Rethinking Mental Health

TOWARDS A BETTER CHARACTERISATION OF SCHIZOPHRENIA

In the complex world of psychiatric disorders, few terms are as contentious as 'schizophrenia'. With symptoms that span delusions, hallucinations, disorganised behaviour, and emotional withdrawal, schizophrenia challenges both medical understanding and societal perception. Diagnosed in 20 million people worldwide, it is a term laden with stigma, fear, and misunderstanding.

In 2015, Moncrieff and Middleton shook the psychiatric community with a paper rejecting the very concept of schizophrenia as a disease, urging a radical shift in how we define and treat this intricate condition. Criticising modern reliance on medical frameworks, they advocated for abandoning the current terminology in favour of more generic terms, arguing that such a shift could foster more transparent and collaborative approaches in healthcare and improve the relationship between caregivers and service users.

Schizophrenia: A Disabling Disorder with Broad Impact

Despite its relatively low median population prevalence, schizophrenia is one of the most complex and heterogeneous psychiatric disorders. Its deteriorating course has dramatic individual and societal repercussions, making it not only a disabling mental health disorder but also a leading cause of early mortality. Individuals with schizophrenia are estimated to die 12 to 15 years earlier than the average population, primarily due to suicide or physical causes stemming from decreased access to medical care or increased routine risk factors. The onset of symptoms occurs during

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adolescence and early adulthood, a period characterised by extensive neuroanatomical, functional, and chemical reorganisation in the brain. These symptoms lead to several impairments in cognitive, perceptual, emotional, and behavioural processes. Diagnosis relies on abnormalities in one or more domains defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5): delusions, hallucinations, disorganised thinking (speech), disorganised or abnormal motor behaviour, and negative symptoms.

The Debate Over Schizophrenia: Stigma, and Misunderstanding

Although many antipsychiatrists and critical psychiatry movements viewed the concept of mental illness as a form of control and stigmatisation, the disturbing manifestations of schizophrenia were never denied. The main criticism against schizophrenia treatment was turned toward the lack of biological evidence to justify the use of medical terminology. The "schizophrenic" label itself is indeed increasingly contested by patients, family members, and clinicians. Interviews have shown that the term is perceived as harmful, stigmatising, and a source of social exclusion, loss of self-esteem for some, and anger and renunciation for others. Furthermore, it has been pointed out that the sole interpretation of schizophrenia as a biological illness and a profound lack of understanding about the condition reduced patients' hope for any change or improvements, increasing their passivity

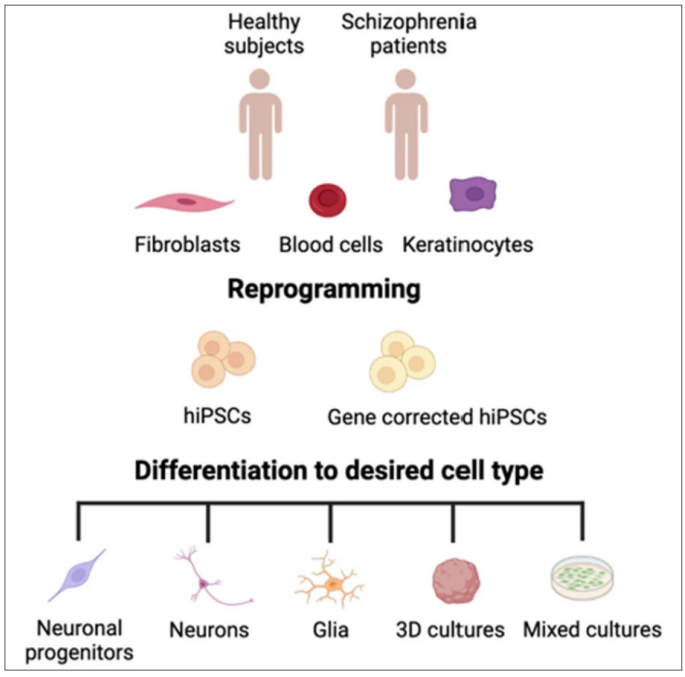
in the treatment process and their reliance on medication.

A better characterisation of schizophrenia and careful use of medical vocabulary seem consequently paramount to improve the communication and the overall perception of schizophrenia among patients, caregivers, and, more generally, in society. However, it seems equally important to highlight that any implementation of new terminology will be ineffective if it is only semantic and not accompanied by legislative and professional changes. Moreover, implementing new and different terms could convey less information about the disorder and be a potential source of confusion among professionals during diagnostic communication, with possible repercussions for the general public. Consequently, any new terminology should be implemented cautiously without disavowing years of research in a well-documented field supported by empirical data.

Decoding Schizophrenia: The Genetic Puzzle

Although twin studies estimate heritability between 80 and 90%, the lack of definitive evidence regarding schizophrenia's genetic basis remains a limitation. Genome-wide association studies have shown that schizophrenia is polygenic, with several genetic variants contributing to only a fraction of the global phenotype and risk. With the first symptoms manifesting in young adulthood, prodromal symptoms that often precede acute psychosis are of particular interest in current research. Studies comparing pre-illness symptomatology in genetically predisposed individuals (i.e., high-risk profile) have shown that affective (i.e., mood disorders) and perceptual (i.e., how to perceive and interpret sensory information) disorders are noticeable before any behavioural changes. Cognitive impairment and attentional deficits could consequently also be helpful as initial steps to detect schizophrenia sooner and prompt early intervention.

Understanding the genetic contributions to schizophrenia provides valuable insights into the hereditary risks and predispositions associated with the disorder. However, genetic findings alone do not account for the full complexity of schizophrenia's manifestation. To gain a deeper understanding, it is essential to explore how these genetic factors translate into observable changes in brain structure and function. This is where neurobiological research plays a crucial role, revealing the pathophysiological changes that occur in the brains of individuals with schizophrenia. By integrating genetic predispositions with neuroanatomical and biochemical abnormalities, researchers can form a more comprehensive picture of how schizophrenia develops and progresses at the cellular and systemic levels.



An overview of human induced pluripotent stem cells (hiPSCs) as a tool to investigate schizophrenia in vitro models. Fibroblasts, blood cells or keratinocytes from control subjects and/or schizophrenia patients are collected and reprogrammed to hiPSCs—some of which may be gene corrected and used as isogenic controls. The established hiPSCs can then be differentiated into the cells of interest, for example, neuronal progenitor cells (NPCs), neurons, and glia or used for 3D or mixed cultures to model schizophrenia in vitro.

Schizophrenia and the Brain: Pathophysiology and Structural Insights

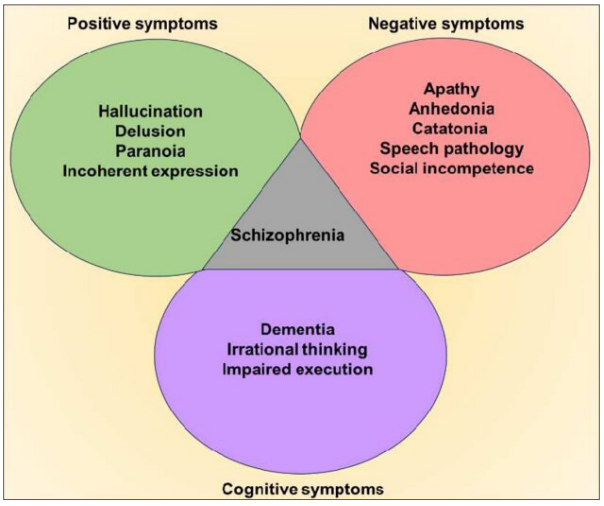
Schizophrenia presents multiple neuropathological abnormalities observable at both macroscopic and microscopic levels. Although not specific to cerebral dysfunction, these early observations highlight the importance of examining the brain for abnormal characteristics. For instance, structural magnetic resonance imaging (MRI) studies have

described one of the first discrepancies observed in schizophrenia patients: the enlargement of cerebral ventricles. The cerebral ventricles are fluid-filled spaces within the brain that contain cerebrospinal fluid (CSF), which helps cushion and protect the brain. In schizophrenia, enlargement of these ventricles is often associated with brain tissue loss or atrophy, pointing to an underlying cognitive dysfunction and possibly a neurodevelopmental origin of the disorder. While it is a common finding, it is not present in all schizophrenia patients, and its exact role in the disease is still being investigated.

Positron emission tomography (PET) studies, a specialised imaging technique used in medical and research settings to observe the metabolic processes in the brain, have been focusing on testing the dopamine hypothesis. The dopamine hypothesis is one of the most prominent theories proposed to explain the neurochemical basis of schizophrenia. It suggests that abnormal dopamine activity in the brain plays a central role in the development of the disorder, particularly in relation to the positive symptoms of schizophrenia, such as hallucinations and delusions, and provides a useful framework for understanding the role of dopamine dysregulation in the disorder. Studies have notably shown an increase in dopamine synthesis, dopamine release, and resting-state synaptic dopamine concentrations, possibly due to a reduced number of GABAergic interneurons providing tonic inhibitory control. This hyperdopaminergic activity suggests abnormal hippocampus activity and correlates with the onset of psychosis. Consequently, these neurochemical findings provide a logical link to the fact that current pharmacological treatments target dopamine receptors to block them, thereby reducing the salience of environmental stimuli and psychotic symptoms.

Finally, the recent use of schizophrenia iPSC-derived neurons in research relying on disease modelling helped circumvent many limitations inherent in animal models, biopsy tissues, post-mortem samples, and cell lines. Thanks to these studies, several structural and functional alterations have been highlighted, such as a decrease in connectivity, synapse number, spine density, and an altered expression of glutamate receptors. Defective neurons also exhibited perturbations in the mitochondrial network and structure, explaining some neuroprogressive changes in schizophrenia and potentially playing a role in prodromal negative symptoms. Taken together, these alterations, which lead to a dysregulation of synaptic pruning and deficits in neuronal circuitry, lead to severe behavioural impairment outcomes.

From this perspective, the current diagnosis of schizophrenia, based on clinical criteria, seems legitimate, given that its pathophysiology exhibits several abnormalities. However, some biological discrepancies between control groups and schizophrenia patients, such as decreased brain volume and lower grey matter volume in individuals with schizophrenia, need careful consideration. As a matter of fact, they could be explained by prolonged exposure to antipsychotic drugs, the initial treatment recommended for the symptoms of an acute schizophrenic episode, or even by differences in intelligence quotient



Clinical symptoms of schizophrenia, a brief summary of the main symptom categories.

and may consequently not be specific to schizophrenia.

Challenges in Treatment: Gaps in Addressing Schizophrenia

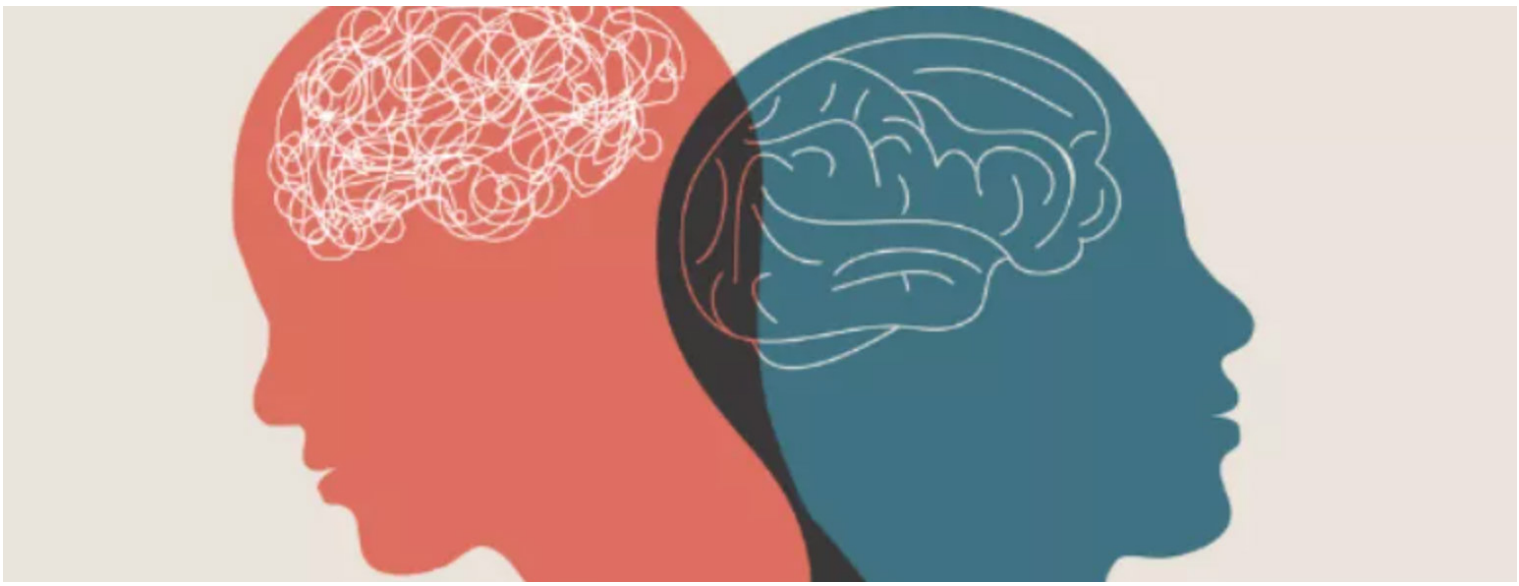
Turning such heterogeneous findings into healthcare practice remains complex. As for now, treatments are predominantly based on observable signs and symptoms rather than on aetiologic and pathogenetic mechanisms. Treatments involving second-generation antipsychotic drugs seem effective in treating positive symptoms but do not address negative and cognitive symptoms. Many patients reported that, while effective for certain symptoms, their treatments often leave them feeling detached or emotionally blunted. Indeed, pharmacological treatments are not harmless and tend to induce a high incidence of metabolic side effects, such as weight gain, increased triglycerides, and cholesterol. A 2019 survey found that over 50% of patients on antipsychotic medication experienced these significant side effects, including cognitive dulling. For these individuals, the promise of improved mental clarity often comes at a significant personal cost. Ultimately, a substantial proportion of patients remain unfortunately symptomatic despite new medications, often leading to unnecessary antipsychotic polypharmacy.

Towards a Holistic Approach: Integrating Models in Schizophrenia Treatment

The ongoing debate over the DSM-5 classifications continues to raise profound interrogations: Should schizophrenia be defined as a distinct psychiatric disorder or as part of a broader spectrum of mental health conditions? The answer could fundamentally reshape clinical practice, influencing everything from diagnostic protocols to treatment funding.

On the one hand, several symptoms of schizophrenia, such as psychosis, overlap with other psychiatric disorders, suggesting a shared underlying aetiology and making diagnosis extremely challenging. On the other hand, experiences associated with schizophrenia manifestations, such as paranoid delusional thinking and auditory hallucinations, are also observed in attenuated and transient forms in healthy people. Although examining psychosis as a continuum is debated, the idea that psychotic experiences occur in the general population could, therefore, undermine the concept of diagnostic categories and slowly transform the future of schizophrenia understanding and practice.

The cognitive dimension and intellectual deterioration involved in disturbed social cognition are unfortunately still often excluded from modern clinical discussions of schizophrenia, even though varied initiatives could contribute to improving patients' ability to understand and interact with the social world. It is urgent to propose community-based case management frameworks involving multidisciplinary teams of mental health professionals engaging with patients, both inside and outside the hospital. Additionally, involving individuals with schizophrenia from the earlier stages



of diagnosis can provide them with a genuine sense of personal choice and acceptance and facilitate their recovery.

Implementing such resources requires consequently reconceptualising the concept of schizophrenia, focusing on non-genetic factors, such as environmental risk factors, without denying the clinical symptoms. Instead, a mixed model should emphasise cognitive-behavioural therapies for patients with drug-resistant symptoms, which could reduce the stress and negative effects of psychotic symptoms. This could involve combining medication with tailored cognitive-behavioral therapies, social skills training, and community support programs. For instance, a patient struggling with paranoid delusions might receive both antipsychotic medication and therapy aimed at addressing cognitive distortions while also participating in a community group to rebuild social connections.

The Future of Schizophrenia Research: A Call for Biopsychosocial Models

Almost ten years after the Moncrieff and Middleton paper, despite significant findings in the pathophysiology of schizophrenia that explain some of its symptoms, there is still no definitive answer regarding its origin, and no treatment has shown consistent efficiency. Is schizophrenia a biological illness, a psychological dysfunction, or a social construct? The answer isn't clear-cut, which is precisely why its classification remains so challenging. Sophisticated biopsychosocial models are required to drive the future of schizophrenia research and practice, with neurobiological findings translated into improved healthcare practice. A sophisticated biopsychosocial model would integrate biological, psychological, and social factors into a comprehensive treatment plan. As we continue to question the very foundation of schizophrenia's definition, one thing remains certain: listening to the voices of those affected is no longer optional — it is essential. Only by embracing their perspectives can we hope to transform understanding and practice for the better. ■

This article was based on the review proposed by Moncrieff and Middleton.

→ Moncrieff, J., & Middleton, H. (2015). Schizophrenia: a critical psychiatry perspective. Current opinion in psychiatry, 28(3), 264–268. https://doi.org/10.1097/YCO.0000000000000151

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