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The right intervention at the right time - Focusing on the timing of autoimmunity and psychosis initiation

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Abstract

Reviewing the clinical and pathophysiological similarities between dysmyelinating diseases and psychosis, we may suggest that the dysconnectivity syndrome of psychosis represents the outcome of a multifaceted dysmyelinating disorder, which is based on a lifelong immunogenetic dysregulation. Issues of 'timing' and 'neuroplasticity' suggest several considerations for therapeutic interventions. The most important principle that emerges from this developmental issue is: 'the right intervention, at the right time'. This means that the intervention should ideally be done at the beginning of the autoimmune processes that affect the neurons. Finding appropriate immunological biomarkers would be the most appropriate effort to early intervention and illness modification of mental disorders. Any immunological or anti-inflammatory agent should therefore be administered at a time when psychopathology is not yet evident or has perhaps given minimal signs. Therapeutic trials can range from anti-inflammatory or antioxidant agents to long-term gene expression modification therapies. Also, early intervention in known autoimmune diseases that are closely related to the development of mental illnesses, such as thyroid diseases, is considered to yield the expected results. The 'temporal dimension', including items such as time, timing, perception of time and timing of perception, could be an important conceptual, research and therapeutic target for mental illnesses, in the future.

Keywords

timing, psychosis, psychiatry, autoimmunity, dys-myelination

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Psychosis is not just in the brain

People with psychotic disorders have disturbances in several systems, beyond the central nervous system (CNS). Studies in patients with first episode psychosis (FEP) have shown dysfunction in the cardiometabolic, immune, and hypothalamic-pituitary-adrenal systems. This suggests that psychotic disorders involve multiple systems from their onset. However, it is unclear how strong the evidence is for abnormalities in these systems, how the alterations compare to CNS abnormalities seen in the disorder, or how they relate to symptoms. To answer these questions, Pillinger et al (2019) **[1]** performed a meta-review using regional markers and compared the findings with representative CNS abnormalities in psychosis. To summarize effect sizes in CNS dysfunctions, the authors focused on parameters of brain structure, neurophysiology and neurochemistry, while for non-CNS dysfunctions they focused on cardiometabolic, immune and hypothalamic-pituitary-adrenal systems, in FEP cases. They statistically compared the summary effect size for total CNS lesions and total non-CNS lesions, as well as for each organ system separately. They also examined how non-CNS lesions correlate with CNS lesions and with psychopathological symptoms.

Data extracted from 165 studies with a total sample of 13,440 first-episode psychotic subjects. Patients showed alterations in (a) immunological parameters, (b) cardiometabolic parameters, (c) HPA parameters, (d) brain structure, (e) neurophysiology, and (f) neurochemistry. Grouping of non-CNS organ systems yielded an effect size for overall non-CNS lesions in patients, that was not significantly different from the overall effect size for CNS lesions. However, the summary effect size for immunological alterations was significantly larger than that for structural and neurochemical brain alterations, whereas the summary effect size for cardiometabolic alterations was significantly smaller than neurochemical, neurophysiological and structural brain alterations. Some limited evidence was found for non-CNS lesions associated with CNS changes, but also symptoms, at first onset psychosis. Findings show that there are consistent alterations in non-CNS systems in psychosis, and that these are generally similar in magnitude to the range of CNS alterations **[1].**

Psychosis has an important autoimmune component

Celiac disease, Graves' disease, systemic lupus erythematosus, multiple sclerosis, autoimmune hepatitis, and psoriasis are higher in psychotic patients, while in patients with autoimmune conditions, the risk of developing schizophrenia increases linearly with the number of severe infectious episodes. Epidemiological and genetic correlations raise the possibility that autoimmune mechanisms may underlie mental illnesses, including psychosis, which may offer potentially new therapeutic approaches. Several immune systems, including the major histocompatibility complex and the B-cell markers CD19 and CD20 show significant associations with schizophrenia. Emerging evidence suggests their role in neurodevelopment, in addition to classical immune pathways. The biology of lymphocytes is increasingly being examined. Some reports note increased levels of peripheral CD19+ and decreased numbers of CD3+ lymphocytes, with altered CD4:CD8 ratios in acute psychosis, while postmortem studies have identified infiltration of CD3+ and CD20+ lymphocytes in brain regions of functional relevance to psychosis. Moreover, significantly higher percentages of thyroperoxidase antibodies have been found in daughters of patients with bipolar disorder, compared to healthy female controls, while children of bipolar parents suffer more frequently from autoimmune thyroiditis, regardless of the development of psychiatric disorders in them **[2]**.

Examples of autoimmune encephalitis with antibodies against NMDAR or GABAßR receptors provide a model of disease development, linking adaptive autoimmunity to psychopathology. NSAbs bind to extracellular signaling molecules such as NMDA and GABA receptors, and this interaction can cause dysfunction of circuits, leading to psychosis and other neurological features, in patients with autoimmune encephalitis. Detection of these cases is critical, as autoimmune encephalitis improves with widely available immunotherapies. At the same time, the frequency and significance of these antibodies in individuals with isolated psychotic disorders is an area of emerging scientific and clinical interest. Collaborative efforts are needed to achieve larger sample sizes and conduct placebo-controlled randomized clinical trials to determine the contribution of autoimmunity to psychosis **[3]**.

Several lines of evidence point to a predisposition towards a pro-inflammatory state in the brain in schizophrenia, and anti-inflammatory drugs could possibly counteract this predisposition. The study by Çakici et al (2019) **[4]** investigated the efficacy of agents with anti-inflammatory activity for schizophrenia symptoms, tested in randomized controlled trials (RCTs). They meta-analysed 56 studies that provided information on the effectiveness of the following components on symptom severity: aspirin, bexarotene, celecoxib, davunetide, dextromethorphan, estrogens, fatty acids, melatonin, minocycline, N-acetylcysteine (NAC), pioglitazone, piracetam, pregnenolone, statins, varenicline, and withania somnifera extract. Aspirin, estrogen, minocycline and NAC were found to be effective agents. The authors observed greater beneficial effects on symptom severity during the first episode of psychosis or during the early phase of schizophrenia.

Dysmyelination as an immunological parameter of information timing disorder

Much research supports the involvement of myelin and oligodendrocyte function in neuronal connectivity, which appears to be a central pathological component of schizophrenia. Neurodevelopmental models involving dysmyelination support their association with various symptoms of schizophrenia. Postmortem studies in patients with schizophrenia report a 14–22% reduction in oligodendrocyte density and quality. There is a mixed picture of peripheral pro- and anti-inflammatory

changes in a large proportion of patients with schizophrenia, while some cytokines, such as IL-12, IFN-γ, TNF-α, and soluble IL-2 receptor, may be trait markers for schizophrenia. Several candidate myelin-related genes have been linked to myelin and oligodendrocyte dysfunction in the manifestation of the neuronal abnormalities of psychosis. Several myelin gene silencing mouse models indicate schizophrenic behaviors, while genomic investigations, particularly GWAS studies, have identified novel schizophrenia gene loci that are associated with genetic polymorphisms involving oligodendrocytes **[2]**.

It is known that myelin acts as electrical insulation of the encased neuron, which helps to maintain the potential range but also to increase the conduction velocity of the current potential in the axon. There is increasing evidence regarding the involvement of dysmyelination in the prefrontal cortex and the development of mental symptoms in patients with psychosis. Neuroimaging studies have linked processing speed with brain anatomical connectivity and have demonstrated its role as a predictor of clinical changes in schizophrenia. This delayed processing speed in patients with psychosis may cause an abnormality in the sensory and information feedback mechanism, which results in prediction error. All these processes may be involved in the development of temporal disturbances seen in the mentally ill, and especially in patients with psychosis.

Myelin abnormalities and resulting processing speed delays have been shown to vary over the course of multiple sclerosis (MS), and the pattern of these variations is likely associated with variation in symptomatology in patients with psychosis. Demyelinating diseases, such as multiple sclerosis, are characterized by a wide spectrum of immune cell involvement that destroys myelin, myelin-producing oligodendrocytes, and the nerve itself. Also of note is that the major histocompatibility complex (MHC) has been shown to exhibit genetic overlaps in multiple sclerosis and schizophrenia. Multiple sclerosis manifests itself with sensory and motor symptoms, while schizophrenia with mental and emotional disorders. But bearing in mind the interdependent relationship between oligodendrocytes, immune cells and nerve cells, we can assume that both multiple sclerosis and schizophrenia have an information processing disordering in the central nervous system, as a common type of disorder. In the case of multiple sclerosis, the infiltration of immune cells mainly affects the myelin, resulting in motor and sensory symptoms, while in the case of schizophrenia, it mainly affects the receptors, resulting in cognitive and emotional symptoms **[2]**.

Disruption in myelination and delays in information processing caused by dysmyelination can produce psychotic phenotypes similar to schizophrenia. Difficulties in distinguishing between relevant and irrelevant information, causes patients to assign the wrong salience to events and possibly results in delusional beliefs. Reviewing the clinical and pathophysiological similarities between demyelinating or dysmyelinating diseases and psychosis, we can consider that the 'disconnection syndrome' of psychosis represents the phenomenological and behavioral outcome of a multifaceted dysmyelinating disorder, based on a lifelong process immunogenetic dysregulation. Recent research suggests that adaptive myelination can normalize neuronal electrical excitability, which in turn modifies myelin plasticity, resulting in modification of neuronal activity and thus behavior. Different myelin enhancing therapies would be potential candidates for large-scale clinical trials in schizophrenia, such as n-3 PUFA, minocycline, clemastine, polyphenols, potential neuro/myeloreparative agents such as sulfasalazine, nano-curcumin, stem cell enhancing therapies, such as Gli-1 inhibitors, and immunomodulators, such as fingolimod. We can therefore assume that interventions that preserve the integrity of the white matter or heal its local or periodic breakdowns, will be able to improve the ability to process information and therefore functionality in psychosis **[5, 6].**

The right intervention, at the right time

Since 1899, Ramon y Cajal had formulated the 'synaptic plasticity hypothesis', which argued that the strength of the synaptic connection is not stable but can be modified by neuronal activity. Emerging research on neuroplasticity processes in psychotic spectrum disorders fills important gaps in models for pathophysiology and opens important perspectives for treatment. In a dialectical review, Vinogradov et al (2023) **[7]** highlighted the changes in spike timing-dependent neuroplasticity and Hebbian-like plasticity that occur during adolescence, the critical period for the development of the prefrontal system. How can early detection of neuroplasticity disorders help in the early diagnosis and treatment of mental disorders? How is the inappropriate 'timing of plasticity' of the brain, associated with the symptoms of 'time deficiency' of the mentally ill, such as difficulties in 'timing of perception' or 'perception of time'? **[8].**

Issues of 'timing' and 'neuroplasticity' suggest several considerations for therapeutic interventions. The most important principle that emerges from this developmental theme is: "the right intervention, at the right time". But this means that the intervention should ideally be done at perhaps an unsuspected time, i.e. at the beginning of the autoimmune processes that affect neurons. Any immunological or anti-inflammatory agent should therefore be administered at a time when psychopathology is not yet evident or has perhaps given minimal signs. Finding or developing appropriate immunological biomarkers would be perhaps the most appropriate effort to early intervention in mental illness. Interventions may range from the use of anti-inflammatory and antioxidant agents to long-term gene expression modification therapies. Also, early intervention in known autoimmune diseases, closely related to the development of mental illnesses, such as thyroid diseases, is expected to yield the expected results **[9]**.

"Life is about timing", said the famous track and field champion Carl Lewis. "Timing is everything", also emphasizes the Swedish endocrinologist Lernmark (2021) **[10],** in his article on the etiology and diagnosis of type 1 diabetes, stating: "Not even the precursor stage of the autoimmune disease of the pancreatic islets, nor does the clinical onset of type 1 diabetes tell us much about etiology. Conversely, islet autoantibody

that appears first and persists, signals the diagnosis of autoimmune islet disease (AID). Many islet autoantibodies without (stage 1) or with impaired glucose tolerance (stage 2) or with symptoms (stage 3) define the pathogenesis of clinical type 1 diabetes. But the etiology concerns the timing of events that occur before the first appearing pancreatic islet autoantibody".

In closing, remodeling the brain function and mental disorders on a phenomenological basis **[11],** can help to reconceptualize, to rethink, or to rename, some main clinical and pathogenetic domains **[12,13],** with the inclusion of the time/timing parameter. For example, the standardized clinical and neuroimaging measures will help to compare different factors, such as immunological comorbidity, brain connectivity, and age (time/timing) of the traumatic events, to find whether there is a specific brain area, brain function, or a 'critical period' (timing) for the childhood emotional trauma **[14].** Moreover, note that any symptom of a mental illness, such as anxiety, grief, trauma, hallucinations, suspicion, agitation, etc., can be experienced by any person in the general population. What leads clinicians to diagnose a mental illness is not the 'presence' but the 'duration' of these symptoms. The 'temporal dimension', including items such as time, timing, perception of time and timing of perception, could be an important conceptual, research and therapeutic target for mental illnesses, in the future.

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