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Impact of Gray Matter Pathology on Cognitive Function in Multiple Sclerosis

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1. Introduction

Multiple sclerosis (MS) is a chronic progressive disease associated with both sensory-motor and psychological symptoms including cognitive deficits, affective disturbances, and fatigue. Intellectual disability of MS patients usually manifests itself as a composition of subtle deficits in certain cognitive domains detectable with sensitive neuropsychological test batteries specially developed for the MS population (Benedict et al., 2006b; Rao, 1990). Nevertheless, the effect of cognitive impairment on everyday life activities, employment status, and social relationships is considerable (Amato et al., 1995; Rao et al., 1991b). Cognitive impairment may occur in the earliest stages of the disease (Achiron & Barak, 2003; Callanan et al., 1989; Deloire et al., 2005; Feinstein et al., 1992; Glanz et al., 2007) even in patients with clinically isolated syndrome (CIS) (Achiron & Barak, 2003; Feuillet et al., 2007; Glanz et al., 2007; Potagas et al., 2008). Cognitive deficits may develop independently from physical disability particularly in the early stage of the disease and in patients with benign MS (Feuillet et al., 2007; Glanz et al., 2007; Portaccio et al., 2009). However, the presence of cognitive decline has been found to predict a more progressive disease course (Portaccio et al., 2009; Zipoli et al., 2010). Detrimental effects on quality of life and poor disease prognosis underlie the importance of neuropsychological assessment of MS patients in clinical practice.

Magnetic resonance imaging (MRI) is one of the most important paraclinical tools used in the diagnosis of MS. 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 MS pathophysiology (Filippi & Rocca, 2010).

Increasing recognition of the functional relevance and prognostic role of MS cognitive impairments has resulted in focused attention on MR correlates of cognitive deficit. Assessment of the global and regional white matter (WM) lesion burden, derived from T2- or T1-weighted MRI shows modest association with cognitive status (Arnett et al., 1994; Hohol, et al., 1997; Patti et al., 2009; Rao et al., 1989; Rovaris et al., 2001; Swirsky-Sacchetti et al., 1992). A stronger relationship has been obtained with quantification of the whole and

regional brain atrophy (Rovaris, et al., 2006; Zivadinov, et al., 2001) considered as a marker of irreversible tissue loss (Miller et al., 2002; Rovaris & Filippi, 1999). Non-conventional MRI techniques assessing diffuse brain tissue damage outside of the MRI-visible lesions provide potent tools to detect pathological changes underlying MS cognitive deficits than lesion-based and atrophy measures (Filippi et al., 2010).

Recent advances in histopathological and imaging techniques have renewed the appreciation of gray matter (GM) involvement in MS (Pirko et al., 2007). New histopathological methods have found demyelinating lesions in significant portions of the cortex (Albert et al., 2007; Bo et al., 2003; Kidd et al., 1999; Kutzelnigg et al., 2005; Peterson et al., 2001; Wegner et al., 2006). In addition, neuroimaging techniques have detected structural changes in the GM (Pirko et al., 2007). In this review, we summarize the results of recent studies correlating MRI-detectable GM abnormalities with various aspects of MS neuropsychological dysfunction.

2. Gray matter pathology in multiple sclerosis

GM pathology is detectable in the earliest disease stages (Chard et al., 2004; De Stefano et al., 2003; Kutzelnigg et al., 2005), and becomes prominent in the progressive phase (Fisniku et al., 2008; Kutzelnigg et al., 2005).

GM damage in MS may result from primary local cortical demyelinating lesions (Bo et al., 2003; Peterson et al., 2001), and from GM atrophy secondary to axonal transections in destructive WM plaques or severe diffuse axonal damage in the normal-appearing WM leading to Wallerian (anterograde or transsynaptic) degeneration, as well as retrograde degeneration (Evangelou et al., 2000; Sepulcre et al., 2009; Trapp et al., 1998). 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 (Sepulcre et al., 2009).

MS is characterized by a significant number of focal cortical lesions (CLs) (Bo et al., 2003; Kidd et al., 1999; Kutzelnigg et al., 2005; Peterson et al., 2001). In addition, demyelination may occur in the deep GM structures, hippocampus, hypothalamus, cerebellum, and spinal cord (Geurts et al., 2009). Pathologically, CLs are characterized by a much milder lymphocyte infiltration, complement deposition, microglial activation, and blood-brain barrier disruption than WM lesions (Bo et al., 2003). 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 (Kooi et al., 2009; Magliozzi et al., 2007).

3. Cognitive impairment in multiple sclerosis

3.1 General intellectual abilities

The estimated prevalence of cognitive impairment in MS ranges between 43 to 70% (Benedict et al., 2006b; Rao et al., 1991a) both in the earlier and later stages of the disease (Beatty et al., 1990; Piras et al., 2003). Cognitive impairment can be seen irrespective of

the duration of the disease and is only mildly associated with physical disability (Patti et al., 2009). However, cognitive disturbances seem to be more severe in patients with chronic progressive disease compared to those in the relapsing-remitting (RR) stage (Patti et al., 2009). Both fatigue and depression have been identified as important contributors to cognitive impairment of MS patients (Arnett et al., 2008; Deluca et al., 2004).

MS affects various aspects of general cognitive functioning, including 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 (Benedict et al., 2006b; Rao et al., 1991a).

3.2 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 additionally 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 cues, 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, such as prosody and social content of speech (Stone et al., 1998). Social cognition might be independent, and dissociable from general intelligence (Shamay-Tsoory et al., 2005). Only a few studies investigated social cognition in MS; all demonstrated deficits in facial emotion recognition (Banati et al., 2010; Henry et al., 2009; Jehna et al., 2010; Krause et al., 2009; Ouellet et al., 2010) In addition, decline in complex cognitive inferences relating to the content of the mental state was also described (Banati et al., 2010; Ouellet et al., 2010).

The neural basis of ToM abilities has been widely investigated using advanced neuroimaging methods in healthy subjects and in several clinical conditions showing social cognitive impairment particularly in high-functioning autism and schizophrenia. These studies support the hypothesis that integrated fronto-temporal and temporo-parietal circuits are dedicated to mentalizing. Main nodes of these networks were found distributed in the posterior superior temporal sulcus, temporo-parietal junction, temporal pole, medial prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex, and inferior parietal lobule, as well as in subcortical areas, particularly in the amygdala (Adolphs et al., 2002; Frith & Frith, 2006; Stone, et al., 1998). Another important neural mechanism participating in social cognitive processes is the activation of mirror neurons during observation of movements of others (Williams, 2008). Mirror neuron activation described first in macaque monkeys produces inner simulation of the viewed action thereby enabling 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) (Williams, 2008).

4. Relationship between gray matter findings assessed by MRI and cognitive dysfunction in multiple sclerosis

4.1 General intellectual function

4.1.1 Neocortical lesions

In vivo visualization of CLs is challenging (Geurts et al., 2005a) 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 (CSF) reducing their conspicuity in boundary areas of GM and CSF. Using conventional imaging techniques, CLs are missed in up to 95% of the cases (Geurts et al., 2005b). 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 (Bagnato et al., 2006; Geurts et al., 2005a; Kangarlu et al., 2007; Mainero et al., 2009; Mike et al., 2011; Nelson Poonawalla et al., 2008; Nelson et al., 2007; Simon et al., 2010). 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 (Bagnato et al., 2006; Kangarlu et al., 2007; Mainero et al., 2009; Mike et al., 2011; Nelson et al., 2008; Nelson et al., 2007; Simon et al., 2010). Recently, the application of the double inversion recovery (DIR) sequence convincingly demonstrated that CLs are frequent in MS patients (Calabrese et al., 2007; Calabrese et al., 2008), as has been long known from pathological studies (Brownell & Hughes, 1962, Lumsden, 1970).

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 to study the relationship between CLs and cognitive performance of MS patients (Mike et al., 2011). 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 (Figure 1.). These 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 (Calabrese et al., 2008; Mainero et al., 2009; Nelson et al., 2008; Nelson et al., 2007; Simon et al., 2010).

We explored the relationship between cognitive performance and lesion load of the WM and cortical GM compartments in an MS patient cohort including RR (n=20) and secondary progressive (SP) (n=6) clinical subtypes. Very few studies have examined this previously (Bagnato et al., 2010; Calabrese et al., 2009; Roosendaal et al., 2009). Therefore, a broad range of neuropsychological variables, which could potentially include cortical contributions (e.g. information processing speed, new learning, verbal and non-verbal memory, executive function) had been assessed. 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 also predicted verbal learning and memory.

These findings suggested that both WM and GM lesions influence cognitive performance in MS. However, CLs may have a particularly important contribution to this relationship, as beside information processing speed performance, CL number also significantly correlated with verbal learning abilities. Two recent studies using DIR sequence yielded similar results (Calabrese et al., 2009; Roosendaal et al., 2009).

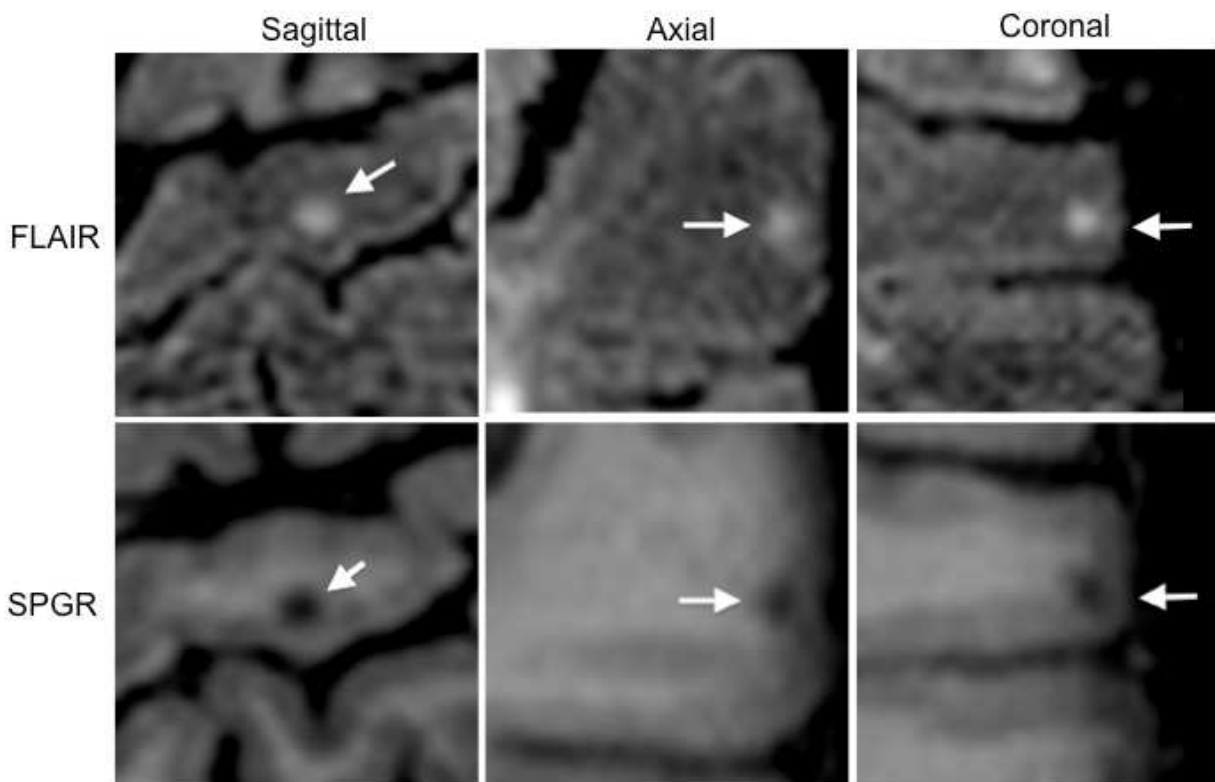


Fig. 1. Cortical lesion shown on multiplanar images

The same cortical lesion involving both the cortex and the adjoining subcortical white matter (Type I lesion) is shown on FLAIR (upper row) and IR-SPGR (lower row) images (arrows), reconstructed in sagittal, axial, and coronal planes. Note that the lesion is conspicuous on FLAIR, while the anatomic location relative to the white matter-gray matter boundary is well defined on the IR-SPGR images.

4.1.2 T2 hypointensity imaging

Iron deposition, a possible sign of neurodegeneration, reduces T2 relaxation times, resulting in hypointensity on T2-weighted images. In MS, T2 hypointensity frequently occurs in the thalamus and basal ganglia. T2 hypointense regions in the GM have been shown to correlate with cognitive impairment of MS patients (Brass et al., 2006; Neema et al., 2007).

4.1.3 Gray matter atrophy

Several cross-sectional and longitudinal studies have reported GM volume reduction in MS using manual or semi-automated segmentation methods, voxel-based morphometry (VBM) approach, and cortical thickness measurement (Grassiot et al., 2009). GM atrophy has been documented both in the deep gray matter structures (caudate nucleus, thalamus) and in neocortical regions. Recently, the relationship between GM volume decrease and cognitive performance of MS patients has been intensively investigated.

Neocortical volume has been found to be significantly reduced in cognitively impaired compared to cognitively preserved patients (Amato et al., 2004). Similar findings have been reported with cortical thickness analyses of the global brain and parcellated brain areas (Calabrese et al., 2010). Compared to healthy controls, a VBM study found significant

decrease in GM volume only in MS patients with cognitive impairment in contrast to patients with normal neuropsychological performance (Morgen et al., 2006). Neuropsychological performance of patients with cognitive decline has been documented to correlate with cortical brain volume (Amato et al., 2004; Benedict et al., 2006a; Morgen et al., 2006), as well as cortical thickness (Calabrese et al., 2010). GM volume assessed longitudinally decreased more progressively in MS patients with deteriorating cognitive performance compared to patients with stable or improving cognitive state (Amato et al., 2007).

The relevance of cortical damage in cognitive dysfunction of MS patients has been highlighted by studies of regional cortical atrophy (Calabrese et al., 2010; Morgen et al., 2006; Tekok-Kilic et al., 2007). In a group of cognitively impaired MS patients, GM volume of fronto-temporal brain areas presumed to be involved in neural processing of working memory, information processing, and divided attention correlated with performance on the paced auditory serial addition task (PASAT) test performance (Morgen et al., 2006). Using a semi-automated parcellation analysis of the neocortex, the prefrontal GM volume resulted the strongest predictor of memory and information processing performance in MS patients (Tekok-Kilic et al., 2007).

Impact of subcortical GM atrophy on MS cognitive performance has also been established. Different methods applied for quantification of deep GM structures including the measure of the bicaudate ratio (Bermel et al., 2002), enlargement of the third ventricular width (Benedict et al. 2004a, 2004b, 2006a, Christodoulou et al., 2003; Sanchez et al, 2008; Tekok-Kilic et al., 2007), semi-automated (Houtchens et al., 2007) and automated (Benedict et al. 2009) segmentation of subcortical GM structures provided convergent evidence for a relationship between deep GM damage and neuropsychological impairment. Reduction of thalamic volume was found to be a reliable predictor of cognitive decline in MS even after correction for WM lesion volume, whole brain atrophy and third ventricular width (Benedict et al., 2009; Houtchens et al., 2007). Strong correlations have been reported between caudate atrophy and impaired information processing speed (Bermel et al., 2002), as well as verbal learning and memory (Benedict et al., 2009). Measure of the third ventricle width has been used to infer the atrophy of adjacent GM structures, such as the thalamus (central atrophy). Enlargement of the third ventricle showed a highly significant relationship with both general cognitive impairment and deficits in specific neuropsychological domains even after accounting for the influence of global lesion load measures and whole brain atrophy (Benedict et al., 2004b; Christodoulou et al., 2003; Sanchez et al., 2008).

A recent study investigated the contribution of different GM compartments to cognitive dysfunction in MS patients, and found both the central and cortical atrophy predictive of the presence of cognitive impairment in MS (Tekok-Kilic et al., 2007).

4.1.4 Non-conventional MRI methods

Beyond focal lesions and atrophy, MS pathology is characterized by diffuse tissue damage. Conventional morphological MRI methods are insensitive to detect these microscopic structural alterations. Quantitative MRI techniques including magnetization transfer (MT) MRI, diffusion tensor imaging (DTI), and proton MR spectroscopy (¹H-MRS) detect brain tissue changes on a molecular level, and thereby are able to measure the degree of structural integrity in diffusely affected brain tissue. Abnormalities in the GM assessed with non-conventional MRI methods have been well established in MS (Filippi et al., 2010; Rovaris et

al., 2006). Studies, addressing the clinical relevance of diffuse GM pathology in the cognitive impairment of MS patients are summarized in the following subsections.

4.1.4.1 Magnetization transfer MRI

The MT ratio (MTR) derived from MT MRI reflects the capacity of macromolecules to exchange magnetization with surrounding water molecules and estimates the relative amounts of free and bound water in the brain (Wolff & Balaban, 1994). In MS, reduced MTR values may indicate a relative increase in the unbound water fraction due to edema and inflammation, or a reduction in the bound fraction, which may reflect demyelination and axonal loss (Schmierer et al., 2007). MTR values derived from the cortical/subcortical brain tissue were significantly lower in cognitively impaired patients than in those with no impairment (Rovaris, et al., 2000). MTR values of the cortical/subcortical regions showed correlation with cognitive performance of RR MS patients (Rovaris et al., 2000). In CIS patients, using voxel-by-voxel statistical mapping, significant correlations were observed between local MTR values and PASAT scores in the right Brodmann (BA) 4 and the left BA40 (Ranjeva et al., 2006; Ranjeva et al., 2005). A recent study investigated GM MRI correlates of cognitive impairment in different stages of MS. In patients with CIS suggestive for MS, mean cortical MTR has been identified as the only independent predictor of decreased mental processing speed. However, in early RR MS cortical atrophy was found as the strongest correlate of the same cognitive task. These findings suggest that both microscopic tissue disintegrations and atrophy of the cortex are important determinants of MS cognitive performance, however their significance changes with advance of the disease (Khalil et al., 2011). In a study including benign MS patients (BMS), total and regional (frontal, temporal, and occipital) cortical MTR values corrected for WM lesion volume were able to differentiate between cognitively impaired and cognitively preserved MS patients. However, MTR values of cognitively preserved MS patients did not differ from healthy controls. These findings support heterogeneity of the brain structural damage in BMS associating with different clinical prognosis (Amato et al., 2008). In patients with primary progressive (PP) MS, significant correlations have been observed between decrease of MTR value in specific cortical regions (right inferior parietal cortex, right inferior occipital gyrus) and PASAT performance (Khaleeli et al., 2007). In a longitudinal study of PP MS patients, GM MTR independently predicted PASAT score at the 5-year follow-up (Penny et al., 2010).

4.1.4.2 Diffusion tensor imaging

DTI measures the diffusion of water molecules in the brain tissue, which is directionally determined along the fiber tracts. Disturbances in the structural integrity of the brain tissue are reflected by the increase of the mean diffusivity (MD) and decrease of the fractional anisotropy (FA), parameters derived from DTI technique (Rovaris et al., 2009).

In RRMS, MD of the NAGM moderately correlated with neuropsychological tests measuring semantic fluency, and information processing-working memory (Rovaris et al., 2002). Structural GM damage of BMS patients with cognitive impairment has been demonstrated in a study comparing GM MD between cognitively impaired BMS patients and SP MS patients. MD of the GM showed no difference between BMS patients with cognitive deficit and low physical disability and patients with SP disease course (Rovaris et al., 2008).

4.2 Mentalization

4.2.1 Focal atrophy of the neocortex impairs mentalization ability of multiple sclerosis patients

Living with MS frequently associates with disturbed social life including insufficiency in partnerships and family roles, as well as employment status (Halper, 2007). Intact social cognition is fundamental for successful social functioning (Penn et al., 1997). Recently, few studies investigating social cognitive abilities of MS patients have reported deficits in emotion recognition and complex perspective taking abilities (Banati et al., 2010; Henry et al., 2009; Jehna et al., 2010; Krause et al., 2009; Ouellet et al., 2010).

To investigate the impact of cortical pathology on social cognitive dysfunction, we performed an MRI study in a cohort of 49 MS patients. We measured the cortical thickness throughout the whole brain, and analyzed its association with mentalization test performance to identify cortical areas involved in neural integration processes of mentalization in MS. Performances on neuropsychological tests were corrected for confounding effects of anxiety and depression. Compared to healthy subjects, MS patients performed significantly poorer in verbal (Irony test) and visual (Eyes test) mentalization tasks. These results are in line with previous reports (Banati et al., 2010; Henry et al., 2009; Jehna et al., 2010; Krause et al., 2009; Ouellet et al., 2010).

Cortical thickness was assessed to quantify cortical atrophy as thinning of the cortex. FreeSurfer software, version 4.5 (<http://surfer.nmr.mgh.harvard.edu>) was applied on 3 Tesla 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) images for automated reconstruction and measure of cortical thickness characterized by preciosity within a submillimeter range (Dale et al., 1999; Fischl et al., 1999). 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 several focal areas. The Eyes test is an advanced and sensitive tool to detect subtle dysfunctions in facial expression recognition (Baron-Cohen et al., 2001). In the Eyes test, participants are required to judge mental states from photographs portraying only the eye region of the face. The identified frontotemporal cortical areas showing significant correlation with the Eyes test were also reported in previous studies documenting a widely distributed brain network engaged in neural processes of facial emotion recognition (Adolphs et al., 2002; Frith & Frith, 2006; Sabatinelli et al., 2011). Simulation theory describes a presumed physiologic mechanism participating in the understanding of observed motor actions, motor learning, and mental state decoding as well as empathizing in social-perceptual processes (Bastiaansen et al., 2009; Williams, 2008). Firing of mirror neurons in the brain of the observer simulates the neuronal activation pattern required to execute the observed movement, and thereby enables the understanding of the underlying action goal (Bastiaansen et al., 2009; Williams, 2008). Mirror neurons were identified in prefrontal and premotor areas, and in the parietal and temporal lobe (Bastiaansen et al., 2009; Williams, 2008). In addition, recent studies found evidence on simulation of observed sensations and emotions through mirror neuron activation in the primary somatosensory cortex, anterior insula, and amygdala contributing to empathic understanding (Bastiaansen et al., 2009; Williams, 2008). Previous fMRI studies demonstrated that viewing emotional facial expressions associates with premotor cortex activation presuming a mirror neuron mechanism (Bastiaansen et al., 2009). Inner simulation of the observed facial muscle group contractions is linked to a matching affective state based on personal experiences.

In conclusion, our study suggests that GM pathology in cortical regions constituting neural networks processing high-level mental information significantly impact the mentalization ability in MS.

4.2.2 Functional MRI study of mentalization in multiple sclerosis

Neuroanatomical correlates of emotional face expression recognition deficit in MS were also investigated in an fMRI study. This approach identified decreased insular and ventrolateral prefrontal cortex BOLD activation in MS patients with impaired recognition performance compared to the unimpaired group (Krause et al., 2009).

5. Conclusion

Cognitive impairment in MS occurs frequently as mild deficit in different neuropsychological domains. Clinical impact of cognitive dysfunction emerges in every day life situations, employment status, and social environment compromising quality of life of the patients. Diagnostic evaluation of neuropsychological performance in MS has also been proved to be significant from prognostic point of view, as presence of cognitive impairment may predict worse disease course. Recently, involvement of the GM in pathological processes underlying MS has been convergent supported by histopathological and MRI studies. The impact of GM damage on clinical course of the disease and its relationship with WM lesions is under intensive research, in which application of different MRI methods plays a highly important role. Application of conventional structural MRI, and non-conventional MRI techniques has been enabled to quantify GM pathology as atrophy, CL load, and degree of microscopic tissue integration disturbances. Cognitive impairment has been demonstrated to correlate all with these different aspects of GM damage highlighting the relevance of MRI evaluation of the GM in MS. Future studies are needed to further refine the MRI-cognition relationship to improve therapeutic decisions and prognosis of MS, and develop potential treatment strategies targeting neuroprotection.

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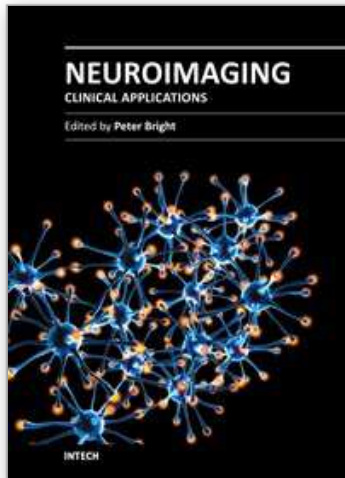
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Modern neuroimaging tools allow unprecedented opportunities for understanding brain neuroanatomy and function in health and disease. Each available technique carries with it a particular balance of strengths and limitations, such that converging evidence based on multiple methods provides the most powerful approach for advancing our knowledge in the fields of clinical and cognitive neuroscience. The scope of this book is not to provide a comprehensive overview of methods and their clinical applications but to provide a "snapshot" of current approaches using well established and newly emerging techniques.

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