History, aetiology, and symptomatology of schizophrenia

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Abstract

Schizophrenia is a severe, chronic, often disabling mental illness with onset characteristically in early adulthood. This article reviews the historical concepts of schizophrenia by Kraepelin and Bleuler, and discusses recent developments in the aetiology of schizophrenia, with an emphasis on the interplay between biological, psychological, and social factors. Genetic factors play an important role in the aetiology, as they 'programme' the early development of the brain's structure, including the neurotransmitter receptor systems. According to the stress–vulnerability model, environmental stress and high 'expressed emotion' can precipitate the onset as well as influence the course and outcome of the illness. Cannabis abuse has a significant impact on the risk of schizophrenia, particularly in individuals with biological vulnerability to develop the illness. Clinically, patients with schizophrenia present with symptoms comprising positive (first-rank) and negative symptoms.

Keywords aetiology; biopsychosocial model; history; negative symptoms; positive symptoms; schizophrenia

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What's new?

- The biological factors involved in the aetiology of schizophrenia have been updated
- Evidence of 'social cognition' impairment in schizophrenia has been included
- The relationship between biological vulnerability and environmental factors (e.g. stress) in the aetiology of schizophrenia is discussed using the stress–vulnerability model

It has long been established that there is an illness with acute episodes characterized by delusions (unshakeable beliefs held on the basis of inadequate evidence) and hallucinations (false perceptions) that affects young adults and often runs a chronically deteriorating course that impacts on normal functioning. This article outlines how such an illness (or syndrome) has come to be called 'schizophrenia', before moving on to discuss its aetiology and describe its symptoms.

History of the concept of schizophrenia

Although 'schizophrenia' is not new, the idea that specific disordered experiences and behaviours (which begin in early adulthood and lead to progressive deterioration) are best conceptualized as a discrete 'illness' is relatively modern. In his work of 1860, *Traité des Maladies Mentales*, Morel used the phrase 'démence-précoce' to refer to an early-onset deteriorating state of bizarre behaviour and abnormal mental function. His notion, essentially of mental degeneration with acute episodes of 'madness' that begins in the young, is central in subsequent accounts of what we now call 'schizophrenia'.

Emil Kraepelin initially used the term 'dementia praecox' to refer to the 'sub-acute development of a peculiar simple condition of mental weakness occurring at a youthful age' and placed it alongside 'catatonia' (a term introduced by Kahlbaum in 1874) and 'dementia paranoides' in his *Lehrbuch der Psychiatrie*. Subsequently, Kraepelin unified these distinct conditions by considering them to represent different expressions of a single, core disorder: dementia praecox.[1] Critically, Kraepelin distinguished dementia praecox from manic–depressive psychosis, a distinction that has been most influential in the development of modern diagnostic classifications.

It was not until 1911 that Bleuler effectively renamed dementia praecox as 'schizophrenia'. Whereas previous terminology had been essentially descriptive (i.e. dementia praecox as a deteriorating illness with early onset), Bleuler's use of 'schizophrenia' was intended to reflect his ideas of causation. Specifically, Bleuler thought that schizophrenia resulted from splitting of the psychic functions (particularly the cognitive and the affective; see Symptomatology, below). The sense of splitting was not (as the term has sometimes been taken to imply) split into two, but more a shattering of the psyche so that its functions cease to be coherent and coordinated. In this regard, it is critical to distinguish

this (historically correct) derivation of 'schizophrenia' from the popular use of 'schizophrenic' as referring to 'split personality' or multiple personality disorder. Such a description of schizophrenia is both historically incorrect and further stigmatizes patients with schizophrenia.

Recently, the Kraepelinian dichotomy of schizophrenia (dementia praecox) versus bipolar disorder (manic–depressive psychosis) has been challenged, based upon increasing evidence for co-aggregation of these conditions within families and upon the identification of genes that appear to have associations across the diagnostic divide, such as *neuregulin-1* (*NRG1*), G72/G30 (D- amino acid oxidase activator (*DAOA*) locus).[2,3] However, in this contribution, the authors continue (for the time being) to regard schizophrenia as critically distinct from affective psychoses.

Aetiology

The term schizophrenia covers a broad range of clinical symptoms. Even those cases that fulfil strict diagnostic criteria, including 'first-rank' symptoms (see below) and core clinical features, are likely to result from diverse aetiological factors. The relative influence of any one aetiological factor may vary from patient to patient. The aetiology of schizophrenia can be divided into three categorical dimensions that make up the 'biopsychosocial model':

- biological
- psychological
- social.

In clinical settings, we are also concerned with patterns of relapse and remission over time. Within the time domain, there are predisposing, precipitating, and perpetuating factors (the 'three Ps'). Table 1 shows an example of how the biopsychosocial model and the three Ps can be combined.

Biological factors

Genetics

The lifetime risk of developing schizophrenia in the general population is approximately 1%. Family studies have shown that first-degree relatives of individuals with schizophrenia have a 2–9% greater risk themselves of developing schizophrenia compared with relatives of controls.[4] Twin studies report that monozygotic (MZ) twin concordance rates for developing schizophrenia are higher than for dizygotic (DZ) twins (41–79% versus 0–17% respectively).[4] Results from adoption studies are consistent in showing that biological relatives of adoptees with schizophrenia have a higher risk of the illness than adoptive relatives. This, together with the observation that the adoptive relatives have a similar risk for developing schizophrenia to that of the general population,[4] demonstrates the predominance of genetic factors over environmental factors in contributing to the risk of schizophrenia.

Recently, associations between schizophrenia and specific genes have been demonstrated, and replicated, in linkage and association studies.[5–7] The genes most implicated are *neuregulin-1*, *dysbindin*, catechol-*O*-methyltransferase (*COMT*), *DAOA* (G72/G30), and *DISC1*. A detailed account of molecular genetics is beyond the scope of this article. However, these genes may contribute to a range of pathogenic effects, including neuronal development, neuronal plasticity, and signal transduction.[6] For example, neuregulin is present in glutamatergic synaptic vesicles and is involved in glutamate receptor expression; DISC1 also plays a particular role in cortical neuron development such as neuronal migration, neurite outgrowth and neuronal maturation.[6]

Neurochemistry

The best-known description of an association between neurochemical factors and the clinical manifestation of schizophrenia is the 'dopamine hypothesis'. Dopamine is released in the central nervous system following intoxication with amphetamine, which can cause a psychosis that resembles schizophrenia. The clinical efficacy of antipsychotic drugs that antagonize dopamine is broadly correlated with their potency at dopamine receptors. Isomers of neuroleptics that do not antagonize dopamine (e.g. β-flupentixol) are not antipsychotic. Although positive psychotic symptoms are thought to occur as a result of secondary dopamine hyperfunction in the striatum,[8] negative symptoms and cognitive deficits in schizophrenia may arise from frontal dopamine insufficiency.[9] Hence, antipsychotic treatment has little effect on negative symptoms.

Some 'atypical' antipsychotic drugs (e.g. risperidone) have significant antagonist effects at serotonin (specifically 5-HT_{2a}) receptors but, unlike dopamine blockade, this property has not been shown to correlate with clinical efficacy. It has been suggested that serotonin may have a modulatory effect on dopamine transmission in schizophrenia.[10]

Glutamate *N*-methyl-D-aspartate (NMDA) receptor hypofunction has been associated with schizophrenia. This hypothesis arose from the observation that phencyclidine (PCP) and ketamine, both of which are NMDA receptor antagonists, have caused a wide range of schizophrenia-like symptoms, both positive and negative.[11] Results of some studies have suggested that subcortical NMDA receptor dysfunction may lead to increased cortical glutamate levels and possible excitotoxicity of neurons.[11]

Neuro-anatomy – pathology and imaging

Neuropathological investigations in schizophrenia suggest that there are subtle cyto-architectural anomalies in entorhinal grey matter and other corticolimbic areas, as well as an abnormally high frequency of aberrant neurons in the white matter underlying prefrontal cortex, temporal, and parahippocampal regions.[6] There is also evidence of a reduction in the volume of cortical neurophil in the absence of comparable neuronal loss.[6]

Dimensional approach to the aetiology of schizophrenia

	Predisposing factors	Precipitating factors	Perpetuating factors
Biological	Genetic risk, obstetric complications	Substance misuse (cannabis, amphetamine)	Non-compliance with medication
Psychological	Schizotypal personality	High expressed emotion	Poor insight
Social	Urban birth, ?migration	Stress and life events	Homelessness

Table 1