD effect exploits the different magnetic properties of oxygenated (diamagnetic, smaller magnetic susceptibility) and deoxygenated (paramagnetic, larger magnetic susceptibility) hemoglobin [Hb]. In a region with enhanced neuronal activity [stimulus condition], the venous blood concentration ratio of oxygenated and deoxygenated hemoglobin increases in favour of oxygenated hemoglobin [Oxy-Hb increase]. This causes a more homogeneous local magnetic field where excited spins dephase more slowly, leading to a less steep T2* curve and thus stronger MRI signal (Buxton, 2010; Jezzard et al., 2001; Kandel et al., 2000).

Following a brief negative BOLD signal (initial dip) and a short overshoot, the positive BOLD response usually occurs 4-6 seconds delayed to stimulus onset. Depending on the duration of the stimulus presentation, the signal value stays on its plateau and is then followed by a post-stimulus undershoot (signal falls below the baseline signal level) (Mullinger et al., 2013; Baert & Sartor, 2005). See also Figure 9.

1.1.4 Neuroplasticity

Brain plasticity is not restricted to critical periods during the ontogenesis: the brain preserves its capacity for plasticity throughout life (Fuchs & Flügge, 2014; Taubert et al., 2012). Thereby, neuroplasticity is defined as the adjustment of the nervous system to changes in the internal (e.g. focal brain injury, inflammation) or external milieu (e.g.

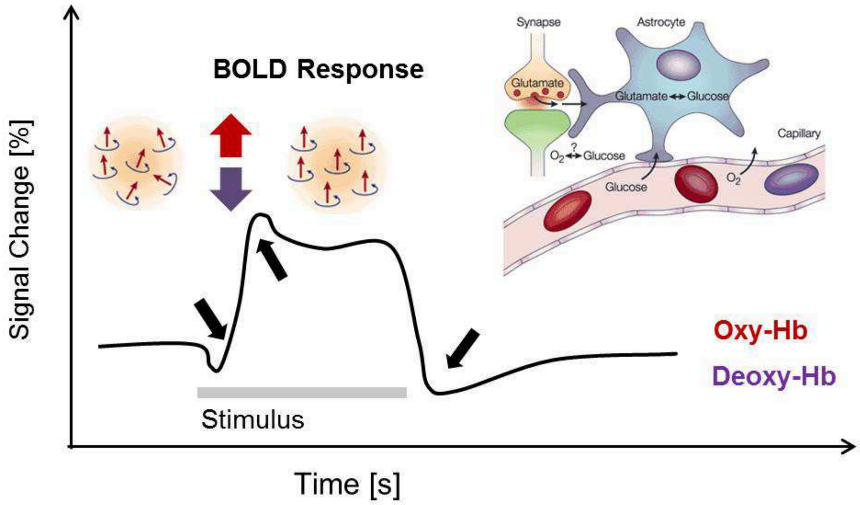

Figure 9. Hemodynamic time course with indication of initial dip, overshoot and undershoot (black arrows). In a stimulated condition, there is an increase of cerebral blood flow [Oxy-Hb], the rotating protons dephase more slowly [less step T2* curve] and the MRI signal is stronger. The inset top right shows the relationship between synaptic activity, neurotransmitter recycling and metabolic demand during stimulation (Illustration based on Baert & Sartor, 2005, Kandel et al., 2000; with inset of Heger & Ress, 2002)

visual-, somatosensory system) (Huttenlocher, 2002; Jacobsen, 1991). It is not restricted to the neurological domain only (e.g. stroke, multiple sclerosis; Pinter et al., 2013; Tomassini et al., 2012), but also affects psychological- (e.g. psychotherapy, schizophrenia; Collerton, 2013; Meisenzahl et al., 2008) and other domains (e.g. chronic pain, loss of olfactory function; Kollndorfer et al., 2014; Seifert & Maihöfner, 2011).

Fundamentally, neuroplastic processes may involve changes in white matter structure, grey matter or extra-neuronal areas. These changes range from white matter fiber organization (as indirectly assessed by DTI FA-values) to grey matter neurogenesis (a supported by VBM volume changes, with the necessity of additional tissue sample analyses) and white and grey matter angiogenesis, respectively (see Figure 10; Zatorre et al., 2012). In reverse direction, the rapidness of neuroplastic processes is highlighted by a study of Langer et al. (2013), where short term limb immobilization of 14 days induced structural changes in motor- and sensory-related areas already (cf. also Hofstetter et al., 2013).

Motor training and motor skill learning have shown to induce changes in white matter microstructure and myelination (Sampaio-Baptista et al., 2013; Dayan & Cohen, 2013; Scholz et al, 2009). Training in juggling over a period of 6-weeks led to increased FA-values in the intraparietal sulcus, a region associated with complex visuo-motor skills (Scholz et al., 2009). But also cognitive training seems beneficial, ameliorating compensation mechanisms seen in older adults (Grady, 2012). The posterior hippocampus has been shown to be significantly larger in London taxi drivers than in controls. The authors argue that this part of the brain is associated with spatial representation of the environment (Maguire et al., 2000).

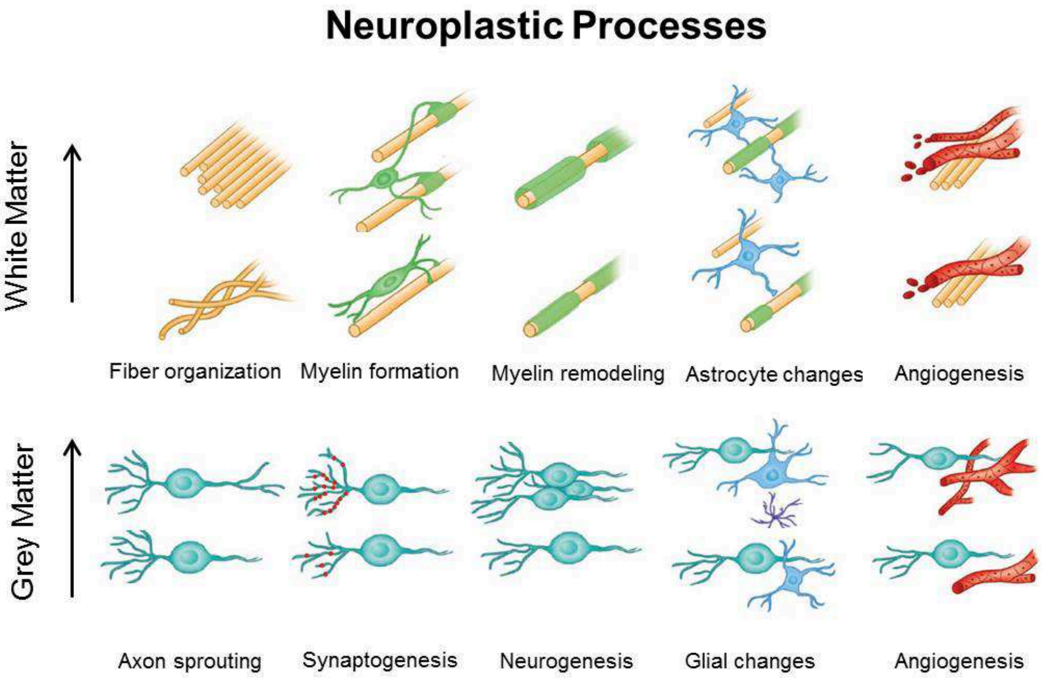

Figure 10. Training-induced neuroplasticity in brain white matter and grey matter (modification of Zatorre et al., 2012).

1.1.5 Neurorehabilitation

In general, rehabilitation aims at the promotion of recovery of function after damage to structure. Neurorehabilitation focuses on enhancement of brain function, using neural plasticity as biological substrate. The focus of neurorehabilitation is directed either towards categorization into groups (e.g. geriatric neurorehabilitation, with cerebrovascular- and demyelinating diseases constituting principal diagnoses in Europe, Eurostat 2014) or domains (depending on symptoms and dysfunction; e.g. training of motor function, cognitive retraining, language processing) (Barrett et al., 2013; Robertson & Fitzpatrick, 2008).

As for motor function, robot-assisted rehabilitation proves to be viable and beneficial tool in addition to or combination with physical therapy in clinics. Current Lokomat-concepts expand on isolated movement execution and add visual feedback, virtual reality and alternations (such as footrests: substrate for climbing stairs) to the device (Swinnen et al., 2014; Calabro et al., 2014; Banz et al., 2008). An efficient and cost-effective home-based intervention technique receiving recent attention is the computer-based exercise training program of the Nintendo WII Fit, used to strengthen muscle force, balance and endurance in interactive manner (Goble et al, 2014). More cost-intensive, also repetitive TMS induces plastic changes in the motor cortex and promotes behavioral motor performance beyond stimulation time and -site (Park et al., 2014)

In the cognitive domain, improvement of motor function can be facilitated using motor observation (mirror neurons) and motor imagery (Lorey et al., 2013; Mulder 2007). Motor-imagery (ERD/S[3])-based Brain-Computer Interfaces enable patients with impaired or lost motor function to either train brain function or control electronic devices (e.g. wheelchair, neuroprostheses, Rohm et al., 2013; Millán, et al., 2010). Further, real-time fMRI assisted control of motor-associated regions can add great value to neurorehabilitation programs (Hui et al., 2014, Berman et al., 2012)

1.2 Studies and Hypotheses

Within the scope of the PhD project, we, as a first step, were interested whether advanced age has any impact on supraspinal gait control. We here used two different analysis approaches. We then concentrated on the (sub)cortical microstructure of WMH. More

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[3] Internally or externally paced events can be traced by changes in the ongoing EEG, in form of an event-related desynchronization (ERD) or event-related synchronization (ERS) (Pfurtscheller & Lopes da Silva, 1999)

precisely, we investigated the association between WMH and grey matter, filtering in information of lesion location and also related grey matter to variables potentially affected with WMH: gait and cognition. The last study aimed at a better objectification of “walking” within the MRI environment, generating a paradigm to be used in individuals with WMH as well as other cohorts. We here also tested for potential sex differences. In the following, the three studies will be discussed separately in more detail. See also Figure 11.

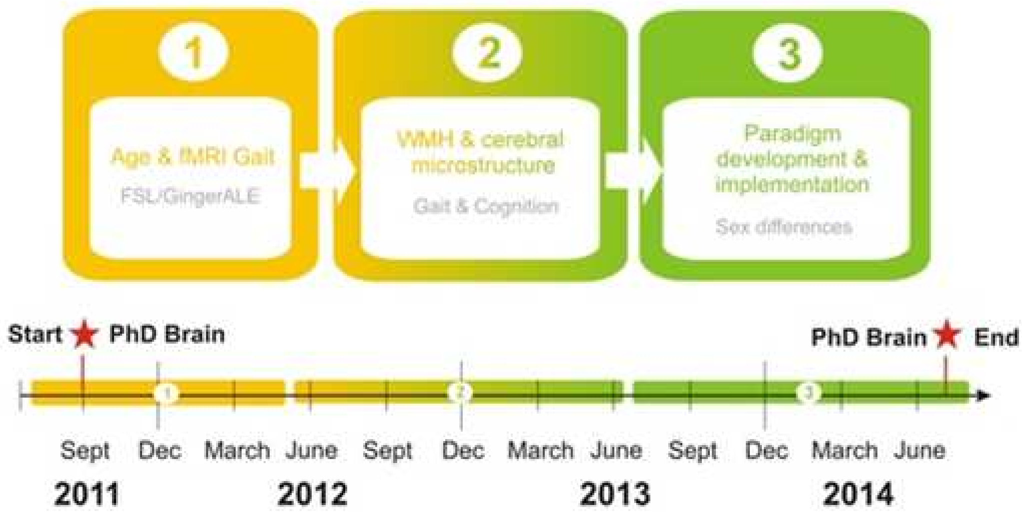

Figure 11 Phases, studies, and objectives of the PhD project, with the corresponding timelines.

1.2.1 Age and fMRI Ankle Movements[4]

Gait and motor performance change with age, as known from several behavioural studies (Seidler et al., 2010). However, the impact of age on the central human motor control has been largely unclear so far, despite the high frequency and clinical relevance of gait problems with ageing (Kreisel et al., 2013; Callisaya et al., 2013).

FMRI studies suggested preceding functional changes of movement representations with older age (Carp et al., 2011) or in the context of age-related white matter changes (Linortner et al., 2012). Advanced age might thus induce compensatory neuroplastic

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[4] Resembling the „Introduction“ section of Linortner et al. (2014).

processes in subcortical motor networks, in response to changes in the neurobiology of motor control systems (Ward, 2006).

Studies on upper limb movements (fine motor skills) showed an increase in neural activity with age, especially in the ipsilateral motor cortex and subcortical (cerebellar) motor areas (Noble et al., 2011; Ward and Frackowiak, 2003; Mattay et al., 2002). Few similar studies focusing on lower limb movements have been reported (Zwergal et al., 2012). These suggested an increase of multisensory cortical control of motor functions with age (Zwergal et al., 2012) and an age-related shift from automated to more controlled movement processing, associated with increased cognitive monitoring involving executive areas (Heuninckx et al., 2008; Heuninckx et al., 2005).

Together, these findings appear to indicate a more conscious locomotor and postural strategy in older adults (Zwergal et al., 2012). However, a direct test for age-effects on cerebral activation during ankle movements, previously used as a probe for gait in clinical and rehabilitation studies (Enzinger et al., 2008 & 2009) has not been performed in larger samples yet.

Within this study, we therefore aimed for two objectives: Primarily, 1. to investigate the impact of age on the neural correlates of ankle movements across various cohorts (big sample approach, with ankle movements as surrogate for gait and walking; Capaday, 2002). 2. to use and compare two different analytic approaches: Standard cluster-based FSL FEAT- and coordinate-based GingerALE meta-analysis (activation likelihood estimation (ALE) mapping; Eickhoff et al., 2009). This was planned in order to detect quantitative inter-study activation consistencies (Biondi-Zoccai et al., 2011; Higgins et al., 2003).

Research Questions and Hypotheses

1. Age Effect: By using a big sample approach, does higher age alter the functional brain response within a proven motor-related fMRI paradigm?

$H1_1$: Higher age is accompanied by BOLD signal changes in (sub)cortical motor areas.

2. FSL FEAT vs. GingerALE: By using two analytic approaches, do both techniques produce robust and similar results as implication for subsequent studies?
$H1_2$: The functional brain response in response to ankle movements using FSL FEAT is similar to the activation cluster as elicited by GingerALE meta-analysis.

1.2.2 WMH and (Sub)cortical Microstructure

Behaviourally, WMH are associated with gait and balance disorders, cognitive dysfunction and depression (Inzitari et al., 2009; Baezner et al., 2008; Teodorczuk et al., 2007). Functionally, people with pronounced WMH showed presumed compensatory brain activation in (higher) motor-related brain regions (Linortner et al., 2012). Partly unresolved are structural changes and deviances, with respect to WMH.

Existing studies showed decreased fiber integrity, especially in the corpus callosum, the major pathway for successful gait (Maillard et al., 2013; Griebe et al., 2011) and linked these results to gait disturbances (De Laat et al, 2011a, De Laat et al., 2011b). Apart from white matter-DTI studies, VBM studies showed a decrease in grey matter volume in proximity to WMH and in frontal regions (Wen et al., 2006; Rossi et al., 2006). Srikanth et al. (2010) used VBM to link WMH and gait, with bilateral frontal and periventricular affected WMH-voxel being associated with poorer gait. Since the affected voxels corresponded to major projection- and adjacent association fibers, the authors concluded that WMH might disconnect motor networks served by these tracts and hence lead to poorer gait.

Which is important in this context: Higher age itself may lead to variations in brain structure such as loss of brain volume and decreased white matter integrity, in both, healthy people and individuals with WMH (Tseng et al., 2013; Bhadelia et al., 2009; Fjell et al., 2009; Schmidt et al., 2005). Also, WMH can cause a confounding effect on the VBM segmentation phase (Brett et al.; 2001). To solve this problem, age-corrections and individual lesion masks (added to the VBM protocol) seem appropriate.

Within this study, we pursued three objectives: 1. To investigate the impact of WMH on grey matter volume and relate those findings to WMH lesion location. 2. To perform correlation analyses with variables potentially affected by WMH: Gait and Cognition.

Research Questions and Hypotheses

1. WMH and Grey Matter Volume: Is there a relationship between WMH and brain grey matter volume, taking age and lesion (location) into account?
$H1_3$: Severe WMH are associated with grey matter volume decreases in frontal and motor-related areas.

2. WMH-Walking/Cognition and Grey Matter Volume: In a WMH cohort, is there a relation between WMH-affected domains such as walking and cognition and grey matter volume, taking age into account?
$H1_4$: Worse walking abilities and cognition, respectively, are associated with grey matter volume decreases in associated brain areas.

1.2.3 fMRI "Walking" Paradigm Development

The last project part aimed at the development of a new (modified) fMRI paradigm to improve existing approaches to study the neural correlates of walking. Until now, active performance of unilateral repetitive ankle movements was mostly used as surrogate for gait (Enzinger et al., 2009; Enzinger et al., 2008; Capaday, 2002). However, gait and walking in particular are complex processes and a closer approximation seems important in the study and understanding of supraspinal gait control.

Some groups approached this aspect by optimizing the device component (simultaneous movement of ankle, hip and knee joints instead of isolated ankle movements; cf. MARCOS design, Hollnagel et al., 2011; Newton et al., 2008). Others concentrated on the improvement of the functional paradigm, whereby gait can be investigated in terms of movement execution, movement observation and movement imagery (cf. Jahn & Zwergal, 2010; Bakker et al., 2007). To date, these movement-associated domains have mainly been studied in an isolated manner (Wang et al., 2009; Wagner et al., 2008; Sahyoun et al., 2004) and have not been combined within one functional MRI run (Lorey et al., 2013; Orr et al., 2008). Integrating the different domains in a single fMRI paradigm feasible for healthy people and clinical populations, hence promises a better understanding of central human motor control in the aging brain (Picard & Strick, 2001). This notion gets support from the results of studies 1.2.1 and 1.2.2 which suggest an inclusion of motoric, visual and cognitive components in an enhanced fMRI motor paradigm for elderly people and individuals with WMH to be useful.

Apart from the primary goal of the fMRI paradigm development, we were interested in potential sex-related differences using the newly developed motor paradigm. Previous studies have shown sex differences in BOLD functions during fMRI tasks that assess functions of language (Vikingstad et al., 2000), creative thinking (Abraham et al., 2014), decision-making (Van den Bos et al., 2013), and visual attention (Semrud-Clikeman et al., 2012). Regarding motor ability, sex differences in behavioural gait performance and kinematics can be considered well-characterized, with men showing higher motor performance speed and women greater non-sagittal motion and a shorter stride length (Jiménez-Jiménez et al., 2011; Chumanov et al., 2008; Kirtley, 2006), However, there is a lack of studies dealing with sex and the functional organization of the motor system.

Along these lines, neuroimaging studies revealed activation differences for movement execution (Silas et al 2010; Lissek et al., 2007); however, these studies concentrated on active upper limb movements. In the movement observation domain and hence, regarding the human mirror-neuron system, women seem to produce neuro-physiologically stronger modulation in spinal excitability when observing bipedal movements (Cheng et al., 2007). Potential sex differences are also discussed in the context of movement imagination. Some authors argue males to be better imagers than females and constitute this on potential differences in brain area activation and inhibition (Schuster et al, 2011; Butler et al., 2006: fMRI mental rotation tasks). Others report on modest sex differences (Ishizu et al., 2009: NIRS motor imagery of hand; Seurinck et al., 2004: mental rotation of hand movements).

Taken together, studies on the influence of sex on lower limb movements are scarce and, to the best of our knowledge, not existing, especially regarding a combined motor execution, -observation and –imagery fMRI foot movement paradigm. However, the relevance of such findings might be particularly interesting since motor observation (mirror therapy) and -imagery are increasingly proposed as tools in neurorehabilitation and sex could trigger outcome effects (Schuster et al., 2011; Zimmermann-Schlatter et al., 2008; Braun et al., 2006; Sharma et al., 2006), in such scenarios.

Research Questions and Hypotheses

1. Paradigm Development: Does the newly developed fMRI gait paradigm produce stable, plausible and reliable activation patterns in the three motor-related domains (execution, observation, imagination)?

$H1_5$: The brain activation associated with a combined motor execution, motor observation and motor imagery fMRI gait paradigm does not differ in the respective conditions from the brain activation reported in isolated paradigms.

2. Sex Differences: By using the newly developed fMRI gait paradigm, are there any sex differences in the brain response in the three motor-related domains (execution, observation, imagination)?

$H1_6$: The brain activation of men and women differs in a combined motor execution, motor observation and motor imagery fMRI paradigm in the respective conditions.

Chapter 2

Methods

For the majority of the content, this chapter provides pertinent information on recruited participants and used methods to answer the research questions and hypotheses outlined in chapter one. To enhance readability, the different parts of the methods section are covered separately for each of the three – concerning study population, experimental design and analysis different yet content-related overlapping and consecutive – studies. The order of the subchapters (2.1-2.3) here follows the logical study order. Subchapter 2.4 covers general statistical analysis (common for all three studies).

2.1 Age and fMRI Ankle Movements

2.1.1 Participants

For the purpose of this study, we pooled data from five previous studies that were performed at the Medical University of Graz and the Centre for Functional MRI of the Brain in Oxford (all using the same fMRI paradigm, see 2.1.3). In total, 102 right-handed healthy subjects aged *M* = 48.7 ± 18.8 years could be integrated for this examination; they all had served as control subjects in the preceding studies (see Enzinger et al., 2009; Katschnig et al., 2011; Linortner et al., 2012; Loitfelder et al., 2011 and Schwingenschuh et al., 2013) and had no history of any neurological or psychiatric disease. Due to various reasons (such as missing T1-weighted structural scans, deviations from the scanning protocol or left-handedness), nine participants of the original data set comprising 111 individuals had to be excluded from further analyses; this resulted in a final cohort of 102 participants. Table 1 lists more detailed information on the contributing study participants.

Table 1. Description of the cohort in terms of data source, participants, age, sex and scanner.

Data source	Participants		Age [years]		Sex, m/f	Field strength & Scanner type
	N	%	*M*	SD	*n*	
Loitfelder et al.	34	33.3	30.6	8.8	16/18	3-T Tim Trio
Enzinger et al.	27	26.5	52.7	17.1	10/17	3-T Varian INOVA
Katschnig et al.	19	18.6	61.5	6.8	10/9	3-T Tim Trio
Linortner et al.	17	16.7	69.7	6.6	4/13	3-T Tim Trio
Schwingenschuh et al.	5	4.9	30.0	5.4	2/3	3-T Tim Trio
Total	102	100	48.7	18.8	42/60	---

Key: f, female; *M*, mean; m, male; *N*, number (population); *n*, number (group); SD, standard deviation

2.1.2 Data Acquisition

Study participants underwent (f)MRI examinations at a Siemens 3-T Tim Trio scanner (*N* = 75, four studies) and a 3-T Varian INOVA (*N* = 27, one study). None showed any morphologic brain abnormalities on structural T1-weighted 3D MPRAGE MRI data [1mm isotropic resolution; TR = 1900 ms, TE = 2.19 ms, inversion time = 900 ms, FA = 9°, and matrix size of 256 x 256]. Functional data were acquired using a single shot EPI sequence [TR = 3000 ms, TE = 30 ms, spin angle = 90°, matrix size 64 x 64], with 3 x 3 x 3 mm voxel dimension for the Tim Trio- and 4 x 4 x 6 mm for the Varian INOVA system, where 180 volumes were acquired within a single 9-min functional run (right vs. left ankle movements, respectively).

2.1.3 fMRI Paradigm

A well characterized and standardized fMRI motor movement paradigm was used in identical form across all sub-studies. Study participants had to perform visually-paced unilateral 1 Hz-rhythmic ankle dorsiflexion movements, separately for the right and left lower limb (different runs). Blocks of active movements alternated with blocks of passive movements (30 sec each), having periods of absolute rest interspersed (21 sec). A wooden apparatus served as study device, allowing ankle movements with a maximum motion displacement of 30° (cf. also Figure 2). Movement performance was facilitated flexing participants' knees approximately to 135° and stabilized using a soft roll beneath the knees and a foam-cushioned holder for the head (Velcro straps fixation). Adherence to the paradigm was traced using a potentiometer and by visual observation. Figure 12 shows the paradigm and the device; see also Enzinger et al., 2008 and 2009.

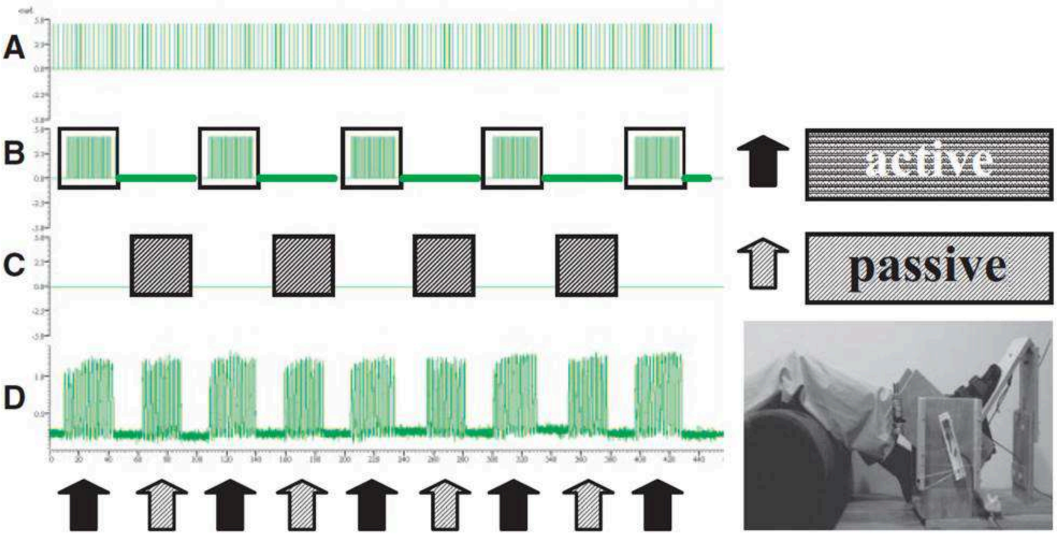

Figure 12. fMRI ankle movement paradigm. A) Scanner triggers (180 volumes). B and C) Active vs. passive movement blocks. D) Potentiometer: Response function. Inset: Ankle movement apparatus. (cf. Enzinger et al., 2008 and 2009)

2.1.4 fMRI Data Analysis

fMRI data analysis was performed using FSL-FEAT (FMRIB Software Library, fMRI Expert Analysis Tool, version 5.92) and GingerALE (BrainMap application for ALE meta-analysis). Both methods required data pre-processing beforehand. Pre-processing was done using FSL with MCFLIRT-motion correction, followed by BET-non-brain removal, spatial smoothing with a Gaussian kernel of FWHM 5 mm and mean intensity normalization by a single multiplicative factor. Pre-processing also included high-pass temporal filtering

(Gaussian-weighted least squares straight line fitting, with sigma = 54.0 sec) and FILM-statistical time series analysis (with local autocorrelation correction). Data were then registered to high-resolution structural and standard space images (with FLIRT) and registration results were checked visually. None of the study participants had to be excluded from further analyses due to artifacts, slice dropouts or over-excessive head motion (defined by > 3mm in x-, y- or z-direction).

FSL FEAT vs. GingerALE

The FSL-FEAT analysis followed several steps. At first, at lower-level, contrasts for active ankle movement vs. rest were computed for each individual (adding head motion parameters as covariates to the model). Using lower-level "copes" (these are contrasts of parameter estimates), higher-level mean group activations were calculated for right and left foot, respectively (FLAME 1+2 mixed effects analysis, $Z > 3.1$, corrected cluster-p threshold of $p = 0.01$). Since data were derived from different scanners and studies, the factors "scanner" and "study" were included independently as covariates of no interest to the model. Subsequent higher level contrast analyses tested for potential differences regarding the effect of the two covariates on activation.

Activation likelihood estimation (ALE) analysis in general allows the detection of quantitative inter-study consistencies in activation by generating maps of activation likelihood estimates. In this study, Ginger-ALE was used to compare the results to those obtained by FSL-FEAT mean group analysis. Here, peak maxima of the mean activation maps of the different study populations (first and second level-FEAT analysis) served as input for the coordinate-based Ginger-ALE analysis. Activation foci were modeled as probability distributions, with the filtered-in coordinates as center and then the overlap between the studies was assessed. So, first, separate group statistics were generated for each study, for right and left foot (ankle) movement. All five studies ($N = 102$ participants and $n = 28$ foci) contributed to ALE meta-analysis, in both conditions. It has to be pointed out, that ALE values are automatically weighted by the sample size of each contributing study. Finally, results were thresholded using false discovery rating (with corrected p-values of $p < .05$), and FWHM value of 9.28 (median value) and a minimum cluster size of 100 mm3 (cf. Eickhoff et al., 2009; Turkeltaub et al., 2012; Turkeltaub et al., 2002).

Effects of Age on Activations

To investigate possible age effects by controlling for "study" as potential source of variance, FSL FEAT higher-level age correlation analyses (demeaning of age) on first level imaging data were performed. Regional brain masks were then defined based on the significant regions of the correlation analyses. Using FEATQUERY region of interest (ROI) analysis, median signal changes were computed within the predefined ROIs, for each individual and for right and left foot movement, respectively.

2.2 WMH and (Sub)cortical Microstructure

2.2.1 Participants

A sample of $N = 59$ individuals ($M = 71.83 \pm 8.18$ years) with presumed cerebral SVD was recruited consecutively from the University Clinic Graz. Participants were then invited to undergo structural MRI, as well as gait and cognitive testing on the same day. MRI data analysis (FLAIR-weighted scans) allowed categorization according to their WMH score: $N = 24$ with no or minor WMH (grades 0+1, respectively) and $N = 35$ with early-confluent or confluent WMH (grades 2+3 respectively). More information on sociodemographical and clinical data of the group is listed in Table 2

2.2.2 Behavioural Assessment

Equilibrioception, gait and motor proficiency were assessed with the Short Physical Performance Battery (SPPB), as well as two additional simple tests measuring the same construct (see Baezner et al., 2008). The first inventory, the SPPB, yields a composite score of maximum 12. The two additional tests, such as the Single Leg Stance Time (SLST) and Gait Velocity, record the maximum stance duration and achieved gait velocity (timed 4-m walkway [m/s]). See Table 3 for information on lower limb function.

Table 2. Characterization of the study cohort in terms of sociodemographic and clinical data; entire study cohort and after grouping by WMH score.

Study cohort	Sociodemography			Clinical profile					
	Age [years]		Sex, m/f	BMI		AH	DM	SC	HC
	M	SD	N	*M*	SD	%	%	%	%
All participants (*N* = 59)	71.8	8.2	19/40	27.1	4.6	74.6	11.9	11.9	40.7
WMH grading									
WMH 2+3 (n_1 = 35)	74.1	6.9	12/23	26.6	4.9	80.0	17.1	11.4	25.7
WMH 0+1 (n_2 = 24)	68.5	8.9	7/17	27.6	4.1	66.7	4.2	12.5	62.5
Test statistic, p-value	**.008**			.504		.167	.118	.663	**.003**

Key: AH, Arterial hypertension; BMI, Body Mass Index; DM, Diabetes mellitus; f, female; HC, Hypercholesterolemia; *M*, mean; m, male; *N*, number (population); N, number (general); *n*, number (group); SD, standard deviation; SC, current smoking; WMH, White matter hyperintensities

Table 3. Characterization of the study cohort in terms of lower limb function; all subjects and grouped by WMH score.

Study cohort	SPPB [total score]		SLST [sec]		Velocity [m/s]	
	M	SD	Med	IQR	*M*	SD
All participants (*N* = 59)	8.3	2.7	15	[3-15]	1.2	0.4
WMH grading						
WMH 2+3 (n_1 = 35)	7.3	2.8	8.5	[3-15]	1.1	0.4
WMH 0+1 (n_2 = 24)	9.7	1.8	15	[13-16]	1.3	0.3
Test statistic, p-value	**<.001**		**.005**		**.021**	

Key: IQR, inter-quartile range; *M*, mean; Med, median; *N*, number (population); *n*, number (group); SD, standard deviation; SLST, Single Leg Stance Time; SPPB, Short Physical Performance Battery; WMH, white matter hyperintensities

Cognitive (i.e. frontal executive) function was assessed using the Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948; Heaton, 1981). For this test, cards have to be sorted correctly with changing stimulus conditions (conceptual reasoning demanded, strategy development and preservative errors interesting). Further, participants had to complete a Word Fluency task (semantic component, Shao et al., 2014), Version B of the timed Trail Making Test (connection of number/letters, TMT-B; Reitan, 1956), the "Lern- and Gedächtnistest (LGT; Bäumler, 1974). Finally, the Mini Mental State Examination (MMSE; Folstein et al., 1975) was used for general cognitive state examination (maximum of 30 points achievable). Table 4 summarizes the performance values for cognitive function.

2.2.3 Data Acquisition

All study participants underwent MRI examinations at a 3-Tesla whole body system (Tim Trio, Siemens Healthcare, Erlangen, Germany) using a head coil array with 12 elements. Structural imaging included a T1 weighted 3D MPRAGE sequence with 1mm isotropic resolution (TR/TE/TI/FA = 1900 ms/2.19 ms/900 ms/9°) and a matrix size of 256 x 256 in all participants. A fast FLAIR sequence was obtained in a subset of 41 individuals (TR/TE/TI = 10 ms/70 ms/2500 ms, in plane resolution = 0.9 x 0.9 mm2, slice thickness = 4 mm and FOV = 220 mm).

2.2.4 Morphological Data Analysis

After rating and identification of WMH by a blinded experienced investigator (CE) on FLAIR-images, a trained technician (PL) segmented WMH (see also Figure A.2). Global lesion volume was calculated by local thresholding and region growing using home-developed software (after instructions by SR). Based on high resolution T1 scans, brain tissue volume was estimated using SIENAX as part of FSL (www.fmrib.ox.ac.uk/fsl). See Table 5 for global-, grey- and white matter volume, as well as white matter lesion load in the two WMH groups.

Table 4. Characterization of the study cohort in terms of cognitive function; all subjects and subgroups defined by WMH score.

Study cohort	MMSE [total score]		Word Fluency [N]		TMT-B [sec]		LGT [total score]		WCST-Corr [N]		WCST-NonpErr [N]	
	Med	IQR	*M*	SD	*M*	SD	Med	IQR	M	SD	M	SD
All participants ($N = 59$)	27	[25-29]	20.3	7.7	165	85.3	22	[20-27]	79.2	13.5	13.5	13.5
WMH grading												
WMH 2+3 ($n_1 = 35$)	27	[24-28]	21.5	8.2	158	87.3	22	[20-28]	75.9	10.1	9.4	9.4
WMH 0+1 ($n_2 = 24$)	28	[26-29]	18.5	6.6	179	82.4	22	[20-26]	83.5	14.1	19.6	15.6
Test statistic, p-value	**.016**		.144		.373		.907		**.045**		**.008**	

Key: IQR, inter-quartile range; LGT, Lern- und Gedächtnistest; *M*, mean; Med, median; MMSE, Mini-Mental State Examination; *N*, number (population); N, number (test score); *n*, number (group); SD, standard deviation; TMT-B, Trail Making Test-Version B; WCST, Wisconsin Card Storting Test - Correct answers and Nonperseverative Errors; WMH, white matter hyperintensities

Table 5. Characterization of the study cohort in terms of morphologic MRI data; entire subject-cohort and grouped by WMH score.

Study cohort	WB volume [mm^3]		GM volume [mm^3]		WM volume [mm^3]		WM lesion load [cm^3]	
	M	SE	*M*	SE	*M*	SE	Med /*M*	IQR / SE
All participants ($N = 59$)	1481642	12433	754963	10352	72667	8160	1.9	[0.8-12.1]
WMH grading								
WMH 2+3 ($n_1 = 35$)	1456142	15577	732317	12871	723825	10759	7.2	[3.1-20.6]
WMH 0+1 ($n_2 = 24$)	1517343	18431	786667	15229	730675	12731	0.7	[0.3-0.9]
Test statistic, p-value	.014		.008		.683		<.001	
After age-correction								
WMH grading								
WMH 2+3 ($n_1 = 35$)	1473694	13210	748751	10099	724944	11185	17.2	3.2
WMH 0+1 ($n_2 = 24$)	1492770	15820	763660	12094	729110	13395	1.8	3.8
Test statistic, p-value	.375		.364		.818		.004	

Key: GM, grey matter; IQR, inter-quartile range; *M*, mean; Med, median; *N*, number (population); *n*, number (group); SE, standard error; WB, whole brain; WM, white matter; WMH, white matter hyperintensities

For display of the lesion load distribution in later analyses/figures, the binary lesion mask (attained by preceding WMH segmentation process) were linearly co-registered to a MNI standard template (2mm, tri-linear interpolation) and threshold with 10%. This means, in the figures of the results section, lesions are displayed if the respective voxel(s) are affected in at least 10% of the population.

Structural T1-data were then analyzed using a modified version of FSL-VBM, an optimised voxel-based morphometry protocol carried out with FSL tools (Smith et al., 2004).

First, structural images were brain-extracted using BET. Since significant WMH can cause a confounding effect on later VBM brain segmentation phase (i.e. misclassification of grey matter segmentation), individual lesions masks were created beforehand to add to the protocol. After registering and resampling, these binary lesion-masks were slightly dilated using modal filtering and a default kernel of 3x3x3 mm, to clear up any problem voxels around the edges. Following an inversion (to remove the lesions and preserve the brain), the masks were then applied to each of the brain-extracted input files. This allowed the brain-extracted, lesion-masked images to be grey matter-segmented using FAST4 and to be non-linearly registered to standard space. The resulting images were used to create a study-specific, left-right symmetric grey matter template, which all native grey matter images were non-linearly registered to (and corrected for local expansion). Smoothing was done using an isotropic Gaussian kernel with a sigma of 3 mm.

Finally, a voxelwise GLM (general linear model) was applied using a permutation-based non-parametric testing correcting for multiple comparisons across space, called TFCE (threshold-free cluster-enhanced) based thresholding. VBM analysis was done comparing the two groups of WMH subjects, additional to whole group correlation analyses based on the SPPB and the WCST scores. In all three cases, the demeaned age was added as covariate of no interest to the GLM. Figure 13 illustrates and summarizes the performed steps.

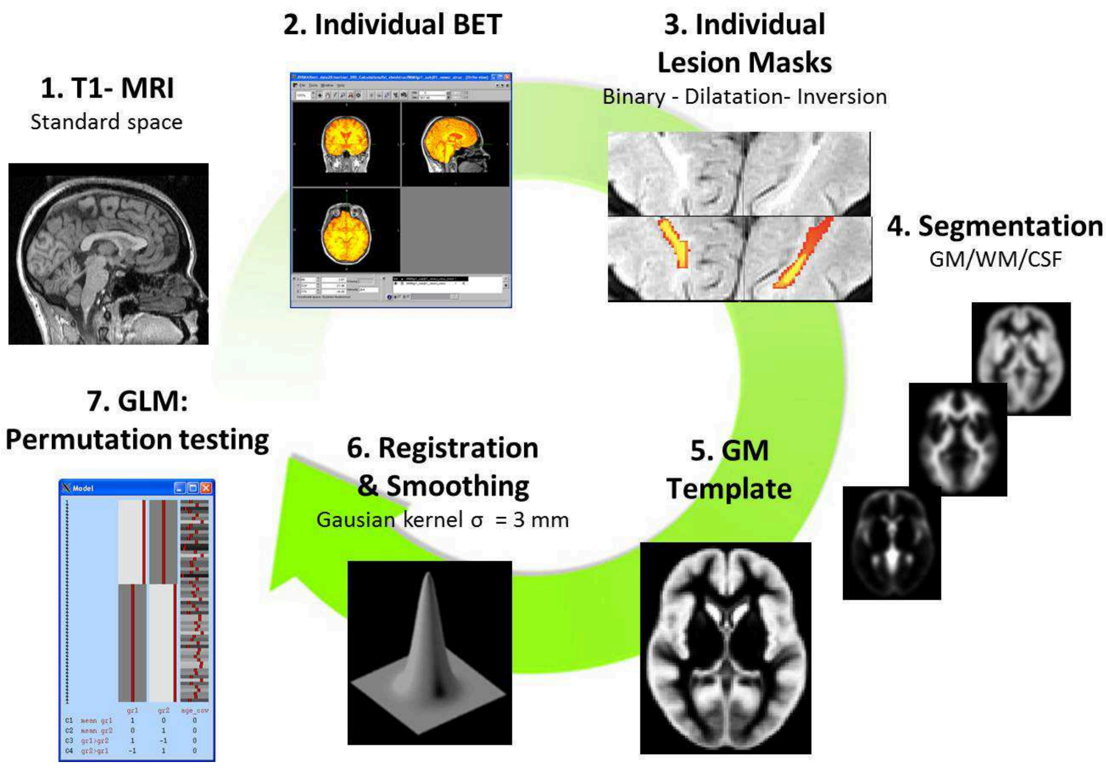

Figure 13. Modified version of the FSL-VBM protocol, with application of individual lesion masking.

2.3 fMRI “Walking” Paradigm Development

2.3.1 Participants

A total of $N = 22$, sex- and age-matched, middle-aged, right-footed, healthy subjects with normal or corrected-to-normal vision were included in the present study ($M = 31.7 \pm 7.4$ years). Due to claustrophobia, data of one subject had to be excluded from further analysis, resulting in a cohort of 11 males and 10 females. Participants reported no history of neuropsychiatric disorders, and declined current or past use of psychoactive medications. We employed the Waterloo Footedness Questionnaire-Revised (WFQ-R; Elias et al., 1998) as used by Grouios et al. (2009), the most reliable items of Schneiders et al. (2010) to assess footedness, and the Movement Imagery Questionnaire (MIQ; Hall & Martin, 1997) to assess motor imagery ability.

2.3.2 Behavioural Assessment

The WFQ-R assessed self-rated foot preference in two categories, the manipulation of objects and the support during actions. In general, according to the WFQ-R, participants were more right-foot (RF) than left-foot (LF) dominant. Based on this self-rating active performance test, 18 subjects had the value 2 (clearly RF), 2 had the value 0.5 (RF) and 1 had the value 0 (RF and LF). Additional, footedness was determined by active foot dominance testing (using the most reliable items of Schneiders et al., 2010). See Table 6 and Annex C.1.

Table 6. Characterization of the study cohort in terms of foot dominance (laterality test and WFQ-R); all subjects and grouped by sex.

Study cohort	Laterality quotient*		WFQ-R**					
			Manipulation		Support		Total	
	Med	IQR	*M*	SD	*M*	SD	*M*	SD
All participants (*N* = 21)	1	[1-1]	1.36	0.85	0.82	0.93	1.09	0.82
Sex-specific								
Male (n_1 = 11)	1	[1-1]	1.21	1.09	0.63	1.11	0.93	1.01
Female (n_2 = 10)	1	[1-1]	1.52	0.44	1.02	0.70	1.27	0.54
Test statistic, p-value	.643		.650					

Key: IQR, inter-quartile range; *M*, mean; Med, median; *N*, number (population); *n*, number (group); SD, standard deviation; WFQ-R, Waterloo Footedness Questionnaire-Revised

* Scores ranging from -1 (left foot dominant) to +1 (right foot dominant)

* Scores (mean) ranging from -2 (left-always) to +2 (right-always)

For the measurement of the motor imagery ability, the MIQ assessed figural and kinesthetic imagination of previously performed actions: Average scores in the MIQ ranged from 3.72 to 7.00 (*M* = 5.85 ± 1.02) on a scale from very difficult to imagine (1) to very easy to imagine (7), indicating that all participants showed good to very good imagery abilities. For details see Tables 7 and Annex C.2

Table 7. Characterization of the study cohort in terms of motor imagery ability; all subjects and grouped by sex.

Study cohort	MIQ					
	Figural*		Kinesthetic*		Total	
	M	SD	*M*	SD	*M*	SD
All participants (*N* = 21)	52.95	9.21	52.43	9.18	105.38	18.29
Sex-specific						
Male (n_1= 11)	55.27	9.55	54.09	9.77	109.36	19.22
Female (n_2 = 10)	50.40	8.55	50.61	8.61	101.00	17.10
Test statistic, p-value			.139			

Key: *M*, mean; MIQ, Movement Imagery Questionnaire; *N*, number (population); *n*, number (group); SD, standard deviation

* Scores (sum) ranging from 9 (very bad imagination ability) to 63 (very good imagination ability)

2.3.3 Data Acquisition

All study participants underwent MRI at a 3 Tesla whole body system (Tim Trio, Siemens Healthcare, Erlangen, Germany) using a standard 12-channel head coil. To minimize head movement, subjects' heads were stabilized with foam cushions. Structural image acquisition consisted of 176 high-resolution 3D-T1 MPRAGE-weighted sagittal images (TR = 1900 ms, TE = 2.2 ms, resolution 1x1x1 mm isotropic). For the fMRI, a total of 314 volumes were obtained using a single shot echo-planar imaging (EPI) sequence covering the whole brain including the cerebellum (TR = 3000 ms; TE = 30 ms; spin angle = 90°; matrix size = 64 x 64, pixel size = 3x3x3 mm; total scanning time ~15 min). The T1-weighted and axial FLAIR sequences served to check for any abnormalities.

2.3.4 fMRI Paradigm

To cover the domains a) motor function, b) visual function and c) cognition within one single fMRI motor paradigm, the following six experimental conditions were created: three exclusive motor execution conditions (1. ME_Right, unilateral right foot movements; 2.

ME_Left, unilateral left foot movements; 3. ME_Bip, bilateral foot movements), two motor observation conditions (4. MO_Bip, observation of bilateral foot movements; 5. MO+ME_Bip, observation and execution of bilateral foot movements) and one motor imagery condition (6. MI_Bip, imagination of bilateral foot movements).

The six experimental conditions (30s each) were presented in six separate runs in the order listed (1.-6.), interspersed with periods of absolute rest (21s, baseline condition, BL). The whole sequence was repeated thrice (starting and ending with baseline condition) resulting in a total scan time of 15m 39s (see Figure 14).

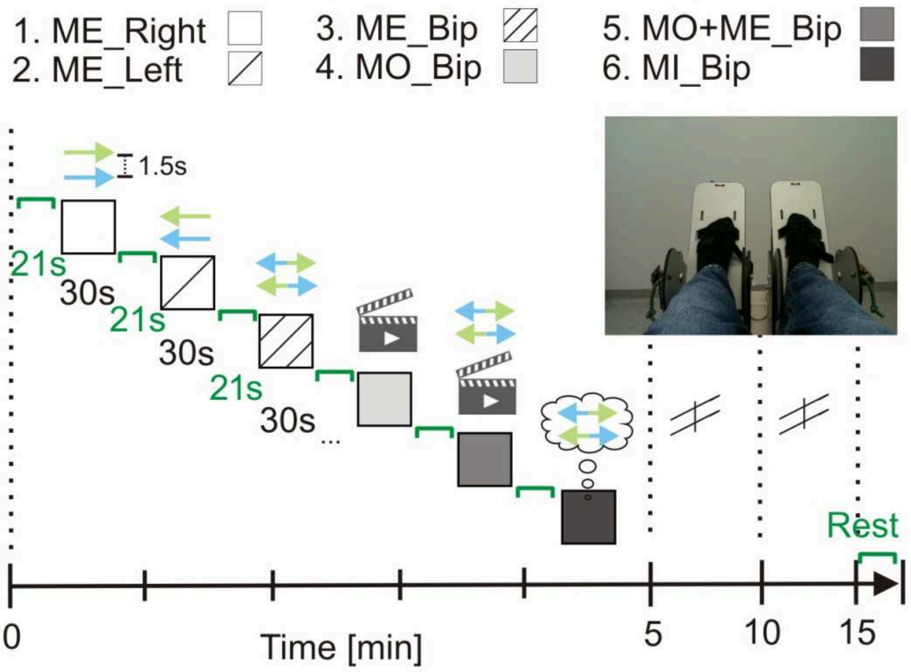

Figure 14. Design of the ankle movement fMRI paradigm, that covers the domains motor function, visual function and cognition. Experimental timing and sequence (conditions) are shown along the x-axis (see text for further details). The small image represents the baseline condition, which is also the basis of the experimental conditions (superimposed by arrows and motion, respectively). [Key: Bip, bipedal; ME, motor execution; MI, motor imagery; MO, motor observation]

A first-person perspective image of one’s feet while lying in the scanner was used as baseline condition. Participants were instructed to rest and refrain from doing anything during presentation of this image. Adding stimuli in form of arrows (and motion, respectively) to the baseline image prompted the experimental conditions, with the direction of the arrow(s) indicating the side of the foot. If the task demanded movement execution, subjects had to perform active unilateral or bilateral (alternating) ankle plantar- (green arrow) and dorsiflexion (blue arrow) movements, at a fixed rate of 1.0 Hz. Observation and imagination of foot movements concentrated on bilateral foot movements exclusively (observation/imagination of the movements performed in 3. ME_Bip).

Execution of foot movements within the fMRI scanner was realized using a purpose-built wooden apparatus that allows separate (unilateral) and simultaneous (i.e. bilateral, alternating, “stepping”) ankle dorsiflexion movements with a maximum motion range displacement of 30° (modified according to Enzinger et al., 2008). To reduce stimulus-correlated motion, subjects’ heads were secured with Velcro straps in a foam-cushioned holder and their knees were flexed to approximately 135° using a soft roll placed beneath the knees.

Prior to the fMRI experiment, participants attended a training session in order to familiarize themselves with the different experimental conditions and the experimental setting. During the fMRI experiment, stimuli and instructions were presented by the PC running Presentation-software (Neurobehavioral Systems, Albany, USA) and projected onto a screen behind the scanner that could be viewed through a mirror attached to the head coil.

2.3.5 fMRI Data Analysis

First, structural MRI data were reviewed in a blinded manner by an experienced observer (CE); there were no morphological abnormalities. Then, fMRI data were analyzed using FMRI Expert Analysis Tool (FEAT, version 5.92, part of FSL, www.fmrib.ox. ac.uk/fsl). The following pre-statistic processing was applied: motion correction using MCFLIRT; non-brain removal using BET; spatial smoothing using a Gaussian kernel of full-width half maximum (FWHM) 5 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least squares straight line fitting, with sigma = 153.0 seconds). Time series statistical analysis was carried out using FILM with local autocorrelation correction. Registration to high resolution structural and/or standard space images was carried out using FLIRT. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p > 0.05$. No subject had to be excluded due to artifacts, slice dropouts, or excessive head motion, as defined by > 3 mm in the x-, y- and z- direction ($M = 0.27 \pm 0.35$ mm) [Male: $M = 0.30 \pm 0.40$ mm, Female: $M = 0.23 \pm 0.30$ mm; $U(n_1=11, n_1=10) = 46.0$, $p = .525$].

In first level analyses, contrasts for all six experimental conditions versus rest were computed for each individual, including head motion parameters as covariates: 1 ME_Right vs. BL, 2. ME_Left vs. BL, 3. ME_Bip vs BL, 4. MO_Bip vs BL, 5. MO+ME_Bip vs. BL and 6. MI_Bip vs. BL. Registration results were checked visually. Mixed effects analyses were used to generate second-level contrasts at the group level. In third level analyses, we tested for differences between subject groups defined by sex.

2.4 General statistical analysis

Across studies, SPSS Statistics (Statistical Package for Social Sciences, Chicago, Illinois, versions 21.0 and 16.0) was used for general statistical analyses. For normally distributed continuous variables, the significance of any differences in means was tested by univariate analyses of (co)variance and Student *t*-tests. Mann-Whitney U-tests were used to test for significant differences of non-normally distributed variables. Any differences in proportions were assessed by X^2 statistics. In study 1, the values for the FEAT age correlation were obtained using z-transformation and by means of feed-forward stepwise linear regression analysis, we assessed which of the ROIs had the greatest magnitude (strongest relation) to age.

Chapter 3

Results

This chapter lists and summarizes the results based on the hypotheses postulated before and the corresponding analyses (see chapters one and two). The main focus lies in structural and functional imaging data. Again, to enhance readability, the different parts of the results section are covered separately for each of the three studies. The order of the subchapters (3.1-3.3) follows the study order.

3.1 Age and fMRI Ankle Movements

3.1.1 FSL FEAT vs. GingerALE

In the first step, we were interested in the mean group activation associated with right (RF) and left (LF) movements. Using FSL FEAT analysis, contrasts of active unilateral foot movements vs. rest showed significant activation in expected somatotopy for movement of both feet (cf. Enzinger et al., 2008). Right and left foot movements elicited activation in the primary motor cortex and supplementary motor area (both bilateral with contralateral activation peak), the primary and secondary somatosensory cortices (contralateral) and cerebellum (ipsilateral; exceeding to the brainstem). Additionally, analyses of left foot movement revealed ipsilateral secondary somatosensory cortex activation and contralateral basal ganglia recruitment.

GingerALE meta-analysis was done to identify locations showing a consistent response in activation across studies (experiments). For both, RF and LF movement, significant activation clusters were found in the bilateral secondary somatosensory cortex, the cerebellum (anterior part/ lobule VIII; both ipsilateral) and the insula (bilateral / ipsilateral). Additionally, movement of the RF activated the contralateral basal ganglia and the medial frontal gyrus. Clusters below a threshold of <100 mm3 included the primary sensorimotor cortex (MI and SI, bi-/ contralateral, RF & LF), the supplementary motor area (SMA, contralateral, RF & LF) and the basal ganglia (ipsilateral, LF) (not reported in table). See Figure 15 and Table B.1 (Annex).

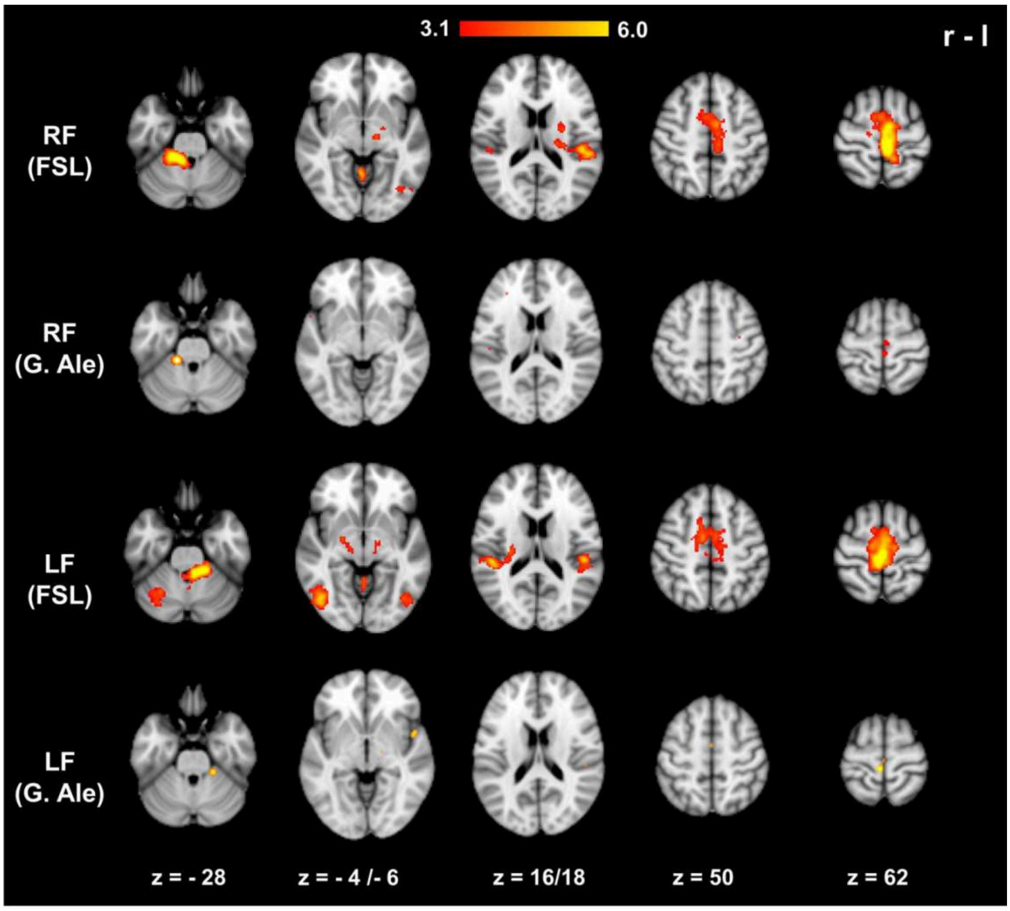

Figure 15. FSL FEAT and GingerALE analyses: Activation maps (selected slices, z-coordinates; where two z-values are displayed, the first represents FSL FEAT results) associated with ankle movement versus rest for RF (upper rows) and LF (lower rows) movement. FSL FEAT shows clusters with Z >3.1, p = 0.01 (*N*=102 subjects), whereby ALE corresponds to cluster peak extremes, p < 0.05 (*N*=96 subjects). The images are shown in radiological convention, where the left side represents the right side of the brain (and vice versa).

3.1.2 Effects of Age on Activations

Using FSL FEAT higher-level correlation analysis, significant results were found testing for a possible effect of age on the neural correlates of foot movement, both for the RF and LF. Correlation analysis elicited enhanced cerebellar (RF and LF, bilateral), occipital (RF and LF, contralateral) and precuneal activation (RF, contralateral and LF, ipsilateral), as well as basal ganglia (RF, bilateral) and frontal activation (LF, bilateral) with increasing age. Computation of the opposite correlation (increased activation with younger age) did not show any significant results.

To examine whether the seen positive correlation effects were driven by activation or deactivation, ROI analyses were performed for the respective regions and their median signal changes were plotted: All structures showed a significant positive correlation with higher age. The cerebellum was the region driven most distinctively by activation (RF and LF), followed by the basal ganglia (RF) and the frontal cortex (LF) (see Table B.2, Annex for listing of local maxima). The occipital gyrus and precuneus were primarily deactivated in younger age, and in contrast activated with higher age (RF and LF).

Finally, a stepwise linear regression analysis provided information on the differences in magnitude across the ROIs. With all 10 ROIs as predictor variables and age as criterion variable, the regions significantly predicting age were: the cerebellum (one cluster each, for RF and LF) and the precuneus (LF). Together, they accounted for 37% of the variation ($R^2 = 0.37$, $p<.015$), with each of the three regions contributing independently to the model: 0.31 (.002), 0.24 (.008) and 0.23 (.015) – values indicate standard coefficients for the analyses on the impact of age (& significance).

Figure 16 summarizes all results for the analyses on the impact of age in detail.

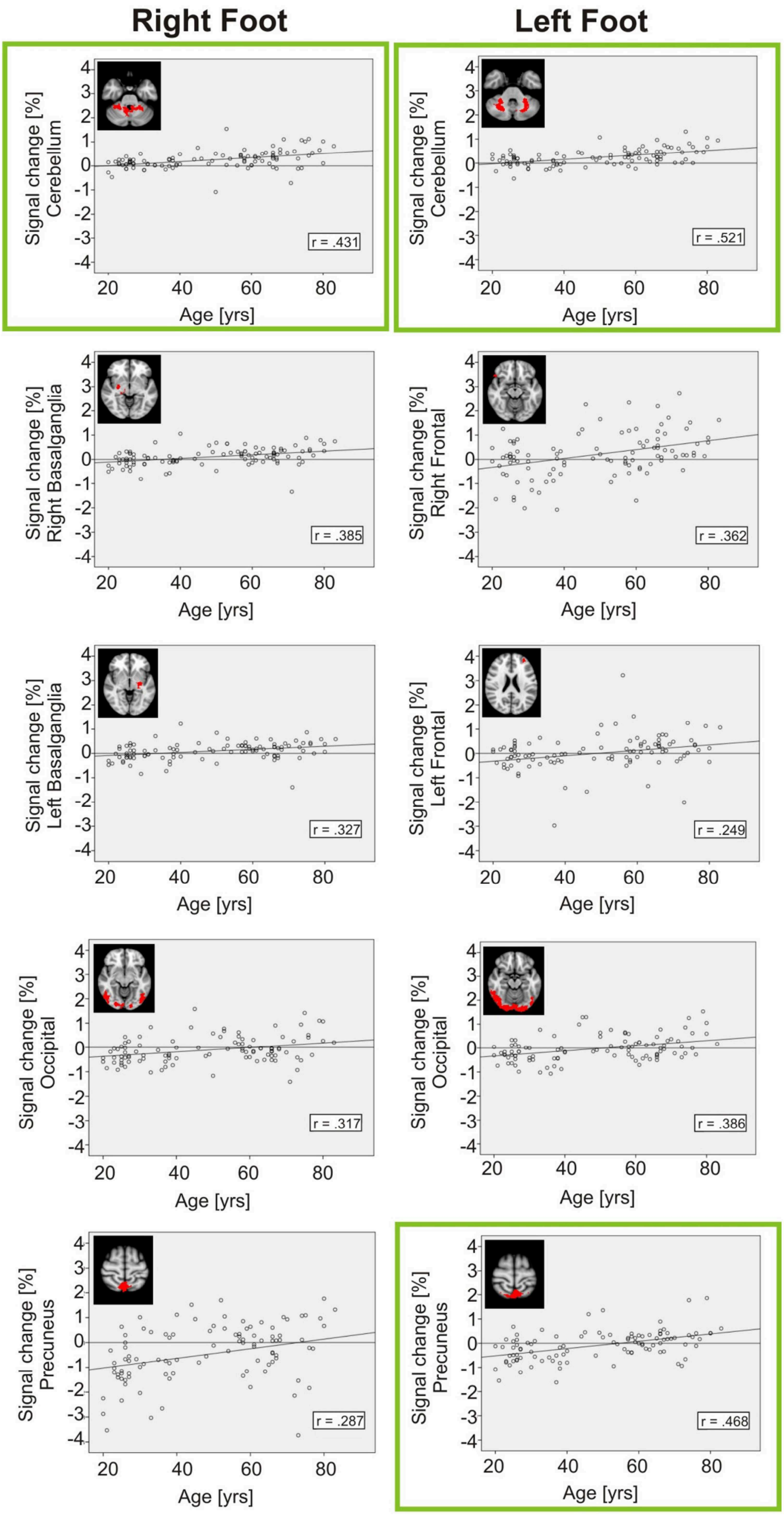
Right Foot
Left Foot
Signal change [%] Cerebellum
r = .431
Signal change [%] Cerebellum
r = .521
Signal change [%] Right Basalganglia
r = .385
Signal change [%] Right Frontal
r = .362
Signal change [%] Left Basalganglia
r = .327
Signal change [%] Left Frontal
r = .249
Signal change [%] Occipital
r = .317
Signal change [%] Occipital
r = .386
Signal change [%] Precuneus
r = .287
Signal change [%] Precuneus
r = .468
4
3
2
1
0
-1
-2
-3
-4
20
40
60
80
Age [yrs]

Figure 16. Based on the pre-defined ROIs (see text for more details), we performed correlation analyses of the respective regions with age; separately for the RF (column on left) and LF (column on right). In each subfigure (different ROI cluster), the median signal change (in percent) is plotted along the y-axis, whereas age (in years) is plotted along the x-axis. Further, each subfigure contains a regression line, the zero-axis, median (md) and correlation value (r). Figures are ranked according to (de)activation (median value), starting top-down with the most prominent activated structures uppermost. The three structures most strongly predicting age (as revealed by stepwise linear regression analysis), are highlighted in green.

3.2 WMH and (Sub)cortical Microstructure

3.2.1 Group Comparison

First, we were interested in potential within-group differences, based on the extent of WMH. As already described in the methods chapter of this study (subchapter 2.3), study participants were grouped according to WMH grades and compared regarding sociodemography, behavioural data and brain morphology.

As for sociodemographical data, the mean age of the participants was $M = 71.83 \pm 8.18$ years. Participants with more severe WMH were significantly older than people with less severe WMH (WMH grades 0+1, respectively; $M= 68.46\pm8.85$ years; WMH grades 2+3 respectively; $M = 74.14\pm6.90$ years), $t(57) = -2.769$, $p = .008$. In line with that, the older the participants were, the higher the white matter lesion load was, $r(58) = .503$, $p < .001$.

Data analysis on lower limb function showed that participants with WMH grades 2+3 performed significantly worse than participants with WMH grades 0+1, as assessed by the three parameters SPPB performance, single leg stance time and gait velocity. According to Baezner et al. (2008), an SPPB score ≤10 points, a single leg stance time <15 seconds and a gait velocity <1.2 m/seconds are considered pathologic. The achieved SPPB score was below a value of 10 irrespective of WMH grade, i.e. in both WMH groups. Additionally, correlation analysis showed that a worse performance in the SPPB was correlated with higher white matter lesion load, *r*(58) = -0.408, p = .001. For single leg stance time and gait velocity, however, only participants with WMH 2+3 showed pathological values.

Regarding cognitive function, participants with WMH grades 2+3 were characterized by worse frontal executive function (WCST) and impaired mental abilities (memory, attention and language; MMSE).

In morphological MRI analyses we observed significantly higher global white matter lesion load and lower whole brain- and grey matter volume in participants with WMH grades 2+3 compared to participants with WMH grades 0+1. After age correction, only differences in WMH lesion load remained significant.

See Tables 2-5 of the methods section (description of the study cohort) for detailed values.

3.2.2 VBM Analyses

VBM comparisons were done using various group- and correlation analyses. Given the reported results of between-group age differences, all subsequent analyses were corrected for age (adding age as a covariate of no interest to the models).

First, we tested for potential WMH group-related differences in regional grey matter areas. Participants with WMH grades 2+3 showed less right hemispheric grey matter volume in the middle- and inferior temporal gyrus, the middle frontal gyrus, the precentral gyrus, the fusiform gyrus, and the posterior part of the cingulum (precuneus) than participants with WMH grades 0+1 (see also Figure 17 and Table B.4, Annex). The opposite contrast revealed no significant results.

Next, we investigated whether WM lesion load correlated with GM volume. The higher the WM lesion load was, the increased grey matter volume was found in the paracentral lobule, precuneus, and cuneus of the left hemisphere. The reverse (negative) correlation showed lower WM lesion load to be paralleled by increased GM volume in most cortical areas. See also Figure 18 and Table B.4 of the annex for details.

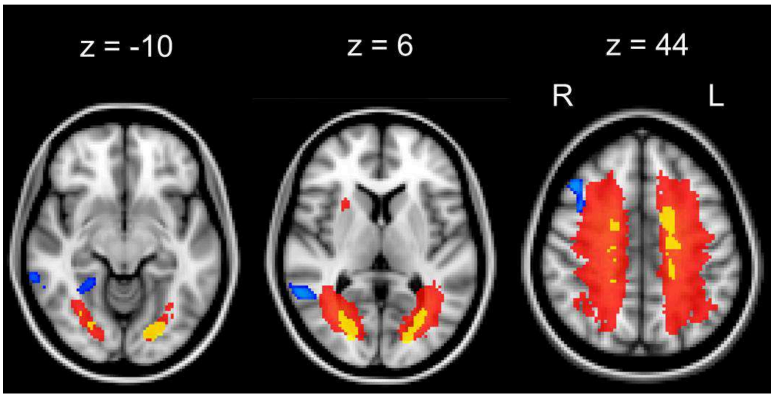

Figure 17. Blue colour: Areas associated with reduced grey matter volume for people with pronounced WMH compared to people with minor WMH (WMH 2+3 < WMH 0+1) (Axial view with z- coordinates, selected slices; corrected for age). Yellow-red colour: Lesion Probability Maps. The image is shown in radiological convention where the left side represents the right side of the brain and vice versa.

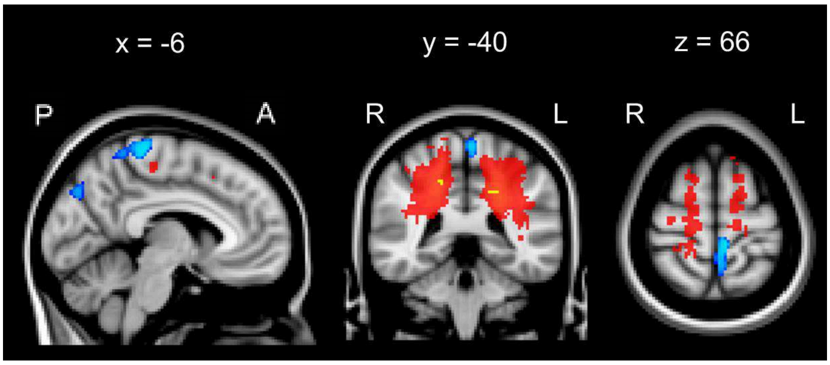

Figure 18. Blue colour: Positive correlation of WM lesion load and GM volume in particular brain areas as found in whole brain analysis (corrected for age). The higher the lesion load, the higher the grey matter volume was in the paracentral lobule, precuneus, and the cuneus. Yellow-red colour: Lesion Probability Maps of WMH. The image is shown in sagittal, coronal and axial view (x, y, z- coordinates). Key: A, anterior part; L, left hemisphere; P, posterior part, R, right hemisphere

Thresholded lesion distribution maps showed that 10% of participants had lesions proximal to the left and right lateral ventricles and in the anterior part of the right putamen. Additionally, the whole centrum semiovale was occupied by lesions in 10% of this group.

Finally, GM volume was correlated separately with three behavioural scores, the motor-related (between-group significantly different) SPPB score and the cognitive-related (between-group significantly different) WCST and MMSE scores. The worse the motor performance was, the less grey matter volume was found in the precentral gyrus, the middle- and superior temporal gyrus, the superior parietal lobule and the occipital cortex (see also Figure 19 and Table B.4, Annex). The reverse correlation showed no significant results. Neither positive- nor negative correlations of cognitive function and GM volume reached statistical significance.

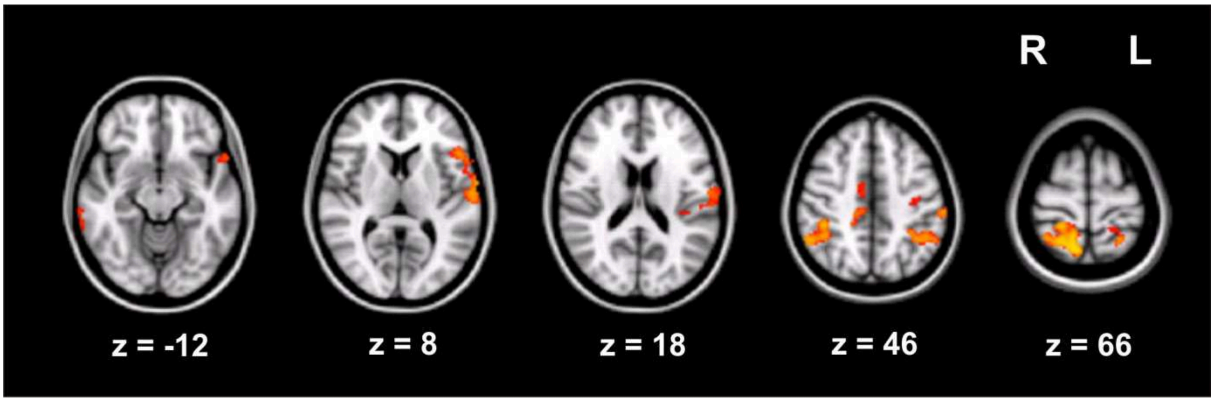

Figure 19. Correlation of the SPPB score and GM volume as defined by whole brain analysis (corrected for age). The better the motor performance, the higher grey matter volume was in the precentral gyrus, the middle- and superior temporal gyrus, the superior parietal lobule and the occipital cortex. The image is shown in radiological convention, where the right side represents the left side of the brain and vice versa. Key: L, left hemisphere; R, right hemisphere

3.3 fMRI “Walking” Paradigm Development

3.3.1 Mean Group Activation

In a first step, fMRI mean group activations were calculated. This was done separately for the six paradigm conditions, i.e. activation maps for active performance of right, left and bipedal ankle movements, as well as movement observation, movement observation and execution and movement imagination vs. rest, respectively.

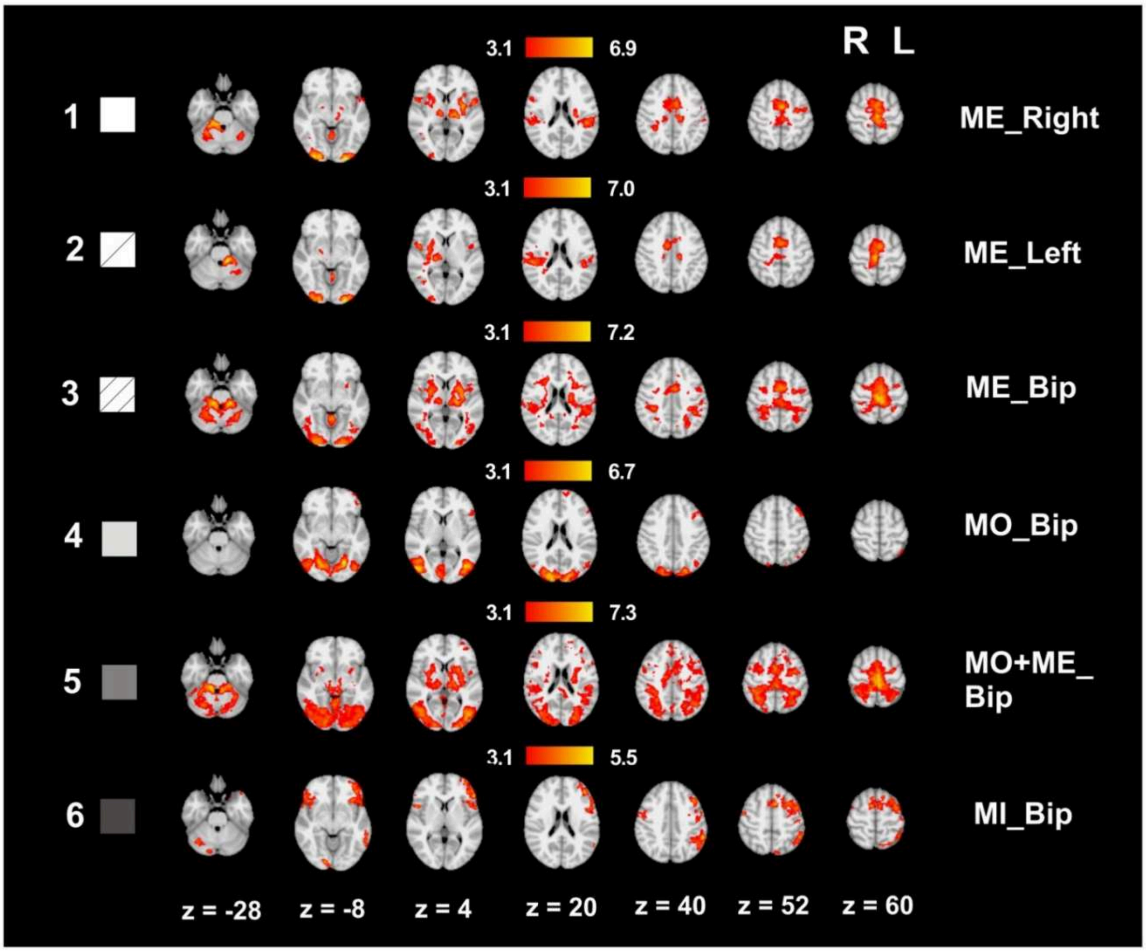

Figure 20. Mean activation maps for all six conditions of the newly developed fMRI motor paradigm (all subjects, Z > 3.1, p = 0.01). The coding refers to three exclusive motor execution conditions (1. ME_Right, unilateral right foot movements; 2. ME_Left, unilateral left foot movements; 3. ME_Bip, bilateral foot movements), two motor observation conditions (4. MO_Bip, observation of bilateral foot movements; 5. MO+ME_Bip, observation and execution of bilateral foot movements), and one motor imagery condition (6. MI_Bip, imagination of bilateral foot movements).

Using FSL FEAT analysis, contrasts of unilateral right foot movements (1. ME_Right), left foot movements (2. ME_Left) and bipedal movements (3. ME_Bip) showed significant brain activation in the primary and secondary sensorimotor areas, the SMA, the basal ganglia, the cerebellum and also the occipital cortex. Regarding lateralization, unilateral active right and left foot movements revealed contralateral signal alterations in the primary motor cortex, bilateral activation for the SMA, sensorimotor cortices and basal ganglia, and ipsilateral cerebellar activation.

Motor observation of the previously performed bipedal movements (4. MO_Bip) activated the occipital and frontal cortex. The combined condition of bipedal motor execution and observation (5. MO+ME_Bip) showed increased signal amplitude in the primary and secondary sensorimotor areas, the SMA, basal ganglia and cerebellum, and additionally occipital and frontal cortices.

For motor imagery of bipedal movements (6. MI_Bip), we found clusters of activation in the postcentral, supramarginal and temporal gyri, as well as in frontal, lingual and cerebellar regions.

See Figure 20 and Table B.5 (Annex)

3.3.2 Sex-specific Analyses

Next, we investigated potential differences in sex, i.e. contrasts for men vs. female and vice versa were computed for all six fMRI motor paradigm conditions.

In three of the six conditions, men compared to female participants showed increased activation in several task-associated regions. These areas included the middle occipital gyrus for the active left ankle movements (2. ME_Left) and the precuneus for bipedal ankle movement execution and observation (5. MO+ME_Bip). For imagination of bipedal movements (6. MI_Bip) differences were found for the superior and middle occipital gyri, the fusiform gyrus, the inferior frontal gyrus, the lingual gyrus, the inferior parietal gyrus and the precentral gyrus.

Women compared to male participants, had increased activation in the inferior frontal gyrus for the active left ankle movements (2. ME_Left), the superior temporal gyrus and the cerebellum for bipedal ankle movements (3. ME_Bip), and the middle temporal gyurs for combined movement observation and execution (5. MO+ME_Bip).

See Figure 21 and Table B.6 (Annex) for mean group activations and contrasts.

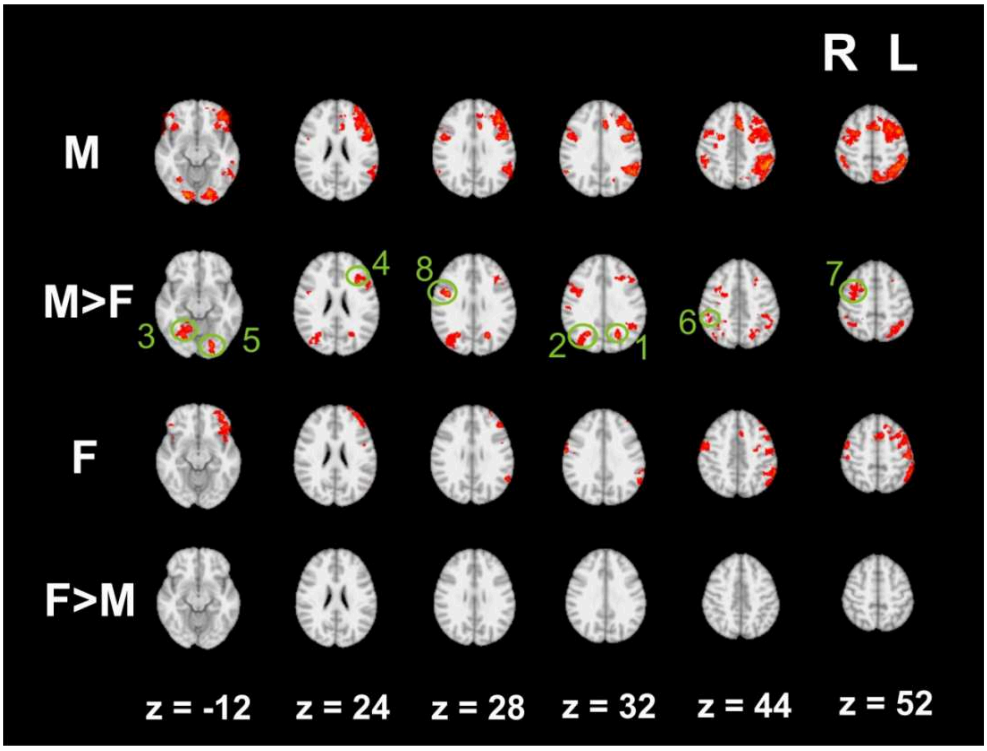

Figure 21. Movement imagery condition (6. MI_Bip); mean activation maps (M, F) and contrasts (M>F, F>M) ($Z > 2.3$, $p = 0.05$). Key: L, left hemisphere; R, right hemisphere; F, female, M, male; 1, Superior occipital gyrus; 2, Middle occipital gyrus; 3, Fusiform gyrus; 4, Inferior frontal gyrus, pars triangularis; 5, Lingual gyrus; 6, Inferior parietal gyrus; 7, Precentral gyrus; 8, Precentral gyrus; L

Chapter 4

Discussion

This last chapter concentrates on the discussion of the gained results and their associated implications. Being divided in two subchapters, the first subchapter separately summarizes and discusses the results of the three different studies. Also chosen further analyses are outlined. Novel aspects are mentioned as well as critical comments on limitations and suggestions for prospective studies. Each study-specific discussion closes with a short summary and conclusion. Subchapter two finally forges a bridge and summarizes the PhD project in general, study-overlapping terms.

4.1 Study-specific Discussion

4.1.1 Age and fMRI Ankle Movements[5]

4.1.1.1 Discussion of Results

Analyzing a large fMRI data set from 102 healthy adults, we here characterized the functional representations of unilateral dominant and non-dominant ankle movements, focusing on the aspect of age. For the first time in a large population, we identified several brain areas with robustly increased activity with aging in clinically asymptomatic healthy participants. Our study provides evidence of age-related increases in brain activity in the cerebellum, precuneus, and occipital cortex, as well as basal ganglia (dominant right foot,

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[5] Corresponding to the „Discussion“ section of Linortner et al. (2014).

RF, only) and precuneal (non-dominant left foot, LF, only) during simple repetitive separate right and left ankle dorsiflexion movements.

We also performed ROI analyses for these areas and created scatter plots of age versus median signal change within these clusters (see Figure 16) to distinguish activation from deactivation. In general, clusters showed a similar pattern with higher activation with increasing age. Exceptions were most clear in the precuneus and occipital gyrus, which appeared to be deactivated relative to rest with younger and activated with older age. Stepwise regression analyses revealed that activation in three regions significantly predicted age, accounting for 37% of the variation: One cluster each in the cerebellum for left and right foot movements and one cluster in the precuneus for left foot movement.

Age, Gait & Cerebellum

The increased cerebellar activation with age is of particular interest as the cerebellum represented the structure with the highest correlation coefficient and an independent prediction of age was also confirmed by formal statistics analyzing the differences among the ROIs. It is widely accepted that the cerebellum acquires and stores internal models of the motor apparatus that are critical for feed forward control and complex coordinated movements (Ebner and Pasalar, 2008). The cerebellum also is involved in the amplification and refinement of motor commands initiated and regulated by the complementary basal ganglia after descending from the motor cortex (Tunik et al., 2009). It also contributes to a great extent to postural and equilibrium control (Ioffe et al., 2007) and plays a key role in motor skill learning (Matsumura et al., 2004; Timmann et al., 2010).

The cerebellum demonstrates clear somatotopic organization and distinct loci of activation have been defined in the anterior lobe for distal and proximal segments of the upper limb (elbow and hand; Grodd et al., 2001) and different segments of the leg (toes, ankle, and knee; Kapreli et al., 2007), suggesting 4 different “homuncular” control regions (Mottolese et al., 2013). In our study, lobules IV-VI, VIII-IX, and crus I were activated with dominant foot movement and higher age, while non-dominant foot movement activated lobules III, VI and crus I. The lobules IV-V are believed to be connected with the sensorimotor cortices. In contrast, crus I has demonstrated functional connectivity with prefrontal and posterior-parietal cortices, possibly relating to the additional frontal activity observed with higher age for LF movements (Mottolese et al., 2013).

Crus I thus is not directly involved in motor or sensory processing but instead appears engaged in cognitive functions (O'Reilly et al., 2010). It is thus tempting to interpret the higher cerebellar activity as a compensatory response to covert age-related declines in sensorimotor network functions for the control of lower limb movement that lead to a higher cognitive demand for non-dominant ankle movements with increasing age.

Age, Gait & Precuneus

The precuneus has been implicated in higher-order cognitive processes such as episodic memory, motor imagery, and spatial aspects of motor behavior control (Cavanna and Trimble, 2006; Grefkes et al., 2004). Precuneus activation has often been reported in functional imaging studies involving the execution (Kawashima et al., 1995) or preparation (Astafiev et al., 2003) of spatially guided behaviors such as goal-directed hand movements like pointing or reaching. Wenderoth et al. (2005) observed precuneus activation with execution of spatially complex bimanual coordination tasks compared with uni-manual subtasks. Reaction time studies suggested involvement in movement control with reference to buffered memory (precuneus activation with reaction time reduction; Oishi et al., 2005).

Another interesting point relates to the fact that the precuneus and occipital gyri belong to structures that become increasingly activated primarily with higher age but are deactivated relative to rest at younger ages. This suggests that simple ankle dorsiflexion movements demand additional compensatory activation of cortico-cerebellar areas with aging, just as is found for more complex and cognitive demanding manual tasks and fine motor skills. Further, the precuneus and surrounding posterior-medial areas are among the brain structures displaying the highest resting metabolic rates, with their tonic activity decreasing transiently during engagement in none self-referential goal-directed actions (Cavanna and Trimble, 2006).

These new findings of age effects for ankle movements generally appear to be in line with findings from other functional imaging studies that have shown that older compared with younger adults activate widespread additional brain networks during performance of (simple) motor tasks (Bernard and Seidler, 2012; Van Impe et al., 2009;Ward, 2006). The increase in the spatial extent of activation with age may reflect decreased distinctiveness of motor representations at older age, or, alternatively, indicate a compensation for age-related subtle declines in cognitive or sensory function (Carp et al., 2011; Heuninckx et al., 2008; Noble et al., 2011; Park and Reuter-Lorenz, 2009). In contrast, neural activation following varying task complexity or body side seems to be independent of age (Van Impe et al., 2009).

FSL FEAT vs GingerALE

To further confirm the robustness of our findings we applied and obtained findings obtained with two different analytical approaches (FSL FEAT and GingerALE).

For both feet, the FSL FEAT analysis showed expected activation in the primary and secondary motor cortices (bilateral with contralateral peak), the bilateral supplementary motor area and basal ganglia, the ipsilateral cerebellum and the contralateral occipital cortex. This pattern is in line with previous studies and emphasizes more bilateral activity (with a lateralized activation peak in most brain regions) associated with lower ankle dorsiflexion compared with the more asymmetrical, lateralized upper limb movements (Enzinger et al., 2009; Huda et al., 2008; Kapreli et al., 2006; Luft et al., 2002; MacIntosh et al., 2004; Zheng et al., 2007). The fact that the cerebellar activation associated with lower limb movement extended to the brainstem (pedunculopontine nucleus) further supports the idea that brain activity related to simple foot movements overlaps with the locomotor network.

The GingerALE analysis also identified significant adjusted activation clusters in the primary sensorimotor cortex (contralateral peak) and the cerebellum (anterior part/lobule VIII, both ipsilateral), for both dominant right- and non-dominant left foot movements. In addition, movement of the dominant foot activated the medial frontal gyrus; movement of the non-dominant foot the secondary somatosensory cortex and the superior temporal gyrus. Generally, ALE meta-analysis facilitates the estimation of consistency across multiple published brain imaging findings, thus presenting a way of assessing spatial reproducibility (Eickhoff et al., 2009; Turkeltaub et al., 2012). Such data pooling allows usage of already existing but statistically frequently underpowered neuroimaging studies to reduce small sample size effects, the variability in the labeling of brain regions, and possible center specific effects such as bias of scanner, image acquisition, and time point (Costafreda, 2009). Following this approach, each activation focus of our five studies was modeled as the peak of a 3D Gaussian probability distribution. The weighted average then allowed estimation of the true effect size as opposed to a less precise effect size derived from a single study under a given single set of assumptions and conditions.

Using FSL FEAT for fMRI data analysis (including the factor “study” or “scanner” as regressor of no interest), for active movement of both feet, larger activation of primary and secondary motor cortices was found than for the basal ganglia and the cerebellum. However, the reverse was seen using ALE meta-analysis, that is, clusters were more prominent for the cerebellum and basal ganglia than for cortical motor areas.

4.1.1.2 Further Analyses

Laterality Analyses

We also tested for potential laterality effects, i.e. dominant vs. non-dominant foot movement, with age. Studies on upper limb movements showed the dominant hand to exhibit large contralateral and small ipsilateral cerebral activation; in contrast, non-dominant hand movement resulted in a stronger bilateral activation pattern (Gut et al., 2007; Dassonville et al., 1997). These findings, esp. ipsilateral recruitment, are reinforced with task complexity (Verstynen & Ivry, 2011; Gut et al., 2007; Verstynen et al., 2005) and suggest inter-hemispheric interaction mechanisms (Newton et al., 2005).

Laterality analysis followed three steps. At single-subject level: 1. Flipping of FSL FEAT first-level left active ankle movement vs. rest imaging data by midline from left to right (LF-F) (flipping performed in standard space). 2. Contrast analysis, computing right foot movement vs. rest minus flipped left foot movement vs. rest (RF > LF-F) and flipped left foot movement vs. rest minus right foot movement vs. rest (LF-F > RF). At group-level: 3. Higher level mean group analysis (Mixed effects analysis, FLAME 1+2, $Z > 3.1$, $p = 0.01$) for the contrasts RF > LF-F and LF-F > R (controlling for a possible “study” or “scanner” effect). Step three was performed with and without age-correction (age as covariate of (no) interest, based on the results of 3.1.2).

Without age-correction, dominant compared to non-dominant foot movement (RF>LF-F) showed increased activation in SMA and secondary somatosensory cortex (ipsilateral), as well as precuneus (contralateral). The opposite contrast (LF-F>RF) revealed significant activation in the cerebellum, inferior parietal and occipital gyri (all contralateral) (Figure A.2). However, no significant laterality effects were found over and above age (adding age as covariate of interest to the GLM; correlation analyses). Since the laterality effects diminished when controlling for age and we also cannot claim anything about "foot dominance" per se (see 4.1.1.4 Limitations), we refrain from a thorough discussion on this aspect.

Lateralization

In this study, the term *laterality* refers to brain activation differences based on dominant vs. non-dominant foot movements. *Lateralization*, in turn, describes the hemispheric activation pattern (ipsilateral, contralateral, bilaterally) associated with these foot movements.

Studies on (upper limb) motor tasks showed contralateral activation in premotor areas in healthy subjects (La Pointe et al., 2009). With age and in patients these pattern seem to become more symmetric (bilateral); (Altamura, 2012; Malandraki et al., 2010). This tendency has been attributed to less efficient transcallosal connections with age (Naccarato et al., 2006). Studying the activation pattern in response to lower limb movements in healthy controls and using a big sample approach, allows the study of deviations from normal.

So, we here additionally to laterality report on the lateralization of activated cluster regions (see Table B.3 for illustration of mean group activations, information on whole cohort). Using FSL FEAT analysis, RF and LF showed a similar activation pattern for the key motor areas. For both feet these regions included the bilateral SMA, primary motor- and secondary somatosensory cortex (with contralateral peak), the contralateral primary somatosensory cortex and basal ganglia, and the ipsilateral cerebellum. LF movement showed additional ipsilateral basal ganglia recruitment and contralateral cerebellar activation.

4.1.1.3 Novel Aspects

This study provides the hitherto largest analysis of participants following the same experimental fMRI protocol for ankle movements. Age-related differences in movement representation have been reported as part of reviews or with small sample sizes, with a stronger, more widespread and bilateral cortical lower limb movement control (Holtzer et al., 2014; Hutchinson et al., 2002). The ankle movement-age effect observed within the framework of this work is even reinforced (i.e. must be stronger), since the BOLD signal itself changes with age as reflected by a decrease of signal amplitude and a change in the hemodynamic time course (Richter & Richter, 2003; Ryan et al., 2001).

Further, meta-analyses help extracting relevant, stable findings. By definition, meta-analyses are systematic reviews that follow certain criteria and pool plus analyze results quantitatively (Walker et al., 2003). Within this study we used GingerALE meta-analysis as secondary analysis approach in addition to FSL FEAT analysis. Latter one was possible due to data availability and by controlling for possible centre- (different scanner) and study (settings) effects, respectively. This allowed a critical comparison of FSL FEAT and GingerALE meta-analysis.

4.1.1.4 Limitations & Future Studies

Foot dominance was assessed as a subcategory of the Edinburgh Handedness Inventory (Oldfield, 1971) while more elaborated inventories on leg dominance are available (Chapman et al., 1986, Schneiders et al., 2010) and discrepancies between hand and foot dominance have occasionally been reported (Spry et al., 1993). Given that only right-footed people were tested, we hence cannot claim anything about “foot dominance” per se. Future work might also wish to examine possible age effects in left-footed participants (Rocca and Filippi, 2010).

Also, a more refined assessment of particular "foot abilities" (such as dancing, playing football, etc.) would have enabled more detailed analyses. Furthermore, as this was not the primary goal of our study, we did not subject participants to refined walking testing which might have revealed subtle preclinical behavioral changes and would have allowed for correlation analyses of variation in these parameters with functional cerebral activation.

In addition, while we excluded participants with severe neurologic or other severe medical conditions, we did not assess age-related medical conditions like well-treated arterial hypertension, obesity, and controlled diabetes. We thus also could not assess the potential effect of these factors on brain functional changes. Further, there is evidence that WMH severity and extent increase with age (Enzinger et al., 2007) and own previous work suggested WMH severity to have an effect on functional activation associated with foot movements (Linortner et al., 2012). However, the aims of the different studies from which the fMRI data have been aggregated were different and scanning protocols therefore did not all include T2-weighted and/or fluid-attenuated inversion recovery sequences needed for WMH analyses in all occasions. We therefore were not able to test the effect of WMH. This limitation of our study should be specifically addressed in future studies.

And finally, when comparing the findings obtained by the two analytical approaches, it needs to be considered that the meta-analytical approach showed relatively lower confidence, most likely because of the overall comparatively small number of individual studies used and their heterogeneity.

4.1.1.5 Summary and Conclusion

In summary, this study highlights increased BOLD-response to be associated with lower limb movements with increasing age and suggests a brain compensatory response to age-related deficits in sensorimotor control of the distal lower limb. Defining the underlying age-related deficits should contribute to a better understanding of factors contributing to impairments of gait with aging. This evidence for a role for compensatory responses provides a framework for understanding pathologic gait changes in the context of diffuse brain vascular or degenerative changes and specific functional systems to target with novel gait and balance training interventions.

4.1.2 WMH and (Sub)cortical Microstructure

4.1.2.1 Discussion of Results

The main purpose of this study was to investigate the impact of white matter hyperintensities (WMH) on grey matter (GM) volume and relate these findings to lesion location. Based on the phenotypical differences of WMH, this in first instance was done by comparing two groups of individuals with WMH, i.e. people without or with punctate WMH (grades 0+1) vs. people with early-confluent and confluent WMH (grades 2+3) (grading according to the Fazekas' Scale; Fazekas et al., 1987). Early confluent and confluent WMH are considered more severe than punctate WMH, showing higher rates of progression (Schmidt et al., 2003), clinical correlates such as gait disturbances (Baezner et al., 2008) or cognition (Van der Flier et al., 2005), and are neuropathologically attributed an ischemic origin with tissue damage in form of perivascular myelin rarefication, loss of fibres and gliosis (Schmidt et al., 2011). In contrast, punctuate WMH are attributed a non-ischemic origin, showing widening of periarteriolar spaces (Fazekas et al., 1991) that is accompanied by reduced myelination with atrophy of the neuropil around fibrohyalinotic arteries (Schmidt et al., 2011). In our study, people with pronounced WMH (grades 2+3) showed reduced grey matter volume in several motor, cognitive and visual areas compared to people without or with minor WMH (grades 0+1). Interestingly, also correlation analysis on walking parameters in individuals with WMH and GM volume, showed reduced grey matter volume in motor, cognitive, auditory and visual areas correlating with worse behavioural gait performance. Given the proximity of pronounced WMH to the cortico-spinal tract, one might speculate an inter-linkage of these parameters. An alternative approach of using lesion load as continuous variable instead of dichotomized grouping, showed grey matter volume increases in motor-related areas with increase of WMH lesion load volume.

GM volume differences depending on walking abilities (and cognition)

On a behavioural level, participants with more severe WMH also showed worse performance in lower limb- and frontal executive functioning (in line with Baezner et al., 2008; Schmidt et al., 2007). Correlation analysis for the whole cohort showed the worse the lower limb function (SPPB), the less GM volume in motor, cognitive, and visual areas was. Here, the largest cluster constituted the bilateral superior- and inferior parietal gyri. While the superior parietal gyrus is responsible for visual-spatial perception and imagination of movements within room and space (Lambrey et al., 2011; Galletti & Fattori, 2002), the inferior parietal gyrus is associated with higher cognitive motor function and movement understanding (Pelgrims et al., 2009). The next cluster, the superior temporal gyrus, has been attributed to movement imitation and the human mirror neuron system (Mengotti et al., 2012; Aziz-Zadeh et al., 2006). The adjoining middle temporal gyrus is involved in motion processing (Joukes et al., 2014; Pitzalis et al., 2010), with single motion-directions coding for single space-regions (Richert et al., 2013). Finally, the precentral gyrus triggers actual movement execution (via possible projection fibers to SMA and cingulate gyrus; cluster < 100 voxel) (Wang et al., 2008). The negative correlation showed no significant results, i.e. worse lower limb function was not associated with higher GM volume. Also, neither positive nor negative correlation analyses with cognitive tests scores (MMSE/WCST) revealed significant results. The results may indicate a stronger connection of WMH, GM volume and gait, than with cognition. Since WMH occur increasingly with higher age (cf. also Pantoni et al., 2010), WMH were considered implicitly as part of the age-corrections (double correction otherwise).

GM volume differences depending on WMH severity - Group comparison

On VBM group analysis, people with pronounced WMH (grades 2+3) showed less GM volume in motor, cognitive and visual areas than people with absent or minor WMH (grades 0+1). The largest cluster here involved the middle- and inferior temporal gyri, regions that have been associated with cognitive function (Scarabino et al., 2005). Atrophy in the temporal lobe is associated with cognitive impairment and memory deficits; and this brain atrophy precipitates cognitive decline in cerebral SVD (Jokinen et al., 2012, Jokinen et al., 2004; Mungas et al., 2001). The second largest cluster involved motor- and cognition-associated regions (Scarabino et al., 2005), i.e. the precentral gyrus for motor execution and the middle- and inferior frontal gyri for action understanding. Here, task difficulty of action understanding modulates the interplay between temporal- and frontal areas (Lingnau & Petris, 2013). Next, GM volume decreases were found in the cingulum and precuneus. The cingulum is involved in enhanced attention (Parks & Madden, 2013; Singer et al., 2004); more precisely, the posterior cingulate cortex is responsible for recognition of familiar objects and places (Sugiura et al., 2005) and, because of its location, is the main connectivity hub for cognitive brain networks (tractography study by Kantarci et al., 2011). The next significant region, the precuneus, serves as substrate for higher-order cognitive motor processes, such as motor imagery and spatial motor control (Cavanna and Trimble, 2006; Grefkes et al., 2004). It also mediates visuo-motor transformations and is part of the default mode network (Dohle et al., 2011). GM volume decreases were also found in the visual fusiform gyrus, a region responsible for the recognition of body parts (Peelen & Downing, 2005). However, the number of voxels here was relatively small. Under the aspect of additional age correction and lesion location filtering-in, the observed results seem plausible and are in line with previous studies. The proximity of WMH to the cortico-spinal tract might account for the GM volume decreases in motor regions (cf. Rossi et al., 2006). In cognitive areas, disruption and disconnection of fronto-cortical networks (deafferentiation processes) might have led to the decrease (Wen et al., 2006). The small visual impact can be explained by worse visual acuity in older age and associated neuron loss (Devany & Johnson, 1980).

GM volume differences depending on WMH severity – Lesion load

Regional GM volume decline in people with WMH and SVD has already been studied and reported (e.g. Wen et al., 2006; Rossi et al., 2006) and linked to gait- (Hoffstaedter et al., 2015; de Laat et al., 2012) and cognitive decline (Mok et al., 2012; Marshall et al., 2006). As an unexpected finding, increase in WM lesion volume across the whole group correlated significantly with increase in GM volume in primary motor areas and the precuneus (functions as mediator for visuo-motor transformations; Dohle et al.; 2011). This paradoxical positive relationship between WM lesion volume and cortical GM “volume” in motor areas might be due to compensatory cellular hypertrophy (water endosmosis) rather than actual volume or density increases (i.e. GM neurogenesis) (Reid et al., 2010). The malfunctioning compensation mechanism-attempt is even more suggested, since people with higher WM lesion load also showed worse behavioural gait performance. Correspondingly, the reverse negative contrast showed most brain regions to be associated with more GM volume in response to absent or minor WMH. So, one might better phrase “more GM voxel” rather than GM volume, density or thickness “increases” in this context.

4.1.2.2 Novel Aspects

Higher age has been reported to be paralleled by loss of brain volume and white matter integrity, in healthy people (Sexton et al., 2014; Tseng et al., 2013; Fjell et al., 2009) and people with WMH (Bhadelia et al., 2009; Schmidt et al, 2005). In healthy people, cerebellar thinning (Salat et al., 2004), ventricular expansion and cortical reductions, esp. in regions of temporal and prefrontal cortices (Fjell et al., 2009), account for these volumetric reductions. In people with WMH, white matter integrity in the genu of the corpus callosum is considered an important marker of gait in elderly (Bhadelia et al., 2009). In line with these reports, in our study higher age was paralleled by decrease in brain volume which is why all analyses were corrected for age. Further, since WMH can cause a confounding effect on the brain segmentation phase of the VBM analysis (i.e. misclassification of grey matter segmentation), individual lesion masks were created and applied to the VBM protocol (Brett et al., 2001). Another novel aspect concerned the correlation analyses with variables affected by WMH (i.e. gait and cognition) to test which voxel groups were independently associated with these parameters. Srikanth et al. (2010) identified worse gait to be associated with WMH in frontal and periventricular regions. Further analyses should be done to evaluate WMH lesions in terms of location and quantity, and test the hypothesis if lesions with proximity to the pyramidal tracts are related to behavioural disturbances.

Finally, this study provided useful information for study 3 of the PhD project, the fMRI motor paradigm development with prospect of testing in individuals with WMH. The decreased regional GM volume in WMH not only affected motor areas, but also regions associated with cognition and visual perception. Thus, motor imagery and motor observation tasks might add additional value to an fMRI motor paradigm, esp. when used for the evaluation of training studies in WMH people.

4.1.2.3 Limitations

Unfortunately our data set did not allow the multimodal approach of testing individuals with WMH in terms of volumetric changes in regional grey matter (VBM) combined with information on microstructural integrity (DTI). This information would have been useful to test for a speculated disconnection of motor-network pathways (cf. Srikanth et al., 2010). Also, longitudinal data on potential regional grey matter volume loss would have been interesting, in order to evaluate which of the found regions is most affected by WMH. With our research we hope to stimulate further research in this area.

Another critical aspect concerns the ambiguously used terms “grey matter volume”, “grey matter density”, “grey matter concentration” and “grey matter thickness” for VBM analyses of the brain. VBM quantifies the amount of grey matter in voxel, hence reports on mesoscopic grey matter volume (changes) (Draganski et al., 2011). However, depending on definition, “grey matter volume” does also describe the amount of grey matter, the lies between the grey-white interface and the pia mater (Winkler et al., 2010). Similar to “grey matter density”, the original term “grey matter concentration” (Ashburner & Friston; 2000) implies changes in the underlying cytoarchitecture. The VBM technique however does not allow disclosure about neurobiological changes or its bases; increases could reflect swollen glia (support function) instead of increased cell size or synaptogenesis (Schmidt-Wilcke et al., 2007). Last, “grey matter thickness” is misleading since with VBM, voxel-by-voxel comparisons are computed and no quantification of tissue thickness such as with FreeSurfer (Fjell et al., 2009).

Finally, we here used a combination of WMH visual severity rating (Fazekas’ Scale, Fazekas et al., 1987) and semi-automated quantity objectification. Qualitative vs. quantitative WMH rating is depending mostly on the research question and purpose of study. In longitudinal studies quantitative measurements are preferred to qualitative measurements (Van den Heuvel et al., 2006). Cross-sectionally however, the Fazekas’ Scale achieves better inter-rater reliability values than other scales (Kapeller et al., 2003). Arbitrary chosen intensity values in computer-based, semi-automated manual outlining may impact the results (triggering WMH number and size). Likewise, higher magnetic field strength leads to an increase in WMH detection (Perri et al., 2013). These aspects have to be considered in the interpretation of WMH study results. The more detailed the rating needs to be (WMH severity level and spatial distribution vs. WMH number and volume), the more adequate a combination of visual- and volumetric measurement appears to be.

4.1.2.4 Future Studies

Studies continuing on this topic might wish to investigate WMH multi-dimensionally. This could be done by looking at microstructural white matter integrity (DTI, TBSS), grey matter volume (or density, VBM), and crosslink the results to elastography measures (magnetic resonance elastography, MRE; Wuerfel et al., 2010) and perfusion data (i.e. total cerebral blood flow, see Van Es et al., 2010). Waveguide elastography (WGE) thereby combines DTI, MRE and anisotropic inversions (for determination of WM elastic properties, Romano et al., 2014). While former techniques are quite commonly used, MRE (or WGE, respectively) is restricted to single research units. The non-invasive MRE technique allows determination of viscoelastic properties of different brain structures and tissues (Green et al., 2008). Here, the cerebellum is physically less stiff than the cerebrum (Zhang et al., 2011), and white matter is more elastic than grey matter (with WM > Corpus Callosum > Caudate Nucleus > Thalamus; Guo et al., 2013; Kruse et al., 2008). In healthy people, atrophy and age cause regional elasticity declines, with softening especially in frontal regions (Arani et al., 2015; Sack et al., 2011); Alzheimer patients show a decreased whole brain stiffness (Wang et al., 2013; Murphy et al., 2011). Magnetic transfer imaging (MTI; Seiler et al., 2014, Ropele et al., 2010) in combination with MRE might aid the detection of WMH, as well as its' understanding of structural consequences (Braun et al., 2014).

4.1.2.5 Summary and Conclusion

In summary, the study shows pronounced WMH to be associated with grey matter volume changes. The results may contribute to a better understanding of the clinical and micro-structural correlates of WMH. Taking age and lesion location into account, the changes affect motor-, cognitive- and visual areas. This might be due to a speculated disruption of fronto-cortical networks within the vicinity of WMH to the corticospinal tract, which should be specifically tested in future studies using multimodal MRI. Advanced training, especially motor training, might ameliorate behavioural performance and even prolong structural grey matter changes. [See Huang et al. (2015) and Sampaio-Baptista et al (2013) for motor training effects on white and grey matter microstructure, but also Section 1.1.4 Neuroplasticity]

4.1.3 fMRI "Walking" Paradigm Development

4.1.3.1 Discussion of Results

The purpose of the last study was to further develop and implement a modified fMRI paradigm as a closer approximation to the complex walking behavior (cf. Enzinger et al., 2009; Enzinger et al., 2008), first in healthy people and later to be used in individuals with WMH such as follow-up intervention studies. Since males and females differ in behavioural gait pattern and -performance (Jiménez-Jiménez et al., 2011; Chumanov et al., 2008), we also tested for potential functional brain activation differences related to sex as an important secondary objective. Using a combined motor execution, - observation and – imagination fMRI paradigm, we were able to show plausible and robust motor activation patterns and identify sex differences, which were most strongly evident in the motor imagery condition.

Paradigm Development

We first looked at condition-specific fMRI mean group activations, to check for plausibility of activation patterns and also to compare the results to previous studies. Here, neuroimaging studies suggested that movement execution, -observation and imagination are associated with shared neural substrates, with substantial regional activation overlap across the three tasks for lower limb movements (Lorey et al., 2013; Orr et al., 2008).

Alternating bipedal movements are considered a closer approximation to gait and stepping (Jaeger et al, 2014) and thus appear especially interesting for intervention studies (Pons et al., 2013). For bipedal movements, activations were found in locotypical motor areas similar to those of unilateral ankle movements (cf. Linortner et al., 2014; Enzinger et al., 2008). In subsequent analyses, direct comparisons showed that merged unilateral right and left foot movements elicited more activation in the pre-SMA, SMA and secondary somatosensory cortex than bipedal movements. These results might reflect enhanced demand during the movement of one foot (Kim et al., 2010; Nachev et al., 2008) compared to a more automatic process like alternating bipedal movements (similar to walking). Comparing right vs. left foot movements (follow-up analyses; RF > LF and vice versa), we found laterality effects with right foot movements showing stronger activations in motor-related areas. This is line with studies on upper- (Pool et al., 2014) and lower limb movements (Huda et al., 2008), suggesting stronger connectivity in the dominant hemisphere.

Motor observation of bipedal movements activated the frontal and occipital cortices; however, no key motor areas were activated. One would expect activation in the mirror neuron system (MNS) for an observation task like this. The MNS is an observation-execution matching system thought to be activated in humans during action observation, motor learning and imitation of actions (Rocca & Filippi, 2010), in upper as well as lower limb movements (Buccino et al., 2001), and includes the premotor cortex, the inferior parietal gyrus and superior temporal sulcus (Rizzolatti & Craighero, 2004). We found BOLD signal increases in the frontal MNS, indicating a possible stimulation of the imitation system (Press et al., 2012; Iacoboni, 2005). Another explanation for the frontal activation could be its operation as inhibitory mechanism (cf. fMRI go/no-go tasks, Smith et al., 2013), coupled with a speculated suppression of activation in key motor areas as result of preceding active movement conditions in the fMRI paradigm. It remains questionable if an isolated movement observation condition adds additional value to the fMRI motor paradigm, and further research in this direction is needed.

Another question was whether movement observation would have a beneficial effect on the movement execution condition, i.e. active bipedal movements while simultaneous watching. With increase in activation in occipital areas, this condition is adequate for motor training studies. In evaluation studies, however, the condition can be left out in favour of paradigm duration.

The motor imagery condition was added to the fMRI paradigm, since motor imagery has proven useful in neurorehabilitation, such as stroke rehabilitation (Morone et al., 2015) and in spinal cord injury patients (Faller et al., 2014). In line with Orr et al. (2008) we observed activation in higher-level motor areas, such as the frontal cortex and the (pre-)SMA. This structures have been associated with successful motor imagery (Van der Meulen et al., 2014; Guillot et al., 2008), with the frontal gyri reflecting executive functioning (Sharma et al., 2006). And the (pre-)SMA reflecting an indirect pathway for the modulation of locomotion rather than actual execution, esp. when coupled with little sensorimotor activation (Nutt et al., 2011; La Fougère et al., 2010). The motor imagery condition thus seems to represent a viable tool for the assessment of ankle movement imagery ability and should remain in the fMRI paradigm.

Sex differences

As a next step, we investigated the effect of sex on the six defined fMRI conditions. To date, explicit studies on sex differences in the functional brain response with (ankle) movements are to the best of the author’s knowledge not existing or still scare, especially regarding a combined fMRI motor execution, -observation and –imagination paradigm. Gorbet & Staines (2011) reported on inhibition of the contralateral premotor cortex in response to reaching movements in men, but emphasized sex differences to be associated with movement planning rather than movement execution. Silas et al (2010) reported men showing larger readiness potentials in response to motor execution and - observation, and women higher mu-power in response to latter one; both part of the neural correlates of the mirror system and linked to motor perception. And as for motor imagery, here men activate more prefrontal, lingual and cingulate cortices when performing upper limb movement imagination tasks (Wadsworth & Kana, 2011; Seurinck et al., 2004)

In our study, the most striking and interesting finding was that men and women differed in terms of motor imagery activation. Men compared to women by tendency showed higher motor imagery ability (self-report inventory, visual and kinesthetic components) and several brain regions were more strongly activated with motor imagery, such as the inferior frontal gyrus, the primary motor cortex, the fusiform, lingual and inferior parietal gyri, and the occipital gyrus. These results resemble the results found for upper limb movements.

They might further reflect proficiency levels, since good compared to bad gait-motor imagery has been associated with higher prefrontal- and primary motor cortex activation, along with thalamic and cerebellar activation (Van der Meulen et al., 2014). Guillot et al. (2008) additionally attributed parietal recruitment to successful motor imagery, a region commonly reported in motor imagery (e.g. Fleming et al., 2010). So there is some indication of men being better motor imager, given the frontal-, parietal- and motor cortex activations. Especially since the opposite contrast revealed no significant results.

The speculated better motor imagery ability in men might have led to the study imbalance in favour to men as reported by Schuster et al. (2011). Men are attributed more visual-spatial imagery abilities and women are believed to be better in cognitively-focused tasks; thus requiring more kinesthetic dorsal than cognitive ventral fibre pathways (Vry et al., 2012). With our results we hope to stimulate sex-specific investigations, especially since motor imagery is an increasingly frequently applied tool in neurorehabilitation (Munzert et al., 2009) and the advantage of men is not consistently granted (cf. Giacobbi 2007; Callow& Hardy 2004).

4.1.3.2 Further Analyses

In subsequent analyses, we tested for the effect of good vs. bad motor imagery ability. We here defined seven ROIs based on the results of the fMRI motor imagery condition (see Annex Table B.5) and correlated these values with self-rated motor imagery ability. The predefined regions have been observed with successful motor imagery (Van der Meulen et al., 2014; Guillot et al., 2008) and seem functionally plausible. Better motor imagery ability was accompanied by significantly less BOLD signal change in the inferior frontal gyrus, and tendencies for the cerebellum, the supramarginal and inferior temporal gyri (see Annex Figure A.3)

The observed results can be interpreted in terms of neural efficiency. Professional car drivers show less recruitment of motor task-related regions yet concurrent stronger interconnection (Bernardi et al., 2013). Similarly, professional musicians show less activation in motor areas (explained by a lower number of active neurons necessary to perform the movements; Jäncke et al., 2000), coupled with a larger corpus callosum (connector of left and right primary motor cortex; Steele et al., 2013) and decreased intra-cortical as well as inter-hemispheric inhibition (Vollmann et al., 2014).

We thus speculate stronger interconnections in motor imagery task relevant areas may account for the less pronounced inferior frontal activation in people with better motor imagery, a region indicating enhanced cognitive effort (Mulder, 2007). Future studies on functional connectivity and structural tractography will be needed to explore this relationship.

4.1.3.3 Novel Aspects

The advantage of the created fMRI paradigm is a consequence of the domains covered: a) motor function, b) cognition and c) motor function and cognition within one single paradigm. Previous studies showed an overall benefit of combining these domains yet showed implementation deficits (Lorey et al., 2013; Orr et al., 2008), focused differently (Halder et al., 2011) or have investigated these domains separate and not combined (Wang et al., 2009; Mulder, 2007). Additionally, it comprises different complexity steps starting with simple unilateral ankle movement execution to the more complex bipedal "stepping" movements and finally the imagination of these bipedal movements. In a final step, this paradigm is applicable in healthy people as well as WMH (patient) groups.

The results have particular impact for rehabilitation research, such as stroke rehabilitation or gait and balance problems in people with WMH. Previous studies suggest differences in primary motor cortex activity with motor imagery and in dependence of age (e.g. Sharma & Baron, 2014). Our study highlights that not only age but also sex might have fundamental impact on the recruited neural network for motor imagery. Hence, motor imagery training neurorehabilitation could address for these differences and implement this relationship in the design.

4.1.3.4 Limitations

Our study does not provide a report on potentiometer data or EMG results. This information would have been useful in order to control for movement displacement (max.

range) and absent movement, respectively. However, a preceding training session was performed to familiarize the participants with the tasks and to intervene accordingly. They were instructed to move the ankle to a full maximum range of 30° during active performance and to rest during the baseline-, observation and imagination conditions. During the fMRI experiment, participants were video monitored and after the measurement, they were interviewed for potential involuntary movements. In the fMRI analysis phase, results were checked for plausibility on individual basis.

Further, the sample size within this study is adequate for calculation of mean group activations across the whole cohort. The network here encompasses a solid and plausible activation pattern across the different domains (motor, visual and cognitive) and regarding the complexity (simple vs. more complex movements). A larger sample size, however, would be necessary to increase confidence in the stability and reproducibility of the sex findings.

Finally, the MIQ assessed the self-evaluated motor imagery ability. For specific proof of concept of motor imagery ability however, specific neuroimaging-based control tasks or behavioural test batteries with evaluation ability would have been necessary (cf. Madan & Singhal, 2013).

4.1.3.5 Future Studies

The developed and implemented novel fMRI motor paradigm inheres room for improvement, especially in the motor domain. There it currently enables variation in terms of complexity (simple vs. complex) and hemisphere (dominant, non-dominant, bilateral). Further studies could expand the design and vary frequency (slow, fast, self-paced), force resistance (no, minor, strong), performance (active vs. passive) and proprioception (sensory feedback, no sensory feedback) (ideas based on the fundamentals of Kirtley, 2006; Orlovsky et al., 2003).

Also, the paradigms could be applied in different study cohorts. The paradigm was developed for clinical use such as in individuals with WMH. Within this context, studies suggest simultaneous action observation and motor imagery to more strongly promote neurorehabilitation (cf. Villinger et al., 2013; Vogt et al., 2013), which could be realized by adding motion to the motor imagery condition for training purposes. But also healthy trained people (expert brains) could be tested to investigate the relationship between cerebral plasticity and (learning of complex) motor skills (Wei & Luo, 2010). Trained subjects such as soccer players might display a (re)organization of the motor system, in terms of neural efficiency (Del Percio et al., 2008). Changes in response to expertise are thereby expected in all domains, including motor observation and -imagination (Wright et al., 2013; Milton et al., 2007; Calvo-Merino et al., 2005). A recent meta-analysis showed sports experts to more strongly use higher motor planning areas, with parietal regions for motor execution and inferior frontal- and precentral gyri for motor observation (Yang, 2014). Further, athletes seem to utilize their kinesthetic imagery more efficiently than novices (more focused prefrontal activation pattern), but only for the expertise activity (Wei & Luo, 2010).

Future studies could also focus on the strong occipital activation across all conditions. Studies have shown 1st compared to 3rd person perspective, to produce stronger occipital activation (Vogt et al., 2013; Filimon et al., 2007).

4.1.3.6 Summary and Conclusion

In summary, the study met the objective of developing a new, modified fMRI paradigm to be used in healthy and clinical cohorts, e.g. individuals with WMH. Adding motor observation and –imagination to a motor execution fMRI paradigm, might allow more specific monitoring of training interventions and detection of deficits in the various domains. This appears especially useful in individuals with WMH, who show domain-associated behavioural-, structural- and functional variations. Sex differences with regard to motor imagery might impact training effects and should be specifically addressed.

4.2 General Summary

The PhD project consists of three separate yet interlinking neuroimaging studies dealing with the interplay of age, cerebral white matter hyperintensities (WMH), and gait (i.e.

walking). Based on the interdisciplinary field research, a range of clinical, technical and neuropsychological assumptions can be stated.

In the first study we found that age-related changes in the cerebral sensorimotor network responsible for the control of limb function do occur in healthy individuals. For the clinician this means that functional alternations in response to lower limb function with age can be considered normal. Whether these changes compensate for other structural or behavioural changes, should be specifically addressed in future studies. In the technical neuroimaging domain, this study was the first to use a big sample approach of more than hundred people. The two different analysis techniques showed that meta-analyses should take into account potential deviations in functional activation, when a small number of studies is filtered in. Neurospsychologically, questionnaires on activities of daily living and level of physical activity could reveal potential influencing factors for the fMRI signal increases.

Study 2 showed brain volume decreases in motor, cognitive and visual areas in people with pronounced WMH. Neurologically most interesting, this supports the assumption of a disconnection of fronto-cortico networks with WMH proximity to the corticospinal tract. A combined analysis on WMH lesion location, microstructural integrity of motor and sensory fibre pathways and behavioural gait performance, could provide additional information. Also, the sum of different markers from MRI, clinical status scales and psychological testing promises a better understanding of the heterogeneity of WMH and more personalized healthcare. Technically, we added lesion masks to the voxel-based morphometry protocol to prevent from potential misclassifications in the brain segmentation phase. And neuropsychological, the observations gain importance in light of future interventional studies (i.e., movement-related training in the motor and cognitive domain) in people with pronounced WMH, aiming to ameliorate existing deficits or even postpone structural changes.

Finally, study 3 met the objective of developing and implementing a refined and stable fMRI “walking” paradigm, as tested in healthy people. Clinically, the paradigm is now ready for future use in individuals with WMH. In the technical domain, the paradigm also allows reduction or alternation of conditions, in favour of a decreased time-to-performance accuracy ratio. Neuropsychologically relevant, we could show indicators for sex-specific differences in functional activation with motor imagery. Mental practise alongside conventional therapy is increasingly used to rehabilitate motor deficits. If a speculated difference in motor imagery processing in men compared to women exists, already used trainings might improve by accounting for sex-specific differences.

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Annex

The annex includes study-relevant tables, questionnaires and figures that add additional information to the studies or simply illustrate the study process. The category order follows an alphabetical listing: A) Figures, B) Tables and C) Questionnaires. As subcategory D) the already published Linortner et al., “Neurobiology of Aging” 2014– paper on study 1 of the PhD project is attached. Within categories, the ordering follows the study order.

A) Figures

A.1 Study 1, Age and fMRI Ankle Movements: Laterality Analyses

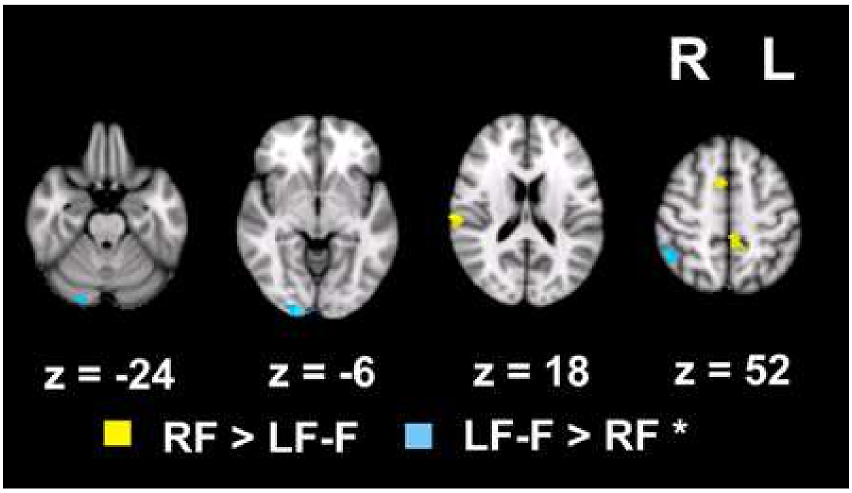

Figure A1. Activation maps (selected slices, z-coordinates; Z>3.1, p = 0.01) associated with right vs. flipped left foot movement (RF> LF-F; yellow) and flipped left vs. right foot movement (LF-F> RF*; blue) [*Back-flip of activation cluster; activation in unflipped hemisphere- flipping as tool for contrast analysis] The image is shown in radiological convention, where the left side represents the right side of the brain

A.2 Study 2, WMH and (Sub)cortical Microstructure: Lesion Masking

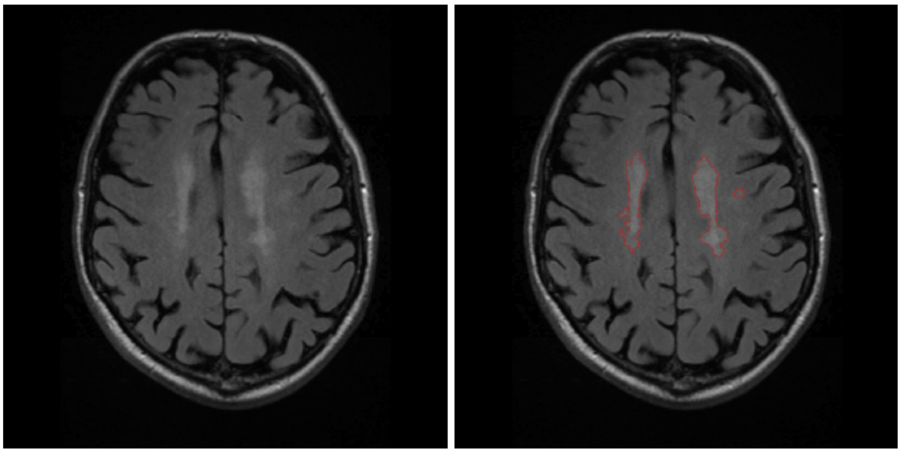

Figure A2. Example of manual WMH masking, as necessary preprocessing-step used in study 2, where WMH were investigated in terms of (sub)cortical microstructure.

A.3. Study 3, fMRI Paradigm Development, Motor Imagery Analyses

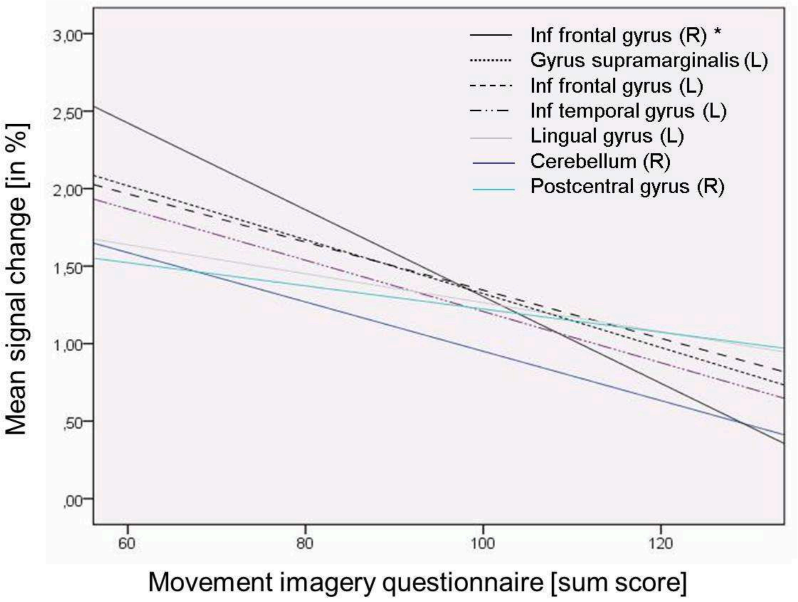

Figure A3. Correlation of the fMRI motor imagery condition (condition 6. MI_Bip, defined ROIs) with the corresponding motor imagery questionnaire (MIQ) values. The higher the cerebellar activation, the worse the behavioural motor imagery ability. Possible MIQ sum scores range from 18 (very bad imagination ability) to 126 (very good imagination ability).

B) Tables

B.1 Study 1, Age and fMRI Ankle Movements

Table B1. Mean activation results for right- and left foot (RF and LF) movements, using I. FSL FEAT and II. ALE meta-analysis. Coordinates (in MNI standard space) and activation significance for I. cluster-based statistical contrasts (z-Statistics; Z >3.1, p = 0.01) and II. voxel-based statistics (ALE value x10^3; False Discovery Rate thresholding, p<.01)

Contrasts	Anatomical region	Hemisphere (L/R)	I. Voxel number, II. Cluster size [mm^3]*	I. Max Z-Score, II. ALE (x10^3)	MNI coordinates I. Max Z-Score [mm], II. Weighted center		
					x	y	z
I. FSL FEAT							
Mean RF	Paracentral lobule	L	3574	7.53	-4	-32	64
	Cerebellum IV-V	R	1526	8.25	16	-38	-26
	Superior temporal gyrus	L	1444	6.07	-52	-32	18
	Middle occipital gyrus	L	326	4.69	-40	-68	0
	Rolandic operculum	R	271	4.61	50	-28	20
Mean LF	Paracentral lobule	R	3770	8.03	2	-26	64
	Cerebellum IV-V	L	1218	7.21	-18	-34	-32
	Superior temporal gyrus	R	1089	5.8	48	-30	18

	Inferior temporal gyrus	R	659	5.57	44	-68	-8
	Superior temporal gyrus	L	367	5.48	-48	-30	16
	Middle occipital gyrus	L	291	4.57	-40	-68	0
	Cerebellum VI	R	223	4.21	28	-60	-26
	Putamen	L	91	3.90	-28	-12	6
II. ALE meta-analysis							
Mean RF	Cerebellum, anterior lobe	R	1216	24.65	16	-36	-28
	Medial frontal gyrus, BA6	L	208	10.61	-2	-18	62
	Paracentral lobule, BA4	L	144	10.76	-2	-30	64
Mean LF	Cerebellum, anterior lobe	L	448	14.92	-20	-34	-32
	Paracentral lobule, BA 4	R	272	12.70	4	-32	66
	Superior temporal gyrus, BA 22	L	200	10.66	-50	4	-2
	Cerebellum, lobule VIII	L	136	9.85	-34	-56	-56
	Cerebellum, lobule VIII	L	101	9.29	-30	-58	-54

Key: ALE, Activation Likelihood Estimation; BA, Broadmann area; L, left hemisphere; LF, left foot; R, right hemisphere, RF, right foot

* Reported are clusters above a threshold of I. > 99 voxel, II. > 100mm^3

Table B2. Correlation analysis for age and right-/left foot (RF/LF) movements, using FSL FEAT. Coordinates (in MNI standard space) and activation significance (Z statistics) for cluster-based statistical contrasts (z-Statistics; Z >3.1, p = 0.01).

Contrasts	Anatomical region	Hemisphere (L/R)	Voxel number*	Max Z-Score	MNI coordinates of Max Z-Score [mm]		
					x	y	z
Positive Correlation							
↑ Age & ↑ RF	Middle occipital gyrus	L	3245	7.51	-44	-76	-22
	Cerebellum, lobule VI	R	1481	6.42	34	-44	-30
	Cerebellum, lobule IV-V	R		6.24	6	-54	-22
	Cerebellar vermis, IV-V	L		5.89	-4	-52	-22
	Cerebellar vermis, IX	R		5.25	0	-54	-30
	Cerebellum, lobule VIII	R		5.18	8	-62	-30
	Cerebellum, crus I	R		4.89	28	-50	-38
	Precuneus	L	496	8.96	-2	-52	68
	Basal ganglia	R	311	5.06	14	-22	-10
	Basal ganglia	L	246	5.27	-28	-16	-6
Positive Correlation							
↑ Age & ↑ LF	Inferior occipital gyrus	R	5322	5.84	4	-82	-16
	Cerebellum, crus I	R	2209	5.56	30	-56	-36
	Cerebellum, lobule III	R		5.53	4	-46	-20
	Cerebellum, crus I	L		5.38	-22	-66	-32

Cerebellum, crus I	R		5.08	22	-64	-34
Cerebellum, crus I	L		5.05	-12	-66	-30
Cerebellum, lobule VI	L		4.82	-28	-54	-34
Precuneus	L	840	6.29	-6	-50	76
Middle frontal gyrus	L	176	5.73	-30	46	22
Inferior frontal gyrus	R	172	4.54	48	24	-14

Key: L, left hemisphere; LF, left foot; R, right hemisphere, RF, right foot

* Reported are clusters above a threshold of > 99 voxel

Table B3. Table-graphic summary of fMRI mean group analyses for major functional regions, using FSL FEAT and ALE meta-analysis. In case of bilateral activation (black box), the after-box dash indicates the hemispheric dominance in the respective cortical area (grey or white box).

Condition (& tool)	Anatomical region							
	Frontal	SMA	MI	SI	SII	BG	Insula	Cereb
RF (Feat)		■ - ▨	■ - ▨	▨	■ - ▨	▨		□
RF (ALE)	▨	[▨]	[■]- □	[▨]	■ - ▨	▨	□	□
LF (Feat)		■ - ▨	■ - ▨	▨	■ - ▨	■ - ▨		■ - □
LF (ALE)		[▨]	[▨]	[▨]	■ - □	[□]	■ - □	□

Key: BG, basal ganglia; Cereb, cerebellum; Frontal, frontal cortex; LF, left foot; MI, primary motor cortex; RF, right foot; SI, primary somatorsensory area; SII, secondary somatosensory area; SMA, supplementary motor area. ■ , bihemispheric; ▨ , contralateral hemisphere; □ , ipsilateral hemisphere; [ ], n.sign

B.2 Study 2, WMH and (Sub)cortical Microstructure

Table B4. TFCE-based thresholded cluster coordinates (in MNI standard space) and activation significance (Z-statistics) of the voxel-based morphometry analysis results. I. Comparing the two groups of individuals with WMH, II. Positive correlation of WMH lesion load and grey matter volume and III. Positive correlation of SPPB score and grey matter volume.

Contrasts	Anatomical region	Hemisphere (L/R)	Voxel number*	Max Z-score	MNI coordinates of Max Z-Score [mm]		
					x	y	z
I. Group comparison							
WMH 2+3 < WMH 0+1	Middle- / inferior temporal gyrus	R	295	0.98	58	-50	6
	Middle frontal gyrus / Precentral gyrus	R	196	0.98	44	22	42
	Fusiform gyrus	R	71	0.96	26	-46	-10
	Posterior Cingulum / Precuneus	R	14	0.96	10	-38	54
II. Correlation analysis							
↑ WMH LL & ↑ GM volume	Paracentral lobule	L	282	0.99	-6	-34	66
	Cuneus / Precuneus	L	120	0.98	-6	-80	36

III. Correlation analysis							
↑ SPPB & ↑ GM volume	Occipital cortex	R	1923	0.99	12	-58	66
	Superior temporal gyrus	L	1117	0.98	-64	-12	4
	Superior parietal lobule	L	702	0.98	-28	-52	54
	Middle temporal gyrus	R	165	0.96	68	-36	-4
	Precentral gyrus	L	100	0.96	-38	-16	40

Key: L, left hemisphere; R, right hemisphere

B.3 Study 3, fMRI Paradigm Development

Table B5. Mean activation results for all study participants (*N* =21) in all six MEMIMO conditions. Coordinates are reported in MNI standard space for cluster-based statistical contrasts (z-Statistics; FLAME 1+2; Z >3.1, p = 0.01).

Contrasts	Anatomical region	Hemisphere (L/R)	Voxel number*	Max Z-score	MNI coordinates of Max Z-Score [mm]		
					x	y	z
1. ME_Right	Supplementary motor area	L	6761	6.43	-8	-14	66
	Thalamus	L	3166	6.3	-18	-20	8
	Cerebellum, IV-V	R	1741	6.02	14	-36	-28
	Paracentral lobule	R	879	4.73	56	6	26

	Inferior occipital gyrus	R	834	6.4	24	-94	-6
	Inferior occipital gyrus	L	795	6.95	-24	-98	-8
	Superior temporal gyrus	R	695	5.31	58	-36	12
	Cerebellum, VI	L	201	4.7	-32	-58	-30
	Thalamus	R	188	4.95	10	-18	4
	Middle temporal gyrus	R	140	4.6	46	-64	2
	Cerebellum, X	L	131	4.22	-6	-34	-42
2. ME_Left	Paracentral lobule	R	7935	7.08	6	-24	68
	Cerebellum, IV-V	L	1442	6.71	-14	-38	-30
	Inferior occipital gyrus	R	769	6.02	24	-94	-6
	Inferior occipital gyrus	L	734	6.66	-24	-96	-10
	Superior temporal gyrus	L	289	4.46	-42	-30	18
	Middle cingulum	L	191	5.01	-14	-24	40
	Inferior occipital gyrus	R	185	4.22	40	-66	-6
	Superior temporal gyrus	L	157	4.04	-52	0	0
3. ME_Bip	Paracentral lobule	R	29807	7.23	2	-26	64
	Middle occipital gyrus	R	376	5.07	32	-62	28
	Post cingulum	L	212	4.45	-6	-42	10
4. MO_Bip	Superior occipital gyrus	R	12099	6.79	16	-94	24
	Middle frontal gyrus	L	640	4.36	-48	26	38
	Inferior frontal gyrus, pars	L	248	4.61	-46	46	0

	triangluaris						
	Superior frontal gyurs	L	144	4.23	-14	62	22
5. MO+ME_Bip	Paracentral lobule	R	50956	7.33	0	-24	62
	Middle frontal gyrus	L	198	4.14	-40	46	8
6. MI_Bip	Inferior frontal gyrus, pars orbitalis	L	7627		-50	30	-6
	Gyrus supramarginalis	L	1792		-60	-44	38
	Inferior frontal gyrus, pars opercularis	R	719		50	10	6
	Lingual gyrus	R	433		14	-88	-8
	Postcentral gyrus	R	345		54	-4	48
	Inferior temporal gyrus	L	267		-56	-52	-12
	Cerebellum, crus I	R	261		34	-60	-32

Key: Bip, bipedal foot movements; L, left hemisphere; R, right hemisphere; ME, motor execution; MI, motor imagination; MO, motor observation

* Reported are clusters above a threshold of > 100 voxel.

Table B6. Mean activation results based on sex-specific contrast analyses (Men n_1=11 & Female n_2=10 subjects) in all six MEMIMO conditions. Coordinates are reported in MNI standard space for cluster-based statistical contrasts (z-Statistics; FLAME 1+2; Z >2.3, p = 0.05).

Contrasts	Anatomical region	Hemisphere (L/R)	Voxel number*	Max Z-score	MNI coordinates of Max Z-Score [mm]		
					x	y	z
I. MEN > FEMALE							
1. ME_Right	---						
2. ME_Left	Middle occipital gyrus	R	304	3.67	32	-88	10
3. ME_Bip	---						
4. MO_Bip	---						
5. MO+ME_Bip	Precuneus	L	577	3.79	-2	-64	26
6. MI_Bip	Superior occipital gyrus	L	1099	4.76	-22	-66	30
	Middle occipital gyrus	R	798	3.98	26	-64	32
	Fusiform gyrus	R	705	4.05	26	-64	-12
	Inferior frontal gyrus, pars triangularis	L	597	3.9	-32	20	24
	Lingual gyrus	L	521	4.22	-20	-80	-12
	Inferior parietal gyrus	R	448	3.58	48	-44	44
	Precentral gyrus	R	437	3.49	42	-4	54
	Precentral gyrus	R	415	4.59	42	4	28

II.FEMALE > MEN

1. ME_Right	---						
2. ME_Left	Inferior frontal gyrus	R	291	3.72	36	46	12
3. ME_Bip	Cerebellum, lobule X	L	764	3.64	-16	-32	-40
	Superior temporal gyrus	L	564	4.01	-52	10	0
4. MO_Bip	---						
5. MO+ME_Bip	Middle temporal pole	R	355	3.92	48	22	-30
6. MI_Bip	---						

Key: Bip, bipedal foot movements; L, left hemisphere; R, right hemisphere; ME, motor execution; MI, motor imagination; MO, motor observation; --- no sign. activation

* Reported are clusters above a threshold of > 100 voxel.

C) Questionnaires

C.1 Study 3, fMRI Paradigm Development, Assessment of Foot Dominance

Active foot dominance testing (using the most reliable items of Schneiders et al., 2010) and German version of the Waterloo Footedness Questionnaire-Revised (WFQ-R, Elias et al., 1998), questionnaire template for the study participants:

VOR- UND NACHNAME(N):

GEBURTSDATUM & ALTER:

AUSFÜLLDATUM:

Liebe Teilnehmerin, lieber Teilnehmer,

Bitte **führen Sie zunächst** alle vier unten genannten Aufgaben **aktiv durch** (1x genügt) und blättern Sie **erst dann** auf die nächste Seite um! Dort erhalten Sie dann auch weitere Informationen.

a. Mit den Zehen eine Murmel hochheben.
(Alternativen: Stein, Radiergummi,…)
b. Mit dem Fuß am Boden Formen ziehen.
c. Mit Schaufel / Spaten ein Graben simulieren (-> Spatenstich mit Fuß).
(*Alternativ kann auch ein Besen/Stiel verwendet werden, mit welchem die Aufgabe durchgeführt wird, als würde es sich um eine Schaufel handeln)*
d. Mit dem Fuß einen Ball schießen / zuspielen.
(Alternativen: Vorrätiger ballähnlicher Gegenstand; Luftballon)

Danke!

Liebe Teilnehmerin, lieber Teilnehmer,

der Ihnen vorliegende Fragebogen dient der Erhebung Ihrer Fußpräferenz. Dabei behandelt der **erste Abschnitt** die **aktive Ausführung** bestimmter fußmotorischer Aufgaben, der **zweite Abschnitt** die **geistige Selbsteinschätzung** (jedoch nicht aktive Ausübung!) solcher.

Um Sie in der aktiven Ausführung nicht mit Vorinformationen zu beeinflussen, haben wir Sie gebeten diesen Part vorab auszuführen und um ihn erst später zu bewerten.

In Anlehnung an bekanntere „Händigkeit“, beschreibt die „Füßigkeit“ bzw. Fußdominanz die Präferenz eines Fußes gegenüber dem anderen.

Bitte beantworten Sie jeder der folgenden Fragen so gut sie können und **achten Sie dabei darauf keine auszulassen**! Die Ergebnisse/Daten werden von uns **anonym** behandelt und nicht an Dritte weitergegeben.

Ihre Einschätzungen sollen nicht dazu verwendet werden, zu erfassen, wie gut oder wie schlecht Sie mit dem jeweiligen Fuß sind. Vielmehr sollen Sie uns Auskunft über Ihre Präferenz/Dominanz geben. **Es gibt keine Antworten, die „richtig“ oder „falsch“ bzw. besser als andere sind.**

Vielen Dank für Ihre Mitarbeit!

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1. Abschnitt - Aktive Ausübung

Bitte **bewerten** Sie die zuvor aktiv ausgeführten Aufgaben!

Welchen Fuß haben Sie für die jeweilige Aufgabe verwendet?
Setzen Sie ein **X** anstatt **R** oder **L** (**R** für: **rechter Fuß**; **L** für: **linker Fuß**).

Wenn Sie eine *Alternative* anstatt der ursprünglichen Instruktion verwendet haben, vermerkten Sie diese bitte.

1	Murmel hochheben *Alternative?:*	L	R
2	Formen ziehen	L	R
3	Spatenstich *Alternative?:*	L	R
4	Ball schießen *Alternative?:*	L	R

2. Abschnitt – Geistige Selbsteinschätzung

Bitte beantworten Sie jeder der folgenden Fragen so gut sie können und lassen Sie keine aus!

Wenn Sie **immer einen Fuß** verwenden (d.h. 95% der Zeit oder mehr) um die beschriebene Tätigkeit auszuführen, setzen Sie ein **X** anstatt **RI** oder **LI** (**RI** für: **rechts/rechten immer**; **LI** für: **links/linken immer**).

Wenn Sie **meistens einen Fuß** verwenden (d.h. ca. 75% der Zeit) um die beschriebene Tätigkeit auszuführen, setzen Sie ein **X** anstatt **RM** oder **LM** (**RM** für: **rechts/rechten meistens**; **LM** für: **links/rechten meistens**).

Wenn Sie **beide Füße gleich oft** verwenden (d.h. jeden Fuß in 50% der Fälle) um die beschriebene Tätigkeit auszuführen, setzen Sie ein **X** anstatt **BG** (**BG** für: **beide gleich häufig**).

1	Welchen Fuß würden Sie wählen, um einen vor Ihnen liegenden Ball in Richtung eines direkt vor Ihnen befindlichen Ziels zu schießen?	LI	LM	BG	RM	RI
2	Wenn Sie auf einem Fuß stehen müssten, welcher wäre dies?	LI	LM	BG	RM	RI
3	Welchen Fuß würden Sie wählen, um an einem Sandstrand den Sand glatt zu streichen?	LI	LM	BG	RM	RI
4	Wenn Sie auf einen Stuhl steigen müssten, mit welchem Fuß würden Sie zuerst auf dem Stuhl treten?	LI	LM	BG	RM	RI
5	Welchen Fuß würden Sie verwenden, um auf eine sich schnell bewegende Wanze zu treten?	LI	LM	BG	RM	RI
6	Wenn Sie mit einem Fuß auf einem Schienengleis balancieren müssten, welchen Fuß würden Sie verwenden?	LI	LM	BG	RM	RI
7	Wenn Sie eine Murmel mit Ihren Zehen aufheben wollen würden, welchen Fuß würden Sie verwenden?	LI	LM	BG	RM	RI
8	Wenn Sie auf einem Fuß hüpfen müssten, welchen Fuß würden	LI	LM	BG	RM	RI

	Sie verwenden?					
9	Welchen Fuß würden Sie verwenden, um mithilfe dessen eine Schaufel in die Erde zu stechen?	LI	LM	BG	RM	RI
10	Wenn wir entspannt stehen, belasten wir anfänglich meist einen Fuß mit unserem Gewicht und lassen den anderen leicht gebeugt. Auf welchen Fuß geben Sie anfänglich das meiste Ihres Gewichts/ welchen belasten Sie stärker?	LI	LM	BG	RM	RI

Ankreuzmodus der nachfolgenden Fragen: **X** anstelle von **JA** oder **NEIN** setzen

11	Gibt es einen Grund (z.B. Verletzung), weswegen Sie die Fußpräferenz für eine der oben genannten Tätigkeiten gewechselt haben?	JA	NEIN
12	Wurden Sie jemals speziell trainiert oder ermutigt, einen bestimmten Fuß für bestimmte Tätigkeiten zu verwenden?	JA	NEIN
13	Wenn Sie Frage 11 oder 12 mit „JA“ beantwortet haben, geben Sie bitte ausführlichere Auskunft dazu:		

C.2 Study 3, fMRI Paradigm Development, Assessment of Movement Imagery Ability

German version of the Movement Imagery Questionnaire (MIQ, Hall & Martin, 1997):

Liebe Teilnehmerin, lieber Teilnehmer,

für das Ausfüllen dieses Fragebogens benötigen Sie etwa 15–20 Minuten. Wir bitten Sie, diesen Fragebogen zügig auszufüllen. Die Ergebnisse/Daten werden von uns **anonym** behandelt und nicht an Dritte weitergegeben.

Dieser Fragebogen befasst sich mit zwei Arten, Bewegungen mental auszuführen, von denen manche Leute mehr als andere Gebrauch machen und die auch in Abhängigkeit vom

Bewegungstyp unterschiedlich gut anwendbar sind. **Die erste Aufgabe betrifft die Bildung eines mentalen (visuellen) Eindrucks oder eines „Bildes“ der Bewegung. Bei der zweiten Art ist man bestrebt, zu spüren, wie sich der Bewegungsvollzug anfühlt, ohne die Bewegung tatsachlich auszuführen.**

In diesem Fragebogen wird von Ihnen verlangt, diese beiden Vorstellungsaufgaben für eine Vielzahl von Bewegungen auszuführen und anschließend zu bewerten, wie schwer/leicht Ihnen diese Aufgabe gefallen ist. Ihre Einschätzungen sollen nicht dazu verwendet werden, zu erfassen, wie gut oder wie schlecht Sie diese mentalen Aufgaben ausgeführt haben. Vielmehr sollen Sie Auskunft geben über Ihr Vermögen, diese Aufgaben bei verschiedenartigen Bewegungstypen auszuführen. **Es gibt keine Antworten, die „richtig“ oder „falsch“ bzw. besser als andere sind.**

Jeder der folgenden Abschnitte beschreibt eine spezifische Bewegung. Lesen Sie jede Beschreibung sorgfältig, und führen Sie anschließend die Bewegung wie beschrieben aus. Führen Sie die Bewegung aber nur **ein einziges Mal** aus. Zur Durchführung der mentalen Aufgabe nehmen Sie dann bitte wieder die Ausgangsposition ein, so, als ob Sie die Bewegung ein zweites Mal ausführen wollten. Führen Sie die dann geforderte mentale Aufgabe aus,

d.h. entweder

- Sie versuchen ein möglichst klares und lebhaftes **Vorstellungsbild** von der Bewegung zu erzeugen, die Sie gerade ausgeführt haben, **oder**
- Sie versuchen wirklich **zu fühlen**, wie Sie die Bewegung ausführen, ohne dies aber tatsachlich zu tun.

Nachdem Sie die **mentale Aufgabe** beendet haben, **beurteilen** Sie bitte die Leichtigkeit bzw. Schwierigkeit, mit der Sie die mentale Aufgabe durchführen konnten. Orientiere Sie sich in Ihrer Bewertung an der nachstehenden Skala (bei jeder Aufgabe jeweils mit angegeben).

Sein Sie dabei so genau wie möglich, und nehmen Sie sich jedes Mal so lange Zeit, wie Sie für nötig halten, um zu einer angemessenen Einschätzung zu gelangen. Sie können dabei jeden Wert für so viele mentale Aufgaben vergeben, wie Sie wollen. Es ist nicht erforderlich, dass Sie das gesamte Spektrum der Beurteilungsskala ausnutzen. **Bitte lassen Sie keine Aufgabe aus**!

Vielen Dank für Ihre Mitarbeit!

1. Ausgangsposition:

Machen Sie mit Ihrer dominanten Hand (die Hand, mit der Sie schreiben) eine Faust, und bringen Sie diese Hand zur gleichseitigen Schulter (z. B. rechte Hand zur rechten Schulter), sodass Ihr Ellbogen direkt nach vorne zeigt.

Aktion: Strecken Sie Ihren Arm im Ellbogengelenk, sodass Ihre Hand die Schulter verlässt und sich nun waagerecht vor Ihnen befindet. Ihre Hand ist weiterhin zur Faust geballt. Führen Sie diese Bewegung langsam aus.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein (genau wie oben beschrieben). Rufen Sie in Ihrer Vorstellung ein möglichst klares und lebhaftes Vorstellungsbild von der Bewegung hervor, die Sie gerade ausgeführt haben. Führen Sie die Bewegung aber nicht mehr physisch aus! Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht vorzustellen	leicht vorzustellen	eher leicht vorzustellen	weder leicht noch schwierig	eher schwierig vorzustellen	schwierig vorzustellen	sehr schwierig vorzustellen

2. Ausgangsposition:

Stehen Sie aufrecht, geschlossene Fußstellung. Die Arme liegen seitlich am Körper an.

Aktion: Heben Sie Ihr rechtes Knie so hoch wie möglich, sodass Sie nun auf dem linken Bein stehen, das rechte Bein im Kniegelenk gebeugt. Nun senken Sie Ihr rechtes Bein, sodass Sie dann wieder auf beiden Füßen stehen. Führen Sie diese Bewegung langsam aus.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein. Versuchen Sie zu fühlen, wie Sie die soeben vollzogene Bewegung ausführen (ohne dies jetzt tatsachlich zu tun)! Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht zu fühlen	leicht zu fühlen	eher leicht zu fühlen	weder leicht noch schwierig	eher schwierig zu fühlen	schwierig zu fühlen	sehr schwierig zu fühlen

3. Ausgangsposition:

Stehen Sie aufrecht, hüftbreite Fußstellung. Die Arme liegen seitlich am Körper an.

Aktion: Gehen Sie tief in die Hocke, und springen Sie dann so hoch wie möglich gerade nach oben, die Arme über den Kopf nach oben ausgestreckt. Landen Sie in hüftbreiter Fußstellung und senken Sie die Arme wieder an Ihre Seiten.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein (genau wie oben beschrieben). Rufen Sie in Ihrer Vorstellung ein möglichst klares und lebhaftes Vorstellungsbild von der Bewegung hervor, die Sie gerade ausgeführt haben. Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht vorzustellen	leicht vorzustellen	eher leicht vorzustellen	weder leicht noch schwierig	eher schwierig vorzustellen	schwierig vorzustellen	sehr schwierig vorzustellen

4. Ausgangsposition:

Stehen Sie aufrecht, hüftbreite Fußstellung. Die Arme liegen seitlich am Körper an.

Aktion: Springen Sie hoch und drehen Sie sich in der Luft links herum, sodass Sie wieder genau in der Ausgangsstellung landen, d.h., Sie vollführen eine Linksdrehung um 360°.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein. Versuchen Sie in Ihrer Vorstellung zu fühlen, wie Sie die Bewegung ausführen (ohne dass Sie die Bewegung tatsachlich physisch ausführen)! Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht zu fühlen	leicht zu fühlen	eher leicht zu fühlen	weder leicht noch schwierig	eher schwierig zu fühlen	schwierig zu fühlen	sehr schwierig zu fühlen

5. Ausgangsposition:

Strecken Sie den Arm Ihrer nicht dominanten Hand waagerecht zur Seite aus, die Handfläche nach unten.

Aktion: Bewegen Sie den Arm vorwärts, bis er sich direkt vor Ihnen befindet (dabei immer noch waagerecht). Lassen Sie Ihren Arm während der gesamten Bewegung gestreckt, und führen Sie die Bewegung langsam aus.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein (genau wie oben beschrieben). Rufen Sie in Ihrer Vorstellung ein möglichst klares und lebhaftes Vorstellungsbild von der Bewegung hervor, die Sie gerade ausgeführt haben. Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht vorzustellen	leicht vorzustellen	eher leicht vorzustellen	weder leicht noch schwierig	eher schwierig vorzustellen	schwierig vorzustellen	sehr schwierig vorzustellen

6. Ausgangsposition:

Stehen Sie aufrecht, die Hände liegen seitlich am Körper an.

Aktion: Heben Sie das gestreckte linke Bein so hoch wie möglich (Sie dürfen das linke Knie nicht beugen). Lassen Sie auch das Standbein (rechtes Bein) gestreckt. Senken Sie nun das linke Bein, bis Sie wieder auf beiden Beinen stehen. Führen Sie diese Bewegung langsam aus.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein. Versuchen Sie in Ihrer Vorstellung zu fühlen, wie Sie die Bewegung ausführen (ohne dass Sie die Bewegung tatsachlich physisch ausführen)! Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht zu fühlen	leicht zu fühlen	eher leicht zu fühlen	weder leicht noch schwierig	eher schwierig zu fühlen	schwierig zu fühlen	sehr schwierig zu fühlen

7. Ausgangsposition:

Stehen Sie aufrecht, hüftbreite Fußstellung. Die Arme sind vollständig über dem Kopf ausgestreckt.

Aktion: Beugen Sie sich langsam im Hüftgelenk nach vorne ab und versuchen Sie, mit den Fingerspitzen Ihre Zehen zu berühren (oder, falls möglich, den Boden). Kehren Sie nun in die Ausgangsposition zurück, d.h. aufrechter Stand mit über dem Kopf empor gestreckten Armen.

Mentale Aufgabe: Nehmen Sie wieder die Ausgangsstellung ein (genau wie oben beschrieben). Rufen Sie in Ihrer Vorstellung ein möglichst klares und lebhaftes Vorstellungsbild von der Bewegung hervor, die Sie gerade ausgeführt haben. Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht vorzustellen	leicht vorzustellen	eher leicht vorzustellen	weder leicht noch schwierig	eher schwierig vorzustellen	schwierig vorzustellen	sehr schwierig vorzustellen

8. Ausgangsposition:

Machen Sie eine Faust mit Ihrer nicht dominanten Hand. Strecken Sie Ihren Arm mit geballter Faust über dem Kopf. Lassen Sie den anderen Arm an Ihrer Seite.

Aktion: Schwingen Sie den empor gestreckten Arm so schnell wie möglich abwärts, sodass auch er seitlich am Körper anliegt. Lassen Sie während der Bewegung den Arm gestreckt und die Faust geballt.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein. Versuchen Sie in Ihrer Vorstellung zu fühlen, wie Sie die Bewegung ausführen (ohne dass Sie die Bewegung tatsachlich physisch ausführen)! Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht zu fühlen	leicht zu fühlen	eher leicht zu fühlen	weder leicht noch schwierig	eher schwierig zu fühlen	schwierig zu fühlen	sehr schwierig zu fühlen

9. Ausgangsposition:

Stellen Sie sich vor eine Gymnastikmatte/einen Teppich, geschlossene Fußstellung. Die Arme liegen seitlich am Körper an.

Aktion: Führen Sie eine Rolle vorwärts auf der Matte/auf dem Teppich aus (Sie dürfen dabei die Hände benutzen) und beenden Sie die Bewegung dann wieder in einer stehenden Position.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein. Versuchen Sie in Ihrer Vorstellung zu fühlen, wie Sie die Bewegung ausführen (ohne dass Sie die Bewegung tatsachlich physisch ausführen)! Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht zu fühlen	leicht zu fühlen	eher leicht zu fühlen	weder leicht noch schwierig	eher schwierig zu fühlen	schwierig zu fühlen	sehr schwierig zu fühlen

10. Ausgangsposition:

Machen Sie eine Faust mit Ihrer dominanten Hand (die Hand, mit der Sie schreiben) und bringen Sie diese Hand zur gleichseitigen Schulter (z.B. rechte Hand auf rechte Schulter), sodass Ihr Ellbogen geradewegs von Ihnen weg zeigt.

Aktion: Strecken Sie Ihren Arm im Ellbogengelenk, sodass Ihre Hand die Schulter verlässt und sich nun gerade, parallel zum Boden, vor Ihnen ausgestreckt befindet. Die Hand ist weiterhin zur Faust geballt. Führen Sie die Bewegung langsam aus.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein. Versuchen Sie in Ihrer Vorstellung zu fühlen, wie Sie die Bewegung ausführen (ohne dass Sie die Bewegung tatsachlich physisch ausführen)! Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht zu fühlen	leicht zu fühlen	eher leicht zu fühlen	weder leicht noch schwierig	eher schwierig zu fühlen	schwierig zu fühlen	sehr schwierig zu fühlen

11. Ausgangsposition:

Stehen Sie aufrecht, geschlossene Fußstellung. Die Arme liegen seitlich am Körper an.

Aktion: Heben Sie Ihr rechtes Knie so hoch wie möglich, sodass Sie nun auf dem linken Bein stehen, das rechte Bein im Kniegelenk gebeugt. Nun senken Sie Ihr rechtes Bein, sodass Sie dann wieder auf beiden Füßen stehen. Führen Sie diese Bewegung langsam aus.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein (genau wie oben beschrieben). Rufen Sie in Ihrer Vorstellung ein möglichst klares und lebhaftes Vorstellungsbild von der Bewegung hervor, die Sie gerade ausgeführt haben. Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht vorzustellen	leicht vorzustellen	eher leicht vorzustellen	weder leicht noch schwierig	eher schwierig vorzustellen	schwierig vorzustellen	sehr schwierig vorzustellen

12. Ausgangsposition:

Stehen Sie aufrecht, hüftbreite Fußstellung. Die Arme liegen seitlich am Körper an.

Aktion: Gehen Sie tief in die Hocke und springen Sie dann so hoch wie möglich gerade nach oben, die Arme über den Kopf nach oben ausgestreckt. Landen Sie mit hüftbreiter Fußstellung, und senken Sie die Arme wieder an Ihre Seiten.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein. Versuchen Sie in Ihrer Vorstellung zu fühlen, wie Sie die Bewegung ausführen (ohne dass Sie die Bewegung tatsachlich physisch ausführen)! Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht zu fühlen	leicht zu fühlen	eher leicht zu fühlen	weder leicht noch schwierig	eher schwierig zu fühlen	schwierig zu fühlen	sehr schwierig zu fühlen

13. Ausgangsposition:

Stehen Sie aufrecht, die Füße sind leicht geöffnet. Die Arme liegen seitlich am Körper an.

Aktion: Springen Sie hoch und drehen Sie sich in der Luft links herum, sodass Sie wieder genau in der Ausgangsstellung landen, d.h., Sie vollführen eine vollständige Linksdrehung um 360°.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein (genau wie oben beschrieben). Rufen Sie in Ihrer Vorstellung ein möglichst klares und lebhaftes Vorstellungsbild von der Bewegung hervor, die Sie gerade ausgeführt haben. Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht vorzustellen	leicht vorzustellen	eher leicht vorzustellen	weder leicht noch schwierig	eher schwierig vorzustellen	schwierig vorzustellen	sehr schwierig vorzustellen

14. Ausgangsposition:

Strecken Sie den Arm Ihrer nicht dominanten Hand waagerecht zur Seite aus, die Handfläche zeigt nach unten.

Aktion: Bewegen Sie den Arm vorwärts, bis er sich direkt vor Ihnen befindet (immer noch waagerecht). Lassen Sie Ihren Arm während der gesamten Bewegung gestreckt, und führen Sie die Bewegung langsam aus.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein. Versuchen Sie in Ihrer Vorstellung zu fühlen, wie Sie die Bewegung ausführen (ohne dass Sie die Bewegung tatsachlich physisch ausführen)! Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht zu fühlen	leicht zu fühlen	eher leicht zu fühlen	weder leicht noch schwierig	eher schwierig zu fühlen	schwierig zu fühlen	sehr schwierig zu fühlen

15. Ausgangsposition:

Stehen Sie aufrecht, die Hände liegen seitlich am Körper an.

Aktion: Heben Sie das gestreckte linke Bein so hoch wie möglich (Sie dürfen das linke Knie nicht beugen). Lassen Sie auch das Standbein (rechtes Bein) gestreckt. Senken Sie nun das linke Bein, bis Sie wieder auf beiden Beinen stehen. Führen Sie diese Bewegung langsam aus.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein (genau wie oben beschrieben). Rufen Sie in Ihrer Vorstellung ein möglichst klares und lebhaftes Vorstellungsbild von der Bewegung hervor, die Sie gerade ausgeführt haben. Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht vorzustellen	leicht vorzustellen	eher leicht vorzustellen	weder leicht noch schwierig	eher schwierig vorzustellen	schwierig vorzustellen	sehr schwierig vorzustellen

16. Ausgangsposition:

Stehen Sie aufrecht, hüftbreite Fußstellung. Die Arme sind vollständig über dem Kopf ausgestreckt.

Aktion: Beugen Sie sich langsam im Hüftgelenk nach vorne ab und versuche, mit den Fingerspitzen Ihre Zehen zu berühren (oder, falls möglich, den Boden). Kehren Sie nun in die Ausgangsposition zurück, d.h. aufrechter Stand mit über dem Kopf empor gestreckten Armen.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein. Versuchen Sie in Ihrer Vorstellung zu fühlen, wie Sie die Bewegung ausführen (ohne dass Sie die Bewegung tatsachlich physisch ausführen)! Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht zu fühlen	leicht zu fühlen	eher leicht zu fühlen	weder leicht noch schwierig	eher schwierig zu fühlen	schwierig zu fühlen	sehr schwierig zu fühlen

17. Ausgangsposition:

Machen Sie mit Ihrer nicht dominanten Hand eine Faust. Strecken Sie Ihren Arm mit geballter Faust über dem Kopf. Lassen Sie den anderen Arm an Ihrer Seite.
Aktion: Schwingen Sie den emporgereckten Arm so schnell wie möglich abwärts, sodass auch er seitlich am Körper anliegt. Lassen Sie während der Bewegung den Arm gestreckt und die Faust geballt.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein (genau wie oben beschrieben). Rufen Sie in Ihrer Vorstellung ein möglichst klares und lebhaftes Vorstellungsbild von der Bewegung hervor, die Sie gerade ausgeführt haben. Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht vorzustellen	leicht vorzustellen	eher leicht vorzustellen	weder leicht noch schwierig	eher schwierig vorzustellen	schwierig vorzustellen	sehr schwierig vorzustellen

18. Ausgangsposition:

Stellen Sie sich vor eine Gymnastikmatte/einen Teppich, geschlossene Fußstellung. Die Hände liegen seitlich am Körper an.

Aktion: Führen Sie eine Rolle vorwärts auf der Matte/auf dem Teppich aus (Sie dürfen dabei die Hände benutzen), und beenden Sie die Bewegung dann wieder in einer stehenden Position.

Mentale Aufgabe: Nehmen Sie die Ausgangsstellung ein (genau wie oben beschrieben). Rufen Sie in Ihrer Vorstellung ein möglichst klares und lebhaftes Vorstellungsbild von der Bewegung hervor, die Sie gerade ausgeführt haben. Bewerten Sie nun die Leichtigkeit bzw. Schwierigkeit, mit der Sie diese mentale Aufgabe ausführen konnten.

☐	☐	☐	☐	☐	☐	☐
sehr leicht vorzustellen	leicht vorzustellen	eher leicht vorzustellen	weder leicht noch schwierig	eher schwierig vorzustellen	schwierig vorzustellen	sehr schwierig vorzustellen

Nochmals vielen Dank für Ihre Teilnahme!