Schizophrenia: Past, Present and Future

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Despite huge advances in modern medicine, schizophrenia remains somewhat an elusive illness, not only due to the relatively poor understanding of its aetiology and pathophysiology, but also because of the lack of availability of effective and comprehensive treatments. Sadly it continues to be described as a chronic, frequently disabling mental disorder of young adults that affects about one per cent of the world's population. Indeed, it continues to place a huge socioeconomic burden throughout the world. Yet, the progress on many fronts towards understanding its nature is being made and the possibility of effective comprehensive treatments remain a realistic goal, though it is hard to predict whether this is likely to happen in the next 20 years. The current knowledge of schizophrenia is far from complete, but what can be said in the light of present knowledge is that it is a heterogeneous disorder, which is characterized by positive and negative symptoms with persisting cognitive deficits. The illness usually has its onset in youth with varying heritability and shows alteration in brain structure and function.

A four-stage model is increasingly being used to encapsulate this complex disorder. These stages include; **stage I**, the risk stage, which begins before any detectable deficits, followed by **stage II,** the prodromal stage, which covers the period before frank psychosis. During this stage, there may be expressions of bizarre ideation, which do not quite reach psychotic intensity, impairment of functioning and social isolation. The **stage III**, represents the psychosis of schizophrenia which is recognized clinically with the presence of delusions, hallucinations, disorganization of thoughts and behaviour, and psychomotor abnormalities. The so-called negative symptoms of this stage, consisting of anhedonia, avolition and poverty of thinking along with cognitive deficits (such as poor cognitive control and worsening of working memory), unfortunately, are likely to lead to poorer outcome and often ends in **stage IV**, which is that of chronic disability of schizophrenia.

Historical perspectives

Description of the symptoms resembling schizophrenia affecting humanity go back thousands of years. Possibly the earliest reference was in 2000 BC by Egyptians in the "Book of the Heart" which described a mental condition with symptoms that resembled schizophrenia. Individuals suffering

from schizophrenia, throughout the centuries may have been thought of, at one extreme as those possessed with evil spirits or the devil to those considered to be saints and mystics. Attempted treatments also varied extremely, from ice-pick surgery to music therapy.

The relatively modern history of this condition began with German psychiatrist Emil Kraepelin who at the end of 19th century used the term 'dementia praecox ' (premature dementia) (1). These thorough descriptions differentiated this condition from the cyclic and non-deteriorating psychosis of manic depression and insanity, which resulted from tertiary syphilis.

The work of Kraepelin was furthered by the Swiss psychiatrist Eugen Bleuler who coined the term 'schizophrenia' in the early 20th century and highlighted what he thought was the plurality of the condition representing a "group of diseases" (2). He was not as convinced as Kraepelin that a terminal state was inevitable. He reiterated it as consisting of delusions and hallucinations ('basic symptoms'), potentially coupled with disorder of affect, ambivalence, autistic isolation and disturbances of associations – the 'four A's' ('accessory symptoms'). It is worth noting that these respectively could be seen as precursors to the modern and commonly used terminology of positive and negative symptoms.

During the mid-20th century another German psychiatrist, Kurt Schneider, gave weight to the so-called "first rank symptoms" in diagnosing schizophrenia (3). These included, audible thoughts, delusions of control, delusions of perception, hearing voices arguing, hearing voices commenting on actions, thought withdrawal, thought insertion and thought broadcast. These still make up part of the diagnostic tools in use today (4,5). The modern day reliability of these has been debated and it should be noted that these symptoms are not necessarily predicative of more severe manifestations of schizophrenia (6).

There was a period during the first part of 20th century when psychoanalytic theories began to predominate and the brain basis of schizophrenia symptomatology was largely ignored. Schizophrenia was considered to be a psychotic reaction to the fragmentation of ego of the sufferer by a rejecting or ambivalent mother.

Arrival of antipsychotics and chemical theories of schizophrenia

With the availability and use of neuroleptic medications in the second half of 20th century, began what many would consider as a start of pharmacological revolution that soon led to the emptying of mental asylums. As the idea of the brain basis of this disorder began to take hold, the researchers looked for explanations with the development of the dopaminergic theory of schizophrenia. This theory had its basis in the findings that dopamine releasing drugs (such as amphetamines) appear to lead to psychosis, whilst many neuroleptics (anti-psychotics) that blocked the dopamine D2 receptors (7), led to alleviation of psychotic (mostly positive symptoms, such as delusions and hallucinations) symptoms.

The classical antipsychotics (often called typical antipsychotics), though effective in alleviating positive symptoms of schizophrenia, had many adverse effects, including extrapyramidal adverse effects (tremor and rigidity) and sometimes relatively permanent adverse effect such as tardive dyskinesia. These clearly were unacceptable to most patients and unfortunately led to further stigmatization as treated patients were easily recognized because of these adverse effects.

The development and use of atypical (not an accurate description) antipsychotics (also known as second- generation antipsychotics) in the 1990s showed that they were also efficacious against positive symptoms (and perhaps against some negative symptoms too). But, whilst generally avoiding the extrapyramidal adverse effects, they had their own sets of adverse effects, such as weight gain (some worse than others) and contributed to the so-called metabolic syndrome. The latter led to the worsening of cardiac risk factors and hence mortality figures for these individuals remained high and in some cases worsened. It is worth noting, in this context, that most individuals with schizophrenia smoke. The research evidence largely suggest that neither first generation nor second generation

antipsychotics have beneficial effects on the cognitive deficits of schizophrenia, which remain a major contributor to poor social outcome.

Simple hyperdopaminergic theory did not explain all the aspects of schizophrenia. More integrative models described as prefrontal-limbic dopamine (DA) imbalance model (8) and phasic–tonic DA imbalance model (9) have been proposed. These models still do not explain all the aspects of the condition, since antidopaminergic treatment does not have much effect on cognitive and negative symptoms.

Another hypothesis, which might explain the cognitive problems of schizophrenia, suggests that there is alteration in the excitatory neurotransmitter glutamate system, particularly involving N-methyl-D-aspartate (NMDA) receptor function (10,11). The glutamate hypothesis (NMDA receptor hypofunction) leaves much unexplained, including the role of dopamine. It integrates the early and late developmental deviations, as well as the post-illness onset deteriorative processes occurring in schizophrenia (11). Additional support comes from the evidence that many genes implicated in schizophrenia appear to relate to the glutamatergic system (12). This model does not explain the lack of generalized neurological impairment in schizophrenia, given that glutamatergic neurons are widely present throughout the brain and therapeutic effect of drugs modifying the glutamatergic system still await confirmation through well-designed double-blind trials.

Evidence also exists for the dysfunction of gamma amino acid butyric acid (GABA) neurotransmission (an inhibitory neurochemical system) (13), the cholinergic system (14) and of the serotonin pathway (15).

Structural and functional changes in schizophrenia

The search for the biochemical basis of schizophrenia, stimulated by treatment findings, was not the only avenue being explored. Post-mortems conducted around the time of the diagnostic inception of schizophrenia were crude and imprecise. In part, researchers expected the abnormalities not only to be as dramatic as the symptoms the patients had, but also as gross as the findings discovered in the brains of those with diseases such as Pick's disease (16).

The development of computerised tomography (CT) scanning in the 1970s allowed for non-invasive imaging of the brain. One of the earliest reported findings was the observation of ventricular enlargement compared with controls (17). The 1980s hailed the advent of magnetic resonance imaging (MRI), which has itself undergone a significant amount of development over the last three decades. Aside from the absence of ionising radiation to the subject, modern MRI provides quite exquisite imaging, particularly allowing the clearer demarcation between soft tissue and fluid structures. Reviews of MRI imaging show not only the relative ventricular enlargement that CT did, but also involvement of the hippocampus, amygdala and neocortical temporal lobe in particular (18). A number of other structures have also been implicated in their involvement to a lesser degree, illustrating the apparent multifocal nature of the disease. Further technological developments, such as diffusion tensor imaging (DTI), use the diffusion properties of water to allow for further detailed imaging of the white matter of the brain (19). DTI studies are still in their infancy. The use of DTI to examine white matter is as a result of the idea that potential variations in the in the myelin producing oligodendrocytes may lead to conduction abnormalities between neurons (16).

Functional MRI (fMRI) assesses the haemodynamic response in relation to activity in the brain or spinal cord. It is increasingly being used to gather information on the neurobiology of the brain in schizophrenia (20). Suggestions have been made that schizophrenia symptomatology results from disruptions in neural connectivity of certain brain regions, possibly as result of white matter pathology (21), as shown by diffusion tensor imaging studies (22), and post-mortem findings that show reduced oligodendrocytes, which synthesize myelin (23). Interestingly, those with metachromatic leukodystrophy (a white matter disease) display the psychosis of schizophrenia (24).

Models relating to developmental abnormalities try to explain the proposed stages of schizophrenia

described above. It is suggested that those with schizophrenia may experience neuronal insults on processes such as neurogenesis during intrauterine or early postnatal life (early development; stage I), leading to the impairment in structure and maturation of the brain and therefore predisposition to pre-morbid dysfunction (late development; stage II) and psychosis emerging later in adolescence or early adulthood (stage III) (25).

Others have proposed that the actual problems occur at the time of onset of schizophrenia, ie adolescence and early adulthood, in processes such as synaptic, axonal pruning or neuronal apoptosis and myelination (26-28). Models incorporating both early and late developmental problems have also been proposed (29). Recently it has been suggested that an increase in corticolimbic glutamatergic activity, resulting from reduced inhibition by GABAergic interneurons, could lead to neuronal loss, explaining the progressive neuropathology and decline in function seen in some patients (30). The explanation for the onset of schizophrenia during adolescence and early adulthood is that this is a critical period, when there is pruning of excitatory synapses, proliferation of inhibitory synapses, increase in myelination (31) and dopaminergic innervation of the prefrontal cortex (32); all designed to optimize inhibitory and excitatory balance in cortical and subcortical regions, and that the resulting impairment leads to an increased risk of developing schizophrenia. The continued deterioration (stage IV) after the onset of psychosis is explained by neurodegeneration or negative neuroplasticity, which represent atrophic processes which continue to occur (33,34) Additional evidence for dysfunctional neuroplasticity in schizophrenia patients comes from transcranial magnetic stimulation studies (35). Along with DTI, further advances in imaging technology, such as use of magnetoencephalography (MEG) has provided information on functional the abnormalities in schizophrenia, such as alteration in the hemispheric interactions in the formation of the short-term memory traces necessary for the integration of auditory stimuli (verbal memory) (36).

Genetics and gene-environment interaction in schizophrenia

Heritability and its role in the aetiology of schizophrenia, has been recognized for some time. However, the situation is complex and resolving the issues is likely to require further advances in molecular genetics. Though the lifetime risk for schizophrenia is around 1%, the risk to siblings rises to 9%, and the risk to children of affected probands rises further to around 13%. The risk to an identical twin of the affected individual (sharing 100% of genes) is around 48%. This clearly suggests that other factors (environmental) must also play a significant role.

Schizophrenia is likely to be polygenic, with multiple genes each contributing a small effect to contribute towards the overall risk and predisposition of the individual. There are a large number of candidate genes which have a number of expressions from synapses to regulation of G-protein signalling that are being examined (37). As a result of the likely small effect size of each candidate gene, research demands large patient numbers and time to be adequately powered to reliably detect differences. An interesting example is provided by the DiGeorge (velocardiofacial) syndrome. This condition arises as a result of a deletion in 22q11 and is phenotypically expressed as abnormalities of the face, palate and heart. Interestingly, 18% of those with this genotype change display symptoms similar to schizophrenia (38). Approaching the issue from the other side, 2% of those with schizophrenia are found to possess 22q11 deletions, which is an 80 fold higher prevalence than found generally (39). This is thought to be because this region houses the catechol-O-methyltransferase (COMT) and proline dehydrogenase (PRODH) genes, which are also under examination (40). The genetic examination does not stop at schizophrenia spectrum disorders. A recent study of over two million families showed that schizophrenia and bipolar affective disorder have common susceptibility genes (41). Further research, given time, may subsequently find more genetic commonalities between neuropsychiatric conditions.

Increasing paternal age has been shown to increase the risk of the offspring developing schizophrenia (42). There is debate, however, as to whether this is truly causative, as there is likely to be an overlap with psychological and social factors as a result of being born to a father with increased age.

As already stated, both genetic and environmental factors play a role in the aetiology of schizophrenia.

The environmental factors thought to increase the risk of developing schizophrenia include, maternal malnutrition during famine (43,44) infections in the second trimester (45), perinatal injury (46) and cytokine exposure (47). However, it is likely that the gene-environmental interaction modifying the biological pathways leading to the development of schizophrenia has far greater effect then environmental or genetic factors on their own (48). This appears to be an exciting area of future research, which is likely to not only improve our understanding of the aetiology of schizophrenia, but also to provide potential opportunities for therapeutic interventions (49).

The discipline of epigenetics suggests that environmental factors have an impact on gene expression through changes in DNA methylation and chromatin structure and may play a role in the aetiology of schizophrenia (50). The epigenetic field in schizophrenia is still in its infancy but holds promise in improving our understanding of schizophrenia and indeed in the development of novel therapeutic approaches by modifying its process (49).

Yet another form of technology, utilizing ideas from stem cell research, has the potential to move forward our knowledge of schizophrenia. In a study reported in Nature (51), popularly described as "schizophrenia 'in a dish'", Brennand and colleagues described how they reprogrammed fibroblasts from schizophrenia patients into human induced pluripotent stem cells (hiPSCs) which were subsequently differentiated in to disorder-specific hiPSCs neurons. These hiPSCs neurons from schizophrenia patients showed diminished neuronal connectivity along with decrease in neurite number, PSD95-protein levels and glutamate receptor expression. Interestingly, use of the antipsychotic loxapine led to an increase in the number of synapses formed by the patient-derived neurons towards normal levels. They also reported differences in gene expression of those with and without schizophrenia and in genes related to synapse function.

Current treatments

Antipsychotic medications have largely been successful in alleviating psychotic symptoms, mostly positive symptoms. The first-generation ("typical") antipsychotics, although effective in treating the positive symptoms, caused severe neurological adverse effects such as parkinsonism, adding to the stigma of the illness. The advent and increased use of second-generation ("atypical") antipsychotics from the 1990s onward has led to the reduction in neurological adverse effects. However, these drugs had their own varying degree of adverse effects, such as weight gain, lipid dysfunction and insulin resistance (52). For treatment resistant cases, many strategies have been used which include, clozapine, augmentation (combination) with various drugs, use of fish oil and transcranial magnetic stimulation (53,54). Neither, the first or the second generation antipsychotics have had significant beneficial effects on cognitive deficits of schizophrenia which clearly contribute to chronic disability. Research is moving forward in this field but as yet no more effective drugs have come through into routine clinical use.

Schizophrenia is clearly a complex disorder in which environmental factors play an etiological role, modify the disease process and have a significant role in the treatment. The role of psychosocial interventions (social and psychological support) in addition to medication cannot consequently be overemphasised (55).

The future

Is the future for schizophrenia bright? Given the pace in scientific advances in molecular biology, we should expect to see major advances in our understanding of this dreadful disease as well as availability of effective and person-centred comprehensive treatments.
The diagnosis of schizophrenia mainly relies on clinical assessment by well-trained experienced psychiatrists. However, research is active in elucidation of various biomarkers (56) (laboratory tests), which could be used to supplement the diagnosis as is the case in many medical illnesses. The routine use of various imaging technologies in clinical practice is rather unlikely due to cost and the practical difficulties involved. However, for greater understanding of structural and functional changes in the brains of those with schizophrenia, it is likely that combined use of technologies (MRI, fMRI, DTI, MEG,

TMS) that have been further refined will be required. Work has begun in the field of neuroimaging (fMRI) genomics, where at-risk genes, such as COMT have shown polymorphism on cognition and prefrontal cortex function in schizophrenia, whilst the neuregulin1 (NRG1) promoter region has been shown to be associated with decreased activation of prefrontal and temporal lobe cortex. Potentially this could be used in at-risk children to establish possible neurodevelopmental abnormalities associated with schizophrenia (57,58).

Prevention is often said to be better then cure. The advent of first-episode psychosis services should help to prevent progression in to stage IV (chronic disability of schizophrenia), whilst early detection programmes theoretically may prevent onset of schizophrenia (stage III). These have begun; however, it is unclear at the moment, whether promise of what they can achieve will be delivered. Perhaps, more time and better understanding is needed of such initiatives before clear judgment can be made (59,60).

As further advances are made in stem-cell technology, prevention at the molecular and cellular levels could be envisaged by modifying aberrant neural networks. Indeed this could be part of early-detection programmes and first-episode services.

Though strides have been made in improving the treatment (largely of positive symptoms) and adverse effect profile of the pharmacological agents that are available to clinicians, this still relies largely on a form of trial and error approach. Progress has begun in the field of pharmacogenetics and indeed there are now some commercially available kits. However, we are still some way from having a situation where the clinician armed with the genetic profile of the patient is able to prescribe the right drug for the required response (61).

Currently the biggest challenge in the pharmacological treatment of schizophrenia is development of effective treatments for cognitive deficits, so as to prevent progression to stage IV of the illness leading to life long disability. The drugs sometimes known as cognitive enhancers have been used. However, none as yet passed the standards required for use in routine clinical practice (62).

Utopia in the field of schizophrenia would be prevention. However, this is unlikely to be achieved fully in the next 10 to 20 years. A more achievable goal is individualized treatment that is incorporated into smooth, accessible, patient-friendly and carer-friendly services which are not multiple and fragmented. These services should be led by the staff who are able to appreciate the biopsychosocial complexities of schizophrenia, make accurate diagnoses and give drug treatment which should lead to good response: alleviation of psychotic, negative and cognitive symptoms, along with other associated psychiatric symptoms such as anxiety, and depression. The overall treatment plan should also address issues of stigma, ethnic, cultural and social factors with psychosocial treatments, educational and occupational provisions. The recovery of those with schizophrenia should be measureable. The aim is to enable affected individuals to function at their pre-morbid level and to contribute to society in a fulfilling way.

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