The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis

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Eine gewaltige Lichtsinfonie spielte in tiefstem, feierlichen Schweigen über unseren Häuptern, wie um unserer Wissenschaft zu spotten: kommt doch her und erforscht mich! Sagt mir, was ich bin!

~ Alfred Wegener ~

Image source
Acknowledgments

To my family, which – to my great delight – has expanded in the years since I began this grand journey. Thank you for always supporting me unconditionally and preparing me to be able to reach my goals. To my mother and father who would never stop believing in me and to my brother for showing me that also the longest project does eventually come to an end. I love you all. Many thanks to my other family members and friends who supported me along the way.

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Abstract

Background:
Among patients with multiple sclerosis (MS) fatigue is the most commonly reported symptom. It can be subdivided into an effort-dependent (fatigability) and an effort-independent component (trait-fatigue).

Objective:
The objective was to disentangle activity changes associated with effort-independent “trait-fatigue”, from those associated with effort-dependent fatigability in patients with MS.

Methods:
The current study employed behavioral measures and functional magnetic imaging to investigate neural changes in patients with MS associated with fatigue. Forty patients with MS and twenty-two age-matched healthy controls performed in a fatigue-inducing N-back task. Effort-independent fatigue was assessed using the fatigue scale of motor and cognition (FSMC) questionnaire.

Results:
Effort-independent fatigue was observed to be reflected by activity increases in fronto-striatal-subcortical networks primarily involved in the maintenance of homeostatic processes and in motor and cognitive control. Effort-dependent fatigue (fatigability) lead to activity decreases in attention-related cortical and subcortical networks.

Conclusion:
These results indicate that effort-independent (fatigue) and effort-dependent fatigue (fatigability) in patients with MS have functionally related but fundamentally different neural correlates. Fatigue in MS as a general phenomenon is reflected by complex interactions of activity increases in control networks (effort-independent component) and activity reductions in executive networks (effort-dependent component) of brain areas.
Zusammenfassung

Hintergrund

Bei Patienten mit Multipler Sklerose (MS) stellt die Fatigue einer der am häufigst genannten Symptome dar. Sie besitzt sowohl eine belastungs-abhängige („fatigability“) als auch eine belastungs-unabhängige („trait“) Komponente.

Ziel:

Das Ziel der Studie war es, die neuralen Aktivierungsmustern der beiden obengenannten Komponenten in Patienten mit MS mittels Kernspintomografie (MRT) zu untersuchen und diese miteinander zu vergleichen.

Methoden:

In dieser Studie wurden sowohl Verhaltensmessungen, als auch funktionelles MRT eingesetzt um die neuralen Veränderungen bei Patienten mit MS und im Zusammenhang mit Fatigue zu untersuchen. Hierzu wurden 40 Patienten mit MS und 22 gesunde Kontrollektierten rekrutiert, welche eine Fatigue-induzierende N-back Aufgabe durchführten während sie im MRT gemessen wurden. Belastungs-unabhängige Fatigue wurde mittels der Fatigue Skala für Motorik und Kognition (FSMC) erhoben.

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<th>Description</th>
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<tr>
<td>18-FDG-PET</td>
<td>[fluorine-18]fluoro-D-glucose Positron Emission Tomography</td>
</tr>
<tr>
<td>9-HPT</td>
<td>9-Hole Peg Test</td>
</tr>
<tr>
<td>ACC</td>
<td>Anterior Cingulate Cortex</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotrophic Hormone</td>
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<tr>
<td>ALS</td>
<td>Amyotrophic Lateral Sclerosis</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>AVLT</td>
<td>Auditory Verbal Learning Test</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
</tr>
<tr>
<td>BDT</td>
<td>Block Design Test</td>
</tr>
<tr>
<td>BICAMS</td>
<td>Brief International Cognitive Assessment for Multiple Sclerosis</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood Oxygenated Level-Dependent</td>
</tr>
<tr>
<td>BPF</td>
<td>Brain Parenchymal Fraction</td>
</tr>
<tr>
<td>BRB-N</td>
<td>Brief Repeatable Battery of Neuropsychological Tests</td>
</tr>
<tr>
<td>BVMT-R</td>
<td>Brief Visuo-spatial Memory Test-Revised</td>
</tr>
<tr>
<td>BVRT</td>
<td>Benton Visual Retention Test</td>
</tr>
<tr>
<td>CC</td>
<td>Corpus Callosum</td>
</tr>
<tr>
<td>CFS</td>
<td>Chronic Fatigue Syndrome</td>
</tr>
<tr>
<td>CIS</td>
<td>Clinically Isolated Syndrome</td>
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<tr>
<td>CIS-FATIGUE</td>
<td>Checklist Individuals Strength Fatigue</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>COWAT</td>
<td>Controlled Oral Word Association Test</td>
</tr>
<tr>
<td>CRF</td>
<td>Corticotrophin-releasing Factors</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<tr>
<td>CTIP</td>
<td>Computerized Test of Information Processing</td>
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<td>CVLT</td>
<td>California Verbal Learning Test</td>
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<td>CWIT</td>
<td>Color-Word Interference Test</td>
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<td>DEX-CRH</td>
<td>Decamethasone/Corticotropin Releasing Hormone</td>
</tr>
<tr>
<td>D-KEFS</td>
<td>Delis-Kaplan Executive Function System</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Dorso-lateral Prefrontal Cortex</td>
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<tr>
<td>DMN</td>
<td>Default Mode Network</td>
</tr>
<tr>
<td>DOT</td>
<td>Digit Ordering Test</td>
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<td>DSCT</td>
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<tr>
<td>DST</td>
<td>Digit Span Test</td>
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<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>ED</td>
<td>Encephalomyelitis Disseminata</td>
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<tr>
<td>EDSS</td>
<td>Extended Disabilities Status Scale</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
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<tr>
<td>FA</td>
<td>Fractional Anisotropy</td>
</tr>
<tr>
<td>FAI</td>
<td>Fatigue Assessment Inventory</td>
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<tr>
<td>FDS</td>
<td>Fatigue Descriptive Scale</td>
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<tr>
<td>FES</td>
<td>Fatigue Descriptive Scale</td>
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<tr>
<td>FEE</td>
<td>Fast Field Echo</td>
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<td>FIS</td>
<td>Fatigue Impact Scale</td>
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<tr>
<td>FLAIR</td>
<td>Fluid-attenuated Inversion Recovery</td>
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<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<tr>
<td>FRS</td>
<td>Fatigue Rating Scale</td>
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<td>FSMC</td>
<td>Fatigue Scale of Motor and Cognition</td>
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<td>FSS</td>
<td>Fatigue Severity Scale</td>
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<tr>
<td>G+</td>
<td>Gadolinium Enhanced</td>
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<tr>
<td>GM</td>
<td>Grey Matter</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamic-Pituitary-Adrenal</td>
</tr>
<tr>
<td>ICA</td>
<td>Independent Component Analysis</td>
</tr>
<tr>
<td>IFG</td>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>IL-1 / IL-6</td>
<td>Interleukin 1 / Interleukin 6</td>
</tr>
<tr>
<td>ISI</td>
<td>Inter Stimulus Interval</td>
</tr>
<tr>
<td>JLO</td>
<td>Judgement of Line Orientation</td>
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<tr>
<td>LPM</td>
<td>Lesion Probability Maps</td>
</tr>
<tr>
<td>MACFIMS</td>
<td>Minimal Assessment of Cognitive Functions in Multiple Sclerosis</td>
</tr>
<tr>
<td>MADRS</td>
<td>Montgomery-Asberg Depression Rating Scale</td>
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<tr>
<td>MFG</td>
<td>Middle Frontal Gyrus</td>
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<tr>
<td>MFIS</td>
<td>Modified Fatigue Impact Scale</td>
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<tr>
<td>MNI</td>
<td>Montreal Neurological Institute</td>
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<tr>
<td>MPRAGE</td>
<td>Magnetization Prepared Rapid Acquisition Gradient Echo</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MS</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>mSDMT</td>
<td>Modified Symbol Digit Modality Test</td>
</tr>
<tr>
<td>MSFC</td>
<td>Multiple Sclerosis Functional Composite Scale</td>
</tr>
<tr>
<td>NAA/Cr</td>
<td>N-acetyl Aspartate to Creatine</td>
</tr>
<tr>
<td>NBV</td>
<td>Normalized Brain Volume</td>
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<tr>
<td>PASAT</td>
<td>Paced Auditory Serial Addition Task</td>
</tr>
<tr>
<td>PD</td>
<td>Proton Density</td>
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<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>PFC</td>
<td>Prefrontal Cortex</td>
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<tr>
<td>PPMS</td>
<td>– Primary Progressive Multiple Sclerosis</td>
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<td>-----------------------------------------</td>
</tr>
<tr>
<td>RA</td>
<td>– Rheumatoid Arthritis</td>
</tr>
<tr>
<td>rANOVA</td>
<td>– Repeated Measures Analysis of Variance</td>
</tr>
<tr>
<td>REM</td>
<td>– Rapid Eye Movement</td>
</tr>
<tr>
<td>RLS</td>
<td>– Restless-Legs-Syndrome</td>
</tr>
<tr>
<td>RRMS</td>
<td>– Relapsing Remitting Multiple Sclerosis</td>
</tr>
<tr>
<td>RSFC</td>
<td>– Resting State Functional Connectivity</td>
</tr>
<tr>
<td>RTs</td>
<td>– Reaction Times</td>
</tr>
<tr>
<td>RWT</td>
<td>– Regensburger Wortflüssigkeitstest</td>
</tr>
<tr>
<td>SIPSR</td>
<td>– Sickness Impact Profile Sleep and Rest Scale</td>
</tr>
<tr>
<td>SLE</td>
<td>– Systemic Lupus Erythematosus</td>
</tr>
<tr>
<td>SMA</td>
<td>– Supplementary Motor Area</td>
</tr>
<tr>
<td>SOA</td>
<td>– Stimulus Onset Asynchrony</td>
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<td>SPART</td>
<td>– Spatial Recall Test</td>
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<td>SPECT</td>
<td>– Single Photon Emission Computer Tomography</td>
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<td>SPL</td>
<td>– Superior Parietal Lobule</td>
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<td>SPM8</td>
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1. Multiple Sclerosis

Multiple Sclerosis (MS), also known under its Latin name *encephalomyelitis disseminata* (ED), represent an exceptionally multifaceted and heterogenic neurological disease affecting approximately 2.1 million people worldwide (DeLuca & Nocentini, 2011). The etiology of the disease has thus far eluded encompassing explanations and is currently viewed as a complex interaction between genetic predispositions, autoimmune reactions and environmental factors (Kroner-Milsch et al., 2012).

The current understanding of the disease sees its definition as an autoimmune-induced, chronic-inflammatory affliction of the central nervous system (CNS). As a consequence of these inflammations, numerous regions within the brain experience demyelization, seemingly arbitrarily with regard to their spatiotemporal characteristics, which cause both axonal and neural damage, equally leading to dispersed and varying functional deficits (Kroner-Milsch et al., 2012). These inflammatory areas are referred to as *plaques* and are clearly distinguishable from their surrounding tissue, often acquiring a round shape with a diameter between 2-10mm. Newly appearing (active) plaques and older plaques with necrotic/sclerotic tissue often appear in close proximity to each other. So called *shadow plaques* refer to plaques that exhibit a certain amount of re-myelination, albeit that the myelin sheath in these cases is vulnerably thin compared to healthy tissue (Hacke & Poeck, 2010; Kroner-Milsch et al., 2012).

According to the world health organization (WHO) (World-Health-Organization, 2008), the mean global prevalence of the disease is estimated to be 30/100 000 with an average incidence of 2.5/100 000 and an average age of onset of 29.2 years. The prevalence is highest in Europe (80/100 000) and greater in high-income countries (89/100 000) than in upper middle (32/100 000), lower middle (10/100 000) and low income countries (0.5/100 000). In 2008, Germany in particular ranked as the country with the third highest prevalence worldwide (149/100 000) (World-Health-Organization, 2008).

Till recently, the total number of persons affected with the disease in Germany has been estimated to be between 120 000 and 140 000, however newer inspections by the German statutory health insurance registers provide estimates of over 200 000 afflicted persons (Dippel, Mäurer, Schinzel, Müller-Bohn, &
Larisch, 2015; Petersen, Wittmann, Arndt, & Göpffarth, 2014). This would increase the prevalence in Germany to roughly 173/100 000. Annual costs per patient in Germany vary between 28,200€ in mild up to 62,700€ for severe disease severity (Flachenecker, Kobelt, Berg, Capsa, & Gannedahl, 2017). When regarding Europe as a whole, annual costs per patient vary between 22,800€ (range of country means: 12,600€-27,300€), 37,100€ (22,500€-54,700€) and 57,500€ (27,500€-77,600€) for mild, moderate and severe disease severity respectively (Kobelt, Thompson, Berg, Gannedahl, & Eriksson, 2017).

The gender-distribution shows an unexplained imbalanced distribution, with women being afflicted between 2 and 3 times more commonly than men (Flachenecker & Zettl, 2006; Flachenecker et al., 2005; Kroner-Milsch et al., 2012).

The clinical appearance of patients with MS often does no present a reliable indicator for the lesion load actually evident within the CNS of the patients. Rather, it is not uncommon, that a multitude of plaques can appear within the CNS without leading to noticeable functional impairment. Commonly the functional impairment associated to a plaque is directly related to its location within the CNS and to the extent of demyelization and damage caused to both the axons and neurons. The conduction of electro-chemical impulses along the axon is drastically impaired or even impossible depending on the extent of demyelization evident (Hacke & Poeck, 2010).

1.1 Classifications in multiple sclerosis

The clinical course of MS can typically be classified into three categories: relapsing-remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS). RRMS is characterized by episodes of acute exacerbations with complete or incomplete remittance. SPMS or PPMS on the other hand are characterized by chronic, continuous disease progression. For an overview, please refer to figure 1 below.

Relapses are defined as the emergence of new clinical symptoms lasting longer than 24 hours, distinguishable from a previous episode by appearing at least 30 days apart and not being attributable to a change in body-temperature or viral infection (Kroner-Milsch et al., 2012; McDonald et al., 2001; Polman et al., 2011).
Multiple Sclerosis

1.1 Classifications in multiple sclerosis

They may also appear as the recurrence of previously exhibited clinical symptoms, however this occurs less frequently.

Clinically Isolated Syndrome (CIS)

The very first manifestation of MS symptoms is termed a clinically isolated syndrome (CIS) (Kroner-Milsch et al., 2012). The likelihood of MS manifesting subsequently to a CIS increases, if magnetic resonance imaging (MRI) scans show signs of multiple cerebral lesions at the time of the CIS (Tintoré et al., 2006). In approximately 21% of patients experiencing a CIS, the incident remains monofocal, whilst in the remaining 79% of patients multiple brain regions are affected (Confavreux, Vukusic, & Adeleine, 2003). CIS are typically associated with symptoms such as inflammation of the optic nerve (optic neuritis), paresthesia or motor deficits in young patients less than 30 years of age. Patients who acquire the disease at a later age however tend to experience a gradually increasing paresis of the lower extremities as the first symptom (Hacke & Poeck, 2010).

Relapsing-Remitting MS (RRMS)

The relapsing-remitting form of MS is characterized by a complete or partial remission following a clearly distinguishable MS episode leading to an aggravation of clinical symptoms. Additionally, a continuous deterioration of the clinical symptoms is not evident between two discriminable MS episodes. Approximately 80% of patients with MS show this form of MS in the initial phase of the disease and early symptoms include paresthesia, visual problems and strain-induced weakness of the legs (Hacke & Poeck, 2010; Kroner-Milsch et al., 2012).

Secondary Progressive MS (SPMS)

In an estimate of 50% of patients (Confavreux et al., 2003) with an initial relapsing-remitting type of MS the disease course develops into a secondary-progressive form within 10 to 15 years, which is characterized by a phase of steadily progressing disability in the patient following an initial phase of RRMS and which may or
may not be accompanied by additional relapses (Kroner-Milsch et al., 2012). The exact moment of transition to this form of MS is difficult to isolate, as a prolonged phase of gradual increase of disability by definition essentially lasts between 6-12 months (Rovaris et al., 2006).

Primary Progressive MS (PPMS)
This form of MS course is defined by the absence of any distinguishable MS episodes whilst patients experience a gradual progression of the symptoms associated with MS. At times, the progression of the disease may encounter a phase of inactivity, termed plateaus, or patients may even experience periods of slight improvement of the symptoms (Kroner-Milsch et al., 2012). This form of MS occurs within approximately 15% of patients with MS (Confavreux et al., 2003).

![Types of MS](www.nationalmssociety.org)

**Figure 1:** Types of MS (Lublin et al., 2014); Image source: www.nationalmssociety.org

EDSS
A well-established scale describing the physical mobility and functional impairments experienced by patients with MS was developed in the early 1980s by John F. Kurtzke (Kurtzke, 1983). The Extended Disability Status Scale (EDSS) is an internationally used measure that rates these impairments on a scale of 0 to 10. Patients are assigned an EDSS score in order to obtain an objective measure of improvement or...
deterioration of their capabilities over the course of the disease. A score of 0 indicates no functional impairments while a score of 10 indicates death as a result of MS. Scores of 7 and above indicate that the patient is not able to walk. For a description of the denotation of the EDSS scores, please see figure 2. Further detailed information on the EDSS can be viewed in Appendix A. The greatest disadvantage of the EDSS however is that it is primarily constituted and influenced by a decrease in mobility. Cognitive functions and functions of upper extremities and of the hands (e.g. grasping) are not taken into account. The Multiple Sclerosis Functional Composite Scale (MSFC) on the other hand takes these factors into account, is however implemented far less often in the field.

**Figure 2: The Extended Disability Status Scale (EDSS) (Kurtzke, 1983)**

Image source: https://my-ms.org/ms_progression.htm

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1.2 Clinical presentation of multiple sclerosis

The clinical presentation of MS is very heterogeneous as the functional impairments provoked by the disease are dependent on location and size of the inflammatory areas and lesions. One of the most common dysfunctions in MS is optic neuritis. This dysfunction is often one of the first symptoms experienced by patients with in the initial phase of the disease additionally to sensory disturbances (Kroner-Milsch et al., 2012). Typical symptoms include a loss of visual acuity including unclear or blurred vision, pain during eye movement, sensitivity to bright light or even blindness. Symptoms often arise within a few days or weeks and can regress within a 3-4 weeks. Visual impairments can also be elicited through a rise in temperature or through physical exertion. This is referred to as the Uhthoff-Phenomenon (Hacke & Poeck, 2010).
Another early manifestation of the MS disease includes sensory disturbances commonly experienced in the hands and feet including miss-sensations such as tingling paresthesia, numbness, a fuzzy feeling and less frequently also a miss-sensation of coldness (Hacke & Poeck, 2010). The Lhermitte Phenomenon, also known as Lhermitte’s sign, refers to an uncomfortable electrical sensation running down the spine and into the limbs when the patients head is bowed forward and the neck is flexed. This phenomenon can serve as a pathological indicator for MS lesions in the cervical spine, if other spinal injuries can be rejected (Kroner-Milsch et al., 2012).

Additionally, patients with MS often suffer from acute or sub-acute pain, mostly in conjunction with spasticity, dysesthesia, back-pain, the Lhermitte phenomenon or even trigeminal neuralgia (Kroner-Milsch et al., 2012).

Early manifestations of motor disturbances and malfunction in the wake of the MS disease include weaknesses in arms and legs (Hacke & Poeck, 2010; Kroner-Milsch et al., 2012). During later stages, proximal paresis and weakness of the limb girdle characterize the disease; whilst inflammations within the pyramidal tract can lead to spasticity appearing simultaneously, as well as the appearance of pathological reflexes such as the Babinski sign (upward response of the hallux). In general, patients with MS display an increase muscle tone and may also suffer from intention tremor, nystagmus, saccaded pursuit eye movement, as well as dysarthria as a result of damage to the cerebellum (Hacke & Poeck, 2010).

Micturition and bladder dysfunction represent dysfunctions of the autonomous nervous system affecting up to 75% of patients predominantly in later stages of the disease. Likewise, sexual dysfunction also appears in many patients during the course of the disease but often remains unreported as a result of patients being ashamed of mentioning them to their medical practitioners (Kroner-Milsch et al., 2012).

Recent studies have shown that cognitive deficits in patients with MS can be identified at early stages of the disease and that in 43-70% of patients these deficits will develop during the course of the disease
The clinical presentation of multiple sclerosis (Chiaravalloti & DeLuca, 2008; Schulz, Kopp, Kunkel, & Faiss, 2006). The type of cognitive impairment depend strongly on the cerebral location and size of the inflammation or lesion, but typically include mnemic and executive functions, attentional processes and information processing speed (Chiaravalloti & DeLuca, 2008).

In addition to the motor and cognitive dysfunctions, affective disorders regularly arise in conjunction with the disease. These may include depressive, panic, anxiety and obsessive-compulsive disorders (Feinstein, DeLuca, Baune, Filippi, & Lassman, 2013; Jones et al., 2012; Korostil & Feinstein, 2007). The comorbidity of depression in patients with MS is especially worth noting, as it is both higher than in the normal population as well as in other neurological diseases (Ghaffar & Feinstein, 2007). The risk of developing a depression is up to three times higher in patients with MS than in the general population (Paparrigopoulos, Ferentinos, Kouzoupis, Koutsis, & Papadimitriou, 2010) and the prevalence varies between an incidence of 25-50% in patients with MS (Feinstein et al., 2013; Piber et al., 2012; Siegert & Abernethy, 2005). The 12-month-prevalency for a major-depressive episode in patients with MS between the ages of 18 and 45 is calculated to be around 25.7% (Patten, Beck, Williams, Barbui, & Metz, 2003). In a large scale survey (N>4000), researchers found that patients with SPMS further showed significantly more depressive symptoms than patients with other forms of MS, independent of gender (Jones et al., 2012). In general however it is uncertain how MS-associated depression is related to disease-specific factors such as disease type, disease duration and physical disability, as the scientific results are very heterogeneous (Feinstein, 2011). Feinstein (2011) concluded that individual coping strategies may manifest more meaningful determinants for the psychological state of patients with MS than physical disability alone (Feinstein, 2011). Although the clinical presentation of MS-associated depression resembles a primary depression not caused by bodily dysfunction, aspects such as irritability, melancholy, despondency, depressiveness, feelings of hopelessness and despair appear to be more characteristic in depressive MS-patients than low self-esteem and feelings of guilt (Ghaffar & Feinstein, 2007). Diagnosing a depression in patients with MS is complicated, as the classical neuro-vegetative symptoms of a depression such as sleeping disorders, change in appetite,
The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis

weariness and exhaustion could also be caused by primary disease mechanisms such as the presence of MS-related fatigue (Braley & Chervin, 2010; Ghaffar & Feinstein, 2007; Paparrigopoulos et al., 2010). This complex interaction may be the reason for depression being generally under-diagnosed and under-treated in patients with MS (McGuigan & Hutchinson, 2006; Schiffer, 2005). Besides being regarded as a central predictor for quality of life in MS (Amato et al., 2001; D’alisa et al., 2006), depression also negatively influence cognitive functioning (Chiaravalloti & DeLuca, 2008; Feinstein, 2006), therapeutic adherence and compliance (Bruce, Hancock, Arnett, & Lynch, 2010; Mohr et al., 1997) and further increases suicidal thoughts and actions to an extent that the prevalence of suicidal tendencies is as high as 28.6% in patients with MS (Feinstein, 2002). Specifically, in addition to the depression, social isolation, young age, male gender, low income, a progressive disease course, severe physical disability and early disease stage constitute risk-factors for suicide in patients with MS (Pompili et al., 2012).

Due to the high comorbidity and clinical relevance of depressive disorders in MS, it is recommended that screening instruments validated for patients with MS (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003; Honarmand & Feinstein, 2009), such as the Hospital Anxiety and Depression Scale (HADS) (Herrmann-Lingen, Buss, & Snaith, 2011) and Beck Depression Inventory (BDI) be employed as a standard when treating patients with MS (Feinstein, 2011; Schiffer, 2005), as early detection and treatment can prove to be critical.

Insomnia, sleep apnea, narcolepsy, Restless-Legs-Syndrome (RLS) and rapid eye movement (REM)-sleep-behavior-disorder are all forms of sleep disorders that may arise and are much more prevalent in patients with MS than in other chronic diseases or in the normal population, arising in approximately 25-54% of patients (Bamer, Johnson, Amtmann, & Kraft, 2008; Barun, 2013).

Disentangling the effects of depression, sleep disorders and fatigue is considered a daunting task (Kroner-Milsch et al., 2012) and the complex relationship should always be acknowledge. In the following sections one of the most prevalent and debilitating symptoms of the disease will be discussed in detail: fatigue.
2. MS-related fatigue

2.1 Definition

According to the Oxford English Dictionary, the word *fatigue* originated in the mid-17th century, refers to “extreme tiredness resulting from mental or physical exertion or illness” and is derived from the French word *fatigue* (noun) which in turn is derived from the Latin word *fatigare* (‘tire out’) (Oxford-English-Dictionary, 2017). With regard to fatigue in Multiple Sclerosis, this definition is suitable, yet should be more precise when viewed in relationship to the disease.

As fatigue is a subjectively experienced phenomenon referring to both cognitive and motor exhaustion, finding a consensus for a unitary definition of this symptom proved complicated (Induruwa, Constantinescu, & Gran, 2012; Penner et al., 2009). It is a phenomenon which is associated with the affective state of the patient to a greater extent than with measures of physical disability (e.g. EDSS) or neurological diagnosis (e.g. neuroimaging) (DeLuca, 2005; DeLuca, Genova, Capili, & Wylie, 2009) A popular definition of fatigue in connection with MS is offered by the Multiple Sclerosis Council for Clinical Practice Guidelines (Multiple-Sclerosis-Council-for-Clinical-Practice-Guidelines, 1998), who define fatigue as

“- a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities”.

A newer and more detailed definition was recently offered by Mills and Young (2008), who defined fatigue as “reversible, motor and cognitive impairment with reduced motivation and desire to rest, either appearing spontaneously or brought on by mental or physical activity, humidity, acute infection and food ingestion. It is relieved by daytime sleep or rest without sleep. It can occur at any time but is usually worse in the afternoon. In MS, fatigue can be daily, has usually been present for years and has a greater severity than any premorbid fatigue” (Mills & Young, 2008). This definition incorporates modern approaches and findings of studies over the last few years and mentions causes, coping mechanisms and therapy approaches.
Similarly to the feeling of exhaustion, fatigue is characterized by the desire for recuperation, restlessness and loss of motivation and is aggravated by physical activity, stress and depression, yet can be moderated by rest, sleep, sexual intercourse and positive experiences (Krupp, Alvarez, LaRocca, & Scheinberg, 1988). MS related fatigue however differs from ordinary exhaustion as it can hinder continuous physical performance or daily duties, can be aggravated by increased temperature and is easily provoked (Krupp et al., 1988). Generally, fatigue is considered substantially greater and more persistent than ordinary exhaustion (Calabrese, 2009), is often not alleviated or reduced by rest and may interfere with the physical and cognitive functioning of the patient to such an extent that occupational as well as requirements of daily life are negatively affected (Barak & Achiron, 2006; DeLuca & Nocentini, 2011; Krupp, 2002). Fatigue experienced by the general, healthy population differs as it can be strongly alleviated by rest and breaks and are predominantly only temporary (Krupp et al., 1988).

In addition to being appreciated as one of the typical feature, MS-related fatigue is one of the most prevalent, most common symptoms of the disease (Rao, Leo, Bernardin, & Unverzagt, 1991). It affects an estimate of 70-90% of all patients with MS, is often mentioned as the most disabling symptom (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Freal, Kraft, & Coryell, 1984; Krupp et al., 1988; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989b; Minden et al., 2006) and is the leading cause of unemployment related to the MS disease (Simmons, Tribe, & McDonald, 2010).

Besides occurring in MS, the probability of fatigue occurring in conjunction with other diseases such as Myasthenia Gravis (75-89%), Amyotrophic Lateral Sclerosis (ALS; 44-83%), post-stroke (36-77%), Morbus Parkinson (28-58%), in Post-Polio-Syndrome (27-91%) and even through traumatic brain injury (TBI; 45-73%) is higher than in the general population (Kluger, Krupp, & Enoka, 2013).

MS-related fatigue is further characterized by the possibility of its emergence at all stages of the disease, displaying a prevalence of being one of the first symptoms to appear of roughly 31-50% of patients (Fisk, Pontefract, et al., 1994; Krupp et al., 1988). Additionally, fatigue may occur prior to or during an episode of increased MS activity or even persist chronically as an enduring symptom (Comi, Leocani, Rossi, & Colombo,
2. MS-related fatigue

2.1 Definition

Case studies have found that an increased MS activity may even manifest itself solely in a significant increase of fatigue in the patient (Flachenecker & Meissner, 2008a). Although fatigue may occur at any time of the day, it usually tends to appear mostly in the afternoon and in the evening (Freal et al., 1984; Krupp et al., 1988; Mills & Young, 2008). Further, fatigue may frequently be experienced when the patient is at rest and is not necessarily linked to cognitive or physical exertion (Comi et al., 2001), although it may also be elicited by these (Claros-Salinas et al., 2013; Krupp et al., 1988). Approximately 40% of patients with MS indicate that fatigue constitutes the most disabling symptom of the disease (Bakshi, 2003). This in turn signifies, that for these patients, fatigue interferes in daily life to a greater degree than other neurological symptoms caused by the disease such as spasticity, paresis, pain, muscle-weakness, and bladder control (Bakshi, 2003). In light of these findings, it is not surprising that fatigue has become one of the factors playing an important role in the evaluation of performance of MS-patients (Hausotter, 2009).

The empirical evidence of sociodemographic and disease associated factors correlating with fatigue is varied. Already over a century ago, it was known, that self-report measures of fatigue correlate poorly with actual physical performance or measures of disease activity (Mosso, 1904; Wessely, Sharpe, & Hotopf, 1998). Although MS-related fatigue is not associated with age or gender (Bakshi et al., 2000; Barak & Achiron, 2006; Mills & Young, 2011), level of education was found to be negatively correlated to fatigue i.e. lower fatigue scores were associated with higher levels of education (Lerdal, Celius, & Moum, 2003). Although some studies have also found a correlation between subjectively experienced fatigue and disease duration (Lerdal et al., 2003), the majority of studies indicates otherwise (Bakshi et al., 2000; Barak & Achiron, 2006; Mills & Young, 2011). Similarly, the empirical evidence concerning the association between physical disability and MS-related fatigue remains uncertain. Some studies have found weak to moderate associations between these two factors (Bakshi et al., 2000; Forbes, While, Mathes, & Griffiths, 2006; Kroencke, Lynch, & Denney, 2000; Krupp et al., 1988), whilst other studies failed to find relationships between the experience of fatigue and physical disability (Barak & Achiron, 2006; Egner, Phillips, Vora, & Wiggers, 2003). Disease type has been found to be closely related to fatigue, indicating that patients with PPMS experience fatigue more often and more pronounced than in patients with RRMS (Hadjimichael,
The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis

Vollmer, & Oleen-Burkey, 2008; Mills & Young, 2011; Patrick, Christodoulou, & Krupp, 2009; Razazian, Shokrian, Bostani, Moradian, & Tahmasebi, 2014). These findings could however be attributed to increased disability in PPMS patients compared to RRMS patients (Ghajarzadeh et al., 2013; Kroencke et al., 2000) or even the manifestation of depressive disorders appearing on connection with serious illnesses (Bakshi et al., 2000).

2.2 Cognitive and motor fatigue

The current understanding of fatigue differs from previous perceptions. It has become ever more established that fatigue, which was previously assumed to be a uni-dimensional construct, should in fact be viewed as the result of the interaction of two distinct dimensions. These dimensions are motor fatigue on the one hand and cognitive fatigue on the other (Penner & Kappos, 2009).

Modern questionnaires take this discrepancy into account and offer differentiated scales for each dimension in their analysis. These values are obtained by employing domain specific questions in these self-report questionnaires.

Motor fatigue can be objectified by measuring decreases in strength, frequency, or persistence of motor reactions over time or following induced strain (Beatty et al., 2003). In recent years, the objectification of motor fatigue has been the scrutiny of many studies and numerous new methods have been found. Amongst others, by using kinematic gait analysis, it was possible to objectively measure and discriminate motor fatigue in patients with MS in the absence of muscular exhaustion (Sehle, Vieten, Sailer, Mundermann, & Dettmers, 2014).

Similarly, cognitive fatigue has been objectified by the deterioration of cognitive functioning over time or following cognitive load (Beatty et al., 2003). In comparison to the well-established and numerous studies found regarding motor fatigue, cognitive fatigue has only come to the attention of researchers in recent years (DeLuca, 2005).
Most patients however tend to experience both motor and cognitive fatigue simultaneously with only a small portion of patients report experiencing only a single dimension of fatigue (Penner & Kappos, 2009). It is unclear at this point, whether these two dimension share mutual pathophysiological correlates or whether they are independent of each other but appear in conjunction.

In their study, Chaudhuri and Behan (Chaudhuri & Behan, 2000) distinguish between these two presentations of fatigue, differentiating physical presentations of fatigue, defined as the inability to sustain a specified force output or work rate during exercise, from the cognitive or mental fatigue which they defined as representing a failure of physical and mental tasks that require self-motivation and internal cues in the absence of demonstrable cognitive failure or motor weakness. The latter form was further also termed central fatigue in contrast to peripheral fatigue, as it represents a form of fatigue which finds its cause in the CNS, rather than the peripheral fatigue which “is attributed to the failure of neuromuscular transmission, metabolic defects of the muscles or a peripheral circulatory failure” (Chaudhuri & Behan, 2000). In their paper, Chaudhuri and Behan hypothesized, that central fatigue was specifically caused by a failure of the non-motor function of the basal ganglia. This hypothesis will be discussed in detail at a later point in the text. Other studies (Claros-Salinas et al., 2013) showed, that central or cognitive fatigue can be induced by both physical and more importantly also cognitive exertion, further supporting the discrimination between central and peripheral fatigue.

Where possible, the discrimination between motor and cognitive dimensions of fatigue will be highlighted in the following sections further describing the essential discrimination between primary and secondary fatigue.

### 2.3 Primary and secondary fatigue

In the following section yet another distinction within the concept of fatigue will be introduced. The concepts of *primary* and *secondary* fatigue were coined to differentiate between primary fatigue as fatigue which manifests itself a direct result of the neuroinflammatory MS disease and the effects on the central nervous system, whilst secondary fatigue refers to fatigue arising as a byproduct by symptoms, disorders or
illnesses related or unrelated to MS such as brain injury, sleep dysfunction, depression or infections to name but a few. In the next section each of these concepts will be discussed in detail.

2.3.1 Primary fatigue

Primary fatigue in MS refers to fatigue caused by primary neural mechanisms and may appear as a consequence of centrally mediated processes which are characterized by the disease. It is often defined as “significant fatigue that persists despite adjustment of medications and management of mobility issues as well as of confounding medical problems such as depression and sleep disruption” (Kinkel, 2000; Multiple-Sclerosis-Council-for-Clinical-Practice-Guidelines, 1998). The cause of primary fatigue as yet remains unclear; however theories toward the pathophysiology of fatigue include demyelination, axonal loss in the CNS, as well as inflammatory processes and immunological actions (Kos, Kerckhofs, Nagels, D’Hooghe, & Ilsbroukx, 2008).

2.3.1.1 Models of fatigue

Basal ganglia dysfunction

One of the most influential models to explain the occurrence of fatigue in MS is offered by Chaudhuri and Behan (Chaudhuri & Behan, 2000) and shall be touched upon numerous in the sections below. In addition to the aforementioned distinction between peripheral and central fatigue, Chaudhuri and Behan further proposed that central fatigue occurs as a dysfunction of structures in the basal ganglia and frontal lobe and that the non-motor functions of the basal ganglia are of pivotal importance for the emergence of fatigue, specifically due to a “dysfunction of the striato–thalamo–cortical loop connecting the neostriatum with the prefrontal cortex” (Chaudhuri & Behan, 2000). Specifically, the functions of the aforementioned areas are important for the maintenance of performance, especially of parietal areas during sustained attention. Although the hypothesis was originally not explicitly developed for fatigue in MS nor for cognitive fatigue, the hypothesis has gained widespread interest and acknowledgment among MS-researchers. Structural MRI studies as well as functional MRI (fMRI) studies have found evidence for structural correlates such as cortical thickness, lesion burden, atrophy or white matter connections between the aforementioned areas
as well as altered functioning therein and offer support for the proposed model. Often functional correlates showed an increased activation in both motor and non-motor areas which was associated with both motor and cognitive fatigue. These studies will be highlighted further below. This hyper-activation was often interpreted as portraying a compensatory mechanism tailed by a failure to uphold this compensation or to compensate for further demands which in turn lead to accelerated declines in performance, also known as *fatigue*.

**Trait and state fatigue**

Recently, a new approach of regarding fatigue in MS has been proposed by Genova and her colleagues (Genova et al., 2013), which has been widely accepted by the scientific community. According to these researchers, the explanation of fatigue can be divided into two distinct forms.

Firstly it is proposed that patients with MS become fatigued following a comparatively simple task due to neurodegenerative or neuroinflammatory processes. This form of explanation can be termed the compensatory state theory of fatigue and suggests that the level of fatigue is *state dependent* and requires some form of exertion to become debilitating. It also implies that patients do not feel fatigued if they are inactive or do not perform tasks. This form of fatigue can be labelled *state fatigue* or *effort-dependent fatigue* (DeLuca, Genova, Hillary, & Wylie, 2008; Hanken, Eling, & Hildebrandt, 2014a) and constitutes a transient dynamic condition, which can vary with time and can fluctuate based on both internal and external factors (Genova et al., 2013). In a call for a unified taxonomy, Kluger et al. 2013 propose a similar form of classification for fatigue and its causes, referring to the abovementioned form of fatigue as *fatigability* (Kluger et al., 2013). Inherent in its definition, *state fatigue* by nature can be elicited by means of fatigue-inducing tasks during which the level of fatigue rises. For an overview of which neuropsychological and day-to-day tasks may elicit fatigue most effectively, please refer to the section entitled *induction of fatigue* on the previous pages.

Secondly, fatigue is proposed to be understood as a neurological and (neuro-)psychological symptom similar to depression. It thus constitutes a *psychogenic trait* and may de facto be the cause of debilitating
behavior rather than the consequence of exertion (Bol, Duits, Hupperts, Vlaeyen, & Verhey, 2009; Hanken et al., 2014a). Trait fatigue may be viewed as an effort-independent component referring to the experience of fatigue across a long period of time, which remains stable and is not likely to change significantly over time (Genova et al., 2013). Similar to depression, trait fatigue may be measured by means of self-report questionnaires and scales which make use of fatigue-specific questions to assess the extent of fatigue in patients with MS. For an overview of the most common questionnaires and scales, please refer to the section entitled measures of fatigue below.

Genova and her colleagues not only proposed a new distinction between different types of fatigue, but additionally performed a combined fMRI and DTI study investigating each of the two domains of fatigue (Genova et al., 2013). The results are described in detail in the section addressing functional studies of fatigue. In short, results obtained in their study offered further support for the model by Chaudhuri and Behan. The study further found evidence underpinning the general understanding that fatigue in MS is not observable in decreases in behavioral or neuropsychological measures as has been observed for over 100 years (Mosso, 1904). Their results showed that no differences between the patient group and the control group were evident in neuropsychological measures. This may however be attributed to the comparatively small group size.

Compensatory activation hypothesis

Based on fMRI findings that CIS patients and patients with MS with mild to moderate cognitive impairment show an increase recruitment of cortical areas, researchers came to two conclusions: firstly, functional changes in diseased brains are already present before any noticeable clinical deficits arise, and secondly, that this increase in cerebral activation is indeed responsible for the compensation of such potential deficits (Penner, Opwis, & Kappos, 2007). The researchers went on to state, that severe cognitive impairment may be a consequence of the failure of the aforementioned compensatory mechanisms. The researchers proposed that the course of this compensatory mechanisms may take on an inverted-U form, meaning that as impairment (i.e. cortical damage due to the disease) increases, so does the functional compensation. At
some point however, the impairment reaches a point at which the compensatory mechanisms fail and can’t counteract the negative effects (see figure 3). The researchers see these compensatory mechanisms as forming the base for potential therapeutic interventions aimed at strengthening already established compensatory hyper-activations and at potentially creating new functional networks (Penner et al., 2007).

Figure 3: Left: functional brain activation during a tonic alertness task in healthy control subjects, mildly impaired and severely impaired patients with MS. Right: The inverted-U shaped curve of compensatory functional brain activation in respect to increasing impairment. Image source: (Penner et al., 2007)

Inflammatory hypothesis

In 2014, Hanken and her colleagues (Hanken, Eling, & Hildebrandt, 2014b) proposed a new model for cognitive fatigue following a review by the same group about the relation between fatigue, cognitive performance and brain atrophy in patients with MS (Hanken et al., 2014a), in which the authors conducted a search on PubMed for articles concerning the relation between fatigue and cognitive performance or brain atrophy or functional MRI. The review found, that of all tested cognitive domains, only tasks assessing alerting/vigilance were strongly related to fatigue. This point will be picked up upon at a later section of this work. From the outset in their review the authors stated, that they proposed that fatigue was neither a compensatory state nor a psychogenic trait, but rather a feeling with behavioral effects caused by brain atrophy or neurochemical dysfunction within the alerting/vigilance system (Hanken et al., 2014a). The later publication elucidated upon this. The proposed model argued that the subjectively experienced sensation of fatigue can be viewed as a consequence of inflammation induced neural processing within interoceptive
and homeostatic brain areas. The model further argues, that fatigue is strongly associated with particular cognitive states, including alertness and vigilance, which are reliant on high levels of endogenous attention and during which distraction by internal events can easily occur (Hanken et al., 2014b). Their model of fatigue also takes into account the discrepancy between subjectively experienced fatigue and objective decrements in behavioral performance. In their model it is hypothesized that subjective experience of fatigue may be a variation of inflammation-induced sickness behavior resulting from cytokine-mediated changes in activity in brain areas such as the insula, anterior cingulate and the hypothalamus, all involved in interoception and homeostasis. Following this statement, the researchers gave a review of studies investigating the neural correlates of peripheral inflammation (Hanken et al., 2014b). Even though the inherent assumption for the cause of fatigue in MS may differ, the authors do acknowledge the role of the cortico-subcortical vigilance network and the role it plays in the objective, measureable decrements of fatigue (Hanken et al., 2014a), thus incorporating the models of Chaudhuri and Behan and many findings of previous studies into their model. Please refer to a graphical overview offered by the authors of the model in Figure 4. The original text to the figure reads:

“Peripherally released pro-inflammatory cytokines IL-1, IL-6, TNF-α, and INF-γ activate immune-to-brain communication pathways such as afferent interoceptive nerve fibers (particularly afferents of the vagus nerve). These afferent nerve fibers innervate interoceptive and homeostatic brain areas including regions of the brainstem, the hypothalamus, the insula, and the anterior cingulate. Inflammation-induced activity changes within these brain regions cause the subjective feeling of fatigue. Furthermore, interoceptive information processing constitutes interoceptive interference resulting in a distraction of cognitive processes such as alertness and vigilance tasks that heavily rely on intrinsic alertness. This specific fatigue-related alertness and vigilance decrement can be exaggerated by focal brain atrophy affecting the alertness/vigilance network” (Hanken et al., 2014b).
In the following sections, various aspects of fatigue in MS shall be described; including pathophysiological and neuroimaging findings, subjective and objective neuropsychological measures and lastly possible treatment options for affected persons. Thereafter the aim and hypothesis of the current study shall be outlined.

2.3.1.2 Pathophysiological concepts of fatigue

Central nervous system (CNS)

It has been found, that patients with MS performing similar activities recruited additional nerve fibers or activated additional brain areas in comparison to healthy individuals performing the same task (Filippi et al., 2002). The reason might be found in the inflammation, demyelination and destruction of axons in the CNS. It has been hypothesized that this may provoke fatigue and that an increased lesion load in the white matter can be related to higher fatigue levels. However, studies investigating both the structural and functional correlates of fatigue in patients with MS, offer diverse and partially contradicting findings.
Structural correlates

Some studies found a correlation between fatigue and brain atrophy as well as higher lesion load (Colombo et al., 2000; Marrie, Fisher, Miller, Lee, & Rudick, 2005; Tedeschi et al., 2007) and others even found a relationship between specific white matter locations, specific cortical or even subcortical areas and fatigue (Achiron et al., 2013; Andreasen, Spliid, Andersen, & Jakobsen, 2010; Calabrese et al., 2010; Pellicano et al., 2010; Riccitelli et al., 2011; Sepulcre et al., 2009). Other studies however did not find an association between fatigue and lesion load, lesion distribution and location or brain atrophy (Calabrese et al., 2010; Codella, Rocca, Colombo, Martinelli-Boneschi, et al., 2002; Genova et al., 2013; Mainiero et al., 1999; Pardini, Bonzano, Mancardi, & Roccatagliata, 2010; Pellicano et al., 2010; Riccitelli et al., 2011; Tomasevic et al., 2013; van der Werf et al., 1998).

Global atrophy

As mentioned previously, co-morbid symptoms such as depression and physical disability can play a role in the experience of fatigue. These variables were controlled for in a study by Colombo et al. (2000) who examined non-depressed and non-disabled MS-patients with (n= 15) and without (n= 15) fatigue (Colombo et al., 2000). Fatigue was assessed by the FSS. The patients were categorized according to their FSS scores, with patients scoring 25 or higher were included in the fatigue group, whilst patients scoring lower were assigned to the non-fatigue group. Proton density and T2-weighted images were acquired using a 1.5-tesla MRI scanner. The analysis of the MRI data allowed for the calculation of lesion burden in global terms and with regard to specific anatomical structures. Results indicated a significant association between scores on the fatigue Severity Scale and the total lesion burden. When viewing specific regional lesion burden, the parietal lobe, internal capsule and periventricular areas showed significant correlations with measures of fatigue (Colombo et al., 2000).

A study by Tartaglia and her colleagues (2004) using proton magnetic resonance spectroscopy to investigate the relationship between diffuse axonal damage and fatigue also found an association between these two factors (Tartaglia et al., 2004). The study investigated 73 patients with MS with RRMS and SPMS.
and evaluated fatigue by means of the Fatigue Severity Scale (FSS). Patients were categorized as high-fatigue (n=34) or low-fatigue (n=26) patients by using a FSS cut-off score of ≥5 or ≤4 respectively, excluding patients scoring between 4 and 5. MRI data acquisition was performed with a 1.5-tesla MRI scanner. Results also indicated that the N-acetyl aspartate to creatine (NAA/Cr) ratio was significantly lower in the high-fatigue than in the low fatigue group. No significant differences were found concerning the T2-lesion volume; although these correlate with disease duration and EDSS score (Marrie et al., 2005).

In a longitudinal study (Marrie et al., 2005) spanning a total of 8 years, Marrie et al., (2005) evaluated a cohort of 134 patients with RRMS at baseline, at a 2-year follow up and 8 years after initial testing. The researchers employed MRI measures to estimate brain parenchymal fraction (BPF). BPF refers to the relation of brain volume to intracranial volume. The studies used the Sickness Impact Profile Sleep and Rest Scale (SIPSR) to evaluate fatigue. Using linear regression analysis, their findings indicated, that an increase in scores in the SIPSR within the first 2 years was significantly associated with progressive brain atrophy over the subsequent 6 years, independent of changes in disability, mood or other MRI characteristics (Marrie et al., 2005).

A large scale study (Tedeschi et al., 2007) including 222 RRMS patients with low disability (EDDS ≤2) investigated the correlations between fatigue and lesion load, white matter (WM) and grey matter (GM). Fatigue was assessed using the FSS and a cut-off score of 4. MRI data consisted of T1 and T2 weighted whole brain images provided by a 1-tesla MRI scanner in 15 slices with a slice thickness of 4 mm. Lesion load, WM and GM were measured using an automated, multi-parametric segmentation method. The results of this study showed, that high-fatigued patients showed higher abnormal WM fraction, T1 and T2 lesion loads and significantly lower WM- and GM fraction (Tedeschi et al., 2007).

Another large scale study (Mowry et al., 2009) including 507 patients with MS investigating similar relationships as described above. This study utilized a 3-tesla MRI scanner to acquire high-resolution T1-weighted isotropic images with a voxel size of 1x1x1mm in 180 slices as well as T2-weighted images. Lesions were identified manually and segmentation took place fully automated. Fatigue scores were
The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis assessed using the Emotional Well-Being and Thinking/Fatigue subscale scores from the Functional Assessment in Multiple Sclerosis, a health-related quality of life questionnaire in MS. Results indicated that higher T1 and T2 lesion load, T1 lesion volume and lower GM volume were related to lower scores for Emotional Well-Being, whilst lower Thinking/Fatigue scores showed a relationship with higher T1 lesion volume, T2 lesion load and lower GM and WM volume (Mowry et al., 2009).

In studies by Yaldizli and colleagues (2011 & 2014), the relationship of fatigue and the progression of the corpus callosum (CC) atrophy was investigated using a 1.5-tesla MRI. Fatigue was measured using the Fatigue Severity Scale (FSS) with a cut-off score of 4. In their first study (Yaldizli et al., 2011) using a cohort of 70 RRMS patients over a mean follow-up of 4.8 years, they found that patients with fatigue (n=28) not only had higher EDSS scores (p=0.01) than non-fatigued patients (n=42), but also found that CC atrophy was more pronounced in patients with fatigue than in patients without. In a later paper (Yaldizli et al., 2014), the same research group further investigated the impact of CC atrophy in certain segments of the CC. In this 113 RRMS patients were recruited and fatigue was assessed by means of the Fatigue Scale of Motor and Cognition (FSMC) (Penner et al., 2009). The researchers found that in general, total CC atrophy correlated more strongly with T2- and T1-lesion volume than with disease duration or EDSS score. Specifically, atrophy in the posterior CC was significantly associated with poor performance in the Paced Auditory Serial Addition Task (PASAT) (Brittain, La Marche, Reeder, Roth, & Boll, 1991; Gronwall, 1977), the verbal fluency test and the Symbol Digit Modalities Test (SDMT), whilst atrophy of the anterior CC was significantly associated with fatigue scores and results in long-term memory tests (Yaldizli et al., 2014).

By analyzing T1-weighted MPRAGE MRI of 172 patients with MS (4 CIS, 122 RRMS, 35 SPMS, 11 PPMS), Weier et al. (2014) investigated the effects of cerebellar abnormalities on cognitive functioning and fatigue in these patients (Weier et al., 2014). MRI data was acquired using a 1.5-tesla MRI scanner obtaining T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) (isotropic kernel 1mm) and T2-weighted images. In their study, fatigue was assessed using the FSMC. Neuropsychological testing included the SDMT and the PASAT. Results showed that age, T2 lesion volume and normalized brain volume
(NBV) constituted a model for the prediction of PASAT scores. Interestingly, the study also found that age and NBV emerged as significant predictors of fatigue, further supporting the notion of the influence of global brain atrophy on fatigue in MS.

**Regional atrophy**

The study by Colombo et al. (2000) mentioned above, further found that specific cortical and sub-cortical areas such as the parietal lobe, internal capsule and periventricular trigone showed a higher lesion load in patients with fatigue than in those without (Colombo et al., 2000).

Support for deep-grey matter damage causing fatigue in MS was found by Niepel and colleagues (2006) who found a correlation between T1 relaxation in the caudate nucleus and fatigue (Niepel et al., 2006), which was measured using the FSS. This was true both when comparing patients with MS with healthy controls as well as when comparing patients with MS with fatigue with non-fatigue patients. A study by Téllez et al. (2008) investigated a group of 41 RRMS with mild disability and 20 control subjects. They assessed fatigue using the FSS and the modified fatigue impact scale (MFIS). Proton magnetic resonance spectra were then obtained from frontal white matter and the lentiform nucleus. No differences were found in the frontal white matter; however results showed, that patients with fatigue showed decrease in NAA/Cr ratio in the lentiform nucleus (Tellez et al., 2008).

A large study investigating a total of 152 RRMS patients and 42 age- and gender-matched controls was conducted by Calabrese and his colleagues (2010). The aim of their study was to the relationship of deep and/or cortical GM atrophy and fatigue in patients with MS. The study made use of the EDSS, FSS, the MFIS and BDI to evaluate the patients and MRI data was acquired using a 1.5-tesla MRI scanner yielding Fluid-attenuated inversion recovery (FLAIR) and 3D-fast field echo (FFE) images (Calabrese et al., 2010). A cut-off score in the FSS of ≥4 (over three examinations over 6 months) was used to categorize the patient cohort into fatigued patients (n=71) and non-fatigued (n=81) patients. The results of the analysis failed to show any significant differences neither in terms of T2-WM-lesion volume, nor in global cortical thickness between fatigued and non-fatigued patients with MS. However, fatigued patients did show a significantly
The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis

greater reduction of volume in the putamen, caudate nucleus and thalamus, as well as more regional
cortical thinning of the superior frontal and inferior parietal gyrus. When correlating the findings with the
scores of the MFIS in the cognitive and physical fatigue domains, it further became evident, that the
cognitive domain correlated with the volume of the striatum and the cortical thickness of the posterior
parietal cortex and middle frontal gyrus, whilst the physical domain correlated with the striatum volume
and cortical thickness of the superior frontal gyrus (Calabrese et al., 2010). The researchers concluded that
their results suggested a relationship between neurodegenerative processes in the striatum-thalamus-
frontal cortex pathway and the development of fatigue in RRMS.

A comparatively large study incorporating a sample of 60 patients with MS and 20 sex- and age matched
healthy controls was conducted by Sepulcre et al. (2009). They employed the MFIS to evaluate fatigue and
used the MFIS-5 criteria to identify fatigue. The MFIS-5 criteria selects only the values of the 5 questions
best correlating to the larger MFIS-21 version score. This form of analysis still provides an evaluation of
fatigue in terms of physical and cognitive fatigue. Following analysis, 43 patients were classified as having
fatigue, most of which reported both physical and cognitive fatigue. Additionally, MRI data was acquired
using a 1.5-tesla scanner. T1-weighted, T2/Proton Density (PD) and gadolinium enhanced (G+) lesion
imaging was conducted and analyzed using voxel based morphometry (VBM) and lesion probability maps
(LPM). Moderate correlations between fatigue scores and lesion load on T2-weighted and T1-weighted
images were found. These correlations were specifically located in the right parieto-temporal and left
frontal WM regions. With regard to the neuropsychological tests, fatigue scores correlated significantly
with the SDMT and the PASAT. Cortical atrophy however, was found to correlate significantly with fatigue
within the left superior frontal gyrus and bilateral middle frontal gyrus. Not only did patients with MS show
increased cortical atrophy in these areas, but fatigued patients further showed more atrophy here than
non-fatigued patients. The authors of the study concluded that their results suggest that the symptom of
fatigue is associated with a disruption of brain networks involved in cognitive and attentional processes
(Sepulcre et al., 2009).
To examine the relationship between fatigue, regional brain atrophy and normal appearing WM in patients with MS, Andreasen et al. (2010) recruited 17 primary fatigued and 17 non-fatigued RRMS patients (Andreasen, Jakobsen, et al., 2010). The participants were assigned to each group according to their subjective fatigue scores measured by the FSS, grouping patients with a score of ≥5 as primary fatigued and patients with a score of ≤4 as non-fatigued. MRI imaging was performed using a 3-tesla scanner acquiring T2-FLAIR, T1 and diffusion tensor (DTI) images. Following quantitative analysis, the researchers found no significant differences in BPF, lesion load, not in NAA/Cr ratio in primary fatigued vs. non-fatigued patients. When investigating the differences in regional atrophy between the two groups, the results showed that primary fatigued patients showed more regional atrophy in 5 clusters located the genual part of the anterior cingulate cortex (ACC), in the left primary visual cortex, and in the ventral complex of the thalamus, partially extending into the ventral parts of the globus pallidus and the internal capsule (Andreasen, Jakobsen, et al., 2010). When correlations were calculated between the regional brain atrophy and objective measures of motor fatigue, clusters within the frontal lobe, left inferior parietal lobe and in the right temporal middle and inferior gyrus showed significant differences between the two groups. However, when comparing mental fatigue results, which were measured using Digit Symbol Coding and subjective fatigue ratings, no differences in regional atrophy became evident between the two groups.

Published in 2010, a study by Pellicano et al. also investigated the relationship of cortical atrophy and fatigue in patients with MS. They recruited 24 patients with MS and 24 healthy volunteers who underwent MRI scanning and fatigue evaluation. Fatigue was evaluated by the MFIS using a cut-off score of 38 to categorize patients into fatigued (n=8) or non-fatigued (n=16) cohorts. MRI data included 3D-MPRAGE sequences, FLAIR and T2-weighted images. Following analysis, the cortical thickness of the parietal lobe proved to be the only area showing a significant correlation to the MFIS scores, explaining 25% of the variance. Further correlation analysis revealed that only the sub-regions of the posterior parietal cortex, the supramarginal gyrus and the inferior parietal cortex showed significant associations with fatigue. The researchers concluded that their results suggested that dysfunctions in higher-order aspects of motor control may be related to fatigue in MS (Pellicano et al., 2010).
A study conducted by Ricitelli et al. (2011) also investigated the relationship between fatigue and GM and WM atrophy (Riccitelli et al., 2011). This study investigated 14 RRMS patients without and 10 RRMS patients with fatigue, as well as 14 healthy controls. High resolution T1-weighted MPRAGE images with a voxel-size of 1x1x1mm, as well as dual-echo turbo spin-echo images were acquired using a 1.5-tesla MRI scanner. Images were analyzed using local thresholding segmentation technique, Structural Image Evaluation with Normalization of Atrophy software and VBM. Results showed that T2 lesion distribution and regional WM atrophy did not differ between fatigue and non-fatigue patients. However, compared to healthy and non-fatigued patients, atrophy was greater in the left central sulcus and precentral gyrus in fatigue patients. The findings of atrophy in the left precentral gyrus showed a significant correlation to fatigue scores (Riccitelli et al., 2011). Once again it is worth noting the small group sizes (n=14 and n=10) in this study.

Recently, a study (Cruz Gomez, Ventura Campos, Belenguer, Avila, & Forn, 2013) investigating the neural correlates of fatigue in 60 RRMS patients using 1.5-tesla MRI scans to assess GM and WM atrophy as well as fMRI scans to assess resting state functional connectivity (RSFC) was conducted. Structural MRI data consisted of a high-resolution T1 image with an isotropic voxel-size of 1x1x1mm. Functional (resting state) MRI was recorded over 9 minutes using a T2*-weighted echo-planar imaging sequence resulting in 270 volumes. Data was analyzed using VBM to investigate GM and WM atrophy, whilst RSFC was investigated with a seed-based method and independent component analysis (ICA). Fatigue was assessed using the FSS. High FSS scores correlated with reductions of WM in the supplementary motor area (SMA) and decreased RSFC between SMA and the associative somatosensory cortex (Cruz Gomez et al., 2013).

In a cohort of 17 RRMS patients, Derache et al. (2013), a French research group, investigated metabolic and density alterations of GM by means of positron emission tomography (PET) and MR imaging. Data was recorded using a 1.5 tesla MRI scanner and consisted of FLAIR images, T1- and T2- weighted images as well as [18F] FDG PET data collected with a resolution of 4.2x4.2x4.6mm. Data was analyzed using VBM and SPMS. Fatigue was measured using the EMI-F-SEP, a validated French version of the Fatigue Impact Scale.
The results of this study indicated, that compared to patients without fatigue, patients with fatigue showed a significant reduction of GM density in clusters located in the bilateral middle, superior and inferior frontal cortex and in the left temporal and parietal cortex (Derache et al., 2013). It is however worth noting, that by dividing their patient cohort into fatigue and non-fatigue patients with MS, the group sizes diminished to n=11 and n=6 respectively, ultimately causing a decrease in validity of the study and its results.

Investigating 77 RRMS patients, a study by Pardini et al. (2015) used DTI measurements to analyze fractional anisotropy (FA) within the WM and their relationship to subjective fatigue scores. DTI data was acquired using a 1.5-tesla MRI scanner and fatigue was evaluated by the MFIS. Disabling fatigue was identified by scores higher than 37 points. The results of the analysis indicated, that two distinct clusters within the WM correlated significantly with global MFIS scores. The clusters were located in the anterior and medial cingulate cortices. Following this, connectivity analysis revealed that damage in these clusters was related with a deficiency of structural connectivity in the medial and anterior cingulate cortices, dorsolateral prefrontal areas and in the left caudate (Pardini et al., 2015).

Although not directly related to fatigue, Achiron and his colleagues (2013) similarly employed 3-tesla MRI scans to investigate the relationship of cortical thickness and cognitive performance in RRMS patients (Achiron et al., 2013). They recruited 20 RRMS patients and 20 age-matched healthy subjects to participate in their study. Cognitive assessment was performed using a test battery measuring numerous cognitive domains including executive function, attention, information processing speed, memory, motor skills, verbal function and visual spatial performance, also yielding a global cognitive score. Although many regions showed less cortical thickness in RRMS patients in comparison to healthy controls, when correlating the cognitive assessment with the data, only the left superior temporal gyrus thickness correlated with motor skills, attention and information processing speed (Achiron et al., 2013). Some of these cognitive domains often reported as being impaired in fatigued patients with MS. Please refer to section 2.4.2 Objective measures of fatigue for an overview.
**Studies which found no evidence of structural differences**

Although many studies mentioned above found evidence for a relationship between fatigue and structural cerebral changes, numerous studies were in fact not able to offer support for these findings.

The focus of the study by van der Werf and colleagues (1998) was to investigate the - at that time - still scarcely examined neural correlates of fatigue in patients with MS (van der Werf et al., 1998). They investigated the relationship of cerebral abnormalities and fatigue in 45 patients with MS (26 RRMS, 19 SPMS). Fatigue was evaluated using three measures, the Checklist Individuals Strength (CIS-FATIGUE), the global average of a subjective rating of fatigue on a 4-point scale completed four times daily over a 2 week period, and subjective evaluation of fatigue frequency in the 3 months prior to examination. Results indicated that 71% of the patient cohort experienced serious fatigue at least several times a week. MRI data was acquired using a 1-tesla MRI scanner obtaining proton density images, T2-weighted spin-echo images, as well as gadolinium-enhanced and unenhanced T1-weighted images. Lesion load was evaluated manually. Brain atrophy was assessed by means of the T2-weighted images and atrophy indexes were measured for frontal, bi-parietal, bi-caudate and for the 3rd ventricle. Results indicated that no correlation was evident between fatigue ratings and T1- or T2-weighted total lesion load, nor with global atrophy indices (van der Werf et al., 1998).

An early MRI study by Bakshi et al. (1999) investigated 71 MS with and without fatigue. Global plaque load (lesion load) and global atrophy were assessed. The results of this study indicated, that no correlation between the abovementioned neuro-structural changes and fatigue was evident in patients with MS (Bakshi et al., 1999).

Another early study conducted by Mainero et al. (1999) recruited 11 RRMS patients and measured lesion load within the brain over a 3 month period using MRI and gadolinium enhanced T1-weighted images acquired using a 1.5-tesla MRI scanner (Mainero et al., 1999). MRI data was acquired at three time-points over the 3 month period and fatigue was assessed using an expanded version of the FSS with the same frequency. Following analysis, the results showed neither a correlation with lesion volume nor with changes...
in MRI activity over the 3 months. The authors concluded that their findings failed to support the then already emerging theory of the involvement of proinflammatory cytokines affecting the blood brain barrier in the development of fatigue in patients with MS (Mainero et al., 1999).

In 2002, an MRI study using brain lesion estimates provided by magnetization transfer and diffusion-tensor imaging acquired by a 1.5-tesla MRI investigated the relationship of these factors to fatigue in 28 patients with RRMS. The patients were assigned to a fatigued (n=14) or non-fatigued (n=14) group by their total score in the FSS. The cut-off for this categorization was 25 points. The results of this study showed that no significant differences with regard to lesion load or WM diffusivity and fractional anisotropy was evident between fatigued and non-fatigued patients with MS (Codella, Rocca, Colombo, Rossi, et al., 2002).

In 2006, a study by Hildebrandt and his colleagues investigated the differential relation between whole brain and central brain atrophy and factors such as memory, cognitive performance, depression, quality of life and fatigue in a cohort of RRMS patients (Hildebrandt et al., 2006). They recruited 45 RRMS patients who underwent MRI scans in a 1.5-tesla MRI scanner yielding T1 images used to calculate BPF and brain volume fraction. Fatigue was evaluated using the FSS and scores were incorporated into correlation calculations. Interestingly, results showed no significant correlations between fatigue scores and BPF or brain volume fraction. Fatigue did however correlate with functional performance, especially in the PASAT (Hildebrandt et al., 2006).

A study by Heesen et al. 2010 investigated the MRI markers of inflammation, lesion load and global atrophy and their relationships with cognitive functioning, fatigue and depression (Heesen et al., 2010). They recruited 25 cognitively impaired and 25 cognitively unimpaired patients with MS and obtained T1-weighted, FLAIR, T2/PD-weighted TSE and MPRAGE images of these patients for analysis. With regard to the relationship of structural changes or damage and fatigue, the study did not mention any correlations (Heesen et al., 2010). The findings of this study regarding the interaction of fatigue and neuropsychological (cognitive) measures shall be mentioned in a later section.
Although previously mentioned above, it is suitable to recollect, that the study by Andreasen et al. (2010) also found no significant differences in brain parenchymal fraction (BPF), lesion load, not in NAA/Cr ratio in primary fatigued (n=17) vs. non-fatigued (n=17) patients. They did however find correlations with regional atrophy.

Müller et al. (2013) investigated the relationship of 3\textsuperscript{rd} ventricle enlargement and motor and neuropsychological deficits (Muller et al., 2013). The researchers employed transcranial sonography (ultrasound) to measure the size of the 3\textsuperscript{rd} ventricle in 54 RRMS and 70 healthy controls. Among other neuropsychological tests, participants were required to complete the FSMC (Penner et al., 2009). Results showed, that although the patient cohort showed extensively more fatigue than the control group, no correlation between 3\textsuperscript{rd} ventricle size and fatigue was evident (Muller et al., 2013).

In an attempt to identify markers sensitive for fatigue in patients with MS, Tomasevic et al. (2013) investigated 20 RRMS patients using MRI scans (Tomasevic et al., 2013). They employed the FSS and the MFIS to evaluate fatigue and conducted T1-MPRAGE, T1-weighted gadolinium enhanced, as well as T2 and FLAIR imaging using a 1.5-tesla scanner. From this data, lesion load, BPF, thalamic volume and cortical thickness was measured. Additionally, electroencephalography (EEG), electromyography (EMG) and electrocardiogram (ECG) recordings were conducted to assess cortico-muscular coherence. On the basis of the FSS and MFIS scores, patients were grouped into fatigued (n=9) and non-fatigued (n=11) groups. Analysis of the MRI data showed no significant differences between the two patient groups with regard to lesion load, BPF, thalamic volume and cortical thickness of the SM1 rolandic sulcus. The study did however find that the CMC functioned at higher frequencies as fatigued increased during a motor task (handgrip). The researchers concluded that brain-muscle functional connectivity may serve as a sensitive marker for the phenomena related to the source of fatigue in patients with MS, influencing central-peripheral communication well before the advent of any impairment in the communication nodes (Tomasevic et al., 2013).
Hulst et al. (2013) also investigated the extent and severity of WM damage and its effect on cognition in 55 patients with MS (Hulst et al., 2013). They additionally recruited a cohort of 30 healthy controls for their study. The aim of their study was to investigate if WM damage offered explanations for cognitive impairment in patients with MS. WM damage was assessed using DTI to investigate FA mean diffusivity, radial diffusivity and axial diffusivity. Results indicated that cognitively impaired patients with MS differed to cognitively unimpaired patients in WM areas highly relevant for cognition, including the corpus callosum, superior and inferior longitudinal fasciculus, corticospinal tracts, forceps major, cingulum and fornices. However, when investigating the correlation to fatigue scores, this study found no relationship between structural WM integrity and fatigue in their patient cohort (Hulst et al., 2013).

The study by Gobbi et al. (2014) set out to investigate the influence of topography of brain damage on depression and fatigue in patients with MS. The researchers were able to recruit a total of 123 patients with MS showing both depression (69) and fatigue (64) as well as 90 control subjects. GM and WM atrophy as well as lesion distribution was estimated by means of VBM and SPM8 on the basis of 3-telsa MRI T1-FFE and dual-echo turbo spin-echo images. In their cohort, fatigued patients showed higher EDSS scores than non-fatigued patients. Results did not indicate a relationship between lesion distribution and WM atrophy. GM atrophy of frontal, parietal and occipital regions showed a combined effect on fatigue and depression, however no specific GM atrophy was found to be related to fatigue (Gobbi et al., 2014).

Recently, a study by Biberacher et al. (2017) also investigated the relationship between MRI and cerebrospinal fluid (CSF) in a large cohort of 233 (34 CIS and 199 RRMS) patients (Biberacher et al., 2017). A 3-tesla MRI scanner was used to obtain T1-weighted and FLAIR images, whilst CSF was taken during routine clinical work-up following lumbar puncture. Fatigue was assessed using the FSMC. Results initially indicated significant negative correlations between motor fatigue and total and cortical GM volume. This result also remained significant even after controlling for depression. However, when correcting for motor disability or disease duration, these results failed to become significant. Furthermore, the study did not find any association between humoral CSF parameters and fatigue (Biberacher et al., 2017).
In 2014, a study of fatigue in patients with post poliomyelitis syndrome (PPS) included a cohort of 49 patients with MS (Trojan et al., 2014). The research group used the FSS to evaluate fatigue using a cut-off score of ≥5 to assign a patient to the fatigue group and ≤4 to assign them to a non-fatigued group. Utilizing high-resolution T1-weighted scans obtained by a 1.5-tesla MRI, the normalized brain volume (NBV) for each patient was calculated. Normal brain volume proved to be less in patients with MS than in healthy controls; however, the study did not mention any structural correlations between fatigue and NBV in patients with MS, although they did report that not significant relation between fatigue and NBV existed for PPS patients (Trojan et al., 2014).

The exact relation and interaction between structural changes and the experience of fatigue in patients with MS remains unclear, however there is evidence for correlations between these two factors. Specifically, a complicated thalamo-striato-cortical network has been suspected of playing a vital role in the pathophysiology of MS-related fatigue (Calabrese et al., 2010; Chaudhuri & Behan, 2000; Engström, Flensner, Landtblom, Ek, & Karlsson, 2013). For an overview of the studies on structural correlates of fatigue mentioned above, please refer to table 1 below.

<table>
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<th>Studies finding global atrophy, lesion load or diffuse axonal injury</th>
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*longitudinal studies

Table 1: Overview of structural MRI studies investigating fatigue in MS (author, year of publication and size of patient cohort (N))
Functional correlates

It has been hypothesized, that the cause of fatigue may also lie within functional changes within the brain caused by the MS disease. These changes have been investigated in numerous studies using functional imaging techniques.

fMRI studies exploring the effects of MS on cognitive functioning such as working memory, attention and executive functions and neural changes have been promising; however the specific effects of fatigue were not dissociated in most of these studies. Bilateral frontal, parietal and temporal cortical activations as well as right cerebellar activations were found when patients with MS performed the PASAT (Au Duong et al., 2005; Audoin et al., 2005; Audoin et al., 2003; Chiaravalloti et al., 2005; Forn et al., 2006; Mainero et al., 2004; Staffen et al., 2002). An interesting approach to evoking and investigating fatigue in patients with MS was conducted in a study by Tartaglia and colleagues, who investigated the neural activations during a finger-thumb apposition task before and after performing an allegedly fatiguing PASAT task (Tartaglia, Narayanan, & Arnold, 2008). The difference in fMRI activation was ascribed to fatigue induced by the cognitively challenging task. Results indicated increased recruitment of brain structures including the bilateral cingulate and left primary sensory cortex while activation of the left premotor and supplementary motor cortex was also observed. The authors concluded that their data offered support for the hypothesis, that the substrate of fatigue may be an increased demand placed on functioning neural circuits (Tartaglia et al., 2008).

Resting state analysis of RSFC seems to show promising results. Nonetheless, studies investigating patients with MS with regard to cognitive impairment in general (not specific to fatigue) have offered contradicting results. Some studies report an increased RSFC within patients with MS specifically within the default mode network and interpret this as the recruitment of reserve capacity to compensate for structural damage (Roosendaal et al., 2010), whilst other studies described reduced RSFC, especially of anterior regions of the brain or the default mode network (Bonavita et al., 2011; Hawellek, Hipp, Lewis, Corbetta, & Engel, 2011; Rocca et al., 2010; Rocca et al., 2012). Furthermore, findings from other studies even contradict the
compensation hypothesis as they provide evidence for a relationship between increased RSFC and worse cognitive performance in patients with MS (Faivre et al., 2012; Hawellek et al., 2011; Schoonheim et al., 2015). A recent study (Hidalgo de la Cruz et al., 2017) using RSFC in a cohort of 122 patients with MS and 94 healthy controls also found abnormalities within RSFC in fatigued patients. Results indicated that higher thalamic RSFC with the precuneus and lower RSFC with the posterior cerebellum correlated with cognitive fatigue measured by the Modified Fatigue Impact Scale. These results once again offer support by the model of Chaudhuri and Behan implicating the basal ganglia as a pivotal area for the occurrence of fatigue. Another study (Cruz Gomez et al., 2013) investigating both cortical atrophy as well as RSFC was mentioned in the section on structural correlates of fatigue. This study recruited 60 patients with MS and objectified fatigue as a score on the FSS. RSFC results indicated that high FSS scores were associated with decreased RSFC between the supplementary motor area and the associative somatosensory cortex (Cruz Gomez et al., 2013).

Studies using positron emission tomography (PET) to depict cerebral glucose metabolism in 47 patients with MS found a reduced metabolism in the frontal cortex, white matter, and basal ganglia in patients with higher fatigue severity scores, independent of the overall disability and depression (Roelcke et al., 1997). It was proposed, that this reduced energy metabolism might possibly represent the pathogenesis of fatigue in patients with MS. It was further found that in fatigue patients, brain areas associated with cognitive and attention tasks showed higher glucose metabolism than in non-fatigued patients. It was suggested that this phenomenon reflects compensatory mechanisms for impaired motor performance, although the study itself could not find more evidence for this hypothesis (Kos et al., 2008; Roelcke et al., 1997).

Leocani and colleagues (Leocani et al., 2001) employed EEG to investigate the effects of fatigue on neural activity in patients with MS. The participants were requested to perform extensions of the thumb whilst under EEG-observation. The data indicated that patients with MS and who complained of fatigue showed increased cortical activation and decreased cortical inhibition compared to other non-fatigued patients or healthy controls. The researchers found hyperactivity during movement execution and failure of the
inhibitory mechanisms intervening after movement termination. Furthermore, it was found that this aforementioned pattern showed a moderate correlation to self-reported fatigue. The authors concluded that these results suggest that fatigue is related to a dysfunction in the cortical organization of motor performance although the causal relationship remains unclear (Leocani et al., 2001).

In their study employing transcranial magnetic stimulation (TMS), Liepert and his colleagues (Liepert, Mingers, Heesen, Baumer, & Weiller, 2005) noted that a reduced inhibition of the primary motor cortex was evident pre- and post-exercise in fatigued patients with MS. This prolonged normalization time following exercise correlated with fatigue scores and in turn suggests a relationship between membrane excitability of the primary motor cortex and fatigue.

Numerous studies (Cader, Cifelli, Abu-Omar, Palace, & Matthews, 2006; DeLuca et al., 2008; Dobryakova, DeLuca, Genova, & Wylie, 2013; Engström et al., 2013; Filippi et al., 2002; Genova et al., 2013; Morris, Cantwell, Vowels, & Dodd, 2002; Petajan & White, 2000; Rocca, Matthews, et al., 2002; Rocca et al., 2009; Sweet, Rao, Primeau, Mayer, & Cohen, 2004; Wishart et al., 2004; Wylie, Genova, DeLuca, & Dobryakova, 2017) have employed functional MRI (fMRI) to investigate the hemodynamic processes in patients with MS and fatigue. Many of these studies focused on the motor aspects of fatigue. One such fMRI study (Rocca, Falini, et al., 2002) examined 30 PPMS patients and compared these to 15 healthy controls. Participants performed three simple motor tasks namely repetitive flexion-extension of the fingers of the right hand, repetitive flexion-extension of the right foot, or both exercises simultaneously. The results showed that patients with MS had increased ipsi- and contralateral cortical activations in non-motor areas in comparison to healthy controls. It was further found, that a strong correlation existed between these observed changes in cerebral activation and the lesion load within the brain. The authors concluded, that due to the fact that these additional cortical activations were normally only present during complex tasks, the increased activation in fact reflects cortical functional reorganization hypothesized to represent adaptive compensatory mechanisms. In other words, to maintain the functional capacity of the damaged brain, more areas are recruited for the same task (Rocca, Falini, et al., 2002). This hypothesis explains the limited
relationship between structural MRI measures of lesion load and clinically manifested disabilities (Kos et al., 2008).

Further fMRI studies suggested a relationship between fatigue in MS and impaired cortico-subcortical interactions responsible for motor planning and execution (Filippi et al., 2002). An additional MRI study using T1 relaxation time offered further support for the involvement of deep grey matter structures, particularly the thalamus, in the pathophysiology of fatigue (Niepel et al., 2006). Other studies showing a reduction of recruited areas and fatigue following motor training are in line with the above findings (Filippi et al., 2002; Petajan & White, 2000; Rocca, Matthews, et al., 2002). Filippi et al. concluded that an explanation for mental fatigue might be found in the increased activation of cortical areas involved in attention tasks (i.e. the anterior cingulate) in patients with fatigue (Filippi et al., 2002). Further studies have found additional support for this hypothesis and are mentioned below. There are however contradicting studies which suggest that the mechanisms regulating motor performance differ from those responsible for perceived fatigue (Morris et al., 2002).

Other studies investigated altered neural activity in cognitively impaired versus cognitively preserved patients with MS by means of fMRI and the Stroop tasks (Rocca et al., 2009). This study found significantly increased activations of several areas involved during the task in cognitively preserved patients. These patients also showed increased connectivity between sensorimotor areas and right inferior frontal gyrus and cerebellum, as well as decreased connectivity between areas including the anterior cingulate.

Chaudhuri and Behan (2000) suggested that the origin of cognitive fatigue in MS may lie within the non-motor functions of the basal ganglia (BG) or an imbalance of neurotransmitters in these areas (Chaudhuri & Behan, 2000). Recent studies have embedded this idea into the theory that fatigue arises from a dysfunction of the cortico-striatal network between prefrontal cortical (PFC) areas and the BG and their implication in the calculations of effort requirements and outcome validation (Dobryakova et al., 2013), including areas of the ACC. Interestingly, these areas are also implicated in the attention network.
A study by DeLuca and his colleagues in 2008 investigated the neural correlates of fatigue by means of fMRI during the implementation of a cognitive task. The study recruited 15 patients with MS and 15 healthy controls and requested them to perform in a modified version of the Symbol Digit Modality Test (mSDMT) in which the subjects were requested to state whether the paring between a symbol and a digit was correct or incorrect according to a key displayed above the pairing in question. Learning effects were countered by changing the key with every presentation. The experiment lasted over 4 runs with a total of 256 trials. Response times and accuracy were recorded. Neuroimaging was performed through a 3 tesla Siemens Allegra scanner using a TR of 2 seconds with an in-plane resolution of 3.75mm$^2$ over 32 axial slices. The whole experiment lasted roughly an hour. Results indicated that with regard to accuracy, there were no group effects across the four runs. With regard to the reaction times (RTs), patients with MS continuously performed with slower RTs than controls. Both groups however showed decreases in RTs over time as they may have become more accustomed to the task. The analysis of the fMRI data indicated increased activation within frontal, parietal and occipital areas as well as in areas of the basal ganglia, in turn offering support for the model proposed by Chaudhuri and Behan mentioned above (DeLuca et al., 2008).

A Swedish study in 2013 used fMRI data to analyze brain activation whilst 15 patients with MS and 11 healthy controls performed a challenging working memory task over a period of 15 minutes (Engström et al., 2013). The working memory task consisted of a presentation of semantically correct or incorrect sentences which the participants were requested to rate as correct or incorrect and remember the last word of the sentence. After the presentation of 5 sentences, the participants were requested to identify the target words from a list of other words presented in sequence. Data was acquired using a 1.5 tesla MRI scanner with a voxel size of 3x3x3mm and a TR of 2.7s. Before and after the experiment, subjects were requested to rate their current levels of fatigue on a visual analog scale. The results indicated that when comparing patients with MS and healthy controls to each other, the patient group exhibited an increased activation in bilateral posterior parietal areas in addition to less activation in the thalamus and several regions of the basal ganglia. The authors further investigated the differences in neural activations when the subjective fatigue ratings from the visual analog scale were included as a covariate. The findings of this
analysis indicated patients with higher ratings of fatigue showed increased neural activation with the right substantia nigra as well as the left posterior parietal cortex. The authors concluded, that their findings offered support for the hypothesis of a dysfunction within the thalamo-striatal-cortical network (Engström et al., 2013) as proposed in the model by Chaudhuri & Behan (Chaudhuri & Behan, 2000).

When using the N-back task as an experimental paradigm, studies have found varying results. A study by Sweet and his colleagues (Sweet et al., 2004) investigated fatigue using the n-back task with 4 different difficulties (N-0;N-1;N-2;N-3). They recruited 15 patients with MS and 15 healthy controls and measured the neural activity using a 1.5 tesla MRI scanner with a TR of 3s and a sagittal slice thickness of 7mm. They found that cortical activation within the premotor, supplementary motor and dorsolateral prefrontal areas was related to task difficulty. For simpler N-1 back tasks, patients with MS displayed greater activity within the aforementioned areas, while the left superior frontal gyrus, anterior cingulate cortex, and parahippocampal gyri were less activated at more difficult tasks than in controls. Interestingly, although the patients with MS responded slower in some but not all of the N-back tasks, they consistently did not differ with regard to accuracy from healthy controls. The authors concluded that patients with MS showed a compensatory hyper-activation of areas required to complete the verbal working memory tasks, however as tasks demands increased, these compensatory mechanisms seem to decrease (Sweet et al., 2004).

A similar study (Wishart et al., 2004) recruited a total of 10 patients with RRMS and 10 healthy controls and requested them to perform the N-back task at two difficulties. Results showed that group differences were evident as both difficulties and that overall, patients showed less activation in prefrontal and parietal regions recruited to manage the working memory task. However, the study also found a greater activation of regions typically not associated with this working memory task which included bilateral medial frontal, cingulate, parietal, bilateral middle temporal and occipital regions (Wishart et al., 2004).

A third study using the N-back task with varying difficulty (N-0;N-1;N-2;N-3) recruited 21 patients with RRMS and compared these to 16 age- and gender-matched healthy controls (Cader et al., 2006). Imaging data were acquired using a 3 tesla MRI scanner and a TR of 3 seconds and 24x8mm coronal slices. The two
groups did not differ with regard to their performance during the tasks. Both groups recruited task specific areas including medial frontal areas and bilateral posterior parietal cortices, inferior frontal gyri and dorsolateral prefrontal cortices (DLPFC). Further analysis of the fMRI data showed however, that patients showed reduced activation in the superior frontal and anterior cingulate gyrus. When including task difficulty into the analysis, it was evident, that patients with MS showed smaller increases in activations in tasks specific areas than healthy controls. The authors concluded these results as indicating impaired functional reserve in patients with MS following increasing tasks demands (Cader et al., 2006).

Very recently, a study (Wylie et al., 2017) investigating the neural correlates of fatigue by means of the N-back task (N-0; N-2) revealed that the anterior cingulate cortex seems to play an important role in the development of fatigue. The study did however not include patients with MS but rather recruited a group of 23 healthy controls that underwent testing. Data was acquired by means of a 3 tesla MRI scanner using T2*-weighted pulse sequence to attain fMRI data with a TR of 2s and a slice thickness of 4 mm. Before and after each block, participants were presented with a visual analog scale on which they could rate their level of fatigue from 0 (no fatigue) to 100 (most fatigued they have ever felt). Results showed that increased activation in the ACC was not only associated with better performance in the N-2 back task, but was also strongly associated with more fatigue after the completion of the task. The researchers attributed the change in ACC activation to a change in effort-reward matrix. The study noted that the ACC had often been found to be involved with fatigue in MS (DeLuca et al., 2008; Genova et al., 2013; Pardini et al., 2010) and suggested that cognitive fatigue in these populations may partially arise from a chronic shift in the effort-reward payoff matrix, predicting that the ACC would be chronically active in the diseased population (Wylie et al., 2017).

Another study worth mentioning was a study conducted by Genova and her colleagues in 2013 (Genova et al., 2013), in which a new dichotomy between so called state and trait fatigue was proposed. These two constructs were explained in detail in the sections covering models of fatigue. In short, state fatigue refers
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to the current level of experienced fatigue which may be exacerbated by motor or cognitive load; whilst the concept of trait fatigue refers to more stable feeling of fatigue over a prolonged period of time.

In their study, the researchers investigated the neural correlates of so called state fatigue (as opposed to trait fatigue) using fMRI during a cognitive fatigue-inducing task switching paradigm, as well as structural lesion load and VBM measures. The researchers recruited 12 patients with MS and 11 healthy controls. The task switching paradigm consisted of a stimulus (colored, rotating rectangles) which was presented either in blue or red and rotate either at quickly or slowly. The participants were requested to judge either the speed/velocity or the color/hue of the stimulus depending on which cue was given before presentation of the stimulus. fMRI scanning was performed using a 3 tesla MRI scanner with a TR of 2s and a voxel size of roughly 3.5x3.5x4mm. The results indicated that the MS group showed increased brain activity specifically in the caudate nucleus when compared to healthy controls. No significant differences of grey matter (GM) volume or lesion load were observed between the groups when viewing the results of the structural measures. Behaviorally, the MS group and the patient group did not differ significantly in regard to accuracy or reaction time. The subjective ratings of fatigue as measured by a visual analog scale (VAS) were recorded in regular intervals and differed significantly across groups; however there was no significant group x time interaction.

To assess correlates of trait fatigue, the study (Genova et al., 2013) used DTI in conjunction with fatigue scores assessed by the FSS (Krupp et al., 1989b). The FSS was used to assess trait fatigue from a subjective point of view, with the aim of finding corresponding neural markers. The patient group showed significantly higher FSS scores than healthy controls, however when investigating the correlation of FSS scores and lesion load or GM volume, no significant results were found. The results of the DTI measurements in correlation with the FSS scores indicated reduced fractional anisotropy within the anterior internal capsule, an area connected to the caudate and thalamus. Both the results of the state fatigue experiment as well as the results of the experiment designed to analyze trait fatigue were interpreted by the authors as
supporting the role of the striatal-thalamic-frontal system in fatigue (Dobryakova et al., 2013; Genova et al., 2013) as proposed by Chaudhuri and Behan (Chaudhuri & Behan, 2000).

A number of studies investigating the neural correlates of subjects with MS, TBI and chronic fatigue syndrome (CFS) suggest, that these patients require more cerebral effort that healthy controls to perform similar complex cognitive tasks. Due to its nature and its relatedness to fatigue in MS, studies addressing CFS are often special interest. Single photon emission computer tomography (SPECT) studies in patients with CFS delivered varying and partially contradicting results. Some studies found an increased perfusion in the lateral frontal cortex and lateral and medial temporal cortex (Schwartz et al., 1994) or more widespread diffuse regional cerebral blood flow in frontal, temporal and thalamic regions relative to controls (Schmaling, Lewis, Fiedelak, Mahurin, & Buchwald, 2003). Other studies also found increased perfusion in the right thalamus and basal ganglia including the pallidum and putamen (MacHale et al., 2000). On the other hand, some SPECT studies found evidence for a decreased perfusion in the brainstem of CSF patients (Costa, Tannock, & Brostoff, 1995), whilst some studies even found no differences in perfusion (Fischler et al., 1996). Some positron emission tomography (PET) studies using 18-FDG-PET found decreased cerebral metabolism in the frontal lobes (Tirelli et al., 1998) or abnormalities in the anterior cingulate cortex and mesial and orbital frontal cortices (Siessmeier et al., 2003). fMRI studies with patients with CFS conducted whilst participants were required to perform challenging cognitive tasks found evidence for increased bilateral activity in frontal and parietal areas (Lange et al., 2005) as well as right prefrontal areas (Caseras et al., 2006). Further, when also taking fatigue scores into account rather than simply comparing patients with CFS and healthy control groups, studies have found increased brain activity within the cerebellum, hippocampus, middle and posterior cingulate regions, inferior frontal gyrus, superior temporal gyrus and parietal regions (Cook, O’Connor, Lange, & Steffener, 2007). Other studies (Tanaka et al., 2006) found no differences in patients with CFS and healthy controls during a cognitive verbal working memory task, however they did notice that during task-irrelevant change in auditory stimulation the patient group did show significantly less cerebral activation which also correlated with subjective fatigue ratings. The authors concluded that this may be an indication that patients with CFS may have less processing capacity and...
therefore less cognitive capacity or resources to process task-irrelevant stimuli than healthy controls. Finally, in a study in which fatigue was induced in both healthy controls as well as patients with CFS by means of videos featuring fatigue-inducing or anxiety-creating scenarios, researchers found that the CFS group was more fatigued than the healthy control group and that the patient group displayed increased activity in the cerebellum and occipito-parietal regions bilaterally extending toward the cingulate cortex, left hippocampus cortex and left caudate nucleus (Caseras et al., 2008).

In summary, evidence for the involvement of specific brain areas gathered from functional studies investigating brain activity is still quite heterogeneous. However, when reviewing the studies mentioned above, a tentative statement can be made that the involvement of attention-related structures (both cortical as well as subcortical) are indicated and may play a role in the occurrence of fatigue in MS.

Evidence for the involvement of neural correlates - both structural as well as functional - although promising, are still wide-ranged and require further investigation. It is with this in mind that the current study investigated the neural correlates of fatigue in patients on a functional level using a cognitively challenging and fatigue inducing task.

2.3.1.2 Immunological factors

Increased feelings of fatigue are often reported in conjunction with a relapse phase of MS (Krupp, 2003a). Furthermore, it has been found that immunomodulatory medications such as interferon-alpha and interferon-beta often lead to fatigue as a side-effect during the treatment of MS and other diseases (Krupp, 2003b; Mainero et al., 1999; Polman et al., 2006). As a result, it has been postulated, that immunological factors appear to be involved in the etiology of MS-related fatigue (Kos et al., 2008). An increased immune activation takes place during a relapse of MS and higher levels of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1) and IL-6 (Kos et al., 2008). Research findings on CFS indicate an involvement of an endocrine dysregulation in the origin of fatigue which has been adopted in research concerning fatigue in MS (Induruwa et al., 2012). In CFS, a low cortisol but also low dehydroepiandrosterone (DHEA) levels were found (Cleare, 2003; Maes, Mihaylova, & De Ruyter, 2005).
2. MS-related fatigue

It was previously found, that during an MS-episode, patients reported experiencing increased fatigue symptoms (Freal et al., 1984). Additionally it is established, that an increased level of proinflammatory cytokines exists during these acute episodes which play a decisive role in the disintegration of the blood-brain-barrier (Raine, 1994). To investigate this context, a study of 11 RRMS patients using intravenous gadolinium (Gd)-contrast MRI investigated the relationship between quantity and size of Gd-enhanced lesions of the blood-brain-barrier and fatigue severity in patients with MS (Mainero et al., 1999). This study found no association between fatigue and the action of proinflammatory cytokines on the CNS. The others however stated a possible effect of cytokines on the peripheral nervous system. These effects were investigated by another study, which found higher levels of TNF-alpha mRNA expression in peripheral blood in individuals with fatigue than in those without fatigue (Flachenecker et al., 2004). This study also found, that the relationship of fatigue and cytokine levels was independent of disease-related variables or autonomic nervous system activity, which in turn suggests the role of MS-related inflammation process in the pathogenesis of fatigue (Flachenecker et al., 2004; Kos et al., 2008). These findings were also reported in a similar study, where the production capacity of proinflammatory TNF-α and interferon-gamma (IFN-γ) following whole blood stimulation in patients with MS was found to be significantly higher in patients with MS with fatigue than in patients with MS without fatigue (Heesen et al., 2006). Further, this study found a significant positive correlation between both TNF-α and IFN-γ levels and fatigue severity (Heesen et al., 2006). Especially interleukin-6 (IL-6) has been suggested as playing a mediating role in fatigue, as increased IL-6 concentrations are evident both during a relapse as well as during the treatment with interferon beta (Goebel et al., 2002; Hautecoeur, Forzy, Gallois, Demirbilek, & Feugas, 1997; Neillley, Goodin, Goodkin, & Hauser, 1996). The possible non-disease-specific involvement of cytokine levels on the experience of fatigue are further underpinned by the fact that similar changes in cytokine levels are evident in other diseases such as human immunodeficiency virus (HIV), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), in which complaints of fatigue are common (Dufour, 2005; Kozora, 2005).
2.3.1.3 Neuroendocrine involvement

Increased activity of the hypothalamic-pituitary-adrenal (HPA) axis can be triggered by elevated levels of proinflammatory cytokines in MS and lead to an increased secretion of corticotrophin-releasing factors (CRF), adrenocorticotropic hormone (ACTH) and cortisol (Goebel et al., 2002; Krupp, 2003a; Navikas & Link, 1996). The interaction is reciprocal however, as a HPA dysregulation may in turn also lead to immune activation (Krupp, 2003a). The role of the HPA axis in MS-related fatigue however still remains unclear (Chaudhuri & Behan, 2004). One study found a hyper-reactivity of the HPA axis in relapsing RRMS patients without MS-specific treatment (Gottschalk et al., 2005). This study found an increased ACTH discharge in the decamethasone/corticotropin-releasing hormone (DEX-CRH) test. In contrast, another study investigating the relation between fatigue and the HPA axis in a heterogeneous MS group not excluding medication-use failed to demonstrate a relationship (Heesen, Gold, Raji, Wiedemann, & Schulz, 2002; Heesen et al., 2006). A dysregulation of the HPA axis was suggested after lower serum levels of the adrenal neurohormone dehydroepiandrosterone and its sulphated ester was found in PPMS patients with high fatigue severity (Téllez et al., 2006). It has been proposed, that homogenous samples of MS-types should be included in future studies investigating the activity of the HPA axis and it’s relation to fatigue, as this activation may be related to the clinical course of the disease (Bergh, Kümpfel, Trenkwalder, Rupprecht, & Holsboer, 1999). Further, the immunomodulatory treatment should be accounted for (Kos et al., 2008).

Fatigue related to RA was found to be associated with higher cortisol levels (Kozora, 2005). In contrast to the findings concerning MS and RA, the HPA axis was found to be hypo-reactive in chronic fatigue syndrome (CFS) which in turn suggests a dissimilar neuroendocrine-related pathogenesis of fatigue (Scott & Dinan, 1999). The effects of modafinil, a wake-promoting agent used predominantly in the treatment of narcolepsy, were at first regarded as a promising intervention in the regulation of MS-related fatigue (Rammohan et al., 2002; Zifko, Rupp, Schwarz, Zipko, & Maida, 2002) as it is thought to manipulate brain areas that regulate wakefulness, such as hypothalamic neurons (Ishizuka, Sakamoto, Sakurai, & Yamatodani, 2003; Lin, Hou, & Jouvet, 1996). Contradictively, recent randomized placebo-controlled double-blind clinical trials showed that the effect of modafinil on fatigue in MS-patients was not superior to
that of the placebo treatment (Kos et al., 2008; Stankoff et al., 2005). However, a positive effect in patients with daytime sleepiness was indicated in post-hoc analysis, suggesting dissimilar origins for fatigue and sleepiness (Stankoff et al., 2005).

The abovementioned results indicate a connection between the pathophysiology of MS-related fatigue and the endocrine system, however the evidence is unclear and the trigger in the interaction of immune activation and HPA axis dysregulation is yet to be clarified (Braley & Chervin, 2010; Induruwa et al., 2012; Kos et al., 2008).

2.3.2 Secondary fatigue

Fatigue as a symptom may arise and be amplified by as a result of numerous factors such as medical conditions including infections, injury to the brain, medication, psychiatric disorders including depression, pain, sleep disorders and even unhealthy lifestyles (DeLuca et al., 2009) (DeLuca, 2005; Kos et al., 2008). This form a fatigue is referred to as secondary fatigue. Triggers of secondary fatigue may be identified by guided interviews to ascertain possible mechanisms leading to fatigue (Ayache & Chalah, 2017). Factors such as depression and anxiety may be identified by key elements such as sadness, anhedonia, motivation loss, social isolation, nervousness and irritability. Sleep disorders such as sleep apnea, nocturia, nocturnal spasms, neuropathic pain, snoring or restless leg syndrome may also be the cause of fatigue. Thyroid dysfunction (hypo- & hyperthyroidism) may also cause factors leading to fatigue such as constipation, diarrhea, restlessness and cold or heat intolerance. Medications such as analgesics, anti-epileptics, anti-spasmodics or even immunosuppressants may have side effects such as fatigue. Other deficiencies such as anemia or vitamin D deficiency have also been shown to lead to feelings of fatigue. Some of these factors will be addressed in more detail in the section below.

A comparatively large study of 151 individuals with MS found no association between fatigue and age, gender, disease duration and clinical activity (Flachenecker et al., 2002). Contrary to these findings, other studies found higher age, lower educational level, longer disease duration and a progressive disease type to
be related to fatigue (Colosimo et al., 1995; Kroencke et al., 2000; Lerdal et al., 2003). Post-hoc calculations of these studies however revealed that disability status was mainly responsible for the differences in fatigue scores when viewing MS types (Kroencke et al., 2000; Pittion-Vouyovitch et al., 2006; Schreurs, de Ridder, & Bensing, 2002). Other factors which may lead to secondary fatigue include side-effects of prescription medication or infections unrelated to the MS disease.

In general, subjective measurements of fatigue have eluded any viable correlation with objective measures such as physical performance or indicators of disease progression (Beatty et al., 2003; DeLuca, 2005; Jennekens-Schinkel, Sanders, Lancer, & Van der Velde, 1988; Johnson, Lange, DeLuca, Korn, & Natelson, 1997; Mosso, 1904; Wessely et al., 1998), nor with functional deterioration in daily life (Kinkel, 2000) or even with indicators of physical fatigue (Gandevia, Enoka, McComas, Stuart, & Thomas, 1995). Please refer to the section entitled “objective measurements of fatigue” below for further information.

Fatigue as a side-effect of medication

Typical symptoms of fatigue can also appear following the intake of medication and has been reported for antispastic and anticonvulsive medication, analgetics, antidepressants, antihistamines, anti-inflammatory medication, neuroleptic drugs, gastrointestinal medication, immune-modulators, muscle relaxants, sedatives and hypnotic drugs (Zifko, 2004).

Fatigue as a result of infections

Symptoms of fatigue have also been found in conjunction with urinary tract infection and infections of the upper respiratory tract (Zifko, 2004). In general, feelings of fatigue and lack of energy are typical symptoms for people suffering from any type of infection as the body attempts to fend off the infection, similar to those feelings experienced when fighting a common cold or flu (Doerr & Gerlich, 2010; Heesen et al., 2006).

Fatigue and physical disability

Although a connection between physical disability (i.e. EDSS scores) and MS-related fatigue may inherently be expected, a consensus on the relationship between these two aspects has not been attained. Some studies have found that the differences in fatigue scores could indeed be explained mainly by the variation
2. MS-related fatigue

2.3 Primary and secondary fatigue

of disability scores (Biberacher et al., 2017; Kroencke et al., 2000; Pittion-Vouyovitch et al., 2006; Schreurs et al., 2002). In contrast however, numerous other studies found no significant relationship between these two variables (Bakshi et al., 2000; Kos et al., 2003; van der Werf et al., 1998). Although yet remaining uncertain, it is crucial for any study investigating fatigue in patients with MS to measure and evaluate the level of physical disability of each subject as correlations to other mental disorders such as depression may also seem reasonable.

Fatigue and reduced activity

Studies have indicated that patients with MS are less active than healthy controls and that this chronically reduced activity (Motl, McAuley, & Snook, 2005; Ng & Kent-Braun, 1997) may in turn offer an explanation for increased fatigability and muscle use. However, when analyzing the correlations between self-reported fatigue and reduced activity levels, no relationship was found (Vercoulen et al., 1997). Even after short exercise interventions lasting between 3-4 weeks, an improvement in fatigue severity scores was not observed (Mostert & Kesselring, 2002; Surakka et al., 2004; Van den Berg et al., 2006). However, training interventions lasting longer (10 weeks) affected the fatigue scores in a positive manner (Oken et al., 2004; Petajan et al., 1996). When investigating the relation between gait pattern and fatigue in the morning and in the afternoon, gait patterns remained unchanged whilst fatigue scores increased (Morris et al., 2002). Results suggest that the mechanisms for motor control and the subjective experience of fatigue are unrelated (Morris et al., 2002; Ng, Miller, Gelinas, & Kent-Braun, 2004; Rietberg, Brooks, Uitdehaag, & Kwakkel, 2005). It was even possible to objectify this component by analyzing the individual kinematic gait patterns of patients with MS and comparing the results on an individual level between the beginning (no fatigue) and end of a motor task (walking on a treadmill) (Sehle et al., 2014). Using intricate mathematical models to calculate a so called “attractor”, it was possible to objectively discriminate fatigue patients from non-fatigue patients after a short time even before muscular exhaustion was evident.
Fatigue and psychological factors

Psychological factors may positively and negatively influence the experience of fatigue in MS. Statements describing changes in personality and affect due to MS were mentioned as early as 1877 by J.M. Charcot (Charcot, 1877) and play an important role in the experience of MS. It has been indicated that in contrast to control subjects, patients with MS showing cognitive impairment and patients with MS-related fatigue show higher neuroticism-scores, meaning they tend to focus their attention and perception more on negative and strenuous emotions as well as physical symptoms than controls (Benedict, Priore, Miller, Munschauer, & Jacobs, 2001; Merkelbach, König, & Sittinger, 2003). Similarly, patients with fatigue were found to be less extrovert, hypersensitive and emotionally less stable (Schwartz, Coulthard-Morris, & Zeng, 1996). Further it was found, that self-efficacy (sense of control) may reduce feelings of fatigue, whilst the focusing on bodily sensations (introspection) on the other hand may aggravate the symptom (Schwartz et al., 1996; Vercoulen et al., 1996). Effects of both cognitive behavioral therapy (CBT), as well as large placebo effects were found in studies investigating the psychological influence on fatigue persistence (Mohr, Hart, & Goldberg, 2003; Mostert & Kesselring, 2005; Prins et al., 2001; Rossini et al., 2001a; Stankoff et al., 2005) and should be included as an additional treatment for fatigue.

Fatigue and depression

The high comorbidity and the additional negative symptoms of depression in patients with MS have been mentioned above. Both depression and fatigue are two components of MS which often appear in conjunction and appear to be strongly related (Bakshi et al., 2000; Chwastiak et al., 2002; Kroencke et al., 2000; Lobentanz et al., 2004; Patrick et al., 2009; Pittion-Vouyovitch et al., 2006; Randolph, Arnett, Higginson, & Voss, 2000; Schreurs et al., 2002; Voss et al., 2002), although the causality of the relationship has not yet been established (Kos et al., 2008). Mood and behavioral changes may already be prominent symptoms at presentation but may remain underdiagnosed (Skegg, Corwin, & Skegg, 1988) and may also be observed in early stages of the disease (Sullivan, Weinshenker, Mikail, & Bishop, 1995). It has for instance also been found, that anxiety and depression levels can be elevated during peri-diagnostic periods (Mattarozzi et al., 2012) or during periods of increased MS activity (Di Legge et al., 2003; Moore et al.,
2. MS-related fatigue

In a longitudinal follow-up study including 236 patients with MS over a period of 5 years, it was found that clinical anxiety, depression and fatigue were already frequent in early stages of the disease and that the co-occurrence of the three outcomes was in total 3.76 times higher than expectation under statistical independence, suggesting these three symptoms tend to cluster together in the disease process (Simpson et al., 2016).

An MRI study investigating the involvement of specific regional patterns of lesion distribution and GM as well as WM atrophy on the experience of fatigue in patients with MS (Gobbi et al., 2014). The researchers recruited 123 patients with MS and 90 control subjects and acquired 3D T1 weighted images on which VBM was performed to assess lesion distribution and as well as GM and WM atrophy. The patient cohort was analyzed with regard to depression and fatigue separately, meaning the same cohort consisted of patients with and without clinical signs of depression (69 patients with depression & 54 patients without depression) as well as a self-reported fatigue (64 fatigued & 59 non-fatigued). The study used the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) as well as the FSS (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989a) to categorize the groups. Their results showed, that within their patient group there was no inherent difference between the depressed and non-depressed group with regard to age, gender, disease duration nor in conventional MRI characteristics, however fatigued patients showed higher EDSS and depression than non-fatigued patients. When comparing the groups, the researchers found that the lesion distribution and WM atrophy were related neither to depression nor to fatigue. Interestingly however, GM-atrophy within the frontal, parietal and occipital lobes showed a mutual effect for depressed as well as fatigue patients. They also found that atrophy specifically in the left middle frontal and right inferior frontal gyrus was solely related to depression. The authors concluded that atrophy within the aforementioned cortical areas is linked to depression and that further distributed GM atrophy contributes to the concomitant occurrence of fatigue and depression in patients with MS (Gobbi et al., 2014). The authors thus emphasize, that neural mechanisms (in this case) GM atrophy should rather be ascribed to depression rather than fatigue.
PET studies (Brody et al., 2001) examined the association between change in depressive symptoms and change in regional brain metabolism following treatment for depression. The findings indicated that a decrease in bilateral ventral prefrontal cortex activity correlated with a decrease in fatigue before and after treatment.

**Interaction and associations between fatigue, depression and daytime sleepiness**

As mentioned above, in addition to the high prevalence of fatigue in patients with MS, depression and sleep disorders are also as prominent in the disease manifestation (Induruwa et al., 2012). All three symptoms can lead to severe impairments in private and occupational life and have a negative influence on quality of life. Diagnosing and treating these symptoms can prove challenging as they can appear individually or in combination with each other and may have reciprocal influences (Bol et al., 2009; Braley & Chervin, 2010).

Regarding fatigue in the sense of a secondary phenomenon appearing comorbidly in conjunction with other disorders such as depression and sleep disorders implicates that treating these primary disorders in turn would have beneficial consequences on the manifestation and experience of fatigue (Bol et al., 2009; Braley & Chervin, 2010; Kos et al., 2008). Numerous studies have found significant correlations between fatigue and depression in MS (Amato et al., 2001; Bakshi et al., 2000; Chwastiak et al., 2002; Ghajarzadeh et al., 2013; Goretti et al., 2012; Kroencke et al., 2000; Voss et al., 2002). Studies have even proven that fatigue symptoms do not remit if the depressive disorder is not treated correspondingly (Krupp, Serafin, & Christodoulou, 2010). Treating the depressive disorder may in turn also positively influence the subjective assessment of the severity of the fatigue (Mohr et al., 2003). It is speculated, that the strong association between fatigue and depression indicates a mutual pathophysiology or a reciprocal interdependency due to their causal relationship (Flachenecker et al., 2002). However, a prominent methodological problem in the objectification of fatigue and depression has been identified. Many items found on self-report questionnaires coincide with each other, which may in turn lead to an artificial increase in the correlation between these two symptoms (Bol et al., 2009). Nevertheless, other studies have found significant
correlations between fatigue and depression even after correcting for the coinciding items (Kroencke et al., 2000).

Fatigue and sleep disorders

Although the exact relationship and interaction between fatigue and disorders of sleep, including the quality and the quantity of sleep, remain to be fully understood (Induruwa et al., 2012), an increasing appreciation for the importance of the influences of sleep disorders on MS related fatigue has arisen over the last few years.

Reports of reduced sleep quality in patients with MS are twice as high as in healthy controls and are often associated with pain, spasms, medication, disorders of bladder control, anxiety and other external factors (Clark et al., 1992; Lobentanz et al., 2004; Stanton, Barnes, & Silber, 2006; Tachibana et al., 1994). Some studies investigating the relationship between fatigue and sleep in patients with MS found no relation between fatigue and sleep-wake rhythm, difficulties falling asleep, early wakening and nocturnal apneas or oxygen desaturations (Stanton et al., 2006; Taphoorn et al., 1993; Wunderlin et al., 1997), whilst moderate correlations between fatigue and disruptions of sleep by nocturnal activity and middle insomnia (i.e. waking during the night) (Stanton et al., 2006) could be identified. Other studies indicated, that disruptions and deviations of circadian rhythm, sleep architecture and cycles, daytime sleepiness, nocturnal activity and waking due to nocturia were important factors in the relationship between fatigue and sleep disorders (Attarian, Brown, Duntley, Carter, & Cross, 2004; Braley & Chervin, 2010; Hossain et al., 2005; Kaminska et al., 2012; Kaminska, Kimoff, Schwartzman, & Trojan, 2011; Kaynak et al., 2006; Niepel et al., 2013; Stanton et al., 2006).

The causality between fatigue and sleep disorders is not explained by the abovementioned relationships (Kos et al., 2008) and many studies have come to the conclusion, that a differentiation between fatigue and daytime sleepiness is necessary (Hossain et al., 2005; Merkelbach et al., 2006; Stankoff et al., 2005; Stanton et al., 2006). In light of the above, the importance and potentially confounding influence of depressive
The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis

symptoms on the complex interaction between sleep disorders and fatigue has often been highlighted (Kaynak et al., 2006).

The relationship between all three MS-related variables – depression, sleep disorders and fatigue – has been the object of scrutiny in only few studies. Significant correlations between fatigue and depression as well as fatigue and sleep disorders were identified in studies investigating prevalence in a small cohort of MS-patients (Nagaraj, Taly, Gupta, Prasad, & Christopher, 2013). Especially noteworthy are the results of a study which found significant correlations between depression and fatigue even when the possible confounding effects of sleep-disorders were corrected for (Ghajarzadeh et al., 2013). The authors of this study came to the conclusion, that fatigue related to MS in a “secondary” fashion may occur as a result of depression or sleep-disorders. The interpretation of the results of this study were however limited, as the directional causality of the relationship could not be established due to the fact that the study was a cross-sectional study as opposed to a longitudinal study. Further, no significant differences were found when contrasting the extent of daytime sleepiness in patients with and without fatigue. Another study investigating the relation of sleep-duration and fatigue were able to illustrate a complex, U-shaped relationship between these two properties (Mills & Young, 2011). They found that a sleep-duration of 7.5 hours improved the experience of fatigue during the day, whilst having either more or less sleep aggravated the fatigue the following day. However, the correlation between fatigue and depression was only found to be moderate in this study. A study investigating the impact of modifiable predictors on fatigue found no correlation between depression and fatigue on the one hand, but was able to identify sleep-quality as an important and potentially modifiable predictor for fatigue (Trojan et al., 2007).

Evidence that depression and sleep disorders are in fact independent influences on MS-related fatigue is also given by a study investigating the relationship between disease-severity, depression and sleep disorders in MS and their potential effects on MS-related fatigue (Strober & Arnett, 2005). The study found, that taken together, all three factors were able to explain roughly 43% of the total variance of MS-related
fatigue. Of the three factors, sleep-disorders proved to explain the most of this variance and disease-severity the least.

When interpreting the abovementioned studies and their results, it is important to keep in mind that these studies varied considerably with regard to their employed methods and materials, aims, patient cohorts and cohort size. Further, most studies were cross-sectional studies, meaning the data was gathered at a single point in time. As a consequence, the direction of the causal relationships between depression, sleep disorders and MS-related fatigue is not possible and a final conclusion regarding their interaction remains elusive.

One longitudinal study investigating the relationship between TBI and fatigue postulated that the experienced fatigue was a direct consequence of neural brain damage (Schönberger, Herrberg, & Ponsford, 2014). Their study included a baseline observation as well as a 6-month follow-up. At both time-points fatigue, depression and daytime sleepiness correlated moderately, indicating that these three factors were de facto independent from each other, yet highly associated. Using a cross-lagged-panel analysis, the study was able to prove that baseline fatigue constituted a significant predictor of depression and daytime sleepiness at follow up, yet these two factors could not significantly predict fatigue at follow up. It was concluded, that although fatigue may have strong associations with depression and daytime sleepiness, the emergence of fatigue is strongly connected with acquired brain damage. This in turn offers support for the notion, that MS-related fatigue should in fact be regarded as a primary symptom of MS (primary fatigue) rather than a secondary symptom (secondary fatigue) brought about by other accompanying disorders such as depression and sleep disorders.
2.4 Measures of Fatigue

The increasing number of studies investigating fatigue in MS reflects the importance of this symptom and the ever growing interest in the scientific explanation of this phenomenon. Specifically, obtaining objective and reliable methods of assessing both cognitive and physical presentations of fatigue have stood in the foreground.

Recently, increasing emphasis has been placed on distinguishing between both physical fatigue and mental or cognitive fatigue as two separate domains pertaining to this debilitating symptom. Many modern questionnaires such as the FSMC (Penner et al., 2009) take this into account and offer separate scales for each domain. This becomes particularly important when contrasting subjective ratings to objective measurements pertaining to either motor or cognitive functions.

2.4.1 Subjective measures of fatigue

In light of the aforementioned importance and consequences of fatigue on the daily functioning and working capacity of patients with MS, much research has been invested in the objective measurement of this aspect of the disease.

The most common methods to quantify fatigue in MS have relied invariably on subjective ratings offered by the patients and are measured using questionnaires. It should be noted, that these subjective scales, as all self-report scales, underlie methodological short-comings, specifically a strong recall bias (Bol et al., 2009). The large variation of self-report instruments in existence reflects the numerous dimensions of fatigue in MS (Kos et al., 2004).

A well-known fatigue scale is the Chalder Fatigue Scale (The Fatigue Scale), which is also known as the Fatigue Rating Scale (FRS). Originally created for chronic fatigue syndrome patients, it is a quick (3-4 minute) 14-item instrument quantifying fatigue intensity in terms of physical and mental domains (Chalder et al., 1993). It uses a 4 point Likert-type scale ranging from 0 to 3 to assess fatigue. A sum score is calculated of which higher scores indicate more fatigue. A shorter version with 11 items is also available.
This questionnaire also differentiates between physical and mental fatigue dimensions. A cutoff of 3/4 is recommended for identifying significant fatigue (Dittner, Wessely, & Brown, 2004).

One of the most commonly employed questionnaires, which has also been mentioned frequently in the sections above, is the Fatigue Severity Scale (FSS) assessing the modality, severity, frequency and impact of fatigue on daily life (Krupp et al., 1989b). It is constituted of 9 items and uses a 7 point Likert-type scale ranging from 1 (‘strongly disagree’) to 7 (‘strongly agree’) for evaluation. The FSS has been validated in a variety of neuroimaging, behavioral and clinical studies investigating fatigue in MS (DeLuca, 2005; DeLuca et al., 2009; Filippi et al., 2002; Genova et al., 2013; Mills, Young, Nicholas, Pallant, & Tennant, 2009; Tedeschi et al., 2007). It also showed a very high internal consistency measured by Cronbach’s coefficient alpha (0.81-0.94) (Kroencke et al., 2000; Krupp et al., 1989b) and satisfactory test-retest reliability (interclass correlation coefficients at 0.82) (Kleinman et al., 2000). It has further been shown to correlate to a high degree with other fatigue scales such as the FDS (see below), the VAS (see below), the FIS (see below), vitality scores in the health-related quality of life questionnaires, as well as the Short Form 36 (SF-36) (Kleinman et al., 2000; Krupp et al., 1989b; LaChapelle & Finlayson, 1998). The questionnaire was developed in 1989 and was applied to 25 patients with MS, 29 patients with systemic lupus erythematosus and 20 healthy controls (Krupp et al., 1989b). As a result of lacking large scale patient studies, no clearly defined cut-off to discriminate normal from pathological results was available. Generally, respondents with scoring a mean score greater than 4 were defined as having severe fatigue (Krupp et al., 1989b). This cut-off score was chosen because less than 5% of healthy control subjects rated their fatigue above this level whilst 90% of patients reported fatigue at or above this level (Krupp et al., 1995). Many studies investigating the cut-off scores of the FSS have come to the same conclusion of using the value greater or equal to four as the cut off score for interpreting results as indicating pathological fatigue (Armutlu et al., 2007; Branas, Jordan, Fry-Smith, Burls, & Hyde, 2000; Hjollund, Andersen, & Bech, 2007; Krupp et al., 1995; Krupp et al., 1989b; Valko, Bassetti, Bloch, Held, & Baumann, 2008; Zifko, 2004).
The Fatigue Impact Scale (FIS) is a 40-item questionnaire designed to assess the impact of fatigue on physical, cognitive and psychological functioning within the last month. A shorter, 21-item version of this scale exists, the Modified Fatigue Impact Scale (MFIS) (Guidelines, 1998). Both scales are considered to have adequate reliability and validity (Fisk, Ritvo, et al., 1994; Kos et al., 2005; Mathiowetz, 2003; Multiple-Sclerosis-Council-for-Clinical-Practice-Guidelines, 1998). These scales use a 0-4 point Likert-scale for evaluation.

The Fatigue Descriptive Scale (FDS) represents a reliable and valid 5-item instrument evaluating severity, frequency, quality of life and the influence of heat (Uhthoff phenomenon) on fatigue. However, an interview is necessary to consider the spontaneity of fatigue complaints (Iriarte, Katsamakis, & de Castro, 1999; Kos et al., 2008). The score range varies from 0-3 per item.

Another questionnaire, the Fatigue Assessment Inventory (FAI) is a 29-item scale designed to assess the severity, pervasiveness, associated consequences and response to sleep of patients with MS. It uses a 1-7 point Likert-type scale, takes roughly 5-10 minutes to administer and was found to be reliable and valid (Schwartz, Jandorf, & Krupp, 1993). Questions applied to experiences of the respondents within the last 2 weeks.

In many cases, the Epworth Sleepiness Scale (ESS) is used to assess excessive daytime sleepiness by rating the risk to fall asleep in 8 situations; however this tool has yet to be validated for patients with MS (Johns, 1991). Answers are given on a Likert-type scale between 0-3 points.

The Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009) is a questionnaire which has recently been developed to specifically assess fatigue in patients with MS. The items were generated by analyzing previous commonly used assessment questionnaires and sorting individual items into cognitive or motor domains. This questionnaire showed good reliability and validity (Penner et al., 2009). It is composed of 20 items using a 5-point Likert-type scale for assessment. Cut off scores for general fatigue, but also specifically for motor and cognitive domains are given. Respondents are specifically requested to rate their level of fatigue independently of their current physical or mental state but rather how they experience
fatigue in their day to day life. The minimum score is 20 and the maximum score 100. The cut off values for fatigue severity are: mild fatigue ≥43 points; moderate fatigue ≥ 53 points; severe fatigue ≥63 points.

A similar questionnaire used in Germany is the *Würzburger Erschöpfungs Inventar* (WEIMuS) developed by Flachenecker and colleagues. This questionnaire also differentiates between cognitive and motor fatigue. It is a 17-item questionnaire using a 5-point Likert-type scale and has been found to be reliable and valid (Flachenecker et al., 2006).

A further form of subjective rating is constituted by a *Visual Analog Scale* (VAS) which allows the patients to rate their subjective appraisal of a specific question along a visually present line (usually around 10cm wide) by indicating their answer with a mark on the line. It has been found, that this method is however only moderately reliable (Kos, Nagels, D'Hooghe, Duportail, & Kerckhofs, 2006; Lee, Hicks, & Nino-Murcia, 1991).

Fatigue diaries such as the *MS Symptom and Impact Diary* (Greenhalgh, Ford, Long, & Hurst, 2004) offer more precise descriptions of the fatigue symptoms experienced by the patients over time. This becomes crucial when investigating the at times greatly varying onsets, durations and intensity of the symptoms and helps to identify patterns in individual experiences of fatigue. These in turn offer useful and crucial information for the development of treatment plans or therapeutic interventions specifically tailored to each individual. Diary entries further offer clues and possible explanations to the cause or co-varying factors of MS-related fatigue (Penner, 2009). Keeping a diary is however very time-consuming and requires a certain level of commitment and insight on behalf of the patient as well as the healthcare practitioner.

Numerous additional subjective fatigue rating questionnaires exists, some of which specifically cater to patients with MS whilst others relate to general feelings of fatigue in non-MS-specific contexts. For a detailed review of these measures we advise referring to the paper by Dittner et al. 2004 which offers a good summary of available subjective assessments of fatigue (Dittner et al., 2004).
2.4.2 Objective measures of fatigue

2.4.2.1 Multiple sclerosis and cognition

Before addressing the neuropsychological measures specifically utilized to investigate fatigue, a brief overview of established neuropsychological measures typically employed to ascertain the possible cognitive impairment resulting from the MS disease is given.

BRB-N

The Brief Repeatable Battery of Neuropsychological Tests (BRB-N) was developed by the Cognitive Function Study Group of the National Multiple Sclerosis Society as an instrument for assessing cognitive functions specifically in patients with MS (Rao, 1990). It derived from a comprehensive neuropsychological test battery which was chosen according to guidelines for neuropsychological assessment and research in MS originally consisting of 23 tests (Peyser, Rao, LaRocca, & Kaplan, 1990; Rao et al., 1991). Of this large number of tests, four tests in particular were found to be most sensitive for detecting cognitive impairment in MS (Rao, 1990). These were the Controlled Oral Word Association Test, the Paced Auditory Serial Addition Test, the 7/24 Spatial Recall Test and the Selective Reminding Test (Rao et al., 1991) resulting in a sensitivity of 71% and a specificity of 94% to detect cognitive impairment. Some of the tests were modified and other tests included expanding the test battery, which finally resulted in the creation of the BRB-N. This battery included the following five tests: the Word List Generation test (WLG), the Paced Auditory Serial Addition Test (PASAT), the 10/36 Spatial Recall Test (SPART), the Symbol Digit Modalities Test (SDMT) and the Selective Reminding Test (SRT) (Bever, Grattan, Panitch, & Johnson, 1995; Rao, 1990). These tests will be described shortly in the following paragraphs.

The WLG test is a timed test of semantic verbal-fluency assessing spontaneous production of as many names as possible within a specified category, either “fruits and vegetables” (version A) or “animals” (Version B) (Rao, 1990). The time limit is 90 seconds and the sum of all adequate names is the score (WLGT).
The Paced Auditory Serial Addition Test (PASAT) evaluates sustained attention and information processing speed by requesting participants to calculate sum values of digit pairs presented at two different tempos (Gronwall, 1977). In total, 60 pairs of digits are presented. The participants are requested to add each number to the one that immediately preceded it and to give the sum-value verbally. The digits are presented by tape, at first with a rate of 1 digit every 3 seconds, thereafter in the second run with a digit every 2 seconds. As the pace is dictated by the tape, the participant has little time to respond and thus encoding of own responses is repressed due to the fact that the participant is occupied with attending to the subsequent stimulus in a sequence. The score is calculated from the sum of correct responses per sequence (PASAT3, PASAT2). The sole difference between the two versions is the presentation rate.

To evaluate visuo-spatial learning and recall following a delay, the 10/36 Spatial Recall Test (SPART) was developed. The 10/36 Spatial Recall Test is an adapted version of the original 7/24 Spatial Recall Test and the board is wider and has more checkers. A board consisting of checker-patterns is presented for a duration of 10 seconds, after which the participant may endeavor to replicate the presented design on a blank board. This procedure is repeated twice and after an intermission of 15 minutes the participant is requested to once again recreate the layout. A sum score is calculated by the number of correct answers over three attempts (SPARTT) and the delayed recall trial (SPARTD).

The Symbol Digit Modalities Test (SDMT) is a measure of sustained attention and concentration (Smith, 1968). It places demands on complex visual scanning and tracking performances. Nine meaningless geometric symbols are paired with the number 1-9 and are permanently presented to the participant. In the written form, the symbols and corresponding numbers are presented at the top of the test page. For the duration of 90 seconds the participant substitutes the presented symbols in a row with the corresponding number as displayed in the original key either verbally or in a written form by filling in a blank space beneath the symbol. The sum of correct substitutions yields a final score (SDMTT). Versions differ in the sequence of symbols. These may also be labeled with a different number. Alternative (reverse) forms of the SDMT require the participants to substitute the numbers with the corresponding symbols.
The Selective Reminding Test (SRT) is a test to assess verbal learning and memory across six trials during which a 12 word-list is presented (Buschke & Fuld, 1974). The presentation frequency is one word every two seconds. Participants are requested to attempt to recall as many words as possible. Following the first trial, only the words that were not recalled are repeated to the participant. Following an intermission of 15 min - during which the PASAT is administered - the participants are once again requested to recall all the word from the word list. The SRT is able to differentiate performance between short-term and long-term components of memory. Analysis is standardized (Buschke & Fuld, 1974). A word is regarded as being represented on long-term memory if it is repeated consistently in two consecutive retrievals. Following 6 presentations, a sum score of all recalled words can be calculated (SRTL). A word named consistently during all recall-attempts is considered as an indication of Consistent Long Term Retrieval (CLTR). The total number of these CLTR-words during all 6 attempts is called the SRTC. The Delayed Recall (SRTD) is sum of words recalled following the delay period.

**MSFC**

The Multiple Sclerosis Functional Composite (MSFC) measure was proposed by the National MS Society’s Clinical Outcomes Assessment Task Force to evaluate clinical functioning in patients with MS (Fischer, Rudick, Cutter, Reingold, & Force, 1999). They sought to create an optimal outcome measure which was multidimensional, widely applicable, valid, responsive, reliable, had an interval scale of measurement, and lastly - and quite simply - was practical for the everyday clinical setting. A consensus was sought on reliable quantitative and objective measures evaluating important clinical dimensions of MS, namely leg function/ambulation, arm/hand function as well as cognitive function. For each of these domains, a suitable measure was proposed. *Leg function/ambulation* was proposed to be objectively and reliably assessed by the T25W, also known was the T8 (Schwid et al., 1997). The test measures the average time taken for a patient to walk a distance of (25-foot; i.e. ~8m) safely. To assess *Arm/hand function*, the task force suggested the use of the 9-Hole Peg Test (9-HPT) (Goodkin, Hertsguard, & Seminary, 1988) during which participants are instructed to insert 9 pegs single-handedly and one-by-one into 9 holes arranged in a square pattern (usually made of wood) before removing these again as fast as possible. The average time
taken with each hand during two consecutive trials is regarded as the dependent variable. As a measure of cognitive functioning, the task force suggested the use of the PASAT to assess information processing speed and flexibility as well as calculation ability (Fischer et al., 1999). For a detailed description of the PASAT, please refer to the section of the BRB-N above.

MACFIMS

The Minimal Assessment of Cognitive Functions in Multiple Sclerosis (MACFIMS) test battery consists of seven standardized neuropsychological tests. It was created in 2001 by an expert panel of neuropsychologists and psychologist from English speaking countries including the United States, United Kingdom, Canada and Australia, who saw the need to create a consensus on the optimal approach of evaluating cognitive functioning of patients with MS (Benedict et al., 2002). They proposed a neuropsychological test battery which takes approximately 90-minutes to complete and encompasses five cognitive domains commonly found to be impaired in patients with MS. These domains include information processing speed, learning and memory, executive functions, visual spatial processing, word retrieval and working memory (Benedict et al., 2002).

Information processing speed & working memory: Both the PASAT and the SDMT are identical to the versions described in the BRB-N above. The SDMT is only administered orally in the MACFIMS.

Learning and memory verbal: The revised California Verbal Learning Test (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000) is employed to assess verbal memory functions. The test consists of a 16-word list (List A) which is presented to the participants orally for a total of five repetitions. Following each repetition, the subject is requested to name all words that he/she can recall. As interference, another 16-word list (List B) is presented with different words and the subject is requested to recall these new words before once again recalling as many words as possible from the first list (LIST A). The total number of recalled words in the first 5 repetitions, as well as the number of interferences and number of words lost from memory due to interference are assessed. Following a 25-minute interval, the participant is once again requested to recall as many words from List A as possible. Finally, the subjects are requested to make a forced yes/no choice
deciding whether they have previously been presented with a word from another list which includes words from List A, List B as well as novel words. Not only can the CVLT-II provide information on verbal memory, it also offers additional information on performance variables such as semantic clustering, susceptibility to interference and depicts a learning curve (Delis et al., 2000).

**Learning and memory non-verbal:** The Brief Visuo-spatial Memory Test – Revised (BVMT-R) (Benedict, 1997; Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996) assesses visuo-spatial learning and memory. It requires the learning of a matrix of 6 simple abstract designs which is presented for a duration of 10 seconds. The matrix is repeated a total of three times. Following each trial, the subject is requested to reproduce the matrix to the best of their ability. Delayed recall is assessed following an intermission of 25 minutes during which other tests are administered. Similar to the verbal memory test, subjects are also requested to make a forced yes/no decision (recognition) of previously presented as well as novel stimuli. The BVMT-R offers a total of 6 alternate forms. Subject’s motor capacities are also taken into account by the examiner when scoring the test.

**Executive functions:** The Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) sorting test (DST) is a measure of conceptual reasoning which allows the differentiation of concept formation from conceptual flexibility (Benedict et al., 2002) and is used within the MACFIMS to assess important components of executive functioning, such as problem solving, concept-formation, explaining abstract ideas, transfer of abstract ideas to action, inhibition, in patients with MS. In the standardized version, both free sorting and structured (cued) sorting is required, although to decrease testing time, only testing the free sorting is also tolerated. Briefly, the examinee is requested to classify six different cards into two categories in as many different ways as possible and to explain rationally why he/she had chosen the category. For a detailed explanation of this test and the administration and scoring, please refer to the manual of the D-KEFS (Delis et al., 2001).

**Language:** The Controlled Oral Word Association Test (COWAT) assesses verbal fluency and mental flexibility (Benton, Hamsher, & Sivan, 1989). In successive 1-min trials, subjects are requested to generate
as many words as possible, beginning with one of the following letters “F”, “A” and “S” depending on the trial. The total number of correct words over all trials is the raw score for this test.

**Visual spatial perception**: To assess this cognitive domain, Benton’s Judgement of Line Orientation Test (JLO) (Benton, Sivan, Hamsher, Varney, & Spreen, 1994) is employed in the MACFIMS. Subjects are required to indicate the angle defined by two stimulus lines from among those defined by a visual array of lines covering 180 degrees (Benedict et al., 2002). The total number of correct responses over 30 trials is considered the dependent variable.

The suggested order of presentation of the neuropsychological tests during the administration of the MACFIMS is displayed in table 2:

<table>
<thead>
<tr>
<th>Suggested presentation sequence MACFIMS</th>
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<tbody>
<tr>
<td>Interview with patient</td>
</tr>
<tr>
<td>1) COWAT</td>
</tr>
<tr>
<td>2) BVMT-R learning trials</td>
</tr>
<tr>
<td>3) PASAT</td>
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<tr>
<td>4) JLO</td>
</tr>
<tr>
<td>5) BVMT-R delayed recall and recognition</td>
</tr>
<tr>
<td>6) SDMT</td>
</tr>
<tr>
<td>7) CVLT-II learning trails and short-delay recall</td>
</tr>
<tr>
<td>8) DST</td>
</tr>
<tr>
<td>9) CVLT-II long-delay recall and recognition</td>
</tr>
</tbody>
</table>

On the basis of the results achieved in the various tests, patients can be classified as mildly, moderately or severely impaired, if two, three or more than three tests are considered as being failed.

**BICAMS**

The Brief International Cognitive Assessment for MS (BICAMS) initiative embarked on creating a brief, cognitive assessment for MS that especially takes into account that small centers treating patients with MS may rely only on few staff with no neuropsychological training (Langdon et al., 2012). It may be regarded as a shortened version of the MACFIMS employing only three of the abovementioned tests, namely the SDMT, the CVLT-II and the BVMT-R. With the aim of encouraging wide-spread and international use of this test
battery, validation studies are currently being undertaken world-wide to promote country-specific translations and norms for the BICAMS tests according to international standards (Benedict et al., 2012). BICAMS norms and validation studies are currently being conducted in many countries including Ireland, Brazil, Hungary, Lithuania, Italy, Canada, Germany, Greece, United Kingdom, Argentina, Netherlands, Belgium and Spanish speaking countries (Burggraaff, Knol, & Uitdehaag, 2017; Giedraitienë, Kizlaitienë, & Kaubrys, 2015; Goretti et al., 2014; O’Connell, Langdon, Tubridy, Hutchinson, & McGuigan, 2015; Orchard, 2013; Penner et al., 2015; Polychroniadou et al., 2016; Sandi et al., 2015; Vanotti, Smerbeck, Benedict, & Caceres, 2016; Walker et al., 2016).

2.4.2.2 Fatigue and cognition

Over and above cognitive impairment directly associated with MS, numerous approaches specifically investigating the effect of fatigue in MS on objective neuropsychological measures have been conducted with varying results. Multiple cognitive domains such as memory, cognitive speed, selective attention, information processing speed, working memory, alertness, vigilance, word fluency and visuospatial processing were investigated. A summary of studies conducted after 2006 is given below. Studies often included more than one neuropsychological measure. The following section is structured according to the neuropsychological domains. Therefore, some studies shall be mentioned repeatedly, however in each case the focus lies on a specific cognitive domain.

Fatigue and memory performance

Karadayi and colleagues (2014) investigated 31 MS patients and 31 healthy controls for neuropsychiatric and cognitive symptoms (Karadayi, Arisoy, Altunrende, Boztas, & Sercan, 2014). Fatigue was assessed by the FSS. Neuropsychological tests included the Mini Mental Status Examination (MMSE), Serial Digit Learning, verbal and non-verbal cancellation, Stroop and Rey Auditory Verbal Learning tests. Results indicated that the memory domain which was impaired in patients with MS independent of fatigue was long-term memory (measured by word list learning and the auditory verbal learning test (AVLT)). Fatigue
however showed no correlation to any cognitive measure, although correlating highly with depressive mood.

Hulst et al. (2013) investigated cognitive functioning during MRI scanning in 50 patients with MS and 30 controls. Variants of the AVLT and SDMT were employed. Results showed that no correlation was evident between fatigue and cognitive performance (Hulst et al., 2013).

Published in 2011, the study by Mattioli et al. was comprised of 255 patients with MS with and without fatigue (Mattioli, Bellomi, Stampatori, Parrinello, & Capra, 2011). Fatigue was measured using the FIS, whilst cognitive performance was assessed by the selective reminding test (SRT), paced auditory serial addition test (PASAT), symbol digit modalities test (SDMT), as well as the controlled oral word associations for phonemes (COWA P) and categories (COWA C). A word recalled on two consecutive trials was regarded to indicate long-term storage (LTS). Consistently recalling this word on all subsequent trials is an indication of consistent long-term retrieval (CLTR). The total number of words recalled following a delay-period is regarded as the direct recall (DR). Regarding memory performance, the results of the correlation analysis indicated a correlation between fatigue and delayed recall performance (CLTR: $\rho=0.32$, $p=0.035$ & DR: $\rho=-0.425$, $p=0.004$).

In a combined neuro-radiological, neuropsychological and immunological study, Heesen et al. (2010) conducted an investigation on cognition and mood in patients with MS (Heesen et al., 2010). The researchers recruited 50 patients with MS, 25 of which were categorized as being cognitively impaired and another 25 were regarded as cognitively preserved. This classification was based on the results of the SDMT which has been proven to be sensitive to cognitive impairment in MS (Benedict et al., 2008). Furthermore, patients underwent a comprehensive neuropsychological testing battery including the Auditory Verbal Learning Test (AVLT) evaluating verbal memory, three subtest of the “Testbatterie zur Aufmerksamkeitsprüfung” (TAP), namely the tonic alertness task, divided attention and cognitive flexibility, the “Regensburger Wortflüssigkeitstest” (RWT) evaluating lexical and semantic verbal fluency and finally the “Wortschatztest” (WST) estimating verbal intelligence level and language comprehension. Fatigue was
evaluated by means of the MFIS. Results indicated a weak correlation between the total learning score of the AVLT and fatigue ($r = -0.28$, $p<0.05$) (Heesen et al., 2010).

Eighty patients with MS were recruited in the study by Bol et al. (2010) investigating patients’ mood, cognitive performance and fatigue. Fatigue was assessed using the physical and mental subscales of the Multidimensional Fatigue Inventory (Smets, Garssen, Bonke, & De Haes, 1995). The extensive test battery which was employed included measures of sustained attention, information processing speed (Letter Digit Substitution Test), mental flexibility and divided attention (Concept Shifting Test), response inhibition and selective attention (Stroop Color Word Test), working memory (Digit Span subtask from the Wechsler Adult Intelligence Scale), verbal learning and verbal memory (California Verbal Learning Test – Dutch version), visual memory (Benton Visual Retention Test), semantic fluency (Groninger Intelligence Test), phonemic and letter fluency (Controlled Oral Word Association Test), concept formation and cognitive flexibility (Wisconsin Card Sorting Test) and non-verbal abstract reasoning (Raven’s Standard Progressive Matrices). The test-battery took about 120 minutes to complete. With regard to memory functions, results showed no correlation between the measured cognitive performance and fatigue when controlling for age, premorbid intelligence, neurological disability, depression and anxiety (Bol, Duits, Hupperts, Verlinden, & Verhey, 2010).

The cognitive performance of 60 patients with MS, as well as their respective fatigue score, was evaluated in a study by Andreasen et al. (2010). A control group consisting of 18 healthy controls was also recruited. Fatigue was evaluated by means of the FSS using a cut-off score of ≥5 for indicating fatigue (n=39) and ≤4 indicating no fatigue (n=21). The researchers even went as far as to further divide the patients group according to the type of fatigue; either as primary fatigued (n=19) or secondary fatigued patients (n=20). Neuropsychological tests included test from the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2008) and the Wechsler Memory Scale (WMS-II) (Wechsler, 1945) test batteries. Specifically, processing speed, auditory memory, perceptual organization and verbal comprehension were evaluated. When regarding
memory performance, the Results showed no correlation with memory performance in the logical memory domain of the WMS (Andreasen, Spliid, et al., 2010).

In a large cross-sectional & longitudinal study, Morrow et al. (2009) investigated 465 patients with MS using the MACFIMS (Benedict et al., 2006) to evaluate cognitive functioning and the FSS to evaluate fatigue (Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009). The cut-off score for the FSS was at ≥5 for fatigue, between 4-5 for borderline fatigue and ≤4 for no fatigue. The MACFIMS is a test-battery specifically developed to assess the cognitive functions often found to be impaired in MS, including tests assessing processing speed (SDMT; PASAT), verbal episodic memory (CVLT2), visuo-spatial memory (Brief Visuospatial Memory Test - Revised (BVMTR)), generative verbal fluency (COWAT), visual/spatial perception (Judgement of Line Orientation Test (JLO)) and higher executive functions (Delis-Kaplan Executive Function System Sorting Test (DKEFS)). Results indicated that a correlation between fatigue and memory and learning was not evident in the collected data, neither for the cross-sectional assessment nor in the longitudinal data (Morrow et al., 2009).

In 2007, Simioni et al. recruited 127 early MS or CIS patients for their study of the relationship between cognitive impairment (long-term memory, executive functions, attention), depression, fatigue and quality of life (QoL). Although a correlation between impaired cognition and fatigue was initially found, when correcting for QoL, fatigue was no longer found to be associated with cognitive deficits (Simioni, Ruffieux, Bruggimann, Annoni, & Schluep, 2007).

The study by Hildebrandt et al. (2006) has previously been mentioned under the investigations of structural MRI changes and fatigue (Hildebrandt et al., 2006). This study also investigated the cognitive performance of 45 patients with MS by means of an extended test battery including measures of cognitive speed (TAP-Alertness), cognitive flexibility (TAP-Flexibility), verbal intelligence (subtests from the WAIS) verbal learning and recall (CVLT-German version), and attention and working memory (PASAT). Fatigue was assessed by means of the FSS. Results indicated that a relationship between fatigue scores and memory functions was not significantly associated (Hildebrandt et al., 2006).
Similarly, Deloire et al. (2006) investigated 57 patients with MS and 44 healthy controls using the Brief Repeatable Battery (Rao, 1990), as well as evaluating the patients on depression, fatigue and quality of life (Deloire et al., 2006). Fatigue was assessed by means of the five-graded fatigue sub-scale of the UK Neurological Disability Scale (UKNDS) (Sharrack & Hughes, 1999). Although a correlation between depression and cognitive performance was evident, no correlation between cognitive performance and fatigue was evident.

Numerous interventional studies were able to induce a positive effect on memory functioning by means of pharmacological intervention or cognitive training (Fink et al., 2010; Hildebrandt et al., 2007). Pharmacological studies administered Armodafinil (Bruce et al., 2012), Lisdexamfetamine (Morrow et al., 2013), Acetylcholine Esterase Inhibitors (Christodoulou et al., 2006) or Donepezil (Krupp et al., 2011). In all of the abovementioned studies, memory performance increased compared to a placebo group, however there were not impacts of the fatigue level of patients.

Fatigue, cognitive speed, information processing and selective attention

A recent Japanese study (2014) recruited 184 patients with MS and assessed them using the BRB-N (Niino et al., 2014). Results showed that although a significant correlation between neuropsychological test scores and depression or apathy was evident, the cognitive measures did not correlate with fatigue scores measured by the fatigue questionnaire.

A Swedish study (Sundgren, Maurex, Wahlin, Piehl, & Brismar, 2013) assessed cognitive impairment and physical disability in 74 patients with RRMS and 89 healthy controls. Fatigue was assessed using the FSS and cognitive functioning was measured using a number of neuropsychological tests which consisted of the COWAT, the Color-Word Interference Test (CWIT) (Delis et al., 2001), the Trail Making Test (TMT) (Delis et al., 2001), the Block Design Test (BDT), Digit Span Test (DST), Digit Symbol Coding Test (DSCT), Symbol Search Test (SST), Benton Visual Retention Test (BVRT-5) and a vocabulary test. Results indicated that of the patient group, 30.5% were regarded as showing cognitive impairment. Importantly, the study found that cognitive impairment was best predicted by depression alone or in combination with physical disability,
whilst subjective fatigue scores did not offer an explanation for cognitive impairment (Sundgren et al., 2013).

In a study by Papadopoulou et al. (2013) 91 MS and CIS patients were recruited to investigate the contributions of cortical and WM lesions to cognitive impairment (Papadopoulou et al., 2013). Cognitive performance was assessed by the SDMT and PASAT, whilst fatigue was evaluated by the FSMC. The researchers found that WM lesions correlated significantly with SDMT scores and showed a trend toward a significant correlation with the PASAT scores. However, a correlation between cortical and WM lesions and fatigue was not evident.

In a large study, Drake et al. (2010) investigated PASAT and SDMT scores for 400 patients with MS and 100 healthy controls (Drake et al., 2010). They also included 115 patients with MS from the large group in a longitudinal analysis of their performance. Results showed that both the SDMT and the PASAT showed low correlations to fatigue scores on the FSS.

Numerous studies which have been mentioned in the section to memory performance also did not find any correlation between cognitive/information processing speed and fatigue scores (Bol et al., 2010; Deloire et al., 2006; Morrow et al., 2009; Yaldizli et al., 2014). To avoid repetition, these studies will not be mentioned in detail again. Further, interventional studies using Modafinil found differing effects on fatigue. Whilst one study (Möller et al., 2011) did not find a benefitting effect of increased vigilance on fatigue or cognitive performance in the SDMT and PASAT, the other study (Lange, Volkmer, Heesen, & Liepert, 2009) showed that receiving Modafinil for 8 weeks improved fatigue scores, visual search performance (d2 test) and visuo-motor speed in the nine-hole peg test. Finally, in an fMRI study, DeLuca et al. (2008) requested subjects to perform the SDMT during 4 fMRI scanning sessions, but found no significant difference in SDMT performance in fatigued patients over time (DeLuca et al., 2008).

Fatigue and working memory

Investigating the relationship between objective cognitive functioning and subjective cognitive fatigue in patients with MS, Walker et al. (2012) recruited 70 patients with MS and 72 healthy controls and requested
them to perform in the PASAT and Computerized Test of Information Processing (CTIP) (Walker, Berard, Berrigan, Rees, & Freedman, 2012). The CTIP is a computerized measure of reaction time for simple attention (press for X), selective attention (chose between left and right key according to presented word) and Semantic Search RT (press left or right key if stimulus word fits or does not fit a semantic category). They further assessed subjective fatigue using the FIS. In total, the PASAT was performed three times with the third administration conducted a whole week after the first two administrations. The CTIP was performed once during the first session and once during the second session a week later. Results indicated that there was no effect between groups in either of the 2 tests in either session. Effects were however found for the PASAT task over time and PASAT performance proved to be negatively correlated to subjective fatigue scores. The study concluded that the PASAT constitutes a more sensitive measure of fatigue than the CTIP (Walker et al., 2012).

The study by Hildebrandt et al. (2006) as mentioned in the above sections investigated the cognitive performance of 45 patients with MS by means of an extended test battery including measures of attention and working memory (PASAT) (Hildebrandt et al., 2006). Fatigue was assessed by means of the FSS. Although no markers of structural changes to the brain correlated with fatigue scores, the study did find a significant correlation between subjective fatigue ratings and the performance in the PASAT test (Hildebrandt et al., 2006).

Also utilizing the PASAT test as a measure of cognitive fatigue, Bryant and her colleagues (Bryant, Chiaravalloti, & DeLuca, 2004) investigated 56 individuals with MS and 39 healthy controls matched with regard to age and education. They obtained their data from two previous studies (Chiaravalloti & DeLuca, 2002; Deluca, Barbieri-Berger, & Johnson, 1994). The researchers divided the patient data into two groups: with or without cognitive impairment as was assessed by means of an array of other neuropsychological measures such as digit span, memory, object-naming, verbal fluency, cognitive flexibility, visual conceptual and visuo-motor tracking, problem-solving ability and verbal learning. Please refer to the study for a concise listing of the measures employed. The main focus of the study lay in the analysis of the PASAT of
and the number of correct responses produced in this test during sustained central executive load. Results indicated that cognitively impaired patients with MS performed significantly worse (i.e. fewer correct responses) than unimpaired patients with MS or healthy controls. The unimpaired group and the healthy controls performed roughly at the same level. The main finding of this paper showed, that both impaired as well as unimpaired patients with MS showed susceptibility to cognitive fatigue significantly earlier than healthy controls (Bryant et al., 2004), meaning they showed drops in performance (correct responses) at an earlier stage than controls.

Another study conducted in 2007 by Bailey et al. found no correlation between subjective fatigue scores and objective results of 14 patients with MS when performing the N-back task over time (Bailey, Channon, & Beaumont, 2007). The authors concluded however, that the level of difficulty (N-0 back & N-1 back), i.e. the demands on working memory, may not have been sufficient enough to induce fatigue in the patient group. For a detailed description of this study, please continue to the section on cognitive fatigue following prolonged effort in this manuscript.

Interventional studies assessing PASAT performance following pharmacological intervention (Rivastigmine) (Huolman et al., 2011), 5-hours of unspecific training (Akinwuntan et al., 2014) or 25 hours of attention or unspecific training (Amato et al., 2014) found a positive effect on PASAT performance, yet did not report a correlation of this performance increase with subjective fatigue scores. A single uncontrolled study by Ruck et al. (2014) treated 54 patients with MS with Dalfampridine and assessed the effects using the MSFC (Fischer et al., 1999; Ruck et al., 2014). Results indicated that patients presented improvements in the PASAT test, walking performance, as well as in cognitive fatigue scores measured by the FSMC questionnaire.

Aforementioned studies which have been described in the above sections have failed to provide evidence for a relationship between subjective fatigue scores and objective measures of working memory performance (Bol et al., 2010; Deloire et al., 2006; Drake et al., 2010; Morrow et al., 2009; Papadopoulou et al., 2013; Yaldizli et al., 2014).
Fatigue, alertness and vigilance

The Attentional Network Test was used to assess three domains of attention in a study of 27 patients with MS and 27 healthy controls (Crivelli et al., 2012). The tested domains included alerting, orienting and executive control. Alerting was assessed by measuring the difference between the RT of a cued and an uncued stimulus in a reaction time task, whilst orienting was calculated in a similar fashion using a spatial cue to the location the target would appear. Executive control was measured using the difference between congruent and incongruent flanking markers to a marker indicating the side where a response was requested. Fatigue was assessed objectively by using the baseline reaction speed of each participant and using linear regression models with the further data. Interestingly, the findings of this study showed, that patients with MS differed from controls only in the alerting test, but not in the orienting and executive control tests although the experimental designs were very similar for the three domains. The results failed to show a relationship between calculated fatigue and performance on alerting tests.

Another study enrolled 49 patients with MS and assessed alertness with the psychomotor vigilance test over a period of 10 minutes and investigated the relationship between this measure and the MFIS used to evaluate subjective fatigue (Rotstein, O’Connor, Lee, & Murray, 2012). The psychomotor vigilance test requires participants to hold a small apparatus and perform a speeded button press when a light signal is shown on the monitor. More than half of the patient sample reported that fatigue had a high impact on their daily lives. On average, patients were significantly slower in this test of alertness and when the results were analyzed using multiple regression analysis, both fatigue and motor disability correlated significantly with RTs. The authors concluded that psychomotor vigilance tests may indeed provide a standardized assessment tool for MS-related fatigue.

In a large study of 110 patients with MS, Weinges-Evres (2010) used the BRB-N, as well as the Faces Symbol Test and the alertness test of the TAP to assess cognitive performance in these patients (Weinges-Evers et al., 2010). Additionally, the researchers also assessed depression, physical disability as well as fatigue. In their study, fatigue was assessed by the FSS. When correcting for age, education, EDSS and depressive
mood, the results showed, that the FSS score was an independent predictor of the performance in the alertness task (Weinges-Evers et al., 2010). These authors also came to the conclusion that simple reaction time task such as the Alertness task from the TAP may provide a suitable tool for assessing fatigue in patients with MS additionally to the subjective FSS.

Another study investigating vigilance test performance and fatigue in 79 RRMS patients and 51 matched healthy controls using the vigilance test from the TAP and the MFIS (Greim, Benecke, & Zettl, 2007). In addition, physical fatigue was also measured using a hand dynamometer. Results indicated that patients with MS showed an inverse relationship between high subjective fatigue scores and below-average objective performance. The authors of this study concluded that vigilance measures may have meaningful comparative value between objective measures and subjective measures of fatigue in patients with MS (Greim et al., 2007).

Studies that have been mentioned in the above sections which also found correlations between measures of vigilance and alertness include the study by Heesen et al. (2010) and Hildebrandt et al. (2006) (Heesen et al., 2010; Hildebrandt et al., 2006).

Due to the comparatively simple implementation and assessment of alertness and vigilance measures, many interventional studies have been conducted. These included studies which assessed alertness performance in 30 patients with MS and 15 healthy controls before and after a 2.5 hour test-battery (Neumann et al., 2014). The study found that patients with fatigue showed markedly slower RTs in the alertness task of the TAP and that there was a significant correlation between these two factors. Similarly, a study by Claros-Salinas et al. (2013) also investigated attention performance (selective attention, divided attention and alertness) in patients with MS following exhaustive physical and cognitive load (Claros-Salinas et al., 2013). Results indicated that the TAP-Alertness task was sensitive to fatigue. Comparative results were published from a study investigating diurnal changes in cognitive (attention) performance conducted at the same research center (Claros-Salinas et al., 2010). Another study initially set out to investigate the effects of wearing a cooling vest on cognitive fatigue and performance in an auditory vigilance task
The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis

(Gossmann, Eling, Kastrup, & Hildebrandt, 2014). This study recruited 31 patients with MS and 10 healthy controls. Results found no effects for the cooling vest. However, the researcher did find that when corrected for depression, fatigue scores and performance on vigilance tests correlated significantly. They concluded that vigilance tests may also present objective measures of fatigue (Gossmann et al., 2014). In a rare single subject case study, Flachenecker & Meissner (2008) reported a case of acute MS relapse in which fatigue was the only manifestation of this relapse (Flachenecker & Meissner, 2008b). Following high-dose corticosteroid therapy not only did fatigue (assessed by the WEIMuS) decline, but in addition the subject improved in RTs in the TAP-Alertness task, possibly indicating a relationship between these two measurements.

In their review of neuropsychological measures employed in the diagnosis of fatigue specifically, Sander and her colleagues (Sander, Voelter, Schlake, Eling, & Hildebrandt, 2017) state that the objectification of fatigue using neuropsychological measures is indeed very complex. They base this statement on two previous reviews on this matter (DeLuca, 2005; Hanken et al., 2014a). The group however does emphasize the promising role of measures ascertaining alertness and vigilance (i.e. TAP-Alertness), yet they also emphasize the importance of interpreting the obtained data within the context of the clinical picture presented by the patient.

Fatigue, language and word fluency

To date, no studies are known that have solely analyzed language and word fluency and their relationship to fatigue in patients with MS. Rather, as these tests form part of many neuropsychological test batteries including the most prominent BRB-N, MACFIMS and BICAMS, they are often assessed peripherally. Results of the aforementioned studies have all failed to show a correlation between fatigue and language and word fluency (Bol et al., 2010; Deloire et al., 2006; Heesen et al., 2010; Morrow et al., 2009; Weinges-Evers et al., 2010).
Fatigue and visuo-spatial processing

In their large cross-sectional & longitudinal study comprised of 465 patients with MS, Morrow et al. (2009) investigate cognitive impairment in patients with MS using the MACFIMS (Benedict et al., 2006) to evaluate cognitive functioning and the FSS to evaluate fatigue (Morrow et al., 2009). As part of the MACFIMS, the JLO (visual/spatial perception) was also assessed. Results found no relationship between this domain and fatigue scores in patients with MS (Morrow et al., 2009).

The table on the following page (table 3) gives an overview of previously conducted studies already mentioned above. Positive studies refer to studies that indicate a relationship between the neuropsychological domain under scrutiny and fatigue, whilst negative studies refer to those studies which reported no such relationship between the two. N refers the number of participants of the study. For an extensive overview of and insight into the operationalization of fatigue, the review by Harrison, Nair and Moss-Morris is recommended (Harrison, das Nair, & Moss-Morris, 2016).
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Table 3: Overview of studies investigating cognitive fatigue, their respective neuropsychological domains, sample size and summary of neuropsychological tests employed in the studies (not allocated to study)
2.5 Induction of fatigue

As mentioned above, due to the low reliability and strong recall-bias associated with subjective measurements of fatigue, the importance of reliable objective measures has often been stressed.

Most measures of cognitive performance are seemingly not affected or show little correlation with subjective ratings. As described above, measures of verbal memory, verbal fluency, working memory, short-term memory, complex attentional measures and executive functions as well as measures pertaining to vigilance have failed to prove reliable relationships with the subjective appraisal of fatigue. When attempting to specifically induce cognitive fatigue in patients with MS, numerous methods have been employed to achieve this. A good working definition of cognitive fatigue has been used in numerous studies and refers to cognitive fatigue as a time-related deterioration of the ability to perform certain mental tasks (Broadbent, 1971). Other authors plead for expanding this definition of fatigue to include cognitive and physical load as aggravating factors for fatigue, leading to a slightly altered definition: a decrease of performance over time or following cognitive or physical load. This allows for an objective measurement and assessment of the effects of MS-related fatigue (Bol et al., 2009; Christodoulou, 2005).

With regard to motor or muscle fatigue, many studies were successful at developing and validating objective measures for its evaluation (Pierce, 2013; Schwid, Covington, Segal, & Goodman, 2002; Schwid et al., 1999). Objective measurements and provocation of cognitive fatigue have however been described less comprehensively although interest in this topic does appear to be growing (DeLuca, 2005). Based on the previously mentioned definition, approaches to the objective measurement and induction of cognitive fatigue can generally be categorized into four approaches. The first approach conceptualizes cognitive fatigue as a decreased performance over a prolonged effort over time. Secondly, resembling methods employed to provoke motor fatigue, cognitive fatigue may be conceptualized as a performance decrease during sustained mental effort. The third approach evaluates cognitive fatigue following challenging mental operations whilst the fourth approach assesses cognitive fatigue following physical strain (DeLuca, 2005).
2.5.1 Cognitive fatigue following prolonged effort

In 1988 one of the first studies investigating cognitive fatigue was conducted by Jennekens-Schinkel et al. who examined RTs in 39 patients with MS and 25 healthy controls prior to and following a 4-hour neuropsychological evaluation. Their results showed that both patients and controls reported increasing fatigue and showed increasing RTs, however the analysis failed to find significant differences (Jennekens-Schinkel et al., 1988).

To induce cognitive fatigue, Johnson et al. (1997) requested their participants to complete a demanding neuropsychological test-battery (Johnson et al., 1997). For their study, they recruited patients with MS (n=15), patients with chronic fatigue syndrome (n=15), patients with a major depression (n=14) and healthy controls (n=15). During the course of the neuropsychological battery, the researchers administered the PASAT test regularly every 30 minutes to investigate the possible development of cognitive fatigue. This yielded results for 4 PASAT administrations. The researchers hypothesized, that through the prolonged effort on a cognitively demanding test-battery fatigue would be induced in all three patient groups but not in the healthy control group and that as a result, the patient groups would not exhibit a learning effect in the PASAT (increasing number of correct answers over the course of the PASAT tests). Interestingly however, although the patients with chronic fatigue syndrome and the major depression patient group did exhibit significantly worse performance that healthy controls, all three patient groups as well as the healthy control group exhibited a significant increase in performance relative to their own starting level over the four PASAT administrations (Johnson et al., 1997). A similar study by Paul and colleagues (1998) found no difference in vigilance tests, learning nor in grip strength between patients with MS and healthy controls following a 30-minute testing session (Paul, Beatty, Schneider, Blanco, & Hames, 1998).

Beatty et al. 2003 investigated the cognitive performance of 17 patients with MS and 12 healthy controls before and after completing a (for them) usual workday (Beatty et al., 2003). Participants were requested to complete four cognitive tests before heading to work and again upon return in the afternoon. The selection of tests consisted of the PASAT, the Letter-Number Sequencing Test, the auditory version of the...
SDMT, and a word-list containing 14 words (learning and direct recall). Although the patient group performed worse in the SDMT and in the word-recall than healthy controls at both the morning and afternoon measurements, a significant decrease of performance in patients with MS in the post-test was not evident in any of the abovementioned tests relative to the initial performance. Interestingly however, patients’ subjective rating of fatigue on the FSS indicated that patients indicated more fatigue at the end of the day than at the beginning with a significantly stronger increase over time than controls (Beatty et al., 2003).

Administering a continuous N-back task, Bailey et al. (2007) compared patients with MS (n=14) to a healthy control group (n=17) with regard to reaction times, accuracy and reported fatigue (Bailey et al., 2007). In their study, fatigue was assessed using both the FSS and 4 ratings on the FRS (scale of 1-8). Participants performed in two testing sessions lasting approximately 1 hour each. Results showed that although patients reported a significant increase in subjective fatigue, the analysis of the objective measures (0-back; 1-back) showed no correlation to these subjective fatigue scores, although in general, patients with MS did perform worse than controls at each time point with regard to accuracy and speed. Also, healthy controls were found to perform at ceiling level in both N-back tasks over time, whilst patients showed tendencies of performance decreases over time in both tasks possibly indicating fatigue, although this decline did not reach significance. Amongst other things, the authors concluded that the cognitive tasks may not have been demanding enough to detect cognitive fatigue and that cognitive fatigue may indeed be comparatively less restrictive in advanced MS than the impact of physical disability (Bailey et al., 2007).

A similar study by Claros-Salinas et al. (2010) investigated diurnal changes in cognitive performance in both patients with MS (n=20) and stroke patients (n=22) compared to healthy controls (n=76) (Claros-Salinas et al., 2010). Fatigue was assessed using a VAS to evaluate subjective fatigue on a scale of 1-10, whilst cognitive performance was measured by the alertness, selective and divided attention task from the TAP. Patients underwent testing at three different times of day (morning, early afternoon, evening) for two consecutive days. Results showed, that both patient groups performed worse than healthy controls on all
tests, however a further diurnal decline of performance was evident only in the patient groups and not in the healthy control group. This objective decline in cognitive performance also correlated to subjective ratings of fatigue. Importantly, the drop in cognitive performance was most evident in the TAP-Alertness task, possibly due to little or no practice effects occurring in this simple reaction time measures following repeated presentation (Claros-Salinas et al., 2010).

2.5.2 Cognitive fatigue during sustained mental effort

Similar to methods employed to induce motor fatigue through sustained repetitive motor activity ultimately leading to a decrease in motor performance over time, various forms of sustained mental effort have been employed in an attempt to induce cognitive fatigue (DeLuca, 2005).

In their study from 1995, Kujala et al. recruited 45 patients with MS and 35 healthy controls and requested participants to complete a short test battery consisting of the PASAT, the Stroop Color Word Test, the auditory As and auditory trails A test, as well as a visual vigilance test (Kujala, Portin, Revonsuo, & Ruutiainen, 1995). In the auditory A’s test, subjects are requested to identify the letter “A” from a series of 160 letters presented auditory in sequence, whilst in the auditory trails A test, subjects are requested to identify an alphabetical sequence (starting with “A”) during another auditory presentation of letters. Both tests are measures of sustained attention and concentration (Lezak, 2004). The visual vigilance test is a timed motor response task during which the subject is required to fixate his gaze on a screen on which 600 letters are presented visually for a total time of 15 minutes during which the subject is required to give a motor response (button press) if either of two target letters (“Y” & “L”) appear. Following the visual vigilance test, a second session was conducted with the other tests. Results showed that patients showed significantly longer RTs in the second session which was interpreted as cognitive fatigue.

In 2000, a study by Krupp et al. investigated cognitive fatigue in 45 patients with MS and 14 healthy control subjects. In their study, participants completed a 4-hour session of cognitive testing including a baseline neuropsychological battery, followed by a uninterrupted effortful cognitive exercise and a repeat of the neuropsychological battery (Krupp & Elkins, 2000). The sustained effortful cognitive exercise consisted of
2. MS-related fatigue

2.5 Induction of fatigue

The Alpha-Arithmetic (A-A) Test which is administered by computer and requires participants to add the numbers 0, 2, 3, or 4 to the letters “A” – “T”. The participant is presented with an equation (e.g., C + 2 = E or F + 2 = I) and judges whether it is true or false (Logan & Klapp, 1991). Although the duration of the A-A test was not indicated in this study directly, a later study by the same research group employed the exercise for a duration of three hours (Krupp, 2002). Both groups showed a decline in subjective rating of fatigue. Interestingly, although no differences in RTs were evident between patients with MS and healthy controls in the first half of the A-A test, the results of the second half of this test revealed that patients with MS performed with significantly longer RTs than controls. The researchers concluded that they were able to induce cognitive fatigue by means of sustained mental effort (Krupp & Elkins, 2000).

The study by Schwid et al. (2003) employed the PASAT test in an investigation into the possibility of objectively assessing cognitive fatigue (Schwid, Tyler, et al., 2003). The study recruited 20 patients with MS and 21 healthy controls. Additionally to the PASAT, the study also employed the Digit Ordering Test (DOT) to measure sustained attention functioning. Both tests were administered four times during a total of three testing sessions. When viewing the results of the fourth session, the researchers found a fatigue effect in the patient group for the PASAT but not for the DOT which was not evident in the control group. Importantly, the results also found a correlation between subjective fatigue measures and the results from the PASAT.

Contradicting previous findings, Bryant et al. (2004) found that when performing repeating administrations of PASAT, the expected deterioration of performance of patients with MS (n=56) compared to healthy controls (n=39) was not evident (Bryant et al., 2004). Fatigue was conceptualized as the significant reduction of correct responses in the second half of a total of 4 presentations of the PASAT test. This drop in performance however was visible in all three groups (cognitively impaired and unimpaired patients with MS and healthy controls) over the course of the examination. However, when comparing dyads between the first two and the last two sessions, it was found, that healthy subjects only showed a drop in
performance during the final PASAT presentation, whilst patients with MS showed this drop earlier during the third presentation (Bryant et al., 2004).

2.5.3 Cognitive fatigue following challenging mental effort

In the study by Krupp and Elkins (2000) mentioned previously, the baseline neuropsychological test battery consisted of tests similar to those found in the BRB-N with a few additions (Krupp & Elkins, 2000). In general, measures of learning and memory, conceptual planning, basic auditory attention, verbal fluency and visuo-spatial memory. This test battery was administered a second time following a 15 minute long sustained cognitive effort (the A-A test). The results of this study indicated that patients with MS did not perform worse than controls at baseline, however following the effortful sustained A-A test, patients with MS showed greater declines in performance in tests assessing visual memory, verbal memory and verbal fluency than healthy controls. There was also a trend to a significant difference in visuo-spatial memory performance (Krupp & Elkins, 2000).

Recently, a study by Claros-Salinas et al. (2013) investigated the effects of both cognitive and physical load in the cognitive performance in patients with MS (Claros-Salinas et al., 2013). Cognitive load was induced by means of a 2.5 hour long assessment battery before and after which attentional measures were administered. Attentional measures included alertness, selective, and divided attention subtests from the TAP. Fatigue was assessed by the FSMC. Results for the effects of cognitive load indicated that patients showed a significant decrease in the RTs in the tonic alertness task which was not evident in the control group. The researchers concluded that simple reaction time tasks seem to be most sensitive to cognitive fatigue (Claros-Salinas et al., 2013). The results for the motor induced fatigue are described in the following section. Corresponding results were found in a later study by a research group at the same facility who similarly investigated RTs before, directly after and following a recovery period after cognitive load (2.5 hour neuropsychological test battery) (Neumann et al., 2014).
2.5.4 Cognitive fatigue following physical exertion

In 1991 a study by Caruso et al. investigated whether cognitive fatigue could in fact be provoked by means of physical exertion (Caruso, LaRocca, Foley, Robbins, & Smith, 1991). They tested patients with MS as well as a group of healthy control subjects by means of a neuropsychological test battery including measures of verbal fluency, lexical retrieval, attention, visual tracking as well as direct and delayed recall (short-term and long-term memory) following strenuous physical exercise. However, the researchers failed to find any significant differences in performance between the two groups (Caruso et al., 1991).

Although the study was conducted with CFS patients, LaManca et al. (1998) examined 19 patients with a neuropsychological test battery prior to, immediately after and 24 hours following an exhaustive treadmill exercise. Although CSF patients performed similar to their respective baseline following the treadmill exercise, this constituted a drop in performance as the control subjects showed marked learning effects and increasing performance upon second testing which the CSF patients did not. In comparison, the cognitive deficits were especially pronounced in measures of information processing speed. Interestingly, subjective evaluations of fatigue did not correspond to objective performance (LaManca et al., 1998). A study which conducted a similar experiment found that CFS patients showed a greater performance decrease in sustained attention tasks following exertion than healthy controls (Blackwood, MacHale, Power, Goodwin, & Lawrie, 1998).

The study by Claros-Salinas et al. (2013), as mentioned above, investigated the induction of cognitive fatigue not only by cognitive load, but also by physical load (Claros-Salinas et al., 2013). Physical load consisted of treadmill training in which subjects were requested to walk until they were exhausted and felt an urgent need for a break or until they began to stumble (Claros-Salinas et al., 2013). Before and after treadmill training, participants would perform in the alertness, selective, and divided attention subtests from the TAP. Similarly to the effects of cognitive load, results showed that the patient group showed a significant increase in RTs in the tonic alertness task. This increase was not evident in the control group.
In conclusion, it can be stated, that tests requiring intensive and sustained attention seem to be most effective in the experimental induction of cognitive fatigue. Nonetheless, there is tentative evidence that cognitive fatigue may also be induced by other means as is evident in some of the studies mentioned above.

### 2.6 Treatment of fatigue

Due to the uncertainty of the pathophysiological mechanisms underlying fatigue in MS as well as the difficulty in objectively, reliably and accurately measuring the symptoms, generating a specific treatment approach remains a challenging task (Induruwa et al., 2012). The approach to the treatment of fatigue should be multidisciplinary and secondary causes of fatigue could be identified by elaborate screenings (Induruwa et al., 2012). If secondary causes are present, these should be treated appropriately (Multiple-Sclerosis-Council-for-Clinical-Practice-Guidelines, 1998) as the effects of the overlap could alleviate fatigue symptoms as a result. Comorbid symptoms aggravating fatigue include deconditioning, depression or sleep disturbances as mentioned previously. Acute infections, current MS episodes and potentially sedating effects of medication should be taken into consideration as possible confounds when assessing fatigue (Greim & Zettl, 2009; Krupp, 2003b). MS and fatigue specific scales should be used in the initial assessment of fatigue severity and as during the course of treatment (Kroner-Milsch et al., 2012).

Persistent fatigue can be treated by nonpharmacological approaches such as a combination of moderate aerobic exercise, a rehabilitation program, body cooling, relaxation techniques, frequent breaks, energy conservation and structured routine strategies, the creation of realistic expectations, as well as psychological and dietary interventions (Bakshi, 2003; Ben-Zacharia, 2011; Branas et al., 2000; Diener et al., 2012; Kos et al., 2008; Krupp, 2003a, 2003b; Zifko, 2004). Unfortunately, due to the lack of large sample sizes ad of detailed contrast in the type of intervention used in experimental groups versus control groups, evidence for the efficacy of aerobic exercise and resistance training on fatigue perception is inconsistent and insufficient (Kos et al., 2008; Rasova et al., 2006; Rietberg et al., 2005; Surakka et al., 2004). With regard to in- or outpatient rehabilitation programs, some controlled studies were able to find a reduction of
fatigue in patients with MS (Asano & Finlayson, 2014; Di Fabio, Choi, Soderberg, & Hansen, 1997; Patti et al., 2002; Rasova et al., 2006). More recent randomized controlled studies however failed to detect any profits of multidisciplinary inpatient rehabilitation measures perceived fatigue nor on disability level (Storr, Sorensen, & Ravnborg, 2006). The effect of active liquid flow cooling vests often utilized by patients with MS on fatigue was investigated by researchers who found a significant effect of these devices on the impact fatigue (Beenakker et al., 2001; Schwid, Petrie, et al., 2003). A positive effect was further established for other cooling strategies such as a cold shower or swimming (Cantor, 2010; Diener et al., 2012). Studies specifically investigating the benefits of environment cooling on fatigue in patients with MS have not been reported, although the interaction between MS and thermoregulation and thermos-sensitivity are well known (Bol et al., 2012; Davis, Wilson, White, & Frohman, 2010). Energy conservation strategies conveyed by occupational therapists resulted in higher self-efficacy as well as lower fatigue impact scores (Mathiowetz, Finlayson, Matuska, Chen, & Luo, 2005). Psychological intervention programs which were not specifically developed for fatigue also proved to be effective. These included group support, individual cognitive behavioral interventions and professionally guided self-care management programs which all proved to significantly decrease feelings of fatigue (Diener et al., 2012; Induruwa et al., 2012; Mohr et al., 2003; O'Hara, Cadbury, De, & Ide, 2002). Patients, family members and caregivers should be informed and sensitized to the fact that rapid fatigability constitutes a disease specific symptom of the MS disease. Studies of dietary influences on fatigue are scarce (Payne, 2001), however one study found that a low cholesterol diet supplemented with olive oil capsules lead to positive effects on fatigue (Weinstock-Guttmann et al., 2005).

A further option in the treatment of fatigue in patients with MS is offered by pharmacological treatments. Three of the most common agents are amantadine, modafinil and pemoline (Ben-Zacharia, 2011; Braley & Chervin, 2010; Branas et al., 2000; Induruwa et al., 2012). The effects of amantadine - an antiviral agent used in Parkinson’s disease (Kos et al., 2008) - on fatigue is unclear and requires further investigation (Branas et al., 2000; Pucci et al., 2007). The effects of modafinil on fatigue are divergent, as some studies found that this wake promoting agent primarily used in narcolepsy reduced MS-related fatigue (Rammohan
et al., 2002), whilst other double-blind, randomized placebo-controlled studies found no advantage of modafinil compared to the placebo (Stankoff et al., 2005). The effect of pemoline - a central nervous system stimulant - did not differ significantly from placebo either (Krupp et al., 1995; Weinshenker, Penman, Bass, Ebers, & Rice, 1992). Other pharmaceutical agents such as 4-aminopyridine - a potassium-channel blocker – also did not show efficacy in PPMS patients (Rossini et al., 2001b), however patients who show temperature dependent aggravation of (fatigue) symptoms in the sense of the Uhthoff-phenomena may benefit from this or similar agents such as 3,4-diaminopyridine (Faiss & Wiethölter, 2012). The effects of glatiramer acetate - an MS specific immune-modulatory drug - also proved to be beneficial (Greim & Zettl, 2009). The antidepressant sertraline was found to have a positive effect on fatigue in RRMS patients (Mohr et al., 2003). However, this may be due to possibly treating fatigue secondary to depression (Kos et al., 2008). Similarly, selective serotonin reuptake inhibitors (SSRIs) have been used in some cases (Kroner-Milsch et al., 2012). One study even found a beneficial effect of aspirin on fatigue (Wingerchuk et al., 2005), although it has to be noted, that the sample size of this study was small and no long-term follow-up was done.

Recently, studies investigating the effects of transcranial direct current stimulation (tDCS) specifically on fatigue in patients with MS have shown mixed results. tDCS consists of delivering a weak electric current to cortical areas through sponge electrodes placed on the scalp. Whilst some studies showed promising results and reported significant fatigue reduction between 3 weeks (Ferrucci et al., 2014) and up to 2 months (Tecchio et al., 2014), others reported mixed results (Chalah et al., 2017) or no effects (Saiote et al., 2014). For a detailed review of interventions to alleviate fatigue in MS, we recommend the review by Ayache and Chalah (Ayache & Chalah, 2017).
3. Aim and hypothesis of current study

The aim of the current study was to investigate the neural correlates of effort dependent and effort-independent fatigue in patients with multiple sclerosis. These constructs are similar to the constructs of fatigability and fatigue (Kluger et al., 2013) or state and trait fatigue (Genova et al., 2013) described in the sections above. Behavioral data as well as MRI data was gathered. Behavioral measures included neuropsychological tasks assessing reaction times as well as concentration, attention and working memory over a prolonged period of time. During the execution of the task, blood oxygen level dependent (BOLD) signals within the brain were measured. To be able to interpret patient data, an age- and gender- matched control group of healthy participants was recruited.

The N-back task was chosen as a behavioral measure performed during fMRI scanning, due to the fact that it places varying degrees of cognitive load on the working memory of participants depending on which N-back task is performed, whilst simultaneously placing demands on vigilance and concentration. Thus by manipulating the difficulty of the N-back task, it would be possible to produce greater cortical activation as a result. The N-back task is also known for its ability to generate robust and consistent neuro-activations (Kearney-Ramos et al., 2014). The N-1 back task was chosen as the simple task (respond when same letter appears directly after each other), whilst the N-2 back task represented the more difficult task (please see the methods section for a detailed description of the N-back task). Using the N-back task allows for comparisons between patients and healthy controls with regard to behavioral measures (RTs and hit ratios) but also to cortical activation firstly in general, secondly during various degrees of cognitive load and thirdly over time as fatigue increases. The N-back task was also chosen as it had been applied in other studies investigating fatigue with fMRI (Cader et al., 2006; Caseras et al., 2006; Sweet et al., 2004; Wishart et al., 2004; Wylie et al., 2017). Structural, as well as resting state data was acquired to prolong the total time participants lay in the MRI in order to support later fatigue induction by the N-back task. Moreover, this additional data was acquired should further analysis of the data, such as lesion load or resting state analysis be desired in order to ensure comparability to the functional data.
It was further hypothesized that initial MRI scans would show little or no task-dependent (state) fatigue which might develop during the course of the examination and thus may represent task-independent (trait) fatigue. It was further hypothesized, that due to the differing nature of the constructs of task-dependent and task-independent fatigue, their neural correlates could possibly also differ accordingly; possibly indicating diverse yet connected neuropathological sources or correlations.

In light of previous research, it was hypothesized that abnormal activations would be evident in networks subserving attention processes, including parietal, frontal, as well as subcortical areas.
4. Methods

4.1 Subjects

4.1.1 Patients
Forty right-handed patients (31 female, ages 27-61) diagnosed with definite MS according to the revised McDonald criteria (McDonald et al., 2001; Polman et al., 2011) and normal or corrected-to-normal vision (acuity >0.4) participated voluntarily in the study. All patients were recruited from the neuro-rehabilitation clinic “Kliniken Schmieder” in Konstanz, Germany. Recruiting took place in the form of neurologists addressing their patients directly and enquiring about their interest in participating in the study which was explained to them. Furthermore a short introduction to the study was given on a regular monthly interval to MS-patients attending an information event as part of their stay in the clinic. Following this, patients willing to volunteer for the study would be contacted within the following few days. The recruited patient group consisted of patients displaying primary progressive (n=2), secondary progressive (n=13) and relapsing-remitting (n=25) types of MS. A broad spectrum of patients with MS was included in the study irrespective of their ratings on the FSMC or MS type in order to be able to perform correlative analysis. Physical disability was rated according to the EDSS (Kurtzke, 1983) employed routinely in the clinical practice. Gait and manual functions were captured post hoc by means of the clinical reports generated by physiotherapists and occupational therapists that treated the patient during their stay. Exclusion criteria for the patient group included other psychological illnesses or other neurological diseases other than multiple sclerosis or any contraindications for the MRI scans. Patients were also excluded if they were unable to lay in the MRI-scanner for roughly one hour (examination time).

4.1.2 Controls
An age- and gender- matched control group consisting of 22 healthy controls (15 female, ages 21-56) was also recruited. Recruitment was done by flyer on notice boards at the clinic and town as well as mouth-to-mouth propaganda. Inclusion and exclusion criteria for the control group resembled those of the patient group, with exception of the MS diagnosis.
Participants received a copy of their structural scans as compensation for their participation. No monetary compensation was given. All participants were given detailed information about the study and were screened for MRI-compatibility before entering the MRI-room. In this screening participants were also requested to state whether or not they would like to be informed about anomalies (especially relevant for healthy volunteers). All participants gave informed consent and the study was approved by the local ethics committee (University of Konstanz, Germany) in accordance with the Declaration of Helsinki (World-Medical-Association, 2013). The forms (in German) pertaining to the detailed information on the study, the informed consent form and the MRI-compatibility screening can be found in the appendix. The characteristics of both groups are shown in table 4 below.
## 4. Methods

### 4.1 Subjects

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<td>7 / 15 (32% / 68%)</td>
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<td>1-5 years</td>
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<tr>
<td>6-10 years</td>
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<td>&gt;15 years</td>
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<tr>
<td>Primary progressive (PPMS)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Depression (BDI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall mean (SD)</td>
<td>10 (± 6.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>minimal (0-9)</td>
<td>23 (57.5%)</td>
<td></td>
</tr>
<tr>
<td>mild (10-19)</td>
<td>12 (30%)</td>
<td></td>
</tr>
<tr>
<td>moderate (20-29)</td>
<td>5 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>severe (≥30)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Fatigue Scale for Motor and Cognition (FSMC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall mean (SD)</td>
<td>70 (± 16.7)</td>
<td>N/A</td>
</tr>
<tr>
<td>no fatigue (20-42)</td>
<td>3 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>mild fatigue (43-52)</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>moderate fatigue (53-62)</td>
<td>5 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>severe fatigue (≥63)</td>
<td>31 (77.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gait function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not impaired</td>
<td>32 (80%)</td>
<td>N/A</td>
</tr>
<tr>
<td>moderately impaired</td>
<td>5 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>severely impaired</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>missing data</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Manual function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not impaired</td>
<td>36 (90%)</td>
<td>N/A</td>
</tr>
<tr>
<td>moderately impaired</td>
<td>3 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>severely impaired</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>missing data</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
</tbody>
</table>

* data gathered post-hoc from medical files

| Table 4: Group characteristics of both the patient group as well as the control group |
4.2 Measures

4.2.1 Depression

Patients were requested to complete the Becks Depression Inventory (BDI) (Hautzinger et al., 1994) at most 24 hours prior to their participation in the examination. The BDI consists of 21 questions concerning how the participant felt in the last week. Each question had four possible responses graded in intensity. Answers are scored from 0-3 points yielding total scores ranging from 0-69. Higher total scores indicate increased depression. The cut-off scores were a score of 9 for no/minimal depression, a score of 18 for mild depression and a score of 29 for moderate and severe depression (score ≥30).

4.2.2 Subjective measures of fatigue

Fatigue scale of motor and cognition (FSMC)

Fatigue was evaluated by means of the FSMC (Penner et al., 2009) which was completed within 24 hours prior to the MRI investigation as was the BDI. Participants were handed the questionnaire and were requested to complete it in their own time without supervision. Questions arising during the completion of the questionnaire were addressed when the patients came in for testing. The FSMC questionnaire can be subdivided into scores for cognitive (FSMC-cog) and for motor (FSMC-mot) fatigue, as well as offering a grand total (FSMC-tot) score. For a detailed description of this questionnaire, please refer to the section on subjective measures of fatigue in the introduction.

Visual Analog Scale (VAS)

To evaluate subjective fatigue during the course of the experiment, all participants were requested to rate their momentary cognitive fitness on a scale ranging from 1-10 between sessions. Where (1) indicated extreme fatigue and (10) indicated no fatigue. The participants gave a rating before the initial fMRI session and after each subsequent session, yielding 7 ratings in total per subject. The exact wording of the question posed to the participants was: “please indicate on a scale of 1-10 how cognitively fit you feel at the moment”; A score of (10) indicating feeling extreme well and very awake, whilst a score of (1) indicated
extreme tiredness, hardly being able to stay awake or concentrated. Participants gave their response verbally and the response was noted by the researcher on the protocol sheet.

4.2.3 Behavioral measures

Alertness measures

Before entering the MRI scanner, participants were initially requested to perform in the Alertness task from the Test-battery of Attentional Performance-Motor (TAP-M-Alertness) (Zimmermann & Fimm, 1993). The task was performed in a separate room where patients were seated before a screen and a response button. The room was situated in a less frequented area of the clinic and outside noises were kept to a minimum to ensure that the participants would not experience any distraction. The response buttons were the standard response buttons used for the execution of the TAP test-battery and were connected as specified via a COM port connection. During the Alertness task, reaction times (RTs) are measured in response to the appearance of a visual stimulus (white ‘X’ on black background). Subjects are requested to fixate their gaze on a white fixation dot presented in the middle of the screen and perform a speeded button press upon presentation of the stimulus. During the task the participants absolve 4 successive runs with a presentation of 20 white-X targets per run and a short interruption between runs. If the participant does not respond to a stimulus or responds too early (before presentation), the presentation of another target is added to the end of the run. This is done for at most 5 incorrect responses, yielding a maximum of 25 possible presentations before the next run begins. A participant is deemed to have missed a target if the response does not occur within 2 seconds following presentation. The TAP-M test battery is similar to the original TAP battery; however it is used for testing the cognitive domains deemed necessary for determining the driving aptitude in neurological patients. With regard to the Alertness task, only tonic alertness is measured in the TAP-M. This means, that the phasic condition present in the original TAP-Alertness is not tested. The phasic Alertness task differs from the tonic Alertness task in that a warning signal (beep) is presented prior to the presentation of the white X-stimulus. Also, the normative data for the TAP-M differs slightly from the original TAP, yet as this study was only interested in the raw data (reaction times in milliseconds), this
difference was negligible. The TAP-Alertness task is a well-established measure of psycho-motor reaction time and tonic alertness and is often employed in routine clinical assessment. The test was conducted prior to the MRI session and repeated thereafter yielding two measurement time points (T1 and T2). The TAP-Alertness task was chosen due to the fact that it has previously been identified as presenting a sensitive measure of cognitive fatigue in numerous previous studies (Claros-Salinas et al., 2013; Neumann et al., 2014; Weinges-Evers et al., 2010).

N-back task

Visual stimuli were presented using the Presentation® software (Version 16.4, www.neurobs.com). Stimuli were displayed foveally at the center of a screen made of opaque glass as letters of white color (color code: 0,0,0) on a grey background (color code: 96,96,96). The font of the letters was Arial font with a font size of 100. The screen was located at the back entrance of the scanner, positioned 60cm from the eye of the participants, who gazed at the screen from a supine position via a mirror mounted above the head coil. The size of the stimuli was 2.4° (height) x 2.4° (width). A fixation cross was not displayed, but participants were requested to fixate on the center of the screen. The standard configuration for displaying visual stimuli in the MRI in the laboratory was used. This meant that the visual information was sent to a beamer which was located outside of the actual MRI-scanner room. The beamer then projected the picture through a so-called wave guide (a copper tube in the wall of the scanner room) via a mirror mounted to the rear wall onto a screen made of opaque glass which acted as a display-screen visible from both sides. The experimental setup is displayed in figure 5 below.
4. Methods

4.2 Measures

Figure 5: Experimental set-up: A) N-back task is transmitted from Stimulation-PC to the beamer B) then projected through the waveguide C) via a mirror D) onto an opaque glass screen E). Participants respond via a response button F) and the response is then transmitted to the Stimulation-PC A). G) All MRI Data is obtained from the MRI scanner and is transmitted to the control-PC G).

4.2.4 MRI measurements

A 3 tesla Siemens Skyra (Siemens, Erlangen) MRI scanner with a standard 32-channel head coil was used for imaging. All testing took place at roughly the same time of day in the afternoon between 16:30 and 18:30 as the clinical routine has priority in this lab. Before entering the MRI room, participants were thoroughly screened for any exclusion criteria for MRI measurement. If the participants had any questions about the equipment or the procedure, these were addressed accordingly. Participants were further briefed to the task and were shown a demonstration version of the N-back task (both N-1 and N-2) on a computer screen. They were requested to state whether they had understood the task and any questions that arose were
promptly addressed and answered to the participant’s satisfaction. Following this, participants were escorted into the scanner room and placed in a supine position on the examination table, head resting in the coil and ears plugged. Each participant was also handed an alarm ball to notify investigators to immediately stop the measurement should they want to interrupt the examination. Participants were also informed that they were free to abort the experiment at any time without naming a reason.

Structural MRI

Three sets of structural MRI-images were obtained before functional data was acquired. These included axial high resolution T1-weighted, T2-weighted, and FLAIR-weighted whole brain scans. For a description of the various settings, please refer to table 5 below.

<table>
<thead>
<tr>
<th>Type of scan (whole brain)</th>
<th>Number of slices</th>
<th>Voxel resolution (xyz)</th>
<th>Orient.</th>
<th>Field of View (FoV)</th>
<th>Repetition time (TR)</th>
<th>Echo time (TE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-weighted</td>
<td>176 no gap</td>
<td>1mm isotropic</td>
<td>axial</td>
<td>256mm</td>
<td>2.7s</td>
<td>7.21ms</td>
</tr>
<tr>
<td>T2-weighted</td>
<td>208 no gap</td>
<td>0.8mm isotropic</td>
<td>axial</td>
<td>205mm</td>
<td>3.5s</td>
<td>316ms</td>
</tr>
<tr>
<td>FLAIR-weighted</td>
<td>192 no gap</td>
<td>1mm isotropic</td>
<td>axial</td>
<td>256mm</td>
<td>5s</td>
<td>395ms</td>
</tr>
</tbody>
</table>

Table 5: Details of the structural magnetic resonance imaging (MRI) sequences

These structural images were acquired for three specific reasons: Firstly, should further investigations such as lesion analysis, brain volume analysis or other VBM be wanted, these could be compared to functional analysis. Due to the heterogeneous results found by previous studies on structural correlated of fatigue in MS - as described in the introduction – these types of analysis were not intended for this study. Secondly, the duration of the entire experiment within the scanner was prolonged by these scans, which was proposed to increase fatigue toward the end of the experiment when the functional scans were acquired. Thirdly, should healthy volunteers show any neurological damage of which they were not aware, structural scans would indicate if the healthy participant did indeed fulfill the inclusion criteria (no previous neurological damage). The structural scans of all healthy participants were reviewed by an experienced
neurologist. If any anomalies or conspicuous features were evident, the participant would have been informed if he/she had wished this (ticked a box in the consent form). Fortunately in this study, no anomalies were found in healthy participants.

Functional MRI

Before the N-back task was performed, resting state data was acquired. This data was acquired for similar reasons as the structural scans. However, the resting state data was included in the analysis to investigate any effects which may be noteworthy. Participants were requested to keep their eyes open during the examination (blinking allowed; lights on). Importantly, the participants received no task in this time and were requested not to think of anything in particular but to let their minds wander. Details of the resting state sequences are detailed in table 6. Following the resting state measurements six functional MRI sessions were acquired whilst the participants performed in the N-back task. Between each session a short break was given to the participants, during which the VAS scores were obtained. The details of these functional scans are also mentioned in table 6. Both resting state and functional scans were acquired using Echo Planar Imaging (EPI) sequences.

<table>
<thead>
<tr>
<th>Type</th>
<th>Number of sessions</th>
<th>Time per session</th>
<th>Number of slices</th>
<th>Slice order</th>
<th>Voxel resolution (x y z)</th>
<th>Orient.</th>
<th>FoV (mm)</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Flip angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting state scans</td>
<td>1</td>
<td>7:07min</td>
<td>34</td>
<td>interleaved</td>
<td>3x3x3.5mm</td>
<td>axial</td>
<td>192</td>
<td>2.5s</td>
<td>30</td>
<td>80°</td>
</tr>
<tr>
<td>Functional scans</td>
<td>6</td>
<td>4:53min</td>
<td>36</td>
<td>interleaved</td>
<td>2x2x3mm</td>
<td>axial</td>
<td>192</td>
<td>2.5s</td>
<td>30</td>
<td>80°</td>
</tr>
</tbody>
</table>

Table 6: Details of the functional magnetic resonance imaging (MRI) sequences

4.2.5 Procedure

Both patients and participants were handed the forms with the detailed information on the study, the informed consent form and the MRI-compatibility screening prior to the day of the experiment.

Patients were requested to complete both the FSMC as well as the BDI questionnaires at most 24 hours prior to arriving for the examination. Upon arrival participants were greeted by the examiner and the
participants were given ample time to question the examiner should any insecurities or questions have arisen. Questions pertaining to the aim of the study were answered in such a fashion as that the participants remained blinded to the objective. Participants were informed to this matter fully at the end of the experiment. Participants were also instructed to make use of the lavatory-facilities as the testing would take some time. During this time, the researcher would inspect all relevant documents and enquire about important exclusion information which might exclude participants from MRI-scanning. Following the reception of the participants, testing was initiated with the first TAP-Alertness measurement (see figure 6). After the participants had completed this reaction time task they were escorted to the MRI-scanner and brought into position for testing.

Initially, participants underwent structural MRI scans (see section above) for the first 30 minutes in the scanner, followed by functional scans. Participants underwent 6 functional scanning sessions lasting 4:53 minutes each in the MRI, during which the N-Back task with 2 difficulty levels (N-1 and N-2 back) was performed. Each session consisted of 8 task blocks (of 33 sec) divided into 4 blocks of for each N-back difficulty respectively (4x 1-back and 4x 2-back). The sequence of task difficulty blocks was distributed randomly. Each block consisted of an initial instruction phase, during which the number “1” or “2” was displayed for 3 seconds, denoting which of the two tasks was to be completed, followed by the successive presentation of 15 letters before the onset of a new block. Letters from A-L, excluding the letter “I” due to the similarity with “J”, were presented in series for 500ms each, with an inter stimulus interval (ISI) randomly distributed between 1-7 seconds following a gamma distribution to create a stimulus onset asynchrony (SOA) which enhances the efficiency of the design for event-related fMRI (Friston, Zarahn, Josephs, Henson, & Dale, 1999; Hinrichs et al., 2000).

For the N-1 task, participants had to perform a speeded button press with their right index finger as fast as possible if the presented letter was identical to the letter previously presented. For the N-2 task, participants were instructed to press the response button if the presented letter was identical to the letter presented 2 trials before the current representation. Each N-back block consisting of 15 letters included 4-5
targets and was designed in that there was no immediate letter repetition in 2-back blocks and no 2-back target occurred in 1-back blocks in order to avoid confusion during the task block (see Fig 1).

Following the functional MRI-scanning, participants were escorted to the separate testing room where they performed the second reaction time measurement in the TAP-Alertness task. Once concluded, participants were briefed to the aim of the study. If needed, participants were finally escorted to the reception area where they were seated and waited for their transportation back to the clinic they were accommodated at.

Figure 6: Study-Design: a) Patients complete the Fatigue Scale of Motor and Cognition (FSMC) and Beck Depression Inventory (BDI) questionnaires; b) all participants complete the Test-battery of Attentional Performance (TAP) alertness task; c) structural scans and resting state scans; d) functional MRI scans whilst performing N-back tasks; in the N-2 task, letter stimuli are presented successively following an instruction as to which task is to be performed. Subjects are requested to press a button if the letter currently shown matches the letter shown two before it. In this example, the second presentation of the letter “A” requires a response. Before and after each session, participants are requested to rate their cognitive fatigue on a visual analog scale (VAS); e) 2nd session TAP alertness test.
4.3 Analysis

4.3.1 Behavioral data

Data on the number of correct hits, false alarms, misses and of course correct-rejections in the N-back tasks was recorded, as well as the corresponding RTs from the false alarms and the correct hits. Hit ratios (HRs) were calculated dividing the number of correct hits achieved by the number of total targets presented in each session. This produced a number between 0 and 1 with 0 indicating that none of the targets had been correctly responded to and 1 indicating a 100% hit-rate. Results were calculated separately for the N-1 back and the N-2 back task. Hit-ratios from the N-back tasks were averaged for patients and controls for each N-back session. Furthermore the RTs for each N-back session as well as each of the two TAP-Alertness measurements were averaged for patients and controls. RTs of the N-back task were inherently only available for false-alarm reactions and correct responses. Only the RTs of correct responses were included in the analysis.

Statistical analysis

Behavioral data was analyzed using IBM SPSS Statistics software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp.).

Exact chi-squared tests were performed on all variables in order to test for normal distribution. The VAS scores and the hit-ratios for the N-back were not normally distributed and were further analyzed using non-parametric tests. Specifically, the Kruskal-Wallis test was used to assess between group differences when more than 2 repeated measures were analyzed, the Wilcoxon test was used to assess within group differences in the variables, and the Mann-Whitney-U test served to test group differences across two samples. Normally distributed data was analyzed by means of standard parametric tests. Firstly, a repeated-measures ANOVA was calculated with the factor group on the average reaction times of the TAP and the N-back task. Bonferroni correction was applied to account for multiple comparisons where needed. Significant group effects were further explored using single factor ANOVAs, whilst interaction effects were
investigated using repeated measures ANOVAs for each group across variables. Correlations were calculated using Pearson’s R for parametric and Spearman’s Rho for non-parametric data.

4.3.2 MRI Data

4.3.2.1 Functional MRI data N-back task

MRI Data was preprocessed and analyzed using statistical parametric mapping software (SPM8, Wellcome Trust Centre for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software).

All scans were resliced using the last slice of the scan as a reference scan, before being realigned to the mean. Reslicing controls for movement errors occurring during the time it takes to acquire a single full brain EPI scan (in this case a TR of 2.5s), whilst the realignment process corrects for movement which occurs during the whole session. Realignment parameters are vectors of 6 movement dimensions (x,y,z, roll, pitch, yaw) and these may be included in the model to account for movement when analyzing the data.

Following this, all images were normalized using the MNI EPI template provided by SPM8. In the normalization process, the images acquired from the participants are modified according to complex algorithms in order to fit into one and the same space in order to be comparable to each other. Finally, the fMRI images were smoothed using a Gaussian isotropic kernel with a full-width at half-minimum (FWHM) kernel of 8x8x8 mm to enhance signal-to-noise ratio and to account for residual differences.

1st level:

For first level linear regression modulation, scans were divided into 5 possible factors: instruction, N-1 hits, N-2 hits, N-1 non-targets, N-2 non-targets, before being estimated. These factors were convolved using the canonical hemodynamic response function (HRF). A high-pass filter of 128s was employed and movement parameters (6 dimensions) obtained during realignment were included in the model as covariates of interest.
2nd level:

Second level group modulation was done using a flexible factorial design with three factors (subjects, group, condition) with an interaction between factor 2 and 3. No violations of sphericity were assumed. Additionally a model was created for the patient group using multiple regression analysis incorporating the FSMC-cog values as covariates (overall mean centering, implicit masking, intercepts included).

Contrasts:

All contrasts on first and second level models were calculated using t-tests. To investigate the neural correlates elicited during the N-back tasks the correct response condition was contrasted vs. the baseline.

Differences in task difficulty of the N-back task were calculated by contrasting all correct responses for both groups for the more challenging N-2 with all correct responses during the N-1 task.

Between group differences were calculated by contrasting neural activations of the patient group with the neural activations elicited by the control group during the correct responses in the N-2 task. The N-2 back task was chosen because it showed greater activations in both groups in areas also active in the N-1 task, as well as activating further cortical and subcortical areas.

The dynamic changes during the course of the experiment were explored by contrasting trials with correct responses from the first two runs sessions of the N-2 back task with those of the last two runs sessions of the N-2 back task across groups. Small volume correction (SVC) was applied in areas known to sub-serve attention and working memory, using anatomical maps (anatomy toolbox version 2.2b of SPM8). These areas included the cingulated cortex (including the anterior cingulated cortex), lingual gyrus, cuneus, superior parietal lobule (SPL), pallidum and amygdala (Merkel, Hopf, Heinze, & Schoenfeld, 2015; Stoppel et al., 2013). To further investigate effort-independent effects within the patient group in relation to fatigue, multiple regression analyses with the FSMC-cog values as covariates was performed.
4. Methods

4.3 Analysis

4.3.2.2 Resting state analysis

The resting state fMRI data was analyzed using the Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm) and the CONN toolbox developed for functional connectivity analysis (http://www.nitrc.org/projects/conn/; (Whitfield-Gabrieli & Nieto-Castanon, 2012)). Preprocessing steps included slice-time correction, realignment, structural data segmentation, normalization into standard stereotactic Montreal Neurological Institute (MNI) space and spatial smoothing using a Gaussian kernel of 6mm full width at half-maximum.

The high resolution T1 images were used for anatomical referencing. Functional data was further analyzed for outliers resulting from head motion over and above the standard realignment parameters offered by SPM8, by means of an artifact detection tool (ART; https://www.nitrc.org/projects/artifact_detect). Noise reduction was further performed using the anatomical component-based noise reduction method available in the CONN toolbox. This so called aCompCor includes the influence of noise as a voxel-specific linear combination of multiple empirically estimated noise sources into the model by deriving principal components from noise regions of interest and by including these as nuisance parameters within the general linear model (Demertzi et al., 2015). This is done by segmenting the structural T1 image into grey matter, white matter and cerebral spinal fluid (CSF) using SPM8 and eroding these masks by one voxel to minimize partial voluming with grey matter. These eroded masks are then used as noise regions of interest and signals resulting from the white matter and CSF were extracted from unsmoothed functional images to avoid contamination of white matter and CSF signals in the grey matter data. Additionally, a temporal band-pass filter of 0.008-0.09 Hz was employed to confine further analysis to low frequency fluctuations, which typify resting state fMRI activity (Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003). The standard six head motion parameters (three translation parameters and three rotation parameters) as well as their first-order temporal derivatives were regressed out in the model.

The analysis of the functional connectivity was performed using a seed-based correlation method, which utilizes the blood oxygenated level-dependent (BOLD) time series from a region of interest (the seed) and
calculates the temporal correlation between this averaged signal and the times series from all other voxels within the brain. The networks chosen for the analysis included the default mode network (DMN), the fronto-parietal network, as well as the cluster of activations found for the effort-independent (trait) Fatigue analysis (see figure 12b further below), the center of which was at the following MNI coordinates (x y z): [02 10 28]. The coordinates of the regions of interest which make up the two networks can be found in the appendices. The location of these seeds are founded upon previous research to function connectivity (DMN: (Raichle, 2011); Fronto-parietal network: (Boveroux et al., 2010; Fair et al., 2009)). For each network, the time-series for the voxels included in each of the regions of the network are averaged to produce a single average time series. Following this, this average time series is used to assess whole brain (all other voxels) correlations r-maps, which are further converted to normally distributed Fischer’s z transformed correlation maps to allow group level-comparisons (Demertzi et al., 2015).

The second level (group level) models are calculated by including the relevant contrasts as regressors into the general linear model. In this study, resting state correlation maps (i.e. resting state connectivity) of the patient group was compared to correlation maps of the healthy subjects. Additionally, the FSMC-cog scores were included as regressors for the patient group to investigate possible effects of effort-independent fatigue on functional connectivity within the patient cohort. This was done in three different fashions. Firstly, the FSMC-cog scores were entered as a raw-score for each patient. Secondly, the 40 patients were ranked from highest to lowest cognitive fatigue score upon a continuum ranging from -20 to 20 excluding “0”. Equal scores were given the same rank and the following scores were adjusted accordingly. This allowed for the data to be contrasted along this continuum. Thirdly, the patient group was divided into 15 low scoring patients and 15 high scoring patients by using the median cognitive fatigue score. The median score was 33.5 with a range of 11-49 and a standard deviation of 8.96. These groups were then directly contrasted to each other. These contrasts were calculated for the aforementioned networks and seeds.
5. Results

5.1 Questionnaires and self-report measures

The results of the FSMC as well as the BDI questionnaires are depicted in the descriptive table 4 in the section 4.1 Subjects. With regard to this data, it is noteworthy that of the patient group roughly ¾ (77.5%) exhibited an EDSS score between 2-4 points, most displayed only a minimal or mild form of depression in the BDI (87.5%) and another ¾ (77.5%) scored as having severe fatigue in the FSMC. The mean FSMC score for the patient group was 70 (±16.7). The further distribution of the FMSC scores within the group is also depicted in table 4 and is similarly depicted in figure 7 below. Although the types of MS were not differentiated during recruitment, the above mentioned facts emphasize the homogeneity within the patient group. No data was acquired for the control group.

The correlation coefficients between the FSMC and its subscales and the physical disability measured by the EDSS was calculated using Pearson’s R and revealed a significant correlation between the EDSS and the total FSMC score (r= .36, p<.05), the FSMC motor subscale (r=.37, p<.05), but not with the FSMC-cognitive subscale (r= .29).

5.1.1 FSMC cognition and FSMC motor

Correlations scores were calculated by means of Pearson’s R between the FSMC scores and the two subscales motor (FSMC-mot) and cognitive (FSMC-cog) fatigue. Results indicated that the FSMC scale highly correlated with both subscales (FSMC-mot: r= .93, p<.000; FSMC-cog: r= .93, p<.000). Similarly, FSMC-mot and FSMC-cog also correlated to a significant degree with each other (r = .73, p<.000). The abovementioned correlations are mentioned in red writing in figure 7.

Notably, the FSMC scores correlated with the BDI scores (r = .57, p<.000). The FSMC scores and the subjective fatigue (VAS) scores neither correlated with the TAP RTs, nor with reaction times or hit ratios in the N-back tasks.
5.2 Behavioral data

5.2.1 TAP alertness

In the alertness task the patients responded slower and with greater variance than controls, who reacted with a mean reaction time (RT) of 240.4 ms (±34.9 ms) before and 241.6 ms (±35.4 ms) following the N-back task in the scanner, whilst patients performed with a mean RT of 284.2 ms (±79.8 ms) before and 312.3 ms (±80.5 ms) after the N-back task in the scanner. This was substantiated by a main effect of group ($F(1,60) = 12.731, p<.001$) in an ANOVA with the factors group and time point in the absence of an interaction between the factors ($F(1,60) = 2.662, p=.108$). The factor time point only showed a trend towards significance ($F(1,60) = 3.165, p=.08$). Between group comparisons at the first TAP measurement using an ANOVA revealed a significant group difference between patients and controls already at the beginning of the experiment ($F(1,60) = 5.948, p<.05$). This difference increased following the MRI session.
(F(1,60) = 15.229, p<.001). A repeated measures ANOVA was used to ascertain differences in the RTs of the TAP Alertness task across time within each group. Whilst the control group was able to perform approximately with the same RTs in the second TAP measurement (TAP T2) as in the first TAP measurement (TAP T1), the RTs of the patient showed a significant decline following the MRI session which included the N-back tasks (F(1,39)= 5.528, p<.05). Figure 8 below depicts the results of the TAP Alertness task.

![Reaction times TAP](image)

**Figure 8:** TAP Alertness mean reaction times for controls (in blue) and patients (in red) for the first measurement (TAP T1) and second measurement following the scans in the MRI (TAP T2)

### 5.2.2 Fatigue measurements

The mean VAS score at the beginning of the MRI session was 7.14 (±1.67) in the control group and 6.75 (±1.93) in the patient group. Whilst both groups showed an increase in Fatigue which was exemplified in a drop in the VAS score, the patient group showed a greater increase in fatigue over time than the control
group. At the last measurement following the final N-back run the control group reported an average VAS score of 5.91 (±1.54) whilst the control group dropped to an average of 4.10 (±2.23).

A repeated measures ANOVA (rANOVA) with the factors group and time point revealed a main effect for each factor (group (F(1,60)=6.54, p=.013); time point (F(1,60)= 44, p<.000)) and a group by time point interaction (F(1,60)=5.924, p=.018). The interaction was caused by a significant group difference at the second (F(1,60)=10.91, p=.002) but not at the first time point (see figure 9) indicating effort-related fatigue.

**Figure 9**: Mean visual analog scales (VAS) scores for fatigue for patients (in red) and controls (in blue) for the first measurement (VAS begin) and the final measurement (VAS end). Low values indicate high fatigue.

**5.2.3 N-back task performance**

**Reaction time:**

The RTs of the patients were over all higher than those of controls. Please refer to table 7 for a detailed listing of the reaction times. The RT data was normally distributed and was submitted to an ANOVA with
the factors group (patients, controls), task (N-1 back, N-2 back) and time point (begin, end). Main effects were observed for the factors group ($F(1,1) = 42.68; p<.001$), task ($F(1,1) = 68.76; p<.001$) and a strong trend for the factor time point ($F(1,1) = 3.84; p=.051$). A significant interaction was found between the factors task and time point ($F(1,1) = 5.30; p<.05$) that was caused by a practice effect in the N-2 task (rANOVA: controls $F(1,21) = 13.52$, $p=.001$; patients $F(1,39) = 13.77$, $p=.001$). No significant effects were found for the N-1 task RTs.

**Accuracy:**

In general, patients achieved a mean hit ratio of .92 (±.08) and .79 (±.14) for the N-1 and N-2 task respectively, whilst controls achieved a mean HR of .96 (±.02) and .87 (±.11) for the N-1 and N-2 task respectively. The HRs for each task at the beginning and at the end of the N-back tasks are shown in table 7. As the HRs for the N-1 task were non-normally distributed, non-parametric tests were used for the analyses. Controls performed with a higher accuracy in the N-1 ($\chi^2(1)=10.68$, $p<.01$) and the N-2 task ($\chi^2(1)=7.53$, $p<.01$). Both groups exhibited a practice effect in the N-2 task (controls: $Z= 3.323$, $p<.000$, $n=22$; patients: $Z= 3.441$, $p<.000$, $n=40$), while patients dropped in accuracy in the N-1 task ($Z= -1.984$, $p<.05$, $n=40$).
## Table 7: Average reaction times (RTs) and standard deviations, as well as median hit-ratios (HRs) and range for the first two (begin) and the last two (end) sessions for the N-1 back and N-2 back task for controls and patients, as well as results from between group comparisons

<table>
<thead>
<tr>
<th>Task: N-1</th>
<th>Reaction times in ms</th>
<th>mean (SD)</th>
<th>patients (N = 40)</th>
<th>controls (N = 22)</th>
<th>between group comparison*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begin</td>
<td>619.93 (±119.19)</td>
<td></td>
<td>535.18 (±99.84)</td>
<td>636.95 (±104.27)</td>
<td>F(1,60) = 8.01</td>
<td>.006</td>
</tr>
<tr>
<td>End</td>
<td>535.18 (±99.84)</td>
<td></td>
<td>529.5 (±71.84)</td>
<td>529.5 (±99.84)</td>
<td>F(1,60) = 18.47</td>
<td>.000</td>
</tr>
<tr>
<td>Hit Ratios (hits/misses)</td>
<td>median (range)</td>
<td></td>
<td>.97 (.53 - 1.0)</td>
<td>1.0 (.79 - 1.0)</td>
<td>χ² = 3.56</td>
<td>.059</td>
</tr>
<tr>
<td>Begin</td>
<td></td>
<td></td>
<td>.97 (.42 - 1.0)</td>
<td>1.0 (.85 - 1.0)</td>
<td>χ² = 10.95</td>
<td>.001</td>
</tr>
<tr>
<td>Task: N-2</td>
<td>Reaction times in ms</td>
<td>mean (SD)</td>
<td>patients (N = 40)</td>
<td>controls (N = 22)</td>
<td>between group comparison*</td>
<td>p-value</td>
</tr>
<tr>
<td>Begin</td>
<td>789.6 (±117.45)</td>
<td></td>
<td>710.00 (±126.70)</td>
<td>690.09 (±116.09)</td>
<td>F(1,60) = 6.17</td>
<td>.016</td>
</tr>
<tr>
<td>End</td>
<td>720.5 (±131.07)</td>
<td></td>
<td>609.09 (±116.09)</td>
<td>609.09 (±116.09)</td>
<td>F(1,60) = 11.09</td>
<td>.001</td>
</tr>
<tr>
<td>Hit Ratios (hits/misses)</td>
<td>median (range)</td>
<td></td>
<td>.79 (.22 - 1.0)</td>
<td>.86 (.36 - 1.0)</td>
<td>χ² = 3.62</td>
<td>.057</td>
</tr>
<tr>
<td>Begin</td>
<td>.89 (.38 - 1.0)</td>
<td></td>
<td>.95 (.51 - 1.0)</td>
<td>.95 (.51 - 1.0)</td>
<td>χ² = 4.88</td>
<td>.027</td>
</tr>
</tbody>
</table>

*reaction times = ANOVA; hit ratios = Kruskal-Wallis-test

### 5.3 Functional MRI data

#### 5.3.1 Task and cognitive load

The fMRI Data gathered during the N-back tasks revealed an activation of a widespread bilateral network incorporating parts of the inferior parietal lobule, middle temporal gyrus, the posterior medial frontal sulcus and the anterior cingulated gyrus. During the N-2 task additional bilateral activation was observed in the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG). In general, activations were more pronounced for the N-2 back task.

To ascertain the neural correlates of task difficulty also referred to as cognitive load, the scans from both groups during the N-2 condition were compared to the scans from both groups during the N-1 condition.
5. Results

5.3 Functional MRI data

This yielded strong bilateral activations in the inferior parietal lobule, IFG, MFG, middle temporal gyrus, the posterior medial frontal sulcus as well as anterior insular cortex (see figure 10).

To ascertain whether group differences existed for task difficulty, the contrasts between the N-2 condition and the N-1 condition as described above were contrasted between the patient and the control group. There this contrast yielded no significant differences.

![Figure 10: Activations elicited by cognitive load (N-2 back versus N-1 back). Additional activation in red in the attention and working memory network elicited by the N-2 back task as opposed to the N-1 task.](image)

5.3.2 Group

To investigate group differences, the hemodynamic activity elicited by the N-1 back and the N-2 back tasks were each contrasted between controls and patients, revealing a decrease in activity within the left fusiform gyrus in the patient group compared to the control group for the N-1 task. However, increased activations for the patient group in the left motor and somato-sensory areas, as well as the left supramarginal gyrus were also observed (figure 11a). For the N-2 task increased activity in patients was also observed in the same motor regions as above, with the addition of increased activity in the right
supplementary motor area (SMA), the right supramarginal gyrus and the right insular lobe. Furthermore, reduced activity in the left caudate nucleus was evident for the N-2 task in the patient group (figure 11b).

5.3.3 Effort-dependent changes of brain activity

To compare the neural activations at the beginning of the experiment with activations toward the end of the experiment, data from the first two sessions were contrasted versus those from the last two sessions during the more difficult N-2 task since behavioral and hemodynamic differences were more pronounced. This contrast revealed activity decreases in the left anterior insula, bilateral lingual gyri, right cuneus, superior parietal lobule (SPL), premotor cortex, pallidum and amygdala (figure 12a).
5. Results

5.3 Functional MRI data

5.3.4 Effort independent fatigue-related brain activity changes

A t-test was performed on patients’ N-2 condition data of the first two sessions (in which effort-related changes are if at all rather small) with the scores in the FSMC-cognition scale as a covariate of interest. The analysis revealed activity in the bilateral ACC, the right middle cingulum cortex and left paracentral lobule to positively correlate with the fatigue scores (figure 12b).

![Figure 12: Effort dependent and effort independent neural correlates](image)

- Effort-dependent correlates: decrease in activation (displayed in blue) in the patient group as opposed to the control group at the end of the experiment versus at the beginning*.
- Effort-independent correlates: activation (in yellow) within the bilateral anterior cingulum cortex (ACC) and left paracentral lobule*

* all activations displayed are small volume corrected (SVC)

The numbers below the images indicate the axial, coronal and sagittal coordinates in MNI space respectively.

5.3.5 Depression and related brain activity

Patients’ N-2 data of the first two sessions, were analyzed as a function of the BDI scores. The areas which showed correlating neural activity much resembled those correlating with fatigue. These were the right precentral gyrus, the left anterior and right middle cingulate cortex as well as the right frontal gyrus.
5.4 Resting state fMRI data

The resting state data analysis which directly contrasted the resting state activity of the patient group to the resting state activity of the control group yielded no significant differences in resting state functional connectivity between the two groups. This was the case for both the default mode network (DMN), the fronto-parietal network and the ROI seed taken from the activations found for the effort-independent analysis in the ACC.

Further analysis included the FSMC-cog score as a covariate for the patient group. When including these scores into the analysis, no significant differences in resting state functional connectivity were found for any of the aforementioned networks and seeds in the patient group. This was the case for both the analysis based upon ranks, as well as the analysis between low-fatigue (n=15) and a high fatigue (n=15) patients.
6. Discussion

The current study employed behavioral and fMRI measures to investigate the neural correlates of fatigue in patients with multiple sclerosis. Patients and age-matched controls performed in a working memory (N-back) task in the MRI scanner as well in an attention task (TAP-Alertness) before and after the MRI session. Furthermore, resting state data was acquired over a period of 07:07 minutes prior to cognitive load. The analysis of the results from these measures indicated a generally lower performance level in patients compared to controls and an additional performance decrease as a function of having performed in the task in patients but not in controls. These findings were paralleled by subjective assessments of fatigue on a visual analog scale, which also indicated a general lower level of self-perceived cognitive fitness in patients compared to controls and a more pronounced drop in patients across the sessions of the N-back task. The aim of this study was to investigate the neural correlates of fatigue in patients with MS in general, but also in relation to a fatigue-inducing cognitive task.

The TAP-Alertness measures have previously been shown to be sensitive in the assessment of fatigue in patients with MS (Claros-Salinas et al., 2013) and are typically not influenced by practice (Bühner, Ziegler, Bohnes, & Lauterbach, 2006). In the current study, the analysis of the reaction times (RTs) of the TAP-Alertness measure showed that the RTs of patients with MS were slower than those of controls. Performing the N-back task in the scanner prolonged the RTs in the TAP afterwards in patients but not in controls indicating that performing the N-back task decreased patient’s alertness level. This was also, at least in part, backed up by the behavioral data of the N-back task, which also showed important differences between patients and controls. While controls performed fast and accurate in the N-1 task patients with MS consistently exhibited slower and less accurate responses across the sessions. The analysis of the behavioral data of the N-2 task also revealed a practice effect for both the control group and the patient group, indicating that both groups performed at their individual ceiling level since they were both able to improve their accuracy and reaction times for the more demanding N-2 task. So far the behavioral data points out to two processes or components that are different between patients and controls. The first is
the difference in performance and alertness already before / at the beginning of the N-back task. This task-unrelated difference could have several reasons. It may be interpreted as reflecting the general decrease of neural resources in patients with MS due to lesions (McDonald, 1974; Sailer et al., 2003; Udupa & Chen, 2013). Alternatively, the lower performance level may be a reflection of the effects of cognitive fatigue in MS, or it may reflect a combination of both. The second process is reflected by the difference in performance that patients exhibit at the end compared to the beginning of the N-back task, which was observed in the behavioral data of the N-back task itself, but also reflected by the performance drop in the alertness task performed thereafter. Importantly, this task-induced difference in performance and alertness was not observed in controls. The subjective measures of cognitive fitness were well in line with these findings. While at the beginning of the experiment there was no difference between patients and controls, the values of the patients decreased with every run of the task. The fact that the objective measures of alertness and task performance, as well as the subjective measures on the VAS are able to capture also the dynamic task-induced changes in patients with MS is important because there are currently no specific measures to do this.

Consistent with previous studies (Nee et al., 2013) the N-back task elicited activity in a series of well-known brain areas involved in attention and working memory. These were motor and somato-sensory areas, as well as the supramarginal gyrus and the right insula, in particular for the more difficult N2-back task that were more active in patients than in controls. Importantly, there were also areas like the bilateral fusiform gyri, the left caudate nucleus and the right middle frontal gyrus that exhibited less activity in patients compared to controls. The activity increase in the motor- and somatosensory-related areas could be due to the fact that patients with MS need higher activity for the same motor function (e.g. pressing the response key) due to cortical and white matter damage, which is well in line with findings from other studies (Buckle, 2005; Filippi, 2003; Filippi & Rocca, 2003, 2004; Filippi, Rovaris, & Rocca, 2004; Genova et al., 2013; Lee et al., 2000; Reddy et al., 2000). The insular cortex was shown to be involved in both interoceptive awareness and homeostasis, as well as to be part of the attention network. Specifically, it was proposed to be a key region for sustaining attention, redirecting endogenous attention, attention control and has been shown to
be part of the salience network (Cauda et al., 2012; Gasquoine, 2014). Furthermore, the insula plays an important role in the verbal component of the working memory, specifically for the short-term memory of letters and was suggested to be associated with selective attention (Augustine, 1996) as a junction point between the selective attention and arousal systems needed during complex cognitive tasks and the basal ganglia (Eckert et al., 2009). In light of the above, the neural correlates which were found when analyzing the N-back task across all sessions are in line with previous research and can also offer support for varies models on fatigue in MS. The increased activation of the right insular lobe offers support for the hypothesis by Hanken and her colleagues (Hanken et al., 2014b), which states that fatigue may arise as a consequence of inflammation induced neural processing within interoceptive and homeostatic brain areas i.e. the insular lobe. As mentioned in the introduction, this model further argues, that fatigue is strongly associated with particular cognitive states, including alertness and vigilance, which are reliant on high levels of endogenous attention and during which distraction by internal events can easily occur. This explains why the TAP Alertness tasks seems to be more sensitive to fatigue than the N-back task, as the N-back tasks, especially the N-2 back task, require greater cognitive resources and incorporate many other neuropsychological domains such as working memory. Thus the interference experienced on the alertness and vigilance level is not as debilitating as it may be if the task would place demands solely on alertness and vigilance. When viewing the results in respect to the compensation hypothesis offered by Penner and her colleagues (Penner et al., 2007), the increased activations in the patient group may reflect the increased neural activation (compensatory hyperactivation) required to perform the same task with comparable behavioral proficiency than healthy controls, at least at the very beginning of the task. During the course of the experiment, changes in neural activation patterns may occur which increase or decrease the neural indications of these mechanisms, which not all patients in the cohort were able to uphold for the entirety of the examination.

In accordance with the two aforementioned theories, the resting state data should also show a difference between the patient cohort and the control group in terms of resting state functional connectivity. This however is not the case. The explanation therefore may lie in the heterogeneity within the patient group
not evident through measurements such as the FSMC or the alertness task. Further, when analyzing the resting state data by comparing the patient group among itself, either by splitting it into a high and low fatigue group or by assigned ranks, the number of patients included into the analysis might not suffice to find significant activations. Nonetheless, that analysis of the resting state MRI data in this study neither showed a difference between healthy controls and patients with MS, nor a difference in resting state functional connectivity within the patient group when controlling for fatigue. These results stand in contrast to previous research investigating resting state functional connectivity in patients with MS with and without fatigue (Bonavita et al., 2011; Cruz Gomez et al., 2013; Faivre et al., 2012; Hawellek, Hipp, Lewis, Corbetta, & Engel, 2011; Hidalgo de la Cruz et al., 2017; Rocca et al., 2010; Rocca et al., 2012; Roosendaal et al., 2010; Schoonheim et al., 2015). Some of these studies however do not specifically investigate fatigue and those that do include it in their analysis report differing results. Studies investigating cognitive impairment independently of fatigue have shown that the RSFC is increased in the DMN (Roosendaal et al., 2010), whilst other studies found a decrease in RSFC in anterior regions and the DMN (Bonavita et al., 2011; Hawellek, Hipp, Lewis, Corbetta, & Engel, 2011; Rocca et al., 2010; Rocca et al., 2012). Further studies found a relationship between increased RSFC and worse cognitive performance in patients with MS (Faivre et al., 2012; Hawellek et al., 2011; Schoonheim et al., 2015). Studies including scores from subjective fatigue questionnaires such as the MFIS and the FSS found a relationship between fatigued patients and increased thalamic RSFC with the precuneus and decreased RSFC in the posterior cerebellum (Hidalgo de la Cruz et al., 2017), but also decreased RSFC in the supplementary motor and associative somatosensory cortex (Cruz Gomez et al., 2013). The results of the analysis performed in this study could not offer support for any of the aforementioned findings.

The present findings also add to the evidence that patients with MS display altered patterns of neural activity during tasks placing demands on information processing, memory and sustained attention (Au Duong et al., 2005; Staffen et al., 2002) and also provide strong support for the model of central fatigue proposed by Chaudhuri and Behan (Chaudhuri & Behan, 2000, 2004). What is not clear from such data stemming from the simple comparison between patients and controls during a cognitive task is whether
the observed changes of neural activity along with the behavioral drop in performance are rather reflecting the fatigue experienced by the patients or the consequences of the disseminated lesions or maybe both.

This is an important issue that the current study aimed to address. There were different neural correlates associated with the task-unrelated and the task-induced performance changes. In order to relate these to the fatigue experienced by the patients the task-unrelated performance changes were analyzed in dependence of the fatigue scores (FSMC-cognitive subscale). For this analysis only fMRI data recorded in the first 2 sessions was analyzed in order to minimize the influence of task-induced fatigue. High fatigue scores were associated with higher activity in the ACC, a region known to be implicated in a number of cognitive functions including error detection, performance monitoring, response selection and attention control (Torta & Cauda, 2011; Walton, Bannerman, Alterscru, & Rushworth, 2003; Yu et al., 2011). It has further been suggested to play a role during the maintenance of set goal-directed behavior, working memory, inhibition, as well to act on a subconscious or automatic level of information processing in a top-down fashion during cognitively challenging conditions involving conflict (Gasquoine, 2013; Wendelken, Ditterich, Bunge, & Carter, 2009). It has previously been proposed that the ACC might be overactive in patients who experience cognitive Fatigue (Dobryakova et al., 2013). Studies using positron emission tomography (PET) had also previously found increased cerebral glucose metabolism within the ACC in patients with MS (Roelcke et al., 1997). The current data is well in line with this view supporting the idea of a close relationship between ACC activity and task-independent fatigue in patients with MS. The right middle cingulum cortex (MCC) also showed increased activity with higher fatigue scores. This area also has been shown to play an important role in cognitive control. Its microstructure predicts performance breakdown in several neurodegenerative diseases (Metzler-Baddeley et al., 2012). Another region that showed increased activity with higher fatigue scores was the left paracentral lobule, a region involved in sensorimotor processing as well as in the regulation of physiologic functions such as micturition, which are also often disturbed in MS (MacKenzie-Graham et al., 2016). The task-independent fatigue of patients with MS most likely corresponds to what has been termed trait component in the literature (Calabrese et al., 2010; Genova et al., 2013; Sepulcre et al., 2009). Extending previous findings suggesting a striatal-thalamic-
The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis

frontal cortical system to underlie the trait component of fatigue, the current study adds frontal attention control and sensorimotor regions to the previously suggested network, thereby proving strong support to the model proposed by Chaudhuri & Behan (Chaudhuri & Behan, 2000, 2004). The aforementioned results also offer further support for the inflammatory hypothesis model of Hanken and her colleagues (Hanken et al., 2014b) as both the ACC and the MCC are, as mentioned above, involved in cognitive control and subconscious or automatic level of information processing which are neuropsychological domains proposed to display dysfunctions as a result of inflammation- or cytokine-induced sickness behavior. With regard to the compensatory hyperactivation hypothesis (Penner et al., 2007), the results could be interpreted as indicating that the compensatory neural activation (which possibly arises as a result of structural WM and GM damage not visible in the MRI) may already be visible at early stages of cognitive load or fatigue as Penner et al. proposed. Similarly to the discussion on the general activation seen across all N-back sessions, the resting state functional connectivity data does not offer support for this notion.

The second fatigue related component refers to the task induced dynamic change of experienced fatigue in patients with MS that has been termed “state fatigue” in the literature (Calabrese et al., 2010; Genova et al., 2013; Sepulcre et al., 2009). Consistent with the literature, the behavioral data indicated that this component was very evident in patients with MS but not in controls. The neural correlates of this fatigue component were assessed by contrasting activations during the N-back tasks in the last versus the first 2 sessions. This contrast revealed activity decreases in the left anterior insula, the bilateral lingual gyri, right cuneus, SPL, cingular cortex, pallidum and amygdala. These decreases in hemodynamic activity were only observed in the more challenging 2-back condition of the task in which the patients performed at ceiling suggesting diminished resources in these areas that become evident when the system is challenged harder. The anterior insula and the cingulum are part of the saliency network that plays an important role in task-level control and focal attention (Menon & Uddin, 2010; Nelson et al., 2010), which are core components of the study task of the current study. The cuneus, parietal areas and the lingual gyri are all heavily involved in visual attention and working memory processes (Merkel et al., 2015; Stoppel et al., 2013). With regard to the subcortical structures, the pallidum is also known to be involved in attentional orienting (Hassler, 1979).
while the amygdala was shown to influence attention (Peck & Salzman, 2014). The subjective increase of fatigue, paralleled by the reaction time increase in the alertness task, was associated with drop of hemodynamic activity in attention-related networks in patients with MS. This suggests that dynamic reductions of activity in salience and attention-related networks underlie the state component of fatigue in MS. These findings may be incorporated into the inverse-U hypothesis of the compensatory activation hypothesis (Penner et al., 2007), which states that the amount of compensatory (hyper-)activation initially rises with increasing impairment (i.e. structural damage to WM and GM) in a linear fashion, but reaches an apex after which the effects of the impairment may be too significant and too widespread for further compensation to be possible, thus with further structural neural damage occurring as a result of the disease, the occurrence of the increased compensatory activation decreases (see introduction). With regard to the findings of this study, the drop in compensatory hyperactivation may de facto occur not merely over a prolonged period of sickness and increasing impairment, but may in fact also be evident during sustained cognitive effort, ultimately leading to increased subjective feelings of fatigue and a drop in performance. If this were in fact the case, then on a behavioral level, alertness and vigilance measures such as the TAP-Alertness task would seem to be most susceptible to this shortfall of compensatory mechanisms, whilst more complex tasks such as the N-back task do not appear to be affected, possibly due to a typically more widespread activation of neural networks and resources which may offer more opportunity for compensation.

In summary, the current study investigated neural changes in patients with MS associated with fatigue with the aim to disentangle the neural changes associated with task-independent “trait” from those associated with task-induced “state” fatigue. In line with previous ideas (Chaudhuri & Behan, 2000; Genova et al., 2013; Hanken et al., 2014b) trait fatigue was observed to be reflected by activity increases in fronto-striata-subcortical networks primarily involved in the maintenance of homeostatic processes as well as in motor and cognitive control. These findings were however not supported by the results of the RSFC analysis, indicating that the difference in brain activation may be subtle during a task-free rest condition but may flare up as soon as any form of cognitive functioning is required.
In contrast, task-induced state fatigue was reflected by activity decreases in attention-related cortical and subcortical networks. These findings clearly show that trait and state fatigue in patients with MS have functionally related but fundamentally different neural correlates. Fatigue in MS as a more general phenomenon appears to be reflected by complex interactions of activity increases in control networks and activity reductions in executive networks of brain areas.

6.1 Outlook and shortcomings

The results of this investigation into the neural correlates of both effort-related and effort-unrelated fatigue, also known as state fatigue / fatigability and trait fatigue / fatigue may be seen as providing the basis for future research wishing to discriminate between these concepts.

Future research should aim at increasing the time spent on task to further increase task-related fatigue. This being said, it was the researchers observation, that many patients with MS had apparently reached their limits of cognitive and physical capacity by the configuration of the current study. Patient well-being should be considered if longer measurements are deliberated. Additionally, as the TAP-Alertness task proves to be the most sensitive behavioral measure for fatigue, it would be of interest to have participants perform the TAP-Alertness task in the scanner instead of outside the scanner. This would allow both the behavioral data as well as functional MRI data to be compared and has the benefit of measuring the reaction times in direct proximity to the cognitive load instead of after a short break (patients exiting the scanner and walking to laboratory for TAP Alertness testing).

Furthermore, effort-unrelated fatigue may be measured more concisely if the measurements were procured whilst no task or only a very simple task was being performed. This form of fatigue may be visible in resting state data; however, due to the complexity of this concept, other forms of analysis may prove more fruitful. It can be argued, that a shortcoming of this study was that the amount of patients recruited for this study was not sufficient for resting state functional connectivity analysis to be conclusive.
In addition, it is advisable that future research should lay more emphasis on trying to disentangle the effects of depression or depressive symptoms from the task-unrelated fatigue, as an overlap in neural patterns may be observed (Gobbi et al., 2014).

Another shortfall of this study was that it neglected to acquire FSMC and BDI values for the healthy participants, thus limiting the comparability of the two groups.

Future research should also aim at increasing the number of patients included within the patient group in order to effectively investigate possible trends or factors which may play a pivotal role. Furthermore, the PASAT and SDMT should be incorporated in the study to include established neuropsychological tests for patients with MS. This could possibly be extended to include other neuropsychological tests typically impaired in patients with MS to assess the cognitive functioning of each participant (see introduction).

The medications which the patients were taking at the time of measurement should be included in the analysis to take into account any possible effects brought about by the medication. Similarly and lastly, factors which may lead to secondary fatigue, a few of which have been mentioned above, should be controlled for more rigorously as they may play an important factor in understanding the results on group as well as individual level.

7. Disclosures

The study was funded by the Stiftung Schmieder für Wissenschaft und Forschung, Allensbach. The authors declare that there are no conflicts of interest. All data acquisition, including the MRI scanning, was undertaken at the Kliniken Schmieder Allensbach. This project was further supported and developed under the umbrella of the Lurija Institute, a collaborative institute between the University of Konstanz and the Kliniken Schmieder.
References


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References


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References


The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis


References


The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis

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## Expanded Disability Status Scale (EDSS):

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Normal neurologic examination (all grades 0 in functional systems (FS*); cerebral grade 1)</td>
</tr>
<tr>
<td>1.0</td>
<td>No disability, minimal signs in one FS (i.e., one grade 1 excluding cerebral grade 1)</td>
</tr>
<tr>
<td>1.5</td>
<td>No disability, minimal signs in more than one FS (more than one grade 1 excluding cerebral grade 1)</td>
</tr>
<tr>
<td>2.0</td>
<td>Minimal disability in one FS (one FS grade 2, others 0 or 1)</td>
</tr>
<tr>
<td>2.5</td>
<td>Minimal disability in two FS (two FS grade 2, others 0 or 1)</td>
</tr>
<tr>
<td>3.0</td>
<td>Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three or four FS grade 2, others 0 or 1)</td>
</tr>
<tr>
<td>3.5</td>
<td>Fully ambulatory but with moderate disability in one FS (one grade 3 and one or two FS grade 2) or two FS grade 3, others 0 or 1, or five FS grade 2, others 0 or 1</td>
</tr>
<tr>
<td>4.0</td>
<td>Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters (0.3 miles)</td>
</tr>
<tr>
<td>4.5</td>
<td>Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest for some 300 meters (975 ft)</td>
</tr>
<tr>
<td>5.0</td>
<td>Ambulatory without aid or rest for about 200 meters (650 feet); disability severe enough to impair full daily activities (i.e., to work a full day without special provisions); usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding specifications for step 4.0</td>
</tr>
<tr>
<td>5.5</td>
<td>Ambulatory without aid or rest for about 100 meters (325 ft); disability severe enough to impair full daily activities; usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding specifications for step 4.0</td>
</tr>
<tr>
<td>6.0</td>
<td>Intermittent or constant unilateral assistance (cane, crutch, brace) required to walk about 100 meters (325 ft) with or without resting; usual FS equivalents are combinations with more than two FS grade 3+</td>
</tr>
<tr>
<td>6.5</td>
<td>Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters (65 ft); usual FS equivalents are combinations with more than two FS grade 3+</td>
</tr>
<tr>
<td>7.0</td>
<td>Unable to walk beyond about 5 meters (16 ft) even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair a full day and transfers alone; up and about in wheelchair some 12 hours a day; usual FS equivalents are combinations with more than one FS grade 4; very rarely pyramidal grade 5 alone</td>
</tr>
<tr>
<td>7.5</td>
<td>Unable to take more than a few steps; restricted to wheelchair; may need aid in transfers, wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair; usual FS equivalents are combinations with more than one FS grade 4+</td>
</tr>
<tr>
<td>8.0</td>
<td>Essentially restricted to bed or chair or perambulated in wheelchair; but may be out of bed much of the day; retains many self-care functions; generally has effective use of arms; usual FS equivalents are combinations, generally grade 4+ in several systems</td>
</tr>
<tr>
<td>8.5</td>
<td>Essentially restricted to bed for much of the day; has some effective use of arm(s); retains some self-care functions; usual FS equivalents are combinations, generally grade 4+ in several systems</td>
</tr>
<tr>
<td>9.0</td>
<td>Helpless bed patient; can communicate and eat; usual FS equivalents are combinations, mostly grade 4</td>
</tr>
<tr>
<td>9.5</td>
<td>Totally helpless bed patient; unable to communicate effectively or eat/swallow; usual FS equivalents are combinations, almost all grade 4+</td>
</tr>
<tr>
<td>10.0</td>
<td>Death due to MS</td>
</tr>
</tbody>
</table>

*FS = „functional systems“: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, cerebral, visual.

---

**Appendix A: The Extended Disabilities Status Scale (EDSS) (Kurtzke, 1983)**
The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis

<table>
<thead>
<tr>
<th>contrast</th>
<th>task</th>
<th>cluster p(FWE-corr)</th>
<th>cluster equivk</th>
<th>peak T</th>
<th>MNI coordinates</th>
<th>corresponding anatomical correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls vs.</td>
<td>N-1 task</td>
<td>.018</td>
<td>5</td>
<td>5.19</td>
<td>-26 -48 -12</td>
<td>L Fusiform Gyrus</td>
</tr>
<tr>
<td>Patients</td>
<td>patients vs. controls</td>
<td>.000</td>
<td>87</td>
<td>6.14</td>
<td>-56 -24 20</td>
<td>L Supramarginal Gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.000</td>
<td>177</td>
<td>6.09</td>
<td>-32 -10 70</td>
<td>L Precentral Gyrus</td>
</tr>
<tr>
<td>controls vs.</td>
<td>patients vs. controls</td>
<td>.018</td>
<td>5</td>
<td>4.92</td>
<td>-44 -28 52</td>
<td>L Postcentral Gyrus</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td>.028</td>
<td>2</td>
<td>4.73</td>
<td>-20 -42 70</td>
<td>L Postcentral Gyrus</td>
</tr>
<tr>
<td>patients vs.</td>
<td>controls</td>
<td>.000</td>
<td>54</td>
<td>6.00</td>
<td>-20 2 24</td>
<td>L Caudate Nucleus</td>
</tr>
<tr>
<td>patients</td>
<td>controls</td>
<td>.005</td>
<td>16</td>
<td>5.18</td>
<td>28 12 52</td>
<td>R mid Frontal G</td>
</tr>
<tr>
<td>patients vs.</td>
<td>N-2 task</td>
<td>.000</td>
<td>242</td>
<td>6.03</td>
<td>-36 -12 66</td>
<td>L precentral</td>
</tr>
<tr>
<td>controls</td>
<td>patients vs. controls</td>
<td>.000</td>
<td>93</td>
<td>6.02</td>
<td>42 2 0</td>
<td>R insular Lobe</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td>.000</td>
<td>77</td>
<td>5.90</td>
<td>-42 -26 18</td>
<td>L Rolandic Operculum</td>
</tr>
<tr>
<td>controls</td>
<td>patients vs. controls</td>
<td>.000</td>
<td>108</td>
<td>5.53</td>
<td>66 -30 24</td>
<td>R Supramarginal G</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td>.008</td>
<td>11</td>
<td>5.25</td>
<td>10 -6 76</td>
<td>R post med Frontal</td>
</tr>
<tr>
<td>controls</td>
<td>patients vs. controls</td>
<td>.012</td>
<td>8</td>
<td>5.18</td>
<td>-38 -12 4</td>
<td>L insular Lobe</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td>.024</td>
<td>3</td>
<td>4.84</td>
<td>50 -6 0</td>
<td>R superior temporal Gyrus</td>
</tr>
<tr>
<td>patients</td>
<td>controls</td>
<td>.024</td>
<td>3</td>
<td>4.79</td>
<td>46 -12 2</td>
<td>R superior temporal Gyrus</td>
</tr>
</tbody>
</table>

Appendix B: Table of activations for group differences in the N-back tasks
### Task-dependent changes of brain activity

#### N-1 task

<table>
<thead>
<tr>
<th>contrast</th>
<th>task</th>
<th>cluster p (FWE-corr)</th>
<th>peak T</th>
<th>MNI coordinates</th>
<th>corresponding anatomical correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-1 task</td>
<td>patients vs. controls - end vs. beg</td>
<td>.033</td>
<td>3</td>
<td>3.54</td>
<td>12 -40 30</td>
</tr>
<tr>
<td></td>
<td>controls vs. patients -</td>
<td></td>
<td></td>
<td></td>
<td>no voxels were significantly activated</td>
</tr>
<tr>
<td></td>
<td>patients vs. controls -</td>
<td>.001</td>
<td>168</td>
<td>4.67</td>
<td>-8 -34 66</td>
</tr>
<tr>
<td></td>
<td>controls vs. patients -</td>
<td>.033</td>
<td>38</td>
<td>3.79</td>
<td>-30 28 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.021</td>
<td>47</td>
<td>3.75</td>
<td>42 28 -12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.039</td>
<td>34</td>
<td>3.74</td>
<td>10 -42 32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.041</td>
<td>24</td>
<td>3.72</td>
<td>-16 -78 24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.026</td>
<td>30</td>
<td>3.63</td>
<td>-18 54 -10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.019</td>
<td>8</td>
<td>3.54</td>
<td>16 2 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.048</td>
<td>11</td>
<td>3.57</td>
<td>30 -14 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.039</td>
<td>16</td>
<td>3.91</td>
<td>20 -8 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.023</td>
<td>4</td>
<td>3.68</td>
<td>32 -2 -12</td>
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</table>

#### N-2 task

<table>
<thead>
<tr>
<th>contrast</th>
<th>task</th>
<th>cluster p (FWE-corr)</th>
<th>peak T</th>
<th>MNI coordinates</th>
<th>corresponding anatomical correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-2 task</td>
<td>patients vs. controls - end vs. beg</td>
<td></td>
<td></td>
<td></td>
<td>no voxels were significantly activated</td>
</tr>
<tr>
<td></td>
<td>controls vs. patients -</td>
<td></td>
<td></td>
<td></td>
<td>no voxels were significantly activated</td>
</tr>
</tbody>
</table>

### Task-independent changes in brain activity

#### N-1 task

<table>
<thead>
<tr>
<th>contrast</th>
<th>task</th>
<th>cluster p (FWE-corr)</th>
<th>peak T</th>
<th>MNI coordinates</th>
<th>corresponding anatomical correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-1 task</td>
<td></td>
<td>.045</td>
<td>21</td>
<td>2.99</td>
<td>0 10 28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.026</td>
<td>46</td>
<td>3.86</td>
<td>2 10 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.045</td>
<td>16</td>
<td>3.85</td>
<td>-2 -36 64</td>
</tr>
</tbody>
</table>

#### N-2 task

<table>
<thead>
<tr>
<th>contrast</th>
<th>task</th>
<th>cluster p (FWE-corr)</th>
<th>peak T</th>
<th>MNI coordinates</th>
<th>corresponding anatomical correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-2 task</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no voxels were significantly activated</td>
</tr>
</tbody>
</table>

---

Appendix C: Table of activations for task-dependent and task-independent activations
Appendix A: Table showing the location of the ROIs (sphere with 10mm radius; *4mm radius) which together form the seed network for the resting state functional MRI analysis (taken from Demertzi et al., 2015)

<table>
<thead>
<tr>
<th>Intrinsic connectivity network</th>
<th>x,y,z, MNI coordinates (centered)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Default mode network (DMN)</td>
<td></td>
<td>(Raichle, 2011)</td>
</tr>
<tr>
<td>posterior cingulate cortex/precuneus</td>
<td>[0 -52 27]</td>
<td></td>
</tr>
<tr>
<td>medial prefrontal cortex</td>
<td>[-1 54 27]</td>
<td></td>
</tr>
<tr>
<td>lateral parietal cortex [left] [right]</td>
<td>[-46 -66 30] [49 -63 33]</td>
<td></td>
</tr>
<tr>
<td>inferior temporal cortex [left] [right]</td>
<td>[-61 -24 -9] [58 -24 -9]</td>
<td></td>
</tr>
<tr>
<td>cerebellum [left] [right]</td>
<td>[-25 -81 -33] [25 -81 -33]</td>
<td></td>
</tr>
<tr>
<td>thalamus*</td>
<td>[0 -12 9]</td>
<td></td>
</tr>
<tr>
<td>brainstem*</td>
<td>[12 -24 -24]</td>
<td>(Boveroux et al., 2010)</td>
</tr>
<tr>
<td>Fronto-parietal network</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dorsolateral prefrontal cortex [left] [right]</td>
<td>[-43 22 34] [43 22 34]</td>
<td>(Fair et al., 2009)</td>
</tr>
<tr>
<td>inferior parietal lobule [left] [right]</td>
<td>[-51 -51 36] [51 -47 42]</td>
<td></td>
</tr>
<tr>
<td>premotor cortex [left] [right]</td>
<td>[-41 3 36] [41 3 36]</td>
<td></td>
</tr>
<tr>
<td>midcingulate cortex</td>
<td>[0 -29 30]</td>
<td></td>
</tr>
<tr>
<td>angular gyrus [left] [right]</td>
<td>[-31 -59 42] [30 -61 39]</td>
<td></td>
</tr>
<tr>
<td>precuneus [left] [right]</td>
<td>[-9 -72 37] [10 -69 39]</td>
<td></td>
</tr>
<tr>
<td>brainstem*</td>
<td>[4 -12 0] [4 -12 0]</td>
<td>(Boveroux et al., 2010)</td>
</tr>
<tr>
<td>cerebellum</td>
<td>[-4 -56 -40]</td>
<td></td>
</tr>
<tr>
<td>thalamus* [left] [right]</td>
<td>[-4 -12 0] [4 -12 0]</td>
<td></td>
</tr>
</tbody>
</table>

References of table:


## Appendix B: The Beck Depression Inventory (BDI) (Hautzinger et al. 1994)

### BDI

<table>
<thead>
<tr>
<th>Name:</th>
<th>Geschlecht:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Geburtsdatum:</td>
<td>Ausfülldatum:</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dieser Fragebogen enthält 21 Gruppen von Aussagen. Bitte lesen Sie jede Gruppe sorgfältig durch. Suchen Sie dann die eine Aussage in jeder Gruppe heraus, die am besten beschreibt, wie Sie sich in dieser Woche einschließlich heute gefühlt haben und kreuzen Sie die dazugehörige Ziffer (0, 1, 2 oder 3) an. Falls mehrere Aussagen einer Gruppe gleichermäßen zutreffen, können Sie auch mehrere Ziffern markieren. Lesen Sie auf jeden Fall alle Aussagen in jeder Gruppe, bevor Sie Ihre Wahl treffen.

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ich bin nicht traurig.</td>
<td>Ich habe nicht das Gefühl, gestraft zu sein.</td>
</tr>
<tr>
<td>1</td>
<td>Ich bin traurig.</td>
<td>1 Ich habe das Gefühl, vielleicht bestraft zu werden.</td>
</tr>
<tr>
<td>2</td>
<td>Ich bin die ganze Zeit traurig und komme nicht davon los.</td>
<td>2 Ich erwarte, bestraft zu werden.</td>
</tr>
<tr>
<td>3</td>
<td>Ich bin so traurig oder unglücklich, daß ich es kaum noch ertrage.</td>
<td>3 Ich habe das Gefühl, bestraft zu sein.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ich sehe nicht besonders mutlos in die Zukunft.</td>
<td>0 Ich bin nicht von mir enttäuscht.</td>
</tr>
<tr>
<td>1</td>
<td>Ich sehe mutlos in die Zukunft.</td>
<td>1 Ich bin von mir enttäuscht.</td>
</tr>
<tr>
<td>2</td>
<td>Ich habe nichts, worauf ich mich freuen kann.</td>
<td>2 Ich finde mich fürchterlich.</td>
</tr>
<tr>
<td>3</td>
<td>Ich habe das Gefühl, daß die Zukunft hoffnungslos ist, und daß die Situation nicht besser werden kann.</td>
<td>3 Ich hasse mich.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ich fühle mich nicht als Versager.</td>
<td>0 Ich habe nicht das Gefühl, schlechter zu sein als alle anderen.</td>
</tr>
<tr>
<td>1</td>
<td>Ich habe das Gefühl, öfter versagt zu haben als der Durchschnitt,</td>
<td>1 Ich kritisiere mich wegen meiner Fehler und Schwächen.</td>
</tr>
<tr>
<td>2</td>
<td>Wenn ich auf mein Leben zurückblicke, sehe ich bloß eine Menge Fehlschläge.</td>
<td>2 Ich mache mir die ganze Zeit Vorwürfe wegen meiner Mängel.</td>
</tr>
<tr>
<td>3</td>
<td>Ich habe das Gefühl, als Mensch ein völliger Versager zu sein.</td>
<td>3 Ich gebe mir für alles die Schuld, was schief geht.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>D</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ich kann die Dinge genauso genießen wie früher.</td>
<td>0 Ich denke nicht daran, mir etwas anzutun.</td>
</tr>
<tr>
<td>1</td>
<td>Ich kann die Dinge nicht mehr so genießen wie früher.</td>
<td>1 Ich denke manchmal an Selbstmord, aber ich würde es nicht tun.</td>
</tr>
<tr>
<td>2</td>
<td>Ich kann aus nichts mehr eine echte Befriedigung ziehen.</td>
<td>2 Ich möchte mich am liebsten umbringen.</td>
</tr>
<tr>
<td>3</td>
<td>Ich bin mit allem unzufrieden oder gelangweilt.</td>
<td>3 Ich würde mich umbringen, wenn ich die Gelegenheit hätte.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>E</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ich habe keine Schuldgefühle.</td>
<td>0 Ich weine nicht öfter als früher.</td>
</tr>
<tr>
<td>1</td>
<td>Ich habe häufig Schuldgefühle.</td>
<td>1 Ich weine jetzt mehr als früher.</td>
</tr>
<tr>
<td>2</td>
<td>Ich habe fast immer Schuldgefühle.</td>
<td>2 Ich weine jetzt die ganze Zeit.</td>
</tr>
<tr>
<td>3</td>
<td>Ich habe immer Schuldgefühle.</td>
<td>3 Früher konnte ich weinen, aber jetzt kann ich es nicht mehr, obwohl ich es möchte.</td>
</tr>
</tbody>
</table>

---

Subtotal Seite 1

Fortsetzung auf der Rückseite
The neural correlates of effort-related and effort-unrelated fatigue in patients with multiple sclerosis

K
0 Ich bin nicht reizbarer als sonst.
1 Ich bin jetzt leichter verärgert oder gereizt als früher.
2 Ich fühle mich dauernd gereizt.
3 Die Dinge, die mich früher geärgert haben, berühren mich nicht mehr.

L
0 Ich habe nicht das Interesse an Menschen verloren.
1 Ich interessiere mich jetzt weniger für Menschen als früher.
2 Ich habe mein Interesse an anderen Menschen zum größten Teil verloren.
3 Ich habe mein ganzes Interesse an anderen Menschen verloren.

M
0 Ich bin so entschlossen wie immer.
1 Ich schiebe Entscheidungen jetzt öfter als früher auf.
2 Es fällt mir jetzt schwerer als früher, Entscheidungen zu treffen.
3 Ich kann überhaupt keine Entscheidungen mehr treffen.

N
0 Ich habe nicht das Gefühl, schlechter auszusehen als früher.
1 Ich mache mir Sorgen, daß ich alt oder unattraktiv aussehe.
2 Ich habe das Gefühl, daß Veränderungen in meinem Aussehen eintreten, die mich häßlich machen.
3 Ich finde mich häßlich.

O
0 Ich kann so gut arbeiten wie früher.
1 Ich muß mir einen Rücken geben, bevor ich eine Tätigkeit in Angriff nehme.
2 Ich muß mich zu jeder Tätigkeit zwingen.
3 Ich bin unfähig zu arbeiten.

P
0 Ich schlafe so gut wie sonst.
1 Ich schlafe nicht mehr so gut wie früher.
2 Ich wache 1 bis 2 Stunden später auf als sonst, und es fällt mir schwer, wieder einzuschlafen.
3 Ich wache mehrere Stunden später auf als sonst und kann nicht mehr einschlafen.

Q
0 Ich ermüde nicht stärker als sonst.
1 Ich ermüde schneller als früher.
2 Fast alles ermüdet mich.
3 Ich bin zu müde, um etwas zu tun.

R
0 Mein Appetit ist nicht schlechter als sonst.
1 Mein Appetit ist nicht mehr so gut wie früher.
2 Mein Appetit hat sehr stark nachgelassen.
3 Ich habe überhaupt keinen Appetit mehr.

S
0 Ich habe in letzter Zeit kaum abgenommen.
1 Ich habe mehr als 2 Kilo abgenommen.
2 Ich habe mehr als 3 Kilo abgenommen.
3 Ich habe mehr als 8 Kilo abgenommen.

Ich esse absichtlich weniger, um abzunehmen:
☐ JA  ☐ NEIN

T
0 Ich mache mir keine größeren Sorgen um meine Gesundheit als sonst.
1 Ich mache mir Sorgen über körperliche Probleme, wie Schmerzen, Magenbeschwerden oder Verstopfung.
2 Ich mache mir so große Sorgen über gesundheitliche Probleme, daß es mir schwerfällt, an etwas anderes zu denken.
3 Ich mache mir so große Sorgen über gesundheitliche Probleme, daß ich an nichts anderes mehr denken kann.

U
0 Ich habe in letzter Zeit keine Veränderung meines Interesses an Sex bemerkt.
1 Ich interessiere mich weniger für Sex als früher.
2 Ich interessiere mich jetzt viel weniger für Sex.
3 Ich habe das Interesse an Sex völlig verloren.

Subtotal Seite 1

Subtotal Seite 2

Summerwert
Appendix C: The Fatigue Scale of Motor and Cognition (FSMC) (Penner et al. 2005)

**Anleitung**

Im folgenden Fragebogen geht es um alltägliche Probleme, die in direktem Zusammenhang mit einer extremen Form von Müdigkeit (Fatigue) stehen. Unter dieser extremen Form der Müdigkeit wird ein nicht zu beherrschender Zustand der Abgeschlagenheit, Erschöpfung und Energie­losigkeit verstanden, der schlagartig eintritt, unabhängig von eindeutigen äusseren Ursachen. Gemeint sind damit nicht Einzelereignisse, wie sie jeder Mensch im Verlaufe des Tages, nach einer Anstrengung oder nach einer schlaflosen Nacht erlebt! Bitte lesen Sie jede Aussage genau durch. Entscheiden Sie dann, inwieweit die entsprechende Aussage auf Sie und Ihren Alltag zutrifft. Bitte treffen Sie Ihre Antwort möglichst unabhängig von Ihrem momentanen Befinden und versuchen Sie uns ein Bild von Ihrem Zustand zu geben, wie sie ihn Tag für Tag erleben. Setzen Sie hierzu bitte ein Kreuz in den entsprechenden Kreis (pro Aussage bitte nur ein Kreuz!).

<table>
<thead>
<tr>
<th></th>
<th>Trifft gar nicht zu</th>
<th>Trifft wenig zu</th>
<th>Trifft teils-teils zu</th>
<th>Trifft ziemlich zu</th>
<th>Trifft völlig zu</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Meine Bewegungen werden im Zustand der Erschöpfung deutlich ungeschickter und unkoordinierter.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Im Zustand der Erschöpfung bin ich unfähig, Entscheidungen zu treffen.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Ich fühle mich heute körperlich schneller erschöpft als früher, wenn ich stressigen Situationen ausgesetzt bin.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Wegen meiner Erschöpfungszustände fällt es mir heute schwerer, etwas Neues zu lernen als früher.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bitte umbilättern

FSMC-cog = ____________  FSMC-mot = ____________  FSMC total = ____________

© Penner et al., 2005
8. Berufliche Anforderungen lassen mich geistig schneller erschöpfen als früher.


11. Meine Konzentrationsfähigkeit nimmt bei Stress beträchtlich ab.

12. Im Zustand der Erschöpfung bin ich weniger motiviert als andere Menschen, Tätigkeiten zu beginnen, die mit körperlicher Anstrengung verbunden sind.

13. Mein Denken verlangsamt sich zusehends, wenn es heiß ist.


15. Wegen meiner Erschöpfungszustände habe ich heute weniger Lust als früher, etwas zu tun, was Nachdenken erfordert.

16. Wenn sich ein Erschöpfungszustand einstellt, bin ich überhaupt nicht mehr in der Lage, schnell zu reagieren.

17. Im Zustand der Erschöpfung kommen mir bestimmte Worte nicht mehr in den Sinn.


20. Im Zustand der Erschöpfung nimmt meine Vergesslichkeit merklich zu.

Bitte vergewissern Sie sich, dass Sie die Initialen Ihres Namens, Ihr Alter und Ihr Geschlecht auf Seite 1 angegeben und bei jeder Aussage ein Kreuz gemacht haben. Vielen Dank.

© Penner et al., 2005
Informationsblatt funktionelle Kernspintomographie


Wichtig:

Diese Untersuchung dient nicht der medizinischen Diagnostik, weshalb die durchführenden Mitarbeiter/innen keine Ausküfte bezüglich möglicher Erkrankungen Ihres Gehirns geben können. In sehr seltenen Fällen kann es aber dennoch vorkommen, dass besondere Auffälligkeiten beobachtet werden. Mit Ihrem ausdrücklichen Einverständnis werden wir Sie gegebenenfalls darauf aufmerksam machen.

Ich möchte über mögliche Auffälligkeiten in meinen Bildern informiert werden.  
Ja □ Nein □

Über die Risiken der Studie bin ich aufgeklärt worden:

1. Hohe Magnetfelder bewirken, dass metallische Implantate oder Fremdkörper (z.B. Gefäßclips, Gebiss, Metallsplitter, etc.) im Körper wandern können, was zu Komplikationen führen kann.
2. Bei Tätowierungen und Make-up können sich entsprechende Hautpartien erwärmen was zu Verbrennungen führen kann.
3. Im Untersuchungsgerät herrscht relative Enge, die von Probanden mit Platzangst (Klaustrophobie) als sehr unangenehm empfunden wird.
4. Das hohe Magnetfeld bewirkt, dass Herztaktmacher und jegliche anderen elektronischen Geräte nicht mehr ordnungsgemäß funktionieren, deshalb dürfen Träger von Herztaktmachern an dieser Untersuchung nicht teilnehmen.
5. Metallteile, die Sie mit sich führen sind eine potenzielle Gefahr für Sie und andere. Bitte leeren Sie Ihre Taschen, insbesondere von metallischen Gegenständen (Schlüssel, Geld, Kugelschreiber, etc.) und legen diese vor Betreten des Untersuchungsraums in ein dafür vorgesehenes Behältnis. Auch müssen wir Sie bitten, Körperschmuck (z.B. Ohrringe, Piercings, etc.) und ein herausnehmbares Gebiss zu entfernen.
7. Uhren und Scheckkarten können durch das starke Magnetfeld zerstört werden.
Bitte beantworten sie folgende Fragen (Zutreffendes ankreuzen)

<table>
<thead>
<tr>
<th>Frage</th>
<th>Ja</th>
<th>Nein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sind Sie Träger eines Herzschnittmachers, einer implantierten</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medikamentenpumpe, sonstiger Implantate oder anderer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>elektromedizinischer Geräte? (z.B. Insulinpumpe, Neurostimulator,</td>
<td></td>
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</tr>
<tr>
<td>Shunt, künstlicher Darmausgang mit Magnetverschluss, künstliche</td>
<td></td>
<td></td>
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<tr>
<td>Herzklappe, etc.)</td>
<td></td>
<td></td>
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<tr>
<td>Befinden sich durch Unfälle oder Operationen möglicherweise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metallische und elektrisch leitfähige Einschlüsse und Implantate in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ihrem Körper? (z.B. Metallprothesen, Cochlear-Implantat, Innenohr-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothesen, Gefäßclips, Osteosyntheseplatten, Stents, Cava-Filter,</td>
<td></td>
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<tr>
<td>Intrauterinpessar, Metall- oder Granatsplitter, Spiralé, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haben Sie Tätowierungen am Kopf- oder Halsbereich, Nikotinpflaster</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oder kosmetische Augenlidmanipulationen?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haben Sie schon mal ein (schweres) Schädelhirntrauma o.Ä. erlitten?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sind Sie jemals an Herz oder Gehirn operiert worden?</td>
<td></td>
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</tr>
<tr>
<td>Könnte bei Ihnen eine Schwangerschaft bestehen?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiden Sie an einer Depression oder anderen psychischen Krankheiten,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>welche offiziell von einem Fachmann bestätigt worden sind?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welche:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benutzen sie eine Spirale (ggfs. aus Kupfer) als Verhütungsmittel?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiden Sie unter Epilepsie?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiden Sie unter chronischen Erkrankungen?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welche:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nehmen Sie zur Zeit Medikamente?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welche:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiden Sie unter Platzangst?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiden Sie unter Bluthochdruck?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Datenschutz:


Die Teilnahme an dieser wissenschaftlichen Untersuchung ist vollkommen freiwillig. Es steht Ihnen jederzeit frei, die Untersuchung ohne Angabe von Gründen, auch nach schriftlicher Zusage der Untersuchung, abzubrechen. Es entstehen Ihnen daraus keine Nachteile.

Mit meiner Unterschrift bestätige ich, dass ich von dem Leiter der Studie über den Inhalt der Studie und dieses Formblattes ausreichend aufgeklärt worden bin, die damit verbundenen Informationen verstanden habe und meine Fragen hinreichend beantwortet wurden.

Allensbach,DatumName in Druckbuchstaben

Unterschrift

Unterschrift Versuchsleiter/in

Bitte noch ausfüllen:

Geburtsdatum (TT/MM/JJJJ): ____________________________

Größe (cm) / Gewicht (Kg): _______________________/
Kliniken Schmieder Konstanz
Projektleiter Prof. Dr. C. Dettmers
Eichhornstr. 68
78464 Konstanz
07531-986-3536

Neuronale Korrelate dynamischer Prozesse bei Patienten mit Multipler Sklerose und Fatigue - eine Untersuchung mittels funktioneller Kernspintomographie

Einverständniserklärung

Ich wurde über Art, Ablauf und Zielsetzung der oben genannten Studie aufgeklärt und stimme zu, dass die im Rahmen der Untersuchungen erhobenen Daten zu wissenschaftlichen Zwecken verwendet und ausgewertet werden. Über die Umstände der Untersuchung mit Magnetresonanztomographie bin ich gesondert aufgeklärt worden. Ich hatte Gelegenheit Fragen zu stellen, und diese sind zu meiner Zufriedenheit beantwortet worden.

Ich bin freiwillig damit einverstanden, an der genannten Studie teilzunehmen. Ich wurde darüber informiert, dass ich jederzeit ohne Angabe von Gründen meine Einwilligung zur Teilnahme an dieser Untersuchung zurückziehen kann.

Die Aufklärung erfolgte durch ______________________ (Name des aufklärenden Arztes).

(Datum und Unterschrift des aufklärenden Arztes)

(Datum und Unterschrift des Patienten) ______________________ (Name des Patienten im Druckbuchstaben)
Neuronale Korrelate dynamischer Prozesse bei Patienten mit Multipler Sklerose und Fatigue - eine Untersuchung mittels funktioneller Kernspintomographie -

Patienteninformation

Sehr geehrter Patient,
sehr geehrte Patientin,

das LuriJa Institut für Rehabilitationswissenschaften und Gesundheitsforschung ist stets bemüht durch neueste Erkenntnisse und Forschung die Rehabilitation für neurologische Patienten zu verbessern. Nur mit Ihrer Hilfe können diese Erkenntnisse erlangt werden und wir würden Sie bitten bei der oben genannten Studie als Teilnehmer mitzumachen. Es folgt eine genauere Beschreibung der Studie um Sie damit vertraut zu machen.


Bei Multipler Sklerose sind oft mehrere Gehirnareale gleichzeitig betroffen, vor allem in der so genannten weißen Substanz des Gehirns. Patienten mit MS, und vielleicht sogar auch Sie selbst, leiden häufig an einer Fatigue, bei der Sie von erheblichen Aufmerksamkeitschwierigkeiten berichten.


Bei der Untersuchung besteht die kognitive Belastung aus einem Test innerhalb der MRTs der während einer Messung durchgeführt wird (fMRT). Dieser Test dauert etwa 30 Minuten. Ihre Aufgabe hier ist es immer auf eine Buchstabenreihefolge zu achten und sobald sich ein Buchstabe in einem vorgegebenen Abstand wiederholt sollen Sie auf einen Knopf drücken. Die Aufgabe wird vorher außerhalb des Scanners mit Ihnen geübt.

Appendix I: Patient information sheet


Wichtig und notwendig ist für uns, dass Sie den ausführlichen Einwilligungsbogen für die Kernspintomographie ausfüllen. Hier werden noch einmal ausführlich die Gründe abgefragt, die die Durchführung einer Kernspintomographie verbieten (Herzschrittmacher, künstliche Herzklappen, Metallsplitter usw.).

Freiwilligkeit der Zustimmung:
Ihre Entscheidung, an dieser Studie teilzunehmen, ist freiwillig. Sie kann zu jedem Zeitpunkt ohne Erklärung und ohne, dass Ihnen hieraus ein Nachteil erwächst, widerrufen werden. Therapeutische Konsequenzen ergeben sich derzeitig für Sie im Einzelfall nicht.

Datenschutzhinweis:
Daten, die von Ihnen verwendet werden, werden im Rahmen der Studie anonymisiert ausgewertet. Dass heißt, der Auswerter weiß nicht, von wem die Daten stammen.

Weitere Fragen?

Hr. Stefan Spiteri
MSc. Psychologie
Wiss. Mitarbeiter Lurja Institut
Kliniken Schmieder, Allensbach
Neuronale Korrelate dynamischer Prozesse bei Patienten mit Multipler Sklerose und Fatigue – eine Untersuchung mittels funktioneller Kernspintomographie –

Probandeninformation

Sehr geehrter Proband,
sehr geehrte Probandin,

das Lurija Institut für Rehabilitationswissenschaften und Gesundheitsforschung ist stets bemüht durch neueste Erkenntnisse und Forschung die Rehabilitation für neurologische Patienten zu verbessern. Nur mit ihrer Hilfe können diese Erkenntnisse erlangt werden und wir würden Sie bitten bei der oben genannten Studie als Teilnehmer mitzumachen. Es folgt eine genauiere Beschreibung der Studie um Sie damit vertraut zu machen.


Bei der Untersuchung besteht die kognitive Belastung aus einem Test innerhalb der MRTs der während einer Messung durchgeführt wird (fMRT). Dieser Test dauert etwa 30 Minuten. Ihre Aufgabe hier ist es immer auf eine Buchstabenreihefolge zu achten und sobald sich ein Buchstabe in einem vorgegebenen Abstand wiederholt sollen Sie auf einen Knopf drücken. Die Aufgabe wird vorher außerhalb des Scanners mit Ihnen geübt.
Die Kernspintomographie wird in Allensbach durchgeführt. Sie dauert üblicherweise 1 Stunde da zusätzlich noch strukturelle Messungen gemacht werden. Sie geht mit keinerlei Strahlenwirkung


Wichtig und notwendig ist für uns, dass Sie den ausführlichen Einwilligungsbogen für die Kernspintomographie ausfüllen. Hier werden noch einmal ausführlich die Gründe abgefragt, die die Durchführung einer Kernspintomographie verhindern (Herzschrittmacher, künstliche Herzklappen, Metallsplitter usw.).

Freiwilligkeit der Zustimmung:
Ihre Entscheidung, an dieser Studie teilzunehmen, ist freiwillig. Sie kann zu jedem Zeitpunkt ohne Erklärung und ohne, dass Ihnen hieraus ein Nachteil erwächst, widerrufen werden.
Therapeutische Konsequenzen ergeben sich derzeitig für Sie im Einzelfall nicht.

Datenschutzhinweis:
Daten, die von Ihnen verwendet werden, werden im Rahmen der Studie anonymisiert ausgewertet. Dass heißt, der Auswerter weiß nicht, von wem die Daten stammen.

Weitere Fragen?
Der behandelnde Arzt oder der Studienleiter stehen Ihnen gerne für die Beantwortung weiterer Fragen zur Verfügung.

Hr. Stefan Spiteri
MSc. Psychologie
Wiss. Mitarbeiter Lurija Institut
Kliniken Schmieder, Aliensbach
Neural correlates of effort-dependent and effort-independent cognitive fatigue components in patients with multiple sclerosis

Stefan Spiteri, Thomas Hassa, Dolores Claros-Salinas, Christian Dettmers and Mircea Ariel Schoenfeld

Abstract

Background: Among patients with multiple sclerosis (MS), fatigue is the most commonly reported symptom. It can be subdivided into an effort-dependent (fatigability) and an effort-independent component (trait-fatigue).

Objective: The objective was to disentangle activity changes associated with effort-independent “trait-fatigue” from those associated with effort-dependent fatigability in MS patients.

Methods: This study employed behavioral measures and functional magnetic imaging to investigate neural changes in MS patients associated with fatigue. A total of 40 MS patients and 22 age-matched healthy controls performed in a fatigue-inducing N-back task. Effort-independent fatigue was assessed using the Fatigue Scale of Motor and Cognition (FSMC) questionnaire.

Results: Effort-independent fatigue was observed to be reflected by activity increases in fronto-striatal-subcortical networks primarily involved in the maintenance of homeostatic processes and in motor and cognitive control. Effort-dependent fatigue (fatigability) leads to activity decreases in attention-related cortical and subcortical networks.

Conclusion: These results indicate that effort-independent (fatigue) and effort-dependent fatigue (fatigability) in MS patients have functionally related but fundamentally different neural correlates. Fatigue in MS as a general phenomenon is reflected by complex interactions of activity increases in control networks (effort-independent component) and activity reductions in executive networks (effort-dependent component) of brain areas.

Keywords: Multiple sclerosis, fatigue, fatigability, state/trait-fatigue, attention, MRI

Date received: 29 March 2017; revised: 5 October 2017; accepted: 18 October 2017

Introduction

One of the most prevalent and most common symptoms in multiple sclerosis (MS) is fatigue1 affecting approximately 70%-90% of patients as one of the most disabling symptoms in MS.2,3 Chaudhuri and Behan4 distinguish between physical fatigue, as the inability to sustain a specified work rate during exercise, and cognitive fatigue, as a failure of physical and mental tasks that require self-motivation and internal cues in the absence of motor weakness. They suggest that the cause of cognitive fatigue can be found in a failure of the non-motor functions of the basal ganglia (BG). Both forms of fatigue can be separated into an effort-independent general subjective sensation of fatigué, and fatigability as an effort-dependent change in performance.5

Functional imaging work on different fatigue types6 provided at least in part conflicting results. Some found a correlation between fatigue and brain atrophy or lesion load. Others described a relationship with white matter lesions in cortical and subcortical areas8,9 or no association between fatigue and lesion load, lesion distribution, lesion location, or brain atrophy at all10

Recent work11 proposed a close link between cognitive fatigue in MS and non-motor dysfunctions of the BG due to a neurotransmitter imbalance. Consequently,...
fatigue was suggested to arise from a dysfunction of the cortico-striatal network between prefrontal cortical (PFC) areas and the BG. This network also comprises the anterior cingulate cortex (ACC) that is also involved in the control of attention as part of a more distributed network.\textsuperscript{11,13} Similar to the abovementioned taxonomy of fatigue and fatigability, Genova et al.\textsuperscript{16} proposed to divide fatigue into two components: “trait” fatigue, referring to the experience of fatigue across a long period of time, which is not likely to change significantly over time, and “state” fatigue, which is referred to as a transient dynamic condition fluctuating based on internal and external factors. The authors employed functional magnetic resonance imaging (fMRI) in conjunction with a cognitive-fatigue-inducing task-switching paradigm and structural measures in MS patients to investigate “state” and “trait” fatigue, respectively. They found higher activity in the caudate nucleus when compared to healthy controls, but no differences in gray matter (GM) volume or lesion load. While there were no differences in task performance (accuracy and reaction times (RTs)) between patients and controls, the subjective ratings of fatigue as well as activity in associated neural networks were higher in patients.\textsuperscript{18} The authors interpreted this discrepancy as supporting the notion that neuropsychological tests do not necessarily offer the most sensitive measure for fatigue. Diffusion tensor imaging (DTI) in conjunction with fatigue scores\textsuperscript{2} revealed a reduced fractional anisotropy (FA) within the anterior internal capsule that is connected to the caudate and thalamus supporting the idea of an important role of the striatal-thalamic-frontal system in fatigue.\textsuperscript{19}

Recent studies provided strong evidence that the performance in alertness and vigilance tasks is more correlated with the subjective feeling of fatigue in MS patients, than other cognitive domains. This was observed following a period of roughly 15 minutes performing a monotonous task, arguing for a depletion of attentional resources.\textsuperscript{14} The neuroanatomical correlates include areas of the brainstem, midbrain, and thalamus, as well as fronto-parietal regions and the ACC. So far, functional imaging was mostly focused on motor fatigue and only few studies investigated cognitive fatigue.\textsuperscript{14} The aim of this study was to investigate the neural correlates of effort-dependent and effort-independent fatigue in MS patients and healthy controls. Effort-independent components correspond to previous definitions of “trait” fatigue, while the effort-dependent components correspond to “state” fatigue. Effort-independent fatigue correlates were assessed using the difference of activity in patients at the beginning of a cognitive task (N-back) that correlated with subjective evaluations of cognitive fatigue. It was assumed that the effects of effort-dependent fatigue would be minimal at the beginning of the task. Effort-dependent fatigue correlates were assessed as the difference between the end and the beginning of the task. Behavioral and fatigue measures were performed before and after an N-back task. Neural correlates of effort-independent fatigue were expected to be reflected by alterations of hemodynamic activity in cortical and subcortical network subserving cognitive and motor control. In contrast, effort-dependent fatigue correlates were expected in cortical executive systems, such as the associative visual cortex, which is more involved in the processing of the task itself.

**Materials and methods**

**Participants**

A total of 40 right-handed patients (31 female, aged 27–61) with definitive MS and normal or corrected-to-normal vision (acuity ≥0.4) participated in the study. We included patients with MS irrespective of their fatigue in order to be able to perform correlational analyses. Gait and manual functions were assessed by means of the clinical reports. Exclusion criteria for the patient group were psychiatric or neurological diseases other than MS or any contraindications for the magnetic resonance imaging (MRI). Age- and gender-matched control group of 22 healthy controls (15 female, aged 21–56) was recruited. The characteristics of both groups are shown in Table 1. All participants gave informed written consent and the study was approved by the local ethics committee (University of Konstanz, Germany).

**Behavioral measurements**

Patients completed the Fatigue Scale of Motor and Cognitive (FSMC)\textsuperscript{17} questionnaire, as well as the Beck Depression Inventory (BDI)\textsuperscript{18} on the day of the experiment. Participants performed in the alertness task from the Test-battery of Attentional Performance (TAP),\textsuperscript{17} a simple visual reaction task shown to be sensitive to cognitive fatigue\textsuperscript{16–20} before and after the MRI measurement.

**MRI.** A 3T Siemens Skyra (Siemens, Erlangen) MR scanner with a standard 32-channel head coil was used for imaging:

**Structural MRI.** A T1-whole-brain-scan: 176 slices, voxel resolution: 1 mm × 1 mm × 1 mm, repetition time (TR) = 2.7 seconds, echo time (TE) = 7.21 ms, no gap.
Table 1. Descriptive statistics for the patient and control cohorts.

<table>
<thead>
<tr>
<th></th>
<th>Patients (N = 40)</th>
<th>Controls (N = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>9/31 (22.5%/77.5%)</td>
<td>7/15 (32%/68%)</td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>46.75 (±7.53)</td>
<td>41.73 (±12.52)</td>
</tr>
<tr>
<td>Range</td>
<td>27–61</td>
<td>21–56</td>
</tr>
<tr>
<td>Formal education in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mean (SD)</td>
<td>11.5 (±1.7)</td>
<td>12.1 (±1.4)</td>
</tr>
<tr>
<td>EDSS</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Overall mean (SD)</td>
<td>3.5 (±1.5)</td>
<td></td>
</tr>
<tr>
<td>0–1.5</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>31 (77.5%)</td>
<td></td>
</tr>
<tr>
<td>4.5–6</td>
<td>4 (10%)</td>
<td></td>
</tr>
<tr>
<td>≥8.5</td>
<td>3 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Disease duration in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.1 (±8.3)</td>
<td>N/A</td>
</tr>
<tr>
<td>1–5 years</td>
<td>10 (25%)</td>
<td></td>
</tr>
<tr>
<td>6–10 years</td>
<td>14 (35%)</td>
<td></td>
</tr>
<tr>
<td>11–15 years</td>
<td>7 (17.5%)</td>
<td></td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>9 (22.5%)</td>
<td></td>
</tr>
<tr>
<td>Type of MS</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Relapsing-remitting (RRMS)</td>
<td>25 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>Secondary progressive (SPMS)</td>
<td>13 (32.5%)</td>
<td></td>
</tr>
<tr>
<td>Primary progressive (PPMS)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Depression (BDI)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Overall mean (SD)</td>
<td>10 (±6.0)</td>
<td></td>
</tr>
<tr>
<td>Minimal (0–9)</td>
<td>23 (57.5%)</td>
<td></td>
</tr>
<tr>
<td>Mild (10–19)</td>
<td>12 (30%)</td>
<td></td>
</tr>
<tr>
<td>Moderate (20–29)</td>
<td>5 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Severe (≥30)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue Scale for Motor and Cognition (FSMC)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Overall mean (SD)</td>
<td>70 (±16.7)</td>
<td></td>
</tr>
<tr>
<td>No fatigue (20–42)</td>
<td>3 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Mild fatigue (43–62)</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Moderate fatigue (53–62)</td>
<td>5 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Severe fatigue (≥63)</td>
<td>31 (77.5%)</td>
<td></td>
</tr>
<tr>
<td>Gait function*</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Not impaired</td>
<td>32 (80%)</td>
<td></td>
</tr>
<tr>
<td>Moderately impaired</td>
<td>5 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Severely impaired</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Manual function*</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Not impaired</td>
<td>36 (90%)</td>
<td></td>
</tr>
<tr>
<td>Moderately impaired</td>
<td>3 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Severely impaired</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; BDI: Beck Depression Inventory; FSMC: Fatigue Scale for Motor and Cognition.

*Data gathered post hoc from medical notes.

Functional MRI: Six functional MRI of 4.53-minute sessions with echo planar imaging (EPI) sequences were acquired: 36 slices per volume, voxel resolution: 2 mm × 2 mm × 3 mm, interleaved slice order: field of view...
Appendices

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vision (FOV) = 192 mm, flip angle = 80°, TR = 2.5 seconds, TE = 30 ms while participants performed in the N-back task.

N-back task. Visual stimuli were displayed at the center of a screen as white color letters on a gray background (Presentation® 16.4, www.neurobs.com). The screen was viewed via a mirror above the head coil. The size of the letters was 2.4° (h) × 2.4° (w) of visual angle.

The N-back task had two difficulty levels (N − 1 and N − 2 back). Each session consisted of K randomized task blocks (33 seconds each, 4×N−1 back and 4×N−2 back) containing a cue phase, displayed for 3 seconds, indicating the task (N − 1 or N − 2) to be completed, followed by 15 successive letter stimuli. Letters from A to L (excluding the letter “T” due to the similarity with “J”) were presented for 500 ms each, with an inter stimulus interval (ISI) randomly distributed between 1 and 7 seconds following a gamma distribution to enhance the efficiency for event-related fMRI.21 Participants performed a speeded button-press with the right index finger when the presented letter was identical to the previously shown (N − 1 back) or to the letter presented two trials before (N − 2 back). Each task block contained four to five targets without immediate letter repetition in N − 2 back blocks. N − 2 back targets were absent in N − 1 back blocks to avoid confusion (see Figure 1). The experiment was performed in six sessions of 4.53 minutes each. For each task, RTs were calculated only from correct responses and were averaged per session. The first two and the last two sessions were combined to produce values for the beginning (beg) and end. Similarly, the hit ratio (HR) was calculated by dividing the number of hits by the number of targets for each task and each session. IRTs were then also combined for the first two (begin) and last two (end) sessions.

Participants rated their momentary fatigue using a visual analog scale (VAS) from 1 to 10 before and after each session in the MRI, where (1) indicated extreme fatigue. VAS scores were initially recorded before and after each session resulting in seven scores, however, for the statistical analysis, only the baseline score and the final score following the last session were used for analysis, yielding two time points.

Analysis

Statistical analyses were performed using IBM SPSS Statistics software (Version 22.0, IBM Corp., Armonk, NY). First, data were tested for normal distribution. Analyses of variance (ANOvas) were performed on the RTs of the TAP and those obtained during the N-back task as well as on the subjective fatigue scores obtained using the VAS. Non-normally distributed data were analyzed using non-parametric tests (Wilcoxon test for within-group and Kruskal-Wallis test for between-group comparisons). Bonferroni correction was applied when needed. Correlations were calculated using Pearson’s R for parametric and Spearman’s Rho for non-parametric data.

MRI. MRI data were analyzed using statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software). All scans were resliced, realigned, normalized, and smoothed using a Gaussian isotropic kernel with a full-width half-maximum (FWHM) of 8 mm. After high-pass filtering (1128 seconds), movement parameters (six dimensions) from realignment were included as covariates into the model. A flexible factorial design with three factors (subjects, group, and condition) was employed for second-level analysis. No threshold was entered for the creation of the model, and the significance thresholds of the various contrasts are mentioned in the results. Sphericity assumption violations were not assumed. All contrasts were calculated using t-tests.

The dynamic changes during the course of the experiment were explored by contrasting trials with correct responses from the first two sessions of the N − 2 back task with those of the last two sessions of the N − 2 back task across groups. Small volume correction (SVC) was applied to areas known to sub-serve attention and working memory using anatomical maps (anatomy toolbox version 2.2b of SPM8). These areas included the cingulated cortex (including the anterior cingulated cortex), lingual and fusiform gyrus, cuneus and precuneus, superior parietal lobule (SPL), as well as structures of the BG.12 To further investigate effort-independent effects within the patient group in relation to fatigue, we performed multiple regression analyses with the FSMM and FSMM-cognitive domain values as covariates.

Results

Fatigue measures

Correlations. The FSMM score and the scores of its subscales, motor (FSMM-mot) and cognitive (FSMM-cog) fatigue, were highly correlated (FSMM-mot: r = 0.93, p < 0.000; FSMM-cog: r = 0.93, p < 0.000). Similarly, FSMM-mot and FSMM-cog were also correlated (r = 0.673, p < 0.000). Notably, the FSMM
Scoring correlated with the BDI scores ($r = 0.57, p < 0.000$). The FSMC scores and the subjective fatigue (VAS) scores neither correlated with the TAP RTs nor with RTs or HRs in the N-back tasks.

**Behavioral measures**

**TAP alertness.** In the alertness task, the patients responded slower and with greater variance than controls, who reacted with a mean RT of 240.4 ms ($\pm 34.9$ ms) before and 241.6 ms ($\pm 35.4$ ms) following the N-back task in the scanner, while patients performed with a mean RT of 284.2 ms ($\pm 79.8$ ms) before and 312.3 ms ($\pm 80.5$ ms) after the N-back task in the scanner. RTs were analyzed using a 2 x 2 ANOVA with the factors group and time point. The results indicated a main effect of group ($F(1, 60) = 12.731, p = 0.001$) in the absence of an interaction between the factors ($F(1, 60) = 2.662, p = 0.108$). The factor time point, however, showed a trend toward significance ($F(1, 60) = 3.165, p = 0.08$). This trend was analyzed using a repeated-measures ANOVA (rANOVA) with the factors TAP time point (T1 and T2). Results showed a significant increase in RTs in the patient group ($F(1, 39) = 5.53, p < 0.05$), but not in the control group ($F(1, 21) = 0.08, p = 0.78$).

**Fatigue measurements.** A rANOVA with the factors group and time point revealed a main effect for each factor group ($F(1, 60) = 6.54, p = 0.013$); time point ($F(1, 60) = 44, p < 0.000$) and a group by time point interaction ($F(1, 60) = 5.924, p = 0.018$) (see Figure 2).
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**Figure 2.** Mean visual analog scale (VAS) scores of fatigue for patients (in red) and controls (in blue) for the first measurement (VAS begins) and the final measurement (VAS end). Low values indicate high fatigue. A bar indicated are the significant differences in both between and within groups.

* *p < 0.05; **p < 0.005; ***p < 0.001.

The interaction was due to the fact that patients reported significantly greater subjective feelings of fatigue than controls at the end of the experiment ($F(1, 60) = 10.91, p = 0.002$) indicating effort-related fatigue. The groups did not differ in their baseline evaluation of subjective fatigue.

**N-back task performance**

**Accuracy.** In general, patients achieved a mean HR of 0.92 (±0.08) and 0.79 (±0.14) for the $N − 1$ and $N − 2$ task, respectively, while controls achieved a mean HR of 0.96 (±0.02) and 0.87 (±0.11) for the $N − 1$ and $N − 2$ task, respectively. The HRs for each task at the beginning and at the end of the $N$-back tasks are shown in Table 2.

As the HRs for the $N − 1$ task were non-normally distributed, non-parametric tests were used for the analysis. Controls performed with a higher accuracy in the $N − 1$ ($z^2(1) = 10.68, p < 0.01$) and the $N − 2$ task ($z^2(1) = 7.53, p < 0.01$). Both groups exhibited a practice effect in the $N − 2$ task (controls: $Z = 3.322, p < 0.000, n = 22$; patients: $Z = 3.441, p < 0.000, n = 40$), while patients dropped in accuracy in the $N − 1$ task ($Z = -1.984, p < 0.05, n = 40$).

**RT.** The RTs of the patients were on average higher than those of controls (see Table 2). The RT data were normally distributed and were submitted to an ANOVA with the factors group (patients and controls), task ($N − 1$ back and $N − 2$ back), and time point (begin and end). Main effects were observed for the factors group ($F(1, 1) = 42.68, p < 0.001$), task ($F(1, 1) = 68.76, p < 0.001$), and a strong trend for the factor time point ($F(1, 1) = 3.84, p = 0.051$). A significant interaction was found between the factors task and time point ($F(1, 1) = 5.30, p < 0.05$) that was caused by a practice effect in the $N − 2$ task (ANOVA: controls: $F(1, 21) = 13.52, p = 0.001$; patients: $F(1, 39) = 13.77, p = 0.001$). No significant effects were found for the $N − 1$ task RTs.

**Functional MRI**

**Group differences.** To investigate group differences, the hemodynamic activity elicited by the $N − 1$ back and the $N − 2$ back tasks was each contrasted between controls and patients, revealing a decrease in activity within the left fusiform gyrus in the patient group compared to the control group for the $N − 1$ task. However, increased activations for the patient group in the left motor and somatosensory areas, as well as the left supramarginal gyrus were also observed (Figure 3(a)). For the $N − 2$ task, increased activity in patients was also observed in the same motor regions as above, with the addition of increased activity in the right supplementary motor area (SMA), the right supramarginal gyrus and the right insular lobe. Furthermore, reduced activity in the left caudate nucleus was evident for the $N − 2$ task in the patient group (Figure 3(b)).

**Effort-dependent changes of brain activity.** To compare the neural activations at the beginning of the experiment with activations toward the end of the experiment, data from the first two sessions were contrasted versus those from the last two sessions during the more difficult $N − 2$ task since behavioral and hemodynamic differences were more pronounced. This contrast revealed activity decreases in the left anterior insula, bilateral fusiform gyr, left precuneus, left SPL, right SMA, right middle cingulated cortex, right caudate, right pallidum, left putamen, and right angular in the patient group (Figure 4(a)).

**Effort-independent fatigue-related brain activity changes.** Patients’ $N − 2$ data of the first two sessions (in which effort-related changes are if at all rather small) were analyzed using a one sample t-test with covariance of interest of the FSMC-cognition scale scores and revealed activity in the bilateral ACC, the right middle cingulated cortex, and left paracentral lobule to positively correlate with the fatigue scores (Figure 4(b)).
Table 2. Average reaction times (RTs) and standard deviations, as well as median hit ratios (HRs) and range for the first two (begin) and the last two (end) sessions for the N – 1 back and N – 2 back task for controls and patients, as well as results from between group comparisons.

<table>
<thead>
<tr>
<th>Task: N – 1</th>
<th>Patients (N= 40)</th>
<th>Controls (N= 22)</th>
<th>Between group comparison</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction times (ms)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>F(1, 60)</td>
<td>p-Value</td>
</tr>
<tr>
<td>Begin</td>
<td>619.93 (±119.19)</td>
<td>555.18 (±99.84)</td>
<td>8.01</td>
<td>0.006</td>
</tr>
<tr>
<td>End</td>
<td>636.95 (±154.77)</td>
<td>579.51 (±71.84)</td>
<td>18.47</td>
<td>0.000</td>
</tr>
<tr>
<td>Hit ratios (hits/misses)</td>
<td>Median (range)</td>
<td>Median (range)</td>
<td>χ²</td>
<td>p-Value</td>
</tr>
<tr>
<td>Begin</td>
<td>0.97 (0.53-1.0)</td>
<td>1.0 (0.79-1.0)</td>
<td>3.55</td>
<td>0.059</td>
</tr>
<tr>
<td>End</td>
<td>0.97 (0.42-1.0)</td>
<td>1.0 (0.85-1.0)</td>
<td>10.95</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Task: N – 2</th>
<th>Patients (N= 40)</th>
<th>Controls (N= 22)</th>
<th>Between group comparison</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction times (ms)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>F(1, 60)</td>
<td>p-Value</td>
</tr>
<tr>
<td>Begin</td>
<td>786.6 (±117.45)</td>
<td>710.00 (±126.78)</td>
<td>6.17</td>
<td>0.016</td>
</tr>
<tr>
<td>End</td>
<td>720.5 (±131.07)</td>
<td>669.09 (±116.09)</td>
<td>11.09</td>
<td>0.001</td>
</tr>
<tr>
<td>Hit ratios (hits/misses)</td>
<td>Median (range)</td>
<td>Median (range)</td>
<td>χ²</td>
<td>p-Value</td>
</tr>
<tr>
<td>Begin</td>
<td>0.79 (0.22-1.0)</td>
<td>0.86 (0.36-1.0)</td>
<td>3.62</td>
<td>0.057</td>
</tr>
<tr>
<td>End</td>
<td>0.89 (0.38-1.0)</td>
<td>0.95 (0.51-1.0)</td>
<td>4.88</td>
<td>0.027</td>
</tr>
</tbody>
</table>

SD: standard deviation; ANOVA: analysis of variance; RT: reaction time; HR: hit ratio.
*ANOVA was employed for reaction time; Kruskal-Wallis test for hit ratios.

Figure 3. (a) Group differences for the N – 1 task*: greater activations in red/yellow in motor areas and left supramarginal gyrus in patients compared to controls for the N – 1 task, less activation in patients (blue) compared to controls in the left fusiform gyrus. (b) Group differences for the N – 2 task*: greater activations in red/yellow in motor areas and right insula in patients compared to controls for the N – 2 task, less activation in patients (blue) compared to controls in the left caudate nucleus and right middle frontal gyrus (rMFG).

The numbers below the images indicate the axial, coronal, and sagittal coordinates in MNI space, respectively. *Please refer to section "Materials and methods."

Depression and related brain activity. Patients’ N – 2 data of the first two sessions were analyzed as a function of the BDI scores. The areas which showed correlating neural activity much resembled those correlating with fatigue. These were the right precentral gyrus, the left anterior and right middle cingulate cortex, as well as the right frontal gyrus.

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Discussion
This study combined behavioral and fMRI measures to investigate the neural correlates of fatigue in patients with MS and found a generally lower performance level in patients compared to controls, further decreasing in specific tasks as a function of task length in patients but not in controls. In parallel, subjective assessments of fatigue showed a higher self-perceived fatigue increasing with task length in patients compared to controls.

Performing the task in the scanner prolonged the TAP RTs in patients but not in controls, possibly indicating an effort-dependent decrease of patient’s alertness level, however, a significant interaction effect was not observed in the statistical analysis. The behavioral data of the N-back task showed that patients’ RTs were generally slower than those of controls. Controls performed faster and more accurately in the N-1 task, and in the N-2 task both groups improved. There was a difference between patients and controls, in performance and alertness already before performing in the N-back task, presumably reflecting the limited neural resources or cognitive fatigue in MS. Performance differences in patients but not in controls at the end versus beginning of the N-1 task were observed in the N-back task itself and insinuated in the alertness task performed thereafter possibly reflecting fatigue. All other behavioral measures showed a practice effect due to successive measurements. The subjective fatigue (VAS) also increased after the task exclusively in patients. In short, the behavioral data clearly indicate a baseline difference in alertness, an effort-dependent performance change, and increase of subjective fatigue in patients and to a significantly lesser degree in controls.

Consistent with previous studies, the N-back task elicited activity in areas involved in attention and working memory. Activity in motor and somatosensory areas, the right supramarginal gyrus, and right insula, particularly for the more difficult N-2 back task, was higher in patients than in controls. Importantly, the left fusiform gyrus and the left caudate nucleus showed less activity in patients. The activity increase in the motor- and somatosensory-related areas in MS patients likely reflects higher activity requirements for the same motor action (e.g., pressing the response key) due to cortical and white matter damage. The insular cortex is involved in both interoceptive awareness and homeostasis, is proposed to be a key region for sustaining and redirecting attention, and is part of the salience network. The insula is required for verbal working memory, specifically for short-term memory of letters and selective attention. It is a junction point between selective attention and arousal systems and the BG recruited during complex cognitive tasks. The present findings add to the evidence that patients with MS display...
altered patterns of neural activity during tasks placing
mands on information processing, memory, and sstained attention, and provide strong support for the
fatigue model proposed by Chaudhuri and Behan, who propose an involvement of the non-motor func-
tions of the BG in the occurrence of fatigue in MS.

We observed different neural correlates associated
with effort-independent and effort-dependent perfor-
man ce changes. The effort-independent changes were
analyzed in dependence of the fatigue scores (FSM-
cognitive subscale). Only fMRI data from the first
two sessions were included to minimize the influence
of effort-dependent fatigue. High fatigue scores were
associated with higher activity in the ACC (see Figure
4b), a region involved in cognitive functions, includ-
ing error detection, performance monitoring, response
selection, and attention control. It plays a role during
the maintenance of goal-directed behavior, working
memory, and inhibition and acts top-down on subcon-
scious automatic information processing during cognitively challenging conditions involving
conflict. It has previously been proposed that the
ACC might be overactive in patients with cognitive
fatigue and MS. The current results support the
idea of a close relationship between ACC activity and
effort-independent fatigue in MS patients. The right
middle cingulum also showed increased activity with
higher fatigue scores. This area is involved in cog-
nitive control, and its microstructure predicts perfor-
man ce breakdown in several neurodegenerative
diseases. Another region that showed increased
activity with higher fatigue scores was the left para-
central lobule, a region involved in sensory-motor
processing as well as in the regulation of physiologic
functions such as micturition, which are also often
disturbed in MS. Similar regions were, however,
also found to correlate with the depression scores
attained from the BDI. These included the right pre-
central gyrus, the left anterior and right middle cin-
gulate cortex, as well as the right frontal gyrus. Since
effort-independent fatigue and depression share many
symptoms, they might also share some neural corre-
lates, which would be in line with findings in the
literature.

The effort-independent fatigue of MS patients most
likely corresponds to what has been termed the
“trait” or general fatigue component. Extending
previous findings suggesting a striatal-thalamic-fron-
tal cortical system to underlie the trait component of
fatigue, this study adds frontal attention control and
sensory-motor regions to the previously suggested
network, thereby proving strong support to the model
proposed by Chaudhuri and Behan.

The second fatigue-related component refers to the
effort-dependent dynamic change of fatigue in MS
patients, which has been termed “state fatigue” or “fat-
igability.” Consistently, the behavioral data indi-
cated that this component was predominantly present
in MS patients. Its neural correlates were reflected by
activity decreases in the right SMA, the left anterior
insula, the bilateral fusiform gyrri, left precentral, left
SPL, right middle cingular cortex, right caudate
nucleus, pallidum, putamen, and amygdala observed
particularly in the more challenging N-2 back task-
condition. The anterior insula and the cingulum are
part of the salience network that plays an important
role in task-level control and focal attention, which
are core components of the task of this study. The pari-
etal areas and the fusiform gyri are all heavily involved
in visual attention and working memory. The pallidum
and the putamen are also involved in attentional
orienting, while the amygdala was shown to influ-
ence attention. In sum, the subjective increase of
fatigue, paralleled by the RT increase in the alertness
task, was associated with a drop of hemodynamic
activity in attention-related networks in MS patients
suggesting that dynamic reductions of activity in sali-
ence and attention-related networks underlie the state
or fatigability component of fatigue in MS.

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C.D. and M.A.S. equally contributed to the
manuscript.

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References
dysfunction in multiple sclerosis. I. Frequency,
patterns, and prediction. Neurology 1991; 41:
685–691.
of fatigue on patients with multiple sclerosis. Can J
fatigue severity scale: Application to patients with
Appendices
Appendices

Additional publications, oral presentations and currently running projects in which the author was and is involved:

Publications:


Oral presentations and workshops:

Presentation GNP Tagung September 2017 – Konstanz
Neurale Korrelate dynamischer und statischer Fatigue bei Patienten mit Multipler Sklerose

Poster-presentation IMSCOGS June 2017 - Düsseldorf
Neural correlates of effort-dependent and independent fatigue components in patients with multiple sclerosis

Presentation November 2015 - Delmenhorst
Neural correlates of „trait“ and „state“ Fatigue in patients with multiple sclerosis - an fMRI study

Presentation August 2014
Neural correlates of dynamic processes in patients with multiple sclerosis and fatigue - an investigation via functional MRI

Presentation in-house 2013 · Konstanz

Workshop (20) DGKNK 2014 - Singen
Anwendungspotentiale und Beispiele der funktionellen Kernspintomographie für die Neurorehabilitation
**Current projects:**

(please note, as these projects are still in the process of development, a specific title has in most cases not yet been chosen)

EEG/ERPs recordings elicited by an N400 paradigm in unresponsive wakeful state, minimally conscious, coma or locked-in patients (patients in appalic state).
(32 channel EEG)

*Collaboration with the Department of Neurolinguistics at the University of Konstanz.*

Balance training induces task specific neuronal plasticity
(Functional and structural MRI measures)

*Collaboration with the Sensorimotor Performance Lab at the University of Konstanz*

Therapeutic study investigating the effects of rigorous training on the neural correlates of stroke patients using the ARMEO training device.
(Functional and structural MRI measures)

*Collaboration with the research group of Prof. J. Liepert, Lurija Institute Allensbach*

Studies investigating the neural correlates of emotional processing and cognitive control in patient with dissociative disorder (German: Konversionsstörung).
(Functional and structural MRI measures; EEG measures using “active” electrodes)

*Collaboration with the research group of Prof. R. Schmidt, Lurija Institute Allensbach/Konstanz*