A Comprehensive Look at Multiple Sclerosis

3 Key Factors to Consider

Worldwide, multiple sclerosis (MS) is the most prevalent chronic inflammatory disease of the central nervous system (CNS).[1,2] MS causes early, permanent neurological damage that can lead to the development of scars, called lesions, on nerve tissues throughout the CNS.[1] When lesions form, a sudden attack of symptoms can follow, known as a relapse.[1] In relapsing-remitting MS—the most common course of the disease—patients experience acute attacks (relapses) that develop over a few days, then plateau and fade away (remit) over time, as damage is addressed by CNS repair mechanisms.[1] To fully understand disease activity in MS, it is important to consider a number of factors that can contribute to CNS damage and impair neurological function. This site explores 3 key factors:

White and Grey Matter

Damage caused by multiple sclerosis can begin early in the course of disease—driven by both inflammatory and neurodegenerative mechanisms.[1,3-5] Although White Matter damage has long been associated with early damage, recent studies have found that Grey Matter damage also occurs early in the disease.[6-12]

See More >>

More Than White Matter

While MS has historically been considered a White Matter disease, a growing body of evidence has shown that Grey Matter pathology plays a major role in both disease pathology and progression.[13-16] Research from numerous longitudinal and imaging studies has shown that Grey Matter damage is widespread, starts early in disease progression, and is strongly correlated with disability.[8,13,14,16-20]

See More >>

Comorbidities/ Lifestyle

With MS, many factors can influence brain health, including comorbidities and lifestyle. Research has shown that multiple sclerosis comorbidities can exacerbate the disease, increasing the likelihood of relapses.[1,21-23] Lifestyle choices can also have a major impact on the overall health of the brain.[1]

See More >>

Examining the Whole Picture in MS

MULTIPLE SCLEROSIS—AN AUTOIMMUNE DISEASE OF THE CNS

This site provides an overview of how MS affects brain and spinal cord tissue, causing **permanent damage** that **starts early** in the course of the disease.[3,6-8,13,14,17-20,24-28] In people with MS, the body's own **immune system** attacks nerve fibers in the brain and spinal cord causing inflammation, demyelination, nerve damage, and the destruction of axons and neurons.[1,20] This **neurological damage** can lead to the development of scars, known as lesions, on nerve tissues throughout the central nervous system (CNS).[1] Although lesions can occur in both **White Matter** and **Grey Matter**, they are most easily seen in the White Matter of the brain, using magnetic resonance imaging (MRI) technology.[2,7,20] Since the year 2000, MRI scans have been the primary means of definitively **diagnosing the disease in people with MS**.[2]

A RANGE OF SYMPTOMS AND PHENOTYPES

Depending on where the MS lesions form, they can disrupt nerve function and lead to a sudden attack of symptoms, known as a relapse.[1] **Early symptoms** commonly include numbness, tingling, burning pain, muscle weakness, stiffness, clumsiness, difficulty walking, visual disturbances, and fatigue.[1] In relapsing-remitting forms of MS, patients experience **acute attacks** (relapses) that develop over a few days, then plateau and fade away (remit) over time, as damage is addressed by CNS repair mechanisms.[1] Relapsing-remitting MS is the **most common** course of multiple sclerosis, with 80% to 90% of MS patients initially starting with this disease phenotype.[1] Other **multiple sclerosis phenotypes** include primary progressive MS, secondary progressive MS, and clinically isolated syndrome.[1,20] All together, there are 2.3 million people with MS worldwide, making it the most prevalent chronic inflammatory disease of the central nervous system.[1,2]

MULTIPLE SCLEROSIS DAMAGE BEGINS EARLY

Another important finding is that the damage caused by multiple sclerosis can begin early in the course of disease—driven by both inflammatory *and* neurodegenerative mechanisms.[1,3-5] While the brain is naturally able to compensate for tissue damage for a period of time, some nerve tissue is irreversibly destroyed, causing permanent injury and a loss of brain volume.[1] Although White Matter damage has long been associated with early damage, recent studies have found that Grey Matter damage also occurs early in the disease.[6-12] Evidence of early *atrophy* has been found in both cortical Grey Matter and Deep Grey Matter.[9-12] In addition, researchers have found evidence of early *lesions* in Grey Matter, too.[20] In one study (n=107), 64% of patients with early RMS were found to have Grey Matter damage caused by cortical lesions.[18] Together, this information gives us a much more robust understanding of the complex pathology of MS. Only by developing a comprehensive understanding of this disease can we promote CNS health, work to protect neurological function, and help maintain cognitive ability in patients with MS.

A DISEASE OF BOTH WHITE AND GREY MATTER

While MS has historically been considered a White Matter disease, a growing body of evidence has shown that **Grey Matter pathology** plays a **major role** in both disease pathology and progression.[13-16] Research from numerous longitudinal and imaging studies has shown that Grey Matter damage is **widespread, starts early** in disease progression, and is strongly correlated with **disability**.[8,13,14,16-20] Among the negative outcomes associated with Grey Matter pathology are **cognitive impairment, physical disability**, painful syndromes, fatigue, and ocular motility disturbances.[16] Grey Matter pathology generally takes the form of cortical **lesions**, cortical **atrophy**, deep Grey Matter lesions, and deep Grey Matter atrophy.[17,18,20,25,26] In particular, recent research has found that **thalamic atrophy** is an especially potent driver of long-term patient disability.[26] Thalamic atrophy has been associated with physical disability, cognitive impairment, and fatigue.[26,29] In a post hoc analysis of 1214 patients with MS, thalamic atrophy was a better predictor of future disability than other regions.[26] Another key area of importance in MS is Grey Matter in the spinal cord, which can be highly predictive of disease progression.[19] One clinical study of 113 MS patients and 20 healthy controls demonstrated that Grey Matter atrophy in the spinal cord was more strongly correlated with physical disability than any other variable examined.[19]

Multiple Sclerosis Mechanism of Disease

A Closer Look at MS Pathogenesis

Inflammation and Neurodegeneration

The pathogenesis of multiple sclerosis (MS) involves a complex and dynamic interplay between the immune system and central nervous system (CNS) resident cells, including neurons and glial cells.[1] These mechanisms contribute to the acute inflammation and diffuse neurodegeneration that characterize MS.[1,2]

View **references** on Mechanism of Disease.

The Role of Glial Cells in Multiple Sclerosis

A Network of Support Cells for the CNS

A Closer Look at Cell Function

Neuroglia are a network of cells in the brain and spinal cord that support the central nervous system by maintaining homeostasis, producing myelin, and protecting neurons from outside attack.[1,3,4]

Glial cells include astrocytes, microglia, and oligodendrocytes.[1]

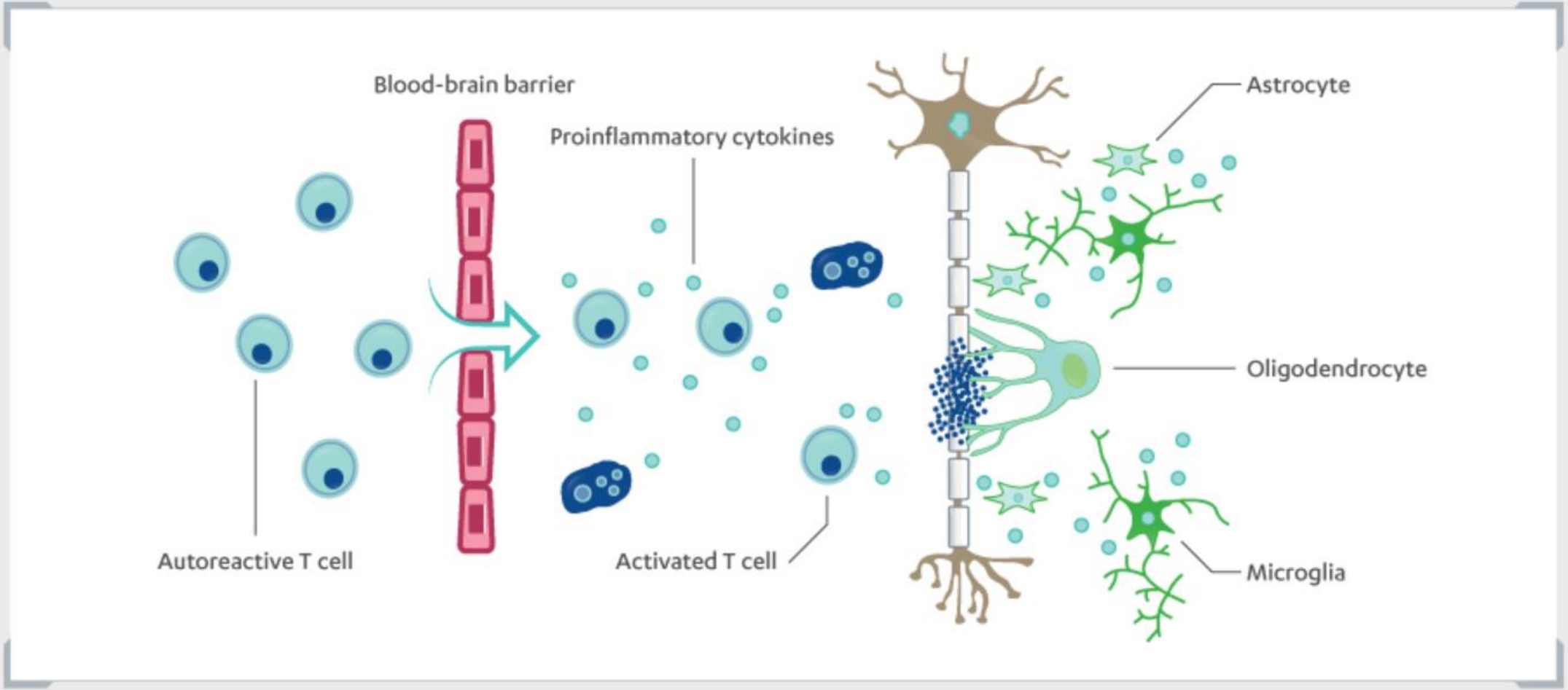
- **Astrocytes** provide synaptic support, neuronal guidance, and maintain the blood-brain barrier[3]
- **Microglia** have an important role in inflammatory and immune responses including clearing cellular debris and repairing tissues[4]
- **Oligodendrocytes** create the myelin sheath that helps insulate axons and allow for efficient conduction of nerve impulses[1]

Glial Cell Activation

Glial cells are activated when immune cells, including T cells, cross the blood-brain barrier and set in motion a chain of cellular reactions.[5-8]

- **Cytokine Secretion:** once inside the central nervous system, autoreactive T cells secrete proinflammatory cytokines[1,8-10]
- **Glial Activation:** in response to these proinflammatory cytokines, resident glial cells, such as microglia and astrocytes, become activated[3,8-10]
- **Axonal Demyelination:** activated microglia and astrocytes produce additional proinflammatory cytokines, such as TNF-α, NO, and IL-6, which play a key role in demyelination and axonal injury[3,4,6,8,9]
- **Oligodendrocyte Loss:** inflammatory activity also results in the extensive loss and apoptosis of oligodendrocytes, which are no longer able to repair and replenish damaged myelin sheaths[1,3,4]

Glial Cell Activity in the Pathogenesis of MS[1,3-10]



Adapted from Duffy SS, Lees JG, Moalem-Taylor G. The contribution of immune and glial cell types in experimental autoimmune encephalomyelitis and multiple sclerosis. *Mult Scler Int*. 2014;2014:285245. Reprinted with permission.

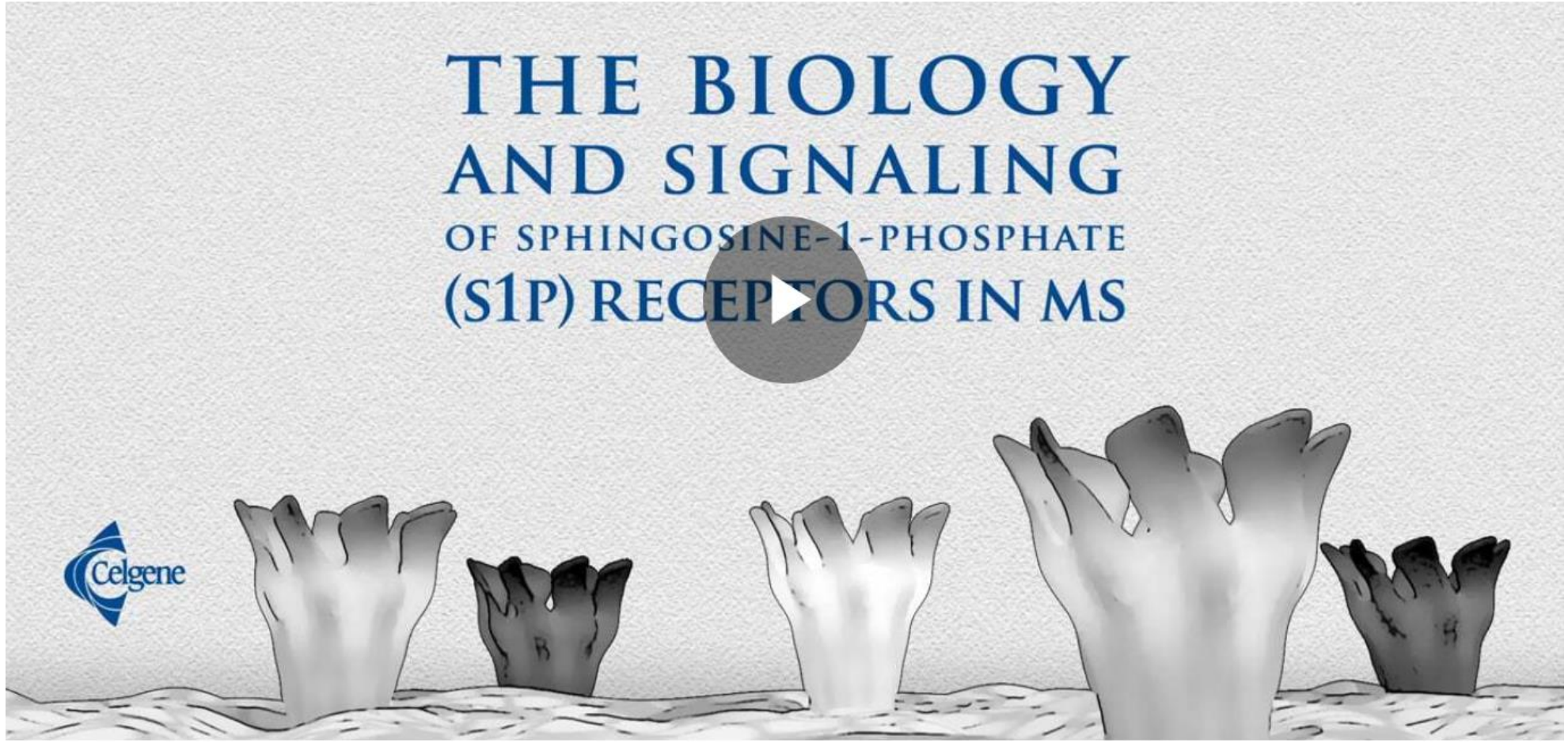
View **references** on the Role of Glial Cells.

Migration and Activation

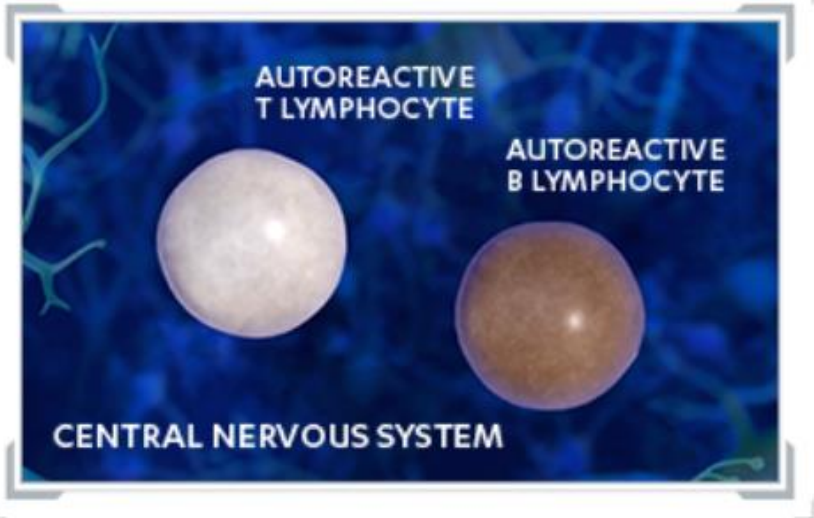
The Biology and Signaling of Sphingosine-1-phosphate (S1P) Receptors

A Range of Biological Functions

A quick overview of the biological mechanisms in multiple sclerosis (MS).



Summary of Key Points

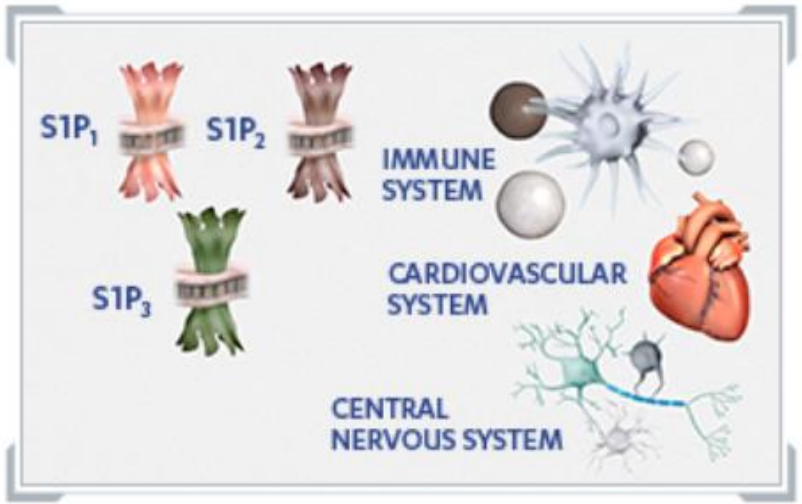


1. Lymphocyte Migration in MS

- In MS, autoreactive T and B lymphocytes cross the blood-brain barrier and cause neurological damage[5]
- Before invading the central nervous system (CNS), autoreactive lymphocytes must first leave lymph nodes and move into circulation[11]
- This may be a pivotal control point in MS. Focusing on the complex mechanisms that drive lymphocyte migration may be key to understanding MS[12]

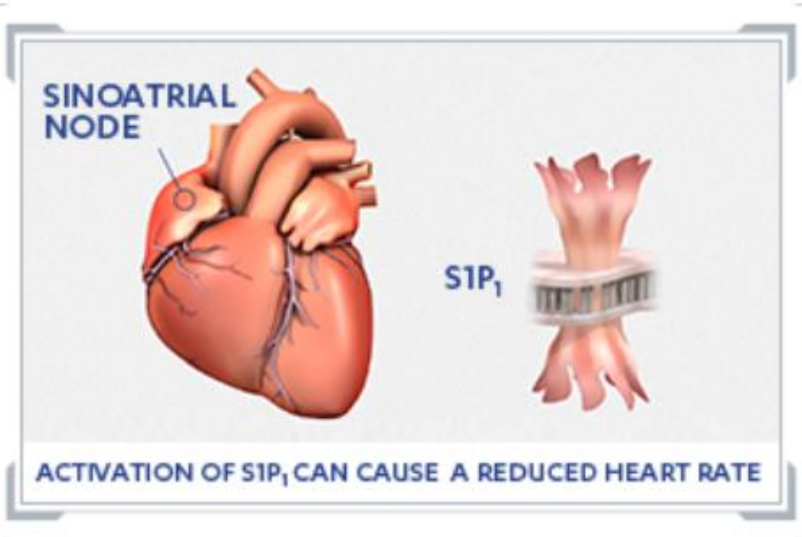
2. S1P and the Role of S1P Receptor-1 in Lymphocyte Migration

- One of those mechanisms involves the signaling of S1P receptors[12,13]
- S1P binds to a family of five S1P receptors—$S1PR_1$ through $S1PR_5$[12]
- $S1PR_1$ is expressed on the surface of lymphocytes and directs their migration from lymph nodes into circulation[13-15]



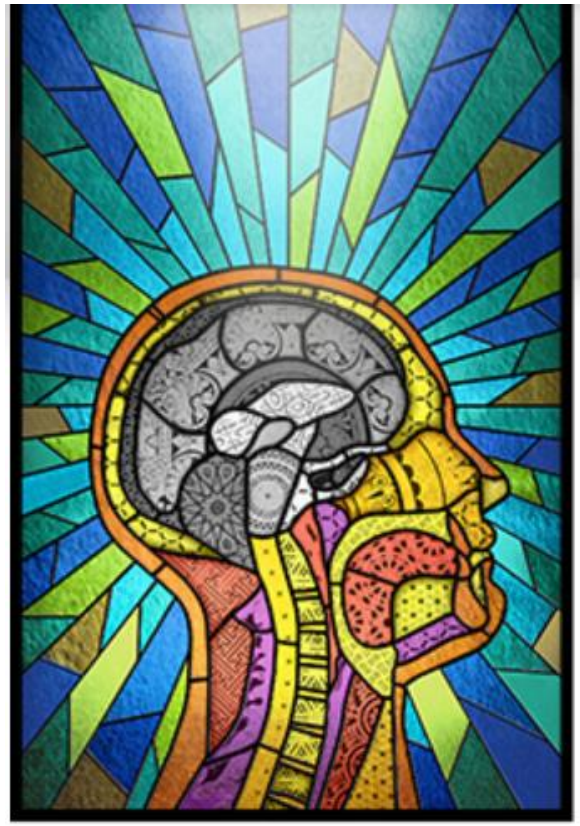
3. **Diverse Biological Functions of S1P Receptors**

- In addition to lymphocyte migration, S1P receptors are involved in other biological functions[16]
- $S1PR_1$, $S1PR_2$, and $S1PR_3$ are broadly expressed in cells of the immune system, cardiovascular system, and CNS[17,18]
- $S1PR_4$ expression is limited to the immune system, while $S1PR_5$ is found primarily in the CNS[17,19]



4. **Role of S1P Receptors in the Cardiovascular System**

- In the cardiovascular system, activation of $S1PR_1$ on cardiac myocytes of the sinoatrial node can cause a reduced heart rate[16]
- $S1PR_2$ causes coronary artery smooth muscle to contract[20]
- $S1PR_3$ is expressed on Purkinje fibers and can alter conduction along the atrioventricular node, leading to cardiac arrhythmias and complete heart block[21]



The Long-Term Consequences of Early Damage to White and Grey

Early Multiple Sclerosis Damage Can Cause Irreversible Harm[1-5]

Early Damage, Permanent Results

In Multiple Sclerosis (MS), permanent damage to White Matter and **Grey Matter (GM)** begins early in the course of disease—driven by both inflammatory *and* neurodegenerative mechanisms.[2-5] Both WM and GM pathologies are important drivers of disease activity in patients with MS.

This central nervous system (CNS) damage includes not only relapses, White Matter lesions, and a decline in physical function, but also whole brain volume loss, **Grey Matter atrophy** (including thalamic atrophy), cortical lesions, and cognitive impairment.[1-8]

Information about More Than White Matter »

Depleting the Neurological Reserve

Exhausting the Brain's Ability to Respond to Multiple Sclerosis Damage

Impact of Early Damage on Neurological Reserve

Evidence shows that early damage can impact Neurological Reserve—the finite capacity of the brain to retain function by remodeling itself after an MS-related injury.[2]

While the brain is naturally able to compensate for tissue damage for a period of time, some nerve tissue is irreversibly destroyed, causing permanent injury and a loss of brain volume.[2]

Ironically, the brain's ability to compensate for early nerve damage may actually mask the ongoing neurodegeneration taking place, causing it to go unrecognized until Neurological Reserve has significantly deteriorated.[2]

View **references** on Neurological Reserve.

> It is therefore important to diagnose MS as early as possible, before Neurological Reserve is exhausted and the progressive stage of the disease begins.
>
> —*Giovannoni et al*[2]

GREY MATTER FACT:
INDEPENDENT

In Multiple Sclerosis, **Grey Matter** demyelination is largely **independent** of White Matter demyelination[9,10]

Beyond White Matter Damage

Together, White and Grey Complete the Picture

White Matter Damage Is Only 1 Component of Disease Activity in Multiple Sclerosis (MS)

Historically, early multiple sclerosis damage has been associated with White Matter,[11,12] with an emphasis on focal demyelinating lesions in White Matter tissue.[10,13] However, while early damage to White Matter is an important contributor to disease activity, it is **just 1 component** of a comprehensive approach to understanding multiple sclerosis and neurological function.

White Matter pathology alone does not fully explain disease activity in multiple sclerosis, as it is only moderately correlated with outcomes (such as disability).[14,15] **Grey Matter pathology** in the central nervous system (brain and spinal cord) has been identified to play an important role.[10,16,17]

View **references** on White Matter pathology.

> ...THE MOST VISIBLE ELEMENT OF PATHOLOGY, WHITE MATTER (WM) LESIONS, REPRESENTS ONLY A FRACTION OF THE DISEASE BURDEN BORNE BY THE BRAIN...
>
> *— CHARD ET AL[18] —*

Information about More Than White Matter »

Grey Matter Atrophy in Multiple Sclerosis

Research Has Shown That Grey Matter Atrophy Begins Early

Evidence of Early Atrophy

- In several studies, researchers found evidence that **Grey Matter atrophy** begins early in the course of disease, with atrophy documented in both cortical Grey Matter and Deep Grey Matter[19-23]
  - Thalamic atrophy is one of the earliest and most prominent subcortical signs of MS pathology[16]
- In a 2-year longitudinal study, researchers found significant **Grey Matter atrophy** in patients (n=21) with a mean disease duration of 2.1 years[20]
- Thalamic atrophy was found to occur early and consistently throughout the course of MS in a 2018 longitudinal study that included 520 patients[24]

> GM atrophy is present early in the disease across different clinical subtypes and is associated with physical disability and cognitive decline.
>
> —*Steenwijk et al*[22]

View **references** on Grey Matter atrophy.

Information about More Than White Matter »

Grey Matter Lesions in Multiple Sclerosis

Grey Matter Lesions Appear Early in the Disease Progression

Evidence of Early Lesions

- Imaging studies confirmed the presence of **Grey Matter lesions** in the earliest phases of disease—even in patients with minimal White Matter pathology[13]
- In some cases, researchers have discovered **Grey Matter lesions** in patients with radiologically isolated syndrome—before any clinical symptoms are present[13]
- In a prospective longitudinal MRI study of 107 MS patients, **64% of RMS patients** were found to have Grey Matter damage caused by cortical lesions at baseline[7]

In a prospective longitudinal MRI study of 107 MS patients,

64% with early RMS had cortical lesions[7]

View **references** on Grey Matter lesions.

Information about More Than White Matter »

More Than White Matter: Grey Matter Is Essential to Understanding MS

Why Grey Matters in Multiple Sclerosis

Damage to Grey Matter in MS—Prevalent and Important

Recent advancements in imaging technology have revealed that Grey Matter pathology in multiple sclerosis (MS) is more important and prevalent than previously realized.[1-4]

Accumulating evidence from numerous longitudinal and imaging studies has shown that Grey Matter damage[2-4]:

- is widespread
- starts early in disease progression
- and is strongly correlated with disability

Strongly Correlated With Disability

Several cross-sectional studies have demonstrated that Grey Matter pathology is significantly correlated with both cognitive impairment and physical disability in MS patients.[8]

Among the negative outcomes associated with Grey Matter pathology are[9]:

- Cognitive decline
- Fatigue
- Motor deficits
- Ocular motility disturbances
- Painful syndromes

View **references** on Grey Matter pathology.

GREY MATTER FACT:
WIDESPREAD

In Multiple Sclerosis, Grey Matter pathology is widespread, progressive, and correlated with disability[5-7]

Why Grey Matters in Multiple Sclerosis

The Impact of Grey Matter Atrophy

A Dominant Driver of Disability

Physical Disability

In a 4-year longitudinal study (n=87), Grey Matter atrophy was correlated with sustained worsening of physical disability in MS patients.[6]

In a 2018 study of patients with multiple sclerosis (N=71), Grey Matter volume (cortical and deep grey) had the strongest association with the extent of walking disability.[10]

Recent findings from a 10-year follow-up study (n=152) suggest that confirmed disability progression (CDP) and Grey Matter atrophy may be inextricably linked.[11]

In a 2-year longitudinal study with more than 1200 patients with multiple sclerosis, researchers found that Deep Grey Matter volume loss was a dominant driver of disability accumulation across all MS phenotypes.[12]

- A post hoc analysis of atrophy in more than 40 different regions of the brain (n=1214) found that the thalamus was a better predictor of future disability than any other region[12]

Cognitive Disability

Data from several cross-sectional studies indicate that Grey Matter damage is significantly correlated with cognitive dysfunction, which can occur early in the course of disease.[5,6,8,9,12-14]

- Even in patients with little or no physical disability, early cognitive deficits have been observed[15]

In a clinical trial with 67 patients with probable MS,

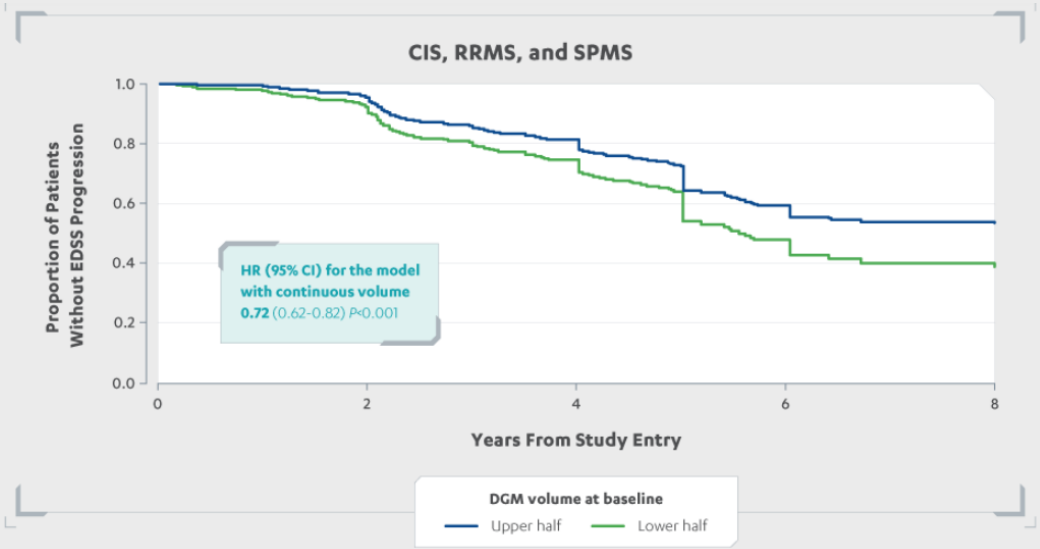
54% of patients exhibited signs of cognitive decline[16]

Fatigue

- Fatigue is a common and debilitating symptom of MS, affecting nearly 80% of patients—with more than half describing it as one of the worst symptoms of the disease[17]
- Studies have shown that fatigue has a major impact on quality of life, adversely affecting a patient's ability to work and socialize[17]

In a retrospective MRI study of 1214 patients with MS,

Patients With Lower Deep Grey Matter Volume at Baseline Had Increased Rates of Physical Disability Progression[12]



Eshaghi A, Prados F, Brownlee W, et al; on behalf of the MAGNIMS study group. *Annals of Neurology*. John Wiley and Sons. © 2018 The Authors Annals of Neurology published by Wiley Periodicals, Inc. on behalf of American Neurological Association. CIS=clinically isolated syndrome; RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis; EDSS=Expanded Disability Status Scale; DGM=Deep Grey Matter.

Grey Matter volume was the strongest independent predictor of physical disability and cognitive impairment*...

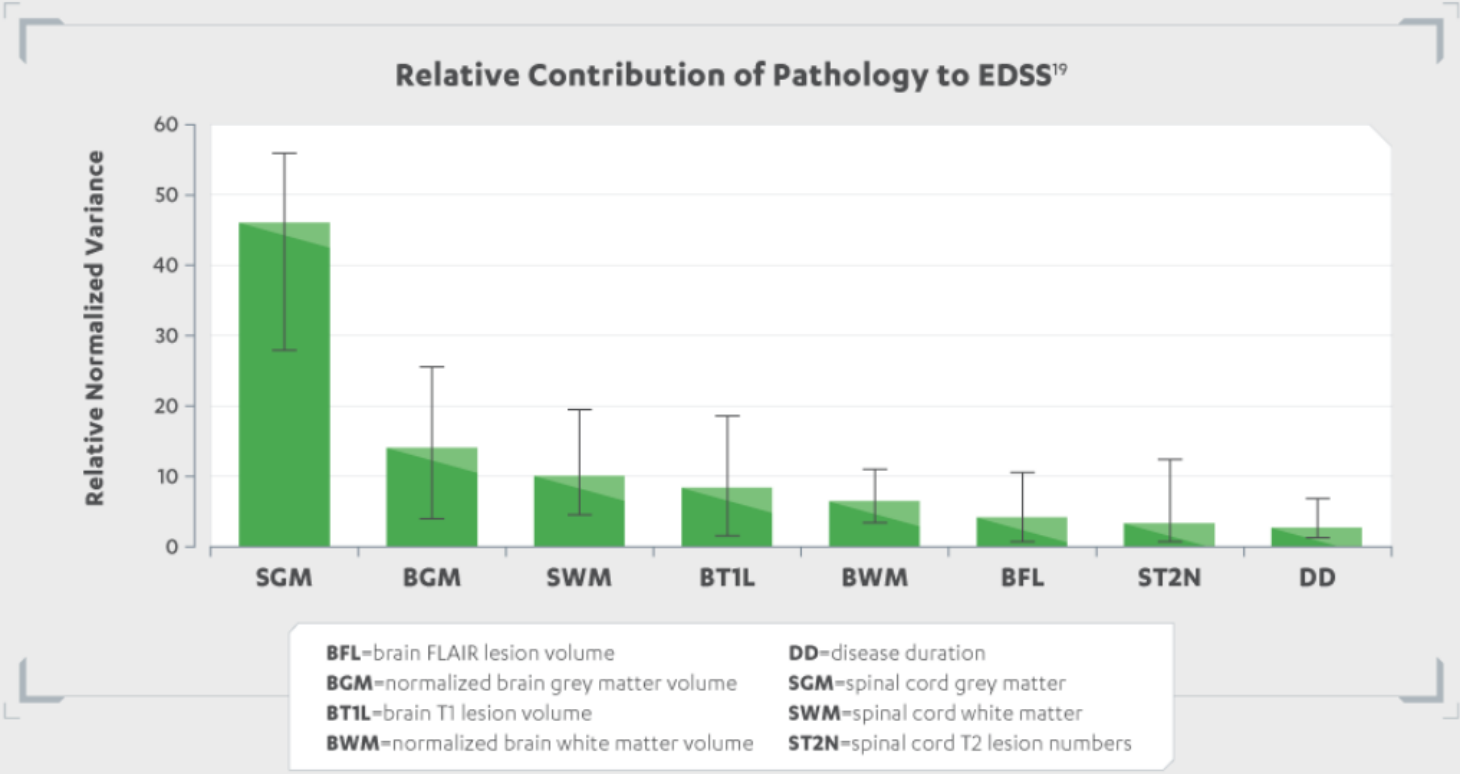
—*Roosendaal et al*[20]

*In a cross-sectional study of 927 MS patients.

The Importance of Spinal Cord Grey Matter

Grey Matter volume loss in the spinal cord was found to be predictive of disease progression[18]

- In an observational study of disability progression (N=113), spinal cord Grey Matter area was more strongly correlated with disability than all other variables examined



Schlaeger R, Papinutto N, Panara V, et al. *Annals of Neurology*. John Wiley and Sons.

A Stronger Correlation Than White Matter?

Research indicates that Grey Matter pathology may be more strongly correlated with cognitive and physical impairment than White Matter pathology.[12,13,19]

Imaging studies that examined a number of key MRI parameters found that Grey Matter atrophy was the single strongest MRI correlate of both clinical disability and cognitive impairment in MS patients.[13,19]

Long Term

reduced odds of more severe EDSS **59%**

A 20-year longitudinal study (n=73) found that Grey Matter atrophy was more strongly correlated with clinical disability over time compared with White Matter atrophy.[19]

In the same study, patients were **59%** less likely to be in a more severe Expanded Disability Status Scale (EDSS) category for every 1 standard deviation increase in their Grey Matter volume.[19]

". . .these data suggest that GM atrophy has more clinical relevance in the long term than either lesion load or WM atrophy . . . " —Fisniku et al[19]

Short Term

Grey Matter atrophy explained physical disability better than White Matter atrophy or even whole brain volume loss.[12]

- Deep Grey Matter volume loss was especially predictive in determining time-to-EDSS progression[12]

View **references** on Grey Matter atrophy.

Why Grey Matters in Multiple Sclerosis

The Impact of Grey Matter Lesions

Driving Both Physical and Cognitive Disability

In a 5-year, prospective, longitudinal study (n=312), MS patients with high cortical lesion load had the worst physical and cognitive prognosis compared with all other patient groups.[13]

- **92% of patients** with high cortical lesion load experienced significant cognitive impairment at study end compared to 23% of patients with low cortical lesion load
- **86% of patients** with high cortical lesion load experienced worsening of physical disability at study end compared to 42% of patients with low cortical lesion load

In a 3-year prospective study (n=107), cortical lesion volume was found to be a strong independent predictor of declining physical disability.[14]

86% of patients with a high cortical Grey Matter lesion load experienced disability progression after 5 years[13]

A Stronger Correlation Than White Matter?

Research indicates that Grey Matter pathology may be more strongly correlated with cognitive and physical impairment than White Matter pathology.[12,13,19]

In a 5-year longitudinal study (n=312), cortical lesion load was a stronger predictor of physical and cognitive decline than White Matter lesion load.[13]

“. . .our data strengthen the concept that disability progression in multiple sclerosis is more related to GM than to WM pathology, in all disease phenotypes.”[13]

View **references** on Grey Matter lesions.

Is Grey Matter Pathology Independent?

The Relationship Between White and Grey Matter Pathologies

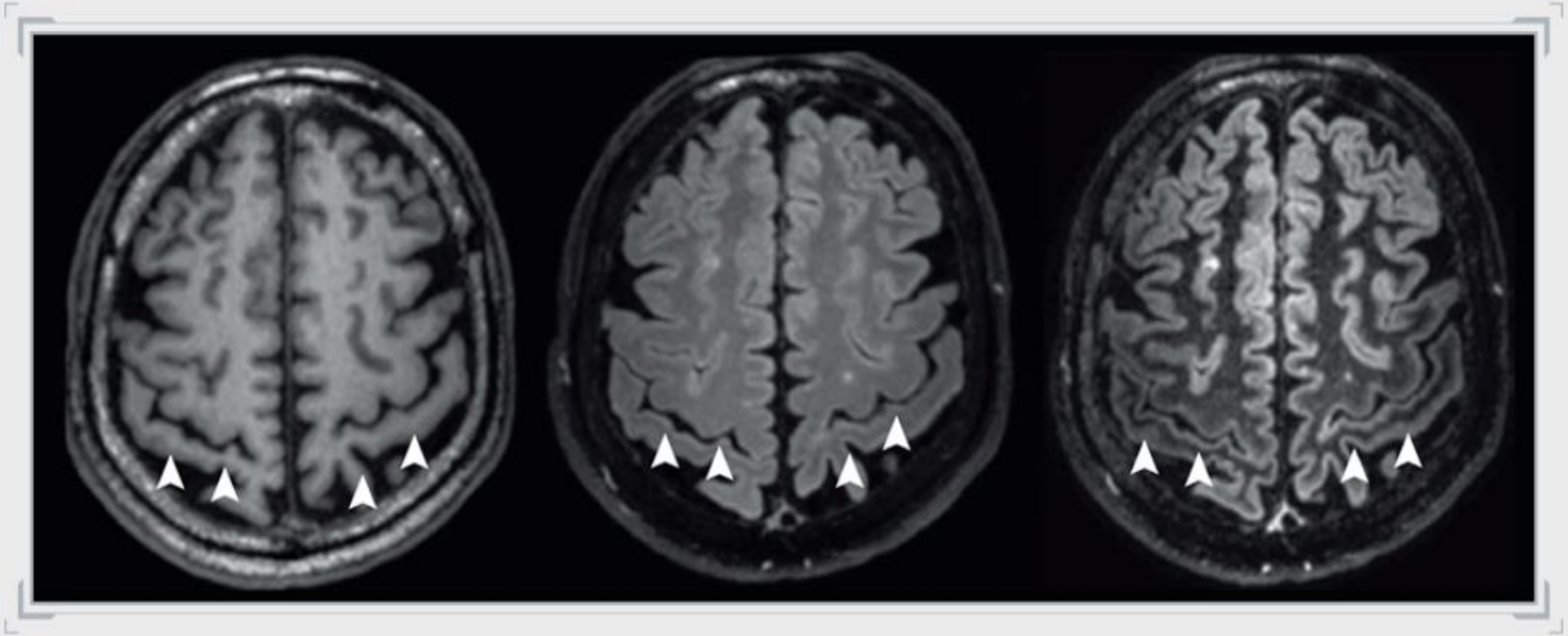
Grey Matter Disease Activity Appears to Be Distinct From White Matter Pathology

In multiple sclerosis (MS), the relationship between White Matter and Grey Matter pathologies in the central nervous system has not been clear.[21] However, evidence suggests that the 2 pathologies can be separate and distinct.[21-23]

Using postmortem, in vivo MRI, and MR spectroscopy techniques, researchers have examined MS activity and observed that White Matter pathology and Grey Matter pathology appear to be largely independent processes.[22,23]

- In a longitudinal, cross-sectional study (N=89) that examined the spatiotemporal topographic distribution of pathology in MS patients, researchers found no direct anatomical overlap between White Matter lesions and Grey Matter pathology[23,24]
- In a comparison of postmortem MRI and histopathologic data in 6 MS patients, the process of Grey Matter demyelination was determined to be largely independent of White Matter demyelination, occurring in different regions and to different degrees[22]

> The presence, distribution, and extent of WM changes were independent of the extent of GM pathological features.
>
> —*Bö et al*[23]

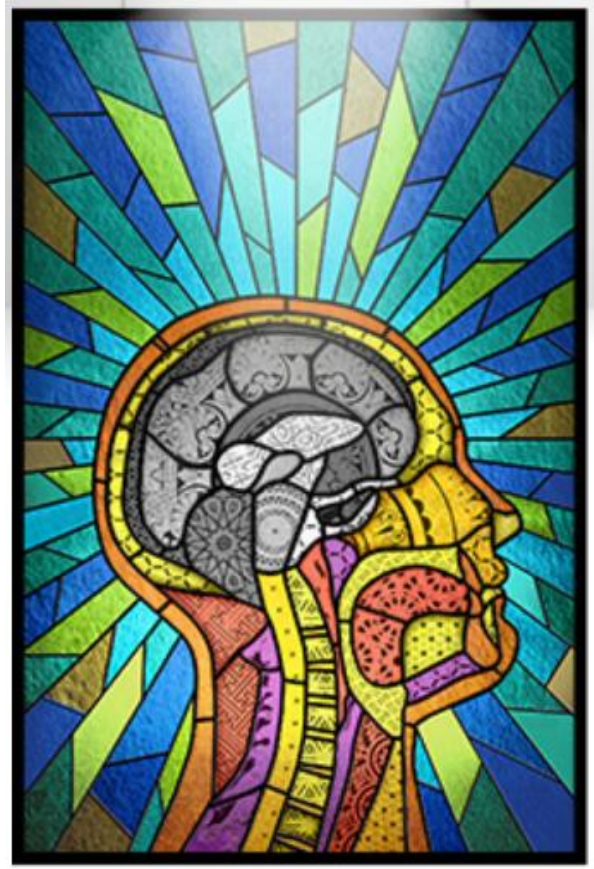


Reprinted by permission from Springer Nature. *Nature Reviews Neuroscience*. Exploring the origins of grey matter damage in multiple sclerosis. Massimiliano Calabrese, Roberta Magliozzi, Olga Ciccarelli, Jeroen J. G. Geurts, Richard Reynolds et al. © 2015.

Cortical atrophy can be present in the absence of visible White Matter or Grey Matter lesions.[23]

In a 5-year prospective study (n=312), MS patients who experienced disease progression had significant increases in the volume and number of cortical lesions, but no significant increase in the volume or number of White Matter lesions.[13]

View **references** on Grey Matter independent pathology.



Considering Comorbidities in Multiple Sclerosis

The Impact of Comorbidities and Lifestyle

Patient Choices and Long-Term Brain Health

For a comprehensive approach to understanding MS, it is important to consider the impact of comorbidities and lifestyle behaviors. Research has shown that multiple sclerosis comorbidities can exacerbate the disease, increasing the likelihood of relapses.[1-4] Lifestyle choices can also have a major impact on the overall health of the brain.[1]

View **references** on Comorbidities/Lifestyle.

The Prevalence of Comorbidities in Multiple Sclerosis

A Common and Exacerbating Problem

A Closer Look at the Multiple Sclerosis Comorbidities

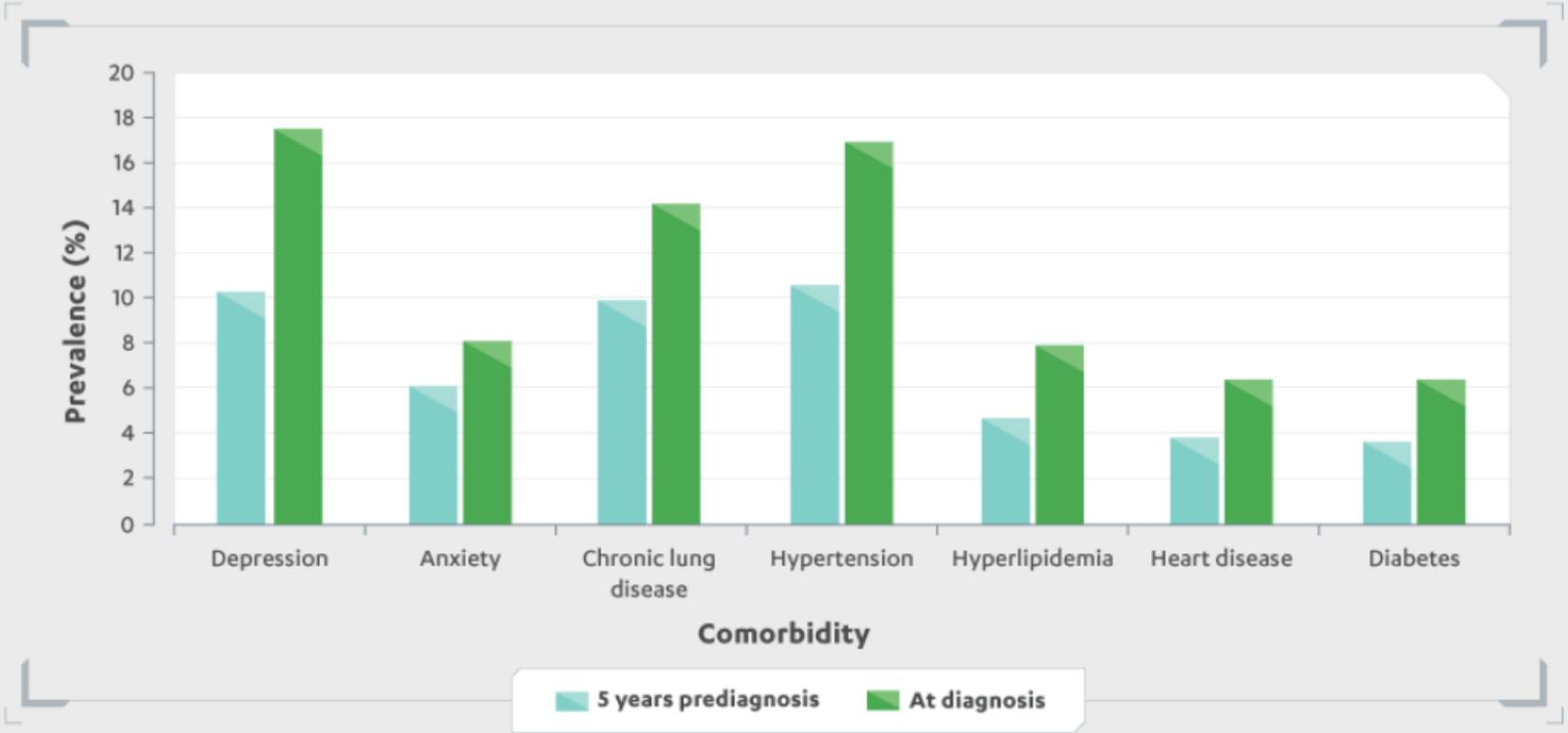
> Comorbid conditions… are frequent in Multiple Sclerosis (MS) and are associated with increased hospitalizations, greater disability progression, mortality risk, and contrast-enhancing lesions on brain MRI.
>
> —*Kowalec et al*[4]

Several adverse health conditions are more prevalent in patients with MS compared with the general population.[5,6]

In a 2016 Canadian population-based study of 23,382 patients with MS, the most common comorbidities were[5,6]:

- Depression
- Hypertension
- Chronic lung disease
- Anxiety

Prevalence of Comorbidity at Diagnosis and 5 Years Earlier[5,6]*



Reprinted by permission from Springer Nature. *Nature Reviews Neurology*. Comorbidity in multiple sclerosis: implications for patient care. Ruth Ann Marrie. © 2017.

*Comorbidities reported in a 2016 Canadian population-based study of patients with MS (n=23,382).[5,6]

Other comorbidities commonly associated with MS include rheumatoid arthritis, psoriasis, irritable bowel syndrome, thyroid diseases, and epilepsy.[2,7]

View **references** on prevalence of Comorbidities.

The Impact of Multiple Sclerosis Comorbidities

An Exacerbating Factor

A Closer Look at the Clinical Consequences

In patients with MS, comorbidities can have significant clinical consequences, including[2,4,7]:

- Increased relapse rates
- More severe MRI outcomes (demyelination and neurodegeneration)
- Accelerated disability progression

> Our main finding was that the presence of comorbidities in patients with MS was associated with more severe MR imaging outcomes of neurodegeneration and demyelination. The tissue injury of patients with MS with comorbidities was localized to the GM and particularly to the cortex.
>
> —*Zivadinov et al*[2]

45%

increase relapse rate

Relapse Rates:

In a prospective observational study of MS patients (N=885), patients with ≥3 comorbidities at baseline had a **45% increased relapse rate (RR)** over 2 years compared with patients with no comorbidities (adjusted RR 1.45; 95% CI: 1.00-2.08).[4]

MRI Outcomes:

Imaging studies have shown that patients with MS who have ≥1 cardiovascular risk factor have **increased lesion burden** and more advanced **brain atrophy**.[2,8]

Information about More Than White Matter »

Disability Progression:

In a retrospective study of 3166 patients with MS, physical disability increased with each additional comorbidity.[7]

Comorbidities and the Brain:

Numerous studies have shown that multiple sclerosis comorbidities can negatively impact the brain.

Cardiovascular System

- **Hyperlipidemia**: increased disability progression and lower brain volume (as measured by brain parenchymal fraction) was associated with higher total cholesterol levels[9]
- **Hypertension**: decreased Grey Matter tissue[10]
- **Heart disease**: reduced cortical and Deep Grey Matter[10]

Metabolism/Nutrition

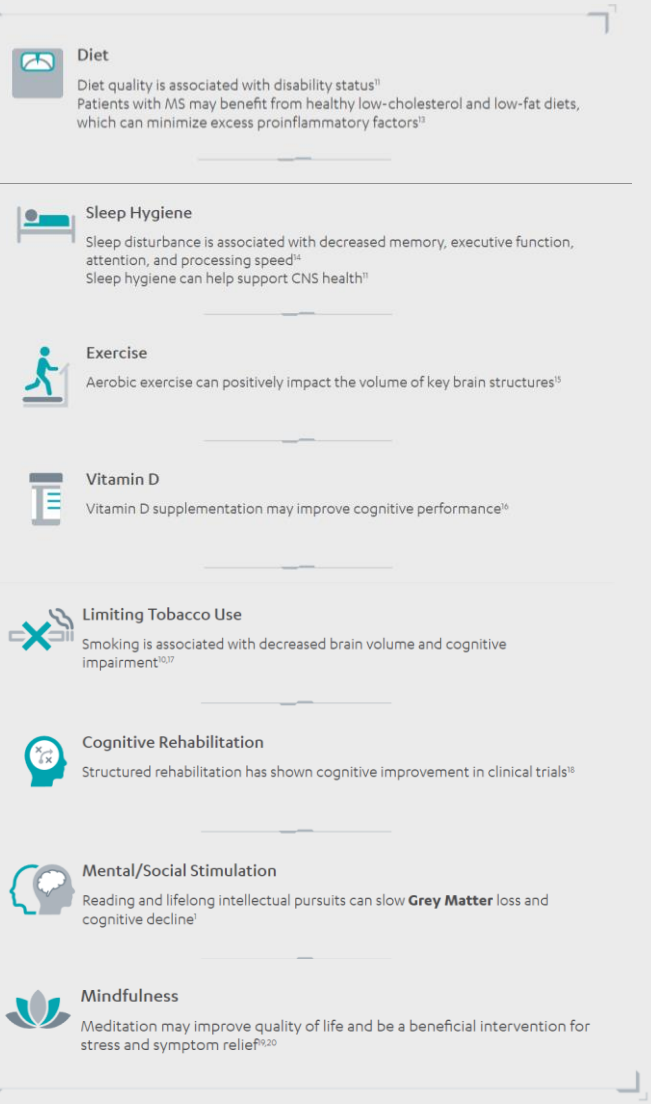
- **Obesity**: increased T1 lesion volume; brain volume loss[10,11]
- **Thyroid disease**: decreased whole-brain volume[2]
- **Type 2 diabetes**: decreased whole-brain volume[2]

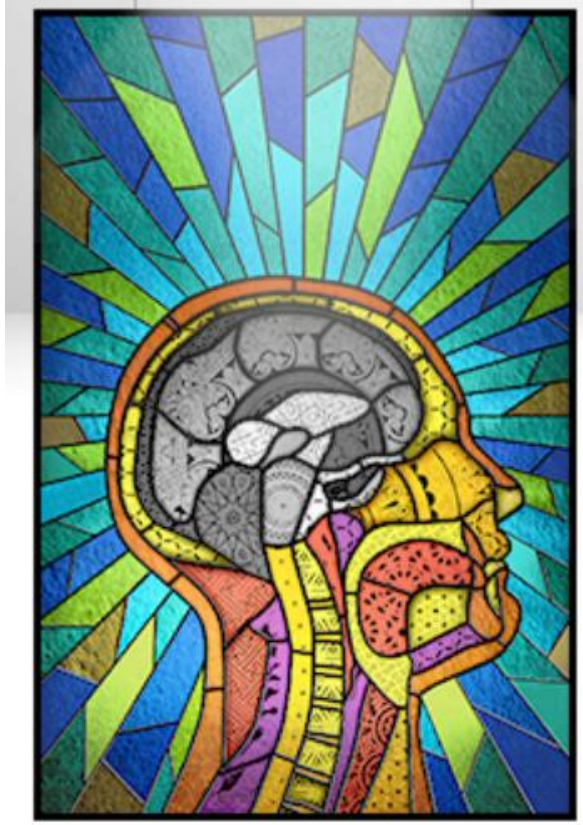
The Benefits of Lifestyle Changes

Empowering Patients to Manage Their Health

How Lifestyle Changes Can Impact Disease Activity

A comprehensive approach to health in MS includes lifestyle changes to manage comorbidities that can impact disease activity.[12]





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Hear What Key Thought Leaders Are Saying About MS

Practitioners with years of experience treating multiple sclerosis share their insights on a variety of important topics in the field, including **cognitive impairment, Grey Matter pathology,** and **early damage**.

Each video features the following 3 HCPs: Adil Javed, MD, PhD; Bhupendra Khatri, MD; and John Kramer, PA

Speakers featured in videos are paid consultants of Celgene, a Bristol-Myers Squibb Company.

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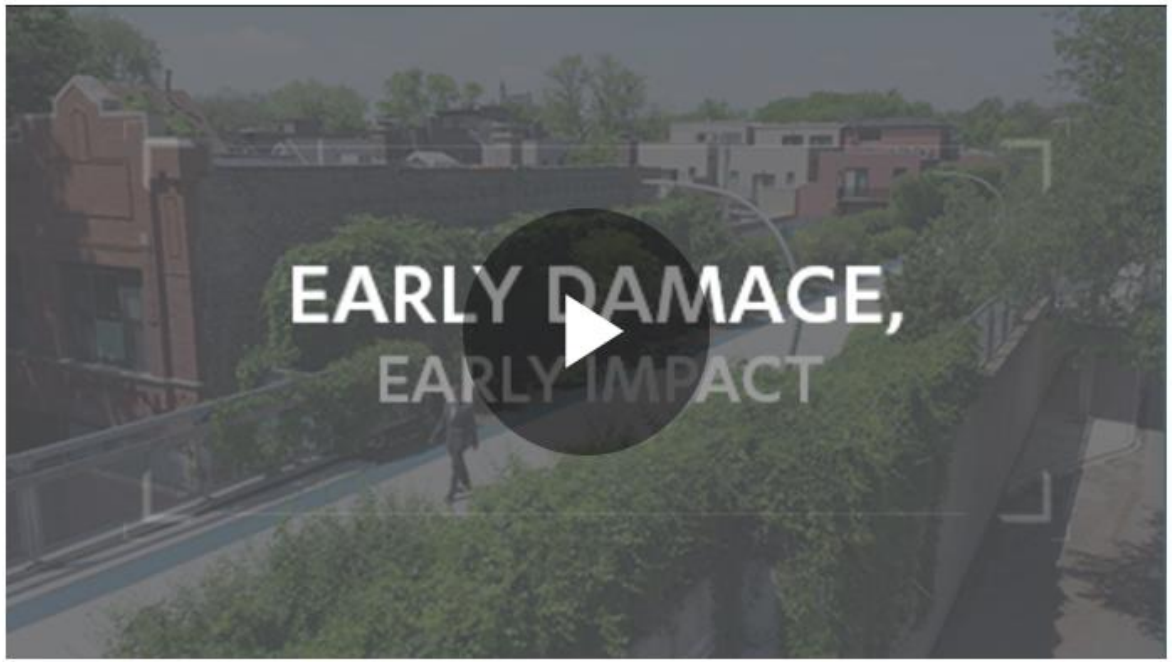

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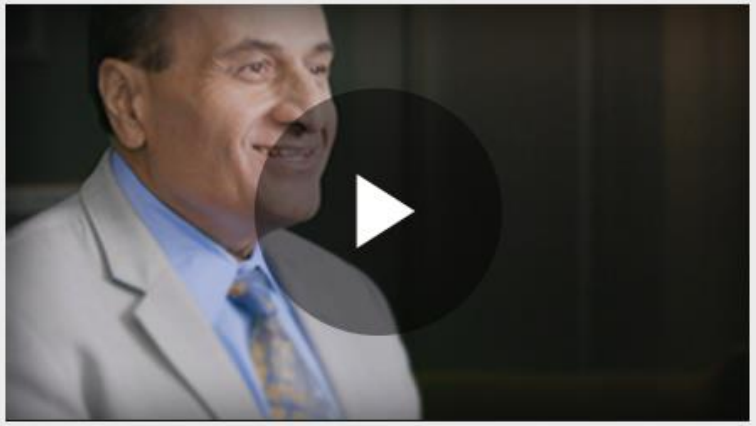

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John Kramer, PA, on Early Damage

John Kramer, PA, emphasizes the need to consider Grey Matter pathology early in the course of MS, noting that deep Grey Matter structures may atrophy faster than other parts of the brain.

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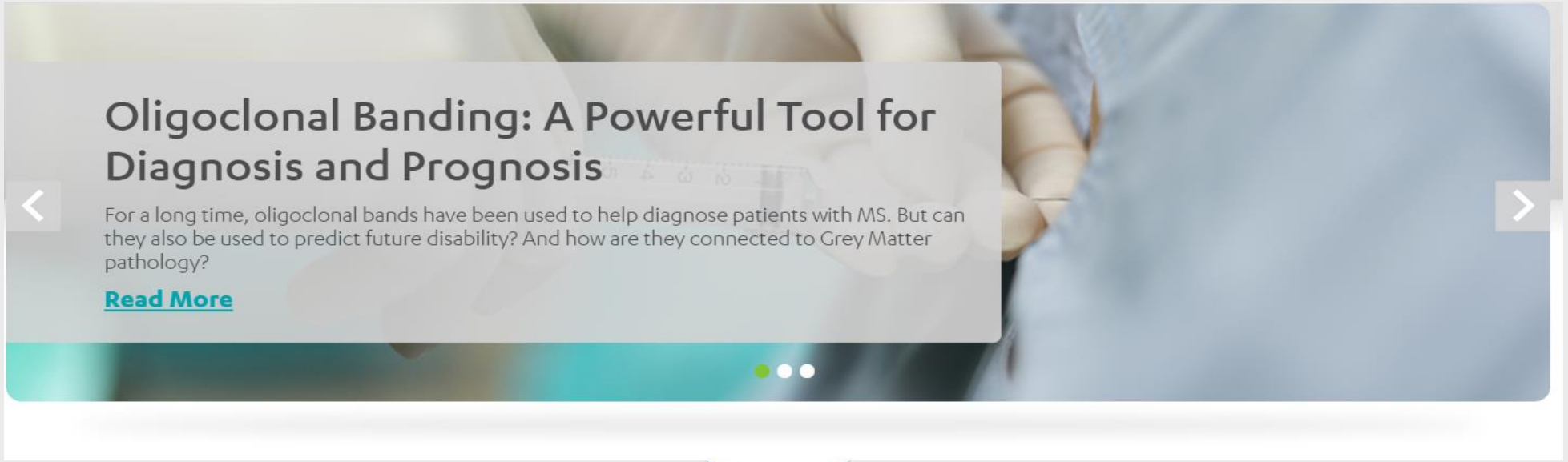
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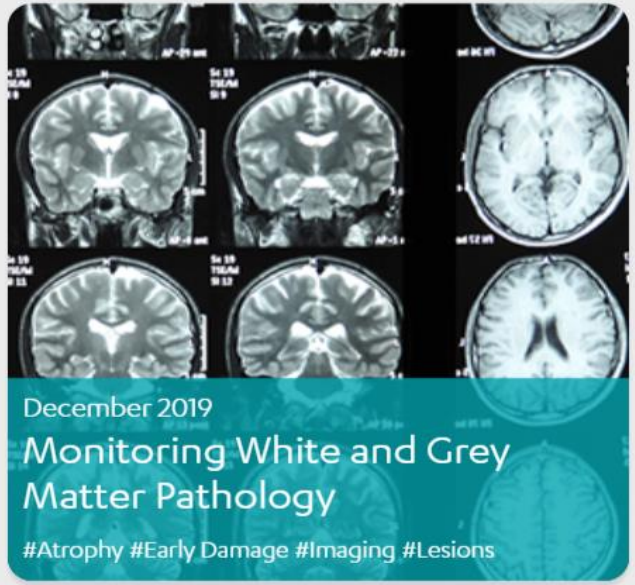
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