Cognitive and brain reserve for mind-body therapeutic approaches in multiple sclerosis: A review
Cristiano Crescentinia, Cosimo Urgesia, Franco Fabbroba and Roberto Eleoprac

Abstract.
Purpose: Cognitive impairment is one of the most disabling symptoms of multiple sclerosis (MS), affecting a large proportion of patients and having a severe impact on their quality of life. Nevertheless, there exists a large variability in the neuropsychological profiles of MS patients and some of them appear to withstand better than others the MS-related brain pathology before showing cognitive decline. In recent years, many studies have made use of concepts such as cognitive reserve and brain reserve to take account of the inter-individual discrepancy between cognitive impairment and MS pathology. Critically, these studies have left open the fundamental issue of the clinical implications of this research for the treatment of cognitive dysfunction in MS.
Methods and Results: We provide an updated and extensive overview of the studies that have explored cognitive and brain reserve in MS and discuss their implications for non-pharmacological therapeutic strategies aimed at potentiating patients’ reserve. In particular, the possible utility of integrated approaches based on mind-body techniques such as mindfulness-meditation is considered.
Conclusions: We conclude that these techniques represent challenging mental enriching activities that may help cultivating cognitive reserve and more systematic research on their efficacy to protect against cognitive degradation in MS is encouraged.

Keywords: Multiple sclerosis, cognitive reserve, brain reserve, cognitive impairment, mind-body medicine, yoga, mindfulness-meditation

1. Introduction
Multiple Sclerosis (MS) is a chronic inflammatory, demyelinating and degenerative disease of the central nervous system (CNS) (Noseworthy et al., 2000). It is the most common nontraumatic neurologic disease among young adults. Long underestimated and under-recognized, the effects of MS on cognition have received increasing scientific credit in recent decades. Nowadays, cognitive disturbances in MS are considered as one of the most disabling symptoms of the disease, occurring at various degrees in 40–65% of patients affected by MS (Rao, 1991; Chiaravalloti and DeLuca, 2008; Jongen et al., 2012; Guimarães and Sá, 2012). The most frequently affected neuropsychological domains in MS are speed of information processing, complex attention/working memory, executive function, and learning and memory. Cognitive changes, especially when coupled with other disabling
symptoms such as depression, fatigue, or anxiety, can profoundly impair patients’ family life and social relationships and hence, more globally, most aspects of health-related quality of life (HRQOL) (Chiaravalloti and DeLuca, 2008).

Recent advances in the methodology of conventional and non-conventional magnetic resonance imaging (MRI) have importantly contributed to a better understanding of the mechanisms of cognitive dysfunction associated with MS, for instance disclosing the correlations between performance on neuropsychological tasks tapping into different cognitive domains and a variety of MRI measures such as T1- and T2-visible lesion volumes and, in particular, atrophy in grey matter critical brain structures (e.g., Rao et al., 1989; Chiaravalloti and DeLuca, 2008; Filippi and Rocca, 2010; Filippi et al., 2010; Shardell et al., 2013; see also Nielsen et al., 2013). However, several recent studies have shown that these correlations fail to capture the full variability of the profiles of cognitive dysfunction observed in patients with MS. Notwithstanding, the application of functional MRI (fMRI) to cognitive impairment in MS has highlighted a high degree of brain plasticity and neurofunctional reorganization of cognitive processing in response to MS-associated brain pathology (e.g., Mainiero et al., 2004, 2006; Filippi and Rocca, 2009; Jongen et al., 2012).

In the last ten years, around twenty studies drew on concepts of “cognitive reserve” (CR) and “brain reserve” (BR) in order to solve at least part of the discrepancy between cognitive impairment and MS-related brain structural damage. This, CR and BR concepts should help explaining why some MS patients are better able than others to compensate for brain damage. The aim of the present article is twofold: i) to give a more updated and extensive review of the studies that have explored CR and BR in patients with MS, relative to past reviews on the topic (Benedict and Zivadinov, 2011; Sumowski and Leavitt, 2013) (see Table 1), and ii) to discuss more thoroughly than hitherto the implications that these studies have for the development of non-pharmacological therapeutic interventions based on mind-body medicine for MS patients.

Key issues that have been addressed by past research on CR (and BR) in MS and that we address here are: i) which are the best proxies of CR and how each of these is able to buffer the effects of MS disease? ii) how and where in the brain are CR and BR implemented? iii) are there limits to the extent to which CR can protect against MS disease progression, and how does this depend on different MS subtypes characterized by varying levels of disability (i.e., relapsing-remitting vs. primary and secondary progressive MS), or on heritable factors associated to BR (e.g., brain size)? iv) which are the implications of the research on CR and MS for mind-body therapeutic approaches aimed at improving CR? The following is organized in two main sections in which we will first review studies exploring CR and BR in MS and second we will turn on the implications for clinical interventions, emphasizing the contribution of integrated mind-body therapies, and in particular the potential utility of interventions based on yoga and mindfulness-meditation (MM), as possible approaches aimed at potentiating reserve.

2. Cognitive reserve and brain reserve in multiple sclerosis

2.1. What are cognitive reserve and brain reserve?

The theory of reserve derives from research on Alzheimer disease and was advocated to account for the discrepancy between clinical manifestation and degree of brain damage (Stern, 2002, 2009; Steffener and Stern, 2012). Essentially, it was proposed that individual differences in brain size, neuronal count, or number of synapses as well as differences in educational and other leisure life experiences protect some people better than others against manifestation of cognitive decline. To put it differently, at a given cognitive status, persons with larger brains/higher neuronal count and/or with higher educational level and engaging more in cognitive leisure should withstand more severe brain pathology than persons with smaller brains and/or with lower educational level and engaging less in cognitive leisure. Among these different factors (or proxies), a useful operational distinction has been made between proxies associated to BR and proxies associated to CR (Stern, 2009; Steffener and Stern, 2012), which in turn reflects a distinction between structural and functional measures of brain networks, respectively.

In more details, proxies such as the maximal lifetime brain volume (MLBV) (estimated with head size or intracranial volume) are considered to be effective measures of BR (Sumowski et al., 2013; Sumowski and Leavitt, 2013). The latter will be the higher the larger the MLBV: specific clinical or cognitive deficits will
<table>
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<th>Study</th>
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<td>Bonnet et al. (2006)</td>
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<td>Sumowski et al. (2009a)</td>
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<td>Premorbid IQ</td>
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<td>SDMT, PASAT, LM-I, LM-II</td>
<td>Higher CR protects from MS-related complex IP inefficiency and verbal learning and memory deficits.</td>
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<td>Sumowski et al. (2009b)</td>
<td>30 RR-MS, 6 SP-MS, 2 PP-MS</td>
<td>VK (V=WAIS)</td>
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<td>SDMT, PASAT</td>
<td>Higher CR attenuates the negative effect of brain atrophy on IP efficiency.</td>
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<td>Benedict et al. (2010)</td>
<td>71 RR-MS, 17 SP-MS, 3 PP-MS</td>
<td>E.A. Premorbid IQ</td>
<td>//</td>
<td>SDMT, PASAT</td>
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<td>Sumowski et al. (2010a)</td>
<td>34 RR-MS, 7 SP-MS, 2 PP-MS</td>
<td>VK (V=WAIS)</td>
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<td>Higher CR lessens the negative impact of brain atrophy on learning and memory.</td>
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<tr>
<td>Sumowski et al. (2010b)</td>
<td>14 RR-MS, 4 progressive MS</td>
<td>VK (V=WAIS)</td>
<td>//</td>
<td>SDMT, N-back Working Memory task during fMRI</td>
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<td>Sumowski et al. (2010c)</td>
<td>26 RR-MS, 2 SP-MS, 2 PP-MS</td>
<td>Premorbid leisure activities</td>
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<td>SDMT, OF-SRT</td>
<td>Premotor cognitive leisure independently contributes to CR and to cognitive status.</td>
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<td>Ghaffar et al. (2012)</td>
<td>59 RR-MS, 9 SP-MS, 4 PP-MS</td>
<td>Premorbid IQ, OA</td>
<td>//</td>
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<td>Amato et al. (2013)</td>
<td>52 RR-MS, 1.6 year follow-up on 35 RR-MS</td>
<td>E.A. IQ, premorbid leisure activities</td>
<td>//</td>
<td>SDMT, PASAT, LM-II, LM-I</td>
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<td>Booth et al. (2013)</td>
<td>57 RR-MS</td>
<td>Active CR, RPS from the SEP</td>
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<td>Feinmam et al. (2013)</td>
<td>79 RR-MS, 45 SP-MS, 26 PP-MS</td>
<td>Premorbid IQ, index of current decline from premorbid IQ</td>
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<td>Higher CR protects from cognitive decline also patients whose cognition falls short of predicted estimates.</td>
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<td>Scarpetti et al. (2013)</td>
<td>50 RR-MS</td>
<td>E.A. OA</td>
<td>//</td>
<td>PASAT, MFS</td>
<td>EA protects against MS-related cognitive impairment.</td>
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<td>Schweizer et al. (2013a)</td>
<td>N=889 from NARCOMS Registry</td>
<td>Passive and Active CR*</td>
<td>//</td>
<td>SI, PS</td>
<td>Active CR is a buffer against symptom burden and onset of progressive disease.</td>
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Table 1 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Schwartz et al. (2013b)</td>
<td>N = 899 (from NARCOMS Registry)</td>
<td>Passive and Active CR</td>
<td>//</td>
<td>//</td>
<td>PS, RPWBM, DLS, PDDS, SAQ-A V</td>
<td>Higher active CR is associated with better functional health, Altruism and active CR acts as buffers to enhance well-being resilience</td>
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<tr>
<td>Schwartz et al. (2013c)</td>
<td>N = 860 (from NARCOMS Registry)</td>
<td>Passive and Active CR</td>
<td>//</td>
<td>//</td>
<td>QOLAP</td>
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<tr>
<td>Schwartz et al. (2013d)</td>
<td>N = 1,142 (from NARCOMS Registry)</td>
<td>Passive and Active CR, O*NET, GLTEQ</td>
<td>//</td>
<td>//</td>
<td>PS, PDRS, PDQ, SF-12v2, BOWMAS, GLTEQ</td>
<td>Higher active and passive CR are associated with better generic and disease-specific PROs</td>
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<tr>
<td>Sumowski et al. (2013)</td>
<td>41 RR-MS, 21 SP-MS</td>
<td>Premorbid leisure activities</td>
<td>MLBV estimated with ICV</td>
<td>T2LL, Brain atrophy measures</td>
<td>SDMT, PSAT, SRT, SRT 1</td>
<td>BR and CR independently protect from MS-related cognitive decline</td>
</tr>
<tr>
<td>Pinter et al. (2014)</td>
<td>92 RR-MS, 12 SP-MS, 33 CIS</td>
<td>EA</td>
<td>//</td>
<td>//</td>
<td>BRB-N</td>
<td>Higher EA reduces the negative effect of disease duration on cognition</td>
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Abbreviations: CR, Cognitive Reserve; BR, Brain Reserve; RR-MS, Relapsing-Remitting Multiple Sclerosis; PP-MS, Primary-Progressive Multiple Sclerosis; SP-MS, Secondary-Progressive Multiple Sclerosis; CIS, Clinically Isolated Syndrome; IP, Information Processing; WAIS-R, Wechsler Adult Intelligence Scale Revised; BNT, Boston Naming test; RFF, Ruff Figural Fluency test; SDMT, Symbol Digit Modalities Test; PNASAT, Paced Auditory Serial Addition Test; SRT 1, Spatial Recall Test; SRT 2, Selective Reminding Test; T2LL, T2 Lesion Load; MLBV, Maximal Lifetime Brain Volume; ICV, Intracranial Volume; BRB-N, Brief Repeatable Battery of Neuropsychological Tests; EA, Educational Attainment (years of education); NARCOMS, North American Research Committee on MS; *Passive CR: Sole-Padulles et al. (2009), Active CR: Scarmeas et al. (2001); O*NET, Occupational Information Network; GLTEQ, Godin Leisure-Time Exercise Questionnaire; SI, Symptom Inventory disability-specific short forms; PS, Performance Scales; PDDS, Patient-Determined Disease Steps; PDQ, Premorbid Deficits Questionnaire; SF-12v2, Short-Form-12 v2; RPWBM, Ruff Psychological Well-Being Measure; DLS, Denver Satisfaction with Life Scale; PROs, Patient-Reported Outcomes; QOLAP, Quality of Life Appraisal Profile; SAQ-A V, Schwartz Altruism Questionnaire-Adult Version; OA, Occupational Attainment; MFIS, Modified Fatigue Impact Scale; MACFIMS, Minimal Assessment of Cognitive Function in MS; RPS, Recreation and Pastimes scale from the Sickness Impact Profile; VK, Vocabulary knowledge (Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence-WWAS-I and Reading subtest of the Wide Range Achievement Test, Third Edition-VRAT-3); LM-I, LM-II, Logical Memory tasks of the Wechsler Memory Scale Revised; CR-RT, operational Selective Reminding Test; TVW, third ventricle width.
Briefly, neural reserve relies on the key concepts of the forms of neural reserve and neural compensation. Stern proposed that CR is neurally implemented into CR proxies on performance. Thus, in his pivotal works, related neural activity that might mediate the effects of nevertheless, CR is derived also from networks of task-based intelligence (IQ) (Stern, 2009; Steffener and Stern, 2012). Cognitive training has also been seen to result in focal structural (and functional) brain changes in task-relevant regions (e.g., see Box 1 in Barulli and Stern, 2013 and below in Section 3). Finally, there is also evidence that higher CR is associated with reduced neural degeneration in aging (Valenzuela et al., 2008).

2.2. Which are the best proxies of CR in MS?

One of the first applications of the CR theory to MS was proposed by Bonnet et al. (2006) (see Table 1 for a summary of the studies investigating CR and BR in MS). In this study, educational level was found to play a critical role for attenuating the effects of cognitive decline in a sample of relapsing-remitting (RR) MS patients. Patients with low educational level (<12 years of schooling) performed worse than paired controls in several neuropsychological measures, derived in part from the Brief Repeatable Battery of Neuropsychological tests (BRB-N; Rao, 1990), that tap into, among others, verbal memory (Selective Reminding Test, SRT), visual-spatial memory (10/36 spatial recall test), sustained and complex attention, information processing speed, and working memory (Symbol Digit Modalities Test, SDMT, and Paced Serial Auditory Addition Test, PASAT 2- and 3-second versions), verbal fluency (Word List Generation Test, WLG), and
Inhibitory/attentional abilities (Go/NoGo and Stroop tasks). By contrast, patients with high educational level (≥12 years of schooling) showed a comparable performance with respect to their paired controls in all tasks, except in the SDMT and PASAT 2-s version in which they showed impaired performance. Moreover, cognitive scores negatively correlated with MRI parameters reflecting atrophy and diffuse brain damage only in more educated patients and such correlations tended to decrease with the severity of brain tissue damage, a set of findings which were held to suggest the presence of limitations for the protective capacities of high educational level; this is an issue that will be addressed in more detail later in section 2.4.

Shortly thereafter, a series of cross-sectional studies by Sumowski et al. (2009a, 2009b, 2010a) and one longitudinal prospective study by Benedict et al. (2010) contributed to further extend the CR hypothesis to MS in that they showed a critical role of intellectual enrichment in protecting against cognitive inefficiency and in mitigating the effect of disease burden on cognition. Overall, in these studies premorbid IQ, which was estimated through word-reading tests, vocabulary knowledge (and also through educational level in Benedict et al., 2010), was used as proxy of CR, while RR-MS patients formed the majority of patients studied. Similarly to the results of Bonnet et al. (2006), in the first of these studies (i.e., Sumowski et al., 2009a), MS patients with low CR performed poorer than healthy controls on measures of complex information processing efficiency (SDMT, PASAT) and verbal learning and memory. By contrast, MS patients with higher CR were as good as controls on the same measures.

In their following studies, Sumowski et al. (2009b, 2010a) went a step further in that they showed that the detrimental effect of MS-related brain atrophy (estimated from computations of third ventricle width) on cognitive status was reduced in MS patients with high vs. low premorbid IQ. This was demonstrated in hierarchical regression models predicting information processing efficiency (mean of SDMT and PASAT performance) (Sumowski et al., 2009b) or learning and memory performance (Sumowski et al., 2010a) that showed significant interactions between CR and brain atrophy. The data, thus, indicated that the MS patients with high CR could withstand better than the MS patients with low CR the brain damage associated to MS without manifesting cognitive impairment. Of note, Pinter et al. (2014) have more recently extended these findings by taking into consideration another important predictor, beyond atrophy measures, of cognitive function in MS, namely T2-lesion load, which estimates white matter damage. It was shown that higher educational attainment (defined by years of education) reduced the negative impact of white matter damage on the cognitive performance (as assessed by the BRB-N battery) of a group of 137 MS patients.

Recently, other cross-sectional research from the same and other groups have reported similar protective effects of CR against disease-related cognitive deficit in (predominantly) RR-MS patients. Nevertheless, this time, different and/or more complete proxies of CR were used; namely, occupational attainment in Ghaffar et al. (2012) and measures of premorbid cognitive leisure activities (including hobbies, playing a musical instrument, reading, producing art and nonartistic writing and playing structured games in patients’ early 20’s before the onset of MS) in Sumowski et al. (2010c) (see also Scarmeas et al., 2001). These studies, thus, assumed that vocabulary knowledge or educational level could not be the only estimates of the benefits of a cognitively stimulating lifestyle (see also below Sumowski et al., 2013; Amato et al., 2013b) and are hence in line with other recent conceptualizations of CR proxy indices such as, for instance, the Cognitive Reserve Index questionnaire (CRIq) (Nucci et al., 2011), which similarly considers life engagement and cognitively stimulating social and intellectual activities such as playing a sport or an instrument. More specifically, in Ghaffar et al. (2012) it was found that occupational attainment significantly predicted information processing speed (PASAT and SDMT), executive function, and memory performance (tests taken from the Minimal Assessment of Cognitive Function in MS (MACFIMS) battery; see in Ghaffar et al., 2012) in hierarchical linear regression models independently from premorbid IQ and brain atrophy. Similarly, Sumowski et al. (2010c) showed that premorbid cognitive leisure also makes an independent positive contribution to cognitive status (processing speed and memory) in MS. Thus, taking part in more early-life cognitive leisure activities was positively correlated with better cognitive outcome after controlling for premorbid IQ, education, and brain atrophy. Concerning occupational attainment, however, another recent study (Scarpazza et al., 2013) has failed to report an influence on RR-MS patients’ cognitive performance (PASAT), while a protective effect against MS-related cognitive decline was...
versions of the PASAT, such a protective effect of education for MS patients’ cognitive profile emerged particularly for high speed versions of the PASAT (≤2.6 sec), while it was not evident for low speed versions (≥3 sec). In other words, MS patients with low education level differed from matched healthy controls at faster, but not at slower, stimulus presentation speed; conversely, MS patients with high education level did not differ from matched healthy controls at any PASAT speed. This study thus indicates that careful attention should be paid to the selection of neuropsychological tests, or different versions of a specific test, in clinical practice with MS patients, as these tests may differ in their suitability for identifying compensatory cognitive capacities in MS patients with varying CR.

2.3. How and where in the brain are CR and BR implemented?

Overall, the studies reviewed above suggest that a possible mechanism through which higher intellectual enrichment can mitigate the negative effects of MS neuropathology on cognitive outcome is linked to greater neural efficiency and compensation (i.e., neural reserve) among MS patients with higher levels of enrichment. A recent study by Sumowski et al. (2010b) showed that this is the case. In this cross-sectional study, the authors elegantly pinpoint the functional anatomy underlying CR. Measures of disease severity (brain atrophy computations of third ventricle width), CR (vocabulary knowledge), and current cognitive status (SDMT) were collected on a sample of mainly RR-MS patients. Moreover, as index of cerebral activity, functional magnetic resonance imaging (fMRI) was employed while the patients had to perform the visual N-back working memory task at three levels of demand (0-, 1-, 2-Back). The authors found that intellectual enrichment (i.e., CR) was critically associated with activity in a main network consisting of default network/resting state nodes (e.g., anterior and posterior cingulate cortices which are generally found more active during rest or passive thought than active cognitive processing) and prefrontal cortex regions. More specifically, during the execution of the working memory task, especially in the most demanding condition (i.e., 2-Back), intellectual enrichment was positively associated with default network activity but negatively associated with prefrontal recruitment. In other words, in order to perform the same cognitive tasks as accurately as MS patients with low CR, those with higher CR required less deactivation of the default/resting state network and less activation of the prefrontal cortex, thus reflecting less use of cerebral resources in general. Moreover, the authors also found evidence that the patients who showed more default network and less prefrontal cortex activation during execution of the working memory task (i.e., high-CR patients) could withstand more severe brain disease (i.e., atrophy) before manifesting cognitive status similar to patients showing to a lesser degree this complex pattern of neural activation (i.e., low-CR patients).

Globally, these data show a direct role of intellectual enrichment in promoting more efficient neurocognitive processing and, in these respects, may be considered to complement the results of previous studies documenting overall differences in neurofunctional recruitment patterns between MS patients and healthy controls during cognitive processing (independently of intellectual enrichment). Thus, the use of IMRI has suggested that compensatory neuroplasticity (e.g., over-recruitment of brain regions), altered functional connectivity between regions normally recruited when performing a given task, or increased activation in task-related brain regions may, separately or together, contribute to limit neuropsychological deficits and maintain normal performance in MS, in the face of both brain damage and reduction in response efficiency of task-related brain networks (Buckle, 2005; Mainiero et al., 2004; Cader et al., 2006; Pantano et al., 2006; Rocca and Filippi, 2007; Rocca et al., 2010; Jehna et al., 2011). Of importance, recent findings (of studies not manipulating intellectual enrichment) show that these adaptive mechanisms in MS also involve prefrontal cortex and default network regions, whose recruitment have been observed to increase and decrease, respectively, in order to maintain cognitive performance relative to healthy controls (see in Sumowski et al., 2010b).

To conclude this section, it is important to note that a considerable research effort is also currently being directed at exploring the possible structural markers of BR. A number of key brain structures primarily involved in neurodegenerative processes such as the hippocampus, the lateral ventricles, and white matter lesions volume have been identified. Abnormalities in these brain regions have indeed proved predictive of subsequent development of dementia (e.g., Alzheimer’s disease) or disability in cognitively intact individuals (see in Cavedo et al., 2012). Moreover,
with the aim of providing normative data, Cavedo et al. (2012) have recently described the distribution of the three mentioned structural markers of BR in a sample of 158 cognitively-intact people ranging from 40 to 90 years of age. Critically, the 5th and 95th percentiles threshold, respectively indicating lower and higher brain reserve, were identified by the authors for each of the three markers. While these data could be effectively used to estimate the brain resilience to neurodegeneration both in cognitively intact subjects and in Alzheimer’s disease, it is hoped that future studies will address the same issue in MS.

This issue appears crucial if one bears in mind that prognosis in MS appears to be age-dependent. Thus, it has been shown that the younger the clinical onset of MS, the younger the age at assignment of disability milestones (e.g., Confavreux and Vukusic, 2006).

More specifically, it appears that onset of progressive phase, i.e. from RR-MS to progressive MS is more dependent on age than on the type or duration of the initial disease course (Be it relapse-remitting or progressive) (Tutuncu et al., 2013; Koch et al., 2007). As specified in more details in the next section, these data suggest the need for early clinical management of MS, including therapeutic interventions aimed at preventing neuronal loss and potentiating CR delivered when the patients could maximally benefit from brain plasticity phenomena (Freitas et al., 2011).

2.4. Are there limits to the extent to which CR can protect against cognitive decline in MS?

Another important issue related to studies on CR in MS concerns the presence of possible limitations in the ability of CR to protect against the cognitive decline related to MS disease progression, and to what extent such limitations depend on different MS subtypes. A very recent study by Amato et al. (2013b; see also in Arnett and Brochet, 2013) suggests that the CR-related positive mediation between cognitive status and brain pathology tends to fail with the progression of damage. This study represents a rare case of longitudinal approach addressing CR in a group of RR-MS patients (see Benedict et al., 2010, for another example). In more details, CR was estimated using an index that integrated three main components, namely, educational level, premorbid IQ, and premorbid cognitive leisure activities; brain atrophy was assessed through quantitative measures of both total and regional brain volumes, respectively normalized brain volume (NBV) and normalized cortical volume (NCV); finally, cognitive function was measured through a broad range of cognitive tests using the BRB-N battery (Rao, 1990).

Importantly, while 52 RR-MS patients were evaluated at baseline, a subset of 35 patients underwent a longitudinal evaluation and measures of changes of cognitive function and brain and cortical volumes were also collected at a 1.6 year follow-up. At baseline, corroborating the results from previous cross-sectional studies showing a buffering effect of CR on the effects of brain atrophy on cognition, an interaction between CR and NCV predicted information processing speed (PASAT) and verbal memory performance (SRT). That is, at lower NCV but not at higher NCV, better cognitive performance was found for patients with high vs. low CR. Nevertheless, over the follow-up period, older age at inclusion and increased gray matter atrophy (change in NCV) were the only factors predicting cognitive deterioration. In fact, premorbid CR failed to buffer the effects of progressing cortical atrophy on cognitive decline in the group of 35 evaluated patients, whose disease course after the follow-up period was still relapsing-remitting. These data were interpreted as evidence of limitations in the protective effect of CR, which would fail in the presence of exceeding levels of brain atrophy (see also before in section 2.2. Bonnet et al., 2006). According to the authors, the data were also suggestive of therapeutic approaches based on potentiation of CR that, in order to be maximally effective, should ideally be employed early on in the MS disease course.

Two recent studies by Sumowski et al. (2012) and Schwartz et al. (2013a) seem to call into question the possibility that CR loses its protective role already during the relapsing-remitting course of the disease. In their cross-sectional study, Sumowski et al. (2012) showed that intellectual enrichment protects against cognitive impairment also in patients with secondary-progressive MS (SP-MS), which is a more advance disease course whereby patients have more evident neuropathology and cognitive deficit (Huibregts et al., 2004). In particular, Sumowski et al. (2012) found differences between healthy controls and SP-MS patients in memory (SRT and logical memory tasks of the Wechsler Memory Scale-Revised) and cognitive efficiency performance (SDMT, PASAT 3 s and 2 s) at lower levels of CR but not at higher levels of CR (estimated through educational level and vocabulary knowledge). More recently, Schwartz et al. (2013a) conducted a study in which cross-sectional
and longitudinal analyses were carried out on a large sample of MS patients (n = 859; with various MS disease course) who provided data into a web-based supplemental survey of the North American Research Committee on MS. It was found that CR was associated with the disease course of MS. More specifically, the rate of progression into progressive forms of MS was directly related to individuals’ CR and in particular to the level of leisure activities concurrent with the comorbidity, that is to active CR in Schwartz et al.’s terms. The authors argued that the onset of progressive disease course, more particularly the conversion from RR-MS to SP-MS, is caused by depletion of one’s own CR. It is important to note, however, that the differences between studies in decreeing the limits of the protective effects of CR could be attributable to differences in the populations studied with respect to a variety of important factors such as educational level (e.g., 11.6 years in Amato et al., 2013b vs. 15.8 years in Sumowski et al., 2012), mean age (e.g., 39.2 years in Amato et al., 2013b; 49.2 years in Sumowski et al., 2012; 54.6 years in Schwartz et al., 2013a), and type of study (longitudinal vs. cross-sectional vs. registry and web-based survey study). Moreover, a factor which could have masked any potential protective role of CR in the study of Amato et al. (2013b) could be the short interval between baseline and follow-up. This may have not allowed cognitive decline to clearly manifest, thus preventing any mediating role of CR (Sumowski and Leavitt, 2013) and thus emphasize the potential utility of rehabilitation techniques designed to improve memory and neuroplasticity in specific brain regions such as the hippocampus.

Finally, a recent study by Sumowski et al. (2013; see also Sumowski and Leavitt, 2013 and Hildebrandt et al., 2007), these findings are in line with evidence showing lower heritability of memory ability and hippocampal volume relative to cognitive efficiency and intracranial volume and thus emphasize the potential utility of rehabilitation techniques designed to improve memory and neuroplasticity in specific brain regions such as the hippocampus. Together with recent evidence showing the existence of specific patterns of regional grey matter volume loss in RR-MS (involving the thalamus, basal ganglia structures, pre/post central and cingulate regions) (Lansley et al., 2013), and a direct association between cognitive deficits in RR-MS and focal cortical atrophy (Morgen et al., 2006), the reviewed findings on reserve and MS suggest that future studies should investigate whether different brain regions are differentially targeted by MS-related neurodegenerative processes and if they benefit to a different extent from BR and CR.

3. Integrated non-pharmacological therapies based on mind-body medicine for the treatment of MS: The link with cognitive and brain reserve

3.1. Improvement of cognitive abilities and well-being in MS patients

Having successfully shown the applicability and extensibility of the concept of CR and BR to MS, an issue emerges about the implications of this research
for clinical care of MS patients (Arnett and Brochet, 2013). A critical aspect raised in many studies concerns the possibility to employ therapeutic interventions aimed at improving CR in newly diagnosed MS patients (fourth question in the Introduction). This appears to be a crucial advance that would allow to reveal, in longitudinal and randomized controlled studies of CR, whether changes in intellectual enrichment moderate decline in MS patients while disease progresses. In fact, in almost all of the reviewed studies only premorbid CR was estimated. However, a few very recent studies have started to show the benefits of estimating the discrepancy between current cognitive function and premorbid IQ (Feinstein et al., 2013) or, more critically, of taking into account current CR of patients already diagnosed with MS. With regards to this, recent studies by Schwartz et al. (2013a, 2013b, 2013c, 2013d; see also Booth et al., 2013) have demonstrated a positive relationship between CR, especially in its active component (i.e., leisure/recreational activities concurrent with the comorbidity), and MS patients’ health, well-being, and cognition.

Based on ideas and concepts related to neuroplasticity obtained in other CNS pathologies, such as stroke or head-injury (e.g., Cumming et al., 2013), or in the elderly (e.g., Optale et al., 2019), a first non-pharmacological therapeutic strategy to protect MS patients against cognitive decline may be cognitive rehabilitation. Although evidence-based research of cognitive rehabilitation in MS is still in its infancy, numerous recent studies have attempted cognitive rehabilitation programs aimed at recovering or remediating impaired cognitive functions in MS (Chiaravalloti and DeLuca, 2008; O’Brien et al., 2008; Guimarães and Sá, 2012; Penner and Sastre-Garriga, 2014). Through the use of computerized programs, cognitive rehabilitation has targeted different cognitive domains. The results are, however, contradictory. Thus, some studies have failed to document any improvement after cognitive rehabilitation in MS patients (Tesar et al., 2005; Solari et al., 2004; Mäntynen et al., 2014; see also in Amato et al., 2013a). For example, in a randomized, controlled trial involving a large number of RR-MS patients with attentional deficits (n = 102), Mäntynen et al. (2014) did not find improved cognitive performance in a group of patients who underwent neuropsychological rehabilitation once a week for 13 consecutive weeks (including, among other forms of psychological support, computer-based attention and working memory tasks). Nevertheless, of interest, the neuropsychological rehabilitation program had an effect in reducing patients’ perceived cognitive deficits in this study.

Some other studies, however, have found improved performance after cognitive rehabilitation in MS, especially in the learning and memory domains, where, nonetheless, some memory-enhancing techniques such as self-generated learning have been observed to be more effective than simple repetition of information for improving learning and memory in MS (see in Chiaravalloti and DeLuca, 2008; see also Chiaravalloti et al., 2005; Bissart et al., 2011). Moreover, in the attention domain, Cerasa et al. (2012) have recently carried out a double-blind randomized controlled study on 23 MS patients providing evidence of enhanced attention abilities in the Stroop task; specific improvements were obtained in an experimental group of patients (n = 12) who underwent an intensive computer-based attention training program of 6 consecutive weeks (1-hour session twice a week) but not in a control group of patients who instead were engaged in a visuomotor coordination task for a comparable period of time and with similar methods. Of importance, using fMRI in both patient groups and both before and after the interventions these authors were able to show that the specific Stroop performance improvement in the experimental group was positively correlated with increased activity in regions such as the superior parietal lobe and the cerebellum during performance of a paced visual serial addition test (PVSAT), a test tapping into attention abilities which can be used as an alternative for the PASAT. These latter findings in particular were held to suggest that intensive cognitive rehabilitation is able to affect neural plasticity and reorganization in specific brain regions involved in the trained abilities (for the first fMRI study documenting effects of cognitive rehabilitation on attention-related brain networks in MS see Penner et al., 2006).

The results of Cerasa et al. (2012) are in line with other recent studies that also used fMRI as a tool to assess the efficacy of neurorehabilitation in MS. For instance, Sastre-Garriga et al. (2011) found increased cerebellar activity during execution of the PASAT test after 5 weeks of cognitive rehabilitation in a group of 15 cognitively impaired MS patients vs. 5 healthy control subjects. Moreover, better performance on a measure of working memory (backward digit span) and on a composite score of neuropsychological outcomes was also found in the patients after vs. before the rehabilitation intervention. More recently, Filippi et al. (2012)
also tried to assess brain changes consequent to 12 weeks of computer-based cognitive rehabilitation of attention, information processing, and executive functions in a group of 10 RR-MS patients, this time using structural, as well as functional, MR imaging. A control group of 10 RR-MS patients not involved in any cognitive rehabilitation intervention was also included in the study. After cognitive rehabilitation, Filippi et al. found in the rehabilitated vs. control patients an increased recruitment of frontoparietal brain regions (especially dorsolateral prefrontal cortex, a key region in “top-down” attentional control) during performance of the attention demanding Stroop interference condition. Critically, in the rehabilitated patients, the fMRI changes after rehabilitation were correlated with the improvements in cognitive performance in all three treated domains. Surprisingly, however, no structural changes (either in the grey matter or in the normal appearing white matter) was observed in any subject groups after cognitive rehabilitation, a finding which was interpreted as potentially suggesting an impairment of structural plasticity in MS patients due to the MS pathologic process.

Finally, in addition to the study of Filippi et al. (2012), it is worth noting that a few other interventions have been designed to improve functioning in domains such as processing speed, working memory, and executive function. Thus, in two related studies Mattioli et al. (2010, 2012) (see also Vogt et al., 2009) have first reported evidence of the efficacy of a cognitive rehabilitation program of 3 months for improving performance in the treated functions of information processing, attention, and executive functions (e.g., PASAT, Wisconsin Card Sorting Test), in a group of 10 RR-MS patients who were compared with 10 RR-MS control patients (i.e., not involved in any cognitive rehabilitation) (Mattioli et al., 2010). Two years later, the same researchers documented the persistence of these effects by showing similar improvements in attention, information processing, and executive functions both immediately after a cognitive rehabilitation program of three months and six months after the end of the training in a group of 13 RR-MS (vs. a group of 11 RR-MS patients with no rehabilitation) (Mattioli et al., 2012).

Overall, besides the many challenges associated with cognitive rehabilitation programs in MS (e.g., see Amato et al., 2013a), a factor which may limit their effectiveness and efficacy concerns their focus on training specific skills in the patients; in fact, this makes unclear how those rehabilitated strategies translate and generalize into more global, real-world, changes in function, such as the ability to maintain employment status. Moreover, it is known that cognitive problems are also mediated by factors such as depression, coping styles, and fatigue (Jongen et al., 2012; Langdon, 2011; Chiaramarli and Deluca, 2008), and this motivates the need of also taking into account psychosocial problems and patients’ quality of life, when trying to remediate cognitive impairment.

Sutvegyi indicate that more than 60% of MS patients have tried one or more complementary and alternative medicine (CAM) approaches to treat their disease, with most patients using CAM as complimentary rather than as an alternative to conventional medicine (Tavee and Stone, 2010; Barnes et al., 2002; Apel et al., 2006; Esmehde and Long, 2008; Horowitz, 2011b). Common reasons for using CAM are patients’ dissatisfaction with conventional medicine, desire for a more holistic, whole-person based approach to treatment, which also includes an interest into taking more self-control over disease management, and a desire to obtain relief from physical and psychological symptoms (Berkman et al., 1999; Nayak et al., 2003; Hunley, 2006; Olsen, 2009; Yadav and Bourdette, 2006). Common types of CAM reported by MS patients include diet (low-fat and gluten-free) and dietary supplements, including antioxidant supplements (e.g., α-Lipoic Acid, vitamin E/selenium, omega-3 fatty acids, and high-dose vitamin D (see review of Horowitz, 2011a), as well as integrative nondietary approaches such as exercise, yoga, meditation, visual imagery, hypnotherapy, biofeedback, magnetic field therapy, neuromuscular electrical stimulation, brain stimulation techniques such as transcranial magnetic stimulation, relaxation techniques, acupuncture, massage, and cannabis (see reviews of Horowitz, 2011b; Senders et al., 2012). For the vast majority of CAM, there is only a paucity of randomized controlled trials evaluating their effectiveness in MS; it is thus difficult to recommend any specific modality or therapy. Nevertheless, recent research is beginning to show that the most commonly practiced form of CAM, namely mind-body medicine, is effective for treating a series of common MS symptoms known to affect cognitive processing, such as fatigue and depression (see in Senders et al., 2012; Wabbeh et al., 2008; see also Vissers et al., 2005 for mind-body medicine in general). Mind-body medicine, which includes forms of yoga and meditation, integrates the mind, brain, body, and behavior with the intent to use the mind to positively influence physical...
Fig. 1. Putative mechanisms through which mindfulness-meditation and yoga may impact cognitive and brain reserve. Mindfulness meditation and yoga practice involve the development and improvements of a number of key mental components including attentional functions and regulatory emotional and cognitive processes (layers 1 and 2 of the figure are based on Fig. 1 of Malinowski, 2013 to which the reader is referred for a more detailed description of the effects of these processes on behavior). Improvements in these core components may influence cognitive and brain reserve through more efficient patterns of task-related neural activity and neuroprotective effects. Changes in task-related activity and cortical thickness affect task performance and clinical outcome (layer 3, in particular the Task-related neural activity box, and layer 4 of the figure are based on Fig. 1 of Steffener and Stern, 2012 to which the reader is referred for a more detailed description of the authors’ model of the neural basis of cognitive reserve). Improvements in cognitive and clinical outcomes also occur through reduced stress, anxiety, and depression promoted by mindfulness meditation/yoga practice.

3.2. Yoga and physical exercise in MS

Yoga is a common mind-body practice that incorporates meditation, breathing exercises (pranayama), and physical postures (asanas) with the aim to positively influence physical and mental well-being. The term yoga summarizes all the techniques of meditation and asceticism developed in ancient Hinduism (Klostermaier, 1998; Fabbro, 2010). According to Patanjali (II BCE), probably the author of one of the most important ancient texts of Hinduism, namely Yoga-Sutra, the goal of performing yoga is the “suppression of the fluctuations and modifications of the mind” (Yoga-sūtra 1.2) (Taimni, 1961). This goal can be reached through, for example, focusing the mind on a particular object with the aim of calming mind wandering, moving concentration from a single object of consciousness to complete meditative absorption, and practicing specific muscular postures and breathing regulation (Fabbro, 2010). Of the many contemporary yoga techniques, Hatha yoga, with some of its forms such as Iyengar yoga, is probably the most common type of Yoga practiced through Western culture. Hatha yoga has in general an emphasis on poses and breathwork, Iyengar yoga, more in particular, focuses on detail, precision and alignment in the performance of posture and breath control with the aim of gaining muscle strength, mobility, and stability. Of note, in order to correctly perform yoga exercises a person has to be aware of his body posture and be focused on breathing; this requires a high level of attention. Thus, yoga globally centers around exercise, relaxation, and attentional components and, hence, it may be potentially helpful for a variety of MS symptoms (e.g., Senders et al., 2012).

Only two studies (Oken et al., 2004; Velikonja et al., 2010), however, have so far investigated the possible effects of yoga on motor and cognitive functions of MS patients. In the study of Oken et al. (2004), consisting of a 6-month, randomized controlled trial of Iyengar yoga and aerobic exercise, 69 patients were randomized to one of three groups: yoga, physical exercise, or wait-list. Yoga was as good as aerobic exercise in leading to improvements (vs. wait-list controls) in energy and vitality on the Short Form-36 (a health survey; Ware, 1993) and in a general fatigue score. Of importance, there were no effects from either of the active groups on cognitive measures focused on attention, a result likely due to the minimal intensity of supervised exercise or poor participations in the weekly classes (see also Moll et al., 2011). However, more recently, Velikonja et al. (2010) compared 10-week sport climbing and Hatha yoga interventions in a randomized prospective study of 20 RR-MS, PP-MS
or SP-MS patients finding an improvement in selective attention performance specifically after yoga. This finding was interpreted in the light of the high level of attention and concentration on breathing, body posture and movement required during yoga practice.

Although preliminary and based on a restricted number of patients, these few studies suggest that yoga may be comparable to other forms of exercise in relieving some of the MS symptoms as well as being specifically effective in improving attention-related cognition. This is a particularly important result which would complement findings from previous studies showing a positive relation between cognition and aerobic fitness in older healthy adults and in MS patients (reviewed in Motl et al., 2011). Physical exercise would affect cognitive function through alterations in brain structure and function. Accordingly, in MS patients, cardiorespiratory fitness was found to be positively correlated with brain volume (regional gray matter volume), integrity of white matter (higher fractional anisotropy), and cognitive efficiency (PASAT and SDMT) (Prakash et al., 2010). Speculatively and with relevance to reserve theory, these results would point to physical activity, possibly in the context of yoga, as an important enriching activity to help patients with MS to defend against cognitive impairment via neuroprotective advantages for brain integrity and efficiency.

In line with this possibility, recent ideas (Fick et al., 2009; Jones et al., 2010; Shelley, 2013) refer to physical activity as a possible useful intervention to improve cognitive reserve, and, thus, for protecting against dementia risk, preventing delirium and slowing the rate of cognitive decline in early-stage Alzheimer’s disease patients. In a similar fashion, other recent researches point to a role of mind-body techniques, and in particular yoga and meditation (for the latter see also next section), in enhancing cognitive reserve capacity, thus potentially preserving brain function and preventing or protecting against age-related brain degeneration and dementia (see reviews by Xiong and Doraiswamy, 2009; Gard et al., 2014; Luders, 2014; Newberg et al., 2014; Marciniak et al., 2014, Table 2). For instance, Newberg et al. (2010) tested the effect on memory of an 8-week yoga/meditation program, based on the practice of Kirtan Kriya (a form of mantra meditation derived from the Kundalini yoga tradition), on a group of older individuals with memory problems ranging from age-related memory difficulties (n = 7), mild cognitive impairment (n = 5), and early Alzheimer’s disease (n = 3). It was found that the yoga/meditation practice (vs. listening to music performed by a group of control subjects) led to improvements on neuropsychological tests of logical memory and verbal fluency and in the Trail making test (part B) measuring working memory and attention. Moreover, these cognitive improvements in the practitioners were correlated with increases in cerebral blood flow in attention- and memory-related prefrontal and parietal regions, a finding suggestive of yoga/meditation-related increases in brain network efficiency/capacity (namely CR) (see Newberg et al., 2014; Marciniak et al., 2014 for the description of two other studies employing Kirtan Kriya techniques in the context of neurodegenerative diseases).

Moreover, a few recent neuroimaging studies on yoga healthy practitioners have shown both functional and structural focal brain changes in areas relevant to task demand. For the functional aspects, a recent study (Wang et al., 2011) has investigated two different forms of meditation deriving from the Kundalini yoga tradition in a group of 10 expert healthy practitioners. It was found that a “focused-based” practice (Kirtan Kriya), which is generally associated with enhanced attention, activated in particular the prefrontal cortex and the left basal ganglia. On the other hand, a “breath-based” practice (Shabad Kriya), which induces a profound state of relaxation, triggered activation in limbic and paralimbic structures such as the insula, the amygdala, and the hippocampus and in the left inferior frontal cortex. More importantly, the authors reported positive correlations between subjective ratings of depth of meditation in the “breath-based” practice and neural activity in areas such as the insula and the inferior frontal cortex, but negative correlations between activity in these regions and perceived stress.

With regards to brain anatomy, in a recent study by Froeliger et al. (2012), Hatha yoga has been found to lead to fewer cognitive failures and greater gray matter volume in several brain regions such as prefrontal, hippocampus, insula, temporo-occipital, and cerebellar regions in a group of healthy Hatha yoga meditation practitioner vs. a yoga-naive control group. Of importance, the scores obtained in the Cognitive Failures Questionnaire (CFQ), the higher the scores the higher the self-reported cognitive failures) were negatively correlated with gray matter volume in many of the above mentioned regions and the latter measure was positively correlated with yoga practice duration. Overall, this study suggests that the practice of Hatha yoga is associated with better cognitive function (i.e., with making fewer errors in memory, attention,
and motor function in everyday tasks as measured by the CFQ) together with thickening of brain structures involved in memory and executive control.

Similarly, other recent findings are relevant for the reserve theory in that they associate the practice of yoga to changes in brain anatomy, connectivity, and function. For instance, Villeneuve et al. (2015) have documented beneficial effects of yoga, as observed in expert yoga practitioners relative to naive matched controls, on pain tolerance, possibly via the learning of more efficient cognitive strategies and emotional reactions focused on insightful awareness. Moreover, the capability to tolerate pain was positively correlated with insular gray matter volume. Finally, the latter was higher in expert yogis than controls (yogis also had increased white matter integrity in left intrinsular regions) and was also positively correlated with yoga experience. Beside these cross-sectional studies, a recent longitudinal study, carried out on a sample of seven healthy elderly subjects undergoing a 6-month yoga intervention, showed increased hippocampal gray matter volume in these individuals after vs. before the intervention (Hariprasad et al., 2013). Although based on a small sample of subjects with no control group, this latter study may suggest potential neuroprotective effects of yoga against Alzheimer-related neural degeneration. Globally, the evidence points to possible links between yoga and cognitive and brain reserve, whereby yoga practice may serve as a useful additional treatment for disorders characterized by gray matter volume loss and cognitive problems.

3.3. Mindfulness meditation in MS

Similarly to Yoga, the most common forms of meditation derive from healing and spiritual traditions, particularly Hinduism and Buddhism, both originated in India several centuries BCE. The term meditation is generally used to refer to complex attentional and emotional regulatory training procedures which are developed and followed for the promotion of well-being and emotional balance (Lutz et al., 2008; Fabbro, 2010). In the past three decades there has been an increase in popular and scientific interest in the psychological and cognitive benefits of meditation and in the study of its influence on the brain. Several research lines have demonstrated that meditation practice can promote improvements in cognitive function and changes in the brain structure (Cahn and Polich, 2006; Newberg et al., 2014; Lutz et al., 2008; Tomasin et al., 2013). Moreover, positive clinical outcomes for anxiety, depression, immune function, pain, and stress-related disorders have been reported in clinical studies employing meditation trainings (e.g., Baer, 2003; Brown and Ryan, 2003; D’Aloisio, 2009). Despite the existence of several types of meditation practices, the two most popular styles within the Buddhist tradition are focused attention meditation and open monitoring meditation (Lutz et al., 2008; see also Tomasino et al., 2013). These two styles are also implicated in common meditation trainings occurring in secular clinical contexts such as the interventions based on mindfulness-mediation (MM).

MM is indeed a form of meditation that can be defined as a way of intentionally paying attention to present moment experience with a non-judgmental attitude of openness and receptivity (i.e., non-reactive monitoring) (Kabat-Zinn, 1990, 2003; Brown and Ryan, 2003; Lutz et al., 2008). A popular formalization of MM for clinical intervention is the mindfulness-based stress reduction (MBSR, Kabat-Zinn, 1982; 1990; 2003), a program in which several mind-body techniques are amalgamated such as MM, yoga postures, breathing exercises, and relaxation techniques. Other important interventions based on or incorporating mindfulness training exist such as the Mindfulness-Based Cognitive Therapy, the Dialectical Behavior Therapy, the Acceptance and Commitment Therapy, and the Relapse Prevention treatment (see in Baer, 2003; Baer, 2010; Chiesa and Serretti, 2011).

With regards to MS, a recent randomized, single-blind, controlled trial by Grossman et al. (2010) has investigated the effects of an 8-week MM program (based on MBSR) compared to usual care on depression (Center for Epidemiologic Studies Depression Scale), fatigue (Modified Fatigue Impact Scale), anxiety (Spielberger Trait Anxiety Inventory), and quality of life measures (German-language Profile of HRQOL in Chronic Disorders as disease-nonspecific measure and the German version of the Hamburg Quality of Life Questionnaire in MS as disease-specific measure) in 150 patients with RR-MS or SP-MS. After the 8-week MM training, Grossman et al. (2010) found improvement across all outcome measures, with the benefits remaining present at the 6-month follow-up. This study has thus provided preliminary evidence that MM is a helpful therapeutic option for persons with MS and extends similar results of other studies conducted in smaller sample of MS patients evaluating the effects of mindfulness of movement (Mills and Allen, 2000),
mindfulness meditation (Tavee et al., 2010), and mindfulness and acceptance (Pakenham and Samios, 2013). There is a mounting body of knowledge in healthy young and old individuals suggesting a role of MM interventions in potentiating cognitive and brain reserve. Several studies link MM and MBSR with enhanced cognitive function, especially memory, attentional regulation and executive control, and brain plasticity (Slagter et al., 2011; Chiesa et al., 2011; Zeidan et al., 2010; Tang et al., 2007; Malinowski, 2013; Newberg et al., 2014). For instance, with regard to the latter phenomena, a series of cross-sectional studies using structural neuroimaging (e.g., voxel-based morphometry) have compared expert meditation practitioners and meditation naive individuals showing increased cortical thickness in experts, in regions related to memory, attention and interoception (Lazar et al., 2005). Yet relevant to reserve theory, more recent longitudinal studies have extended these findings in normal participants engaged in an 8-week MBSR program (Hölzel et al., 2011) and have also shown meditation-related improvement in white matter efficiency (i.e., increased myelin and axonal density) (Tang et al., 2012).

More critically, other recent studies have found that regular practice of meditation positively affects normal age-related decline of cerebral gray matter volume and of cognitive (attentional) performance, a result suggestive of a neuroprotective effect of meditation against age-related cognitive decline and neural degeneration (see previous section; see also Pagtam and Cekic, 2007; see Lazar et al., 2005 for similar results; see also Xiong and Doraiswamy, 2009; Luders, 2014; Gard et al., 2014; Newberg et al., 2014; and Marciniak et al., 2014). Further evidence to support a protective effect of meditation comes from cognitive and functional neuroimaging studies in young participants. For instance, Jha et al. (2010) have explicitly referred to MM as a way to cultivate a cognitive reserve (working memory capacity) that could be used in demanding, high-stress contexts (e.g., military predeployment interval) to protect against functional impairments (cognitive failures and emotional disturbances). Finally, MRI studies on healthy individuals have shown that increases in brain network efficiency (namely CR) in functional activation patterns within attention-related regions of the prefrontal cortex during attention-demanding tasks are related to lifetime hours of meditation practice (Irifetzynski-Lewis et al., 2007; see also Chan and Woollacott, 2007 for related arguments). Similarly, a more recent study (Korasa et al., 2012) has reported that, in spite of comparable behavioral performance in an attention task (Stroop task), meditation naive healthy participants, relative to regular meditators, showed an increased pattern of functional activity in attention-related brain regions during the error-prone, incongruent trials of the task. Importantly, this finding was attributed to a role of meditation in promoting neural efficiency, a key concept related to neural implementation of CR (cf. section 2.1), through improved sustained attention (Korasa et al., 2012).

4. Conclusions

To conclude, the existent literature on mind-body medicine involving yoga and especially MM trainings suggests that these techniques represent challenging mental enriching activities that may help cultivating a cognitive reserve to protect against cognitive degradation occurring in physiological (e.g., aging) and pathological (e.g., MS) contexts. The reviewed evidence on the neurocognitive effects of yoga and MM in young and older adults, as well as the positive clinical outcomes for physical and psychological health reported in clinical contexts (within and beyond MS), may indicate that there is adequate justification to encourage more systematic examination of the effects of mind-body medicine and especially MM on cognitive decline in MS. Longitudinal research and randomized controlled trials adopting research methods and practices from MM research (e.g., MBSR and behavioral and MRI functional/morphometry testing) should be designed for testing the beneficial effects on improving cognitive function in MS, either directly or indirectly through the effects on other psychosocial symptoms (see Fig. 1). At this regard, it is important that the effects of mindfulness-based trainings on the personality traits of MS patients should also be taken into account (for the relation between mindfulness and personality traits see for example Giluk, 2009; Haimerl and Valentine, 2001; Campanella et al., 2014). The issue of the association between personality traits and mood/anxiety difficulties and their overall relation with cognition in MS has indeed been very scarcely explored (Bruce and Lynch, 2011). Of note, however, the protective role of specific personality variables (conscientiousness) against the development of Alzheimer disease and cognitive decline in mild cognitive impairment has recently been shown (Wilson
et al., 2007), and it may be worth addressing similar issues in MS patients engaged in MM trainings. In a similar manner, future studies testing the putative protective effects of mind-body techniques against MS disease-related cognitive decline should also consider the influence that factors such as perceived fatigue in MS have in determining patients’ cognitive profiles. As already mentioned, although the issue of the relation between perceived fatigue and cognitive impairment in MS is debated, several studies suggest that fatigue negatively affects cognitive processing in MS (e.g., see in Chiaravalloti and DeLuca, 2008 and Scarpazza et al., 2013). Nevertheless, a recent study in MS patients (Scarpazza et al., 2013) has shown that this influence appears to be mediated by factors such as age, disease duration and, more importantly, educational level, hence emphasizing the need to further explore the links between perceived fatigue, cognitive status, and more generally cognitive reserve in MS. Mind-body interventions in MS could be conceptualized as forms of intensive training aimed at complementing disease-modifying benefits of medical therapies in newly diagnosed MS individuals by increasing reserve and helping patients to withstand better brain pathology in order to modulate disease progression. According to the claims of the theory of reserve (Sumowski and Leavitt, 2013), to consider MM as a proxy of CR, the results of these trials should demonstrate that patients undergoing MM can withstand MS pathology without cognitive impairment or with less cognitive impairments as compared to other MS patients with the same disease course and with no MM practice (eventually allocated to usual care or active control trainings). Indeed, rather than protecting from the progression of the MS pathology, which is the aim of medical therapies, yoga and MM trainings may increase the cognitive reserve of MS patients, allowing them to better cope with the burden of the disease at the cognitive and psychosocial levels, thus attenuating the relationship between the disease progression and cognitive decline. Similarly to very recent attempts to put into relation meditation with neurodegenerative diseases (Marciniak et al., 2014; Newberg et al., 2014) and in keeping with similar efforts made for other types of disorders affecting cognitive functioning (e.g., attention-deficit/hyperactivity disorder; Grant et al., 2013) and for MS patients undergoing a stress management therapy (Mohr et al., 2012), these suggested lines of inquiry would be needed before making more specific clinical recommendations regarding the use of mental training therapies based on mind-body techniques to protect MS patients against disease-related cognitive decline.

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