

Is psychosis, at least in part, an immune-related dysmyelination disease?

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Abstract

Epidemiological studies have borne out the association between psychotic disorders and autoimmune disease, while the immunogenetic contribution in psychosis is largely dominated by the major histocompatibility complex genetic diversity. On the other hand, demyelinating diseases, like multiple sclerosis, are characterized by a large array of invading immune cells that degrade the myelin sheath, the myelin producing oligodendrocytes and the nerve itself. Schizophrenia has been proposed to be a dysconnectivity syndrome, and numerous lines of evidence implicate myelin and oligodendrocyte function as critical processes that could affect neuronal connectivity. Disruption in myelination and dysmyelination-induced delays in information processing can produce phenocopies of psychosis similar to schizophrenia. Rethinking the clinical and pathophysiological similarities between de- or dysmyelination diseases and psychosis, we may consider that the dysconnectivity syndrome of psychosis represents the phenomenological and behavioral result of a multiple-faces dysmyelination disorder, which is based on a lifelong immunogenetic dysregulation process.

Key-words: psychosis, schizophrenia, multiple sclerosis, myelin, demyelination, dysmyelination, dysconnectivity syndrome

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Myelin

Myelin, the lipid membrane that ensheathes axons, is essential for the efficient conduction of action potentials, which supports the integrity of axons. In terms of evolution of the nervous system, the myelin sheath is the most recent of nature's structural inventions. The first myelin-like ensheathed axons may have appeared about 400 million years ago. The number of glial cells increases during evolution and they constitute 25% of total cells in the *Drosophila*, 65% in rodents, and 90% in the human brain. Glial cells may well constitute 50%–90% of the cells in the human and rodent CNS. Myelination begins after 30 weeks gestation, occurs mainly in the post-natal period and is largely complete by young adulthood, although fine tuning of the pathways may continue as myelin internodes continue to be created into adulthood. PNS myelinated fibers are separated from each other by an extracellular compartment, the endoneurium, whereas the CNS myelinated fibers are in close contact. Some of the components of PNS myelin, lipids, and proteins are different **1, 2**.

High-speed conduction, fidelity of transfer signaling on long distances, and space economy are the three major advantages conferred to the vertebrate nervous system by the myelin sheath. In the invertebrate nervous system rapid conduction is accompanied by increased axonal calibers. The conduction velocity in a myelinated fiber is linearly correlated with diameter and at a given diameter, but there is a particular myelin thickness that maximizes conduction velocity. There is a myelin gradient, with the axons of the deeper cortical layers to be more uniformly myelinated and intermittent unmyelinated axonal segments in superficial layers of the cortex interspersed with myelinated internodes **3**.

Oligodendrocytes is the myelin-forming cells of the central nervous system. Glutamate is involving in the shaping of the oligodendrocyte population. The main ionotropic glutamate receptors expressed by oligodendrocytes belong to the dl- α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate classes. It has been shown that non-NMDA glutamate receptor agonists are able to inhibit oligodendrocytes progenitor proliferation in cell cultures. Oligodendro-

cytes express opioid receptors, μ -receptors are apparent at the earliest stages of oligodendrocyte development, while κ -receptors are detected later. There is also a proliferative response to μ -receptor stimulation **1**.

Microglial cells share certain characteristics with macrophages and contribute to immune-surveillance in the central nervous system. M1 polarized microglia can produce pro-inflammatory cytokines, while M2 polarized microglia express cytokines and receptors that are implicated in inhibiting inflammation and restoring homeostasis. Based on these aspects, Nakagawa & Chiba (2014) **4** propose a possibility that M1 and M2 microglia are related to relapse and remission, respectively in psychiatric disorders, such as major depressive disorder and bipolar disorder **5**.

Multiple Sclerosis (MS) is characterized by a large array of invading immune cells that attack and degrade the myelin sheath, the myelin producing oligodendrocytes and the nerve itself. These lesion sites develop with time and initially result in clinically benign symptoms but can progress in to profound disabilities. Suggesting the concept of an autoimmune predisposition there have been reports hypothesizing shared risk and increased statistical susceptibility for people with one of autoimmune disorder to develop another. There has been an extensive research for pathophysiological mechanisms that may underlie autoimmunity resulting in the frequent co-occurrence of autoimmune disorders, such as MS and Hashimoto's thyroiditis among others. Given that MS currently remains incurable and the immunomodulatory therapies do not completely prevent disease progression in most patients, the final option for managing patients who do not respond to immunomodulatory treatment is to use a chemotherapeutic agent. Azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, mitoxantrone, cyclophosphamide and rituximab are the most utilized agents **6**.

Neurogliobiology or the myelin-neuron interaction

The term "neurogliobiology" refers to the concept that neurons and glia (including microglia) in the nervous system are

inseparable partners **1**. Neurons and glia cooperate to build a complex network during development. Numerous studies have demonstrated an interdependent relationship of oligodendrocytes and the axons they myelinate **7**. The reciprocal communication between neurons and oligodendrocytes is essential for the generation of myelin, a multilamellar insulating membrane that ensheathes the axons. Neuron-derived signalling molecules regulate the proliferation, differentiation and survival of oligodendrocytes. Moreover, signals from oligodendrocytes to neurons direct the assembly of specific subdomains in neurons at the node of Ranvier. Heterogeneous neuronal populations may have differential signaling patterns modulating localized oligodendrocyte myelination. The interaction of these neurons and oligodendrocytes may regulate plasticity in the adult brain **8**. Moreover, not only does the thickness of the myelin coating on axons affect conductance speed but synaptic activity influences the activity and replacement of oligodendrocytes in the brain throughout life **9**.

New myelin is being generated in the healthy adult brain, and adding new myelin internodes in areas of discontinuous myelination may be a mechanism for local plasticity **10**. Altered or inadequate myelination in the adult could also be a component in some of the psychiatric or neurodegenerative disorders that involve white matter **11**. Oligodendrocytes provide essential trophic support to axons. Aerobic glycolysis in oligodendrocytes is sufficient to maintain the myelin itself and the structure and function of the myelinated axons. The lactate produced by these cells is rapidly utilized by the axons, except when neuronal function is reduced as under anesthesia, at which point lactate accumulates in the tissue **12**.

Adaptive myelination implies that neuronal electrical excitability modifies myelin plasticity and that myelin plasticity in turn feeds back to modulate neural activity and behavior **11**. Some studies suggest a critical period in which neuronal function impacts myelination, either during early or late development. Neural activity, either in the medial prefrontal cortex or the barrel cortex of the somatosensory cortex, impacts myelination. Social isolation for as little as 2 weeks in the early post-weaning period has a dramatic effect reducing myelin-

ation in the prefrontal cortex, although motor activity is unaffected. Reintroduction of mice to a social environment at the end of the two weeks does not improve myelination. In these studies, 30 days social isolation in the adult has little impact on myelin content. Moreover, it was myelination per se that is reduced, since the number of oligodendrocytes themselves was normal in these tissues **13, 14**.

Dysfunction of neurotransmitters is one of the primary aetiologies of schizophrenia, while antagonists or selective-agonists of dopamine, serotonin and/or glutamate receptors were developed and used as major antipsychotic drugs. Concerning the action of antipsychotic drugs on white matter, a recent neuroimaging study using diffusion tensor imaging (DTI) assessed the myelin integrity among normal control and acutely psychotic, drug-free schizophrenics, before and after antipsychotic drugs treatment. It was found that a decrease of myelin integrity was partially restored in drug-responding schizophrenic individuals, whereas the poorly responsive schizophrenics did not appear to be related to a disordered myelin **15**. Moreover, it seems that haloperidol and olanzapine stimulate proliferation but inhibit differentiation of oligodendrocytes via different molecular mechanisms. Quetiapine, however, is diametrically opposed to the above processes, although it targets the similar receptors as does olanzapine. Therefore, Ren et al (2013) **16** proposed that the improvement of myelin/oligodendrocyte dysfunction by antipsychotic drugs may not rely on canonical neurotransmitters but rather that cross-communication may exist through different molecular mechanisms.

Demyelinating diseases

There are many causes of demyelination in human diseases. The main causes of primary demyelination are genetic, immune mediated, viral such as HIV, and toxic; they may also be secondary to neuronal dysfunction. Some genetic diseases may give rise to leukoencephalopathies in which demyelination is secondary to vascular, mitochondrial, or neuronal alterations or may be linked to a metabolic disease. Demyelination, breakdown of myelin, is characteristic of metabolic leukodystrophies, such as Krabbe's disease, metachromatic leukodystro-

phy, ALD, Canavan disease, Alexander disease, orthochromatic leukodystrophy, or mitochondrial disorders. Dysmyelination and hypomyelination are failure to myelinate occurring during fetal life or early infancy, as observed in different forms of Pelizaeus-Merzbacher disease **1**.

Multiple sclerosis (MS) is a chronic and inflammatory demyelinating disease. In MS, there is a loss of myelin in defined areas (lesion sites) in the brain and spinal cord. Current evidence shows that the etiology of MS and other demyelinating diseases may involve a combination of viral and autoimmune factors. MS is an autoimmune disorder that is characterized by muscle weakness and numbness as well as problems with vision and bladder control. There is a profound heterogeneity of pathology and immunopathogenesis of the lesions. There is a high interindividual but a low intraindividual variety of MS lesions. It is caused by the immune system attacking the nerve-insulating myelin sheath, which disrupts the communication between brain and peripheral parts of the body **6**.

In chronic MS lesions, oligodendrocyte precursor cells are present; however, they appear to be quiescent, not expressing a nuclear proliferation antigen. In MS, remyelination occurs, but it is incomplete and poorly sustained. After a demyelinating lesion, remyelinated myelin never regains its normal thickness, and the normal linear relationship between axon and sheath thickness is also never regained. It is not clear whether the mechanism of remyelination is identical to myelination. Normal appearing white matter in MS tissue often has reduced axonal density, which is generally attributed to inflammation. This normal appearing white matter may well have dysfunctional myelin that cannot provide the necessary trophic and metabolic support for axons. This suggests that altered myelin and oligodendrocyte function in human brain could be just as important as myelin loss in neurodegeneration **11**.

In addition to the well-known demyelinating and dysmyelinating diseases such as MS, neuromyelitis optica, and the leukodystrophies, myelin deficits resulting from altered glial structure/function and or glial/neuronal interactions are seen in human psychiatric disorders and developmental disorders including autism spectral disorder (ASD), sensory processing

delay disorder, and attention deficit hyperactivity disorder **17, 18, 19**.

Clemastine, a Food and Drug Administration-approved antimuscarinic compound that has been shown to enhance myelination under demyelinating conditions, successfully reversed social avoidance behavior in adult socially isolated mice. This was associated with enhanced myelination and oligodendrocyte differentiation in the prefrontal cortex through epigenetic regulation. Thus, enhancing myelination may be a potential means of reversing depressive-like social behavior **20**. Clemastine also have been suggested as a potential therapy for hypoxic brain injuries associated with white matter injury and oligodendrocyte precursor cell maturation arrest **21**.

Multiple Sclerosis vs psychosis

MS and schizophrenia have numerous similarities in terms of the onset and cause. SCZ affects the same age distribution as MS; however, it has a 10- to 100-fold higher estimated prevalence rate **22**. Both schizophrenia and MS are substantially more widespread in the northern and temperate regions of the world than in the tropics **23**. Concordance rates in identical twins range from 30 to 80% for MS and approximately 50 to 60% for schizophrenia. Moreover, dizygotic twins exhibit approximately 5–10% concordance rate only **24**.

MS and schizophrenia may be present together in the same patient. In a recent review, 91 cases were identified in the literature in which both MS and psychotic disorders or mood disorders with psychotic features were present in the same patient. In most cases (> 60%), frontotemporal lesions were present and, in 26 cases, corticosteroids were successfully used for therapy **25**. The inflammatory process that occurs in MS patients is directly associated with human leukocyte antigen (HLA) class I and II loci. The major histocompatibility complex (MHC) is responsible for the genetic overlap in both MS and SCZ, since a GWAS noted the involvement of similar HLA alleles in MS and SCZ **26**.

The pathophysiologies of MS and schizophrenia are similar but not identical. MS is more prevalent in females than males,

whereas the incidence of schizophrenia is equal in males and females. For MS, the pathophysiology appears to lie in an autoimmune reaction directed against the myelin sheaths of the nerves, which disrupt the transmission of information. On the other hand, only in a subgroup of patients with schizophrenia, autoantibodies cause the disease, which are directed against receptors on the perikarya of the nerve cells (NMDA receptors) **27**. Additionally, the HLA genes involved appear to be the same; however, alleles or mutations within these genes appear to have opposite effects in MS and schizophrenia **25**.

Genetics

The etiological significance of genetic factors in psychotic disorders is substantial: the heritability of schizophrenia spectrum and bipolar disorders is around 65–85%. Numerous studies have correlated variants in schizophrenia candidate genes with phenotypic features, sometimes also with outcome measures. However, recent genetic studies have questioned the validity of previously suggested schizophrenia candidate genes **28, 29**.

A number of myelin gene knockout mice models exhibit schizophrenia-like behaviours **30, 31**. Genomic, especially GWAS, studies identified new schizophrenia loci related to oligodendrocyte genetic polymorphisms **32**. The candidate marker for schizophrenia Neuregulin-1 is possibly related to oligodendrocyte dysfunction and defective myelination **33**, while several other myelin-related candidate genes have been linked oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia **34**.

Neuregulin 1 (NRG1) risk genotypes or haplotypes have been associated with schizophrenia **35**. The potential pathophysiological role of NRG1 is further supported by its diverse neurobiological functions, including neuro-glial trophic effects and myelination **36**. Genetic evidence also supports ERBB4 – the NRG1 receptor – as a candidate susceptibility gene and suggests positive epistatic interactions between NRG1 and ERBB4 in schizophrenia **37**. Disrupted-in-schizophrenia 1 (DISC1) is a strong candidate gene for schizophrenia **38** followed by ad-

ditional genetic evidence for association with sporadic cases of schizophrenia **39**. The DISC1 SNPs is also associated with white matter integrity as measured by DTI **40**. Reticulon 4 receptor (RTN4R) is a myelin-associated protein that inhibits the outgrowth of neurites and nerve terminals and is upregulated in the brains of patients with schizophrenia **41**. Genetic association analysis of oligodendrocyte lineage transcription factor 2 (OLIG2), which encodes a transcription factor central to oligodendrocyte development, is associated with schizophrenia, having also an epistatic effect with 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) and ERBB4 **42**. No OMR genetic association reached genome-wide significance; however, a handful of OMR genes (ANK3, ERBB4, and NRG1) show suggestive association **43**. The above observations suggest that genetic alterations underlying oligodendroglial and myelin related cell type functions increase susceptibility to schizophrenia and provide evidence that the “neuron-centric” hypothesis of schizophrenia should be extended to include a role for glia in the etiopathogenesis of the disease. The oligodendroglial and myelin related gene and protein expression abnormalities can hamper saltatory conduction by affecting node of Ranvier integrity, which may result in failures of saltatory conduction, disconnection of higher-order association areas, and finally to the disconnectivity syndrome **7**.

Patients with a deletion at chromosome 22q11.2 (22q11DS) have 30% lifetime risk of developing a psychosis. People fulfilling clinical criteria for ultra-high risk (UHR) for psychosis have 30% risk of developing a psychosis within 2 years. Both high-risk groups show white-matter abnormalities in microstructure and volume compared to healthy controls, which have been related to psychotic symptoms. Bakker et al (2016) **44** found that UHR and 22q11DS patients were characterized by distinct patterns of white matter alterations, in relation to healthy controls. Interestingly, while UHR patients were typified by signs suggestive of aberrant myelination, 22q11DS subjects showed signs suggestive of lower axonal integrity.

Dysregulated immune response and psychosis

The association of a dysregulated immune response and

psychosis is well-established. Several pro-inflammatory cytokines are elevated in first episode psychosis (FEP) patients. The changes are similar in the cerebrospinal fluid (CSF) and blood, and they occur across severe mental disorders **45**. While meta-analyses initially suggested that antipsychotic medication might decrease pro-inflammatory activation, a later meta-analysis did not find a significant medication effect **46**. C-reactive protein (CRP) has been the most commonly used measure of inflammation. CRP levels are increased in both drug-naïve and unmedicated patients, as well as after the onset of psychosis, although it has been studied and suggested as a biomarker for numerous acute and chronic diseases **47**. The question remains open regarding to what extent inflammation might be secondary to metabolic changes, or vice versa **48**.

Autoimmune disorders occur after the failure of self-recognition processes with consequent production of pathogenic autoantibodies directed against specific or multiple organs. They are heterogeneous disorders, representing more than 80 different diseases. The “immunogenetic” contribution is largely dominated by the major histocompatibility complex (MHC) genetic diversity and, at a lesser extent, by mutational events affecting cytokines encoding genes **49**. Several genome-wide association studies (GWAS) confirmed an association between the MHC region (chromosome 6) and psychosis **50, 51**.

Autoantibodies, specifically against the central nervous system, have been found in schizophrenic patients. These patients have a higher prevalence of circulating antibodies against hippocampus and hypothalamus as compared to healthy control **52**. A systematic review demonstrated that among patients with established schizophrenia, 20 autoantibodies (including antinuclear antibody [ANA], anti-cardiolipin, anti-N-methyl-d-aspartate receptor [NMDAR], and anti-serotonin) were present at higher rates than among controls. Rates of anti-cardiolipin and anti-NMDAR antibodies were also present in patients with first-episode psychosis **53**.

Schizophrenic patients are three times more likely to have high levels of anti-glutamate receptor antibodies, N-methyl-d-aspartic acid receptor (NMDAR), compared to controls (Pearlman et al, 2014). In at least a subgroup of schizophrenic

patients, led us to propose the concept of “autoimmune psychosis” **54**. The anti-N-methyl-D-aspartate-type glutamate receptor (anti-NMDAR) encephalitis can in some cases present with prominent psychotic symptoms. The identification of encephalitis in patients with early psychosis is crucial, as over 75% of patients with classic anti-NMDAR encephalitis have substantial recovery with specific treatments, while antipsychotic treatment is not effective. Other than anti-NMDAR antibodies, autoantibodies detected in autoimmune encephalitis seem to remain negative in patients with isolated early psychotic symptoms **55**.

Peripheral monoamines and their metabolites have been studied as candidate biomarkers for treatment response in FEP. Tryptophan metabolite kynurenine acid (KYNA) has been studied extensively in recent years. A meta-analysis found that KYNA levels are elevated in CSF, but not in plasma, in patients with schizophrenia, and KYNA elevation is linked to proinflammatory activation **56**.

An immunohistochemical study revealed that a marked activation of microglia and astrocytes in the middle frontal and anterior cingulate gyri and cerebellum is obtained at autopsy from Autism spectrum disorder (ASD) subjects **57**. Similarly, microglial cells are markedly activated in the dorsolateral prefrontal cortex of ASD individuals **58**. Risperidone in combination with a cyclooxygenase-2 inhibitor, celecoxib, showed a superior efficacy as compared with monotherapy of risperidone in a randomized double-blind placebo-controlled clinical study in ASD children **59**. Neuroinflammation mediated by M1 microglia appears to be associated with ASD and schizophrenia and a drug that selectively suppresses polarization of M1 microglia may provide a beneficial therapy these disorders **5, 60**.

Is psychosis an immune-dysregulation dysmyelination disorder?

Environmental stressors are of major importance for the onset of autoimmunity. The occurrence of infections by pathogens such as, influenza, herpes simplex type 2, cytomegalovirus, and *Toxoplasma gondii* and/or increased C-reactive protein plas-

ma levels during pregnancy are known to be associated with an increased risk of developing schizophrenia in adulthood **61**. Childhood autoimmune diseases as well as inflammatory diseases, such as asthma, are known to be associated with an increased number of psychotic experiences in adolescence. Epidemiological studies have borne out the association between psychotic disorders and autoimmune disease. Rates of autoimmune disorders such as celiac disease, Graves' disease, systemic lupus erythematosus, multiple sclerosis, autoimmune hepatitis, and psoriasis are higher in those with schizophrenia **62, 63**. Moreover, in patients with autoimmune conditions, the risk to develop schizophrenia increases linearly with the number of severe infectious episodes **64**. Recent research also have been suggested that neuroinflammation plays a role in the with matter processes associated with catatonia **65**.

Dizocilpine (also known as MK-801), an N-methyl-d-aspartate receptor [NMDAR] antagonist and pharmacological model of schizophrenia seem to affects the metabolic processes of oligodendrocytes rather than neurons in vitro **66**. Interestingly, clozapine counters the metabolic effects of MK-801 and promotes glycolysis and myelin lipid synthesis in cultured oligodendrocytes **67, 68**. A number of putative myelin enhancing therapies would be potential candidates for large-scale clinical trials in schizophrenia. These include myelin-enhancing agents such as n-3 PUFA, minocycline, clemastine, polyphenols, and potential neuro/myeloreparative agents such as sulfasalazine, nano-curcumin, stem cell enhancing therapies such as Gli-1 inhibitors, and immunomodulators, such as fingolimod **69**.

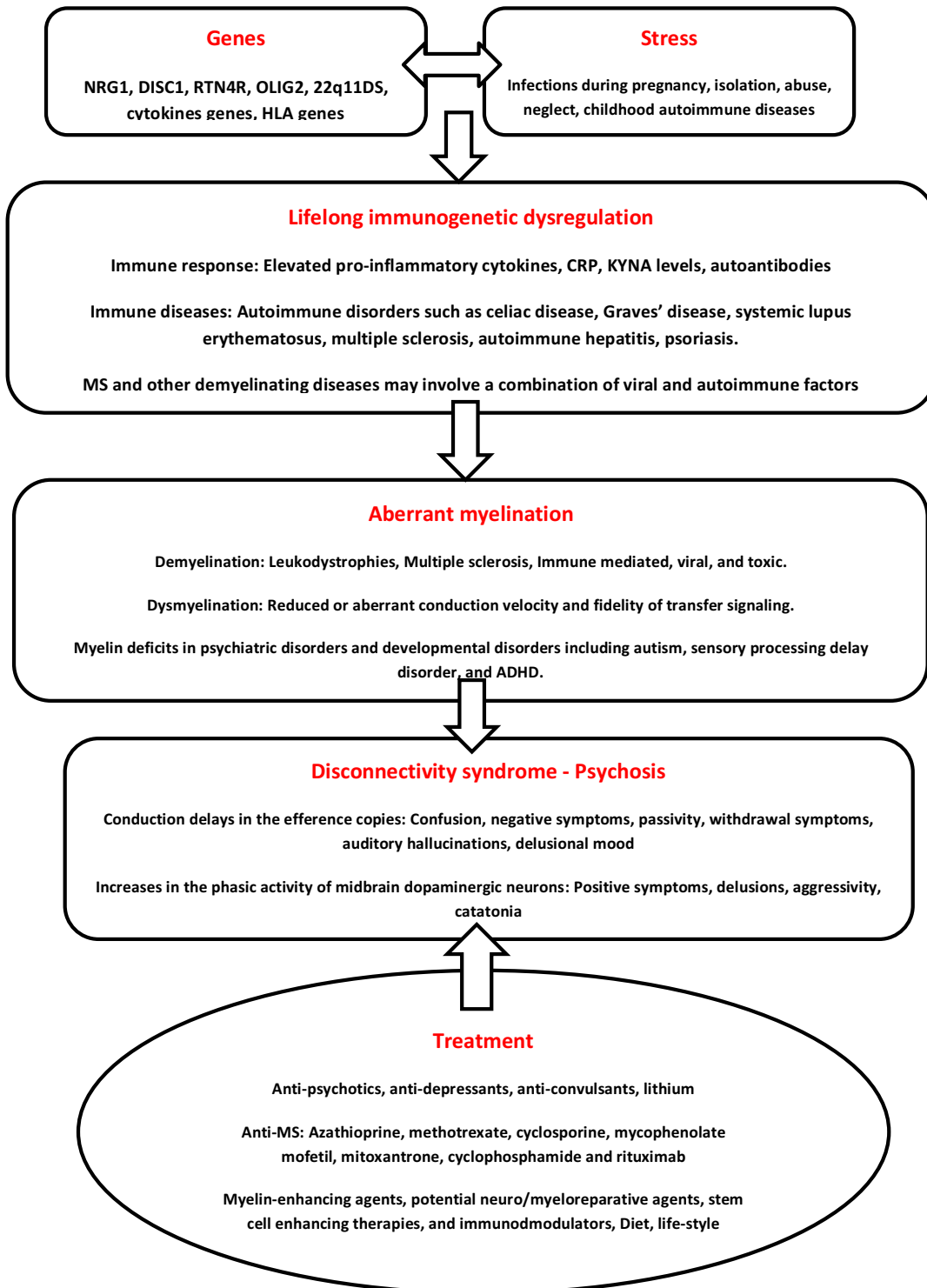
The neurodevelopmental hypothesis for schizophrenia posits that mis-wiring the cortex including the with matter connections is the underlying pathology of schizophrenia **70**. Several studies have suggested that some prediction aspects are impaired in psychotic patients **71, 72, 73, 74**. They manifest confusion at the initiation of the actions, and hence passivity experiences in the case of willed motor actions, and auditory hallucinations in the case of willed cognitions. Research suggests that changes in white matter integrity occur in schizophrenia and these may be more associated with cognition and even negative symptomology. Some studies have been shown

that the dysmyelination-induced delays may cause a discrepancy in sensory feedback mechanisms, which may represent a prediction error and a phenomenological and neurophysiological salient event **75**. Extending this aspect, Whitford et al (2012) **76** suggested that passivity or negative symptoms and auditory hallucinations could arise initially because of dysmyelination-induced conduction delays in the efference copies. The resultant increases in the phasic activity of midbrain dopaminergic neurons could amplify these symptoms and concurrently trigger additional psychotic symptoms. The authors concluded that on a phenomenological level, these prediction errors cause confusion, giving rise to passivity experiences and auditory hallucinations. On a neurophysiological level, these prediction errors give rise to a second cause of psychotic symptoms, by increasing the phasic activity of midbrain dopaminergic neurons **76, 77** (Fig 1).

Summarizing, while not clear if white matter changes are a cause or an effect of underlying pathology, it is clear that white matter integrity is affected in schizophrenia. The pathophysiology of MS and schizophrenia show some similarities. MS is characterized by a large array of invading immune cells that attack and degrade the myelin sheath, the myelin producing oligodendrocytes and the nerve itself. On the other hand, schizophrenia has been proposed to be a dysconnectivity syndrome. Disturbance in neuronal connectivity between different brain regions, rather than abnormalities restricted to individual brain regions, may be responsible for the clinical symptoms and cognitive dysfunctions observed in psychosis. In addition, the association of a dysregulated immune response and psychosis is well-established, and autoantibodies, specifically against the central nervous system, have been found in schizophrenic patients. Myelin and oligodendrocyte dysfunction affect neuronal connectivity, which has been implicated as a central abnormality in schizophrenia, resulting in prediction errors and dysconnectivity. Clinical and neuropathological studies have shown that disruption in myelination and dysmyelination-induced delays in information process can produce a high fidelity phenocopy of psychosis similar to schizophrenia **78, 79, 80, 81, 82, 83, 84, 85, 86**.

Recently, Boyle et al (2017) **87** found that disease risk is driven mostly by genes with no direct relevance to disease, but which act as modifiers of more fundamental biologic processes, perhaps related to individual genetic backgrounds and environmental experience. Based on these findings, Weinberger (2017) **88** reported: "This proposal echoes the question of whether psychiatric disorders are really "diseases" rather than varying states of brain development that have a particular way of expressing difficulties in particular environmental contexts, based on genomic background, development and experience". Rethinking the relative research findings and suggestions on psychosis, we may further suggest that the above described dysconnectivity syndrome in psychosis represents the phenomenological and behavioral result of a multiple faces dysmyelination disorder, which is based obviously on a lifelong immunogenetic dysregulation process.

Fig 1. Factors implicating in the immune-related dysmyelination process of psychosis



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