Lateralization of visuospatial attention

Ph.D. Thesis Summary

Krisztián Kocsis

Clinical and Experimental Neuroscience Program,
Doctoral School of Clinical Medicine,
Faculty of Medicine, University of Szeged

Supervisor:
Zsigmond Tamás Kincses, M.D., Ph.D., DSc
Department of Radiology, Albert Szent-Györgyi Clinical Center,
University of Szeged

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Introduction

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 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? 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). 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.

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; thus, 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).

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 (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).

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. 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. 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.

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). Different 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).

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 (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 diagnose MS, dissemination of symptoms in time and space must be proved based on clinical or paraclinical evidence. 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. Due the damaged blood-brain barrier, contrast enhancing lesions 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).

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). 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).

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. 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. All patients and controls had normal or corrected-to-normal (20/20) visual acuity and all subjects were right-handed. Both studies were approved by the ethical committee of the University of Szeged (Reference number: 87/2009; and 000002/2016/OTIG, respectively), and all the subjects gave their written informed consent prior the participation according to the Declaration of Helsinki.

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 (exactly in the middle-bisected lines; left elongated; right elongated lines). 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. 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). 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).

MRI acquisition

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); 60-direction diffusion-weighted images with 6 non-diffusion-weighted reference volumes.

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)) and CUBE T2 FLAIR for lesion detection.

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 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

In Study 1, we aimed to investigate the reproducibility of pseudoneglect measured by Landmark task also. 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. 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. However, there were subjects who judged the right segment consistently longer. The intraclass correlation was ICC = 0.744 (CI: 0.547–0.879), which, according to Cicchetti, shows a good-excellent reproducibility.

Study 1 - White matter integrity and visuospatial attentional bias

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. 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).

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.

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. The independent-samples T-test revealed no differences on average between controls and MS patients in Fierro scores ($t(59)=0.007$, $p=0.99$), but the variability of the bias was higher in the patient population ($F(34,25)=2.18$, $p=0.04$) as revealed by the F-test.

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. No significant correlations were found between the clinical or cognitive variables and the individual Fierro scores.

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. 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**.** Patients with lesioned left superior longitudinal fascicle tended to underestimate the right side of space and err towards left in Landmark task.

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.

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.

Thesis points:

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.