Lateralization of visuospatial attention

Ph.D. Thesis

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Original publications related to the thesis

I. **Krisztián Kocsis**, Gergő Csete, Zsombor Erdei, András Király, Nikoletta Szabó, László Vécsei, Zsigmond Tamás Kincses. Lateralization of the white matter microstructure associated with the hemispheric spatial attention dominance. PLoS One. 2019 Apr 26;14(4): e0216032. doi: 10.1371/journal.pone.0216032. PMID: 31026280; PMCID: PMC6485922.
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I. András Király, Nikoletta Szabó, Eszter Tóth, Gergő Csete, Péter Faragó, **Krisztián Kocsis**, Anita Must, László Vécsei, Zsigmond Tamás Kincses. Male brain ages faster: the age and gender dependence of subcortical volumes. (2016) Brain Imaging and Behavior, 10 (3) e901-e910; doi: 10.1007/s11682-015-9468-3
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Abbreviations

BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BVMT	Brief Visuospatial Memory Test
CVLT	California Verbal Learning Test
EDSS	Expanded Disability Status Scale
FA	Fractional Anisotropy
FAST	FMRIB's Automated Segmentation Tool
FDT	FMRIB's Diffusion Toolbox
FLIRT	FMRIB's Linear Image Registration Tool
FNIRT	FMRIB's Non-linear Image Registration Tool
FSL	FMRIB's Software Library
FWE	Family-Wise Error correction
GLM	General Linear Model
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SDMT	Symbol Digit Modalities Test
TBSS	Tract-Based Spatial Statistics
TFCE	Threshold-Free Cluster Enhancement
VBM	Voxel-Based Morphometry

Summary

Background: Lateralization of visuospatial attention, referred as pseudoneglect manifests as a mostly leftward attentional bias in healthy people, and is established by the lateralized activation of attentional network. Due MS, the forming lesions in white matter and the atrophy affecting the gray matter alters patient's cognitive ability.

Objectives: In this thesis, we aim to demonstrate how invariant the visuospatial attention in healthy people is, and how the brain laterization on microstructural level contributes to the behavioral manifestation. Furthermore, we set out to reveal how visuospatial attention differs in MS patients, and what structural brain alterations can be identified in association with the behavior.

Methods: In Study 1, tract-based spatial statistics was used to investigate how lateralization of white matter microstructure, characterized by fractional anisotropy, associated with visuospatial attentional bias in 20 healthy controls. Structural connectivity of white matter tracts associated with the extent and lateralization of visuospatial attentional bias was also investigated. In addition, healthy subjects performed Landmark task on three consecutive days in order to measure the reproducibility of pseudoneglect. In Study 2, Fierro scores of 35 multiple sclerosis patients and 20 healthy controls were compared. Using voxel-based morphometry and lesion-symptom mapping, we aimed to identify the structural background of the altered attentional bias in MS patients. Association between visuospatial attention and clinical or cognitive scores of MS patients were also analyzed.

Results: In Study 1, the integrity of white matter microstructure in parietal lobe significantly correlated ($p<0.05$) with the visuospatial attentional bias in healthy controls. The more the parietal white matter was integrated in one hemisphere, the more lateralized and extended the visuospatial attention to the contralateral side was. The significant parietal clusters showed connectivity towards the dorsal and ventral nodes of the attentional network. Furthermore, our results revealed good-excellent reproducibility of the attentional bias in healthy patients (ICC=0.74). In our second study, we found that the variability of visuospatial attention differed in MS patients compared to healthy controls ($F(34,25)=2.18$, $p=0.04$). Our lesion-symptom mapping analysis showed that lesion probability in the superior longitudinal fascicle in the left hemisphere is associated with the

leftward shift of visuospatial attention ($p<0.05$). There was no significant correlation between gray matter atrophy nor the clinical as well as cognitive scores and the visuospatial attentional bias.

Conclusions: Our work revealed that visuospatial attentional bias in healthy people is highly consistent over time. Due this consistency we hypothesed that the microstructural correlates of visuospatial attention can be identified. The positive correlation found in the parietal white matter between the individual bias and the microstructural integrity supported our hypothesis. In our second study we set up to reveal whether visuospatial attentional bias alters due the damaged white matter integrity in MS patients. We found that the variability of attentional bias is higher in MS patients compared to healthy controls, and this increased variability is associated with the presence of lesions located in the superior longitudinal fascicle. Our results might be substantial in order to understand how visuospatial attention functions, and how alterations in healthy brain structure and lateralization affect visuospatial attention.

Introduction

Laterality of human brain

Structural and functional brain lateralization is a well-known principle of human brain that enables effective parallel and complementary information processing (Duboc et al., 2015; Gunturkun and Ocklenburg, 2017), even though the left-right lateralization of the brain is not only peculiar to humans but also prominently present in different animal species from nematodes to vertebrates (Corballis, 2019; Gunturkun and Ocklenburg, 2017). Several genetic, environmental and epigenetic factors contribute to forming hemispheric asymmetry. In a genom-wide association study McManus and colleagues identified over forty gene loci that are associated in determining handedness (McManus et al., 2013). From epigenetic perspective, hemispherical differences in methylation of DNA might be accountable for hemispheric asymmetry, also during the disease course of Parkinson disease, alteration in methylation pattern contributes to changing in hemispheric lateralization (Li et al., 2020). Even though the exact cohesive mechanisms resulting brain lateralization are still unexplained, since Broca and Wernicke's revelation, investigating structural and functional brain lateralization became a subject of spacious research (Broca, 1865; C, 1874). Left sided brain damage affecting Broca's area leads to impaired language production, whilst lesioned Wernicke's area in the left temporo-parietal regions is associated with inability to comprehend written or spoken language (Heilman and Scholes, 1976; Mohr et al., 1978). But how lateralized brain circuits could evolve from a basically symmetric structural system? The Bilateria, involving humans as well are symmetrized about the midsagittal plane. The asymmetric arrangement of internal organs might lead by efficiency, but from functional point of view, the effect of functions remain symmetric. As the human brain evolved in complexity and size, asymmetric arrangement of functions became necessary in order to preserve and improve efficacy in a limited space. Because of bipedalism, specialization of the two hands began to differ and in the course of time, the complexity of manual skills and fine cooperation between the two hands could be achieved using asymmetrical settings rather than duplicated between the two hemispheres. Nevertheless, functionally shifting from symmetric to asymmetric coding, reduced redundancy and duplication, thus improved capability and complexity could be developed (Corballis, 2017). Based on these principles, we could assume, that in order to achieve higher efficacy, different functions, e.g., handedness and language, get lateralized in association with each other. In other words, to avoid higher load of one hemisphere, lateralization of different functions does not

interfere. Still, the cerebral asymmetry of handedness, language or attention poorly correlates suggesting the multifactorial background of lateralization. Based on Corballis work, new lateralized circuits could evolve from the already existing symmetrical arrangement through expansion and separation, through the fusion of modified circuits into a new function, or if an already existing circuit get copied and differential modified (Corballis, 2017). Lateralization of handedness and language illustrates prominently how lateralized brain functions are determined on functional (Lehericy et al., 2000; Ziemann and Hallett, 2001) and structural level (Dorsaint-Pierre et al., 2006; Sun et al., 2012), however the right hemisphere dominant attentional functions in human brain also became increasingly acquainted.

Visuospatial attention

Attention could be defined as a process that enables us percept different sensory stimuli more emphasized whilst other stimuli got suppressed in order to select relevant information (Karnath, 2015). Our capacity to receive and process different sensory information is limited, thus attention is crucial in how and what we perceive from the encompassing world (Gaillard and Ben Hamed, 2020). The attentional selection applies to all sensory modalities, furthermore we can distinguish its spatial and temporal components. The spatial domain of attention enhances the representation of stimuli at the determined location, whilst selective temporal attention operates on analogue manner to spatial attention just in the temporal domain. As a result of concurrent spatial and temporal attention domain, the perceptual noise and reaction time reduces, whilst the discriminability of the attended stimuli will be enhanced (Correa et al., 2006; Ruffino et al., 2014; Seibold et al., 2020).

Albeit, our attention selects the incoming information permanently, its capacity is finite. Grimes in an image manipulation study showed that the large percentage of participants were not able to detect large-scale changes in a scene presented on photographs (Akins, 1996). This phenomenon called change blindness, that also observable using auditory stimuli (Simons and Rensink, 2005; Vitevitch, 2003). Change blindness might be the consequence of information selection, thus we attend to stimuli that are perceived important whilst changes in marginal stimuli won't be processed. Also in temporal domain, the capacity of our attention is restrained. If two stimuli in a close time-range presented, mostly the perception or identification of the second stimulus is impaired. This phenomenon called attentional blink. However, increment of the inter-

target-intervals restitutes the identification deficit (Snir and Yeshurun, 2017; Willems and Martens, 2016). Next to the finite capacity of selective attention (differentiating and enhancing relevant stimuli from irrelevant information set), performing two or more parallel information-processing task presents difficulty as well. In this case, we divide our attention and allocate our attentional resources by either splitting it or rapidly shifting our attentional focus between the tasks. It should be noted that losing details of the incoming stimuli can't be avoided in case of divided attention (Hahn et al., 2008).

Interestingly, in order to allocate our attentional focus to a predefined part of space, we do not need to move our gaze necessarily. This phenomenon is called covert attention. As against overt attention, where our gaze points towards a predefined location in order to enhance processing of stimuli perceived or expected from it, covert attention operates with inhibition of saccadic eye movements. The efficacy of covert attention was proved by Posner and colleagues using a paradigm in which a cue appears before target stimulus presentation. The cue indicates where the subsequent target will be located spatially. During cueing, participants must fixate a central fixation point. The subsequent target appears in a location either accordingly or not to the cue. Posner and colleagues showed that the reaction time decreased in a condition in which the cue and target location were congruous, whilst in the inverse condition, reaction time increased (Findlay, 2003; Posner MI, 1980). We can distinguish exogen and endogen visuospatial covert attention. Exogen covert attention is involuntary and stimulus-driven (also called bottom-up) that enables us to shift our attention towards external events (salient stimuli) located outside our gaze, and is transiently deployed within 100 ms, approximately. Contrarily, endogen covert attention is a voluntary, goal-driven process (also called top-down), sustained with the peak efficacy around 300 ms. Endogen covert visuospatial attention enables us to willfully screen information in a predefined location without moving our gaze towards it. We use our covert spatial attention every day (e.g.: driving, crossing the street, etc.), in order to monitor our peripheral visual field selectively. Covert visuospatial attention conducive to enhancing the spatial resolution of the attended location, the contrast sensitivity, the speed of information accrual and grouping also (Anton-Erxleben and Carrasco, 2013; Carrasco, 2011). However, the underlying exact mechanisms that determine our visuospatial attention are more complex.

More than thirty years ago, Posner and colleagues divided the attention system into three networks, each responsible for different aspects of attentional processes. The three networks

included the alerting, orienting and executive network (Petersen and Posner, 2012). Alerting can be defined as a process that arouse and maintain attention to incoming stimuli involving the ascending reticular activating systems' noradrenergic projections towards the frontal and parietal cortices. We can distinguish tonic and phasic alerting. Tonic alerting is the baseline, resting-state arousal, showing circadian rhythm, whilst phasic alerting is referred as preparation for detection and responding to an expected stimulus if it is preceded by a warning clue. Thus, phasic alerting, through altering the tonic state, facilitates the response to the expected stimulus, as reduces the time of attentional orientation. The phasic alerting functional loop involving projections from locus coeruleus, superior colliculi via thalamus and amygdala to the anterior cingulate cortex and anterior insula is involved in face and subliminal fear stimuli recognition, as well as in emotion processing. Phasic alerting mechanisms show a strong left hemisphere dominance, whilst tonic alerting shows explicit right hemisphere involvement (Bast et al., 2018; Petersen and Posner, 2012).

Orienting can be defined as a process that selects sensory inputs and facilitates reaction to a target stimulus appearing in a predefined spatial location. Two main factors are distinguished as contributors to the selection process. The endogen, top-down factors (goal-directed, voluntary) are related to personal intentions and aims, whilst the exogen, bottom-up factor (stimulus-driven, involuntary) are related to external salience stimulus detection without intention of orienting attention towards an object or location. The synergy of these two factors, or rather the underlying networks determine the extent and lateralization of visuospatial bias (Chica et al., 2013). Likewise, the orienting network, also called fronto-parietal attention network, is subdivided into two subnetworks, namely the dorsal (top-down, endogen) and ventral (bottom-up, exogen) fronto-parietal network. Notably, top-down visuospatial attention can be measured using line-bisection or the Landmark-task (Cavezian et al., 2012). In the Landmark-task, horizontal lines, that were previously bisected at the midpoint with a vertical line, are presented for the participants. Participants are asked to judge, whether the left or right segment of the bisected line is longer (or shorter, depending on the given task instructions during the experiment) (Milner et al., 1993). Contrarily, during line-bisection task, participants are asked to bisect manually the presented lines. It must be noted that the two tasks eventuate different activation patterns in the fronto-parietal network due the necessity of premotor (line-bisection) and perceptual components (Landmark-task) required to perform the tasks, respectively (Harvey et al., 2002). Functional MR imaging and event related potential studies identified the underlying brain regions contributing to the top-down

and bottom-up attentional control. The dorsal attention network includes the bilateral medial intraparietal sulcus (IPS), superior parietal lobe (SPL), as well as the supplementary and frontal eye field (SEF and FEF, respectively). The ventral attention network includes the temporo-parietal junction (TPJ) (inferior parietal lobule and superior temporal gyrus) and the ventral frontal cortex (VFC) (inferior frontal gyrus (IFG) and middle frontal gyrus (MFG)) and is typically lateralized to the right hemisphere (Corbetta and Shulman, 2002; Macaluso and Doricchi, 2013; Petersen and Posner, 2012; Shulman et al., 2010). The dorsal network generates top-down endogen signals and forwards them to the visual areas and the ventral network (in order to avoid distracting salience stimuli). Thus, the activation of the ventral network restrains to the previously determined, relevant stimuli. Contrarily, the ventral network is responsible to detect salience stimuli, and forwards signals to the dorsal network, thus the endogen attention will be oriented towards the new, salience stimuli (Bast et al., 2018; Corbetta et al., 2008).

The third network, executive control is engaged in conflict resolving, establishing focal attention that allows us to maintain our attentional focus on the detected target, whilst slowing down the detection of other stimuli. The neural basis of executive control involves the medial frontal and anterior cingulate cortices (Petersen and Posner, 2012; Posner, 2008).

The distribution of visuospatial attentional functions (as determined by the dorsal and ventral fronto parietal network) between the two hemispheres shows disproportion both in healthy controls and patients. Well known, that visuospatial attention shows right hemisphere dominance, leading to asymmetrical visuospatial attention. Albeit the exact mechanism explaining how asymmetry in visuospatial attention forms, is not known. There are more hypothesis that account for the lateralized visuospatial attentional bias. According to the hemispatial theory, the right hemisphere directs attention towards both visual hemifield, whereas the left hemisphere deals with the right hemifield only. This hypothesis was based on the symptoms of left hemineglect patients as well as the right hemifield selectivity of the left hemisphere was also proved (Corbetta et al., 1993; Heilman and Valenstein, 1979; Mesulam, 1981, 1999). Another theory states, that both hemispheres are engaged in the direction of the visuospatial attention towards the contralateral visual hemifield, but the left visual hemifield is more preferred. Following stimulus presentation in left visual hemifield, more synchronized activation in bilateral FEF, dorsolateral prefrontal cortex and IPS was shown, compared to the inverse condition (Siman-Tov et al., 2007). The third theory, the so-called interhemispheric competition theory, states, that the lateralization of the

visuospatial attentional bias is determined by interhemispheric interactions. Namely, each hemisphere directs visuospatial attention towards the contralateral visual hemifield, but via reciprocal inhibition, the extent and lateralization of visuospatial bias is determined by the activity pattern of the two hemispheres (Kinsbourne, 1970).

Neglect syndrome

The visuospatial attentional bias is determined by the dorsal and ventral fronto-parietal networks, the former showing bilateral, whilst the latter showing right hemisphere dominance. In severe cases, for example after right parietal cortex damage due ischemic stroke, patients with neglect syndrome show no ability to detect or respond to stimuli in the contralesional visual hemifield (Fruhmann-Berger and Karnath, 2005). Due neglect syndrome, patients show heterogeneous symptoms including maladaptive spatially asymmetric movements of the head and eyes, pointing towards the side of their lesion. They are also unable to respond, detect or orient towards stimuli presented in the contralesional hemifield. In addition, after performing a memory task, neglect patients fail to recall details presented also in the contralesional hemifield (Barrett and Houston, 2019; Umarova, 2017). Lesion-symptom mapping studies revealed that damage of the right temporo-parietal junction, superior temporal cortex, inferior parietal lobule, insula, also damages in white matter tracts connecting the parietal and frontal regions involving the superior longitudinal fascicle and inferior occipital-frontal fasciculus is accountable for hemineglect (Karnath et al., 2009; Verdon et al., 2010). Neglect like syndromes can be induced in healthy people as well by temporarily disrupting the right posterior parietal cortex using transcranial magnetic stimulation (Fierro et al., 2001). But which of the two orienting network and how exactly they contribute to visuospatial impairment in neglect patients? Corbetta and Shulman argued that the anatomy of neglect better matches with the ventral stimulus driven network, including the temporo-parietal junction and ventral frontal cortex. They reasoned that those lesions leading to neglect are located more ventrally, affecting the temporo-parietal junction. Also in frontal lobe, lesions that are associated with neglect syndrome were in the right ventral prefrontal and opercular cortices, rather than in the FEF. Second, neglect syndrome occurs more frequent after right hemisphere damage, and the ventral network shows more prominent rightward lateralization than the dorsal network. They also reasoned, that in neglect syndrome, the goal-directed orienting is more preserved that the stimulus-driven attentional orienting (Corbetta and Shulman, 2002). In

neglect syndrome, egocentric and allocentric attentional impairments can be distinguished. Egocentric neglect refers to the inability to detect or respond stimuli in contralesional hemifield (viewer-centered, repartition occurs along the observers' midline), whilst allocentric neglect refers to the inability to detect the contralesional side of any object, regardless of the object's position to the viewer (object and stimulus centered) (Leyland et al., 2017). Corbetta and Shulman in another work deducted, that spatial neglect is characterized by a spatial gradient of impaired attention within the egocentric reference frame, and that the irresponsiveness to salient stimuli occurs due the shift in egocentric reference matrix, that is determined via several proprioceptive signals, derived from for example the position of the eyes, neck, vestibular system. They also deducted, that neglect syndrome is determined by the impaired interactions between the dorsal and ventral frontoparietal networks (Corbetta and Shulman, 2011; Karnath, 2015).

Pseudoneglect

In neurological intact adults, there is a weak lateralization of visuospatial attention, known as pseudoneglect, which refers to a mostly leftward visuospatial attentional bias, measured with the line-bisection, or Landmark-task (Heilman and Scholes, 1976). This subtle visuospatial bias mostly towards the left visual hemifield could be defined, as a slight underestimation of a right end of a symmetric line, thus the attentional focus shifts leftward (Bellgrove et al., 2008; Fierro et al., 2001). Functional MRI studies showed, that during the performance of the Landmark-task, increased activation in the right intraparietal sulcus, lateral peristriate cortex, anterior cingulate and posterior parietal cortices can be seen. Interestingly, during line-bisection task, the frontal eye field showed increased task-related activation (Cicek et al., 2009; Fink et al., 2000). For these task-related differences in activation patterns the perceptual (measured with Landmark-task) and premotor components (measured with line-bisection task) of visuospatial attention are responsible (Harvey et al., 2002). Szczepanski and colleagues showed that the fronto-parietal areas in both hemispheres generate and determine the overall visuospatial bias towards the contralateral visual hemifield, supporting Kinsbourne's interhemispheric competition theory (Szczepanski and Kastner, 2013; Szczepanski et al., 2010). These former and also other studies revealed that healthy people not just tend to err leftward, but also rightward or even no visuospatial attentional bias can be measured (Friedrich et al., 2018). With aging, a subtle shift from no bias to leftward bias in the

line-bisection task, whilst no effect of aging on the performance of Landmark-task was revealed (Learmonth and Papadatou-Pastou, 2021).

Multiple sclerosis

Multiple sclerosis (MS) is a progressive autoimmune disease in the central nervous system affecting young adults leading to demyelination and axonal loss (Kincses et al., 2019). Typically, numerous glia scars in different locations of the central nervous system develop, thus the multiple sclerosis denomination. MS affects mostly young adults decreasing the quality of life of the patients. Despite the constant improvements of disease modifying therapies, the etiology of MS remains pending. Currently, more than two million people suffer in MS, and still the world-wide incidence of MS is rising. Furthermore, MS shows a north-south gradient with higher prevalence in north countries (Grant and Mascitelli, 2012; Walton et al., 2020). In Hungary, the male: female ratio is 1:3, and the standardized prevalence of MS is 101.8/100.000 (Biernacki et al., 2020).

Albeit the exact patomechanism leading to MS is still unexplained, several environmental and genetic risk factors were already identified contributing to the immune dysregulation. Large percentage of MS patient are Epstein-Barr virus seropositive leading to increased number reactive T-cells. Smoking was shown to be associated with elevated disease progression and with higher risk of conversion between the clinical forms of MS. Exposure to ultraviolet-B radiation, thus mediately the level of vitamin D is also determined as a risk factor. Genetic polymorphisms of human leukocyte antigen, interleukin and tumor necrosis factor genes contribute to MS patomechanism as well (Ascherio, 2013; Browne et al., 2014; Massimo Filippi, 2018).

Autoimmune processes in MS involves CD4+ myeline reactive T- and B-cells mediated autoimmune reaction against the central nervous system's antigens. Persistent autoreactive T-cell activation on the periphery, induced by viral or bacterial infections, is followed by increased production of proinflammatory cytokines by T-helper cell, that is resulted in the damage of the blood-brain barrier. T-helper cells pass into the central nervous system, leading to inflammation, immune cell proliferation as well as micro- and macrophage activation. These processes result in the impairment of the myelin sheet and axonal injury (Garg and Smith, 2015).

Regarding the clinical manifestation of MS, four main clinical courses, namely the clinically isolated syndrome (CIS), relapsing-remitting (RRMS), secondary and primary progressive (SPMS and PPMS, respectively) MS can be distinguished. In CIS, a one-off

inflammatory episode occurs with demyelination and with symptoms peculiar to MS. However, symptoms cease in days or weeks (Allen et al., 2020). In PPMS clinical form, symptoms severity continually deteriorates, patients occasionally experience a plateau phase or the amelioration of the symptoms (Miller and Leary, 2007). More than 80% of MS patients suffer in the RRMS clinical form. During RRMS disease course, relapses (reversible episodes with neurological symptoms) and remitting (with stable clinical state without neurological symptoms) periods intermit. Relapses, involving symptoms like weakness, altered sensation or vertigo, occur due to perivascular lymphocyte infiltration and the consequent demyelination and axonal injury. The relapse periods sustain more than 24 hours, that for example can be provoked by infections, following by remitting phase in which remyelination occur. Despite remission, in numerous cases patients experience residual symptoms, leading to gradually worsening clinical state over time. Conversion from RRMS to SPMS clinical form occur in up to thirty percent of RRMS patients. In the SPMS clinical form, active phases (progressive-unprogressive) and inactive phases (progressive-unprogressive) vary leading to neurodegeneration and axonal damage, as well as increment of lesion volume and atrophy due persistent inflammation and mitochondrial dysfunction (Klineova and Lublin, 2018).

Disseminating neurological symptoms in time and space vary during the disease course. To determine and follow-up the severity of clinical symptoms, the Expanded Disability Status Scale (EDSS) is used (Kurtzke, 1983). EDSS point range from 0 to 10 points. 0 point means symptom free clinical state, whilst 10 point refers to deceasing due MS. From 1 to 4.5 EDSS points, patients' walking ability is preserved, whilst walking impairment is present from 5 EDSS point and above. EDSS scores characterize the severity of pyramidal, cerebellar, brain stem, sensory, the bowel and bladder, visual and cerebral functions' impairment (Fuvesi, 2019). In order to control the worsening clinical state of MS patients' due relapses or conversion to progressive clinical forms, disease modifying, or symptom therapies are used. Disease modifying therapies involve medication with immunosuppressive or immune modulatory effect. The appropriate medication must be carefully chosen based on the patient's relapse rate, present of novum findings on MR scans, etc.

In order to diagnose MS, dissemination of symptoms in time and space must be proved based on clinical or paraclinical evidences. Such paraclinical examinations are the MRI, CSF examination and electrophysiological studies. Liquor immunology aims to reveal the presence of oligoclonal gammopathy using electrophoresis and immunoblot techniques. Measuring visual or

somatosensory evoked potential, deceleration of the nerve conduction velocity due demyelination can be detected (Dobson and Giovannoni, 2019; Kiiski et al., 2016). Furthermore, MR imaging plays a crucial role in establishing the diagnosis (confirming the dissemination in time and space, that is currently based on the revised McDonald criteria (Thompson et al., 2018)), and in follow-up of MS. During the disease course, T2 hyperintense white matter lesions evolve in various location, most frequently in the periventricular and juxtacortical white matter, in the corpus callosum (these lesions form the so-called Dawson fingers), as well as in the infratentorial region and spinal cord. Some of the T2 hyperintense lesions are also depicted on the T1 weighted images as hypointensities. These permanent black holes are thought to represent severe tissue damage and axonal degeneration. Due the damaged blood-brain barrier, contrast enhancing lesions (with the duration up to 8 weeks) can be distinguished from inactive lesions on T1-weighted images (Filippi and Agosta, 2010). Next to the white matter lesions, atrophy of the gray matter also evolves from the early stages of the disease. It was shown that the atrophy rate in MS patients is higher than in controls and is associated with the clinical state (Andravizou et al., 2019). From clinical aspects, using the T1- and T2-weighted images, as earliest as possible detection of white matter lesions and atrophy is the main purpose (Filippi et al., 2019; Hemond and Bakshi, 2018; Miller et al., 2002).

Relation of brain pathology to cognitive impairment in MS patients

Next to the clinical symptoms, up to 70% of patients develop various degree of cognitive dysfunction during disease span, thus the quality of life of the patients decreases (Daniel et al., 2017). Cognitive impairment affects most frequently the information processing speed, verbal and working memory, attention and executive functions as well (Giorgio and De Stefano, 2010). Cognitive impairment also presents from the early stage of disease course in all clinical forms (Filippi et al., 2010). MR imaging is the cornerstone of the diagnosis and follow-up in MS. Conventional (T2- and T1-weighted images) and advanced (diffusion tensor imaging, voxel-based morphometry, etc.) imaging and analysis techniques allow physicians to detect already subtle brain pathologies in MS involving white matter (lesions in various locations, normal appearing white matter) and gray matter (cortical, subcortical) alterations. More and more evidence from MS related studies showed that gray matter atrophy progressively develops during the disease course and notably contributes to clinical disability and cognitive dysfunction (Kincses et al., 2014). Albeit a plethora of studies investigated the relation of gray matter atrophy and cognitive

impairment, only a few examined alterations in visuospatial attention and the underlying brain pathology in MS patients (Gilad et al., 2006; Graff-Radford and Rizzo, 1987). Gray matter atrophy was shown to be better associated with clinical disability and cognitive impairment than white matter pathology (Sanfilipo et al., 2006). In addition, numerous studies revealed that cortical and subcortical (thalamus, putamen, caudate nucleus, hippocampus) atrophy contributes to the cognitive impairment (Nasios et al., 2020; Paul, 2016), as well as to clinical disability, notably (van Munster et al., 2015). While the key characteristic of MS is the presence of T2 hyperintense white matter lesions, its association with the severity of clinical symptoms is often sparse, that is called the clinico-radiological paradox (Barkhof, 2002; Kincses et al., 2011). Numerous studies investigated and showed association between lesion location and clinical state as well as with the impairment of different cognitive domains in MS patients with varying clinical forms. Albeit the rate of the association varies across studies, in the background of cognitive impairment, structural and functional damage of cognitive related networks was shown, also the individual differences in the level of impairment shows variability due the cortical reorganization and neural plasticity (Altermatt et al., 2018; Charil et al., 2003; Reuter et al., 2011; Rossi et al., 2012; Sepulcre et al., 2009b; Vellinga et al., 2009). For example, lesion probability in the periventricular white matter and forceps major was associated with the clinical disability and inversely with the information processing speed in MS patients, respectively (Charil et al., 2003; Rossi et al., 2012).

Connecting function to structure: the role of advanced MRI techniques

It is well known that function is tightly interconnected with the anatomical structure, and behavioral performance is strongly associated with the properties of the underlying brain structure. Neuroscientist and physicians are concerned long to connect functions to structure in healthy and to understand how structural alteration, should it be brain damages due various reasons or adaptive plasticity, affect functions vice versa. Continuous advancement of MR imaging techniques and thriving possibilities of methodology used in image analysis enabled researchers to understand in more details how structure and function is related. While a plenty of neuroimaging techniques and tools are available, in the subsequent paragraphs, short methodical description of neuroimaging techniques related to this thesis only will be delineated.

The microstructural integrity of white matter as defined by diffusion tensor imaging can reveal the coupling of structure and function. Diffusion-weighted imaging depict the diffusion

pattern of water molecules in the brain. Because the diffusion of water molecules is hindered along membranes and axonal fibers, using diffusion-weighted images, the organization and integrity of the white matter tracts in-vivo can be characterized. If water molecules can diffuse freely, the shape of diffusion is spherical, that is called isotropic diffusion. In all direction, one diffusion constant is sufficient to characterize the diffusion pattern. If the diffusion is hindered by membranes and axonal fibers, the diffusion becomes ellipsoid, that is called anisotropic diffusion. Anisotropic diffusion can be characterized using diffusion tensor field derived from diffusion-weighted images. In order to characterize anisotropic diffusion, three diffusion tensors, namely the axial, radial and perpendicular, are used. Diffusion tensors (also called eigenvectors) measures the extent (also called eigenvalues, representing the magnitude of diffusion) of diffusion in all directions in the three-dimensions and are perpendicular to each other. Axial diffusivity (λ1) is the longest tensor, representing the least hindered diffusion. Radial (λ2) and perpendicular tensors (λ3) are shorter and by averaging them, radial diffusivity can be calculated. Mean diffusivity (that is the average of λ1, λ2 and λ3) describes the molecular diffusion rate. In order to characterize the integrity of white matter, fractional anisotropy can be calculated, that is the normalized fraction of the three tensors' magnitude, as follows:

$$FA = \sqrt{\frac{3\sum_{i=1}^{3}(\lambda_i - \overline{\lambda})^2}{2\sum_{i=1}^{3}\lambda_i^2}}$$

Fractional anisotropy ranges from 0 (completely isotropic diffusion) to 1 (completely anisotropic diffusion). Fractional anisotropy is very low in the gray matter, whilst much higher in the white matter. Using the diffusions tensors, the main direction of diffusion can be determined in each voxel, referring to the main fiber direction. Connecting the main diffusion directions in each voxel, white matter tracts can be depicted. As a first step during tractography, either in a region-of-interest or in a whole brain, seeds must be appointed from which the fiber bundles will be drawn. During propagation, white matter fiber tracts are generated, either on deterministic or probabilistic manner. During probabilistic tractography, a probability map is created representing the uncertainty of diffusion direction in each voxel due crossing fibers or lower signal-to-noise ratio. Lastly, termination criteria must be determined in order to avoid propagation of fibers through voxels not

inhering to the white matter tracts. That is usually achieved by thresholding the fractional anisotropy at a determined minimum value or thresholding the turning angle (Qiu et al., 2015; Soares et al., 2013).

In order to reveal the association between function and gray matter morphology in both healthy and patients with different neurological diseases, whole brain voxel-based morphometry is frequently used. Contrary to region-of-interest studies, whole brain morphometric analyses allow researchers to characterize and compare gray matter content voxel-by-voxel between controls and patients using the statistical approach of parametric mapping. Firstly, segmentation of the brain is carried out into three tissue components (white and gray matter, cerebrospinal fluid) based on their intensity profile and spatial neighborhood information. This is followed by spatial normalization of individual partial volume effect images into standard space, thus individual images become comparable directly. Lastly, smoothing the standard space images results the normal distribution of the data and reduced interindividual variability. Hereby, voxel-wise non-parametric or parametric permutational statistical testing can be carried out with the proper correction methods in order to reveal group level association or differences between behavior and gray matter morphology or pathology (Beaton, 2018; Dickie et al., 2015; Shi et al., 2014).

From the cognitive aspects of neuroscience, lesion-behavior mapping studies have broadened our knowledge enormously about the contribution of different brain regions to human cognition and function. Albeit lesion-symptom mapping is more of a computational approach, since the initiative studies, the underlying methodical approaches have improved drastically. Novel computational and statistical approaches include Bayesian statistics, graph theory, multivariate decoding techniques as well as perfusion and metabolic mapping (Achilles et al., 2017; Jha et al., 2020; Yuan et al., 2017; Zhang et al., 2014).

Objectives

Our aim was to identify novel structural MRI markers of visuospatial attention in healthy and MS patients. In Study 1, we hypothesized that the lateralization of white matter microstructural integrity is associated with the lateralization of visuospatial bias in healthy controls. In addition, we aimed to demonstrate that visuospatial attention measured by Landmark task, is a reliable and reproducible phenomenon on individual level. In Study 2, we aimed to explore whether the

visuospatial attentional bias differs between MS patients and healthy controls and identify structural MRI markers responsible for the behavioral alterations.

Methods

Participants

In Study 1, twenty healthy subjects were recruited (mean age ± SD = 25.85±2.94 years). All healthy subjects were right-handed as measured by the Edinburgh Handedness Inventory (mean score ± SD = 9.21±2.08). None of the subjects suffered from any neurological or psychiatric diseases. All of them had normal or corrected-to-normal (20/20) visual acuity. The study was approved by the ethical committee of the University of Szeged (Reference number: 87/2009), and all the subjects gave their written informed consent prior the participation according to the Declaration of Helsinki.

In Study 2, 35 RRMS patients were enrolled. All patients were treated as outpatients at the Multiple Sclerosis Outpatient Clinic at the Department of Neurology, University of Szeged. All RRMS patients were diagnosed according to the revised McDonald criteria (Polman et al., 2011). The following inclusion criteria were applied: RRMS disease course, EDSS > 6 points, no relapse or EDSS progression in the previous 6 months, right handedness, normal or corrected to normal visus, whilst exclusion criteria were: pregnancy, relapse or EDSS progression in 6 months following the MR scanning, or presence of other neurological or psychiatric disorders. Clinical symptoms scored by EDSS, were evaluated before scanning. Cognitive performance, as measured by the BICAMS (Langdon et al., 2012) (including the three subtests: SDMT, CVLT and BVMT) which was available from the clinical reports within 6 months of scanning. In order to compare the spatial attentional bias of MS patients, 26 age-, and sex-matched healthy controls from relatives and university staffs were recruited. Similarly, to the first study, none of the healthy subjects suffered from any neurological or psychiatric disease. Their visual acuity was normal or corrected-to-normal (20/20), and all subjects were right-handed. Important to note, that in the second study, there was no comparison of the imaging data of patients and controls. This study was approved by the Ethical Committee of the University of Szeged (Reference Number.:

000002/2016/OTIG). All study participants gave their written informed consent in accordance with the Declaration of Helsinki.

The main clinical and demographic parameters of the patient population and healthy controls enrolled in both studies are depicted in Table 1.

	Study 1	**Study 2**	
Group	**HC**	**MS**	**HC**
Number of patients	20	35	26
Females (%)	7 (35%)	21 (60%)	14 (53.8%)
Age (years) (mean±SD)	25.85 (±2.94)	40.9 (±8.5)	36.23 (±11.25)
EDSS (median/range)	-	(1.5/0-6)	-
Disease duration (year) (mean±SD)	-	11.3 (± 6.3)	-
Treatment regimen (percent /number of patients)	-	**DF**: (2.85%/1), **Te:** (20%/7), **IFNb:** (20%/7), **GA:** (22.85%/8), **F:** (22.85%/8), **A:** (11.42%/4)	-
Lesion load (cm^3) (mean±std)	-	6.561 (±5.731)	-

Table 1. **Demographic and clinical data of participants in Study 1 and Study 2.** Abbreviations: MS=multiple sclerosis patients, HC=healthy controls; EDSS=Expanded Disability Status Scale, SD=standard deviation; DF=dimethyl fumarate, Te=teriflunomide, IFNb=interferon beta 1a, GA= glatiramer acetate, F=fingolimod, A=alemtuzumab.

Stimulus presentation and experimental design

In order to measure the extent and lateralization of visuospatial attentional bias, custom-made Landmark task with the same parameters and experimental design in both Study 1 and Study 2 was used. Landmark task was presented on a Tobii Pro TX300 23" Eye Tracker TFT monitor (maximal screen resolution of 1920x1080) thus an accurate fixation during the task could be achieved. The custom-made Landmark task was programmed in Matlab R2012b with Psychophysics Toolbox (version: 3.0.10. PTB-3). The Landmark task consisted of 1mm thick horizontal black lines, that were previously bisected with a 10 mm high vertical black line centered in the middle of the monitor. In random order, five lines with different lengths were presented

during the task (Figure 1A.): (a) exactly in the middle-bisected lines; (b-c) left elongated; (d-e) right elongated. Participants were seated in a chair in front of the monitor in the distance 55-60 cm. In order to achieve accurate fixation during the task, Tobii Pro TX300 Eye Tracking system was used (gaze sampling rate: 300 Hz; operating distance: 50-80 cm; binocular and dark pupil tracking technique). Prior to the stimulus appeared, patients had to fixate a central fixation dot placed in the middle of the screen. The fixation accuracy was checked for 400 ms. In the case of correct fixation, the dot disappeared, and the main stimuli were presented on the screen for 50 ms duration. A white blank screen with 4000 ms intertrial interval followed the stimulus presentation, and during this time period, the patients were asked to make forced-choice decision about the respective length of the two segments of the bisected lines using three keyboard buttons (answers: left-left segment longer; right-right segment longer; down arrow key-equal segments) (Figure 1B.). Prior the Landmark task, patients were instructed to judge which segment of the bisected line was longer by pressing the corresponding button. All lines were presented 10 times, thus altogether, 50 stimuli were presented in Study 2. In Study 1, during the reproducibility measurement, the subjects repeated the Landmark task in three consecutive days. The performance of the patients was scored according to Fierro (Fierro et al., 2001) as follows: 0= correct response; 1 and 2= rightward errors due to left underestimation; -1 and -2= leftward errors due to right underestimation. The detailed calculation of Fierro scores based on the subjects' answers is shown in Table 2.

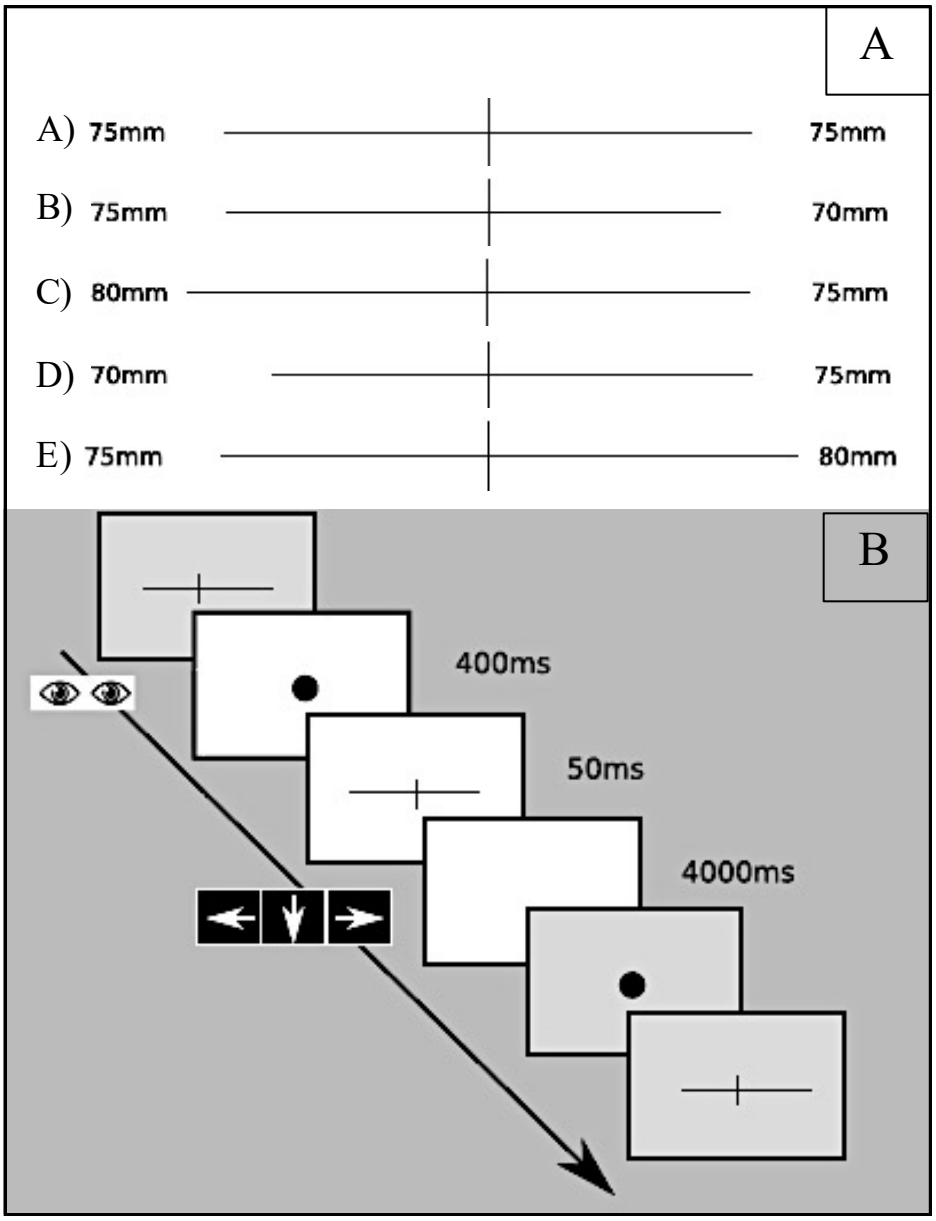

Figure 1. Stimulus presentation and experimental design. ***A:*** *Stimulus set used in Landmark task*. Line (A): equally elongated; Line (B) and Line (C): right and extreme right bisected; Line (D) and Line (E): left and extreme left bisected. ***B:*** *Landmark task*. After correct fixation (checked for 400 ms) the main stimulus was presented for 50 ms. Afterward subjects had to judge which segment of the line was longer or equal using the proper arrow keys on keyboard.

	Elongation	Participants' response		
		Left longer	Equal	Right longer
Line A)	Equal	-1	0	1
Line B)	Left	0	1	2
Line C)	Left	0	1	2
Line D)	Right	-2	-1	0
Line E)	Right	-2	-1	0

Table 2. Fierro's scoring system to evaluate the extent and lateralization of spatial attentional bias in Landmark task.

MRI acquisition

Study 1

MRI images in Study 1 were acquired within one month to the behavioral testing on a 1.5T GE Signa Excite HDxt MR scanner (GE Healthcare, Chalfont St. Giles, UK). The following sequences were acquired: Three-dimensional spoiled gradient echo images (FSPGR: echo time [TE]: 4.1 ms; repetition time [TR]: 10.276 ms; matrix: 256x256; field of view [FOV]: 25cmx25cm; flip angle: 15˚; in-plane resolution: 1x1mm; slice thickness: 1mm) and 60-direction diffusion-weighted images with 6 non-diffusion-weighted reference volumes (TE: 93.6 ms; TR: 16.000 ms; matrix: 96x96; FOV: 23x23cm; flip angle: 90˚; in-plane resolution: 2.4mmx2.4 mm; slice thickness: 2.4mm; b: 1000 s/mm2; number of excitations [NEX]: 2; array spatial sensitivity encoding technique [ASSET]).

Study 2

In Study 2, MR imaging was performed on a 3 T GE Discovery 750w MR scanner (GE Healthcare, Chalfont St. Giles, UK). The following sequences were acquired: high resolution T1 weighted anatomical images (3D spoiled gradient echo images with inversion recovery (3D FSPGR IR: echo time [TE]: 5.4 ms; repetition time [TR]: 2 ms; inversion time: 450 ms; matrix: 256x256; field of view [FOV]: 25.6 x25.6 cm; flip angle: 12 degree; slice thickness: 1mm; PURE intensity correction), CUBE T2 FLAIR for lesion detection (TE: 135 ms; TR: 6700 ms; TI: 1827 ms; matrix: 256x224; FOV: 25x22.5 cm; slice thickness: 1.4 mm; post processing: ZIP512, ZIP2)).

Image analysis

Study 1 - Correlation of diffusion parameters with spatial attentional bias

Using the first non-diffusion-weighted reference image, diffusion data were corrected for eddy currents and movement artefacts by twelve degree of freedom affine linear registration. An algorithm included in FDT of FSL (v.4.0) fits diffusion tensors at each voxel (Smith et al., 2004). FA was computed for the whole brain. In order to reduce the possible errors due to misalignment of the images, the TBSS method was used (Smith et al., 2007). The FA images of all subjects were aligned into a common space, using the non-linear registration algorithm, FNIRT, which use a b-spline representation of the registration warp field. Afterward, a mean FA image was created by averaging the aligned FA images. The mean FA image was fed into a tract skeleton generation deriving a mean FA skeleton representing the 1 voxel-wide centers of all tracts common to the group. The FA skeleton was thresholded at FA=0.2 in order to get good tract correspondence across the participants. Finally, the participants' aligned FA images were then projected onto the skeleton (Smith et al., 2006).

In order to test for asymmetries in FA characteristics we projected the data to a symmetric skeleton using the FSL's tbss_sym algorithm. This algorithm thickens the original asymmetric skeleton, then the mean FA image is flipped along the y axis, then the flipped and non-flipped images were averaged. This averaged, symmetrized mean FA image is fed into the skeletonization program and then masked by the dilated original skeleton. Finally, this skeleton is flipped along the y axis also and masked by the original non-symmetrized skeleton. The prealigned FA data are projected onto the symmetrized skeleton, left-right flipped and the resulting images are subtracted from the non-flipped. Since the same information present on the two sides of the images the right hemisphere is masked out and only the left side is subjected to further voxel-wise cross-subject statistics and presented in the results. Modelling and inference using standard GLM design set-up was accomplished using permutation-based cluster analysis (n = 5000) as implemented in FSL (Nichols and Holmes, 2002). The design encoded for the average spatial bias scores across the three measurements on consecutive days, whilst the age and gender were used as nuisance variables. Statistical thresholding was carried out with TFCE, and all results were FWE corrected for multiple comparisons.

Study 1 - Structural connectivity

The connectivity of regions that significantly correlate with the visuospatial attentional bias, was defined by probabilistic tractography (FDT, part of FSL: www.fmrib.ox.ac.uk/fsl/fdt). A Multifiber diffusion model was fitted that estimates probability distribution on the direction of 1 or more fiber populations at each voxel. Probabilistic tractography was then performed from any brain voxel by tracing streamline samples through these probabilistic distributions of fiber direction. For tractography, 5000 streamline samples were generated from each seed voxel to build up a connectivity distribution. The number of these samples passing through each brain voxel is interpreted as proportional to the probability of connection to the seed voxel. Fitting a multifiber model to the diffusion data enables to trace pathways through regions of fiber crossing (Behrens et al., 2007). Seed masks were the binary masks, derived and thresholded at the significance level from the TBSS analyses. The result of the tractography was standardized by the total number of generated tracts (waytotal), then thresholded at 10% probability. In order to reveal a group level connectivity map, the individual standardized and thresholded maps were registered to the standard space, binarized and summed over subjects.

Study 2 - Voxel-based morphometry

A VBM-style analysis was used as implemented in the FSL, complemented with the Lesion Filling algorithm. The Lesion Filling algorithm reduces the impact of white matter lesions on brain volume and atrophy measurements (Battaglini et al., 2012; Jenkinson et al., 2012). First, non-brain parts were removed from all structural images then tissue-type segmentation was carried out by FAST. The resulting gray matter partial volume images were registered to standard space (MNI152) using linear transformation (FLIRT), which was followed by a non-linear registration (FNIRT). The resulting images were averaged to create a study-specific template, to which the native gray matter images were then non-linearly (FNIRT) re-registered. The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 2 mm. Finally, voxelwise GLM was applied using permutation-based non-parametric testing. The design coded for the spatial attentional bias of the patients as measured by the Fierro score. Thresholding was carried out with TFCE technique. Following FWE correction for multiple comparisons, the statistical images were thresholded at $p<0.05$.

Study 2 - Lesion probability mapping

The lesion-symptom mapping was carried out using a method described in our earlier publication (Kincses et al., 2011). The lesions were outlined manually on the CUBE T2 FLAIR images for each patient, then binary lesion masks were created. The quality of the manual lesion marking was visually checked and corrected if needed by Z.T.K. The patient's FLAIR images were registered to the high resolution T1 weighted images with 6 DOF linear registration (FLIRT) using the lesion masks as weighting volumes. The high-resolution T1 images were registered to the standard space (MNI152) with 12 DOF affine registration, followed by non-linear registration (FNIRT). Binary lesion masks were transformed to the standard space by using the previously derived linear and non-linear registration transformation matrices and warp fields. The registrated masks were thresholded at an intensity of 0.5 and binarized to avoid size increment. The standard space binary lesion masks were concatenated into a 4D matrix that was subjected to voxelwise GLM using permutation based non-parametric testing. The design coded for the spatial attentional bias of the patients as measured by the Fierro score. Thresholding was carried out with a TFCE technique (statistical images were then thresholded at $p<0.05$) (Lett et al., 2017; Smith and Nichols, 2009). Following this step, FWE correction was used to correct for multiple comparisons. Using FWE-correction, the likelihood of false positives (Type I errors) occurring in the uncorrected statistical image is kept at the probability of 5%. That means that with a 95% confidence, no false positive errors occur in the corrected statistical image (Han et al., 2019; Winkler et al., 2014).

Statistical analysis

Study 1

Apart from analyzing the association between the diffusion parameters and spatial attentional bias in healthy subjects in Study 1, we aimed to investigate the reproducibility of pseudoneglect measured by Landmark task also. Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS 20.0.0 for OS X, SPSS Inc., http://www.spss.com). In order to calculate intraclass correlation coefficient, subjects performed the Landmark task on three consecutive days repeatedly. In the reliability measures, intraclass correlation coefficient (ρ) was calculated with the following equation:

$$\rho = \frac{MS_{BS} - MS_{WS}}{MS_{BS} + (k-1)MS_{WS}}$$

where MS_{BS} is the between subject mean of squares and MS_{WS} is the within subject mean of squares, and k is the number of observations. In order to interpret the reproducibility measure Cicchetti's guideline was followed (Cicchetti et al., 2006).

Study 2

In Study 2, differences on average of the individual Fierro scores between MS patients and healthy controls was compared using independent-samples T-test. In order to test whether the variances of Fierro scores are equal between the two groups, two-samples F-test was calculated. Following Shapiro-Wilk normality test, we calculated Spearman rank or Pearson correlation coefficients between the individual Fierro score of MS patients and the SDMT, BVMT, CVLT and EDSS scores.

Results

Study 1 - Reproducibility

In Study 1, on average the healthy subjects judged the left segment of the line slightly longer (mean score: -4.48), similarly to the findings of Fierro and co-workers (Fierro et al., 2001). However, it is clear from our results that there were people who judged the right segment consistently longer. The reproducibility of the attentional bias as measured with Landmark task was evaluated by repeating the task on three consecutive days. The intraclass correlation was ICC = 0.744 (CI: 0.547–0.879), which, according to Cicchetti, shows a good-excellent reproducibility. The reproducibility of visuospatial attentional bias is depicted on Figure 2.

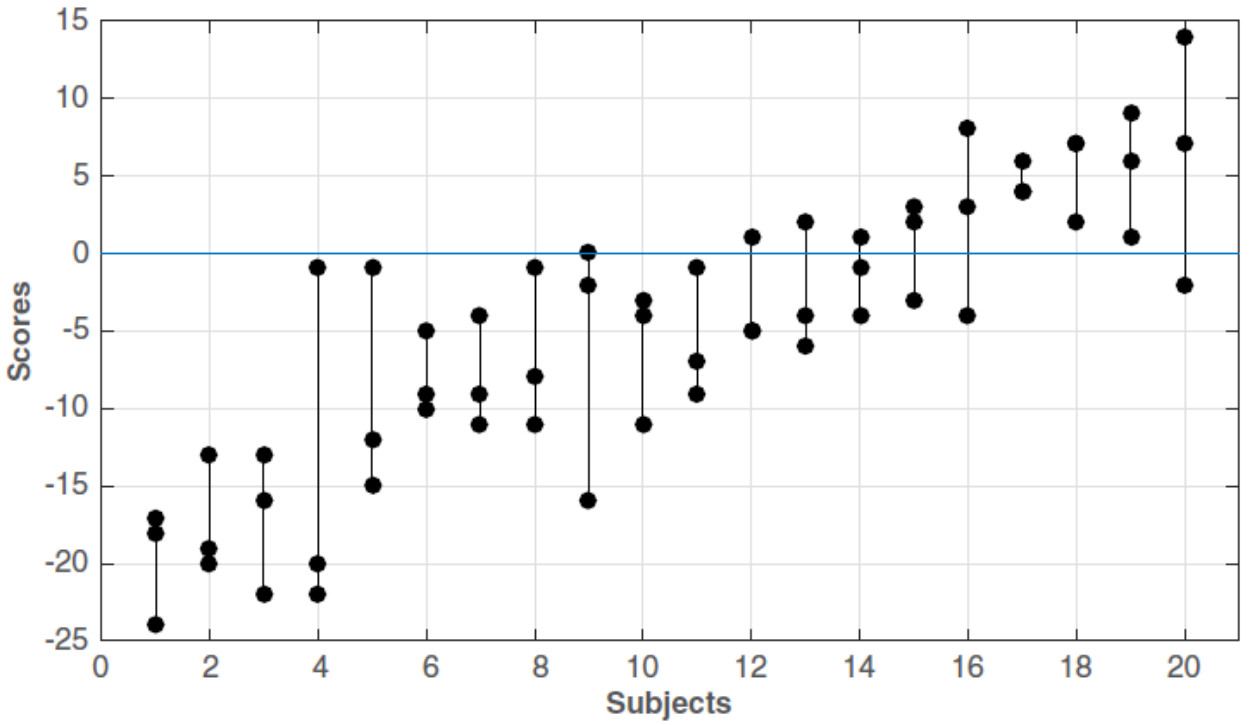

Figure 2. Reproducibility of visuospatial attention in healthy controls. Fierro scores (y-axis) of the three consecutive measurements plotted for each subject separately (x-axis). The subjects are sorted on ascending order based on the individual Fierro scores. Where are only two data points, Fierro scores from two measures are virtually inseparable.

Study 1 - White matter integrity and visuospatial attentional bias

In order to test, whether the lateralization of white matter microstructure correlates with the extent and lateralization of visuospatial attentional bias, we calculated the hemispheric differences of fractional anisotropy in a symmetric white matter skeleton and correlated the difference with the average spatial bias scores. In our symmetrized-flipped-subtracted FA images higher values represented higher values on the left in the original space. Positive correlation means higher FA values on the left comes along with more positive spatial bias scores (rightward bias/neglecting the left side of the space). Looking at it from the other direction leftward bias (neglecting the right side of the space) correlate with higher FA values in the right hemisphere (negative values in the subtracted FA image). Our analysis showed that there was a cluster of positive correlation in the parietal white matter (peak p-value = 0.04, x = -29mm, y = -44mm, z = 36mm, 49 voxels) (Figure 3.), whilst no negative correlation was found.

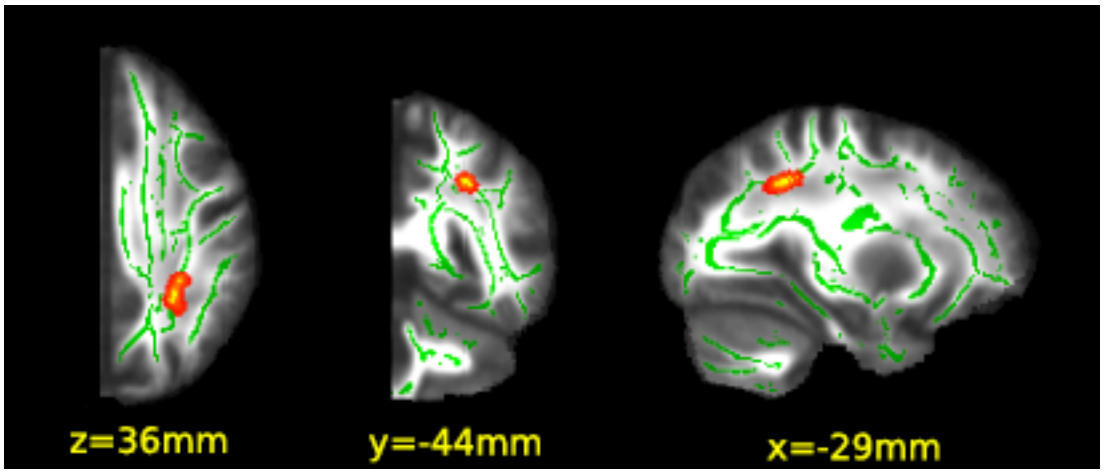

Figure 3. Correlation between the Fierro scores and symmetrized-flipped-subtracted FA parameters. Statistical images are overlaid on the FMRIB58_FA standard image. The mean FA skeleton, thresholded at 0.2, is depicted in green shades. Significant cluster is indicated in red-to-yellow ($p<0.05$, corrected for multiple correlations). A thickened version of the significant cluster is used to facilitate visualization. Positive correlation in the parietal lobe indicates leftward bias correlating with higher FA in the right hemisphere.

Study 1 - Structural connectivity of correlations

The above-described parietal cluster showed connectivity along the superior longitudinal fascicle on one end to the posterior parietal cortex and anteriorly to the putative frontal eye field at the junction of the superior frontal sulcus and the precentral sulcus. In the posterior parietal lobe, the white matter fibers run under the bottom of the intraparietal sulcus. Connection travelled to the lateral and medial bank of the intraparietal sulcus, also towards the inferior parietal lobule and to the temporoparietal junction (Figure 4.).

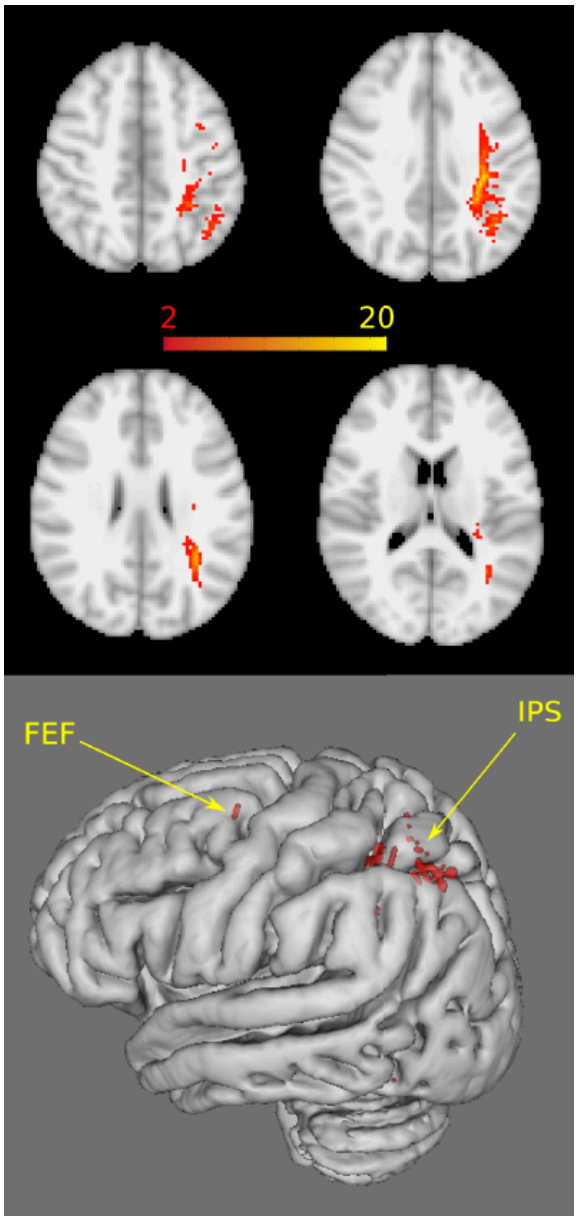

Figure 4. The connectivity of the cluster showing correlation between FA and behavioral data. In the upper section axial slices at standard space coordinates z = 46mm, 36mm, 26mm and 16mm are shown. In the lower section the cortical projections of the tracks are shown. The binary cluster masks were used as seed mask for each subject. Five thousand streamline samples from each seed voxel were drawn to build up a connectivity distribution that was standardized by the total number of generated tracts, thresholded at 10% and binarized. Population connectivity maps were derived for controls by adding these masks together and thresholding at two (Pathways passing through the given voxel in at least two subjects). Abbreviations: FEF=frontal eye field, IPS=intraparietal sulcus.

Study 2 - Visuospatial attentional bias in MS patients and healthy controls

MS patients in our study showed significant spatial bias as indicated by the non-zero Fierro scores (median: -8, range: -27/28.5). Most of the patients had a leftward bias, but some patients had a spatial bias to the right, as it can be seen on the boxplots (Figure 5.). Fierro scores of the MS patients were compared to the Fierro scores of healthy control group (group comparison of age: (t(59)=1.863, p=0.067); and sex: (X^2(1)=0.231, p=0.63). The independent-samples T-test revealed no differences on average in Fierro scores (t(59)=0.007, p=0.99, Cohen's effect size value (d=0.05) suggested a low practical significance), but the variability of the bias was higher in the patient population (F(34,25)=2.18, p=0.04, Cohen's effect size value (d=0.56) suggested a moderate to high practical significance), as revealed by the F-test.

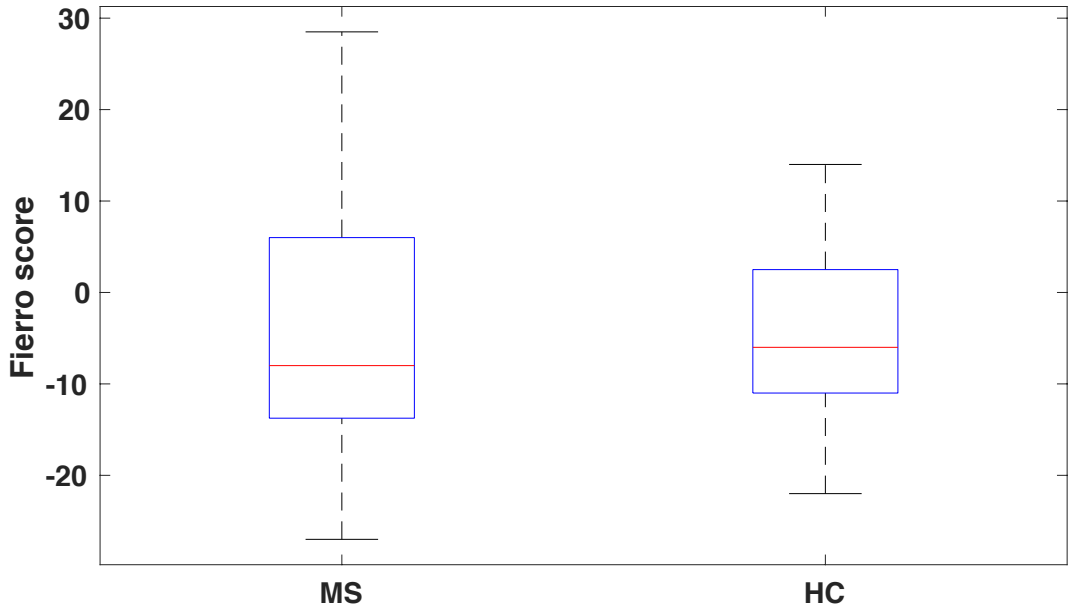

Figure 5. Distribution of visuospatial attentional bias. Patients (MS) are presented on the left. For comparison the Fierro scores of healthy controls (HC) are presented on the right. There was no significant difference between the mean, but the variability of the bias was higher in MS patients. The central mark on the boxplot shows the median, the boxes represent 25 and 75% percentiles, the whiskers extend to the most extreme data points not considered outliers. Abbreviations: MS=multiple sclerosis patients, HC: healthy subjects.

Following the Shapiro-Wilk normality test, Spearman rank or Pearson correlation coefficients were calculated between the individual Fierro scores and the SDMT, BVMT, CVLT and EDSS scores of MS patients. The EDSS and BVMT scores failed the normality test ($p<0.05$). No significant correlations were found between the clinical or cognitive variables and the individual Fierro scores. Table 3. summarizes the descriptive statistics and the correlation coefficients values.

A)	Mean (± Standard deviation) of cognitive tests			
SDMT	50.15 (±12.8)			
BVMT	27.73 (±6.7)			
CVLT	58.84 (±10.3)			
EDSS	1.5 (0-6) *			
B)	**SDMT**	**BVMT**	**CVLT**	**EDSS**
Fierro scores	R=-0.002, p=0.994	rho=-0.069, p=0.738	R=-0.046, p=0.824	rho=0.065, p=0.753

Table 2. Part (A) shows the results of the BICAMS test. Part (B) shows the results of the correlation between individual Fierro scores and the SDMT, BVMT, CVLT as well as EDSS scores. No significant correlation was found between clinical or cognitive scores and visuospatial bias (the represented p-values are uncorrected). Abbreviations: BICAMS: *Brief International Cognitive Assessment for Multiple Sclerosis*, SDMT: *Symbol Digit Modalities Test*, BVMT: *Brief Visuospatial Memory Test-Revised*, CVLT: *California Verbal Learning Test*, EDSS: *Expanded Disability Status Scale*)

* The description of EDSS scores includes the median and range.

Study 2 - Lesion-symptom mapping and visuospatial attention

The lesion probability map showed that the highest lesion occurrence could be seen in the bilateral periventricular white matter (Figure 6A.). The result of lesion-symptom mapping was visualized as an overlay on the MNI152 2mm brain. After thresholding the FWE-corrected statistical image at $p<0.05$ (eventually the output statistical image is a 1-P image, where a value 1 is the most significant, thus the FWE-corrected statistical image must be thresholded at =0.95 that equals to $p<0.05$), the JHU White Matter Tractography Atlas was used to determine the exact location of the significant cluster. Based on the JHU White Matter Tractography Atlas, we found

that the individual Fierro scores correlated with the lesion probability along the left superior longitudinal fascicle (Figure 6B.). Namely, the higher the probability of lesions over the left superior longitudinal fascicle, the lower the Fierro scores were. This meant that patients with lesioned left superior longitudinal fascicle tended to underestimate the right side of space and err towards left in Landmark task.

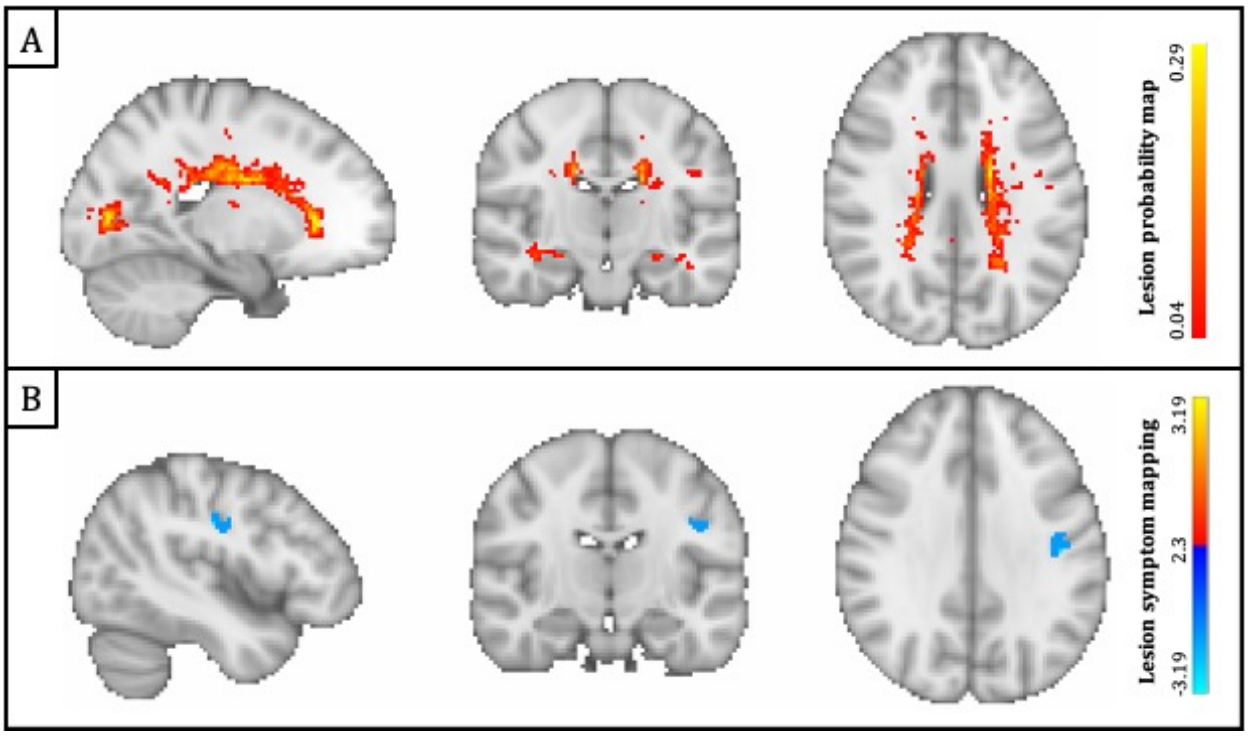

Figure 6. Lesion probability map and result of the lesion-symptom mapping. ***A:*** Most of the lesions appeared in and around the periventricular white matter. The color bar on the right represents the probability of lesions. ***B:*** Lesion-symptom mapping showed significant correlation between the lesions, affecting the left parietal white matter and the lateralization of the visuospatial bias. Standard space coordinates for the significant cluster are (x=-44, y=-19, z=31). The color bar represents Z-values.

Study 2 - Voxel-based morphometry and visuospatial attention

In our VBM analysis, we found no significant correlation between the individual Fierro scores and the gray matter density of the patients.

Discussion

In our two studies we aimed to demonstrate that (i) the individual visuospatial attentional bias, measured by the Landmark task, is a reproducible and reliable phenomenon in healthy people over time, (ii) we can determine the white matter microstructural correlates of the individual visuospatial attentional bias in healthy people. We assumed, that if the extent and lateralization of visuospatial attentional bias is consistent over time, it will be partly hardwired in our brain, thus we could identify the underlying lateralization in the white matter microstructure, (iii) the visuospatial attentional bias differs in MS patients due to the evolving brain pathology affecting the gray and white matter, eventually altering the lateralization pattern of the healthy brain.

The most important results of our studies can be summarized as follows:

(1) In line with the literature, healthy people showed mostly a leftward visuospatial attentional bias on average in our first study. However, we showed that there are individuals who constantly underestimate the left side of the space. The good-excellent reproducibility of visuospatial attentional bias in healthy people, measured on three consecutive days, supported our hypothesis that it is consistent over time.

(2) Lateralization of white matter microstructural integrity in superior longitudinal fascicle correlated with the extent and lateralization of visuospatial bias in healthy. Namely, the more organized the white matter in the right parietal white matter was, the more lateralized visuospatial attentional bias was measured towards the contralateral side of space (leftward spatial bias).

(3) The above-mentioned relationship between the spatial attentional bias and white matter microstructure was found in the superior longitudinal fascicle showing connectivity towards the posterior parietal cortex and rostrally to the putative frontal eye field, whilst fibers also run towards the intraparietal sulcus, inferior parietal lobule and to the temporoparietal junction. The results of the tractography suggest that the visuospatial attentional bias in healthy is determined mainly in the dorsal fronto-parietal network and in the white matter fibers connecting the nodes of the dorsal and ventral fronto-parietal network.

(4) In our second study we found, that not on average but higher variability of the visuospatial attentional bias can be observed in MS patients compared to healthy controls.

(5) Furthermore, this altered variability in visuospatial bias in MS patients is highly related to the white matter pathology. Namely, higher probability of white matter lesions affecting the left superior longitudinal fascicle was associated with the extent of leftward visuospatial bias.

In our studies we have replicated the results of Fierro and colleagues. They found that on average, healthy people tend to overestimate the leftward segment of a bisected line (Fierro et al., 2001). In line with the literature, that report mostly leftward visuospatial bias in healthy, known as pseudoneglect, most of our healthy participants in both studies and MS patients in the second study as well, tended to underestimate the right segment of the bisected line (Fierro et al., 2001; McCourt and Jewell, 1999; McCourt and Olafson, 1997; Werth and Poppel, 1988). It must be noted that there are several studies, which reported rightward visuospatial attentional bias of their study population as well (Manning et al., 1990; Szczepanski and Kastner, 2013). Furthermore, the visuospatial bias depends on which task (Landmark or line bisection task) is used during measurement, and the task instruction has a significant effect on it as well (Cavezian et al., 2012; Fink et al., 2002; Garcia-Perez and Peli, 2014; Harvey et al., 2002; Harvey and Olk, 2004). As our results and former studies indicated, the direction of spatial bias seems to be more of a spectrum. This was supported by Szczepanski and colleagues in a functional MR imaging study enrolling healthy participants. They found that the individual variability of visuospatial attentional bias is strongly associated with the lateralization of brain activation in the key nodes of the fronto-parietal attentional network (Szczepanski and Kastner, 2013). In our first study we found that the attentional bias was consistent over three consecutive days in healthy, suggesting that this consistency is not an immediate result of a constantly changing cerebral activity, but at least partially hardwired in our brain. Our hypothesis was supported in the first study, namely the higher the white matter microstructural integrity in the superior longitudinal fascicle was, the more lateralized the visuospatial bias towards the contralateral side of space was. These results indicate that a more integrated structure, which possibly provide a base for a more coherent functional activation in the fronto-parietal network, is overdriving the function of the contralateral hemisphere. Furthermore, the tractography in our first study revealed, that white matter fibers originated from the significant cluster connected the posterior parietal lobe, putative eye-field and ventrally the temporo-parietal junction. These regions are the key hubs and streams of the fronto-parietal attentional network, namely the largely bilateral dorsal fronto-parietal network including the frontal eye-field, posterior parietal cortex, and the mostly right-lateralized ventral attentional network including the temporo-parietal junction and the ventral frontal cortex. The dorsal nodes are responsible for the goal-directed, top-down attentional modulation of lower-level centers, whilst the ventral nodes are responsible for the stimulus-driven, bottom-up attentional modulation.

Even though we distinguish the dorsal and ventral stream of attentional network, still on network level there is a tight functional interaction. On closer examination the connection between the nodes of dorsal and ventral attentional network, the three segregated branches of the superior longitudinal fascicle are referred to compose its base. The most dorsal branch (SLF I) connects the nodes of the dorsal attention network, whilst the projections of the most ventral part (SLF III) is a link between the nodes of the ventral attention network. The third branch (SLF II) partially overlaps with the dorsal and the ventral attention network, connecting the inferior parietal lobule/temporo-parietal junction and the frontal eye-field (Thiebaut de Schotten et al., 2011). Thus, SLFII possibly composes the structural link between the two systems, with redirection of the goal-directed attention mediated by the dorsal network to the events identified as salient by the ventral network. Based on the results of the tractography in our first study, our tracts coincide with the SLFII. Considering the different connection patterns of the three branches of superior longitudinal fascicle, we assume that SLFI and SLFII stipulate visuospatial attentional bias in healthy people (Corbetta and Shulman, 2002; Thiebaut de Schotten et al., 2011). In case this delicate functional balance between the nodes of fronto-parietal attentional network or the underlying connections alters, that basically determines the individual attentional focus in time and space, eventuates altered visuospatial bias, and in severe cases neglect syndrome (Corbetta and Shulman, 2002; Hattori et al., 2018). In our first study we aimed to find connection between function and structure, that is in most cases tightly interconnected. Still this interaction is volatile, since the pre-existing structure that determines our behavior, can be altered by adaptive or maladaptive plasticity over time (Draganski et al., 2004; Sampaio-Baptista et al., 2013; Sampaio-Baptista et al., 2014; Scholz et al., 2009). Several other studies proved this relation. More organized white matter microstructure, described by fractional anisotropy, in the corpus callosum, Broca's area or fornix was associated with better bimanual coordination, artificial grammar learning and recollection memory, respectively (Floel et al., 2009; Johansen-Berg et al., 2007; Rudebeck et al., 2009). Also, integrity of white matter in cerebellar peduncle, also in the ventral and dorsal visual pathways was associated with better visuo-motor adaptation and audio-visual integration (Della-Maggiore et al., 2009; Kaposvari et al., 2015). Notably, motion detection threshold was also associated with white matter integrity in the posterior part of the right superior frontal gyrus, the right juxta-cortical superior parietal lobule, the left parietal white matter, the left superior temporal gyrus and the left optic radiation (Csete et al., 2014). The question might arise, how white matter integrity contribute

to functionality? Even though the exact underlying diffusion properties must be better explored, nerve diameter, myelination presumably determines behavioral performance through better conduction velocity. Since precise timing and proper spreading of the neural signal is crucial between the network nodes to improve or keep efficiency, myelination thus mediately the integrity of white matter fibers, characterized by fractional anisotropy values, has a decisive impact on behavior (Fields, 2015; Hodgkin and Huxley, 1952; Zatorre et al., 2012). In our first study, using symmetrized fractional anisotropy skeleton, we demonstrated, that microstructural lateralization of healthy brain correlates with behavioral bias in healthy participants.

However, the physiological structural and functional brain lateralization might alter in different neurological diseases. Compared to controls, Altarelli and colleagues found rightward asymmetry of planum temporale in dyslexic children (Altarelli et al., 2014). Thompson and colleagues early work shed light on the Alzheimer-disease related structural alterations of the commissural system connecting temporal and parietal regions bilaterally (Thompson et al., 1998). Altered structural hemispheric lateralization was also revealed in autism, attention deficit/hyperactivity, psychotic and mood disorders (Eyler et al., 2012; Shaw et al., 2009; Yucel et al., 2009; Yucel et al., 2003). Albeit there is a plethora of studies investigating the relationship between atrophy or lesion location in white matter and the clinical or cognitive disability in MS patients, still just a few studies aimed to examine how functional and structural intact brain lateralization pattern alters in MS. From functional aspects, Gomez and colleagues revealed reduced functional connectivity between the nodes of fronto-parietal network in the left hemisphere, regardless of whether MS patient were cognitively preserved or impaired. In patients with cognitive decline, they found reduced functional connectivity between the nodes of fronto-parietal network in the right hemisphere (Cruz-Gomez et al., 2014). Alteration in lateralization pattern and its association with clinical disability of MS patients was also revealed by Reddy and colleagues. Examining the functional lateralization of motor cortices, they found that during a motor performance, the ipsilateral activation of motor cortex increases compared to healthy controls. In other words, reduced hemispheric lateralization in the motor-task related activity was found between the two hemispheres in MS patients. Also, the amplitude of the ipsilateral motor cortex activation correlated with the severity of clinical disability (Reddy et al., 2000; Reddy et al., 2002). Presumably, alterations in hemispheric activation patterns during motor task performance occur due to lesioned white matter tracts, gray matter atrophy leading to maladaptive plasticity

(Ksiazek-Winiarek et al., 2015; Peterson and Fling, 2018). Even in the spinal cord, asymmetry alterations of microstructural integrity in the normal-appearing white matter in cervical lateral funiculi correlated with the central motor conduction time to abductor digiti minimi and tibialis anterior muscles (von Meyenburg et al., 2013). Structural lateralization patterns also alter during the disease course of MS. Worsening clinical state of MS patients over a 5-year follow-up period was associated with left-lateralized white matter lesions and gray matter atrophy in almost all brain regions including cortical (frontal, temporal, parietal and occipital cortices), and subcortical regions, compared to MS patients with clinically stable state (Preziosa et al., 2017). In our second study we found that MS patients had higher variability of visuospatial attentional bias compared to healthy controls. Albeit no group differences were shown on average in attentional bias, still the probability of white matter lesions in the superior longitudinal fascicle were associated with the extent and lateralization of spatial attentional bias of MS patients. In the background of higher behavioral variability in MS patients, the altered structural lateralization patterns of the attentional network due the presence of white matter lesions is presumed.

Though the relation between T2 white matter lesion burden and clinical or cognitive symptoms is modest at most (known as clinico-radiological paradox) (Barkhof, 2002), yet several studies aimed to reveal association between white matter lesion-location and clinical or cognitive disability in MS patients. Comparing cognitively preserved and impaired MS patients, Rossi and colleagues found that higher lesion volume and frequency bilaterally in forceps major and in splenium of the corpus callosum was associated with the rate of cognitive impairment. They also found significant inverse association between patients' performance on SDMT, that measures information processing speed, and lesion frequency in bilateral forceps major and splenium of corpus callosum, also with lesion frequency in forceps major and inferior fronto-occipital fascicle in the left hemisphere (Rossi et al., 2012). Higher lesion probability in the left internal capsule, periventricular white matter, also in prefrontal, posterior parietal and medial temporal lobe was associated with disease severity and mentation scores, respectively (Charil et al., 2003). It must be noted, that several different methods are used to segment multiple sclerosis lesions, also in statistical analyses binary masks or probability distribution of voxels inside the lesion can be used (Mortazavi et al., 2012). Using lesion probability maps containing voxels with higher probability in the center, and lower probability at the periphery of the lesions, Sepulcre and colleagues found inverse relation between the scores of Paced Auditory Serial Addition Task (PASAT), measuring

verbal working memory performance, and lesion probability in bilateral prefrontal, anterior cingulate and parietal cortex, in the genu of the internal capsule on left, as well as in the ponto-mesencephalic tegmentum and cerebellar peduncle on the right hemisphere (Sepulcre et al., 2009b). Another study also revealed association between PASAT scores and lesion location in different brain regions including frontal, temporal and limbic lobes, corpus callosum, corona radiata and in the posterior thalamic radiatia. In the background of the cognitive performance on PASAT the relative widespread and separate white matter lesions affecting the large-scale network involved in attention and concentration required to fulfill PASAT task is presumed (Altermatt et al., 2018). Using the same lesion probability mapping calculation published by Sepulcre and colleagues, Reuters and coworkers found inverse correlation between lesion probability in Broca's area, frontal lobe, splenium in the right hemisphere, and deep white matter and worse verbal and spatial learning performance in cognitively impaired clinically isolated syndrome patients as compared to healthy controls, respectively (Reuter et al., 2011). In order to resolve the clinico-radiological paradox, lesion-symptom mapping studies showed relation between lesion location for example in the periventricular white matter and the disease severity in MS patients (Altermatt et al., 2018; Vellinga et al., 2009). Albeit several studies investigated the relationship between different cognitive functions and the evolving structural brain pathology in MS, only a few examined the neglect syndrome and the underlying structural alterations in MS patients. The first case reported an MS patient with hemispatial neglect due lesioned right supramarginal, angular, and cingulate gyri originate from 1987 (Graff-Radford and Rizzo, 1987). Gilad and colleagues found significantly larger rightward bisection error in MS patients using line bisection task, but the rightward bias did not correlate with lesion burden or the laterality of lesions (Gilad et al., 2006). However, later studies showed association between lesion volume and location in intracortical, parietal, occipital, paracentral and superior frontal lobe and the visuospatial bias measured by Judgement of Line Orientation task (Louapre et al., 2016; Stankiewicz et al., 2011). Lesion-symptom mapping studies in stroke patients already showed that damages in the right perisilvian cortical regions and white matter are responsible for visuospatial neglect (Karnath and Rorden, 2012). Ad interim inhibition using transcranial magnetic stimulation of the parietal lobe, 150 ms after stimulus onset also induced neglect-like symptoms in healthy people (Fierro et al., 2001). In our second study we showed that lesions disrupting the integrity of the left superior longitudinal fascicle leads to altered visuospatial attentional bias towards the left side of space in MS patients.

Albeit right hemispheric lesions are the most frequent cause of neglect, but less frequently, left hemispheric stroke can also cause underestimation of the contralesional hemifield (Becker and Karnath, 2007). Our results might be in correspondence with the interhemispheric competition theory, wherein each hemisphere, in relation to each other's' activity, directs attention towards the contralateral visual field (Kinsbourne, 1977).

Next to the white matter and cortical/subcortical lesions, gray matter atrophy also presents from the early stage in MS. Recent studies claim that atrophy progresses in determined patterns not randomly (Bergsland et al., 2018). Cortical areas that are functionally and structurally connected shows similar atrophy patterns. In the background of this might the retrograde and anterograde degeneration following demyelination and axonal loss presumed (Bergsland et al., 2018; Sepulcre et al., 2009a). Although several studies aimed to reveal the impact of gray matter atrophy on cognition and the severity of clinical symptoms, the reported results varied. Hyncicova and colleagues found no correlation between cognitive functions, involving visuospatial attention as well, and gray matter atrophy in clinically isolated syndrome patients (Hynicova et al., 2017). However, other studies proved the relation between different cognitive domains and gray matter atrophy of different cortical and subcortical regions (Batista et al., 2012; Houtchens et al., 2007; Kincses et al., 2014; Mineev et al., 2009; Sanchez et al., 2008; Sumowski et al., 2009; Zivadinov et al., 2001). Interestingly, in our second study we found no correlation between focal cortical atrophy and visuospatial bias in MS patients. In the background of our result might the higher variability of different MRI parameters contributing to the clinical and cognitive symptom severity could be presumed.

Limitations

Undoubtedly, our two studies summarized in this thesis have limitations. The Landmark task measures the perceptual component of visuospatial attention whilst direct comparison of the microstructural background of line-bisection task, that measures the premotor component of visuospatial attention as well, could give further insight into the physiology of pseudoneglect. During stimulus presentation, we did not use post-stimulus masks in order to avoid retinal aftereffect, that might influence our results. Increasing the number of patients and healthy controls could increase the robustness of our results. With moderate effect size, only in a post-hoc analyses, we found higher variability of visuospatial bias in MS patients compared to healthy controls.

Enrolling patients with different clinical forms of MS with different the rate of cognitive impairment could specify more the underlying mechanisms of visuospatial attention and improve our knowledge.

Conclusion

Our work showed that visuospatial attentional bias in healthy people is more of a spectrum and is partially hardwired in the white matter microstructure, namely, physiological microstructural lateralization of the superior longitudinal fascicle contributes to the individual variability of visuospatial attention. We were able to support, that function and brain structure are tight interconnected. Alterations in normal brain lateralization due the lesioned superior longitudinal fascicle in MS patients, despite stable clinical state, eventuate higher variability of visuospatial attention. Even subtle behavioral changes can be mapped in the underlying brain structure. Our findings help us to understand how physiological and pathological alterations in the brain structure determine human psychophysiology.

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