

**COGNITIVE FUNCTION IN MULTIPLE
SCLEROSIS ASSESSED WITH
NEUROPSYCHOLOGICAL AND MULTI-MODAL
MRI METHODS**

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PhD Thesis

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I. INTRODUCTION

Multiple sclerosis

In the western hemisphere of the Earth multiple sclerosis (MS) is the most common central nervous system disease in young adults leading to disability. Prevalence of the disease in Hungary is 62/100.000, i.e. about 6000 Hungarians are affected by the disease.

Pathologically, MS affects the central nervous system with multifocal and diffuse inflammatory and neurodegenerative changes, but their exact etiology and pathogenesis remains uncertain. Currently, MS is considered to result from immunological, genetic, and environmental factors. Traditionally, inflammatory demyelination has been seen as the main disease process, however, axonal loss is increasingly being documented to occur early in the disease and results in permanent disability.

Clinically, MS is a chronic progressive disease, characterized by both sensory-motor and psychological symptoms including cognitive deficits and affective disturbances, and accompanied by fatigue.

Magnetic resonance imaging (MRI) is one of the most important paraclinical tools used in the diagnosis of MS mainly due to its high sensitivity for detecting the focal central nervous system abnormalities of the disease. Quantitative measures derived from conventional and advanced MRI methods have been developed to monitor and predict the course of the disease, as well as for in vivo non-invasive investigation of the pathophysiology.

Gray matter pathology in multiple sclerosis

Recent advances in histopathological and imaging techniques have renewed the appreciation of gray matter (GM) involvement in MS. New histopathological methods have found demyelinating lesions in significant portions of the cortex. In addition, neuroimaging techniques have detected structural changes in the GM. GM pathology is detectable in the earliest disease stages, and becomes prominent in the progressive phase.

GM damage in MS may result from primary local cortical demyelinating lesions, and from GM atrophy secondary to axonal transections in destructive white matter (WM)

plaques or severe diffuse axonal damage in the normal-appearing WM leading to Wallerian (anterograde or transsynaptic) degeneration, as well as retrograde degeneration. However, the exact relationship between primary and secondary processes leading to GM damage remains poorly understood. Finally, other primary neurodegeneration independent from focal WM or GM lesions has been presumed in the early development of GM atrophy in MS.

In the cortex of the MS brain significant number of focal demyelinating lesions are detectable. Pathologically, cortical lesions (CLs) are characterized by a much milder lymphocyte infiltration, complement deposition, microglial activation, and blood-brain barrier disruption than WM lesions. Cortical demyelination can occur in conjunction with subcortical WM plaques or as small perivascular intracortical lesions. However, the most extensive cortical demyelination is seen as widespread and band-like subpial lesions, which span the cortex over long distances affecting several adjacent gyri and sulci. This type of CL is associated with chronic inflammation of the meninges.

Assessment of CLs in vivo is of great significance because it is still not fully elucidated how CLs impact clinical manifestation and progression of MS, and how CLs are related to WM pathology and GM atrophy. To understand these questions would improve our understanding of MS pathogenesis, and might open new perspectives for novel therapeutic innovations.

Cognitive impairment in multiple sclerosis

The estimated prevalence of cognitive impairment in MS ranges between 43 to 70%. Typically, the intellectual dysfunction manifests itself as a composition of subtle deficits in different cognitive domains involving the efficiency of information processing, verbal and visuo-spatial memory, executive functioning, attention, and visual perceptual processing. Processing speed, and visual learning and memory seem to be most commonly affected. Both fatigue and depression may impact the cognitive performance of MS patients. Cognitive decline may be detected by sensitive neuropsychological test batteries specially developed for the MS population.

Cognitive impairment may occur in the earliest stages of the disease even in patients with clinically isolated syndrome. Cognitive deficits may develop independently from physical disability particularly in the early stage and in patients with benign MS. However, the presence of cognitive decline has been found to predict more

progressive disease course. Cognitive impairment may compromise the everyday life activities, employment status, and social relationships. Detrimental effect on health-related quality of life and association with worse disease prognosis underlie the relevance of neuropsychological assessment of MS patients in clinical practice.

Recognition of the clinical relevance and prognostic role of MS cognitive impairment has been motivated MS research to focus on MRI correlates of the cognitive deficit. Assessment of the global and regional WM lesion burden, derived from T2- or T1-weighted MRI showed modest association with the cognitive status. Stronger relationship was obtained with quantification of the whole and regional brain atrophy considered as a marker of irreversible tissue loss.

Social cognition, Theory of Mind

Deficits of general intellectual abilities significantly interfere with everyday life activities and decision-making. In addition, loss of employment status, restriction in social activities, and difficulties in inter-personal relationships frequently occur during the disease. Deficits of social cognition may significantly account for all of these functional limitations. Social cognition is a human mental ability involving the capacity to interpret and predict mental states of other people in terms of thoughts, intentions, desires and beliefs known as Theory of Mind (ToM), also referred as mentalizing and mindreading. ToM ability involves social-perceptual processes that enable mental state decoding from nonverbal clues, such as facial expression, eye gaze, and body postures. Furthermore, ToM involves social cognitive processes that enable complex abstract reasoning about the mental state of others using prosody and social content of speech. Social cognition might be independent, and dissociable from general intelligence.

The neural basis of ToM abilities has been widely investigated using advanced neuroimaging methods. These studies support the hypothesis that integrated fronto-temporal and temporo-parietal circuits are dedicated to mentalizing. Another important neural mechanism participating in social cognitive processes is the activation of the mirror neuron system. Mirror neurons activate during observation of a motor action with an identical firing pattern required for the execution of the observed movement. Thus, inner simulation of a viewed action enables the understanding of its intended goal. Electrophysiological studies of monkeys and human functional MRI (fMRI) studies found mirror neurons in the premotor cortex

(frontal mirror system), as well as in the inferior parietal cortex and posterior temporal cortex (parietal mirror system).

II. AIMS

Aims of the studies were to investigate cognitive aspects of MS using neuropsychological evaluation and quantitative MRI methods.

Our hypotheses were:

- In MS, cognitive dysfunction develops both in fields of general intelligence and social cognition. These deficits may manifest independently or dissociated from each other.
- In MS, pathological processes of both the GM and WM independently contribute to the manifestation of the cognitive decline.
- In MS, evolution of cortical GM pathology relates both to processes primary taking place in the cortex and to the WM pathology resulting in secondary neurodegeneration.

We tested these hypotheses by:

Identification and clinical impact of cortical lesions in multiple sclerosis

1. We evaluated the ability of a routinely available MRI protocol to capture CLs and their different subtypes.
2. We studied the relationship between CL load and WM lesion load.
3. We investigated the association between CLs and physical disability, as well as CLs and cognitive performance of MS patients.

Study of social cognition in multiple sclerosis

4. We evaluated the social cognitive performance of MS patients compared to healthy control subjects using comprehensive social cognitive tests.
5. We studied the impact of physical disability, disease duration, and disease progression rate on the social cognitive performance.

Neuroanatomical substrates and connectivity of mentalization: a multi-modal MRI study in multiple sclerosis

6. We tested whether brain pathological changes of MS patients impact the mentalization ability. Without a priori hypothesis about possible anatomical substrates relating to social cognitive performance using multi-modal MRI methods we assessed cortical thickness of the whole neocortex and regional WM lesion loads in the interconnecting fiber bundles to find correlations between WM as well as cortical GM changes and mentalization.
7. To extend the general neuroanatomical knowledge about mentalization we identified neural substrates in the brain of MS patients, which if damaged, associate with impaired social cognitive performance in individuals, whose primary brain development was normal.
8. The relationship between focal cortical thickness and lesion load of WM fiber bundles projecting to the atrophic cortical area, both related to the same cognitive function was statistically analyzed to better understand neurodegenerative processes in the neocortex of MS patients.

III. EXPERIMENTS

1. Identification and clinical impact of multiple sclerosis cortical lesions as assessed by a routine 3 Tesla MRI

1.1. Identification of cortical lesions using a routine MRI protocol

In vivo visualization of CLs is challenging because CLs are typically small compared to the usual resolution of MRI in clinical practice, have poor contrast with the surrounding normal GM, and have similar signal properties to those of cerebrospinal fluid reducing their conspicuity in boundary areas of GM and cerebrospinal fluid. Using conventional imaging techniques, CLs are missed in up to 95% of the cases. In the past few years, large efforts have been devoted to the development of MRI techniques capable of visualizing at least a portion of CLs in vivo. Novel MRI methods have been deployed to address these challenges, including novel pulse sequences, multi-channel and high-resolution imaging, and ultra-high magnetic field strength. Recently, the application of the double inversion recovery (DIR) sequence

convincingly demonstrated that CLs are frequent in MS patients, as has been long known from pathological studies.

We employed a high-resolution 3 Tesla brain MRI protocol that combined multiplanar display of 3 dimensional (3D) fluid attenuated inversion recovery (FLAIR) and T1-weighted 3D inversion recovery spoiled gradient-recalled echo (IR-SPGR) sequences. This approach took advantage of the high contrast sensitivity of FLAIR for imaging CLs combined with IR-SPGR to delineate the boundary between cortex and WM. The multiplanar display of our isotropic resolution IR-SPGR images allowed precise visualization of the lesions in relation to the GM-WM junction and cortical folding patterns, which is important in assigning lesions to their proper subtype during anatomic lesion classification. The acquired sequences are widely available on clinical scanners from multiple vendors and can be integrated in clinical routine with reasonable scan times.

Using this clinically applicable MRI method the detected CL load was comparable with the bulk of CLs assessed by specialized MRI methods developed for sensitive CL delineation. We detected CLs in 92.3% of the patients, supporting the notion that focal CLs are highly prevalent in MS. CLs occurred both in the early and late relapsing-remitting MS subtype, as well as in the secondary progressive subtype. CLs were detectable in 85.7% of patients with relapsing-remitting MS in the early stage.

CL measures showed moderate correlations with WM lesion volume, suggesting that the underlying pathogenic processes might be related.

1.2. Impact of white matter lesion and cortical lesion load on physical disability and cognitive performance in multiple sclerosis

Twenty-six MS patients including relapsing-remitting (n=20) and secondary progressive (n=6) clinical subtypes were tested with a comprehensive neuropsychological test battery to evaluate broad range of cognitive domains. Physical disability was quantified with the Expanded Disability Status Scale (EDSS). Physical disability showed significant correlations with the CL number and CL volume, but not with the WM lesion volume, although a trend was apparent.

After controlling for age, depression and pre-morbid intelligence, CL number, CL volume and WM lesion volume independently predicted the performance of information processing speed and working memory. In addition, CL number predicted verbal learning and memory. These findings suggested that both WM and GM lesions

influence cognitive performance in MS, and CLs have a particularly important contribution to this relationship.

2. Social cognition and Theory of Mind in multiple sclerosis

Forty MS patients with relapsing-remitting (n=37) or secondary progressive (n=3) disease course and 35 gender- and age-matched healthy controls were investigated with non-verbal and verbal mentalization tests, as well as an empathy questionnaire was applied. Non-verbal tests included the Faces test and the Eyes test requiring emotion recognition and mental state decoding from facial expressions, and eye gazes, respectively. Perspective taking and reasoning about mental and emotional states of others was evaluated with the Faux Pas test. Psychometric assessment of the participants included measure of the general intelligence, depression, and anxiety with validated tests.

After controlling for confounding effects of age, gender, general intelligence, depression, and anxiety, performance of MS patients in the Eyes test was significantly poorer compared to healthy controls. Physical disability correlated with non-verbal mentalization (Eyes test) and cognitive perspective taking (Faux pas test) independently from the confounding factors. Progression rate of the disease was related to both aspects of mentalization: compared to healthy controls, more rapidly progressing patients performed significantly poorer in visual (Eyes test) and verbal (Faux pas test) mentalization tasks independently from the confounding factors. MS patients with shorter disease duration, and with faster disease progression rate reported higher level of empathic ability.

Mentalization dysfunction in MS may be considered a significant contributor among the factors defining health-related quality of life. In addition, social cognitive dysfunction may require more cognitive effort to perform successfully in social situations. This higher cognitive demand in everyday life may contribute to cognitive fatigue. Furthermore, constant cognitive compensation of social cognitive disabilities may interfere with other cognitive domains, such as information processing speed, verbal and visuospatial memory, and executive function known most frequently impaired in MS.

3. Neuroanatomical substrates and connectivity of mentalization: a multi-modal MRI study in multiple sclerosis

We performed an MRI study with a cohort of 49 MS patients to investigate the impact of WM lesion burden and cortical atrophy on mentalization ability in MS. In addition, we explored brain regions, which if damaged associates with impaired mentalization performance in individuals, whose primary brain development was normal to map neural substrates of mentalization. Finally, we aimed to explore the relationship between focal cortical atrophy and regional WM lesion load taking part in the same cognitive function and anatomically connected to better understand neurodegenerative processes in MS.

After correction for confounding effect of anxiety and depression, our MS patient cohort performed significantly poorer in verbal and visual mentalization tasks (Irony and Eyes test) compared to a group of 24 healthy subjects.

T1-weighted three-dimensional Magnetization Prepared Rapid Gradient Echo (MPRAGE) and diffusion-weighted images were acquired on a 3.0 Tesla MRI scanner. MRI analysis included the assessment of the total and regional WM lesion load, diffusion tensor imaging (DTI) fiber tractography, and measure of the cortical thickness.

After correction for anxiety and depression, no associations were found between total T1 WM lesion load and mentalization performance. This finding converges with previous studies reporting modest correlations between cognitive performance and total WM lesion volume. As assessment of the total WM lesion load may mask the identification of strategically important WM pathways, which if damaged impair mentalization abilities, WM lesions were parcellated with the use of a WM fiber tract atlas, and regional T1 lesion loads of each individual major fiber bundle were measured. After correction for depression and anxiety, and adjusting for multiple comparisons, T1 lesion volume of the splenium of corpus callosum (SCC) showed correlation with the Eyes test performance. Next, using DTI fiber tractography we traced the tracts of the SCC affected by the T1 lesions to explore their cortical projections. These tracts projected to the occipital, parietal, and temporal lobes of both hemispheres corresponding to the anatomical fiber tract endings in healthy subjects. These results suggest that damage of the SCC in MS impairs the inter-

hemispheric integration of signals containing mainly visual information associating with poorer mental state decoding performance from visual clues. This finding points out the importance of WM integrity in cognitive processes, and suggests that disconnection of cortical areas involved in neural networks impairs cognitive processing.

Cortical thickness was measured throughout the whole brain to quantify cortical atrophy as thinning of the cortex. For the assessment FreeSurfer software was applied, which is an automated method for reconstruction and measure of cortical thickness within submillimeter preciosity. After correcting for confounding effects of age on cortical thickness, and effects of depression and anxiety on mentalization significant correlations were found between the Eyes test performance and cortical thickness of focal areas in the right premotor cortex (caudal middle frontal gyrus, Brodmann area [BA] 8), left anterior inferior temporal gyrus, close to the temporal pole (BA20), and in the fusiform face area (FFA) of the fusiform gyrus (BA19). The identified cortical areas were also reported in previous studies documenting a widely distributed brain network engaged in neural processes of facial emotion recognition. The premotor BA8 area regulates the voluntary and involuntary eye movements. Majority of the photographs in the Eyes test depict averted eye gaze. We propose that correlation between Eyes test performance and cortical thickness of the premotor eye region reflects the role of somatotopic-organized mirror neurons in simulation of portrayed eye gazes. Eyes test performance significantly correlated with cortical thickness of the left temporal pole, which integrates social and emotional signals with stored autobiographical memory content and social scripts. Integration of general knowledge about the world with actual new situations is required to understand mental states of others. The fusiform face area is crucial in visual processing of faces, and participates in emotional perception.

Stepwise linear regression analysis suggested that mentalization performance is independently compromised by WM tract injuries presumably causing disconnection of distant cortical areas, and focal damage of the cortex measured as cortical thinning. To explore the contribution of secondary neurodegeneration to cortical atrophy, we statistically analyzed the relationship between T1 lesion load of the SCC and cortical thickness of focal areas lying in the projection field of the SCC tracts (left temporal pole, left fusiform face area). In this approach both the WM and the GM pathologies were found to associate with the same mental function. Our results suggest that

regional WM lesions only partially account for focal cortical atrophies, and processes independent from axonal damage in the WM lesions also play a part in the pathogenesis of GM neurodegeneration

IV. SUMMARY OF THE THESES

Identification and clinical impact of multiple sclerosis cortical lesions as assessed by a routine 3 Tesla MRI

1. Using a clinically applicable 3 Tesla MRI protocol combining 3D FLAIR and IR-SPGR sequences, the detected CL load was comparable with the bulk of CLs assessed by specialized MRI methods developed for sensitive CL delineation.
2. The multiplanar display of the IR-SPGR images with isotropic resolution allowed precise anatomic lesion classification in relation to the GM-WM junction and cortical folding pattern.
3. CLs were detectable in different progression stages of MS including early relapsing-remitting MS.
4. Our CL measures showed moderate correlations with WM lesion load, suggesting that the underlying pathogenic processes might be related.
5. CL load showed significant correlations with MS physical disability. We did not find this correlation with the WM lesion load, only a trend was apparent.
6. Cortical lesion load and WM lesion load independently predicted the information processing speed and working memory performance. In addition, CL number was found to contribute to verbal learning and memory performances. Cognitive performance of MS patients is impacted by both WM and cortical GM pathology. CL load seems to play a particularly important role in this relationship.

Social cognition and Theory of Mind in multiple sclerosis

7. Compared to healthy control subjects, visual mentalization ability of MS patients is impaired unrelated to confounding effects of age, gender, general intelligence, and affective co-morbidities (depression, anxiety).
8. More advanced physical disability and faster progression rate of the disease predicted more extended mentalization deficit affecting both the social-perceptual and the complex perspective taking abilities.

9. MS patients with shorter disease duration, and with faster disease progression rate reported higher level of empathic ability suggesting complex mechanisms contributing to empathic understanding of patients with chronic disease.

Neuroanatomical substrates and connectivity of mentalization: a multi-modal MRI study in multiple sclerosis

10. Pathological changes in the brain of MS patients significantly impact the mentalization ability. Cognitive performance deteriorates with the increase of the WM lesion load located in strategically important WM tracts, presumably due to disconnection of cortical nodes in neural networks. Focal atrophy of the neocortex causes disturbance in neural networks as well associating with deficits in mentalization.
11. Our results suggest that mentalization from facial expressions requires inter-hemispheric integration of visual signals mediated by the splenium of corpus callosum. In addition, focal fronto-temporal areas are involved in processes of mentalization decoding visual signals. We propose that among these cortical areas the premotor eye field interprets social content of eye gazes by simulation mechanism based on mirror neurons organized somatotopically.
12. We statistically analyzed the relationship between focal cortical atrophy and lesion load of tracts projecting to the atrophic cortical area. We found that focal cortical and regional WM damage both associated the same cognitive process are only in part related. This result suggests that pathology of the cortical neurodegeneration is partly independent from WM demyelination.

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