Multiple Sclerosis Phenotypes as a Continuum: The Role of Neurological Reserve

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ABSTRACT

Purpose of review

This review presents the hypothesis that loss of neurological reserve explains onset of progressive multiple sclerosis (PrMS).

Recent findings

Evidence supporting the separate classification of PrMS and relapsing multiple sclerosis (RMS) is limited and does not explain PrMS or the response of these patients to therapy.

Summary

We argue that MS progresses along a continuum from RMS to PrMS, with differing levels of neurological reserve accounting for phenotypic differences. In early MS, inflammation causes brain atrophy with symptoms buffered by neurological reserve. As brain loss from normal aging and MS continues, reserve is depleted and effects of subclinical MS disease activity and aging are unmasked, manifesting as PrMS. Most therapies show limited benefit in PrMS; patients are older, have fewer inflammatory events and the effects of aging cause continued loss of neurological function, even if inflammation is terminated. Loss of neurological reserve means patients with PrMS cannot recover function, unlike patients with RMS.

TAKE-HOME MESSAGES

- There are no confirmed genetic or immunological differences between relapsing and progressive forms of MS.
- The reported pathological and radiographic differences between these apparent MS subtypes represent quantitative differences on a pathological spectrum, influenced by patients with progressive disease generally being older, with longer disease duration rather than being pathognomonic to relapsing or progressive MS.
- We propose that loss of neurological reserve owing to MS-related inflammation explains the onset of PrMS, and the level of neurological reserve may explain why some patients with MS develop progressive disease earlier than others.
- We propose that reducing comorbidities, through strategies such as a healthy diet or active lifestyle, may help to protect neurological reserve, and could therefore prove beneficial in the care of patients with MS.

SEARCH TERMS

[41] Multiple sclerosis
Background

Multiple sclerosis (MS) involves inflammatory processes (believed to be mediated by lymphocytes and astrocytes) that ultimately lead to oligodendrocyte and neuronal loss, as illustrated in Figure 1. However, neuronal loss (evidenced by brain volume loss) is increasingly acknowledged as the primary driver of neurological disability in patients with MS and correlates with declines in motor, cognitive, and sensory functions, as assessed by the Expanded Disability Status Scale (EDSS).

The first attempt to differentiate MS types was done by international expert consensus and was based on common clinical courses of the disease. This classification was revised in 2013 by Lublin et al. as our understanding of MS increased owing to new insights into clinical relapse rate and imaging data (Table 1). Briefly, this update removed progressive-relapsing MS (PRMS), introduced clinically isolated syndrome (CIS), and the concept of active and non-active MS subtypes to all stratifications. Additionally, the terms “worsening” and “disease progression” were differentiated, the former to describe advancing symptoms for any reason and the latter reserved specifically for “true progression” rather than relapse. Although the revised Lublin criteria were devised to help to diagnose progressive forms of MS and aimed to distinguish between clinical phenotypes, in our opinion some of the definitions are difficult to apply consistently in clinical practice, resulting in a lack of consensus on this method of differentiation. Furthermore, the phenotype definitions do not address a number of issues: most MS-related CNS inflammation occurs at the onset of MS; over 80% of new brain MRI lesion formation detected by 0.6 Tesla MRI is subclinical; in patients with radiologically isolated syndrome (RIS), thalamic atrophy (neuronal loss or neurodegeneration) has been identified; and MS-related brain atrophy is already present at the CIS stage of MS. It should also be remembered that, after the age of 30 to 40 years, humans lose neurons at an increasing rate because of aging, a process which also consumes neurological reserve. Once neurological reserve is exhausted, aging will also contribute to slowly progressive neurological disability.

As our understanding of the biology of MS has increased, it has become apparent that there are no confirmed genetic or immunological differences between relapsing forms and progressive forms of MS, and that the reported pathological and radiographic differences between primary and secondary progressive MS subtypes and between progressive and relapsing disease are quantitative rather than qualitative, supporting the view that these apparent subtypes are part of a spectrum of disease rather than different biological entities. What, then, causes the onset of progressive disability in patients with MS? We propose that applying the concept of brain or neurological reserve (Figure 2A) may help to address this question.
Is there evidence that progressive and relapsing MS are distinct conditions?

**Diagnostic evidence**

To date, no diagnostic tests have been discovered that can identify a patient with progressive versus relapsing disease. There may be some quantitative differences in markers of disease that correlate with and could possibly predict progressive disease; however, there is a lack of data to support the view that it is possible to distinguish the two states by genetic, immunological, pathological, or radiographic findings.\(^{11, e5}\)

**Are there genetic differences between MS phenotypes?**

There is limited evidence to suggest that there are genetic differences between progressive and relapsing MS. The human leukocyte antigen (HLA) class II region has been identified as having a strong influence on the susceptibility to MS.\(^{12, e6}\) Associations have been reported between genes in this region and both progressive and relapsing forms of MS, suggesting that HLA-related mechanisms contribute to both phenotypes.\(^{12}\) Furthermore, two large studies in patients with MS could not find an association between disease progression and various non-HLA disease-susceptibility genes.\(^{e7, e8}\)

Further evidence that there is no genetic difference between MS phenotypes comes from studies within families, in which the chance of having progressive disease has been shown to be the same as that in people who are unrelated.\(^{e9, e9}\) Furthermore, if there were differences, one would expect the prevalence of one phenotype within a family to be different from the general population, but this is not the case. A study of a family with 15 members affected with MS showed that the clinical characteristics of the affected individuals were indistinguishable from those seen in sporadic MS, and the frequency of primary progressive MS (PPMS) was approximately 13%, which is the same as in the overall population.\(^{11, 13}\)

**Are there pathological/radiographic differences between MS phenotypes?**

There are no qualitative differences in brain pathology between relapsing and progressive forms of MS (Table 2).\(^{11}\) Ultrahigh field MRI analysis of gray and white matter lesions demonstrated that lesion morphology does not differ in PPMS and relapsing-remitting MS (RRMS).\(^{e10}\) Age-adjusted analyses of gadolinium-enhancing (Gd+) T1 lesion load and normalized total brain, gray, and white matter volumes showed no differences between RRMS and secondary progressive MS (SPMS).\(^{14}\) Likewise, no significant differences were found in MRI measures of lesion activity or brain volume loss between PPMS and SPMS.\(^{e11}\) Rates of annualized brain volume change were not statistically different in patients with PPMS, RRMS, or SPMS when adjusted for baseline normalized brain volume.\(^{9}\) Indeed, what differences there appeared to be in relapsing and progressive MS can be explained by the
longer disease duration that characterizes progressive forms of MS.\textsuperscript{15-17,e12-e14} Notably, two prominent neuropathologists specializing in MS were asked to write review papers, one arguing for different pathologies between relapsing and progressive disease and the other arguing for no difference.\textsuperscript{15,17} In fact, both authors reached the conclusion that the pathology is not different between patients with progressive or with relapsing MS.\textsuperscript{15,17}

Retinal changes are observed in patients with MS, with some studies suggesting differences between progressive and relapsing MS subtypes based on optical coherence tomography (OCT) data;\textsuperscript{e15–e17} however, analyses are complicated by the effects of aging, because thinning of the retinal layers is part of the normal aging process, and rates of thinning may increase with age, suggesting that much of the retinal atrophy observed in older patients with MS could be attributable to normal aging.\textsuperscript{e15} A recent study showed that progressive MS was associated with faster retinal layer atrophy than RRMS, even after adjusting for age, disease duration and severity; however, it is unclear whether this reflects differences in the pathobiological mechanisms between phenotypes or an increased susceptibility to neurodegeneration in individuals with progressive MS.\textsuperscript{e15}

\textit{Are there immunological differences between MS phenotypes?}

Inflammatory activation in early MS leads to demyelination and neuronal destruction (Figure 1).\textsuperscript{1,6,e18} However, the frequency of new inflammatory events decreases with age such that patients in their seventh decade have only approximately 30\% of the disease activity of patients in their third decade.\textsuperscript{e19} Although the cause of this decline in the frequency of new inflammatory events in the CNS of aging patients with MS is not known, it is important to keep this observation in mind when considering reports of immunological differences between RRMS and progressive forms of MS.\textsuperscript{18} Tissue-resident memory T cells (\(T_{\text{RM}}\) cells) have been observed invading the perivascular space in patients with progressive MS;\textsuperscript{e20} however, \(T_{\text{RM}}\) cells have also been detected in acute MS cases with short disease duration, suggesting that population of the perivascular space may start in the early stages of MS.\textsuperscript{e21,e22} Chronic white matter lesion activity (smoldering lesions) has been shown to predict clinical progression in PPMS, but these lesions are also observed in RRMS.\textsuperscript{e23,e24}

Indeed, several studies report immunological differences between relapsing and progressive forms of MS.\textsuperscript{18} However, none of these studies confirms the findings of any of the others. One potential explanation for this inconsistency is that all but one study did not control for age. Another is that all the studies are relatively small and made multiple comparisons without making Bonferroni-type corrections. This could mask any differences in early MS, and the differences could therefore have been a result of older patients having had MS longer and lower rates of immunological activity.\textsuperscript{6} Furthermore, the immune system ages and goes into senescence, which could also explain differences within patient groups of
different ages. It is noteworthy that, to date, no immunological or biomarker tests have been identified that can clearly distinguish between progressive and relapsing MS. Although neurofilament light chain (NFL) is considered a promising biomarker for MS, analysis suggests that it is useful as a marker of disease activity and does not clearly distinguish MS subtypes. NFL levels are known to increase as part of the normal aging process, even in healthy individuals, limiting its value as a marker of progression or progressive MS. Thus, the only way to distinguish between relapsing and progressive forms of MS is to interview the patient and/or examine the patient serially over time.

**What does explain the different MS phenotypes?**

Duration of disease and age are two factors that correlate with evolution to progressive disease. Reviewing the natural history of MS is necessary to help us to understand the cause of PrMS. MS tends to start in late adolescence or early adult life. Studies have demonstrated that most inflammatory lesions (approximately 80%) occurring in the CNS are clinically silent but are causing MS plaque formation, and that lesion volume is associated with accelerated brain atrophy, representing loss of neurons. This phenomenon is seen at the CIS stage and even at the RIS stage. This pattern of preclinical and subclinical progression of neurological injury before development of clinically apparent neurological symptoms is seen in other CNS diseases, including Alzheimer disease and asymptomatic traumatic brain injury, as well as in normal aging. Most humans demonstrate the onset of brain atrophy owing to loss of neurons after the age of 20 years but maintain normal neurological function into late life through brain and cognitive reserve. In healthy individuals, brain atrophy is slow at first but accelerates in the sixth and seventh decades (Figure 2B). This process of cerebral atrophy is accelerated in Alzheimer disease and repetitive closed-head injury. Work in these fields has focused primarily on cognitive dysfunction and has developed the terms “brain reserve” and “cognitive reserve” as concepts to help to explain the ability of the brain to buffer for injury, at least in the early phase of disease. The brain reserve concept proposes that maximal lifetime brain volume protects against cognitive decline, with impairment occurring when this falls below a critical threshold; the cognitive reserve concept suggests that intellectual enrichment and activities and behaviors that keep the brain active also offer protection against cognitive decline. These concepts have been shown to extend to MS. Brain reserve can protect against disease-related declines in cognition in MS. A larger brain reserve, estimated from intracranial volume (ICV), reduced the impact of disease burden on cognition, while a longitudinal study showed that a larger ICV protected against the decline in cognitive efficiency seen in patients with MS. Similarly, higher lifetime intellectual enrichment
(cognitive reserve) can attenuate the effects of brain atrophy on cognition in patients with MS.\textsuperscript{e34,e35} Furthermore, the protective effects of intellectual enrichment on cognition were shown to be independent of the beneficial effects of brain reserve against cognitive decline.\textsuperscript{e32} We propose to use the term “neurological reserve” in MS to expand the concepts as used in dementia, which focus on cognition, to include most other neurological functions that are affected by MS, including motor and sensory function.

If we apply this same concept of the ability of the brain to buffer for injury to MS, then the onset of progressive disease represents the point at which neurological reserve has been depleted or exhausted.\textsuperscript{32} At this point two things happen: the brain can no longer compensate for subclinical MS disease activity and we have unmasked the effect of normal aging on the brain (Figure 2B).\textsuperscript{33} In addition, as the biology underlying neurological reserve (mostly related to cortical remodeling) and neurological resilience (the ability of the brain to recover function after injury) has also declined, it would follow that progressive patients would be less able to recover function with exercise or other interventions than patients with RRMS.

**Neurological reserve**

The concept of neurological reserve has been used to explain why similar levels of brain injury may lead to different degrees of clinical impact.\textsuperscript{31} Is it possible that level of neurological reserve may explain why some patients with MS develop progressive disease earlier than others?

It is well established that brain volume correlates with age, MS duration, level of disability, and MRI markers.\textsuperscript{2,23} Diminishing functional/neurological reserve is a potential biological explanation for what happens to patients when they transition to progressive disease from RMS. The inflammatory phase of MS tends to start early,\textsuperscript{15} when most manifestations of the disease are subclinical. The brain begins to shrink early in the disease owing to loss of neurons, regardless of MS phenotype,\textsuperscript{9} and it has been shown that rate of brain loss is a predictor of subsequent disability.\textsuperscript{2} In the early phase of MS, symptoms may be buffered if there is adequate neurological reserve. Indeed, Schwartz et al. showed that patients with MS with high-active cognitive reserve had less symptom burden than those with low-active cognitive reserve and were more likely to have RRMS rather than progressive disease.\textsuperscript{32} Others have also shown that cognitive reserve and brain reserve (the latter measured by brain volume) protect against cognitive disability in MS.\textsuperscript{e32} As brain loss continues, the neurological reserve is used up and patients enter the progressive stage of the disease, in which the effects of subclinical inflammatory disease and the effect of normal aging are unmasked. Thus, the occurrence of progressive disease will be determined to some extent by the initial neurological reserve of the patient (Figure 2C). This is broadly in line with the
topographical model of MS proposed by Stephen Krieger, which suggests that clinical signs and disability in MS are driven by the relationship between focal lesion formation and the loss of neurological reserve.\textsuperscript{34}

We propose that MS phenotypes are part of a disease continuum. As described in Figure 1, inflammation is initially the cause of brain atrophy in MS; however, as inflammation declines with age, brain loss due to normal aging becomes more important. There are data to indicate that, by the time patients are approximately 60 years old, over half of brain loss observed is due to normal aging, that is, not due to MS (Figure 3A–D).\textsuperscript{35} One group looked at the nature of lesions as a function of age in patients with MS at autopsy compared with age- and sex-matched controls, and found that the frequency of acutely active lesions, chronically active lesions and burnt-out lesions is steadily shifting in the direction of the burnt-out lesions as patients age.\textsuperscript{6} Furthermore, when investigating the whole brain of post-mortem patients with progressive disease, they could be divided into two categories: those with pathologically active disease, characterized by classical active or slowly expanding lesions, and those with pathologically inactive disease, who only showed inactive, burnt-out lesions. Patients with inactive disease were older and had longer disease duration than those with active disease. Adding support to this concept of the impact of normal aging, markers of neuronal death such as amyloid precursor protein in patients with inactive disease indicated that the rate of neuronal death was the same as in age-matched controls, thereby contradicting the concept of progressive disease being a result of accelerated neuronal loss.\textsuperscript{6} MS prognosis is in part age-dependent, uninfluenced by an initial relapsing or progressive disease course.\textsuperscript{10} The brain shrinks at an accelerated rate in patients with young-onset MS,\textsuperscript{35} and at any given age patients with earlier onset have smaller brains and increased disability, adding strength to the hypothesis that neurological reserve is a key element of defining MS phenotypes and that age-related changes affect cellular vulnerability.

The assessment of cognitive reserve and its effects on outcomes in patients with MS provides a good basis for considering how to evaluate neurological reserve in MS. Several measures have been used to evaluate active and passive aspects of cognitive reserve.\textsuperscript{e36} Passive reserve refers to factors that precede disease onset, and typically relies on measures of education, occupation and childhood activities to quantify intellectual enrichment. Active reserve relates to current activities and behaviors that keep the brain active, and includes leisure activities and hobbies (Supplementary Table, http://links.lww.com/CPJ/A248).\textsuperscript{e36} Schwartz et al. suggested a broader view of reserve extending beyond cognition to encompass factors such as physical activity, social/community participation and spiritual/religious practices, as well as personal characteristics, such as attitudes, values and socio-emotional skills that may enhance a person's resilience.\textsuperscript{32}
Reducing MS comorbidities and protecting neurological reserve through diet and physical activity

MS is associated with numerous comorbidities, which may lead to greater disability, increased mortality, and reduced quality of life.\textsuperscript{36,37} For example, registry analysis showed that vascular comorbidity (diabetes, hypertension, heart disease, hypercholesterolemia, and/or peripheral vascular disease) was associated with an increased risk of disability progression in patients with MS.\textsuperscript{37} As such, there is great interest in lifestyle choices that may help to reduce the burden of common comorbidities in patients with MS, such as hypertension, diabetes, hyperlipidemia, ischemic heart disease and chronic lung disease,\textsuperscript{37} and so potentially benefit patients by helping to protect neurological reserve. Physical activity has been associated with increased brain volume in patients with MS,\textsuperscript{38} and it has been suggested that physical activity provides an important “reserve-building activity” by expanding the synaptic network and ensuring that more areas of the brain and interconnections remain active and fit.\textsuperscript{39} Therefore, we suggest that physical activity may be able to develop an increased buffer against injury by expanding the synaptic network of the brain, as has been documented in Alzheimer disease.

Pharmacological treatment of progressive MS: what do clinical trial results suggest?

Several issues need to be considered in clinical trial design for disease-modifying therapy (DMT) interventions in progressive forms of MS. First, patients with progressive disease are on average 15 years older than those with RRMS. Thus, they are experiencing far fewer acute inflammatory events as measured by new T2 or Gd+ lesions or by relapse rate. Second, as we contend, these patients have exhausted neurological reserve, which means they can no longer mask the effect of subclinical inflammatory disease due to MS or the effect of age-related neuronal loss that begins in the fourth decade of life in humans.\textsuperscript{30,32} Finally, unlike patients with RRMS, patients with PrMS have little ability to recover function on highly effective DMTs, as was demonstrated in a study by Coles et al.\textsuperscript{38} When treated with alemtuzumab, patients with RRMS steadily recovered function over 3 years of observation, whereas patients with PrMS showed a slowing in the rate of disability progression but continued to progress slowly (Figure 3E).\textsuperscript{38} We would propose that this is due to the unmasking of the effect of aging on the brain because of premature consumption of neurological reserve by MS. Moreover, the neurobiology of neurological reserve is primarily mediated through cortical remodeling, as is recovery of function or neurological resilience.\textsuperscript{32}

If we delay the use of highly effective therapies until patients have developed significant disability and are entering the progressive phase of MS, the best outcome (without
reparative therapies) will be a slowdown in the decline in function.\textsuperscript{22} Early treatment of RRMS with highly effective DMTs is associated with better long-term outcomes than delayed treatment and it generally results in improvement, if not resolution, of MS-related disability.\textsuperscript{39}

To date, most therapies have shown limited benefit in patients with progressive forms of MS, with the exception of ocrelizumab (approved for PPMS in Australia, Europe and the USA), siponimod (approved for active SPMS in Europe and the USA, SPMS in Australia and Japan), and cladribine (approved for active SPMS in the USA).\textsuperscript{40,40–47} While other potential therapies for the treatment of PrMS are still under investigation,\textsuperscript{40} our therapeutic goal in the management of MS is to treat as early as we can with the most effective DMT with an appropriate safety profile to minimize further neuronal loss, and to preserve neurological reserve both to avoid entry into the progressive phase of MS and to buffer against normal aging effects on the CNS in later life.

Conclusions

In summary, we believe there is a lack of genetic, pathological, and immunological evidence to justify stratifying progressive and relapsing forms of MS as two separate entities. Furthermore, there appears to be no simple classification that can accurately distinguish between the two forms. Instead, we believe that MS progresses along a continuum from RMS to PrMS, with phenotypic differences along this spectrum accounted for by differing levels of neurological reserve. This is a concept well developed in other fields, notably Alzheimer disease. When applied to MS, it explains the pattern of treatment response seen when patients are treated with the various DMTs that cannot be accounted for by consideration of genetic, pathological, or immunological differentiators. It also provides the scientific rationale for early intervention with highly effective DMTs, helping patients with MS to adopt active and healthy lifestyles to build reserve and improve their neurological function over their lifetime.

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Appendix 1: Authors

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<tr>
<th>Name</th>
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<th>Contribution</th>
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<tr>
<td>Timothy Vollmer, MD</td>
<td>Department of Neurology, University of Colorado, and Rocky Mountain Multiple</td>
<td>Design/conceptualization of the study; acquisition, analysis/interpretation of</td>
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<td>Author</td>
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<td>Analysis/interpretation of data; drafting/revising the manuscript for intellectual content</td>
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<td>Design/conceptualization of the study; acquisition, analysis/interpretation of data; drafting/revising the manuscript for intellectual content</td>
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### Tables

**Table 1** Phenotype descriptions for RRMS and PrMS<sup>5,4,48</sup>

<table>
<thead>
<tr>
<th>RRMS</th>
<th>CIS</th>
<th>RRMS</th>
<th>PrMS</th>
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|        | • Clear-cut syndrome such as optic neuritis, brain stem/cerebellar dysfunction or partial myelitis  
• Characteristics of inflammatory demyelination are present, but McDonald 2010 criteria of dissemination in time are yet to be fulfilled | • MRI evidence of dissemination in space, as well as gadolinium-enhancing and nonenhancing T2 lesions on a single MRI scan and/or a subsequent event | Progressive accumulation of disability from onset  
Progressive accumulation of disability after initial relapsing course |
|        | Active<sup>a</sup> | Active<sup>a</sup> | Active<sup>a</sup>, without progression  
Active, without progression  
Not active, with progression  
Not active, without progression (stable disease) |
|        | Not active | Not active | |

<sup>a</sup>Clinical relapses and/or MRI activity (gadolinium-enhancing MRI lesions or new/enlarged T2 lesions) assessed at least annually.  
<sup>b</sup>Measured by clinical evaluation at least once yearly.  
Abbreviations: CIS = clinically isolated syndrome; MS = multiple sclerosis; PPMS = primary progressive MS; PrMS, progressive MS; RRMS = relapsing-remitting MS; SPMS = secondary progressive MS.
Table 2 Summary of imaging and histopathological findings in different MS disease courses\textsuperscript{11,14-16}

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<tr>
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<td>Gadolinium enhancement\textsuperscript{a}</td>
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<td>Reduced axonal density (lesion)</td>
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+, ++ and +++ indicate the relative extent of changes observed.

Abbreviations: APP = amyloid precursor protein; NAWM = normal appearing white matter; ND = not detected.

\textsuperscript{a}Predicts progression of clinical disability.

\textsuperscript{b}Correlates with physical disability.

\textsuperscript{c}Correlates with cognitive impairment.

Adapted from Antel et al., 2012.\textsuperscript{11}
FIGURES

Figure 1 Inflammatory activation in early MS leads to astrocyte activation, demyelination and neuronal destruction

A) The dura mater and subarachnoid space of the brain are well connected to the circulation, filled with blood vessels and lymphatic vessels across which immune cells, such as B and T lymphocytes, can enter and exit the CNS. B) Autoreactive B cells and T cells mature in the lymph nodes, including the deep cervical lymph nodes, and enter the circulation, where C) these cells cross the blood–brain barrier and enter the CNS. Effector functions of autoreactive B cells include antibody and cytokine production, and antigen presentation to T cells, which further drives CNS inflammation. The proinflammatory cytokines released by these cells drive the activation of CNS resident cells, including astrocytes. The inflammatory processes mediated by activated astrocytes include the release of TNF-α, production of reactive oxygen species including NO (via iNOS) and other toxic intermediates, leading to oligodendrocyte damage and apoptosis, neuronal/axonal damage, and the loss of astrocytes themselves. Oligodendrocyte damage may be compounded by the fact that some patients with MS can be predisposed to factors that inhibit oligodendrocyte maturation, and loss of normal astrocyte function may also impact the blood–brain barrier, microglial activation and neuronal damage. Indeed, repair in lesions is accompanied not only by regeneration of oligodendrocytes but the reappearance and maturation of astrocytes. Interestingly, the role of astrocytes was elucidated by studies with the S1PRm fingolimod. S1PRms are also thought to be potentially neuroprotective in the CNS through their direct effects on astrocytes, as well as neurons and oligodendrocytes. Autoreactive B cells are able to leave the CNS, crossing the blood–brain barrier by draining through the deep cervical lymph nodes and on into the peripheral lymphatic system, where further rounds of maturation and clonal expansion can occur before repopulating the CNS and driving pathological process further.

iNOS = inducible nitric oxide synthase; NO = nitric oxide; S1PRm = sphingosine-1 phosphate receptor modulator; TNF= tumor necrosis factor.
Figure 2 The concept of brain/neurological reserve in MS

A) Cross-sectional relationships between components of reserve and performance. This model provides a roadmap for the nomenclature and expected relationships among reserve-related constructs at a specific point in time. Going counter-clockwise from left, genetic and inborn factors refer to inborn or background determinants of brain function (e.g. single nucleotide polymorphisms). These factors are the only direct causes of (innate) brain reserve, which represents a patient’s potential brain structure (e.g. head size, intracranial volume, synapse count, CNS structure). Regardless of a patient’s brain reserve, the patient’s neuronal network function represents the present level of functioning of a patient (e.g. functional connectivity as measured by functional magnetic resonance imaging). Then the combination of a patient’s present neuronal network function, environmental factors (e.g. socioeconomic adversity or advantage; stressful events) and disease burden (e.g. diagnosis, symptoms, treatment side effects, progressive disability) determines the patient’s expected performance on a task. Finally, the difference between observed and expected performance is affected by the person’s expected performance, (acquired) reserve and reserve-related person characteristics. Reserve and reserve-related person characteristics are each hypothesized to lead to larger differences between observed and expected performance, but through different mechanisms. Whereas reserve relates specifically to compensatory or protective brain function, reserve-related person characteristics refer to attitudes, values or socioemotional skills that are posited to enhance an individual’s resilience in the face of adversity and/or disease. Both reserve and reserve-related person characteristics are posited to be directly affected by the individual’s past and current reserve-building activities. Such activities are hypothesized to include a multidimensional array of activities that promote brain health, including cultural/intellectual pursuits, physical activity, social/community participation, spiritual/religious practices and dietary/lifestyle habits. B) Brain reserve as a function of normal aging and in MS. In healthy people, brain reserve is initially high, but slowly declines as people age. Only at advanced ages would cognitive/brain health be affected by the loss of brain reserve. In people with MS, brain reserve can initially buffer/compensate for the effects of disease (preclinical phase). However, in MS, brain reserve is depleted more rapidly by the effects of aging and disease processes. Brain reserve is lowered to a level at which it can no longer compensate and the impact of disease on cognitive/brain health becomes apparent, manifesting as disease progression. C) As described above, brain reserve buffers/slows disease progression. Patients with lower levels of brain reserve may progress through all the “classically defined” stages of disease progression, with overt “unbuffered” symptoms at each stage that are easily diagnosed (top line). Those with intermediate levels of brain reserve may appear asymptomatic for longer, with the disease progressing in the background before the loss of reserve manifests as overt relapsing-remitting symptoms prior to progressive disease (middle line). Patients with very high brain reserve may appear functionally asymptomatic even while the clinical effects of the relapsing phase are ongoing, buffered until disease processes overcome reserve and manifest overtly as primary progressive disease (bottom line).

MS = multiple sclerosis.
Figure 3 Rates of brain atrophy in MS and in normal aging and rates of disability worsening in RRMS and SPMS.\textsuperscript{35,38}

Stacked histograms showing the trend of brain atrophy slopes by age in HCs (red) and MS-specific atrophy (blue). The total rate of atrophy in patients with MS is represented by the total height of each histogram bar (combining colors). For SIENA (A) and the thalamus (B), the contribution of MS-specific atrophy and normal aging to the total atrophy slope changed significantly across decades, whereas normal aging was stable across decades in the caudate (C) and the putamen (D). The rates of disability worsening in RRMS and SPMS are depicted in (E), in which mean annualized EDSS scores indicate that disability worsening is significantly higher in patients with SPMS in the first 3 years after initiating treatment than in those with RRMS. Data are annualized to allow comparison between time epochs of different duration.

*\(p < 0.5\), **\(p < 0.01\), ***\(p < 0.001\), Mann–Whitney U test.

EDSS = Expanded Disability Status Scale; HC = healthy control; MS = multiple sclerosis; RRMS = relapsing-remitting MS; SIENA = structural image evaluation using normalization of atrophy; SPMS = secondary progressive MS.

Adapted from (A–D) Azevedo et al., 2019,\textsuperscript{35} and (E) Coles et al., 2006.\textsuperscript{38}
Multiple Sclerosis Phenotypes as a Continuum: The Role of Neurological Reserve

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