Maternal immune activation: Implications for neuropsychiatric disorders

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Epidemiological evidence implicates maternal infection as a risk factor for autism spectrum disorder and schizophrenia. Animal models corroborate this link and demonstrate that maternal immune activation (MIA) alone is sufficient to impart lifelong neuropathology and altered behaviors in offspring. This Review describes common principles revealed by these models, highlighting recent findings that strengthen their relevance for schizophrenia and autism and are starting to reveal the molecular mechanisms underlying the effects of MIA on offspring. The role of MIA as a primer for a much wider range of psychiatric and neurologic disorders is also discussed. Finally, the need for more research in this nascent field and the implications for identifying and developing new treatments for individuals at heightened risk for neuroimmune disorders are considered.

The Zika virus and its accompanying risk of microcephaly (1) have finally turned public attention to the detrimental effects of maternal infection. Although images of microcephalic newborns evoke outcry and require government action, the direct effects of Zika are only one part of a much larger global health hazard. An acute maternal immune response initiated by many common viruses is sufficient to cause lifelong changes in brain function and behavior of offspring in animal models (2). Although Zika and other pathogens may confer higher risk of specific disorders, growing evidence suggests that maternal immune activation (MIA) in the absence of a pathogen may increase the risk of a broad spectrum of central nervous system (CNS) disorders in humans (3) (Fig. 1).

Maternal infection and psychiatric disorders

The association between maternal infection and neurodevelopmental disorders is long-standing but not without controversy. After the 1964 rubella pandemic, the incidence of two neurodevelopmental disorders, autism (ASD) and schizophrenia (SZ), rose from less than 1% in the unexposed population to about 13 and 20%, respectively (2). Subsequent studies charting historic outbreaks of flu, measles, mumps, chickenpox, and polio revealed an association with ASD, SZ, and several mood disorders (4). However, not all ecological studies have replicated these associations (5). The differing conclusions may stem from differences in estimating the exposed population (6). Nevertheless, several prospective studies following birth cohorts (3, 6) are consistent with an association between viral infection and psychiatric disorders in offspring and add other classes of pathogens to the list: namely, bacterial infections—including pneumonia, sinusitis, and tonsillitis—and the parasite Toxoplasma gondii (2, 3).

How can such a diverse group of pathogens confer similar risks of neurodevelopmental disorders? Common to the implicated pathogens is the maternal immune response. In support of this possibility, enduring fevers above a certain threshold pose the greatest risk (6). It follows that immune system activation above that threshold due to any environmental insult or genetic predisposition would also increase risk. Indeed, maternal autoimmune disorders, allergies, asthma, acute stress, and exposure to environmental pollutants—all of which lead to elevated immune responses—have been linked to an enhanced risk of ASD and SZ (3, 6). These findings may help to contextualize two recent prospective studies that failed to find a significant association between prenatal infection and SZ after adjusting for parental infection in general, parental psychiatric disorder, and socioeconomic status (7, 8). For example, in one study, the modest association between prenatal infection and SZ was not significantly different from an association with a generalized familial liability to develop severe infection (8). This finding may again point to the importance of the maternal immune background. A paternal association implicates the immunogenetic background of the fetus. Thus, the immune status of both mother and child determines the vulnerability to MIA. A second study found a synergism between maternal infection and maternal psychiatric disorders (7). Since many individuals with SZ have immune abnormalities, this association could point to maternal immune status, as well as synergism with genetic risk factors. If MIA is a primer for a wide array of disorders, then further work is necessary to identify additive (9) and synergizing risk factors (7) that may be hidden in the adjusted models typically used in these studies.

Explosive growth in the human population, urbanization, and climate change combine to drive emerging infectious diseases like Zika (10). Simultaneously, pervasive poverty that limits access to childhood vaccinations, together with baseless fear of vaccinations within affluent groups, has led to a resurgence in infectious diseases of the past, like measles, mumps, rubella, whooping cough, and even polio (11). Increased exposure to new and old viruses heightens the risk of pregnant women contracting one of these diseases and thereby may increase the likelihood that their children will develop CNS disorders. Together, the increased presence of communicable diseases, combined with an uptick in autoimmune disorders (5), would account for a large proportion of the concerning recent increase in incidence of neurodevelopmental disorders (12).

Animal models of maternal infection

Evidence for these associations has been growing steadily more compelling, but epidemiology alone cannot establish a causal relationship between MIA and risk of neurodevelopmental disorders. Thus, this association in humans will likely remain controversial at least into the near future. Humans are genetically, ecologically, and behaviorally heterogeneous, all of which can influence susceptibility to disease and therefore complicate and undermine detection of causal relationships. Clinical research is also limited in its ability to identify the molecular pathways downstream of maternal infection because humans cannot be subject to invasive experimentation. Moreover, there is currently not an effective way to identify the at-risk pregnancies. The majority of pregnancies, even those at high risk, will lead to healthy offspring, and the resulting CNS disorders in offspring often do not appear for many years after birth and appear to be influenced by postnatal risk factors that synergize with genetic and prenatal risk to act as “second hits” (3, 13–15). Clearly, there is a compelling need for long-term and large prospective studies to identify the specific aspects of infection during pregnancy (e.g., the type of pathogen, extent of fever, and timing of infection), as well as synergies with postnatal exposures, that lead to heightened risk of CNS disorders in offspring.

Because of these challenges of studying MIA in humans, animal research is therefore essential for identifying causal mechanisms and developing new diagnostic tools and therapeutics. Indeed, a causal relationship between maternal infection and ASD- and SZ-related behavioral abnormalities has been clearly demonstrated using rodent models and, more recently, nonhuman primate (NHP) animal models. In these models, pregnant animals are exposed to an immunological manipulation at a specific gestational stage. The behavior and brain structure and function of MIA offspring are then compared with those of control offspring. The most common immunogens used in these studies include influenza infection and exposure to viral (polyinosinic-polycytidylic [poly(I:C)]) and bacterial (lipopolysaccharide (LPS)) mimics that cause MIA (16). These MIA animal models meet all of the criteria required for validity for a disease model: They mimic a known disease-related risk factor (construct validity), they exhibit a wide range

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of disease-related symptoms (face validity), and they can be used to predict the efficacy of treatments (predictive validity). Each specific MIA model has important advantages and disadvantages. Differences in gestational age, immunogen, dose, and timing lead to overlapping and distinct phenotypic signatures that are critical factors in evaluating their use as preclinical models. The common principles revealed by these models are included in this overview of the field. See other recent reviews for details on each model (4, 14), as well as additional maternal immune (14), maternal antibody (16), autoimmune (17), and stress (18) models.

**Rodent MIA models**

The rodent MIA models manifest a comprehensive range of SZ- and ASD-related behavioral abnormalities. Offspring from the poly(I:C) rodent model, in particular, exhibit most of the core behavioral symptoms of ASD—abnormal communication, abnormal social behaviors, and increased repetitive behaviors (2–4, 6, 14). Offspring from these MIA models also show many additional SZ- and ASD-related behaviors, including decreased sensorimotor gating (which measures the ability of the brain to filter out extraneous information), deficits in working memory and cognitive flexibility, increased anxiety, and enhanced sensitivity to amphetamines (2, 3, 14). Importantly, many of these behaviors can be alleviated by antipsychotic drugs, supporting the disease relevance of these models (3, 4, 14).

In addition to these aberrant behaviors, adult MIA offspring also exhibit neuropathologies emerging at specific developmental ages, especially SZ-associated reduced cortical thickness and hippocampal volume and increased ventricular size, as well as ASD-associated aberrations in Purkinje cells (2–4, 14). Several studies have also recently reported deficits in dendritic spine density, levels of synaptic proteins, synaptic transmission, long-term plasticity, and cortical malformations (4, 19–24). However, most of these measures have been studied in single brain regions from single models at a single age. So, although it is likely that MIA causes changes in synaptic connectivity, function, and plasticity, elucidating the details and common principles remains an important goal for the future.

Recent work has also uncovered neurochemical changes in adult MIA offspring that are characteristic of SZ and ASD (3, 4, 14, 25) (Fig. 2).

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Serotonin and dopaminergic signaling is altered in MIA offspring across models (3, 4, 14). Additionally, specific changes in inhibitory neurotransmission have been linked to both SZ and ASD (26), and similar reductions in several components of the γ-aminobutyric acid (GABA) system are present in the brains of MIA offspring (3, 4, 14, 25, 27–29). One of the most exciting recent advances in the MIA field is the discovery of deficits in the function of parvalbumin (PV) cells, known to be selectively altered in SZ, in the brains of adult MIA offspring (3, 14, 22, 30). MIA causes a specific reduction in inhibition from PV cells onto pyramidal neurons that is sufficient to cause deficits in attentional set shifting and enhance anxiety-related behavior in offspring (30), similar to behavioral changes in SZ patients with confirmed evidence of gestational infection (31). Consistent with predictions from a loss of perisomatic inhibition of pyramidal cells in the prefrontal cortex (PFC) (4), MIA offspring exhibit increased power in the theta band (32) and reduced electroencephalogram coherence, specifically between the hippocampus (HC) and the medial PFC (4). These findings mirror reductions in long-range signaling in SZ (33).

**NHP MIA models**

Even though these rodent models have remarkably strong face, construct, and predictive validity for SZ and ASD, the potential of using rodents to tell us about psychiatric disorders that are so inherently human has remained controversial. To bridge the gap between rodents and humans, several groups have established rhesus macaque MIA models. Some of these NHP models display behavioral symptoms of ASD and SZ—increased repetitive behaviors, abnormal communication, and impaired social interactions—that start at weaning and increase in intensity with age (4, 14, 34). MIA also alters gray- and white-matter volume in an immunogen-specific manner (4) and causes subtle changes in dendritic arborization (35) in neonatal NHP offspring. An outstanding question that can be addressed uniquely by NHP models is whether molecular signatures of MIA identified in rodent models underlie phenotypes similar to ASD and SZ in humans. Answering this question in the future will be a major advantage for generating new therapies.

**Considerations in interpreting MIA models**

MIA models use a surprisingly wide range of protocols that vary in the type, as well as the timing, mode of delivery, and dose, of immunogen used. The type of immunogen dictates the nature of the immune response and downstream phenotypes. The timing of exposure is also key in determining the nature and severity of the outcomes (Fig. 3) (14). MIA in early versus late gestation causes distinct fetal brain cytokine responses and changes in neuropathology and behavior in...
Fig. 2. Mechanisms underlying the effects of MIA on brain function. Aberrations in the microbiome after MIA can lead to altered development of peripheral immunity, both of which can alter brain development. Deficits in long-range connections between brain regions implicated in SZ and ASD, including the HC, PFC, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and amygdala (AM), have been reported in MIA (3, 4, 14). Specific alterations in activity of glutamatergic neurons in the cortex caused by decreased function of dopaminergic (DA) neurons in the ventral tegmental area (VTA) and decreased GABAergic input also occur in SZ and ASD, as well as in the MIA models (3, 4, 14). Changes in expression of immune molecules in the brain and even at synapses, including cytokines and MHCI molecules, alter synaptic plasticity and function and contribute to the changes in circuitry and connectivity between brain regions that characterize these disorders (6). Finally, alterations in immune and neuronal signaling due to MIA may converge upon the mTOR pathway, which regulates synapse formation, growth, translation, survival, and autophagy (68). mTORC1, mTOR complex 1.

MIA as a disease primer

In humans, most maternal infections do not lead to SZ or ASD in offspring (40); thus, it is currently thought that multiple “hits” (exposure to more than one risk factor) may be required for disease induction (Fig. 1). MIA appears to act as a “disease primer” (14) to make an individual more susceptible to the effects of genetic mutations and environmental exposures in triggering disease-related symptoms later in life (41). Consistent with this idea, the incidence of both ASD and SZ is much higher in families with autoimmune disorders (2, 6), and the effect of maternal infection in increasing SZ risk is greater in families with a history of SZ (3). Indeed, low-dose poly(I:C) MIA synergizes with mutations in SZ- and ASD-associated genes, including DISC1, NRGI (encodes Neuregulin-1), NR4A2 (encodes Nurrl), and TSC2, to cause greater effects than either insult alone (3, 4, 14).

Although studies of interactions between MIA and environmental risk factors have only recently begun, the results thus far using animal models suggest that even subclinical maternal infection can make offspring much more vulnerable to second “hits” (Fig. 1). Subthreshold MIA increases the likelihood of environmental risk factors, such as stress and drug use, to cause SZ and ASD-related phenotypes in offspring (3, 14). Peripubertal stress causes synergistic effects in subclinical poly(I:C) MIA offspring on a wide range of SZ- and ASD-related behaviors and molecular phenotypes (3, 4, 14). Similarly, adolescent cannabinoid exposure causes synergistic effects in subclinical MIA mice (4, 42). Combined insults can even change the nature of the phenotype. LPS MIA alone results in N-methyl-D-aspartate receptor hypofunction and a loss of hippocampal long-term plasticity in adolescent rats, but, when combined with restraint stress, the outcome switches to the opposite phenotypes (4). Although the molecular mechanism of MIA as a disease primer is unknown, brain region–specific alterations in epigenetic marks at several loci, including DISC1, could be a molecular signature of its priming effect (43, 44).

There is also growing evidence that MIA is associated with a much wider array of psychiatric and neurologic disorders than just ASD and SZ. Recently, MIA has been linked to anxiety, major depressive disorder (MDD), and bipolar disorder (BPD) in people (3, 45–47). These seemingly distinct disorders share a surprising number of genetic and environmental risk factors, behavioral abnormalities, and alterations in brain structure and function (3, 48, 49). MIA animal models also exhibit behavioral and neurochemical alterations consistent with depression and anxiety (3, 47, 50). MIA has even been shown recently to prime mice for degenerative diseases during aging, including Alzheimer’s disease (51).

These links of MIA to an increasing array of diseases as diverse as neurodevelopmental disorders (e.g., ASD) and neurodegenerative diseases (e.g., Alzheimer’s disease) that afflict individuals at nonoverlapping stages of life and result in distinct...
symptoms have been surprising. This conundrum is not an issue for MIA alone but rather has surfaced in the field of genetics as well, with increasing evidence for associations between specific genes and a similarly wide range of CNS disorders (52–54). How MIA or genetic mutations can cause such a wide range of disorders is unknown, but both may act to prime an individual for second hits, and the nature and timing of those second hits may determine when and which disease will result, if any (Fig. 1).

The fact that MIA is associated with such a broad range of disorders indicates that MIA animal models can be used to identify common molecular pathways that are shared among them. This is good news from a treatment perspective because it suggests that new therapies could have efficacy in a wide range of human diseases. When, where, and how the common pathways are disrupted may be critical to understanding disease-specific vulnerabilities and can be manipulated and identified using the MIA animal models. Perhaps most important, the larger the family of MIA-associated CNS disorders, the greater the public health implications for initiatives aimed at preventing maternal infection in high-risk populations.

**How does MIA alter brain function and behavior in offspring?**

Immune activation within the maternal compartment likely influences the developing fetal CNS through inflammatory mediators found in the blood and amniotic fluid of ASD and SZ mothers (2, 3, 6, 14) (Fig. 1). Whether or not these proteins cross the placenta and act directly upon the fetal brain is unknown. MIA somehow induces alterations in multiple cytokines within the fetal brain in a matter of hours (6, 14). Although MIA triggers unequivocal inflammation within the mother, the limited cytokine profiles that have been measured in the fetal brain do not by themselves signify a classic inflammatory response (29, 55). Whether, and how, these changes in fetal brain cytokines are related to MIA neuropathologies are critical questions for the field. More research is needed to address these issues and to quantify the dynamic changes in a large number of immune molecules across brain regions and age, with the ultimate goal of identifying immune signatures associated with specific disease-related neuropathologies and behaviors.

Nevertheless, several maternal cytokines have already been identified as critical mediators of MIA on disease-related phenotypes in offspring (Fig. 1). Injection of a single inflammatory cytokine (interleukin (IL)–6, –17, or –2) is sufficient to induce several ASD- and SZ-like behaviors in offspring (14, 19, 56). Moreover, coadministration of poly(I:C) with an IL-6 or an IL-17 function blocking antibody, or with overexpression of the anti-inflammatory cytokine IL-10, partially prevents the effects of MIA in offspring (3, 19). However, little is known about how these maternal cytokines alter brain development. One possibility is that MIA leads to long-lasting changes in expression of immune molecules known to regulate neural connectivity and function in offspring (6). Indeed, the levels of numerous cytokines are altered throughout development and into adulthood in the brain of MIA offspring in a region- and age-specific manner (6, 57). These cytokines are likely to regulate the expression of other classes of immune molecules on neurons, including major histocompatibility complex I (MHCI) molecules (Fig. 2). In the immune system, MHCI levels are controlled by cytokines as an important early step in the immune response. In the healthy brain, MHCI is found on neurons, where it negatively regulates synaptic plasticity required for activity-dependent synaptic pruning (6, 58, 59). Alterations in synaptopathies and pruning are associated with a range of neurodevelopmental disorders and are thought to play a central role in the etiology of ASD and SZ (60, 61). MIA causes a dramatic change in MHCI levels on neurons in the brains of neonatal offspring (6, 21), and the resulting increase in MHCI at birth is required for the dramatic MIA-induced deficit in the ability of newborn neurons to form synapses (62). Outstanding questions for the field include determining whether these changes in cortical connectivity are long-lasting and causally related to the disease-related behaviors emerging at later stages of development.

MHCI is one of several immune proteins present at the synapse capable of mediating responses to infection while concurrently regulating activity-dependent plasticity and circuit formation. These versatile proteins—part immune defense, part...
synaptic structure—are the most likely suspects to bring about changes in brain development in response to maternal infection (63). Although studies on this topic are only just beginning, MIA presumably alters the expression and function of these immune proteins in the brain as it does for cytokines and MHC-I. The alterations may be acute, reflecting the nature, intensity, and duration of infection, or chronic through epigenetic changes that may synergize with other risk factors at different stages of life. With such heterogeneity from onset to phenotype, could there be a unifying converging pathway underlying MIA’s priming effect?

If immune molecules act through similar pathways in the brain (and the same intracellular machinery is present, which remains an open question), then it is possible that immune signaling in neurons may converge upon mammalian target of rapamycin (mTOR) signaling. In the immune system, mTOR acts as a regulatory hub integrating inputs from numerous upstream intracellular signaling pathways—including cytokines, trophic factors, and synaptic scaffolding proteins—many of which are altered in the brains of MIA offspring, as well as individuals with ASD, SZ, MDD, and AD (64-69). Dysregulation of protein synthesis due to alterations in the mTOR pathway has been implicated in several mono-genetic forms of ASD, as well as the SZ-associated DISC-1 mutation in animal models (68, 69). Hyper- or hypoactivation of mTOR signaling imparts mutation-specific alterations in neuronal morphology and synaptic plasticity, as well as the synthesis of many synaptic proteins and glutamate receptors (70), which are common features of several MIA models. mTOR signaling also regulates macroautophagy, a homeostatic process leading to the breakdown of unused proteins and structures within cells that has been implicated in several neurodegenerative diseases and, recently, idiopathic forms of ASD (67). Although direct evidence for a role for mTOR dysfunction in MIA is lacking, this is a plausible exemplar of several potential signaling hubs that have been implicated in a similar wide range of disorders as MIA. These hubs could be altered by underlying genetic mutations or postnatal environmental risk factors to cause distinct responses in individuals after MIA, leading to the growing list of disorders associated with maternal infection.

The gut-immune-brain axis in MIA

Several intriguing studies indicate that some MIA-induced neuropathologies may emanate from outside the nervous system (Fig. 2). MIA mice exhibit peripheral immune abnormalities, including T and myeloid cell skewing to inflammatory phenotypes (38), or maternal dietary supplementation with zinc (79, 80), n-3 polyunsaturated fatty acids (80, 81), or N-acetyl-cysteine (NAC) (82). Finally, one of the most exciting potential treatments is antipruriginous therapy, which completely reverses several ASD-related phenotypes in MIA offspring (4). The future

If MIA is a disease primer for numerous CNS disorders, as mounting evidence suggests, then MIA animal models are critical for determining the molecular pathways that mediate the resulting neuropathology and abnormal behaviors. Although the field is in its infancy, newly identified convergent pathways are already starting to serve as targets for development of new therapeutics. The altered signaling in these molecular pathways is age-, region-, and gender-specific, a critical finding that helps explain the considerable individual differences in vulnerability to MIA-related disorders. Tailoring therapies to different stages of these disorders requires MIA animal models in which dynamic changes can be quantified and related to specific symptoms. Effective use of these new treatments in humans will depend in large part on new, yet undiscovered, approaches to identify the at-risk individuals. MIA models are already uncovering synergizing genetic and environmental risk factors that will help define these populations. The ultimate goal, which is now within sight, is to use new therapeutic interventions before deleterious symptoms appear, decreasing the incidence of, or even preventing the emergence of, immune-mediated psychiatric illness in adulthood.

REFERENCES AND NOTES

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How neuroinflammation contributes to neurodegeneration

Richard M. Ransohoff

Neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and frontotemporal lobar dementia are among the most pressing problems of developed societies with aging populations. Neurons carry out essential functions such as signal transmission and network integration in the central nervous system and are the main targets of neurodegenerative disease. In this Review, I address how the neuron’s environment also contributes to neurodegeneration. Maintaining an optimal milieu for neuronal function rests with supporting cells termed glia and the blood-brain barrier. Accumulating evidence suggests that neurodegeneration occurs in part because the environment is affected during disease in a cascade of processes collectively termed neuroinflammation. These observations indicate that therapies targeting glial cells might provide benefit for those afflicted by neurodegenerative disorders.

The human central nervous system (CNS) might represent the most complex entity in existence, although conclusive evidence to support or falsify that hypothesis will probably forever be elusive. Nonetheless, the CNS is beyond question the most elaborate system of which we have daily experience. CNS disorders alter and often degrade the structure and function of this intricate organ. Neurodegeneration is a common (but not invariable) component of CNS disorders and includes processes by which previously established CNS functions such as mobility, memory, and learning, judgment, and coordination are progressively lost. Neurodegenerative diseases primarily occur in the later stages of life, positioning time as an essential cofactor in pathogenesis of the major neurodegenerative disorders in a mechanism-driven fashion (4–7). The achievements of medicine and public health efforts in reducing early- and midlife mortality from certain cancers, infectious diseases, and cardiovascular disorders mean that a larger number of individuals are aging and therefore susceptible to neurodegenerative disease by virtue of their survival. The large cohort of aging people in the developed world threatens society with a substantial burden of care for those afflicted with neurodegeneration (4). Moreover and most poignantly, these diseases rob affected persons of those attributes that make long lives worth living: thinking, feeling, remembering, deciding, and moving. How and why neuroinflammation in neurodegeneration, a topic that comprises most of the nonneuronal contributors to the cause and progression of neurodegenerative disease. The study of this topic is animated by our hope that meaningful action, in the form of novel treatments, will follow understanding.

Review

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What is neurodegeneration?

Neurons are the primary cells of the CNS and endow it with its distinctive functions. Connec-

“Neuroinflammation has been famously difficult to define in relation to neurodegenerative disease.”

tions between neurons are enacted at synapses, where neurotransmitters are released in quanta to deliver an excitatory or inhibitory signal to the synaptic-target neuron. Cell processes that deliver these signals are termed axons, whereas dendrites receive synaptic inputs. Each of the ~1015 neurons in the human brain integrates many synaptic inputs from other neurons and, for each input received, may or may not initiate an axonal action potential and thereby provide synaptic input to its target neuron—a system comprising 1023 connections in all.

Neurodegeneration by definition disturbs the properties of the CNS and therefore affects neuronal function, as well as the structure or survival of neurons. Unlike primary cells from skin, the liver, or muscle, neuronal cells of the CNS do not regenerate after damage by disease, ischemia (deprivation of oxygen, glucose, or blood flow), or physical trauma. Because the complexity of the human CNS is so great, neurodegenerative disorders that derange its function have been challenging to understand and treat: No therapeutics ameliorate the natural course of neurodegenerative disease.

Major neurodegenerative diseases include Alzheimer’s disease (AD), frontotemporal lobar dementia (FTLD), Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS). Individuals diagnosed with multiple sclerosis (MS) are also at risk of developing a neurodegenerative course, typically at later stages of the disease; such cases are termed progressive MS (P-MS). One might consider that AD, PD, and ALS are primary neurodegenerative diseases, in which the initial