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Brain mapping in multiple sclerosis: Lessons learned about the human brain

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ABSTRACT

The application of structural and functional magnetic resonance imaging (MRI) techniques in patients with multiple sclerosis (MS) has certainly helped to improve our understanding of the mechanisms responsible for clinical disability and cognitive impairment in this condition.

The numerous studies performed in MS patients have also provided many lessons on the structure-function relationships in the human brain, which could be applied to healthy subjects and to patients affected by other neurological conditions. The findings have allowed a better understanding of the processes involved in the loss of function after central nervous system (CNS) damage, and clarified the substrates of specific symptoms (e.g., cognitive impairment and fatigue), which should aid clinical recovery and help in the monitoring of disease progression.

In this review, important examples of how the application of different MRI techniques in MS might provide relevant information on the human brain are discussed. These include how damage to strategic white matter tracts can cause symptoms due to a disconnection mechanism and how involvement of a specific brain network, independent of the underlying pathological substrate, might determine certain symptoms. The role of functional and structural plasticity in clinical recovery (following an acute relapse or promoted by rehabilitation) and the mechanisms that might become the target of treatment aimed at function recovery are also considered. The ways in which network- and system-based analysis can reshape current understanding of the brain structure-function relationships are discussed. Finally, there is speculation about the relevance of inherited or acquired factors, such as age, comorbidity, brain reserve and cognitive reserve, which are likely to influence the relation between CNS damage and disease clinical manifestations.

1. Introduction

Brain functions are based on local processing and effective integration of information between different regions. The study of structural and functional brain abnormalities occurring in neurological diseases is allowing us to identify the mechanisms associated with their clinical manifestations. For many conditions, we are also seeing improvements in our knowledge of human brain structure-function relationships, which could be applied to healthy subjects and to patients affected by other neurological conditions. This might not only permit a better understanding of the processes related to loss of function after central nervous system (CNS) damage and a clarification of the substrates of given symptoms, but also allow us to identify the mechanisms of recovery which could become the targets of specific interventions.

From this perspective, multiple sclerosis (MS) represents an ideal model for analysis, because of the presence of structural damage to the CNS which can result in acute symptoms and/or accumulation of disability. Studies of CNS functional and structural abnormalities in MS patients at different phases of the disease or following therapeutic intervention have helped to identify processes related to recovery (or stability) of clinical functions or to disease progression. The assessment of patients with specific symptoms (e.g., fatigue, cognitive impairment), that are not unique to this condition, has provided important insights into the pathophysiology of these symptoms, which might inform their treatment. Finally, it has been demonstrated that many factors, including age, comorbidity, brain reserve and cognitive reserve, influence the relationship between CNS damage and clinical manifestations of the disease.

Starting from findings derived from the application of magnetic resonance imaging (MRI) in MS, this review will use MS as a model to

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discuss recent advances in the understanding of the structure-function relationship in the brain that could be applied to healthy subjects and other neurological diseases.

2. Tissue damage causes disconnection syndromes

Since the human brain is characterized by specialized areas that are strongly interconnected, direct damage not only to specific brain regions, but also to their connections, is likely to have a significant impact on brain activity and clinical function (Fig. 1).

The term "disconnection syndrome" has been used to describe all possible conditions that are related to the occurrence of focal lesions or microscopic damage to white matter (WM) connections. It was introduced by Wernicke in the 19th Century to describe conduction aphasia (Wernicke, 1874), which is a condition caused by damage to associative connections. Since then, it has been suggested that this pathological substrate is found in several other neurological and psychiatric conditions, including callosal disconnection syndrome (Sperry et al., 1969), cerebrovascular diseases (Jang et al., 2013), neurodegenerative diseases (Wang et al., 2015; Galantucci et al., 2017), schizophrenia (Friston and Frith, 1995), autism (Niculae and Paval, 2016) and dyslexia (Demonet et al., 2004).

MS is classically characterized by the formation of macroscopic focal WM lesions and diffuse damage to the so-called normal-appearing WM (NAWM) (Filippi et al., 2012a). As a consequence, it has been suggested that disconnection mechanisms are likely to be involved in some of the clinical manifestations of the disease (Rocca et al., 2015a). In particular, cognitive impairment, which affects between 40% and 70% of MS patients (Rocca et al., 2015a; Chiaravalloti and DeLuca, 2008), might be explained, at least partially, by multiple disconnection syndromes during the course of the disease, disrupting the proper integration of different brain functions.

In line with this view, correlative clinical-lesional studies have demonstrated that the location of lesions in WM tracts or structures that are critical for cognition helps to explain global cognitive dysfunction and deficits in individual cognitive domains in MS patients (Arnett et al., 1994; Vellinga et al., 2009; Kincses et al., 2010; Sepulcre et al., 2009a; Rossi et al., 2012).

The introduction of quantitative imaging techniques capable of depicting WM architecture and organization (based on diffusion-weighted imaging *in primis*) has allowed the demonstration that microscopic damage in WM tracts related to cognition partially accounts for cognitive deficits in MS. Using diffusion tensor (DT) tractography (Audoin et al., 2007; Mesaros et al., 2009, 2012; Rocca et al., 2009a; Lin et al., 2005; Llufriu et al., 2012; Ozturk et al., 2010) or voxel-wise methods (Dineen et al., 2009; Roosendaal et al., 2009; Hulst et al., 2013; Preziosa et al., 2016; Llufriu et al., 2014), several associations have been found between performance of global cognitive functions and of specific cognitive domains, including information processing speed, attention, memory, and executive functions, and abnormal tract-derived DT MRI metrics in relevant WM tracts, such as the corpus callosum, cingulum and fornix (Fig. 2).

Interestingly, by applying a random forest analysis to classify and rank several MRI measures that might explain cognitive deficits in these patients, one study (Mesaros et al., 2012) showed that DT MRI measures of lesional damage in WM tracts "critical" for cognition, such as the cingulum, better explained global cognitive impairment and deficits in single cognitive domains than diffuse NAWM abnormalities.

The notion that disconnection mechanisms are relevant in MS-related cognitive impairment has also been supported by a recent study using a tractography-based parcellation of the thalamus and its WM connections, which found that damage to specific cortico-thalamic tracts, rather than thalamic damage itself, explained cognitive impairment (Bisecco et al., 2015).

Several recent investigations have highlighted the importance of focal WM lesions in determining secondary gray matter (GM) damage or

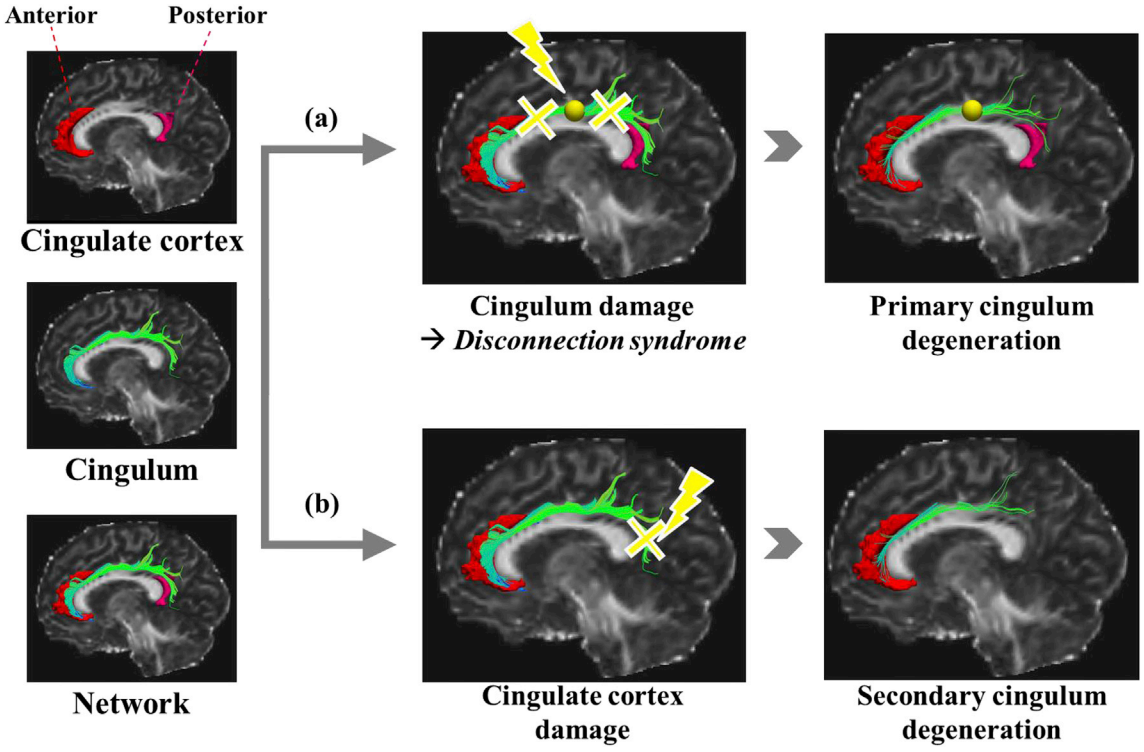

Fig. 1. Illustration of the possible substrates of network dysfunction in neurological diseases. Each network is based on specific brain regions and their interconnections. Network damage might be the consequence of: (a) primary damage to a white matter (WM) tract, due for example to the formation of a demyelinating lesion (yellow ball), causing a disconnection of two or more brain regions not directly affected by the disease; or (b) primary damage to one or more brain region(s), causing secondary damage to their WM connections. In some conditions, such as multiple sclerosis, various combinations between these two mechanisms may occur.

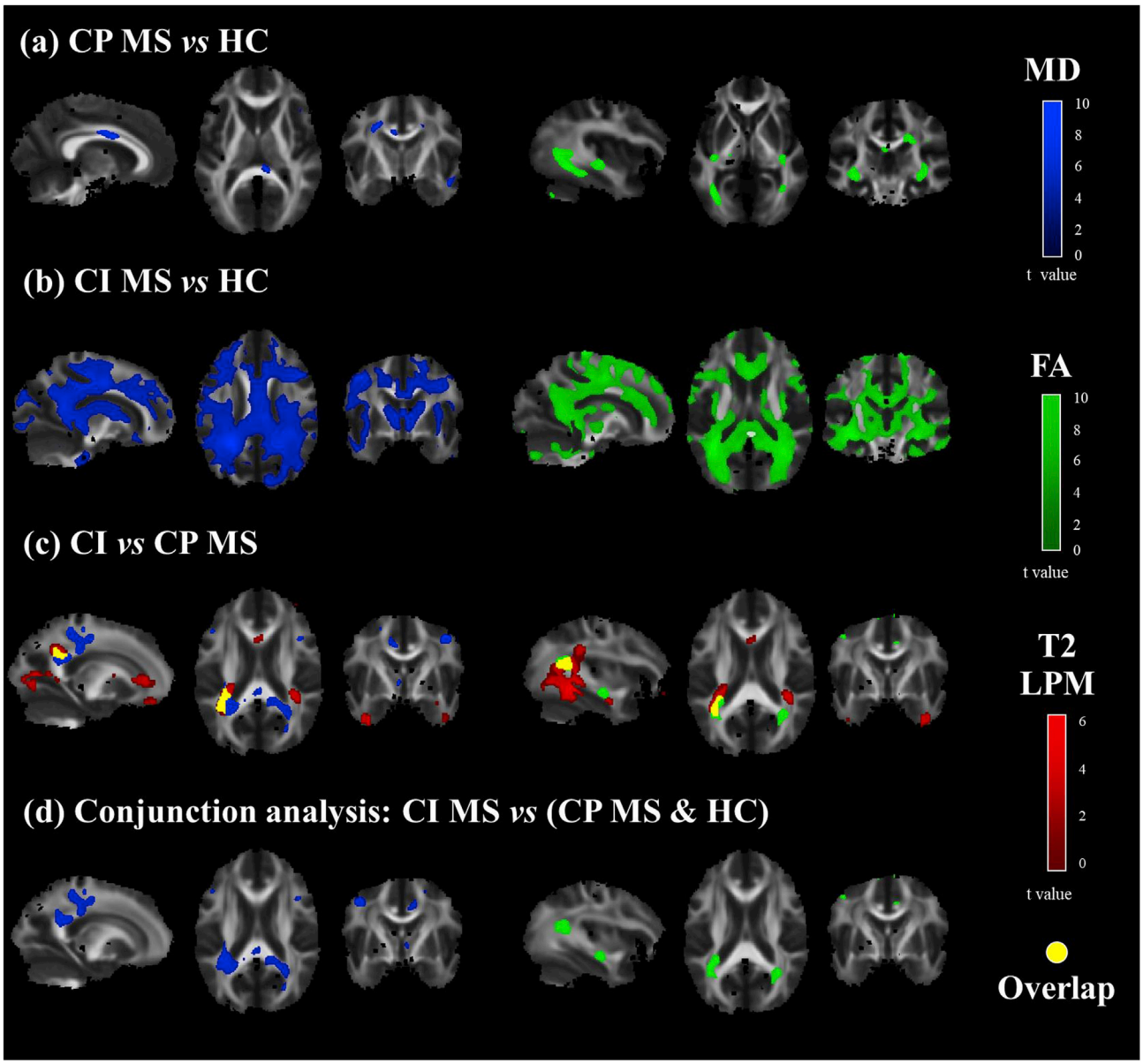

Fig. 2. Statistical parametric mapping (SPM) analysis showing regions with increased mean diffusivity (MD) (coded blue), reduced fractional anisotropy (FA) (coded green) and T2 lesion probability map (LPM) differences (coded red) superimposed on a customized FA template, comparing multiple sclerosis (MS) patients with and without cognitive impairment with healthy controls (HC) ($p < 0.05$ family-wise error corrected for multiple comparisons; cluster extent = 5 voxels): a) significantly increased MD and decreased FA in cognitively preserved (CP) MS patients *vs* HC; b) significantly increased MD and decreased FA in cognitively impaired (CI) MS patients *vs* HC; c) significantly increased MD and decreased FA and regions with higher T2 lesion occurrence in CI *vs* CP MS patients (the overlaps between diffusivity differences and T2 LPMs differences are coded yellow); d) significantly increased MD and decreased FA in CI MS patients *vs* both HC and CP MS patients. Images are presented with neurological convention (right side of the images is right side of the brain). From Preziosa et al (Preziosa et al., 2016). with permission.

dysfunction, which might be clinically relevant. In patients with primary progressive MS followed-up for two years, WM lesion abnormalities predicted NAWM damage and consequent GM atrophy (Bodini et al., 2016). In cognitively-intact MS patients, focal WM lesions contributed to a functional disconnection within the hippocampal-centered network, that was associated with depression (Rocca et al., 2015b) (Fig. 3).

Clearly, GM damage may also be a primary phenomenon in MS, since GM abnormalities seem to proceed, at least partially, independently from the accumulation of WM damage (Calabrese et al., 2015).

3. Central fatigue: a symptom due to damage of a specific brain circuit

Probably everyone during their life complains of a lack of energy, feelings of exhaustion, and the perception of an inability to perform mental and physical activities. However, fatigue is also a chronic and frequent manifestation of several diseases, with a strong impact on patients' quality of life (Chaudhuri and Behan, 2004). It has been described as a typical symptom of systemic (e.g., anemia, cancer (Barsevick et al., 2010), human immunodeficiency virus infections (Jong et al., 2010), immunomediated conditions (Morris et al., 2016)) and neurological diseases (e.g., post-stroke (Staub and Bogousslavsky, 2001; Winward et al., 2009), chronic fatigue syndrome (Fukuda et al., 1994), Parkinson disease (Beiske et al., 2010; Friedman et al., 2011), MS (MacAllister and Krupp, 2005; Ayache and Chalah, 2017) and traumatic brain injury (Cantor et al., 2013; Mollayeva et al., 2014)), the manifestation of psychiatric diseases (e.g., depression) or a side-effect of drugs prescribed for the previous disorders (e.g., anti-hypertensive agents, beta interferons, anxiolytics, antipsychotics) (Chaudhuri and Behan, 2004).

The term "central fatigue" has been introduced to describe the loss of

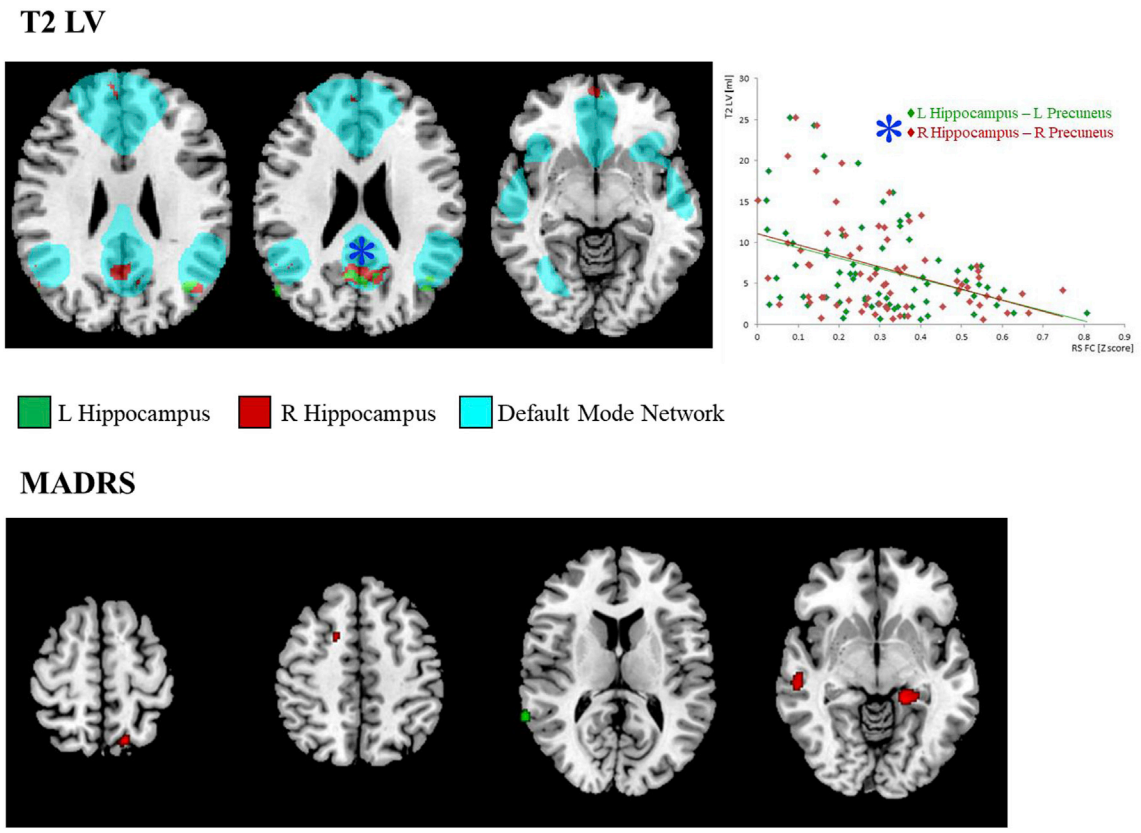

Fig. 3. Results (and illustrative scatterplots) of the analysis of correlation in multiple sclerosis (MS) patients between reduced resting state (RS) functional connectivity (FC) of the left (L) (green) and right (R) (red) hippocampus and brain T2 lesion volume (LV) and Montgomery-Asberg Depression Rating Scale (MADRS). The T2 LV results are superimposed onto a standard template mask of the default mode network (light blue areas) (Franco et al., 2009). Green scatterplots refer to correlations with L hippocampal RS FC, while red scatterplots refer to correlations with R hippocampal RS FC. Images are presented in radiological convention. Modified from (Rocca et al., 2015b), with permission.

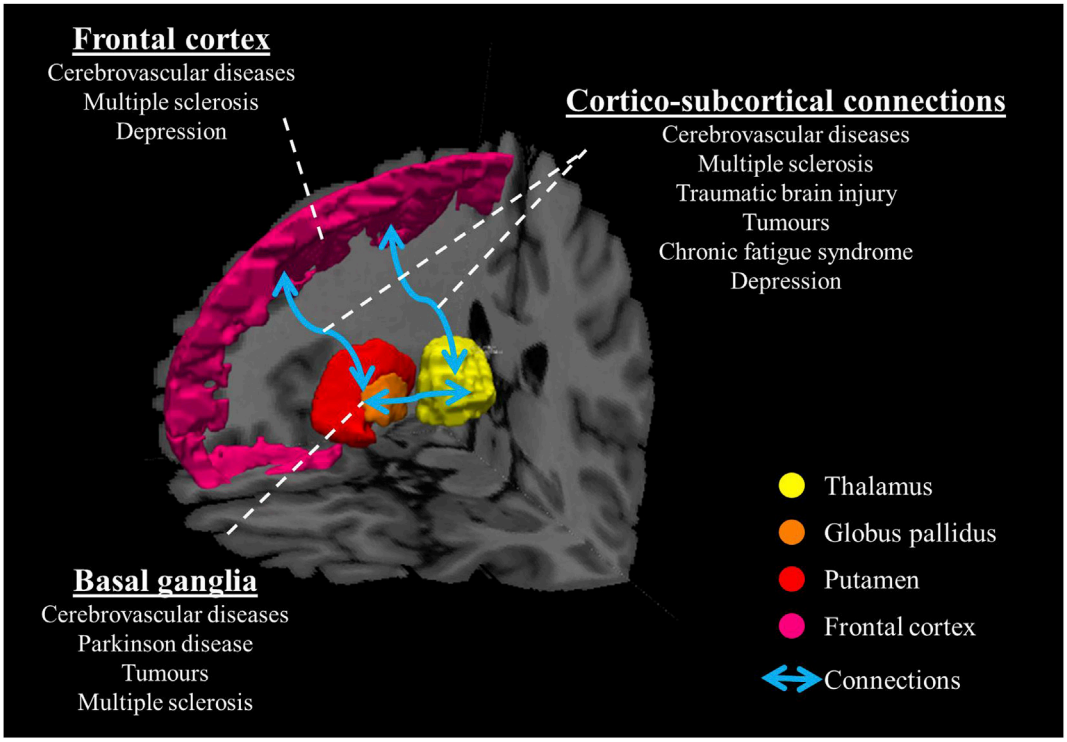

Fig. 4. Illustration of the possible substrates of central fatigue in different neurological diseases. Damage to cortico-subcortical circuits and basal ganglia connections is likely to be the common pathological substrate of central fatigue in several different conditions.

endurance in both physical and cognitive tasks in the absence of serious weakness or dementia (Chaudhuri and Behan, 2000). Several pieces of evidence arising from different diseases suggest a role for structural and functional abnormalities of specific brain circuits in the genesis of this symptom (Chaudhuri and Behan, 2000, 2004; Morris et al., 2016; Ayache and Chalah, 2017; Dobryakova et al., 2015), with the failure of basal ganglia connections, particularly with the prefrontal cortex, playing a major role (Chaudhuri and Behan, 2000, 2004) (Fig. 4), possibly due to an imbalance in the dopamine axis (Dobryakova et al., 2015).

In MS, fatigue is one of the most frequent and disabling symptoms, present in up to 80% of patients and being independent of the clinical form and stage of the disease (MacAllister and Krupp, 2005). Neurophysiological (Sheean et al., 1997; Leocani et al., 2001), metabolic (Roelcke et al., 1997; Tellez et al., 2008; Tartaglia et al., 2004) and functional imaging (Filippi et al., 2002; Rocca et al., 2007, 2009b; Finke et al., 2015; Rocca et al., 2016a; DeLuca et al., 2008; DeLuca et al., 2009; Cruz Gomez et al., 2013; Pravata et al., 2016; Sepulcre et al., 2009b; Tartaglia et al., 2008; Engstrom et al., 2013; Genova et al., 2013) studies

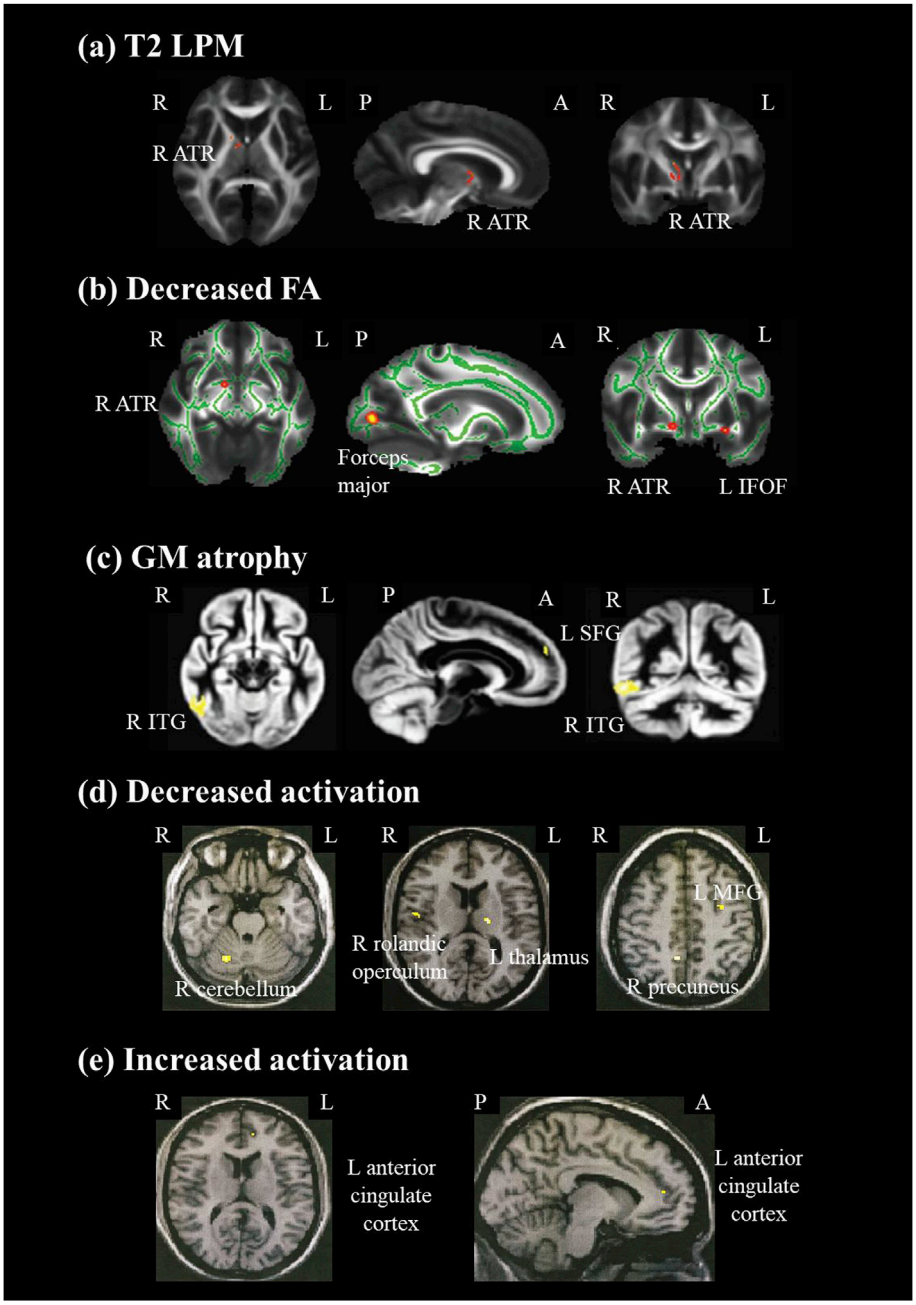

Fig. 5. Summary of the main structural and functional MRI findings in multiple sclerosis (MS) patients with fatigue. (a) Clusters of voxels (red) where fatigued MS patients had higher frequency of lesion occurrence compared with non-fatigued MS patients ($p < 0.01$, uncorrected), adapted from Rocca et al (Rocca et al., 2014). with permission; (b) clusters of voxels with significantly decreased fractional anisotropy (FA) (red-yellow) superimposed on a FA atlas (green) in fatigued vs non-fatigued MS patients ($p < 0.01$, uncorrected), adapted from Rocca et al (Rocca et al., 2014). with permission; (c) clusters of gray matter (GM) atrophy (yellow) superimposed on a customized GM template in fatigued vs non-fatigued MS patients and healthy controls ($p < 0.001$, uncorrected), adapted from Rocca et al (Rocca et al., 2014). with permission; (d) cortical activations of right-handed non-fatigued MS patients during a motor task in comparison to right-handed fatigued MS patients performing the same task ($p < 0.05$, corrected for multiple comparisons), adapted from Filippi et al (Filippi et al., 2002). with permission; (e) cortical activations in fatigued MS patients during a motor task in comparison with right-handed non-fatigued MS patients performing the same task, adapted from Filippi et al (Filippi et al., 2002). with permission. Abbreviations: A = anterior, L = left, P = posterior, R = right; T2 LPM = T2 lesion probability map, ATR = anterior thalamic radiation; IFOF = inferior fronto-occipital fasciculus; ITG = inferior temporal gyrus; SFG = superior frontal gyrus.

have consistently supported the hypothesis of a central origin of MS-related fatigue by showing a dysfunction of cortico-subcortical circuits, mainly involving fronto-parietal regions and the basal ganglia. In particular, these studies showed abnormal recruitment of core motor areas, such as the primary sensorimotor cortex, supplementary motor area and cerebellum, as well as of cortico-subcortical circuits, which are part of the sensorimotor network and are central to motor planning and execution (Fig. 5).

Several structural MRI studies have provided discordant or negative results on the presence of structural MRI abnormalities (in terms of lesions, NAWM damage or GM damage) that might explain the presence and severity of fatigue in MS patients (Bakshi et al., 1999; Mainero et al., 1999; Tedeschi et al., 2007; Marrie et al., 2005; Codella et al., 2002a, 2002b). Several factors may help to explain these inconsistencies in the literature, including the definition used for of fatigue, the scale applied to quantify its severity, the characteristics of the MS patient cohorts recruited, the type of MR images acquired and methods used for their analysis. However, with the use of multiparametric approaches and advanced methods of analysis, recent evidence has supported the role of structural damage to anterior cortico-subcortical networks in the pathogenesis of fatigue. Indeed, fatigue in MS patients has now been associated with more severe diffusivity abnormalities of the forceps minor, anterior thalamic radiation and uncinate fasciculus (Genova et al., 2013; Gobbi et al., 2014a; Rocca et al., 2014; Bisecco et al., 2016; Pardini et al., 2010), the thalamus (Wilting et al., 2016) as well as atrophy of several WM and GM regions located in the frontal (Cruz Gomez et al., 2013; Riccitelli et al., 2011) and temporal lobes (Rocca et al., 2014; Gobbi et al., 2014b; Pellicano et al., 2010; Calabrese et al., 2010) (Fig. 5).

4. Neuroplasticity and restoration of function after acute relapses and rehabilitation

It had long been believed that the human brain does not change substantially after the initial phase of development, but it is now accepted that structural and functional modifications of brain organization and connections (plasticity) occur throughout life, allowing cognitive and motor skill learning, memory formation and consolidation, enabling us to face everyday challenges by adapting dynamically to environmental and pathological stimuli (Dayan and Cohen, 2011; Zatorre et al., 2012).

The term “neuroplasticity” refers to the ability of the CNS to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function, and connections, and it includes a variety of mechanisms that modify neurons and neural pathways, including the strength of synaptic transmission, the sprouting of novel synapses, changes to glial cell numbers and WM fiber features (e.g., degree of myelination, membrane voltage-gated ion channel distribution, axonal diameter and fiber packing density), and the induction of angiogenesis and neurogenesis (Zatorre et al., 2012).

Spontaneous clinical recovery and compensatory mechanisms may occur after CNS injury associated with different neurological conditions, not only following an acute insult, as in the case of stroke (Ward, 2006; Price and Crinion, 2005), but also in chronic and degenerative conditions (Masdeu et al., 2005; Appel-Cresswell et al., 2010).

The formation of acute symptomatic lesions in MS patients offers the ideal model to study *in vivo* the effects of acute damage to a specific neuronal pathway related to a loss of function, and to identify the mechanisms associated with functional recovery. In addition, the study of the correlation between disease clinical manifestations and measures derived from functional and structural MRI techniques helps to clarify the processes that determine the clinical outcome. All of this may provide fundamental insights that guide the development of intervention procedures, particularly in the field of rehabilitation.

A longitudinal functional (fMRI) study of motor system recruitment in MS patients with an acute motor relapse secondary to the formation of pseudotumoral MS lesions along the motor pathways has demonstrated that functional plasticity is a dynamic phenomenon and that the role (adaptive *vs* maladaptive) played by the different brain areas in terms of compensation or restoration of function may vary according to the time of the investigation (Mezzapesa et al., 2008). In particular, at the onset of the relapse, increased recruitment of motor areas located in the contralesional (healthy) hemisphere was detected upon movement of the impaired upper limb. After 1-year of follow-up, patients with good clinical recovery had relateralization of motor network function to the previously affected hemisphere, whereas those patients with poor clinical recovery continued to show recruitment of motor areas in the contralesional hemisphere. Thus, restoration of function in motor areas of the affected hemisphere may be classified as an adaptive mechanism with a critical role in favorable clinical outcomes following acute CNS insults. On the other hand, recruitment of parallel existing pathways in the undamaged hemisphere may be a protective phenomenon, replacing functional activity of the affected hemisphere, in the early stages of the acute insult. The persistence of this activation over time, which may be due to the lack of recovery of the affected hemisphere, is likely to represent a maladaptive mechanism, contributing to poor clinical recovery.

Outside the acute relapse, many other factors (discussion of which is beyond the scope of this review) have been shown to modulate the patterns of fMRI recruitment and the clinical manifestations of MS, including the burden and location of focal lesions, and the involvement of the NAWM, GM and spinal cord (see (Filippi and Rocca, 2009; Rocca et al., 2016b) as comprehensive reviews). A cross-sectional study of motor system recruitment in relapse-onset MS patients at different phases of the disease without impairment in the performance of the task investigated has suggested that, with disease progression, there may be a sort of hierarchy of mechanisms of functional reorganization (Rocca et al., 2005). In early phases of MS, when tissue damage was limited, areas in the contralateral primary sensorimotor cortex typically devoted to motor tasks were activated. With initial accumulation of disability, bilateral activation of these regions was noted. With further accumulation of disability, additional recruitment of areas related to the motor network, such as the secondary somatosensory cortices and thalamus, was observed. Finally, in disabled secondary progressive MS patients, a distributed recruitment of many areas, located within the frontal, parietal and temporal lobes was detected (Rocca et al., 2005).

Promoting restoration of function and competence of dysfunctional brain networks is one of the main goals of motor and cognitive rehabilitation. Even though the mechanisms underlying clinical improvement after rehabilitation are not yet fully understood, by applying different rehabilitation procedures, several studies in MS patients have consistently demonstrated that motor and cognitive rehabilitation results in an improvement of the rehabilitated function (i.e., motor functions, attention, memory, and executive function) and that this improvement is somehow mediated by modification of recruitment and/or functional connectivity occurring in function-related networks (Chiaravalloti et al., 2015; Prosperini et al., 2015; Filippi et al., 2012b; Parisi et al., 2014; Sastre-Garriga et al., 2011; Cerasa et al., 2013; Bonavita et al., 2015; Chiaravalloti et al., 2012; Leavitt et al., 2014a; Dobryakova et al., 2014a; Dobryakova et al., 2014b; Hubacher et al., 2015).

In line with this, three-months of computer-assisted cognitive rehabilitation of attention, information processing and executive functions in relapsing-remitting MS patients with selective deficits in these functions resulted in cognitive improvement through enhanced recruitment of brain networks subserving the trained functions (Fig. 6) (Filippi et al., 2012b).

Interestingly, since the results of fMRI analysis of the previous study (Filippi et al., 2012b) pointed towards a role for the left dorsolateral prefrontal cortex in improving cognitive functions, this region was selected, in a subsequent study, as a target for an anodal transcranial direct current stimulation, in combination with attention training in MS patients impaired in attention/speed of information processing (Mattioli et al., 2016). Transcranial direct current stimulation can modulate cortical excitability through the application of a direct current of

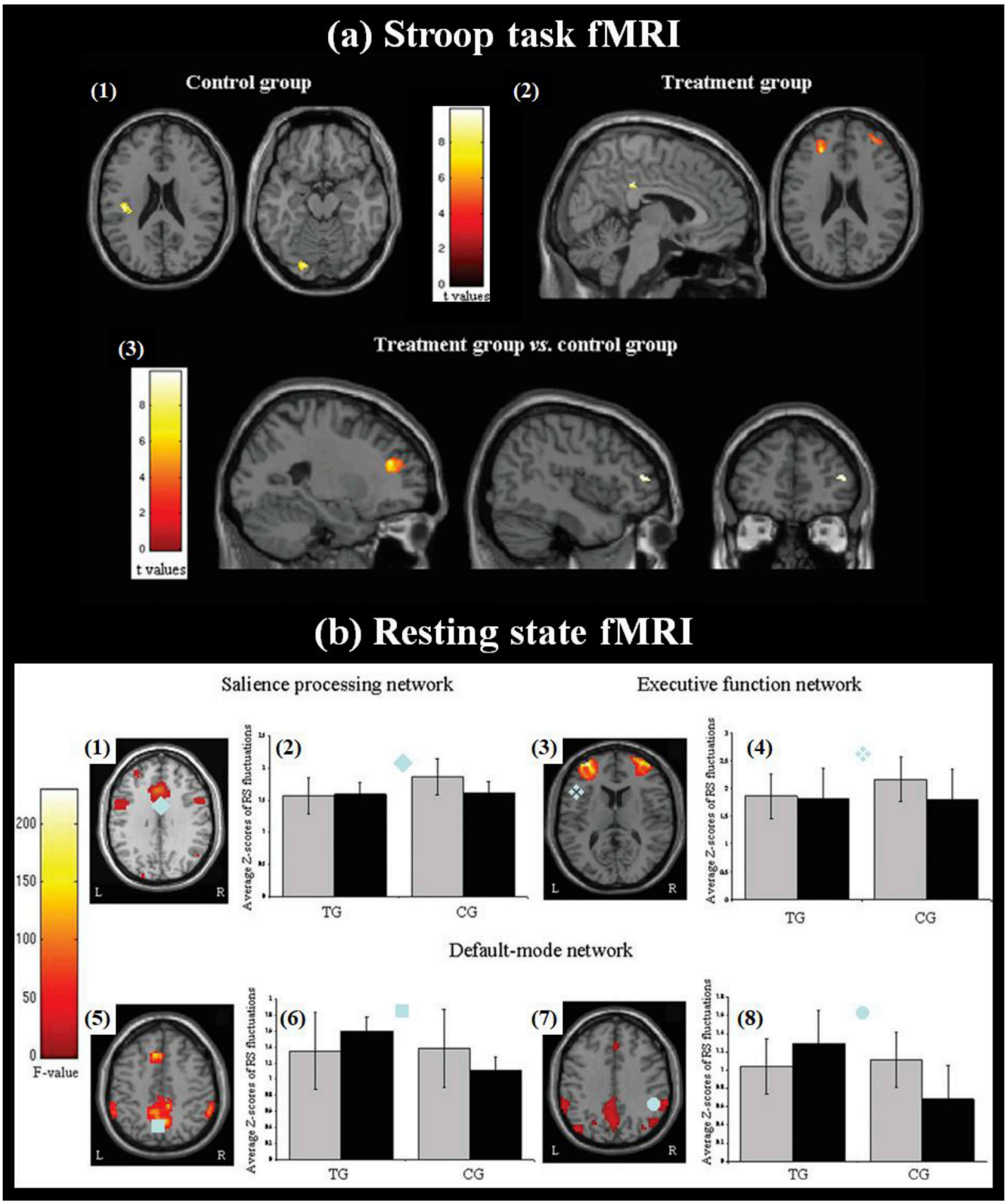

Fig. 6. (a) Statistical parametric mapping results (color-coded for t values) overlaid on high-spatial resolution T1-weighted MR images showing changes of functional MRI activations during the Stroop interference condition in (Wernicke, 1874) control group (CG) (patients not undergoing cognitive rehabilitation) (Sperry et al., 1969), treatment group (TG) (patients undergoing cognitive rehabilitation), and (Jang et al., 2013) in TG *vs* CG. Images are presented in neurological convention ($p < 0.05$, corrected for multiple comparisons). (b) Axial spatial maps and corresponding graphs show average z-scores of resting-state functional connectivity (FC) that were significantly different between the TG and CG over the three months of the study (gray bars = baseline values, black bars = follow-up values). A significant increase (or a stability) of resting-state FC over time in the TG *vs* a significant decrease of resting-state FC in the CG was found in (Wernicke, 1874; Sperry et al., 1969): the anterior cingulate cortex for the salience processing network ($p = 0.02$) (Jang et al., 2013; Wang et al., 2015); the left dorsolateral prefrontal cortex for the executive function network ($p = 0.01$) (Galantucci et al., 2017; Friston and Frith, 1995); the right posterior cingulate cortex and/or precuneus for the default-mode network ($p = 0.006$) and (Niculae and Paval, 2016; Demonet et al., 2004) the inferior parietal lobule for the default-mode network ($p = 0.02$). Adapted from Filippi et al (Filippi et al., 2012b). with permission.

low-level intensity via electrodes placed on the subject's scalp. This current determines changes in the permeability of the neural membrane, influencing neuronal polarization and glutamatergic *N*-methyl-D-aspartic receptors which can persist after the direct stimulation. This procedure exerted positive results in several neurological and psychiatric conditions (Lefaucheur et al., 2017; Stagg and Nitsche, 2011). In the study of MS patients, the combination of cognitive training with an anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex during ten daily sessions fostered improvements in attention and executive function, which persisted up to 6 months after the intervention (Mattioli et al., 2016).

Recent lines of evidence in healthy individuals undergoing motor and cognitive training have shown that CNS plasticity is not limited to modifications of function of specific brain areas, since structural changes at the level of GM morphology and WM architecture (i.e., structural plasticity) also occur (Zatorre et al., 2012) at the level of regions involved in the trained function. In healthy subjects, structural CNS reshaping seems to occur after just a few days of training (Driemeyer et al., 2008; Taubert et al., 2010), is preserved in elderly subjects (Boyke et al., 2008), is strictly modulated by the type of exercise, duration and timing (Taubert et al., 2010; Ceccarelli et al., 2009; Draganski et al., 2004; Filippi et al., 2010; Hamzei et al., 2012; Rocca et al., 2016c), and is functionally relevant, since it has been correlated to functional improvements in the trained function (Taubert et al., 2010; Draganski et al., 2004; Hamzei et al., 2012; Rocca et al., 2016c).

Studies of structural plasticity following rehabilitation in MS patients are scant, and limited by the lack of enrollment of comparable groups of healthy controls. While a cognitive rehabilitation study (Filippi et al., 2012b) has suggested that there is impaired structural plasticity in MS patients (since no modifications of WM/GM structural measures were detected following rehabilitation), studies of motor training in this condition have found amelioration or stabilization of microstructural tissue measures in relevant WM tracts, including the corpus callosum (Bonzano et al., 2014; Ibrahim et al., 2011), corticospinal tract (Bonzano et al., 2014) and cerebellar peduncles (Prosperini et al., 2013) after motor training, which were related to improved motor function. However, these changes to WM microstructural properties, as well as clinical improvements, tended to disappear a few weeks after the termination of the motor rehabilitation procedures (Prosperini et al., 2013), suggesting that the extensive and distributed damage to the WM and GM, distinctive of MS, is likely to impair the structural plasticity potential of these patients.

One structure that may escape this rule is the hippocampus. Several pieces of evidence suggest that the dentate gyrus (DG) of the hippocampus is one of the few brain regions with preserved neurogenesis in adults (Eriksson et al., 1998). Hippocampal damage (lesions, atrophy and microstructural tissue abnormalities) characterizes MS patients, with an uneven distribution at the level of the different hippocampal subfields. Adaptive structural plasticity of the hippocampus (which may reflect neurogenesis) might represent a "physiological" response to disease-related damage in the early phases of the disease and a potential target for intervention. In line with this, using MR-based radial mapping analysis of the hippocampal surface, a recent study detected an expansion of the DG of the hippocampus in relapse-onset MS patients, which was more pronounced in the relapsing-remitting than in the secondary progressive phase of the disease, and was associated with better cognitive performance and the volume of focal WM lesions, suggesting a functional compensation role for this finding (Rocca et al., 2015c). A seminal study in two MS patients demonstrated an enlargement of the hippocampus with concomitant improvement of memory functions after three months of aerobic training (Leavitt et al., 2014b). Even though these results need to be verified in other patient samples, they are of great interest since they may point to a tool for monitoring reparative mechanisms following CNS inflammation.

Clearly, despite the encouraging results, major efforts are still needed to help understand the substrates promoting neuroplasticity following acute relapses and rehabilitation. The studies available share several limitations, including the small sample sizes, the lack of proper control groups, their study designs, which are often not randomized nor blind, and the application of MRI techniques which are not specific for the mechanisms underlying neuroplasticity (Prosperini et al., 2015). Furthermore, between-study comparisons are hampered by differences of type and duration of the interventions, clinical outcomes and MRI parameters analyzed (Prosperini et al., 2015).

5. Network- and system-based analysis to assess brain structure-function relationship

Since sensorimotor, cognitive and behavioural functions rely on large-scale network interactions, with specific brain systems involved in different functions, mapping structural and functional brain networks is likely to improve our understanding of the brain structure-function relationship and of the pathophysiological aspects of neurological and psychiatric disorders.

Graph theory approaches are currently being applied in an attempt to

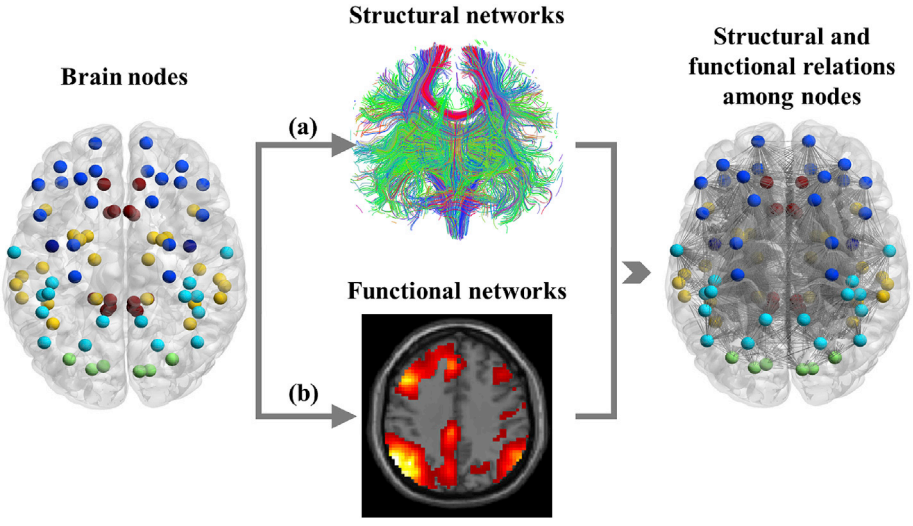

Fig. 7. Schematic showing the possibilities for (a) structural and (b) functional connectomic analyses with MRI. Brain nodes, which correspond to different brain regions, are identified by division of the brain into regions using several different strategies (e.g. *a priori* anatomical templates). Maps of structural or functional connectivity can be generated by (a) diffusion tensor imaging or (b) functional MRI. Inter-regional connectivity is then measured using brain tractography for diffusion tensor imaging or with analyses of dependencies in regional-activity time courses for functional MRI.

comprehensively map brain neural connections (the so-called human connectome) (Fig. 7) (Bullmore and Sporns, 2009; Filippi et al., 2013), to evaluate developmental trajectories of brain networks, their physiological modifications during ageing and their pathological changes due to several conditions (Filippi et al., 2013).

Only a few studies have used these methods to analyze network functional and structural alterations in MS patients (He et al., 2009; Shu et al., 2011, 2016; Schoonheim et al., 2012; Rocca et al., 2016d; Li et al., 2013; Muthuraman et al., 2016; Fleischer et al., 2017). A study of 246 MS patients and 55 matched healthy controls (Rocca et al., 2016d) found that global network properties were abnormal in MS patients compared to controls, and helped to distinguish cognitively impaired MS patients from controls, while they did not allow the main MS clinical phenotypes to be differentiated. Regional analyses of brain hubs, which represent regions with a high number of connections with other areas and with a central position in network organization, showed that, compared to controls, MS patients also had a loss of hubs in the superior frontal gyrus, precuneus and anterior cingulum in the left hemisphere; a different lateralization of basal ganglia hubs (mostly located in the left hemisphere in controls, and in the right hemisphere in MS patients); and the formation of hubs, not seen in controls, in the left temporal pole and cerebellar lobule IV-V. This modification of regional network properties was found to contribute to cognitive impairment and phenotypic variability of MS. The role of network functional abnormalities in cognitive deficits in MS patients has been confirmed by other studies, in smaller groups of subjects. In early MS patients, diminished functional integration between separate functional modules contributed to worse performance in a dual task (Gamboa et al., 2014). Another study has suggested an influence of gender on this line of research, since decreased network efficiency (which was correlated with reduced visuospatial memory) was found in male MS patients only (Schoonheim et al., 2012).

Structural network abnormalities, usually quantified from DT MRI and/or 3D T1-weighted volumetric scans, revealed a decreased network efficiency which was related to the extent of WM lesions and the severity of clinical disability (He et al., 2009; Shu et al., 2011). Interestingly, a study that assessed both structural and functional network abnormalities in patients with clinically isolated syndromes (CIS) and MS showed that CIS patients had only structural network abnormalities, while in MS patients both the structural and functional networks were altered. This suggests that in WM diseases, modification of network structure may precede modification of network function (Shu et al., 2016), possibly as consequence of this structural alteration. Another study, which analyzed structural connectivity of the WM and GM networks, showed that concomitant increase of local and modular structural connectivity of WM and GM networks can contribute to a preservation of clinical function in the first year after disease onset. A divergence of WM and GM network trajectories (with continuing GM network reorganization and a plateauing of WM reorganization after the first year) was accompanied by clinical disability (Fleischer et al., 2017). By applying an approach that can infer structural connectivity loss using a large reference set of healthy tractograms, without requiring tractography in pathological brains (Kuceyeski et al., 2013), another study has demonstrated that WM abnormalities are associated with atrophy of connected deep GM regions and that both contribute to processing speed performance in patients with early MS (Kuceyeski et al., 2015).

While the application of advanced methods of analysis to DT MRI and fMRI to model connectivity is providing interesting and novel insights into the relationship between brain structure and function and their role in the clinical manifestations of neurological diseases, several challenges still remain. These imaging modalities are not pathologically specific. Therefore, we need to improve our understanding of the biological information underlying the structural and functional abnormalities that they detect. Additionally, there are inconsistencies between existing studies, which might be attributable to the clinical heterogeneity of the patient groups as well as to differences in imaging parameters and methods of analysis.

6. Factors affecting investigation of the structure-function relationship

Many factors can influence the assessment of the relationship between structural and functional abnormalities of the CNS and their clinical manifestations, not only in MS, but also in the majority of neurological and psychiatric conditions.

Clearly, an appreciation of these factors and of their role in the structure-function relationship is of the utmost importance, not only to give a better understanding of the mechanisms responsible for disease clinical manifestations, but also for establishing strategies aimed at minimizing negative factors and potentiating positive ones.

In MS, aging is one of the stronger predictors of the accumulation of severe disability, of entry into the progressive phase and of the development of more severe brain damage (Confavreux and Vukusic, 2006; Scalfari et al., 2014; Enzinger et al., 2005). Among the mechanisms associated with aging, reduced efficiency in the repair of damage and in neuroplasticity (Burke and Barnes, 2006), iron accumulation (Ward et al., 2014) and metabolic abnormalities, including mitochondrial dysfunction and oxidative stress (Currais, 2015) are likely to play a role.

Risk factors typically associated with aging, including hypertension (Enzinger et al., 2005; Beauchet et al., 2013), diabetes mellitus (Enzinger et al., 2005; Climie et al., 2015; Cho et al., 2016), hyperlipidemia (Meyer et al., 1999) and elevated plasma homocysteine (Hooshmand et al., 2016) have been correlated with more severe structural brain damage, clinical disability and cognitive impairment. Cerebral small vessel disease (Pantoni, 2010), a condition which affects cerebral small arterioles and capillaries, is another age-related phenomenon that may influence MS course (Geraldes et al., 2016), since vascular comorbidities contribute to MS progression (Marrie and Horwitz, 2010), higher load of WM lesions and brain atrophy (Kappus et al., 2016).

Genes are another factor to be considered. In line with studies in neurodegenerative diseases, allelic variations affecting the gene coding for apolipoprotein E (*APOE*), a protein implicated in lipid homeostasis, have been associated with more severe brain atrophy in ApoE ε4 carriers (Enzinger et al., 2004, 2005). Polymorphisms in genes involved in immune response (Liguori et al., 2011; Okuda et al., 2009; Jensen et al., 2010; Kalincik et al., 2013; Sombekke et al., 2011; Van der Walt et al., 2011; Gourraud et al., 2013), epigenetic functions (Inkster et al., 2013), glutamate signal (Strijbis et al., 2013; Matsushita et al., 2015) and neuronal development and survival (Gourraud et al., 2013; Matsushita et al., 2015; Dinacci et al., 2011) influence disease course and brain damage accumulation.

In MS, systemic and neurological comorbidities, together with negative lifestyle factors, are common and can impact the delay between symptom onset and diagnosis, the disease clinical phenotype, disability progression, and health-related quality of life (Marrie and Horwitz, 2010). Systemic comorbidities, including disimmune, psychiatric (e.g., depression), cardiopulmonary and sleep disorders, can further worsen clinical disability and brain damage (Marrie and Horwitz, 2010). Smoking, alcohol intake, and obesity are all associated with increased risk of disability progression and more severe accumulation of brain damage, as measured by focal WM lesion load and atrophy (Enzinger et al., 2005; Marrie and Horwitz, 2010).

Many MS patients withstand severe brain damage without significant clinical disability or cognitive impairment. Similar pathological-cognitive dissociations have been found in patients with other neurological diseases, such as Alzheimer's disease (Bennett et al., 2006, 2012) and have promoted the theories of “brain reserve” (Satz, 1993; Sumowski and Leavitt, 2013; Staff et al., 2004) and “cognitive reserve” (Sumowski and Leavitt, 2013; Stern, 2002, 2012) as possible mechanisms to explain such findings.

The theory of reserve suggests that both heritable/genetic and environmental (the “cognitive reserve”) (Stern, 2002) factors contribute to reserve against disease-related cognitive decline, such that patients with higher reserve are better able to withstand disease burden without

clinical disability and cognitive impairment.

It has been suggested that subjects with higher maximal lifetime brain growth (MLBG) due to developmental differences, defined as "brain reserve" (Satz, 1993; Staff et al., 2004), are able to withstand more severe disease burden without clinical disability and cognitive impairment. It is thought that they can accumulate more brain damage before reaching a threshold at which clinical manifestations occur (Satz, 1993; Sumowski and Leavitt, 2013). Larger MLBG is linearly related to higher neuronal and synaptic count (Haug, 1987). As a consequence, it may result in more robust neural networks resistant to disease-related disruption. Unfortunately, in the current literature, only a rough estimate of brain reserve is usually obtained, by quantifying head size or intracranial volume. Alternative measures of brain reserve, including imaging measures closer to synaptic count, or size of specific brain structures, should be considered in the design of future studies.

Acquired/environmental factors largely based on the product of life experience (intellectual enrichment, educational attainment, vocabulary, and occupational activities), defined as "cognitive reserve" (Sumowski and Leavitt, 2013; Stern, 2002, 2012), also seem to protect against cognitive decline. Several studies in MS patients have shown that increased intellectual enrichment attenuates the negative effect of MS disease burden (T2 lesions and brain atrophy) on cognitive status, particularly memory difficulties, independently from maximum lifetime brain growth and education (Sumowski et al., 2010, 2013; Pinter et al., 2014; Amato et al., 2013; Benedict et al., 2010; Sumowski et al., 2014). The protective role of a large MLBG (a largely heritable component of reserve) in the moderation or attenuation of the negative effect of disease burden on clinical disability and cognition has also been recently demonstrated (Sumowski et al., 2013, 2014, 2016).

An important aspect that requires further investigation is the generalizability of the results on cognitive reserve in MS patients, considering that many of these patients present with the first clinical attack at ages where the acquisition of this reserve is still occurring, particularly since there is evidence that pathological tissue alterations may even precede the first demyelination event.

7. Conclusions

Due to the complexity of its pathological substrates and the heterogeneity of disease clinical manifestations, MS represents a good model to map the relationships between abnormalities of structure and function in the CNS. During the past few years, extensive application of structural and functional MRI methods to patients with MS at different stages of the disease and with different clinical symptoms, has led to both the identification of the mechanisms associated to spontaneous recovery of function, and an improvement in our understanding of the factors leading to fixed neurological deficits. These achievements may be easily translated to other neurological conditions. All of this is pivotal for the development of intervention strategies for the preservation or restoration of function.

Declaration of interest

M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer's Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

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