Review

Schizophrenia: from phenomenology to neurobiology

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Abstract

Schizophrenia is a common and debilitating illness, characterized by chronic psychotic symptoms and psychosocial impairment that exact considerable human and economic costs. The literature in electronic databases as well as citations and major articles are reviewed with respect to the phenomenology, pathology, treatment, genetics and neurobiology of schizophrenia. Although studied extensively from a clinical, psychological, biological and genetic perspective, our expanding knowledge of schizophrenia provides only an incomplete understanding of this complex disorder. Recent advances in neuroscience have allowed the confirmation or refutation of earlier findings in schizophrenia, and permit useful comparisons between the different levels of organization from which the illness has been studied.

Schizophrenia is defined as a clinical syndrome that may include a collection of diseases that share a common presentation. Genetic factors are the most important in the etiology of the disease, with unknown environmental factors potentially modulating the expression of symptoms. Schizophrenia is a complex genetic disorder in which many genes may be implicated, with the possibility of gene–gene interactions and a diversity of genetic causes in different families or populations. A neurodevelopmental rather than degenerative process has received more empirical support as a general explanation of the pathophysiology, although simple dichotomies are not particularly helpful in such a complicated disease. Structural brain changes are present in vivo and post-mortem, with both histopathological and imaging studies in overall agreement that the temporal and frontal lobes of the cerebral cortex are the most affected. Functional imaging, neuropsychological testing and clinical observation are also generally consistent in demonstrating deficits in cognitive ability that correlate with abnormalities in the areas of the brain with structural abnormalities. The dopamine and other neurotransmitter systems are certainly involved in the treatment or modulation of psychotic symptoms. These broad findings represent the distillation of a large body of disparate data, but firm and specific findings are sparse, and much about schizophrenia remains unknown.
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1. Prelude

Several assumptions are required in order embark upon a thorough consideration of schizophrenia. First is that schizophrenia is a disease, in the classical sense. It has a pathology that may be found, that in turn upsets the normal physiology of the brain, and leads to the symptoms that anyone can recognize. Second, that it may be possible, with the tools available, to find this pathology, specify its features and to use this understanding to make the connection between pathology and clinical presentation. And third, that understanding what causes schizophrenia, why people get it, and how it works, will lead to better treatments.

Some non-scientific but important issues are raised by schizophrenia and the study of it. The rest of this review will be more rigorous in its text, but perhaps some expansive reflections beforehand will be useful. The modern conceptualization of schizophrenia is usually credited to Kraepelin [1] and Bleuler [2] whose descriptions in the early 20th century emphasize the features of the illness that are codified in contemporary diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) [3] and International Classification of Disease (ICD-10) [4]. Debate about the prevalence of schizophrenia in earlier times continues [5], but is unlikely to be resolved given the paucity of reliable documentation. Although Hippocrates, for example, gives descriptions of epilepsy and depression that any medical student would recognize, no such description of schizophrenia is found in his writings [6]. The question of whether the existence or prevalence of schizophrenia has changed over time is material to the search for the cause of this illness, since current mainstream scientific opinion is that schizophrenia has a neurobiological and genetic basis, with environment being a modulating factor but not the primary cause [7]. Certainly, descriptions of madness [8], insanity and psychotic experiences such as hallucinations, permeate non-medical writings from many cultures since ancient times.

It may be that the epistemological climate of Western thought in the 19th century was required to see schizophrenia as an illness. A materialist view of the mind as the product of a functioning brain [9], and the idea of unintentional abnormal mental experiences, is central to a medical approach to all mental illness, not just schizophrenia. The very definition of delusions is problematic without our current scientific and largely secular world-view [10]. Themes that arise often in schizophrenic delusions include ideas of external control, that today can be manifest as the belief that a microchip has been implanted in one's teeth, brain or other body part. The microchip is being used to control the patients' actions or thoughts and might be directed by the same source from which the auditory hallucinations emanate. Patients tell of telepathic mind control, witches casting spells, epic battles between good and evil waged with the patient as protagonist and being the Messiah, Mohammed or Bhudda. These are obviously delusions to doctors and scientists today, but why? We think these things are 'false, fixed beliefs'. But much of mainstream religious belief, and past scientific theory, is qualitatively very similar to common delusions. Hippocrates explained that 'moisture' aversely affected brain function to produce madness [6], Christ rose from the dead on Easter Sunday, and Apollo spends each day dragging the reluctant sun across the sky. The bible relates the story of water turned into wine, sundry cults promise reincarnation and voodoo rituals are still practiced in some areas of the world.

We exclude beliefs as delusional if they are congruent with 'cultural norms', and this highlights the importance of

context in the definition of psychosis. How would one demonstrate psychotic thinking in a prehistoric era where language was not even an idea [11], and the weather and seasons were entirely mysterious. Much of symptom definition in schizophrenia relies on the presence of language and other advanced, and presumably unique human abilities. It is impossible to find animal schizophrenia using our present diagnostic criteria—in contrast to 'non-psychiatric' diseases like diabetes or neoplasm, for which the same diagnostic criteria can identify the disease in both humans and animals. Crow proposes that the evolution of language was necessary to develop schizophrenia, because cerebral dominance, language and schizophrenia are inextricably linked to a single brain system [12]. So, perhaps schizophrenia has always been there, but no-one noticed, or maybe schizophrenia is a new disease.

The relationship of human behavior to free will, volition and consciousness has been a rich source of material for philosophers [13], priests, the courts and now psychiatrists. These issues, while perhaps not controversial among most neuroscientists today, have not been entirely resolved. In recent history, rather dramatic shifts in the conceptualization of insanity and schizophrenia have included everything from evil spirit possession [14] to psychodynamic neurosis [15]. The assumption that some kind of molecular, cellular or other pathology underlies serious mental disorders will only be confirmed when the pathology is found.

Schizophrenia could be more accurately referred to as 'the schizophrenias' [16]. Two people who have the symptoms of schizophrenia, and are diagnosed as such do not necessarily share the same brain pathology or disease etiology. Metachromatic leukodystrophy [17], mitochondrial encephalomyophathies [18] and complex partial epilepsy of temporal lobe origin [19] can produce psychotic symptoms without obvious physical symptoms. This demonstrates that diagnostic criteria for schizophrenia can be met by diseases of disparate origin, and these diseases would have been diagnosed as schizophrenia before their causes were understood [20]. In fact these three examples would be diagnosed as schizophrenia today, if not for the explicit exclusion criteria of symptoms due to a 'general medical condition'. Indeed the DSM criteria themselves harbor an interesting paradox. If schizophrenia is diagnosed only in the absence of organic pathology, then why are we using these criteria in research studies aimed at finding the presumably neurobiological cause of schizophrenia? The 'cause' of schizophrenia is unlikely to be a singular 'discovery', but rather a process of erosion in which the etiology of symptoms in subsets of people with schizophrenia is discovered, until gradually, more causes of chronic psychosis are known.

Genetic studies of schizophrenia almost always use standard DSM or ICD diagnostic criteria to define cases. If schizophrenia really is a collection of diseases that share a common phenomenology, then grouping them together as a single diagnosis in genetic studies raises important questions. Significant association or linkage between the syndrome of 'schizophrenias' and a given gene or chromosomal region may identify genes that affect vulnerability to psychosis in many conditions, that are not responsible for the unique pathology of each 'type' of schizophrenia. The grouping of all cases of chronic psychosis of unknown origin together as schizophrenia also has the potential to reduce the power of genetic studies in general, since the effect of a given gene in causing a particular type of chronic psychosis may be diluted by the inclusion of other types of psychosis that have a different etiology.

Another assumption in neuroscience and psychiatry research is that the prevailing paradigm in modern biology is sufficient to understand something very complex like the brain. The link from gene to protein to structure to function (genetic determinism) may not be sufficient to understand the complex mental functions that are affected by schizophrenia [21,22]. Computer simulated neural networks have emergent properties that cannot always be determined by the starting parameters [23]. Thus, although there is nothing unscientific in the workings of these nets, their behavior can be unpredictable in more than a stochastic sense. Admittedly, these neural networks are simplistic and not very accurate simulations of brain function, but that is the point. Even simple systems can have complex emergent properties, and our current conception of biological functioning does not yet have a suitable way of describing these phenomena. In chemistry and physics, this problem of emergent properties is well known, but still unsolved. Superconductivity, the behavior of glass, and the self-assembly of micelles cannot be explained on the basis of the constituent elements [24]. This 'mesoscopic' [25] organization is poorly understood, and while the connection to problems of thought and consciousness may be circumstantial, the analogy is that brain organization, far more complex than that of these simple systems, may not be understandable within our current principles.

The above seem to argue that the study of schizophrenia neurobiology is futile. However, even if the pathophysiology of psychotic experience cannot be understood in terms of genes, or protein function, there is much to learn about brain function from a conventional perspective. Uncovering genes related to schizophrenia may not lead to a complete understanding of the illness, but may provide the foundation for studying emergent brain properties, that do after all, require knowledge of the constituent parts.

2. Schizophrenia: phenomenology

Schizophrenia is a devastating illness that strikes at some of the most advanced functions of the human brain. Symptoms can be divided into three main categories: psychotic or 'positive' symptoms, deficit or 'negative'

symptoms, and cognitive impairment [26]. Psychotic symptoms are a feature of many brain diseases but are often the most unsettling and obvious symptom to others when interacting with a patient who has schizophrenia. Psychotic symptoms fall into three main groups: hallucinations, delusions, and thought disorder. The negative symptoms consist of severe disturbances in social interaction, motivation, expression of affect, ability to experience pleasure, and spontaneous speech [27]. Cognitive impairment in schizophrenia affects executive function, attention, memory, and general intellectual functioning [28]. The negative and cognitive symptoms are more persistent and chronic, while the psychotic symptoms have an episodic pattern, that when active are usually the impetus for hospitalization [29]. The DSM-IV diagnostic criteria for schizophrenia are summarized in Table 1 [3].

Hallucinations in schizophrenia are usually in the form of auditory hallucinations of human speech: 'hearing voices'.

Table 1
Diagnostic criteria for schizophrenia [3]

A. *Characteristic symptoms*: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
  (1) delusions
  (2) hallucinations
  (3) disorganized speech (e.g. frequent derailment or incoherence)
  (4) grossly disorganized or catatonic behavior
  (5) negative symptoms, i.e. affective flattening, alogia, or avolition
  Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.
B. *Social/occupational dysfunction*: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).
C. *Duration*: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A, and may include periods of prodromal or residual periods. During these prodromal or residual periods the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form.
D. *Schizoaffective and Mood Disorder exclusion*: Schizoaffective Disorder and Mood Disorder with Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood symptoms have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
E. *Substance/general medical condition exclusion*: The disturbance is not due to the direct physiological effects of a substance or a general medical condition.
F. *Relationship to a Pervasive Developmental Disorder*: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

These voices may be single, or multiple; they may be clear or unintelligible, and they may be the voices of family, friends, strangers or God. The voices may comment on the patient's actions or thoughts, or multiple voices may converse about the patient in the third person. Perhaps most dramatic are voices that command the patient to action, sometimes to commit terrible, ego-dystonic violence [30,31]. The voices may be intimately connected to the content of the delusions, and may even be perceived as the voice of the instigator of the delusional system of thought. Ironically, patients may see the voices as the entity 'that is driving me crazy' or 'that gave me schizophrenia'. One of the author's patients, who is congenitally deaf, gives a clear description of hearing voices that command him not to read his bible, as he likes to do. This patient, similar to many with schizophrenia, believes that the voices belong to his neighbors, and that they conspire to monitor and interfere with his life inside his apartment. This case illustrates that hallucinations do not depend on a functioning sensory system, and that the pathophysiology of hallucinations may involve other brain areas.

The delusions typical of schizophrenia are labeled paranoid, and include delusions of persecution, grandiosity, external control, having thoughts inserted or withdrawn from one's head, ideas of reference and mind-reading. Delusions of persecution may become entrenched in a delusional system, in which most everyday events take on significance as part of a conspiracy against the patient. The content of the delusions takes cues from the patient's life and culture [32,33]. Muslim patients may believe they are Mohamed, while Christian patients think they are Jesus. If originally from the former Soviet-bloc countries, they may fear the KGB or Stassi, while Canadian patients perceive surveillance from the RCMP and Americans think the CIA is following them. The delusions may be bizarre, and contain supernatural or paranormal ideas gleaned from movies or TV. Extraterrestrial alien interference, implanted electronic devices, and other science fiction topics seem to be common in the substance of delusions [34].

Thought disorder may be described along a spectrum of severity, with tangential and circumstantial thinking at the milder end, and loosening of associations and word salad at the more extreme end. These thought form abnormalities can be seen as a progressive fragmentation of the normative, logical progression of ideas characteristic of an intact intellect. Thinking and behavior may also be extremely disorganized, with significant impact on patients' ability to attend to basic needs [29].

None of these symptoms alone are diagnostic for schizophrenia, and in fact the way the DSM criteria are structured allows for the possibility that two patients with schizophrenia may not overlap in their presentation [35]. The question of what clinical deficit is central to schizophrenia remains unanswered. Attempts to sub-classify schizophrenia as predominantly disorganized ('hebephrenic'), paranoid or catatonic [36], or into

predominantly positive or negative subtypes, have not produced correlations with response to treatment or other outcomes [37]. Problems of a cognitive nature—difficulty in filtering and sorting sensory experience, or in correctly attributing meaning to events and the intentions of others—may be a more fundamental, if less striking deficit in schizophrenia [7]. Cognitive abnormalities are discussed further in Section 5.

3. Schizophrenia: a major public-health concern

Schizophrenia has a lifetime prevalence of 1.4–4.6 per 1000 in all populations in the world, and an annual incidence of between 0.16 and 0.42 per 1000 population [38]. Symptoms usually begin in late adolescence or early adulthood, but later onset cases are possible. Males have been thought to develop schizophrenia at an earlier age, but this finding is not consistent across different countries and all ages of onset [38]. The proportion of patients who improve or recover increases with length of follow-up, reaching 60% at 32-years in a retrospective follow-up study of patients from a state hospital [39]. These figures are in contrast to the traditional view that patients face a deteriorating and chronic prognosis. Outcome in industrialized countries is usually worse than in developing or 'Third World' countries [40,41]. The WHO 10-country study found significantly better outcomes (based on a combined index of the course of illness, total duration of psychotic episodes, quality of remissions, and degree of social impairment) in Nigeria, India and Columbia in comparison to developed countries including the United States, Japan and England. Better outcomes were seen in female patients and in those with more social supports [42].

Neuroleptics in conjunction with psychosocial rehabilitation have a substantial effect in reducing relapse [43]. Newer antipsychotic medications may have some advantages over conventional neuroleptics, mainly in reduced extrapyramidal side effects, but appear to be equally effective [44]. Despite the clear effects of antipsychotics in reducing the symptoms of schizophrenia, many patients continue to experience relapses and require hospitalization throughout the course of their illness [45].

Because of the chronic nature of schizophrenia, its severity, and its early onset, the financial costs to society outpace more common illness. Direct costs of care have been estimated at US $17.3 billion in the United States in 1990. These figures are disproportionate to the cost of affective disorders, which are almost 10 times more common (prevalence 9.5%), but had direct costs of US $19.2 billion [46,47]. In the UK in 1992–93, direct costs incurred in caring for people with schizophrenia were UK £810 million, accounting for 2.76% of total health expenditures by the National Health Service. Inpatient care for schizophrenic patients accounted for 5.37% of the total hospital costs in the UK [48]. Income lost due to

the illness, and expenses borne by the family, the legal system, and charitable and community organizations are difficult to estimate, but are in addition to the cost of providing medical care, medications and government social services. In contrast, diabetes in the UK and Wales in 1984 was estimated to cost UK £259.5 million in both direct and indirect costs, excluding lost wages due to illness-related absenteeism [49]. Years of life lost to disability are greatest for mental illnesses in general, as compared to years of life lost, which are mostly due to cardiovascular illness and cancer [50]. In Canada, direct costs of care totaled $1.12 billion in 1996, with another $1.23 billion in lost productivity attributed to schizophrenia [51]. The landmark World Bank and WHO study *The Global Burden of Disease*, reported that in the 15–44 age group, schizophrenia ranks 5th among leading causes of disability (as measured by Disability-Adjusted Life Years or DALY) in established market economies and 9th worldwide [52].

Schizophrenia is an expensive illness, especially in industrialized nations where the symptoms are incompatible with the highly structured nature of the workplace, and where social expectations are high. Of course, patients and their families are more than debits in the ledger of health care costs, and suffer, as all victims of serious illness do. Yet the disease has uniquely painful consequences as well. Schizophrenia starts just at the time in life when promise and potential are at its height, making the emergence of symptoms all the more devastating. Entering college, leaving home and joining the army are common precipitating scenarios. The symptoms alter personality and disrupt or sever close relationships with family and friends. Thus, while cancer is a terrible disease, the affected patient is still able to be the same person, with their illness. Schizophrenia changes the person who has it, and families want treatments not just to improve symptom rating scales and quality of life indices, but to restore the person they once knew. By this measure, our current treatments are surely lacking [53].

4. Neuropathology of schizophrenia

No diagnostic neuropathology has been identified for schizophrenia, despite extensive investigations for over 100 years. Group differences between schizophrenics and normal or other mental illness controls have been documented, but the degree of overlap with controls, and the non-specific nature of these differences preclude the use of these abnormalities clinically [54,55]. The findings are discussed in this section, and are grouped into the following categories: macroscopic pathology, histology, neurochemical findings, functional neuroimaging, and gene expression. The most consistent findings are summarized in Table 2.

Post-mortem studies in schizophrenia are confounded by several factors, largely unavoidable features of the illness. Although schizophrenia usually appears in the late teens or

Table 2
Neuropathological findings in schizophrenia with selected references, adapted from Ref. [54]

Neuropathological finding	Positive findings	Negative or equivocal findings
Decreased cortical volume especially in temporal cortex and increased ventricular size (pathological studies)	Bogerts et al. [56] Brown et al. [58] Pakkenberg [60] Falkai et al. [62] Bruton et al. [64] Vogeley et al. [65]	Rosenthal and Bigelow [57] Heckers et al. [59] Pakkenberg [61] Dwork [63]
Decreased cortical volume especially in temporal cortex and increased ventricular size (imaging studies)	Johnstone et al. [66] Haug [67] Zipursky et al. [68] Lim et al. [69] Cannon et al. [70] Gur et al. [71] Lawrie and Abukmeil [72] Reviewed by McCarley et al. [73]	
Decreased hippocampal and cortical neuron size	Benes et al. [74] Arnold et al. [76] Zaidel et al. [78]	Benes et al. [75] Christianson [77]
Gliosis absent as an intrinsic feature	Roberts et al. [79] Stevens et al. [81] Casanova et al. [83] Arnold et al. [84]	Fisman [80] Stevens [82]
Fewer neurons in the thalamus	Pakkenberg [61] Blennow et al. [85] Danos et al. [86]	
Abnormal laminar distribution of neurons in temporal cortex	Jakob and Beckmann [87] Arnold et al. [89] Benes et al. [74] Conrad et al. [91] Akbarian et al. [92] Zaidel et al. [78]	Akil and Lewis [88] Krimer et al. [90]
Decreased perfusion and metabolism in frontal regions	Ingvar and Franzen [93] Kurachi et al. [95] Berman et al. [97] Weinberger et al. [98] Geraud et al. [99] Mathew et al. [100]	Gur et al. [94] Gur [96]
Increased striatal D2 receptors	Reviewed by Laruelle [101]	
Increased dopamine content or metabolism	Laruelle et al. [102] Breier et al. [103] Abi-Dargham et al. [104] Ginovart et al. [105]	
Decreased 5-HT$_{2A}$ receptors	Reviewed by Harrison [54]	
Decreased expression of synaptic and neuronal marker genes and proteins	Arnold et al. [106] Cotter et al. [107] Harrison and Eastwood [108] Young et al. [109] Karson et al. [110] Eastwood et al. [111]	

in early adulthood, the disease is not directly fatal, and although life expectancy is reduced significantly in schizophrenia [112], patients die from the same causes that affect the general population. Post-mortem tissue is usually available only from relatively older individuals, meaning that any findings are complicated by changes related to aging and the proximate cause of death. The brain changes at the time of symptom onset are only observable

by imaging technology, which is still unable to provide the detailed microstructural and molecular information that tissue can. Suicide is of course a fatal outcome in schizophrenia [113], but may represent a distinct subtype of the illness that may not be generalizeable to the disease as a whole. Another significant confounding factor is that of antipsychotic treatment. Post-mortem tissue from neuroleptic-naïve patients is essentially unavailable, so again, brain imaging studies are the only option in this population, and the information gained is therefore limited. Attempts to compare schizophrenic post-mortem tissue to neuroleptic-treated controls are the only realistic compromise, but of course raise the issue of a common liability for psychosis in other brain disorders (e.g. mood disorders and dementia) that sometimes requires treatment with antipsychotics.

4.1. Macroscopic neuropathology in schizophrenia

Most post-mortem studies of schizophrenics reveal decreased brain weight and increased ventricular volume. These studies also suggest that the temporal lobe and the corresponding temporal horn of the lateral ventricle are the most affected [56,58,60,62,64,65]. Other studies, however, find no significances in brain or ventricular size [57,59,61,63].

A large number of studies using computed tomography (CT) and more recently magnetic resonance imaging (MRI) have confirmed that there are widespread cerebral gray matter volume deficits in schizophrenia when compared to normal control subjects [68,70,73]. These are present even in first-episode cases before treatment might have affected the findings [69,71,114]. Lateral and third ventricular volume is increased in schizophrenia [66,67], although there is no correlation between ventricular size and degree of cortical volume loss [115]. The magnitude of the increased ventricular size in schizophrenics varies among reports, but a meta-analysis shows an effect size of 0.70, indicating that 43% of cases and controls do not overlap [116]. This effect is not due to a subgroup of cases, but rather is distributed normally among schizophrenic patients [117]. The decrease in cortical volume appears to be most pronounced in the temporal lobe [118], especially in the medial structures [72].

Relatives of schizophrenics also have decreased cortical volumes [119] and enlarged ventricles [120–123]. In monozygotic (MZ) twins discordant for schizophrenia, the affected twin tends to have less cortical volume [124], and larger ventricles [125,126]. These finding suggest that the macroscopic structural changes seen in schizophrenic brain may reflect the underlying genetic vulnerability to the illness, and that the magnitude of the changes is correlated with clinical expression of symptoms. In fact, the degree of thought disorder and severity of auditory hallucinations is inversely correlated with superior temporal gyrus size [127–129].

4.2. Histological pathology in schizophrenia

There are robust histological findings in schizophrenia, although meta-analyses have yet to confirm them as with structural imaging findings. Neurons in the cortex and the hippocampus are reduced in size, gliosis is not an intrinsic feature of schizophrenia, and there are fewer neurons in the dorsal thalamus. Less robust findings include reduction in synaptic and dendritic markers, and maldistribution of white matter neurons. More controversial are reports of disarray and loss of hippocampal neurons, and of dysplasia in the entorhinal cortex [54].

The reduced size of hippocampal neurons in schizophrenia was reported in several well-executed studies [74, 76,78], and supported by findings of decreased presynaptic and dentritic markers such as SNAP-25 [109], complexin II [108], and microtubule associated protein MAP-2 [106, 107]. Magnetic resonance spectroscopy (MRS) studies of N-acetyl-aspartate (NAA) as a neuronal marker are consistent with the above studies as well. Reduced levels of NAA have been found in the dorsolateral prefrontal cortex (DLPFC) and hippocampus in schizophrenia [130–133], and are present in unmedicated patients [134,135]. The number of thalamic neurons is consistently reduced in both the mediodorsal nucleus [61], and among parvalbumin-positive thalamocortical projection neurons [86]. This is bolstered by immunoblot experiments documenting decreases in rab-3a, a synaptic protein [85].

Some earlier studies reported gliosis [80,82], but more recent and numerous reports refute this. Gliosis is traditionally associated with degenerative disease, and not usually seen before the third trimester [136]. The absence of gliosis is a convincing argument for a neurodevelopmental rather than neurodegenerative process underlying schizophrenia, and is supported by a number of studies [79,81,83, 84]. Furthermore, the presence of gliosis, when observed in the brains of schizophrenic patients, may be due to other concurrent pathology [64]. Different techniques are used to assess the presence of gliosis, and the anatomical regions studied have varied, so the results of different groups are not always directly comparable [54].

There are intriguing reports of cytoarchitectural abnormalities in the cortex of schizophrenic patients [78,137–139]. Experiments with Nissl stained sections have found: a disorientation of pyramidal cells in the hippocampus [91]; a decrease in cell density in layers I and II of the rostral entorhinal cortex (in the amygdala and pes hippocampus); incomplete glomerular clustering in layer II; and abnormal clustering in deeper cortical layers [74,87,89]. There are also decreased numbers of GABAergic neurons in the prefrontal cortex (PFC), with more pyramidal cells in deeper layers [140]. Histochemical assay with NADPH-diaphorase identifies a sub-population of neurons that are shifted inwards (into deeper layers) in their laminar distribution, with reduced density in superficial layers and increased density in deeper layers [92,141]. However, two

carefully designed studies did not find significant cytoarchitectural abnormalities in schizophrenia [88,90].

These findings have led to interesting computer-simulation neural net experiments, in which the decrease in cell density in the superficial cortical layers has been modeled [23]. In simple pattern-recognition nets designed to simulate auditory word recognition, the pattern of cell loss seen in schizophrenia results in spontaneous mis-identification of words that had not been sent as inputs [142]. These mis-recognitions could be interpreted as similar to hallucinations, in which sensory stimuli from the environment are perceived in the absence of any real sights or sounds [143]. While the biological accuracy of these neural net models is limited, these experiments suggest an explanation for how the diffuse and non-specific pathology of schizophrenia might lead to complex symptoms.

The convergent findings of neuroimaging and pathological studies represent some of the most robust data in schizophrenia research. Their importance in demonstrating that schizophrenia is a brain disease rather than primarily a problem with psychological origins should not be understated. However, the traditional paradigm used to elucidate the neuroanatomy of basic nervous system functions does not seem to apply in schizophrenia and psychiatric disease in general. Motor and sensory functions, for example, are segregated neatly into the pyramidal and spinothalamic tracts, with corresponding cortical areas that are well defined. Diseases or lesions affecting these areas produce fairly consistent clinical patterns of paralysis or paresthesia and make the diagnosis satisfyingly precise. Psychosis, on the other hand, can result from lesions in many anatomical regions, and from many different causes, diffuse and focal [144,145]. The structural brain abnormalities in schizophrenia involve the frontal, temporal and limbic regions and point to the conclusion that schizophrenia is a disease of multiple brain regions, with subtle microscopic changes producing a rich variety of clinical manifestations. One of the current challenges is to establish the pathophysiological mechanisms by which these non-specific brain changes lead to the psychotic and other symptoms of schizophrenia.

4.3. Neurochemical pathology in schizophrenia

Antipsychotics are effective most of the time in reducing psychotic symptoms, and dopamine (DA) receptors are a major target for these drugs. Amphetamine and cocaine can induce psychosis, and these drugs release or inhibit the reuptake of DA, respectively. These observations led to the 'dopamine hypothesis' of schizophrenia, which posits that hyperactivity of the DA system is responsible for the psychotic symptoms [146]. However, evidence that an overactive DA system is significant in the etiology of schizophrenia remains inconclusive.

DA receptors are part of the superfamily of G protein coupled receptors. The D2-like receptors include the D2, D3 and D4 receptors, and the D2 receptor is targeted by most antipsychotics, including the atypical antipsychotics. These receptors couple via Gi/o to inhibit adenylyl cyclase [147], but can also signal to other effectors, including Kir3 channels [148,149] and pathways involving the platelet-derived growth factor receptor, that modulate extracellular receptor kinase activity and N-methyl-D-aspartate (NMDA) receptor activity [150,151].

Recent evidence from positron-emission tomography (PET) studies has suggested that hyperactivity of dopaminergic transmission is present in schizophrenics. Amphetamine-induced DA release in the striatum, DOPA decarboxylase activity, and D2 receptor density in the striatum appear to be elevated in patients with schizophrenia as compared to normal controls [102–105]. A meta-analysis of studies with drug-free and neuroleptic-naïve patients confirms these results [101]. Abnormal presynaptic DA metabolism in drug-free schizophrenic patients has also been demonstrated [152]. However, much of the increase in receptor number and metabolic activity may be related to antipsychotic treatment [153], since some studies in neuroleptic-naïve patients do not confirm these findings [154]. D4 receptor density was reported to be elevated in schizophrenic patients, independent of medication effects, but was subsequently attributed to binding to raclopride insensitive D2-receptor sites [155–157]. A variant of the catechol-O-methyltransferase (COMT) gene has been reported to increase prefrontal DA catabolism, impair prefrontal cognition and is associated with a slightly increased risk for schizophrenia [158].

The serotonin neurotransmitter system has also been studied in schizophrenia, partly because serotonin receptors are targeted by some newer antipsychotic drugs. Serotonin receptors are found in at least 14 different subtypes, categorized into 7 subfamilies (5-HT$_x$) and most are also part of the superfamily of G-protein linked receptors. 5-HT receptors signal through a wide variety of mechanisms including Gi/o to inhibit adenylyl cyclase, PLC-β, and adenylyl cyclase, and are expressed in many peripheral tissues and the central nervous system (for review see Ref. [159]). Decreased cortical 5-HT$_{2A}$ receptor density [160], and increased 5-HT$_{1A}$ receptor density have been reported in schizophrenia [161,162], while 5-HT$_6$ receptor binding was found to be unchanged in schizophrenia [163]. Overall, the evidence for primary serotonin system abnormalities in schizophrenia is not a strong as for the DA system.

Glutamate is the primary excitatory neurotransmitter in the brain, and it binds to two main types of receptor: ionotropic and metabotropic. Excitatory effects are mediated by three types of ionotropic receptors: NMDA, amino-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainic acid (KA) [164]. The 'glutamate hypothesis' of schizophrenia arose out of observations that NMDA antagonists such as phencyclidine [165] and ketamine can cause or exacerbate psychotic symptoms [166]. Proposed mechanisms include excitotoxic damage to hippocampal and cortical neurons [167], interactions

between the DA and glutamate systems [168], and abnormal pruning of glutamatergic innervation during neurodevelopment [169]. The expression of hippocampal non-NMDA receptors may be decreased [170–172], and in the cortex, the expression of some NMDA receptor subunits may be increased. Some evidence of increased glutamate uptake in the frontal cortex, and decreased cortical glutamate release has also been found [173]. Conflicting evidence of AMPA receptor changes in schizophrenia has been reported [174,175].

4.4. Functional imaging in schizophrenia

Functional imaging studies may be divided into those that measure activity in the resting state, during the presence of symptoms, during cognitive tasks, and with task or pharmacological provocation of psychotic symptoms [176]. [113]xenon inhalation cerebral blood flow (CBF) studies have shown less anterior CBF in schizophrenia, referred to as 'hypofrontality' [93]. The normal pattern of CBF is increased in anterior relative to posterior regions. Although results are not entirely consistent [94,96], most groups have replicated the original findings [95,97–100].

PET studies confirm that hypofrontality is seen in both chronic [177–179] and never medicated first-episode patients [180], and is also correlated with negative symptoms [181]. Some studies find that the PFC [180] or the left frontal cortex [182], are particularly affected, although there are many studies that do not find hypofrontality in schizophrenic patients [183–185]. Treatment with antipsychotic medication appears to increase activity in the basal ganglia [179,183,186,187], leading some to suggest that hypofrontality in the resting state is an effect of antipsychotic treatment [188].

Decreased activity in frontal cortex in schizophrenic patients is observed during various cognitive tasks known to involve the frontal lobes [189,190], and is also found in anatomically connected temporal and parietal regions [191]. In some studies, the perfusion deficit in frontal regions may be correlated with decreased performance of the cognitive task. Hypofrontal metabolic activity measured with ^{18}F-fluoro-deoxyglucose ([18]FDG) PET is seen during a serial verbal learning and recall task in unmedicated schizophrenic patients, and the degree of deficit correlates with impairment in some functions [192]. Schizophrenic patients asked to perform a graded memory task showed decreased prefrontal CBF only when their performance deteriorated, in one study using $H_2^{15}O$ PET to measure regional CBF [193]. Another study found no hypofrontality in schizophrenic patients during cognitive tasks in which their performance is matched with controls. However, these schizophrenic subjects failed to show a normal reduction in superior temporal CBF when the task changed from verbal fluency to word repetition [194].

Some studies find hypofrontality in schizophrenic patients with cognitive tasks in which their performance is matched with that of controls. Schizophrenic patients show less activation of the anterior cingulate regions during an auditory recognition task in which their performance is the same as controls [195]. Results are similar during the recognition of novel visual stimuli: attenuated right thalamic and right prefrontal activation [196]. The abnormal activation of PFC during working-memory tasks has been linked to the neuronal pathology in the same area in a recent study in which ^{1}H-MRS of NAA was used as a neuronal marker, and $H_2^{15}O$ PET was performed during a working-memory task [197]. Specific links have been demonstrated between DLPFC activity and the associative components of working memory in schizophrenia using functional MRI (fMRI) and the 'n-back' task [198], and other working-memory tasks [199], and between the inferior frontal cortex and verbal working-memory tasks using fMRI [200]. A de-coupling of cognitive performance and cerebral functional response during working-memory tasks has also been found [201]. Decreased activation in the left mesial frontal cortex was also observed in both neuroleptic-naïve and treated schizophrenic patients with the Tower of London task, assessed with single photon-emission tomography (SPECT) [181]. The impaired cognitive activation of frontal cingulate cortex in schizophrenic patients can be partially corrected with DA agonists as demonstrated in a PET study [202].

The presence of psychotic symptoms may affect the pattern of CBF and activation during functional imaging tests. A $H_2^{15}O$ PET study comparing normal controls to schizophrenic subjects found decreased left prefrontal activation in the schizophrenic subjects while psychotic. This hypoactivation pattern normalized when the patients' clinical symptoms remitted, although the role of medication is unclear [203]. Studies aimed at capturing brain activation with [18]FDG-PET during the experience of auditory hallucinations have found decreased metabolism in lateral temporal language regions [204]. Direct comparison of the hallucinating and hallucination-free state showed increased left inferior frontal CBF to Broca's area [205], and in the striatum, thalamus and medial temporal cortex [206]. All of these studies show changes in activation in cortical areas related to speech and auditory processing, which is an interesting correlate of the subjective experience of hearing voices.

There are a few functional imaging studies of pharmacological provocation of psychotic symptoms. Ketamine administration in schizophrenic patients resulted in an increased anterior cingulate cortical CBF, and a reduction in hippocampal and primary visual cortical CBF, as measured with $H_2^{15}O$-PET. These CBF changes were seen in conjunction with transient psychotic symptom exacerbation, but with no comparison to a control challenge [207]. Metabolic hyperfrontality is seen with [18]FDG-PET in healthy volunteers during ketamine-induced psychotic symptoms [208,209].

Neuroimaging techniques have also been applied to the investigation of the affective disturbances long observed by

clinicians. Social interactions require the accurate assessment of the facial expressions of others, and this task is associated with increased activation in the face movement areas of the motor and pre-motor cortex of schizophrenics, measured with fMRI [210]. The amygdala activation patterns of schizophrenic patients were also different than that of controls when asked to judge the emotional intensity of facial expressions [211]. A novel PET study of possible mechanisms of anhedonia in schizophrenia exposed subjects to pleasant and unpleasant odors. The schizophrenic subjects had impairment in the experience of pleasant odors, and changes in limbic/paralimbic region activation with unpleasant odors [212]. In another fMRI study, patients with schizophrenia had reduced activation of limbic regions (amygdala and hippocampus) during a facial emotion discrimination task in comparison to controls, although task performance itself was not impaired [213]. Similar findings were reported in a $H_2^{15}O$-water PET study, where schizophrenic subjects had abnormal amygdala activation with exposure to non-aversive emotional stimuli, and where left amygdala activity correlated with positive symptoms [214]. These recent studies demonstrate a neural basis for the negative symptoms of schizophrenia that complement the more extensive literature on the functional imaging abnormalities associated with psychotic symptoms and cognitive deficits.

4.5. Gene expression in schizophrenia

The robust evidence for gross and microscopic structural abnormalities in schizophrenia has led some investigators to examine gene expression in the brain tissues of those affected by the illness. Gene expression in general is influenced by many factors, which may be environmental or intrinsic in origin, but that ultimately rely on a molecular mechanism to control gene transcription and translation. The precise timing and location of gene expression is fundamental to the development and functioning of complex, multicellular and multiorgan organisms. The most well known regulators of gene transcription include dedicated promoter, enhancer, suppressor, and repressor genes or regions of the chromosome, often located in close proximity to the genes they regulate [215]. Some families of genes, such as the homeodomain transcription factors, have more general regulatory functions, and are important in neurodevelopment, for example, Ref. [216]. Epigenetic factors can affect gene transcription, without changes in nucleotide sequence, and exert their effects through two main mechanisms: DNA methylation and chromatin structure [217].

Many abnormalities in both mRNA and protein expression have been found in post-mortem studies of the brain in schizophrenia, and some are shown in Table 3. Candidate genes studied include those involved in synaptic function, neurotransmitter systems, and neurodevelopment. Reduction in synaptic protein expression may reflect the reduction in cortical volume that post-mortem and imaging

studies have shown. Neurodevelopmental genes that influence the cytoarchitecture or size of the cerebral cortex, or regulate the positioning and migration of neurons are obvious choices for investigation in light of the histopathology of schizophrenia described in Section 4.2. Studies of neurotransmitter system genes, especially the DA system, are particularly vulnerable to the confounding effects of antipsychotic treatment.

Overall, the examples of studies listed in Table 3 illustrate the diversity and number of gene expression changes associated with schizophrenia, and this variety of findings raises further questions. Not surprisingly, the gene expression abnormalities correspond with the neuropathological and neurochemical findings discussed in the previous sections; they are the molecular correlate of the macroscopic changes in the schizophrenic brain. However, while interesting data have emerged, these candidate-gene studies rely on an a priori selection of genes to be examined. This approach can be limited by our very incomplete understanding of the molecular basis of neurodevelopment, neurotransmitter and synaptic functioning. Microarray technology has recently been used to analyze the mRNA expression patterns of thousands of genes simultaneously, allowing the identification of clusters of genes that may be altered together. Microarray studies have also suggested novel candidate molecular systems for investigation that had not been suspected of being involved in schizophrenia.

Microarray analysis of post-mortem tissue from schizophrenic patients has demonstrated dysregulation of myelination-related genes, suggesting a disruption in oligodendrocyte function. Genes involved in synaptic plasticity, neuronal development, neurotransmission and signal transduction are also altered in expression levels [240]. Another microarray study found that genes involved in the regulation of pre-synaptic function were altered in expression; the two genes most consistently involved were N-ethylmaleimide sensitive factor and synapsin II [241]. The same group also found changes in regulator of G-protein signaling 4 (RGS4) expression [242] and in genes related to energy metabolism [243]. Another study also found genes related to synaptic signaling, but identified other types of genes related to proteolytic functions, as well as specific genes: tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (14-3-3), eta polypeptide; sialyltransferase; proteasome subunit, alpha type 1; ubiquitin carboxyl-terminal esterase L1; and solute carrier family 10, member 1. These data came from analyzing both cerebellum and PFC from drug-naïve and treated patients in comparison with a matched control group [244].

These molecular studies in schizophrenia have demonstrated that the gross and histological brain abnormalities correlate with changes in gene expression. Although this information is significant, it also complicates our understanding of the illness. The complexity of genetic regulation makes it difficult to determine whether these gene expression changes are a primary feature of the illness,

Table 3
Selected studies demonstrating gene expression differences in schizophrenia

Gene name	Protein versus RNA	Gene expression in schizophrenia	Control or comparison group/anatomical area	References
Complexin II	Both	Decreased	Non-schizophrenic/medial temporal lobe	[108]
MAP-2 and 5	Protein	Decreased	Normal controls, neurodegenerative disorder/hippocampus/hippocampus	[106,107]
Synaptophysin	Both	Decreased	Non-schizophrenic patients/cortical Brodmann Areas (BA) 10 and 17	[110,111]
Synapsin IIa and IIIa	Protein	Decreased	Normal controls/hippocampus	[218]
SNAP-25	Protein	Decreased	Normal controls/hippocampus	[109]
PSD 95	mRNA	Decreased	Normal controls/prefrontal cortex	[219]
Glutamic acid decarboxylase	mRNA	Decreased	Matched controls/prefrontal cortex	[220,221]
GABA transporter-1	mRNA	Decreased	Matched controls/prefrontal cortex	[222]
5-HT$_{2A}$ receptor	mRNA	Decreased	Normal controls/left superior frontal gyrus	[223]
Cholecystokinin	mRNA	Decreased	Non-psychotic suicide, and normal controls/entorhinal cortex	[224]
NMDA R1 receptor	mRNA	Decreased	Cognitively impaired schizophrenic patients versus normal controls/superior temporal cortex	[225]
NMDA R1 receptor	mRNA	Decreased	Neuroleptic-free schizophrenics versus normal controls/superior frontal cortex	[226]
Kainate gluR6 and KA1 subunits	mRNA	Decreased	Normal controls/hippocampus	[172]
AMPA	mRNA	Decreased	Normal controls/hippocampus	[175]
gluR1 and 2 subunits	mRNA	Decreased	Normal matched controls/medial temporal lobe	[227]
gluR2 subunit: flip and flop isoforms	mRNA	Decreased	Normal matched controls/hippocampus	[228]
AMPA receptors	Protein	Decreased	Normal matched controls/medial temporal lobe	[171]
Excitatory amino acid transporter 2 (EAAT2)	mRNA	Decreased	Normal controls/parahippocampal gyrus	[229]
EAAT3	mRNA	Decreased	Normal and mood disorder controls/striatum	[230]
Ca(+)/calmodulin-dependent protein kinase II (CaM kinase II)	mRNA	Increased	Normal controls/frontal cortex	[231]
Dopamine D3 receptor	mRNA	Decreased	Normal and Alzheimer's disease controls/parietal cortex	[232]
Growth-associated protein 43 (GAP-43)	mRNA	Decreased	Normal controls/medial temporal lobe, primary visual cortex and anterior cingulate gyrus	[233]
GAP-43	Protein	Increased	Normal controls/visual association and frontal cortices (BA 20 and 10)	[234]
Wnt-1	Protein	Increased	Normal controls/hippocampus	[235]
Reelin	Both	Decreased	Normal controls/PFC (BA 10 and 46), temporal cortices (BA 22), hippocampi, caudate nuclei, and cerebella	[236]
Mitochondrial genes	mRNA	Decreased	Normal controls	[237]
BDNF	Protein	Increased	Anterior cingulate cortex and hippocampus	[238]
NCAM	Protein	Increased	Normal and non-psychotic suicide controls/hippocampus and prefrontal cortex	[239]

result from antipsychotic treatment, or are secondary to the main pathophysiology of schizophrenia. At the other end of the methodological spectrum are neuropsychological studies that demonstrate abnormalities in schizophrenia that are more closely linked to the main symptoms of psychosis and poor functioning.

5. Cognitive and neurological abnormalities in schizophrenia

Schizophrenia is associated with global intellectual impairment and deficits in executive functioning, memory and attention [28]. Current diagnostic criteria and early descriptions of schizophrenia include attentional, motivational and affective disturbances as part of the illness [1]. Neuropsychological abnormalities in schizophrenia range from relatively primitive and subcortical phenomenon such as auditory evoked potentials (AEP) and prepulse inhibition (PPI), to higher order, cortically based functions like working memory, affect recognition and other elements required for social functioning. Some deficits have been demonstrated in first-episode patients, suggesting that cognitive and emotional dysfunction are not due to neuroleptic treatment, but are intrinsic to schizophrenia [245]. The performance of schizophrenic patients differs from controls by approximately one standard deviation, and greater cognitive deficits are associated with more severe negative symptoms, worse psychosocial functioning, and the presence of soft, non-localizing neurological signs [246–248]. These subtle neurological abnormalities are present even in never-treated, first-episode patients [249,250], and include extrapyramidal signs and dyskinesias [251]. Furthermore, the type of cognitive impairment seen in schizophrenia, and the association with negative symptoms, are consistent with frontal lobe impairment. General functions of the frontal lobes include the sequencing, planning and initiation of complex behavior [252].

Patients with schizophrenia have a variety of neuropsychological abnormalities demonstrable in a non-clinical, laboratory setting. For example, deficits in sensorimotor gating are evident in impaired PPI, a test measuring the startle response to a loud tone. In normal controls, a lower volume 'warning sound' (the prepulse), is able to attenuate the startle response. The prepulse is less effective in reducing startle in schizophrenics [253], and with amphetamine treatment in normal subjects [254]. Patients with schizotypal personality disorder and relatives of schizophrenic patients also show reduced PPI in comparison with controls [255].

Event-related potentials (ERP) can measure the surface component of brain electrophysiological response to specific attention tasks, and include the p50 and p300 waves discussed below [256]. Mismatch negativity (MMN) is a specific pattern seen in response to 'deviant' stimuli embedded in a background of homogeneous stimuli. For example, a series of repeated tones of the same pitch may have a deviant tone of a different pitch inserted periodically. Patients with schizophrenia have a reduced MMN amplitude and an altered MMN topography that is not diagnostic when compared with other conditions that show altered MMN such as stroke and Alzheimer's disease [257,258].

Measurement of AEP reveals a characteristic pattern of response to test sounds. 50 ms after stimulation, a p50 wave is observed and 300 ms after stimulation there is a p300 wave. Normal subjects show a marked reduction in p50 amplitude after the second of a pair of sounds. Schizophrenic patients, in contrast have an attenuated suppression of p50 after the second stimulus [259], as do their relatives [260], consistent with their abnormal PPI response. The amplitude of the p300 wave seen in AEP measurements is reduced in schizophrenia, and appears to be a trait marker independent of clinical status [261]. Increased latency of the p300 AEP in schizophrenia has also been reported [262]. These evoked potential abnormalities indicate some impairment in processing of sensory information even before it reaches the cortex, and may represent an endophenotype of schizophrenia [259]. Genetic linkage between abnormal p50 AEP and the α-7 nicotinic receptor gene has been reported [263]. However, as with many of the findings in schizophrenia, these electrophysiological abnormalities are not specific, and can be demonstrated in other brain disorders.

Anatomical evidence of PFC and medial temporal lobe (MTL) involvement in schizophrenia is strengthened by functional imaging and neuropsychological studies implicating the same brain regions. Extensive evidence exists for deficits in working memory, which is subserved in part by the DLPFC, and long-term memory, for which the MTL and hippocampus are crucial (reviewed in Ref. [264]). Working memory is vital for maintaining representations of sensory information in current use that are needed to guide behavior [265]. Semantic memory is also impaired, a likely substrate for the thought disorder and disorganized speech that many schizophrenic patients have [266]. The MTL is also implicated in the abnormal smooth pursuit eye movements found in many schizophrenic patients and in about 40% of their first-degree biological relatives [267].

Impaired social functioning is an obvious clinical feature of schizophrenia, and recent work has begun to illuminate the neuropsychological components of this problem. While incompletely understood, normal interpersonal interactions require that a variety of cognitive tasks be completed successfully, and that the emotional content of the interaction is accurately interpreted. 'Social cognition' is likely mediated by a variety of brain regions including the PFC, cingulate gyrus, amygdale, and temporal cortex; and includes tasks like emotional affect perception, emotion processing, understanding the mental representations of others (sometimes called 'theory of mind'), self-reference and working memory (reviewed in Ref. [268]).

Schizophrenic patients have difficulty in correctly perceiving the affect displayed in facial expressions and vocal communication (reviewed in Ref. [269]), and this deficit is specifically related to decreased social functioning (as opposed to just face recognition, which is also impaired) [270]. 'Affective reactivity', or the tendency to have more disorganized thinking with emotionally negative topics, is increased in schizophrenia, and this abnormality is associated with increased startle response [271]. Having a theory of mind or being able to 'mentalize' is to be able to understand the mental states of others, and to use that understanding to influence the behavior of others. Humans are usually able to do this, but most other animals are not. Great apes have a rudimentary ability to mentalize, but this seems to be at the limit of their cognitive capacity (reviewed in Ref. [272]). This ability is also impaired in schizophrenia [273,274], and may play a role in both disrupting social interaction and in the genesis of delusions of reference or persecution.

6. Schizophrenia and neurodevelopment

Basic questions about the pathophysiology of schizophrenia remain unresolved, including whether schizophrenia is a neurodevelopmental or neurodegenerative disorder, or a mix of the two. The basic problem of defining the diagnosis and scope of the concept we label schizophrenia is highlighted whenever conflicting findings are considered [275]. Different features of the illness may have different explanations—explanations that need not be exclusive, if one allows that schizophrenia is a heterogeneous collection of diseases with a common clinical presentation. However, this diagnostic uncertainty confounds information from all types of experiments from neuropathology to treatment response to genetics.

Evidence for a neurodevelopmental etiology includes premorbid subtle, non-clinical abnormalities in cognitive and social functioning. These are present early in life and are later expressed as the full disorder [276]. In an elegant case-control study, Walker et al. [277] had neurologists observe the play and social interactions of children in home movies (the neurologists were blind to the future diagnosis and other information about the child). Children who would later develop schizophrenia showed a higher rate of neuromotor abnormalities, occurring primarily on the left side of the body, similar to the motor signs described in schizophrenic patients. A retrospective cohort study examining the associations between adult-onset schizophrenia and childhood sociodemographic, neurodevelopmental, cognitive, and behavioral factors found impairments in those who would later develop schizophrenia. The schizophrenic cohort was slower to reach developmental milestones, had more speech problems, and had lower educational achievement and test performance. Self and teacher reports of social functioning were also lower in the schizophrenic group, and they were more likely to prefer solitary play [278].

The consistent findings of ventricular enlargement and cortical volume loss may be explained by either developmental or degenerative hypotheses. In support of a developmental origin to schizophrenia is the presence of gross structural brain changes in first-episode patients, before neuroleptic treatment, and before symptoms have been present for a significant time. However, if the brain volume changes are progressive, at a rate faster than with normal aging, this argues for an ongoing degenerative process that begins before the onset of clinical illness and continues throughout life. No comprehensive, longitudinal, controlled studies exist to resolve this question with certainty. Although there is some evidence that the brain volume changes are progressive [279–282], various confounding factors such as technical artifacts, drug treatment or physiological epi-phenomenon may also account for the progression [283]. If brain volume deficits are associated with the underlying disease process, and if this pathology is progressive, then one might expect a correlation between duration of illness and degree of brain volume change, as in Alzheimer's disease. However, there does not appear to be such a correlation in schizophrenia, which argues against a neurodegenerative hypothesis [284].

Histology does not provide a definitive answer to the question of whether schizophrenia is a primarily degenerative versus developmental disease. Gliosis is a marker of past inflammation [285], and therefore is an indicator of damage and response to damage after the second trimester of gestation. As mentioned in Section 4.2, there is disagreement about the presence or absence of gliosis. Some groups find gliosis in diencephalic regions while more recent studies concentrating on the cerebral cortex, do not [54]. The absence of gliosis in the cortex tells us nothing about other ongoing pathology that may be mediated by apoptosis [286]. So, although current evidence suggests that gliosis is absent, this does not establish conclusively that schizophrenia is a neurodevelopmental disorder.

The cytoarchitectural abnormalities seen in schizophrenics include abnormalities of the rostral and intermediate portions of the entorhinal cortex, aberrant invaginations of the cortical surface, disruption of cortical layers, heterotopic displacement of neurons, and a paucity of neurons in superficial layers [89]. The subplate is a transient layer in the developing cortex from which neurons migrating to cortical layers II–VI originate, including those affected in schizophrenia. The subplate may have considerable importance in the development of cortical circuitry, and plays a crucial role in guiding thalamocortical and other long-range cortical projections to their destinations in the developing cortex [287]. Corticogenesis and the migration of neurons to their cortical target layers occur prenatally, so disrupted cortical cytoarchitecture in schizophrenia argues strongly for a neurodevelopmental process. The well-known but relatively weak associations between schizophrenia and

obstetrical complications [288], and minor congenital physical anomalies postulated to result from uterine insults [289], might represent a subgroup of patients with schizophrenia that have a traumatic or other pre/peri-natal etiology.

Human brain functions, especially those related to language, are lateralized, leading some to consider the role of brain asymmetry in the development of schizophrenia. Some structural imaging studies have found asymmetrical reductions in brain volume but these have not been replicated [12]. The imaging findings of asymmetry, however, correlate with post-mortem findings of decreased left parahippocampal width [58], and left-sided temporal horn enlargement [290]. The degree of right–left preference or 'handedness' is also abnormal in children who will later develop schizophrenia [291]. This has led to speculation about the abnormal development of hemispheric dominance in schizophrenia, which would be consistent with a neurodevelopmental hypothesis.

Neurodevelopmental and neurodegenerative explanations for schizophrenia are not necessarily exclusive. These semantic distinctions obscure some important but largely unexplored questions. Evidence from non-human primates suggests that significant remodeling of dendritic arbors, and cortical connections occurs throughout childhood and adolescence, likely in concert with the learning of language and other complex developmental tasks [292]. It has been hypothesized that the emergence of symptoms in late adolescence may be related to abnormalities in pruning that either reveal the latent cytoarchitectural abnormalities or act synergistically with these earlier developmental abnormalities [293].

7. Drug treatment for schizophrenia

7.1. Conventional neuroleptics

First discovered in the 1950s, the phenothiazine neuroleptic chlorpromazine led to a dramatic improvement in the management of the positive symptoms of schizophrenia. Over the next two decades, different chemical families of neuroleptics (e.g. butyrophenone and benzamide) were identified and introduced as antipsychotic drugs. Common antipsychotics include haloperidol, perphenazine, trifluoperiazine, and fluphenazine, to name just a few. This class of drugs decreased the length of hospitalizations, and with maintenance treatment, reduced the risk of relapse and re-hospitalization [43].

Although antipsychotics are effective in reducing psychotic symptoms, they have significant shortcomings. For a significant portion of schizophrenic patients, these drugs are ineffective ($\sim$30%), produce intolerable side effects (5–10%) [294], or even exacerbate symptoms (reviewed in Ref. [295]). Even patients who respond to and comply with treatment have a 20% annual relapse rate

[296]. The negative symptoms and cognitive deficits associated with schizophrenia are not improved by the conventional neuroleptics [297,298]. All conventional neuroleptics cause a variety of neurological, gastrointestinal, and cardiovascular side effects that are often debilitating. The neurological side effects include extrapyramidal or Parkinsonian symptoms (tremor, rigidity, akinesia or bradykinesia, and a festinating gait), akathisia, and a decreased seizure threshold. Early expression of extrapyramidal symptoms (EPS) significantly increases the chance of later developing tardive dyskinesia [251], a long-term and potentially irreversible movement disorder. Severe EPS can exacerbate negative symptoms and cognitive deficits, and contributes to non-compliance. Cardiovascular side effects include orthostatic hypotension and in large doses, impaired cardiac conduction. Other side effects of classical neuroleptics include erectile and orgasmic dysfunction [299], and persistent elevations in serum prolactin (PRL), which can result in menstrual irregularities and galactorrhea.

7.2. Mechanism of antipsychotic action

The antipsychotic action of neuroleptics is linked to blockade of DA receptors [300]. Conversely, DA receptor agonists induce a schizophrenia-like psychosis [301–303], and these effects are inhibited by dopamine D2 receptor antagonists [300]. Additionally, the clinical potency of different classes of antipsychotic drugs, despite different chemical structures, correlates well with their in vitro binding affinities for the dopamine D2 receptor [300, 304–306] suggesting that this receptor is a common target for antipsychotics.

These discoveries formed the basis of the DA theory of schizophrenia: that the positive symptoms arise from hyperdopaminergic activity [146]. The reversal of positive symptoms or psychosis by antipsychotics is probably mediated by blockade of D2 receptors in the mesolimbic region, and EPS probably results from blockade of these receptors in the basal ganglia. In vivo imaging studies have shown that 60–80% D2 receptor occupancy in the basal ganglia is required for antipsychotic effect, whereas EPS emerges when D2 receptor occupancy exceeds 80% [307]. PET studies with selective DA receptor ligands show that phenothiazine-treated patients with acute EPS had higher D2 receptor occupancy in the basal ganglia than those who did not experience those side effects [307]. In general, antipsychotics with higher D2 affinity tend to produce more EPS and akathisia than those with a lower D2 affinity, at the same effective dose.

7.3. The prototypical atypical antipsychotic: clozapine

In 1988, Kane et al. demonstrated that clozapine was effective in a significant portion ($\sim$30%) of schizophrenic patients who were refractory to typical neuroleptic

treatment [308]. Clozapine is effective in treating not only the positive symptoms of schizophrenia, but also in reducing negative symptoms and cognitive deficits [309–313]. More importantly, clozapine does not induce the EPS, and PRL elevation commonly seen with typical neuroleptics. Unfortunately, clozapine is limited by a severe side effect (agranulocytosis) in about 1% of recipients, necessitating frequent leukocyte and granulocyte count monitoring. Clozapine is now used in patients who have failed to respond to two conventional neuroleptics from different chemical classes, or who have severe neurological side effects. Clozapine's effectiveness in treating refractory symptoms has been pivotal in stimulating research aimed at developing new, effective atypical antipsychotics that do not cause agranulocytosis.

Much of clozapine's atypical properties have been attributed to its unique pharmacological profile, that includes an affinity for serotonin (5-HT$_{2A}$, 5-HT$_{1A}$ and 5-HT$_{2C}$, 5-HT$_7$, 5-HT$_6$), adrenergic (α1, and α2), dopamine (D1, D2, D3 and D4), histamine (H1), and muscarinic receptors (M1 and M4) (reviewed in Refs. [295,314]). The D2 dopamine receptor affinity of clozapine is much lower than that of most classical neuroleptics, which are predominantly selective D2 blockers, with variable adrenergic, histaminergic and anticholinergic affinity. Clozapine is able to reverse catalepsy induced by the atypical antipsychotics olanzapine and loxapine [315]. This suggests that an additional mechanism may influence clozapine's reduced liability for motor side effects, since olanzapine, loxapine and clozapine are almost equipotent in blocking the various serotonin, DA and muscarinic sites [315]. The atypical antipsychotics risperidone, olanzapine, sertindole, quetiapine and ziprasidone, are discussed below.

7.4. Other atypical neuroleptics

None of the existing atypicals is as effective as clozapine in treatment-refractory patients, nor are they as free of neurological side effects. Atypical antipsychotics were initially marketed as being effective in the treatment of negative symptoms, and having fewer side effects. Recent evidence suggests that while atypical drugs do cause less EPS, they are no more tolerable or effective than conventional antipsychotics [44], and may produce more weight gain [316]. Furthermore, the advantages originally attributed to atypical drugs were partially the result of the higher doses of conventional neuroleptic used in the past. There is insufficient data to predict the risk of tardive dyskinesia in atypical neuroleptics, or to properly assess quality of life concerns [44].

Risperidone (Risperdal), is a benzisoxazole derivative, with a high affinity for serotonin 5-HT$_{2A}$, 5-HT$_7$, dopamine D2 receptors, α1 and α2 adrenergic and histamine H1 receptors [317]. Unlike clozapine, risperidone is a relatively potent D2 antagonist, although its 5-HT$_{2A}$ affinity is much higher than its D2 receptor affinity. In lower doses (2–6 mg/day) risperidone produces less EPS than conventional antipsychotics, but the risk of EPS at a dose of 8–12 mg/day, is similar to haloperidol at 10–20 mg/day [318,319]. Risperidone can also cause akathisia, tardive dyskinesia and PRL elevation [320].

Olanzapine (Zyprexa) has a pharmacologic profile similar to that of clozapine, with affinity for D1, D2, D4, 5-HT$_{2A}$, 5-HT$_{2A}$, 5-HT$_6$ and 5-HT$_7$ serotonergic, histamine H2, α1-adrenergic, and M1 muscarinic receptors. Its affinity at all these receptors is greater than that of clozapine, as is its clinical potency [321,322]. However, the relative affinity of olanzapine for 5-HT$_{2A}$ versus D2 receptors (i.e. pK_i ratio of 5-HT$_{2A}$/D2) is less than that for clozapine. There is some evidence that olanzapine can improve negative symptoms [323,324]. Quetiapine (Seroquel) is a clozapine congener that acts as a 5-HT$_{2A}$ receptor antagonist, with relatively weak D2 receptor affinity. Both clozapine and quetiapine (unlike other atypicals) have a high affinity for α2 receptors that is greater than their D2 receptor affinity [325]. Ziprasidone (Geoden) and zotepine (Zoleptil) show atypicality in dopaminergic models and have a high affinity for 5-HT$_{2A}$ and D2 receptors, similar to that of risperidone. Sertindole (Serlect) is an imidazidoline derivative with a relatively restricted receptor binding profile. It has a high affinity for 5-HT$_{2A}$ and 5-HT$_{1A}$, moderate affinity for D2 and low affinity for 5-HT$_{1A}$, D1, cholinergic muscarinic or α-adrenergic receptors [326,327]. It is an effective antipsychotic that has been reported to produce less EPS than haloperidol [328].

7.5. D2 receptor blockade by atypical antipsychotics

Although atypical neuroleptics are D2 receptor antagonists, the nature of their interaction with this receptor may be different from that of conventional neuroleptics. PET studies show that 60–80% D2 blockade is required for antipsychotic response, while over 80% D2 receptor occupancy in the basal ganglia produces EPS [307,329]. At clinically effective doses, typical antipsychotics usually occupy between 70 and 90% of D2 receptors, while atypical drugs have a D2 receptor occupancy of 60–80% [330,331]. At higher doses, and at corresponding higher D2 receptor occupancy (i.e. >80%), even the atypical drugs (risperidone, olanzapine, sertindole and ziprasidone) tend to cause EPS [331]. Recent findings suggest that D2 receptor occupancy by clozapine and quetiapine peaks shortly after administration (to 80 and 59%, respectively) and then falls rapidly. It has thus been suggested that fast dissociation from the D2 receptor may be sufficient for mediating antipsychotic action with reduced side effects and may underlie the superior clinical profile of these drugs [332].

Atypical agents may have a lower D2 affinity or a faster dissociation rate from D2 receptors ($>K_{off}$) than conventional neuroleptics [333]. Atypical antipsychotics might then be displaced more easily from D2 receptors in

the striatum by the presence of high levels of endogenous DA, thereby reducing EPS. However, in mesolimbic and mesocortical areas where the endogenous DA level is lower, sufficient receptors would still be occupied (between 70 and 80%) to elicit antipsychotic effects [334,335]. To compensate for low potency, higher doses of most atypical antipsychotics are required (10–500 mg/day). While the low potency atypicals have some advantages over conventional neuroleptics, patients taking them may have a higher risk of relapse [333].

7.6. Atypical antipsychotics and other receptors

It has been suggested that other dopamine D2-like receptors (D3 and D4) may mediate some of the features of atypical antipsychotics. These subtypes are more restricted to the mesocorticolimbic areas than D2. Since clozapine has a higher D4 affinity compared to D2, it was proposed that D4 receptor antagonism may be responsible for the therapeutic effects of clozapine and its low incidence of EPS [336]. Unlike other antipsychotics, the clinical potency of clozapine is correlated better with D4 rather than D2 affinity [336]. This observation prompted the synthesis of several compounds with high D4 and varying D2 and 5-HT2a affinity, but studies suggest that D4 blockade alone is insufficient for antipsychotic action [157]. Clinical trials with a selective dopamine D4 receptor antagonist, L-745,870, found it ineffective in neuroleptic-responsive inpatients with acute schizophrenia [337]. Fananserin (RP62203), a potent D4 and 5-HT2a antagonist, was also ineffective in treating positive and/or negative symptoms in schizophrenic patients [338].

The PFC is a brain region where lesions impair cognitive functions, including spatial working memory (reviewed in Ref. [339]). D4 receptors are enriched in the GABAergic interneurons of the primate PFC [340]. Clozapine, a D4 antagonist, has been shown to alleviate benzodiazepine inverse agonist-induced working-memory deficits [341,342] and cognitive deficits exhibited after long-term phencyclidine (PCP) treatment in monkeys [343]. Jentsch et al. showed that the potent and selective D4 receptor antagonist NGD94-1 could reverse the cognitive deficits in PCP pretreated monkeys [344], suggesting that this receptor subtype may modulate the cognitive functions of the frontostriatal system. Similarly, the selective D4 antagonist PNU-101387G, prevents benzodiazepine inverse agonist-induced working-memory deficits [345].

It has been difficult to determine the role of D3 receptors in antipsychotic action. The D3 receptor-preferring antagonist nafadotride, increases locomotion in rodents (unlike most neuroleptics) [346], and produces catalepsy at high doses [347]. Another D3 selective antagonist, (+)-UH232, exacerbated psychotic symptoms in 4 of 6 patients with schizophrenia, without producing EPS [348]. In the marmoset, dopamine D3 receptor activation results in selective impairment of cognitive function [349]. The D3

antagonist, (+)-S 14297, blocked haloperidol-induced catalepsy in animal models, but was ineffective in altering conditioned avoidance response in rats [350], a test often used to predict antipsychotic response. However, in another study (+)-PD 128, 907, a D3 receptor agonist, blocked stereotypy produced by MK-801 without catalepsy [351] suggesting a possible role for D3 receptors in antipsychotic action. More selective D3 receptor compounds may provide more insight about the potential role of this receptor in mediating antipsychotic action.

Negative symptoms and cognitive dysfunction have been associated with structural impairment in the PFC. Negative symptoms may be related to a cortical hypodopaminergic state, and cognitive dysfunction can arise from both a deficit or a marked increase in DA levels in the PFC [339,352]. The dopamine D1 receptor, which is highly expressed in the PFC, has been implicated in the control of working memory, a cognitive function impaired in schizophrenia [353–356]. Both reductions [339,357] and increases [358] in PFC D1 receptors have been reported in schizophrenic patients, independent of medication treatment. Nevertheless, decreases in D1 activity in the PFC have been correlated with severity of negative symptoms and cognitive impairment [339,357], suggesting that D1 agonists may have a role in treating these symptoms. Others have suggested the opposite, that the D1 antagonist activity of clozapine at low doses preferentially enhances the extracellular concentration of DA in the PFC [359], and that this is responsible for beneficial effects on cognition and negative symptoms.

Meltzer hypothesized that a high relative 5-HT$_{2A}$ to D2 receptor affinity is important for less EPS and improving negative symptoms [360], since pure 5-HT$_{2A}$ antagonists such as ritanserin improved negative symptoms and reduced EPS when used in combination with classical neuroleptics [361,362]. Risperidone was the first antipsychotic with combined 5-HT$_{2A}$ and D2 blockade. In lower doses (<6 mg/kg) risperidone did display an atypical profile, but at high doses risperidone produced a dose-dependent increase in EPS [318,319]—likely related to its high D2 affinity. 5-HT$_{2A}$ blockade may reduce neuroleptic-induced EPS, since risperidone and the other atypicals do not cause EPS to the same degree despite an almost complete occupancy of D2 receptors. 5-HT$_{2A}$ blockade with a concomitantly low D2 receptor blockade (i.e. low affinity and occupancy) seem to reduce these side effects. 5-HT$_{2A}$ blockade may be sufficient, but is not necessary, to reduce the EPS produced by atypical neuroleptics. Sulpiride and remoxipride are antipsychotics with no appreciable 5-HT$_{2A}$ affinity, yet they have a low tendency to produce EPS [363]. The mechanism by which 5-HT$_{2A}$ blockade might reduce EPS is still unclear, but may be related to disinhibition of nigrostriatal dopaminergic pathways [364,365].

Muscarinic receptors may reduce the D2-mediated side effects of antipsychotics. Muscarinic receptor activation

induces EPS [366,367], while muscarinic receptor antagonists are used to treat neuroleptic-induced EPS. Muscarinic M1 receptor blockade by some atypical antipsychotics, including clozapine and olanzapine may reduce the EPS that would otherwise result from D2 receptor blockade. However, other atypical drugs like quetiapine, ziprasidone and sertindole are weak muscarinic antagonists, but still have low potential to cause EPS. Therefore, blockade of muscarinic receptors is not necessary for this feature of atypical drugs. In addition, muscarinic receptor blockade is associated with anticholinergic side effects such as constipation, dry mouth, blurred vision, urinary hesitancy and cognitive impairment [368,369]. Note that the sialorrhea associated with clozapine is likely related to muscarinic M4 receptor affinity [370].

The glutamatergic hypothesis of schizophrenia has led to some experiments exploring the effects of antipsychotics on the glutamate system. The results suggest that many components of glutamate system may be affected by antipsychotics, but do not provide a clear picture of the overall impact of antipsychotics on glutamatergic function. Glutamate release can be altered by antipsychotic treatment in rats [371–373]. In humans, clozapine was reported to elevate serum concentrations of glutamate [374], while olanzepine had no effect on CSF levels of glutamate [375]. Fluspirilene is an antipsychotic drug with Ca-channel blocking properties that appears to inhibit glutamate release in synaptosomes [376]. In addition to these immediate effects on glutamate release, antipsychotics appear to elevate AMPA receptor subunit mRNA expression [377], to regulate NMDA receptor mRNA levels [378], and to down regulate glutamate transporter GLT-1 expression in the rat cortex, effectively increasing extracellular glutamate levels [379]. Intracellular interactions between the DA and glutamate systems have also been reported, in which D2 antagonists increase phosphorylation of NMDA NR1 subunits [380]. These DA receptor–glutamate interactions may mediate antipsychotic-induced EPS, and may be one factor differentiating atypical from conventional antipsychotics [381]. Novel drugs that directly target the glutamate receptor system have the potential to improve cognitive functioning and negative symptoms in schizophrenia, given that these deficits can be induced by NMDA blockers (reviewed in Ref. [382]).

8. Schizophrenia genetics

8.1. A genetic component to schizophrenia?

Since the identification of schizophrenia in contemporary medicine, various theories have arisen to explain its etiology, including poor mothering, family dynamics, psychological defenses and a host of biological mechanisms [5,383]. Although obstetrical complications, prenatal insults and viral infection have been reported to contribute to the disorder, these insults probably account for only a small proportion of cases or contribute only a small effect to the phenotype [383,384]. Twin, adoption and family studies have established that there is a significant genetic, inherited component to schizophrenia [5].

The risk of developing schizophrenia in the general population is clearly lower than that of relatives of patients with schizophrenia. Family studies show that the risk of developing schizophrenia is highest in first degree relatives of the schizophrenic proband (5–15% average lifetime morbid risk), and that the risk to relatives diminishes in second degree (2–6%) and third degree (2%) relatives [5, 385]. These figures show that schizophrenia runs in families, but not necessarily that there is an inherited component to this familial aggregation.

Adoption studies can help to distinguish inherited from environmental factors in the etiology of familial disorders. Children of schizophrenic parents, adopted by non-schizophrenic parents, are less likely to be exposed to the postnatal environment they would experience with their biological parents. Adoption studies with large government registries in Denmark [386], and Finland [387], and family studies in the United States [388], for example, confirm that some vulnerability to schizophrenia is inherited [389].

MZ and dizygotic (DZ) twins presumably share much of their prenatal and childhood environment, but MZ twins have a concordance rate for schizophrenia around 30–50%, while DZ twins have a concordance rate similar to non-twin siblings of ~10% [390,391]. The exact concordance figures vary from study to study, but the concordance rate for MZ twins is consistently higher than for DZ twins. The discordance of MZ twins for schizophrenia, however, indicates that factors other than the inherited gene sequence influence the development of schizophrenia [392]. The family and twin studies also show that schizophrenia is not transmitted in the classical Mendelian pattern associated with highly penetrant single gene disorders such as cystic fibrosis [393].

8.2. Genetic linkage and association findings

Linkage studies so far have identified loci on chromosomes 1 [394], 2, 4, 5, 6, 7, 8, 9, 10, 13, 15, 18, 22, and X, as evaluated at the Sixth World Congress on Psychiatric Genetics [395–407], and reviewed by Riley [408]. But, these linkage results either require replication, have contradicting reports or do not meet the statistical criteria for significant linkage [409]. Screening candidate genes to test may be a better strategy than hypothesis-free genome scanning approaches [410], but again there are no definitive results. Despite the clear involvement of DA receptors as a therapeutic target in schizophrenia, genetic studies have been unable to confirm linkage between schizophrenia and DA receptor or transporter genes [411–416]. However, a variation in the COMT gene has been reported to be associated with a slightly elevated risk for schizophrenia

[158]. Serotonin receptor genes have also been assessed for association with schizophrenia, suggesting that the 5-HT$_{2A}$ receptor may contribute to susceptibility to schizophrenia [417], but there have been negative reports as well [418]. The 5-HT$_{2A}$ receptors in the PFC may have an important role in working memory functions that are affected in schizophrenia [419]. The search for genetic association with candidate genes has included neurodevelopmental genes, but some studies of neurotrophin-3 [420], and brain-derived neurotrophic factor (BDNF) [421] have not demonstrated an association.

There is an area of chromosome 22q11-13 that has interesting connections to psychosis and schizophrenia. Several chromosomes including 5q, 11q, 18q, 19p and 22q have abnormalities that are associated with schizophrenia and psychosis [422]. The 22q11.2 region is subject to deletions that are associated with the DiGeorge and velo-cardio-facial syndromes [423]. This syndrome is characterized by variety of phenotypes involving midline structures, but also with an increased risk (24–30%) of developing schizophrenia and psychotic symptoms [424]. Microdeletions in 22q11.2 are significantly associated with schizophrenia [425], and the 22q11-13 region has also been implicated in both linkage analysis and linkage disequilibrium (LD) studies with a variety of markers [406]. The COMT and 14-3-3η (see below) genes are also located in this region of chromosome 22. The possible connection between chromosomal abnormalities and psychiatric disease is illustrated by a recent report of a region on chromosome 15 as a susceptibility factor for panic and phobic disorders [426].

Some interesting candidate genes have recently been demonstrated to have an association with schizophrenia. The 14-3-3η-chain gene is a member of a family of regulatory protein genes that have been reported to have mRNA abnormal expression levels in schizophrenia [244], and to have a genetic association with schizophrenia [427–429]. A gene named DISC-1 (disrupted in schizophrenia, located at 1q42) appears to have an association with schizophrenia in two distinct populations studied so far: Scottish [430,431] and Finnish [432]. The function of this gene has not been well characterized. As often is the case in schizophrenia genetics, there are reports of linkage (1q21-22) [394] and no linkage on chromosome 1 [433]. A significant association between the dysbindin gene on 6p22.3 and schizophrenia was recently reported ($P < 0.01$) [434], and this gene is within a susceptibility region (6p34-21) previously linked to the illness [435]. Neuregulin (NRG1) was identified as a candidate gene for schizophrenia in a genome-wide scan, followed by fine-mapping and a transmission-disequilibrium test. NRG1 and NRG1 receptor (ErbB4) heterozygote knock-out mice have behaviors that overlap with other mouse models of schizophrenia, and clozapine can partially correct the abnormal phenotype [436]. The genetic association was also replicated by the same group of researchers in a separate study population [437].

8.3. Models of inheritance

If schizophrenia does indeed have a genetic cause, at least in part, then why have the linkage studies failed to find these genes? Several factors hamper the search for genes linked or associated with schizophrenia in particular, as compared with other complex diseases. First of all, the practical aspects of family genetic studies are problematic in schizophrenia. Compliance with treatment, motivation, and insight are all affected adversely by this disorder, and so a lack of cooperation with genetic studies is often encountered. Even case finding is difficult, again because the ill may not seek treatment, and so sampling of affected cases is biased against those who may be the most ill. The social stigma associated with schizophrenia and mental illness in general does not encourage participation in genetic studies, either by patients or their families. Diagnosis through collateral history for deceased or unavailable family members is haphazard at best. As discussed in Sections 1 and 2, the fundamental issue of accurate and valid diagnosis remains a problem in genetic studies of schizophrenia, leading to the possibility that 'phenocopies' will confound results. Despite these caveats, several models, which may coexist, may explain the familial pattern of inheritance, including MZ twin discordance, and the lack of definitive linkage results. The polygenic, monogenic, multiplicative multilocus, environmental, epigenetic and integrative models are discussed below.

A polygenic model posits that multiple genes, each having a small effect, predispose an individual to developing schizophrenia. In polygenic, or genetically 'complex' disorders or traits, linkage and association studies require an enormous number of families even from isolated populations to achieve the necessary power [409]. Other common disorders such as diabetes and bipolar disorder are likely complex genetic disorders as well [410]. If there are more than 'a few' genes involved or if the disease arises out of epistasis between two or more genes, then the linkage approach may yield conflicting results even in large studies [438]. Thus, the fact that many loci have both positive and negative linkage reports with schizophrenia, is consistent with a polygenic model of inheritance [439].

A monogenic, or single gene hypothesis is not consistent with the pattern of relative risk seen in the families of schizophrenic patients [438]. The lack of definitive linkage results in schizophrenia [408], is also more consistent with a polygenic rather than monogenic pattern of inheritance. Current opinion then, is that "we can now conclusively reject that there is one gene of major effect that causes schizophrenia" [440], and furthermore, that we can "exclude the possibility that schizophrenia is a single gene disorder or a collection of single gene disorders even when incomplete penetrance is taken into account" [418].

Polygenic models may be additive multilocus or multiplicative multilocus models. In the multiplicative multilocus model, there is interaction or 'epistasis' among the genes,

whereas in the additive model, it is the cumulative, 'additive' effect of many genes that do not interact. λ_R is defined as the relative risk ratio of developing the illness in a relative of someone with schizophrenia ($\lambda_R = K_R/K$, where K_R is the risk to a relative of type R, and where K is the population prevalence). In a single gene or an additive multilocus model, $\lambda_R - 1$ would be expected to decline by a factor of two for each degree of relatedness. In a multiplicative multilocus model, $\lambda_R - 1$ decreases at a greater than 2-fold rate [438], which is consistent with the risk to relatives in schizophrenia [5]. However, the number of loci involved, the risk contributed by each locus, and the degree of interaction are unknown [441].

A second hypothesis is that non-genetic factors contribute to the cause of schizophrenia. The heritability of an illness may be calculated from family studies, and twin studies in particular, and is a measure of the proportion of phenotypic variance that is due to genetic variance. Heritability is defined as the ratio of the total multilocus aggregate polygenotype variance and the total phenotypic variance. Heritability may be estimated by the ratio of the observed phenotypic correlation to the theoretical genotypic correlation in related individuals [442]. Various studies have put the heritability of schizophrenia between 58 and 89%, indicating that other factors, perhaps environmental, may influence the expression of the illness [408,443]. Viral infection, season of birth, maternal stress, urban birth and obstetrical complications have all been linked with a higher incidence of schizophrenia [444]. As yet unknown environmental factors may also have a role in affecting the CNS, and may contribute to the histological, structural, or functional pathology of schizophrenia.

Another possible explanation for the complex inheritance pattern seen in schizophrenia and diabetes is that of epigenetic factors. Epigenetic factors include non-gene sequence based factors that influence the regulation, timing and location of gene expression. Epigenetic mechanisms include changes in DNA methylation and chromatin structure that can produce parent-of-origin effects (genomic imprinting), irregular monoallelic gene expression (polymorphic genomic imprinting), and variations in gene expression (epigenetic polymorphism) [445]. Several features of schizophrenia are consistent with epigenetic mechanisms: the discordance of MZ twin pairs, the relatively late and variable age of onset, sex differences in age of onset and course of illness [446], parent-of-origin effects, and fluctuations during the course of the illness [447]. However, no evidence was found for parent-of-origin effects in a study of over 400 families with at least 2 ill siblings [448].

None of these models have, at present, provided a satisfactory explanation for all of the genetic, neurobiological and epidemiological data about schizophrenia that is currently available. An integrative model, though complex, is arguably more useful in the search for the cause of this complex disease. Schizophrenia could arise from a significant multiplicative multilocus genetic vulnerability, modified at various stages of development by epigenetic and environmental factors. Simple models of schizophrenia etiology, though compelling, have led to a huge number of studies that have yet to verify any hypothesis. An integrative model, similar to those of other common diseases like cardiovascular disease and cancer, acknowledges the complex interplay between genes and environment that results in highly variable disease phenotypes [449].

8.4. Parametric linkage analysis

Strategies for finding disease genes may be categorized into linkage and association analyses. Linkage analysis may take the form of parametric linkage studies, or nonparametric analyses, and association studies may use case-control or family based approaches. Parametric linkage analysis has been applied with great success to Mendelian single-gene disorders, while association strategies are a more recent approach being applied to complex genetic disorders. The main features, strengths and weakness of these strategies are discussed below.

Parametric linkage analysis is applied to large multiplex families (families with multiple affected members), to ascertain the likelihood that a given gene or locus is responsible. As the name implies, parametric linkage analyses depend on a model of inheritance seen with single gene Mendelian disorders, in which the disease gene must be inherited from a parent with a family history of the illness. The basic assumption being that the disease gene will be found close to a marker allele that segregates with the disease phenotype. The usual statistic used to express the strength of evidence for linkage is the LOD score, short for logarithm of the likelihood (or 'odds') ratio [442]. Linkage analysis may incorporate multiple markers simultaneously—multipoint parametric linkage analysis—to yield multipoint LOD score maps of a given chromosomal region spanned by the markers. A problem arises in determining significance levels with the massive numbers of markers across the genome, and with different populations being studied. Too high a threshold for significance risks obscuring biologically important information (false negatives), while more lenient thresholds have produced a large number of contradictory results from almost every chromosome. One proposed standard for LOD score significance is $P = 0.00005$ (LOD ≥ 3.6), which across the genome would be equivalent to a 5% chance of randomly finding linkage [409]. Replication by independent groups is still required. This threshold is consistent with the traditional classical two-point linkage LOD score threshold of 3 [409].

No linkage studies in schizophrenia have yet met this threshold, likely because of the large sample sizes needed to detect genes with a low genotype relative-risk (GRR), defined as the relative risk of disease in individuals with a given genotype versus the general population. GRR and allele frequency both influence the power of linkage analysis [408]. Theoretical calculations predict that in

order to detect a susceptibility allele with a GRR of 4 that has a population frequency of 10–50%, a sample size of 200–300 families is required. However, if the same allele confers a GRR of 2, then 2500–4000 families are required, and a GRR of 1.5 requires 18,000–68,000 families to demonstrate linkage [410], which is not very realistic. The lack of replication in many of the positive reports in schizophrenia may partly be related to the problem of sample size. Although some of the positive reports may be real findings, the probability of finding linkage with one of several loci is always higher than the probability of replicating linkage at given locus [439].

If schizophrenia is a polygenic disease, then parametric strategies have several potential pitfalls. Parametric linkage studies require the specification of model parameters such as penetrance, relative genetic contribution, and mode of inheritance; that are often unknown in a polygenic disease. Misspecification can lead to false positive or false negative results. Parametric LOD score methods can be made more robust to misspecification of parameters by testing both a dominant and recessive model, and by using high disease allele frequencies [450]. Other genetic parameters that may confound such analyses include phenocopies, genetic heterogenetity, epistasis and varying allele frequencies. Linkage studies in multiplex families may be able to detect genes that are required for disease expression, but have limited power to detect genes that confer a moderate risk or susceptibility [451]. Although parametric linkage analysis would theoretically be able to identify a single major locus contributing to vulnerability, even in a polygenic disease, the linkage results to date, in combination with statistical arguments, point strongly to the absence of a single major gene locus in schizophrenia [449,452].

8.5. Association methods

In the search for complex disease genes, other strategies include association studies that may also incorporate an analysis of LD. Association studies do not require the specification of a model of inheritance, but rely instead on determining simple association between significant increases in disease risk and the presence of certain genotypes. Tests of association may be applied to unrelated case-control populations, sib-pairs or other affected–unaffected relative pairs, trios consisting of an affected proband and the parents, and small nuclear families with affected and unaffected members. Statistical approaches include: the haplotype relative-risk (HRR) [453], transmission disequilibrium (TDT) [454], or family based association tests (FBAT) [455]. However, association-based tests are not able to distinguish between a major 'necessary' gene and minor 'susceptibility' genes [456].

Case-control association studies analyze polymorphic regions in or near candidate gene regions, and compare genotypes of affected patients and controls matched by age, race and sex. Case-control studies in schizophrenia have yielded contradictory results, with two examples being the studies of the dopamine D3 [457,458] and the 5-HT$_{2A}$ receptor genes [417,459]. Despite a large number of patients from different research groups, results with these two genes remain inconclusive. However, subjects for case-control studies are much easier to recruit than for family based studies, so although other methods of studying association may be theoretically more powerful, they are limited by sample size [460].

Population-based association studies are vulnerable to population stratification effects, since spurious associations with the disease may arise from genes that are associated with ethnic composition or sampling bias in the cases versus controls. Family based studies control for this in part, by sampling families that of course share a common genetic background, and are therefore matched with respect to population of origin [455].

9. Animal models for schizophrenia

At the present time, there are no animal models that capture all the features of schizophrenia, or indeed any mental illness. Animal models of psychiatric illness are difficult to assess, since the core symptoms are abnormal internal states, which may exist while a patient appears outwardly normal. However, a number of pharmacological, structural lesion, environmental and genetic models have been developed that mimic certain aspects of the illness and are used in the screening of potential antipsychotic drugs. None of these is able to model the full spectrum of abnormalities in schizophrenia, especially since they are usually applied to rodents, although non-human primates are occasionally used. Animal models may be used to help understand pathophysiological mechanisms in psychosis and schizophrenia, but with the exception of the genetic models none can model the etiology. It may not be possible to recreate the diversity and complexity of schizophrenia in a single animal model, but the combination of these different models does help to understand the neurobiology of schizophrenia.

9.1. Pharmacological animal models

Pharmacological models include acute challenge and chronic treatments with DA agonists (amphetamine, apomorphine) [461,462], hallucinogens such as PCP, lysergic acid diethylamide (LSD), MK-801, psilocybin and ketamine [463–466], and neurotoxins (methylazoxymethanol acetate, 6-hydroxydopamine, p-chlorophenylalanine) [467,468]. The drugs may be given to adult animals or targeted to specific periods in development. The behavioral tests used to evaluate the animal models may be grouped into the following categories: DA-mediated unconditioned behaviors, conditioned DA-mediated behaviors, attention/information-processing deficits, and negative symptom

paradigms [469]. DA-mediated unconditioned behaviors are commonly evaluated by observing locomotor activity, DA-induced circling behavior, catalepsy, limb retraction time, and alterations in stereotyped behavior. Conditioned DA-mediated behaviors include operant responding for reward (either food or brain stimulation), conditioned place preference, conditioned activity, and conditioned avoidance response. Attention and information processing ability are often measured with PPI [470,471] and evoked potentials. Animal correlates of negative symptoms may be observed in social isolation/interaction protocols and the elevated plus-maze.

Using dopaminergic drugs in pharmacological models of schizophrenia leads to some circular reasoning in the screening of novel neuroleptic agents. If an animal phenotype that results from a manipulation of the dopaminergic system (e.g. amphetamine treatment) is normalized by a given drug, then that drug is deemed to have antipsychotic potential. These models establish only that the drugs in question are DA antagonists, which is not surprising since all existing antipsychotics are DA antagonists. However, considering that many of these behaviors are the result of activation of all DA receptor subtypes, the potential of DA receptor selective ligands (and ligands that indirectly modulate the DA system) can be assessed. These studies are also useful in identifying potential side effects of novel drugs.

PCP is a hallucinogenic drug of abuse; a single dose can produce psychotic symptoms in humans, similar but not identical to psychotic episodes in schizophrenia. It is an antagonist of NMDA glutamate receptors, but also interacts with sigma, dopamine D2 and 5-HT$_2$ receptors [472]. Sigma receptors have not been fully characterized, but they may mediate the modulation of ion channels by psychoactive drugs through protein–protein interactions [473]. Sigma receptor ligands can both alter NMDA-induced currents [18], and modulate the cognitive effects of PCP [474]. Some of the behavioral effects of PCP and other NMDA channel blocking drugs, like MK-801, are similar to those of amphetamine. In rodents, these effects include increased locomotor activity and stereotypic behavior, and persist with chronic administration [475]. However, in contrast to amphetamine, chronic PCP treatment produces tolerance rather than sensitization in acoustic startle, intracranial self-stimulation, and Y-maze performance. PCP-induced sterotypies and hyperactivity are reversible with neuroleptic treatment, but alterations in stimulus discrimination and social behavior are not [475].

Chronic PCP administration produces lasting psychotic symptoms in humans, including auditory hallucinations, paranoid delusions, and cognitive impairment. Non-human primates, when exposed to phencyclidine, show reduced prefrontal cortical DA transmission associated with frontostriatal cognitive dysfunction, similar to the findings in schizophrenia [476]. Chronic exposure in monkeys produces enduring deficits that persist after phencyclidine is discontinued, and the cognitive deficits are improved by clozapine treatment [343]. Non-human primates also exhibit changes in locomotor activity and social behavior, with preservation of motor function; features that capture more of the complexity of schizophrenia than other pharmacological models [477].

9.2. Lesion models for schizophrenia

Lesion models have contributed to our understanding of the pathophysiology and neurodevelopmental functions of various brain regions in relation to schizophrenia. Animal lesion models permit highly controlled interventions in the developing or adult brain that can be correlated with behavior or neurobiological markers used in human studies. However, most of these lesion paradigms are not naturalistic insults, and therefore cannot potentially model etiology in the way that genetic models can. Lesions in the hippocampus [478], frontal cortex [479], dorsolateral PFC, and intracerebroventricular KA injection [480,481] have been used to create structural models of psychosis in animals. Exposure to certain toxins can also create lesions in populations of vulnerable neurons. For example, fetal exposure to methyl-azoxymethanol acetate (MAM) results in destruction of rapidly dividing neurons. At gestational day 15, MAM administration disrupts the cytoarchitecture of the hippocampus and PFC, and results in hyperactivity, perseveration, cognitive impairment and disruption of latent inhibition [467].

The neonatal ventral hippocampal (VH) lesion model is of particular interest because it incorporates many diverse features of schizophrenia. This region is a primary target in lesion models because of the gross and histological hippocampal pathology found in schizophrenia (see Sections 4.1 and 4.2), and because the hippocampal innervation of the striatum is involved in regulating subcortical DA release [482]. Lesions of the VH enhance DA-mediated behaviors and DA levels [482], which is consistent with the DA hypothesis of schizophrenia. The VH lesion produces behavioral and biochemical abnormalities similar to those seen in pharmacological animal models used to test antipsychotic drugs, and in patients with schizophrenia. Although initially normal, these rats develop hyperactivity spontaneously and after stimulation with amphetamine or with stress, when compared with controls. Haloperidol blocks the emergence of hyperactivity in the lesioned animals. In addition, these animals have impaired PPI that develops at day 56 but not day 35 post-injection [478], decreased haloperidol-induced catalepsy, decreased apomorphine-induced stereotypy [483,484], increased startle amplitude, and persisting deficits in spatial learning and working memory [485]. The lesioned rats also have attenuated extracellular DA levels in the striatum after stress and amphetamine exposure [486]. Intracerebral tetrodotoxin (TTX) infusion can produce transient and reversible disruption of the hippocampus during

development without the structural damage induced by excitotoxic lesions. These TTX-infused rats had behaviors similar to those of rats with neonatal VH lesions, but not when infusions were performed in adult rats [487].

Of relevance to the genetic factors contributing to schizophrenia is that the abnormalities induced by VH lesions are strain dependent. Fischer 334 rats display changes in locomotion at post-operative day 35, and effects at day 56 were exaggerated in comparison with Sprague–Dawley rats, that are normal at day 35. Lewis rats, in contrast, appear to be resistant to the behavioral effects of VH lesions, consistent with the considerable differences between the two strains, including responsiveness to stress, preference for psychoactive drugs and vulnerability to inflammatory disease [488]. F344 and Lewis rats are also distinguished by neurochemical and neuroendocrine differences, the genetic basis of which is the subject of ongoing investigation [489]. There is also evidence that early maternal environment may be a more powerful influence than genes on the behavioral differences between these rat strains [490].

Excitotoxic lesions of the medial prefrontal cortex (MPFC), created with intracranial ibotenic acid injection in neonatal day 7 rats, have also been investigated as potential animal models of psychosis. The MPFC has also been implicated as having structural abnormalities in schizophrenia, and projections from the MPFC regulate striatal DA levels [491]. At day 56, MPFC-lesioned Sprague–Dawley rats demonstrate enhanced locomotor activity spontaneously and with *d*-amphetamine, in comparison to sham-lesioned animals. Dopamine D2 receptor expression is persistently increased in striatal and limbic areas, and there is a small, transient elevation in DA transporter expression in the shell of the nucleus accumbens [479]. Others, however, report contradictory findings: attenuated locomotor activity in response to novelty, amphetamine and MK-801, and no change in striatal dopamine D2 receptor expression [492]. These authors also find increased apomorphine-induced sterotypies as a result of the lesion [492]. No changes in startle amplitude or PPI are seen with neonatal MPFC lesions [493]. Adult lesions of the MPFC do not seem to affect latent inhibition, but there are reports of both inhibition [494] of and enhancement [495] of PPI. Other abnormalities associated with adult rat MPFC lesion include: abolishment of the partial reinforcement extinction effect and transient hyper-locomotion [494].

The MPFC and the VH are part of the two areas most consistently implicated in the pathology of schizophrenia, and are closely interconnected [496,497]. Afferents from the hippocampus to the PFC transmit excitatory signals mediated by glutamate and/or aspartate acting on NMDA and AMPA receptors [498]. These brain areas also mediate the major neuropsychological deficits seen in schizophrenia, and animals with lesions in either of these areas share some phenotypic features. Lesions targeting either the PFC or the hippocampus have effects on the neural functions mediated by both areas, and this must be considered in interpreting these lesion studies.

9.3. Environmental animal models of schizophrenia

Environmental manipulations include isolation-rearing [499], pre-weaning non-handling [500], hypoxia [501], and prenatal maternal malnutrition [502], all of which have been proposed as etiological factors in schizophrenia. Isolation-rearing produces enhanced DA-agonist induced stereotypic movement, spontaneous hyperactivity, impaired PPI and impaired schedule-induced behaviors similar to those seen in amphetamine-treated animals. These abnormalities are reversible with re-socialization [468]. Hypoxia increases stereotypic movements and impairs PPI, but reduces locomotor activity. Maternal malnutrition produces diffuse morphological changes in the brain that result in learning, attentional and adaptation deficits that are permanent. All of these environmental models are associated with neuro-chemical changes in the DA system [468].

9.4. Genetic animal models for schizophrenia

The dopamine transporter knockout (DAT-KO) mutant mouse as a model for schizophrenia fits with the DA hypothesis of schizophrenia (reviewed in Ref. [503]). The homozygous $(-/-)$ mice have elevated extracellular DA levels because reuptake is inhibited [504], and they show hyperlocomotion [505], and increased stereotypic behaviors [506]. They also have deficits in sensorimotor gating and spatial cognitive function [506], but do not have deficient social interaction [507]. The hyperlocomotion is reversed with antipsychotic drugs [507]. The heterozygous DAT-KO $(+/-)$ mouse may be a better approximation of reduced DAT activity in schizophrenia [508], since the DAT is not completely absent in schizophrenia. Heterozygote DAT-KO $(+/-)$ mice have raclopride-induced increases in PPI similar to null $(-/-)$ mice, locomotor abnormalities intermediate to the null $(-/-)$ and wild-type $(+/+)$ mice [506], and potentiation of hyperactivity by MK-801 [503]. As with the pharmacological models of schizophrenia that rely on dopaminergic agents, the DAT-KO mouse may be useful in understanding some of the behavioral abnormalities associated with schizophrenia, and the consequences of a hyperdopaminergic state, even if no pathology in the DAT itself is found in schizophrenia.

The NR-1 knockdown (NR1-KD) mouse is deficient in NMDA receptor expression due to a mutation in the NR1 subunit gene [509]. It has behavioral abnormalities similar to these seen in PCP-treated animals, such as hyperlocomotion, increased stereotypy, and impaired social interaction [509]. The hyperlocomotion is reduced by antipsychotics, and the social impairments are improved with clozapine treatment [509]. Other knockout mice, including the DVL1 (*dishevelled* homolog), and the NCAM-180, have

abnormalities that are similar to those seen in other models of schizophrenia, such as impaired PPI [510,511]. The DVL1-KO mice also have deficits in social interaction [510] and the NCAM-180 mice have increased ventricular size [511].

Some of the abnormally expressed genes in schizophrenia have mouse knock-out transgenic models (see Section 4.5). The *reeler* mouse has a characteristically ataxic gait that results from the deletion of the gene encoding for the *reelin* (*Reln*) protein. Similar in both behavioral and histological phenotype is the *scrambler* mouse, which has a mutation in the gene *disabled-1* (*Dab*-1), thought to function as an adaptor molecule in the transduction of protein kinase signals [512]. *Reln* affects the position of Purkinje cells and interneurons, regulates cortical pyramidal neurons, and affects the growth and migration of neurons during development [513]. Deletion of either the *Dab*1, or the *Reln* gene results in widespread abnormalities in laminar structures throughout the brain, which are relevant to schizophrenia because of the observed cytoarchitectural abnormalities. In particular, both genes appear to be involved in the migration of neuronal precursors into the preplate. Deletion of these genes can prevent alignment with the cortical plate, and interfere with subsequent laminar positioning [512].

The coloboma (*Cm/+*) mutant mouse has 1–2cM deleted from chromosome 2, in a region that includes the genes for SNAP-25 and phospholipase C isoform β-1. Coloboma mice exhibit delayed neurobehavioral developmental milestones [514] and profound spontaneous locomotor activity [515]. This parallels the hyperactivity seen with the VH-lesioned F344 rats [516], and is also similar to the hyperactivity induced by amphetamine treatment [517]. The *Cm/+* mouse hyperactivity was corrected when a SNAP-25 transgene was bred into the strain, showing that the hyperactivity was due to the SNAP-25 deletion [518]. Coloboma mice also exhibit regional and transmitter-specific deficits in neurotransmission, notably in glutamate and DA release [519].

Genetic animal models, some examples of which were mentioned earlier, are useful in understanding the impact of particular genes on the behavior and development of the animal as a whole, providing insights not available from purely molecular or cellular experiments. The neurochemical and histological abnormalities in these animals can also be instructive when compared to the abnormalities seen in humans with schizophrenia. When specific etiological genes are conclusively linked to schizophrenia, then genetic animal models will be of paramount importance in understanding how the genetic cause is translated into adult structural and functional deficits. If, as is expected, many genes are eventually implicated in schizophrenia, the challenge will be to generate animal models that have a similarly complex genotype. Until then, the genetic animal models, and indeed all the existing animal models can represent only part of the complex picture of schizophrenia.

10. A core schizophrenia phenotype?

There is considerably more freedom in designing experiments with animal as opposed to human subjects. Many more variables can be controlled, and the previously mentioned problems with human post-mortem tissue studies can be avoided. An inherent assumption in using animal models in studies of schizophrenia is that the animal phenotype captures some important aspect of the human disease. The parallels between the animal model and schizophrenia can presumably tell us something about the biology of schizophrenia in a simplified experimental system. However, if these assumptions about the fidelity of the animal model are true, then what about studying the same behavioral phenotypes in humans?

Many diseases of the brain and general medical illnesses can cause psychotic symptoms. So can a good proportion of street drugs. Mood disorders can often have a psychotic component, especially in severe episodes of mania or depression. Psychosis is a highly non-specific but very obvious feature of schizophrenia. The presence of chronic psychosis without a demonstrable cause is central to our diagnosis and clinical management of schizophrenia, but is it a core phenotype? Is it perhaps a final common pathway of a variety of brain dysfunctions, and therefore a rather distal and unpredictable effect of the presumably genetic etiology [520]. The problem lies, of course, in figuring out which of all the abnormal findings in schizophrenia is most proximal to the underlying genetic pathology.

Functional imaging offers a powerful way of demonstrating the effects of genes on information processing in the brain, as recent studies have demonstrated [158,521], and may help to define a phenotype that is more specific to schizophrenia. Some schizophrenia studies have incorporated eye-tracking abnormalities [522] and p50 evoked-potential measurements [263] as phenotypes in genetic linkage analysis. Another study found a LOD score of 3.55 for a composite inhibitory phenotype in schizophrenic multiplex families that included both the p50 and anti-saccade oculo-motor performance [523]. The p50 and other neurobiological dysfunctions may be relatively non-specific to schizophrenia, but the use of a combined phenotype of schizophrenia with some of these neurobiological measures may narrow the phenotype and facilitate more powerful linkage analysis [443]. Continued research into the phenomenology and neuropsychological abnormalities of schizophrenia may reveal novel phenotypes that represent core abnormalities in schizophrenia that can assist in the search for schizophrenia genes.

11. Summary

The most robust findings in schizophrenia include epidemiological, phenomenological, pathological and pharmacological data. Schizophrenia is a brain disease that

affects 1 out of every 200 people of all races, social classes, countries and both sexes. Health-care and social costs of the illness are disproportionately greater than the prevalence of schizophrenia would suggest. The cerebral cortex of people with the disease is reduced in volume, especially in the frontal and temporal areas, and the cellular architecture of the cortex is disrupted. Patients not only have psychotic symptoms, but a variety of non-specific cognitive and neuropsychological abnormalities. Antipsychotics and psychosocial interventions reduce relapse of psychotic symptoms, but negative symptoms are a powerful determinant of outcome. The DA system is undoubtedly involved in modulating psychotic experiences, but is not necessarily involved in the cause. The most important element of vulnerability to schizophrenia is genetic, accounting for 80% of the risk for developing the illness, but environmental or epigenetic mechanisms may also confer vulnerability.

Less certain are conclusions based on these findings. Schizophrenia is likely a neurodevelopmental disorder that may also be affected by ongoing changes in brain structure. It is unlikely that a single gene causes schizophrenia, and more likely that a group of many genes, possibly interacting, are responsible. However, no genes have yet been shown to definitively increase the risk of developing the illness. Animal models share some, but not all of the features of schizophrenia, and have helped in understanding more of the neurobiology. A unitary animal model is unlikely, however, and so a major tool in the usual approach to disease research is constrained by the unique features of psychiatric illness and its basis in the unique human brain.

Much of the previous sections have mentioned various studies that report a wide variety of abnormalities associated with schizophrenia. However, none of the findings in schizophrenia, whether histological, biochemical or neuropsychological, are diagnostic. In other words there is significant overlap between schizophrenic subjects and controls that prevents the application of these findings as a diagnostic tool. This is not just a clinical problem of interest only to psychiatrists, but rather, it reflects a deeper issue in the study of schizophrenia. As Heinrichs carefully establishes in his recent book [524], the effect size in these disparate studies comparing some feature of schizophrenic versus control subjects ranges from around 1 to 0.5 (expressed as Cohen's d) [525]. These effect sizes roughly correspond to an overlap between schizophrenic and control subjects in the order of 45–65%. Furthermore, the effect size is greatest for comparisons of neuropsychological measures, and least for more biological findings like imaging [524].

The problem of overlap between schizophrenia and control groups, and the lack of a robust diagnostic 'test' leads us to question the concept of schizophrenia introduced at the beginning of this review. Schizophrenia is considered a disease, or a collection of diseases, and has been subjected

to the usual research methods for studying diseases. Unfortunately the large amount of data accumulated over the years has served sometimes to clarify, but also to confuse our understanding of schizophrenia. In some ways we are not much further ahead than Kraepelin; diagnosis is based on the same clinical observations, and treatment with antipsychotics may be somewhat effective, but have not led us to the etiology or pathophysiology of the illness. Several general strategies that may address these difficulties including work on establishing phenotypic assays, for example, through functional imaging studies, that may identify subsets of schizophrenic patients that have a more homogenous etiology for their symptoms. These subgroups may then yield more convincing results in genetic studies. Ongoing studies of the mechanisms of antipsychotic action may eventually intersect with studies directed the pathophysiology of psychotic symptoms, and may thereby result in an understanding of 'how' if not 'why' someone may have psychotic symptoms. What is needed is not just more data, but experiments that demonstrate disease mechanisms, studies that map a path from candidate gene to histology or cognitive deficit, for example. We must go beyond just making associations between certain findings and schizophrenia to developing more detailed disease models that can be tested experimentally [526].

The findings reviewed above are not comprehensive; the selection of topics and depth of coverage is necessarily biased towards information pertinent to the focus of this article. Many scientific investigations in schizophrenia are in areas outside the scope of this review, and include psychosocial research aimed at non-medical treatments and support for patients with schizophrenia and their families [527]. As research in non-industrialized and developing countries suggests, outcomes may be improved through social and environmental interventions that do not rely on sophisticated knowledge of the neurobiology of schizophrenia. Nevertheless, a cure or at least better treatments are sorely needed, and a greater understanding of the neurobiology of schizophrenia is crucial to both destigmatizing the illness and advancing clinical care.

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