General article
Γενικό άρθρο

Is psychosis a dysmyelination-related information-processing disorder?

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Numerous lines of evidence implicate myelin and oligodendrocyte function as critical processes affecting neuronal connectivity, which is a central abnormality in schizophrenia. Neurodevelopmental models related to dysmyelination have suggested its relation with different schizophrenia-like symptoms. Post-mortem studies in patients with schizophrenia have reported 14–22% reduction in the density and the quantity of oligodendrocytes. Several myelin-related candidate genes have been linked oligodendrocyte and myelin dysfunction with neurocircuitry abnormalities in schizophrenia. A number of myelin gene knockout mice models exhibit schizophrenia-like behaviours, and genomic, especially GWAS, studies identified new schizophrenia loci related to oligodendrocyte genetic polymorphisms. It is known that myelin acts as electrical insulation for the ensheathed axon, which helps to preserve the amplitude and to increase the conduction velocity of the propagating axon potential. A growing body of evidence points towards the involvement of dysmyelination of the prefrontal cortex in the development of the cognitive symptoms of psychosis. Neuroimaging investigations have linked processing speed to brain anatomical connectivity, and have pointed the role of processing speed among the predictors of clinical changes in schizophrenia. The dysmyelination-induced delays in patients with psychosis may cause a discrepancy in sensory feedback mechanisms, which results in prediction error. The myelin abnormalities and the resulting conduction delays vary during the course of the multiple sclerosis and this type of cycles are possibly associated with fluctuations in conduction velocity in psychosis. It is worthy of note that the major histocompatibility complex (MHC) is responsible for the genetic overlap in both multiple sclerosis and schizophrenia. Multiple sclerosis manifests sensory and motor symptoms, and schizophrenia disordered cognition and emotion. Having in mind the interdependent relationship of oligodendrocytes and the axons they myelinate, we could suggest that both multiple sclerosis and schizophrenia may use in central nervous system a common pathway of disordered information-processing. Recent research suggests that adaptive myelination could normalize neuronal electrical excitability, which in turn can modify myelin plasticity, resulting to neural activity and behavior modulation. We may suggest that interventions that preserve white matter integrity or ameliorate white matter disruption may enhance information-processing and functional outcome in psychosis.

Key words: Schizophrenia, dysmyelination, information-processing, conduction velocity, processing speed.

Psychosis and cortical dysmyelination

Schizophrenia is a severe and chronic mental disorder that afflicts approximately 1% of the world's population. Typically, the age of onset is late adolescence to early adulthood, with a tendency for earlier occurrence in males. Clinical manifestations of the disorder display great heterogeneity ranging from positive, such as delusions or hallucinations, to negative symptoms, such as affective blunting, poverty of speech or lack of motivation. Other aspect of schizophrenia that has an impact on patients' life is the progressive emergence of neurocognitive dysfunction.[1]

The prefrontal cortex has a central role in cognition, by being the region that integrates highly processed information. A characteristic feature is its relatively slow maturation process, which is not complete until early adulthood, the age that marks the refinement of cognitive functions, such as reasoning and executive functioning. This timing also coincides with the onset of schizophrenia, suggesting that developmental abnormalities of the prefrontal cortex could contribute to the psychosis etiology. Many studies have demonstrated a correlation between the distortion of these maturational processes and the emergence of schizophrenia, leading to the hypothesis that schizophrenia is a disorder of the cortex.[2]

A recent review suggested that the neurological soft signs scores stay in between the low values characteristic for healthy controls and elevated values typical for patients with chronic schizophrenia, i.e., the subjects with an increased genetic vulnerability toward the disorder.[3] Neurological soft signs refer to changes in the whole motor system in particular a cerebello-thalamo-prefrontal network rather than to deficits in discrete cerebral sites.[4] Neuroimaging studies identified the sensorimotor cortices, the supplementary motor area, the basal ganglia, the thalamus and the cerebellum as important sites for neurological soft signs.[5] Moreover, neurological soft signs are associated with cognitive deficits ranging from attention/psychomotor speed and executive dysfunctions to complex neuropsychological abilities, such as logical memory, autobiographic episodic memory, and theory of mind.[6]

On the other hand, many neurodevelopmental models related to dysmyelination suggested its relation with different schizophrenia-like symptoms. Zhang et al,[7] suggested the myelination deficit in a phencyclidine-induced neurodevelopmental model of schizophrenia. Evidence suggests a critical role for dysmyelination in patients with schizophrenia. Intracortical myelination have been found reduced in patients with schizophrenia, while certain antipsychotic agents can restore this defect.[8] Post-mortem studies in patients with schizophrenia have reported 14–22% reduction in the density and the quantity of oligodendrocytes.[9]

Maternal immune activation induces changes in myelin and metabolic proteins, some of which can be prevented with risperidone in adolescence,[10] while abnormal expression of myelination genes is related with prenatal viral influenza infection in mice.[11] A number of myelin gene knockout mice models exhibit schizophrenia-like behaviours.[12,13] Genomic, especially GWAS, studies identified new schizophrenia loci related to oligodendrocyte genetic polymorphisms.[14] The candidate marker for schizophrenia Neuregulin-1 is possibly related to oligodendrocyte dysfunction and defective myelination,[15] while several other myelin-related candidate genes have been linked oligodendrocyte and myelin dysfunction with neurocircuitry abnormalities in schizophrenia.[16]

Dizocilpine (also known as MK-801), a 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*.[17] Moreover, clozapine counters the metabolic effects of MK-801 and promotes glycolysis and myelin lipid synthesis in cultured oligodendrocytes.[18,19]

Information monitoring

The supervisory attentional system incorporates the prefrontal cortex as a core structure. Indeed, the prefrontal cortex seems to play a role in this system in various ways.[20] Both the visual perceptual process and visual mental imagery seem to stimulate similar neural networks, such as the primary visual cortex, the posterior parietal cortex, temporal areas and the dorsolateral prefrontal cortex. An important distinction arises in the fact that neural networks involved in imagery result to the triggering of top-down processes, whereas neural networks in perception are

associated with bottom-up processes.[21] Movement behavior begins with projections from the prefrontal cortex to the striatum, followed by the globus palidus and from there to the anteroventral and ventrolateral thalamic nuclei, which in turn project to the premotor area and the supplementary motor area and to the anterior cingulate.[22,23] Malfunction in any of these areas may lead to disorders such as Parkinson's disease, while the positive symptoms of schizophrenia have also been associated with a failure in monitoring movements, accounted for by deficits between premotor areas and the striatum. This is supported by the symptom of a sense of movement, as if controlled by external forces, in patients with metachromatic leukodystrophy, where the white matter connectivity of several cortical areas, and in particular the frontal cortex is upset.[24]

Cortical lesions and damage in the medial part of the mid-dorsolateral prefrontal cortex (BA 46 & 9/46) lead to deficits in tasks of the monitoring of information in working memory, where the capacity for an epoptic processing of information is evaluated, while the architectonic areas 46 & 9/46 of the prefrontal cortex appear to be linked with specific segments of the inferior parietal lobe through the superior longitudinal fasciculus. The inferior part of the posterior parietal cortex seems to be a crucial area for the updating of information in the working memory and the BA 46 & 9/46 encode it into an "abstract/symbolic form", in order to achieve the controlled monitoring in the active mnemonic process. This system has the capacity to hold symbolically coded information in an active state, in order to supervise the between them relation and their relation with the intended programmed behavior.[25]

Computer generated models on information-processing attempted to describe mechanisms through which the development of some symptoms takes place. The isolation of some computer parts led to several consequences, such as leading to conclusions irrelevant to the incoming data or the independent uncontrolled functioning of some parts. Applying these observations to cognitive contexts, Hoffman & McGlashan[26] hypothesized that if, for instance, some brain areas responsible for speech were isolated from the network of movement initiation, such as the supplementary motor area during the period of cortical pruning, the development of some form of subvocal speech would be possible perceived by the patient as independent of other intellectual processes and thus interpreted as a hallucination or as some thought deficit. A similar proposal was made by David in 1994,[27] who supported that the excessive neural activity between two brain areas, known as dysmodularity, provides a more accurate explanation for the pattern of cognitive deficits and neuroanatomical findings in patients with schizophrenia. This also presupposes the burdening of the cognitive system and reduced brain hemispheric asymmetry, as suggested by Crow in 1990.[28]

Saliency detection and error prediction

Patients with schizophrenia suffer from predictive coding impairments.[29] In the context of predictive coding, information-processing is updated every 50 ms and this time window is longer in patients, which suggests that updating is slower in patients with schizophrenia.[30,31] This displays a connectivity disorder, which account for disturbances in recurrent loops subtending the constant updating of information-processing and the detection of prediction errors.[32,33] Patients with schizophrenia display a disturbed ability to detect new and unexpected stimulus, and the amplitude of the EEG response to these stimulus is reduced.[34] This results in difficulties distinguishing between relevant and irrelevant information, causes patients to assign the wrong salience to events,[35] and possibly results in delusional beliefs.[36] All these difficulties may be explained in the context of predictive coding.[37]

Theories of self-monitoring and error-checking agree with the theory concerning the use of a salience network. According to Corlett et al,[38] there are two types of error prediction associated with schizophrenia and the development of delusional beliefs, playing opposite roles: one that overweights the prediction versus and one that underweights the prediction. The over-weighting of the prediction may be prioritized due to its pathogenetic nature, occurring first, and is followed by the under-weighting of the prediction, which bears as a result a state of fatigue and withdrawal. Neurobiologically, the hyperactivation of the salience network is likely followed by the hyper-activation of the default mode network and subsequently by the suppression of the salience and attention network. This initial hyper-

activation seems to be normalized by antipsychotics, since they dampen the salience of these abnormal experiences and by doing so permit the resolution of symptoms.[35]

Several studies have suggested that some prediction aspects are impaired in patients with schizophrenia.[29,39,40] They manifest a 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. 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.[41] Extending this aspect, Whitford et al[42] suggested that passivity 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.[42]

Myelination and conduction velocity

Myelin ensheath the axons of nearby neurons. Myelinated axons with similar destinations tend to bundle together into white matter fasciculi. The myelin acts as electrical insulation for the ensheathed axon, which both helps to preserve the amplitude and increase the conduction velocity of the propagating axon potential.[43] Myelinated axons typically have higher conduction velocities than unmyelinated axons of the same caliber and damage to the myelin can result in conduction delays in neural discharges. Such conduction delays might be expected to result in a temporal discoordination between the activities of spatially discrete populations of neurons.[42,44] The myelin abnormalities and the resulting implication in conduction delays vary in magnitude over the course of the multiple sclerosis and this possibility would be akin to the cycles of demyelination and remyelination often experienced by patients with multiple sclerosis.[45] These cycles have been shown to be associated with fluctuations in conduction velocity[46] and symptomatology, including psychotic symptomatology.[47,48] A similar idea has previously been proposed by Garver and colleagues (p. 49)[49] who suggested that the patients in their study may have experienced "compromised myelin integrity during psychosis with repair during remission".

Pharmacology studies suggest that dysfunction of neurotransmitters is one of the primary etiologies of schizophrenia, while antagonists or selective-agonists of dopamine, serotonin and/or glutamate receptors were developed and used as major antipsychotic drugs in clinical practice during recent years. 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 patients with schizophrenia, before and after antipsychotic drugs treatment. It was found that a decrease of myelin integrity was partially restored in drug-responding schizophrenia patients, whereas the poorly responsive patients did not appear to be related to a disordered myelin.[49] 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, 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.[50]

Dysmyelination and psychopathology

Waller et al in 2017[51] reviewed findings from 22 studies that examined the relationship between white-matter microstructure and antisocial behavior across development. They found that adult antisocial behavior was associated with greater diffusivity across a range of white-matter tracts, including the uncinate fasciculus, inferior fronto-occipital fasciculus, cingulum, corticospinal tract, thalamic radiations, and corpus callosum. The pattern of findings among

youth studies was inconclusive: both higher and lower diffusivity found across association, commissural, projection and thalamic tracts.

There is preliminary evidence for a role of lipid biology in the onset of psychosis, along with well-established evidence of its role in myelination of white matter tracts. Several lines of evidence suggest that polyunsaturated fatty acids (PUFAs) play a role in myelination, and there is substantial evidence documenting decreased PUFA concentrations in schizophrenia. Reviewing the relative studies, Vijayakumar et al[52] pointed that there is growing evidence of reduced polyunsaturated fatty acids (PUFA) concentration in ultra-high risk for psychosis (UHR) samples, highlighting the need for research to examine the relationship between PUFA and white matter integrity in high-risk samples and age-matched healthy controls. Peters et al[53] assessed in 30 male patients with a recent-onset psychotic disorder, erythrocyte membrane PUFA concentrations and diffusion tensor imaging was performed with voxelwise analysis. Membrane PUFA concentrations appeared to be robustly related to brain white matter integrity in early phase psychosis. The authors suggested the possible effects of PUFA supplementation on white matter integrity and associated symptomatology in early psychosis.

Patients with a deletion at chromosome 22q11.2 (22q11DS) have 30% lifetime risk of developing a psychosis, while people fulfilling clinical criteria for ultra-high risk (UHR) for psychosis have 30% risk of developing psychosis within 2 years.[54] 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)[54] found that UHR and 22q11DS patients share a susceptibility for developing psychosis yet were characterized by distinct patterns of white-matter alterations. While UHR patients were typified by signs suggestive of aberrant myelination, 22q11DS subjects showed signs suggestive of lower axonal integrity.

Fujino et al[55] found impaired empathic abilities and reduced white matter integrity in patients with schizophrenia. The patients showed a significant white matter fractional anisotropy (FA), a measure of white matter integrity, reduction in bilateral deep white matter in the frontal, temporal, parietal and occipital lobes, a large portion of the corpus callosum, and the corona radiata. The authors suggested that disrupted white matter integrity in these regions constitutes a pathology underpinning specific components of empathic disabilities in schizophrenia, highlighting that different aspects of empathic impairments in the disorder would have, at least partially, distinct neuropathological bases.

Summarizing, evidence implicate myelin and oligodendrocyte function as critical processes that could affect neuronal connectivity, which has been implicated as a central abnormality in schizophrenia. Phenocopies of schizophrenia with a known pathological basis involving demyelination or dysmyelination may offer insights into the biology of schizophrenia itself. While classical clinical-neuropathological correlations have established that disruption in myelination can produce a high fidelity phenocopy of psychosis similar to schizophrenia, the role of dysmyelination in schizophrenia remains controversial.[56]

Dysmyelination and cerebral communication in psychosis

Evidences suggest that the normal integration of cerebral communication may be compromised in schizophrenia and white matter abnormalities are integral to these functional deficits. Diffusion tensor imaging (DTI) is a neuroimaging technique which has increasingly been used to study white matter through quantitative indices of its structural and orientational characteristics. Identifying the white matter differences early in the course of schizophrenia may assist in prevention, early diagnosis and identification of treatment targets. Davis et al[57] found white matter changes and evidence for myelin-related dysfunction in schizophrenia. In schizophrenia patients it is possible an aberrant myelination of the frontal white matter fasciculi during periadolescent neurodevelopment causes. Several studies also have observed white matter abnormalities in patients with schizophrenia, either postmortem, with electron microscopy, or in vivo with structural MRI or DTI.[41,58–60] Especially, schizophrenia patients exhibit a range of myelin-specific abnormalities, including reduced numbers of oligodendrocytes or irregular myelin microstructure,[58,59] subnormal expression of myelin-related genes,[61] and irregularities in the nor-

mative processes of periadolescent myelination.[62] Abnormalities in the white matter fasciculi have been implicated in schizophrenia, particularly by disconnectivity theories that emphasize the role of abnormal interactions between brain regions in the etiology of psychosis.[63–65]

Samartzis et al[66] reviewed white matter integrity in the early stages of schizophrenia as inferred by DTI, in relation age, duration of illness and treatment. Although the pattern of white matter differences is not totally consistent frontal, fronto-temporal and fronto-limbic connections, with tracts including the superior longitudinal fasciculus, cingulum bundle, uncinate fasciculus and corpus callosum seem to be affected. The authors suggested that these differences may depend on the developmental stage of the subjects, the duration of illness and exposure to antipsychotic medication. Patients with bipolar disorder also showed lower fractional anisotropy than healthy controls in several white matter tracts. However, compared with schizophrenia patients, bipolar disorder patients showed lower fractional anisotropy in the cingulum, internal capsule, posterior corpus callosum, tapetum, and occipital white matter including posterior thalamic radiation and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus. The findings suggested that different pathophysiological mechanisms may underlie white matter microstructural abnormalities in bipolar disorder and schizophrenia.[67]

Dysmyelination and information-processing in psychosis

Neuroimaging investigations have also linked processing speed to brain anatomical connectivity. Sánchez et al[68] first pointed the role of processing speed among the predictors of longitudinal changes in schizophrenia. Individuals in the early stages of psychosis appear to have less consistent white matter as well as grey matter changes than chronic patients. There is also a 5-year period following the first psychotic episode, called the "critical period" by Birchwood and colleagues,[69] during which the most severe brain changes appear to occur. Karbasforoushan et al[70] found that white matter integrity of the corpus callosum, cingulum, superior and inferior frontal gyri, and precuneus was reduced in schizophrenia. The authors concluded that cognitive impairment in schizophrenia is mediated by reduced white matter integrity and that diffusion-weighted imaging (dMRI) are important in explaining deficits in the processing speed.

Mediation analyses and structural equation modeling were used by Kochunov et al[71] to analyze the associations among processing speed, working memory, and white matter microstructures. Their findings suggested that information-processing speed contributes to the association between white matter microstructure and working memory in schizophrenia. Moreover, the white matter impairment in schizophrenia was found to be regional tract-specific, particularly in tracts normally supporting processing speed performance. It should be noted that processing speed is a cognitive ability that could be defined as the time it takes a person to do a mental task. It is related to the speed in which a person can understand and react to the information they receive. Processing speed implies a greater ability to easily do simple or previously-learned tasks. This refers to the ability to automatically process information, which means processing information quickly and without doing it consciously.

White-matter alterations that occur in the early stages of psychosis may parallel the course of the illness and differentiate the clinical subtypes.[72] In their recent study, Griffa et al[73] suggested that inter-subject white matter variability in connections vulnerable to psychosis could mediate inter-subject variations in the processing speed. The study revealed an association between white matter-connectivity alterations and clinical stages in schizophrenia. These alterations were spatially diffused in the brain but they converged on a vulnerable subnetwork that spans frontal, inter-hemispheric, cortico-thalamic and striatal circuits. This vulnerable subnetwork includes the main brain-network hubs, namely, the superior frontal and superior parietal cortices, precuneus, insula and thalamus, which are implicated in schizophrenia pathophysiology. Moreover, within the subnetwork, the most significant effects have been found in the left hemisphere, in the superior parietal and frontal cortices, which are associated for developing psychosis,[74] and in the pars opercularis of the inferior frontal gyrus, a language area that, to-

gether with the Heschle's gyrus, has been related to auditory hallucinations[75] (figure 1).

Furthermore, we could suggest that both multiple sclerosis and schizophrenia may use in central nervous system a common pathway of disordered information-processing. Multiple sclerosis results in sensory and motor symptoms and schizophrenia in disordered cognition, perception, and emotion. The major histocompatibility complex (MHC) is responsible for the genetic overlap in both multiple sclerosis and schizophrenia, since a GWAS noted the involvement of similar HLA alleles in multiple sclerosis and schizophrenia.[76] In addition to the well-known demyelinating and dysmyelinating diseases such as multiple sclerosis, neuromyelitis optica, and the leukodystrophies, myelin deficits resulting from altered glial structure/function and or glial/neuronal interactions are seen in human psychiatric disorders[77] and developmental disorders including autism spectral disorder, sensory processing delay disorder, and attention deficit hyperactivity disorder.[78] Numerous studies have demonstrated an interdependent relationship of oligodendrocytes and the axons they myelinate. Moreover, adaptive myelination implies that

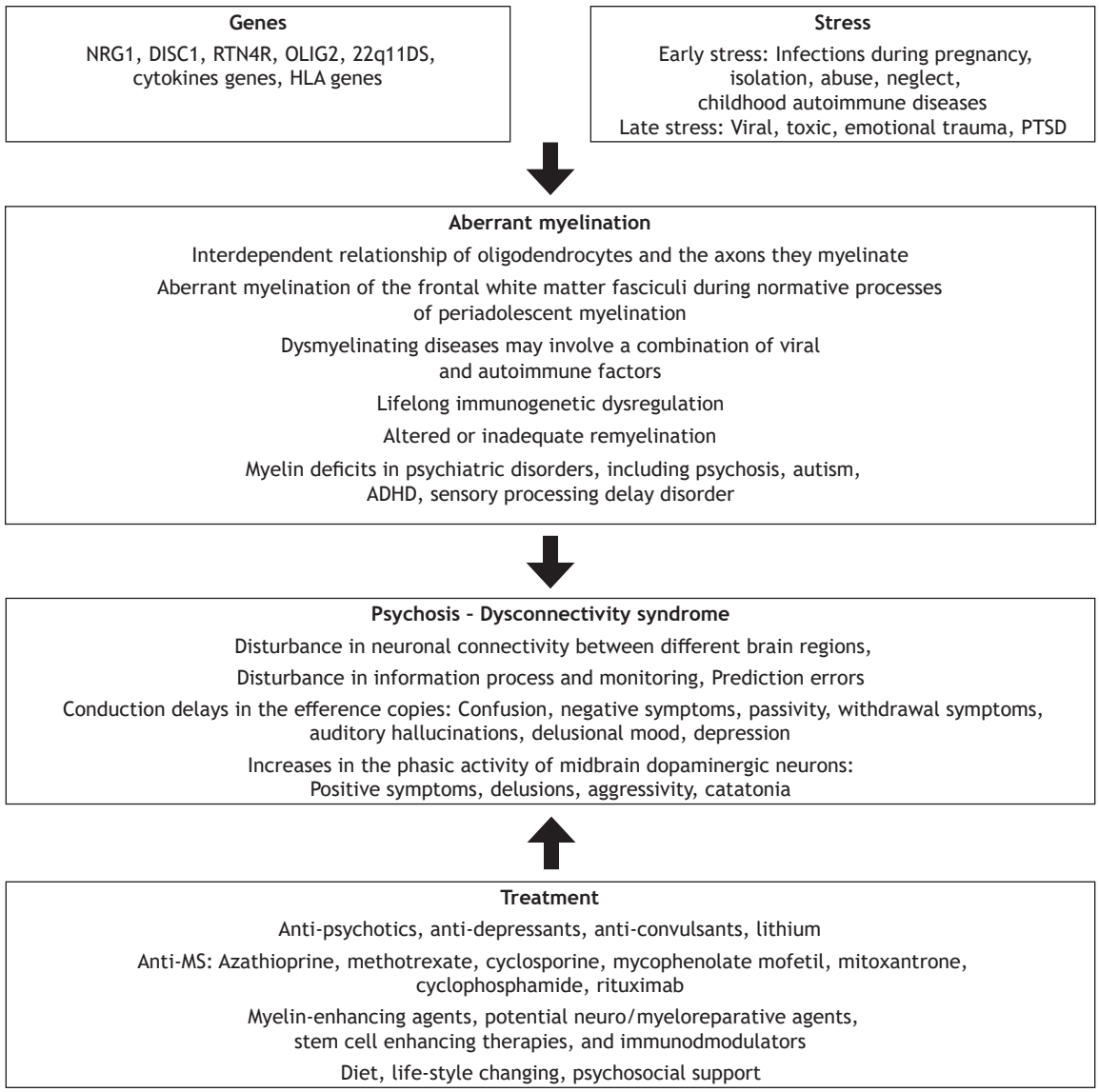

Figure 1. Dysmyelination, brain dysconnectivity, and the resulting information-processing disorder in psychosis.

neuronal electrical excitability modifies myelin plasticity and that myelin plasticity in turn feeds back to modulate neural activity and behavior.[79]

Conclusion

Summarizing, multiple lines of evidence now converge to implicate oligodendroglia and myelin in pathophysiology of schizophrenia. Neuroimaging investigations have linked processing speed to brain anatomical connectivity, and have pointed the role of processing speed among the predictors of longitudinal changes in schizophrenia. The dysmyelination-induced delays in patients with psychosis may cause a discrepancy in sensory feedback mechanisms, which may represent a prediction error and a salient event. A number of myelin gene knockout mice models exhibit schizophrenia-like behaviours, while genomic, especially GWAS, studies identified new schizophrenia loci related to oligodendrocyte genetic polymorphisms. Palaniyappan et al[80] pointed the need to revise our current "deficit-oriented" models of neurobiology of psychosis to the concept of a dynamic process of cortical reorganization, suggesting that early deficits are temporally restricted to the first few years but ameliorate with time, probably owing to a reorganization process. Future studies that employ additional dMRI-techniques for white matter microstructural assessment could better characterize the neurobiological processes that underlie macro-scale connectivity alterations across psychosis stages. Establishing the neural basis of processing speed impairment may inform the treatment and etiology of schizophrenia and interventions that preserve white matter integrity or ameliorate white matter disruption may enhance information-processing and functional outcome in schizophrenia.[72,73,81,82]

Είναι η ψύχωση μια διαταραχή επεξεργασίας της πληροφορίας που σχετίζεται με δυσμυελίνωση;

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Πολλές έρευνες υποστηρίζουν την εμπλοκή της λειτουργίας της μυελίνης και των ολιγοδενδροκυττάρων στη νευρωνική συνδεσιμότητα, η οποία φαίνεται να αποτελεί κεντρικό παθολογικό στοιχείο της σχιζοφρένειας. Νευροαναπτυξιακά μοντέλα που περιλαμβάνουν τη δυσμυελίνωση, υποστηρίζουν τη σχέση της με διάφορα συμπτώματα της σχιζοφρένειας. Μεταθανάτιες έρευνες σε ασθενείς με σχιζοφρένεια αναφέρουν μείωση 14–22% της πυκνότητας και της ποιότητας των ολιγοδενδροκυττάρων. Αρκετά υποψήφια γονίδια που σχετίζονται με τη μυελίνη έχουν συνδεθεί με δυσλειτουργία της μυελίνης και των ολιγοδενδροκυττάρων στην εκδήλωση των νευρωνικών ανωμαλιών της ψύχωσης. Ένας αριθμός μοντέλων γονιδιακής σίγασης της μυελίνης σε ποντίκια υποδεικνύει σχιζοφρενικόμορφες συμπεριφορές, ενώ οι γενομικές έρευνες, ιδιαίτερα οι μελέτες GWAS, έχουν ταυτοποιήσει νέες γονιδιακές θέσεις για τη σχιζοφρένεια, οι οποίες σχετίζονται με γενετικούς πολυμορφισμούς που αφορούν στα ολιγοδενδροκύτταρα. Είναι γνωστό ότι η μυελίνη δρα ως ηλεκτρική μόνωση του επενδεδυμένου νευρώνα, γεγονός που βοηθά στη διατήρηση του εύρους δυναμικού αλλά και στην αύξηση της ταχύτητας αγωγής (conduction velocity) του διατρέχοντος δυναμικού στον νευράξονα. Υπάρχουν συνεχώς αυξανόμενες ενδείξεις σχετικά με την εμπλοκή της δυσμυελίνωσης στον προμετωπιαίο φλοιό την ανάπτυξη νοητικών συμπτωμάτων σε ασθενείς με ψύχωση. Οι νευροαπεικονιστικές έρευνες έχουν συνδέσει την ταχύτητα επεξεργασίας (processing speed) με την ανατομική συνδεσιμότητα (anatomical connectivity) του εγκεφάλου και έχουν αποδείξει τον ρόλο της ως προγνωστικό παράγοντα των κλινικών αλλαγών

στη σχιζοφρένεια. Αυτή η καθυστέρηση ταχύτητας επεξεργασίας στους ασθενείς με ψύχωση μπορεί να προκαλεί ανωμαλία στον μηχανισμό ανατροφοδότησης των αισθήσεων, γεγονός που καταλήγει σε σφάλμα πρόβλεψης (prediction error). Έχει φανεί ότι οι ανωμαλίες της μυελίνης και οι απορρέουσες καθυστερήσεις ταχύτητας επεξεργασίας ποικίλλουν στην πορεία της νόσου της πολλαπλής σκλήρυνσης (multiple sclerosis), και η μορφή αυτών των διακυμάνσεων συνδέεται πιθανόν με τη διακύμανση της συμπτωματολογίας στους ασθενείς με ψύχωση. Να σημειωθεί επίσης ότι το μείζον σύμπλεγμα ιστοσυμβατότητας (MHC) φάνηκε να παρουσιάζει γενετική αλληλεπικάλυψη στην πολλαπλή σκλήρυνση και τη σχιζοφρένεια. Η πολλαπλή σκλήρυνση εκδηλώνεται με αισθητικά και κινητικά συμπτώματα, ενώ η σχιζοφρένεια με νοητικές και συναισθηματικές διαταραχές. Έχοντας όμως υπόψη την αλληλοεξαρτώμενη σχέση μεταξύ ολιγοδενδροκυττάρων και νευρωνικών αξόνων, μπορούμε να υποθέσουμε ότι τόσο η πολλαπλή σκλήρυνση όσο και η σχιζοφρένεια έχουν στο κεντρικό νευρικό σύστημα ως κοινό τύπο διαταραχής την επεξεργασία της πληροφορίας (information processing disorders). Η πρόσφατη έρευνα υποστηρίζει ότι η προσαρμοστική μυελίνωση (adaptive myelination) μπορεί να ομαλοποιήσει τη νευρωνική ηλεκτρική διεγερσιμότητα, η οποία με τη σειρά της τροποποιεί τη μυελινική πλαστικότητα, γεγονός που καταλήγει σε τροποποίηση της νευρωνικής δραστηριότητας και συνεπώς της συμπεριφοράς. Μπορούμε λοιπόν να υποθέσουμε ότι παρεμβάσεις οι οποίες διατηρούν την ακεραιότητα της λευκής ουσίας ή επουλώνουν τις κατά τόπους ή κατά περιόδους διασπάσεις αυτής, θα είναι σε θέση να βελτιώσουν τη δυνατότητα επεξεργασίας της πληροφορίας και επομένως τη λειτουργικότητα στην ψύχωση.

Λέξεις ευρετηρίου: Σχιζοφρένεια, δυσμυελίνωση, επεξεργασία πληροφορίας, ταχύτητα αγωγής, ταχύτητα επεξεργασίας.

References

1. Schultz SH, North SW, Shields CG. Schizophrenia: a review. *Am Fam Physician* 2007, 15:1821–1829, PMID: 17619525
2. Catts VS, Fung SJ, Long LE, Joshi D et al. Rethinking schizophrenia in the context of normal neurodevelopment. *Front Cell Neurosci* 2013, 15, 7:60, doi: 10.3389/fncel.2013.00060
3. Toro P, Schröder J. Neurological Soft Signs in Neuropsychiatric Conditions. Front. *Psychiatry* 2019 doi.10.3389/fpsyt.2018.00736
4. Zhao Q, Li Z, Huang J, Yan C, Dazzan P, Pantelis C et al. Neurological soft signs are not "soft" in brain structure and functional networks: evidence from ALE meta-analysis. *Schizophr Bull* 2014, 40:626–641, doi: 10.1093/schbul/sbt063
5. Kong L, Bachmann S, Thomann PA, Essig M, Schröder J. Neurological soft signs and gray matter changes: a longitudinal analysis in first-episode schizophrenia. *Schizophr Res* 2012 134:27–32, doi: 10.1016/j.schres.2011.09.015
6. Herold C-J, Duval C, Lässer MM, Schröder J. Neurological soft signs (NSS) and cognitive deficits in chronic schizophrenia. *Schiz Res Cog* 2019, 16:17–24, doi: 10.1016/j.scog.2018.12.002
7. Zhang R, He J, Zhu S et al. Myelination deficit in a phencyclidine-induced neurodevelopmental model of schizophrenia. *Brain Res* 2012, 1469:136–143, doi: 10.1016/j.brainres.2012.06.003
8. Bartzokis G. Neuroglialpharmacology: myelination as a shared mechanism of action of psychotropic treatments. *Neuropharmacology* 2012, 62:2137–2153 doi: 10.1016/j.neuropharm. 2012.01.015
9. Kochunov P, Hong LE. Neurodevelopmental and neurodegenerative models of schizophrenia: white matter at the center stage. *Schizophr Bull* 2014, 40:721–728, doi: 10.1093/schbul/sbu070
10. Farrelly L, Focking M, Piontkewitz Y et al. Maternal immune activation induces changes in myelin and metabolic proteins, some of which can be prevented with risperidone in adolescence. *Dev Neurosci* 2015, 37:43–55, doi: 10.1159/000368305
11. Fatemi SH, Folsom TD, Reutiman TJ et al. Abnormal expression of myelination genes and white matter volume abnormalities following prenatal viral influenza infection at E16 in mice. *Schizophr Res* 2009, 112:46–53, doi: 10.1016/j.schres. 2009.04.014
12. Savonenko AV, Melnikova T, Laird FM et al. Alteration of BACE1-dependent NRG1/ErbB4 signaling and schizophrenia-like phenotypes in BACE1-null mice. *Proc Natl Acad Sci USA* 2008, 105: 5585–5590, doi: 10.1073/pnas.0710373105
13. Dries DR, Zhu Y, Brooks MM et al. Loss of nicastrin from oligodendrocytes results in hypomyelination and schizophrenia with compulsive behavior. *J Biol Chem* 2016, 27, 291:11647–11656, doi: 10.1074/jbc.M116.715078
14. Ripke S, Sanders AR, Kendler KS et al. Genome-wide association study identifies five new schizophrenia loci. *Nat Genet* 2011, 43:969–976, doi: 10.1038/ng.940
15. Roy K, Murtie JC, El-Khodor BF et al. Loss of erbB signaling in oligodendrocytes alters myelin and dopaminergic function, a potential mechanism for neuropsychiatric disorders. *Proc Natl Acad Sci USA* 2007, 104:8131–8136, doi: 10.1073/pnas.0702157104
16. Takahashi N, Sakurai T, Davis KL et al. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. *Prog Neurobiol* 2011, 93:13–24, doi: 10.1016/j. pneurobio.2010.09.004

17. Guest PC, Iwata K, Kato TA et al. MK-801 treatment affects glycolysis in oligodendrocytes more than in astrocytes and neuronal cells: insights for schizophrenia. *Front Cell Neurosci* 2015, 12:180, doi: 10.3389/fncel.2015.00180. eCollection
18. Cassoli JS, Iwata K, Steiner J et al. Effect of MK-801 and clozapine on the proteome of cultured human oligodendrocytes. *Front Cell Neurosci* 2016, 10:52, doi: 10.3389/fncel.2016.00052
19. Steiner J, Martins-de-Souza D, Schiltz K et al. Clozapine promotes glycolysis and myelin lipid synthesis in cultured oligodendrocytes. *Front Cell Neurosci* 2014, 8:384, doi: 10.3389/fncel.2014.00384
20. Shallice T. *From neuropsychology to mental structure*. Cambridge University Press, Cambridge, 1988
21. Giotakos O. Poor insight and psychosis. *Psychiatriki* 2017, 28:332–341, doi: 10.22365/jpsych.2017.284.332
22. Frith CD, Friston K, Liddle PF, Frackowiak RSJ. Willed action and the prefrontal cortex in man: A study with PET. *Proc Biol Sci* 1991, 244:241–246, doi.10.1098/rspb.1991.0077
23. Giotakos O. Poor insight in psychosis and meta-representation models. *Dial Clin Neurosc Mental Health* 2018, 1:12–24, doi: 10.26386/obrela.v1i1.5
24. Hyde TM, Ziegler JC, Weinberger DR. Psychiatric disturbances in metachromatic leukodystrophy: Insight into the neurobiology of psychosis. *Arch Neurol* 1992, 49:401–406
25. Petrides M. The mid-dorsolateral prefronto-parietal network and the epoptic process. In: Stuss FT, Knight RT (eds) *Principles of Frontal Lobe Function*. Oxford University Press, New York, 2013:79–89
26. Hoffman RE, McGlashan TH. Parallel distributed processing and tire emergence of schizophrenic symptoms. *Schizophr Bull* 1993, 19:119–140, doi: 10.1093/schbul/19.1.119
27. David AS. Dysmodularity: A neurocognitive model for schizophrenia. *Schizophr Bull* 1994, 20:249–255, doi.10.1093/schbul/20.2.249
28. Crow TJ. Temporal lobe asymmetries as the key to the etiology of schizophrenia. *Schizophr Bull* 1990, 16: 433–443, PMID: 2287933
29. Ford JM, Palzes VA, Roach BJ, Mathalon DH. Did I do that? Abnormal predictive processes in schizophrenia when button pressing to deliver a tone. *Schizophr Bull* 2014, 40:804–812, doi: 10.1093/schbul/sbt072
30. Lalanne L, Van Assche M, Giersch A. When predictive mechanisms go wrong: Disordered visual synchrony thresholds in schizophrenia. *Schizophr Bull* 2012, 38:506–513, doi: 10.1093/schbul/sbq107
31. Schmidt H, McFarland J, Ahmed M, McDonald C, Elliott MA. Low-level temporal coding impairments in psychosis: Preliminary findings and recommendations for further studies. *J Abnorm Psychol* 2011, 120:476–482, doi: 10.1037/a0023387
32. Fogelson N, Litvak V, Peled A, Fernandez-del-Olmo M, Friston K. Functional anatomy of schizophrenia: A dynamic causal modeling study of predictive coding. *Schizophr Res* 2014, 158:204–212, doi: 10.1016/j.schres.2014.06.011
33. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci* 2010, 11:100–113. doi: 10.1038/nrn2774
34. Nagai T, Tada M, Kirihara K, Araki T, Jinde S, Kasai K. Mismatch negativity as a "translatable" brain marker toward early intervention for psychosis: A review. Front. *Psychiatry* 2013, 4:115, doi: 10.3389/fpsyt.2013.00115
35. Kapur S. Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry* 2003, 160:13–23, doi: 10.1176/appi.ajp.160.1.13
36. Schmack K, Gòmez-Carrillo de Castro A, Rothkirch M. Delusions and the role of beliefs in perceptual inference. *J Neurosci* 2013, 33:13701–13712, doi: org/10.1523/JNEUROSCI.1778-13.2013
37. Garrido M.I, Kilner J.M, Stephan K.E, Friston K.J. The mismatch negativity: A review of underlying mechanisms. *Clin Neurophysiol* 2009, 120:453–463, doi: 10.1016/j.clinph.2008.11.029
38. Corlett PR, Taylor J, Wang X et al. Toward a neurobiology of delusions. *Prog Neurobiol* 2010, 92:345–69, doi: 10.1016/j.pneurobio.2010.06.007
39. Franck N, Farrer C, Georgieff N. Defective recognition of one's own actions in patients with schizophrenia. *Am J Psychiatry* 2001, 158:454–459, doi: 10.1176/appi.ajp.158.3.454
40. Frith C. The neural basis of hallucinations and delusions. *C R Biol* 2005, 328:169–175, PMID: 15771003
41. Whitford TJ, Grieve SM, Farrow TF et al. Volumetric white matter abnormalities in first-episode schizophrenia: a longitudinal, tensor-based morphometry study. *Am J Psychiatry* 2007, 164:1082–1089, doi: 10.1176/ajp.2007.164.7.1082
42. Whitford TJ, Ford JM, Mathalon DH, Kubicki M, Shenton ME. Schizophrenia, Myelination, and Delayed Corollary Discharges: A Hypothesis. *Schizophr Bull* 2012, 38:486–494, doi: 10.1093/schbul/sbq105
43. Baumann N, Pham-Dinh D. Biology of Oligodendrocyte and Myelin in the Mammalian Central Nervous System. *Physiologic Rev* 2001, 81:871–927, doi: 10.1152/physrev.2001.81.2.871
44. Waxman S, Swadlow H. The conduction properties of axons in central white matter. *Prog Neurobiol* 1977, 8:297–324, doi: 10.1016/0301-0082(77)90009-0
45. Kesselring J. *Multiple Sclerosis*. Cambridge University Press, New York, NY, 1997
46. Brusa A, Jones S, Plant G. Long-term remyelination after optic neuritis: a 2-year visual evoked potential and psychophysical serial study. *Brain* 2001, 124:468–479, doi:10.1093/brain/124.3.468
47. Matthews P. An update on neuroimaging of multiple sclerosis. *Curr Opin Neurol* 2004, 17:453–458, PMID: 15247542
48. Reiss J, Sam D, Sareen J. Psychosis in multiple sclerosis associated with left temporal lobe lesions on serial MRI scans. *J Clin Neurosci* 2006, 13:282–284, doi: 10.1016/j.jocn.2005.02.017
49. Garver D, Holcomb J, Christensen J. Compromised myelin integrity during psychosis with repair during remission in drug-responding schizophrenia. *Int J Neuropsychopharmacol* 2008, 11:49–61, doi: 10.1017/S1461145707007730
50. Ren Y Wang H, Xiao X. Improving myelin/oligodendrocyte-related dysfunction: a new mechanism of antipsychotics in the treatment of schizophrenia? *Int J Neuropsychoph* 2013, 16:691–700, doi: 10.1017/S1461145712001095
51. Waller R, Dotterer HL, Murray L, Maxwell AM, Hyde LW. White-matter tract abnormalities and antisocial behavior: A systematic review of diffusion tensor imaging studies across development. *Neuroimage Clin* 2017, 14:201–215, doi: 10.1016/j.nicl.2017.01.014. eCollection 2017
52. Vijayakumar N, Bartholomeusz C, Whitford T et al. White matter integrity in individuals at ultra-high risk for psychosis: a systemat-

ic review and discussion of the role of polyunsaturated fatty acids. *BMC Psychiatry* 2016, 11:287, doi: 10.1186/s12888-016-0932-4

53. Peters BD, Machielsen MW, Hoen WP et al. Polyunsaturated fatty acid concentration predicts myelin integrity in early-phase psychosis. *Schizophr Bull* 2013, 39:830–838, doi: 10.1093/schbul/sbs089
54. Bakker G, Caan MW, Schluter RS et al. Distinct white-matter aberrations in 22q11.2 deletion syndrome and patients at ultra-high risk for psychosis. *Psychol Med* 2016, 46:2299–2311, doi: 10.1017/S0033291716000970
55. Fujino J, Takahashi H, Miyata J, Sugihara G, Kubota M, Sasamoto A et al. Impaired empathic abilities and reduced white matter integrity in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2014, 3, 48:117–123, doi: 10.1016/j.pnpbp.2013.09.018
56. Mighdoll MI, Tao R, Kleinman JE, Hyde TM. Myelin, myelin-related disorders, and psychosis. *Schizophr Res* 2015, 161:85–93, doi: 10.1016/j.schres.2014.09.040
57. Davis KL, Stewart DG, Friedman JI et al. White matter changes in schizophrenia: evidence for myelin-related dysfunction. *Arch Gen Psychiatry* 2003, 60:443–456, doi: 10.1001/archpsyc.60.5.443
58. Uranova N, Vostrikov V, Orlovskaya D, Rachmanova V. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res* 2004, 67:269–275, doi: 10.1016/S0920-9964(03)00181-6
59. Uranova N, Vostrikov V, Vikhreva O, Zimina I, Kolomeets N, Orlovskaya D. The role of oligodendrocyte pathology in schizophrenia. *Int J Neuropsychopharmacol* 2007, 10:537–545, doi: 10.1017/S1461145707007626
60. Kubicki M, McCarley R, Westin C et al. A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res* 2007, 41:15–30, doi: 10.1016/j.jpsychires.2005.05.005
61. Hakak Y, Walker J, Li C et al. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proc Natl Acad Sci USA* 2001, 98:4746–4751, doi: 10.1073/pnas.081071198
62. Bartzokis G. Schizophrenia: breakdown in the well-regulated lifelong process of brain development and maturation. *Neuropsychopharmacology* 2002, 27:672–683, doi: 10.1016/S0893-133X(02)00364-0
63. Fields R. White matter in learning, cognition and psychiatric disorders. *Trends Neurosci* 2008, 31:361–370, doi: 10.1016/j.tins.2008.04.001
64. Friston K. Schizophrenia and the disconnection hypothesis. *Acta Psychiatr Scand Suppl* 1999, 395:68–79, PMID: 10225335
65. Walterfang M, Wood S, Velakoulis D, Copolov D, Pantelis C. Diseases of white matter and schizophrenia-like psychosis. *Aust N Z J Psychiatry* 2005, 39:746–756, doi: 10.1080/j.1440-1614.2005.01678.x
66. Samartzis L, Dima D, Fusar-Poli P, Kyriakopoulos M. White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. *J Neuroimaging* 2014, 24:101–110, doi: 10.1111/j.1552-6569.2012.00779.x
67. Lu LH, Zhou XJ, Keedy SK, Reilly JL, Sweeney JA. White matter microstructure in untreated first episode bipolar disorder with psychosis: comparison with schizophrenia. *Bipolar Disord* 2011, 13:604–613, doi: 10.1111/j.1399-5618.2011.00958.x
68. Sánchez P et al. Predictors of longitudinal changes in schizophrenia: the role of processing speed. *J Clin Psychiatry* 2009, 70, 888–896, doi: 10.4088/JCP.08m04294
69. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl* 1998, 172:53–59, PMID: 9764127
70. Karbasforoushan H, Duffy B, Blackford JU, Woodward ND. Processing speed impairment in schizophrenia is mediated by white matter integrity. *Psychol Med* 2015, 45:109–120, doi: 10.1017/S0033291714001111
71. Kochunov P, Coyle TR, Rowland LM, Jahanshad N et al. Association of White Matter With Core Cognitive Deficits in Patients With Schizophrenia. *JAMA Psychiatry* 2017, 74:958–966, doi: 10.1001/jamapsychiatry.2017.2228
72. Bartholomeusz CF, Cropley VL, Wannan C, Di Biase M, McGorry PD, Pantelis C. Structural neuroimaging across early-stage psychosis: Aberrations in neurobiological trajectories and implications for the staging model. *Aust NZJ Psychiatry* 2017, 51:455–476, doi: 10.1177/0004867416670522
73. Griffa A, Baumann PS, Klauser P, Mullier E et al. Brain connectivity alterations in early psychosis: from clinical to neuroimaging staging. *Transl Psychiatry* 2019, 9:62 , doi: 10.1038/s41398-019-0392-y
74. Peters BD, Karlsgodt KH. White matter development in the early stages of psychosis. *Schizophr Res* 2014, 161:61–69, doi: 10.1016/j.schres.2014.05.021
75. Curcic-Blake B et al. Interaction of language, auditory and memory brain networks in auditory verbal hallucinations. *Prog Neurobiol* 2017, 148:1–20, doi: 10.1016/j.pneurobio.2016.11.002
76. Bush WS, Moore JH. Genome-wide association studies. *PLoS Comput Biol* 2012, 8:e1002822 doi: 10.1371/journal.pcbi.1002822
77. Haroutunian V, Katsel P, Roussos P, Davis KL, Altshuler LL, Bartzokis G. Myelination, oligodendrocytes, and serious mental illness. *Glia* 2014, 62:1856–1877, doi: 10.1002/glia.22716
78. Li Q, Sun J, Guo L, Zang Y, Feng Z, Huang X et al. Increased fractional anisotropy in white matter of the right frontal region in children with attention-deficit/hyperactivity disorder: a diffusion tensor imaging study. *Neuroendocrinol Lett* 2010, 31:747–753, PMID: 21196923
79. Bercury KK, Macklin WB. Dynamics and mechanisms of CNS myelination. *Developmental Cell* 2015, 32:447–458, doi 10.1016/j.devcel.2015.01.016
80. Palaniyappan L, Das T, Dempster K. The neurobiology of transition to psychosis: clearing the cache. *J Psychiatry Neurosci* 2017, 42:294–299, doi: 10.1503/jpn.170137
81. Palaniyappan L, Al-Radaideh A, Mougin O, Das T. Aberrant myelination of the cingulum and Schneiderian delusions in schizophrenia: a 7T magnetization transfer study. *Psycholog Med* 2019, 49:1890–189, doi: https://doi.org/10.1017/S0033291718002647
82. Giotakos O. Is psychosis, at least in part, an immune-related dysmyelination disease? *Dial Clin Neurosc Mental Health* 2019, 2:116–129, doi: 10.26386/obrela.v2i2.118

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