Neurotransmitter Receptors in Actions of Antipsychotic Medications

Edited by
Michael S. Lidow
Neurotransmitter Receptors in Actions of Antipsychotic Medications
Pharmacology and Toxicology: Basic and Clinical Aspects
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Preface

Schizophrenia is a debilitating mental disease affecting more than two million people in the U.S. alone. The drugs used in treatment of schizophrenia are referred to as antipsychotic medications. It is now well established that the therapeutic effects of these medications are related to their interactions with dopaminergic receptors. The classic antipsychotic drugs, however, are capable of alleviating only the florid symptoms of schizophrenia, particularly hallucinations and delusions. They are only marginally effective in treatment of chronic symptoms of the disease, such as apathy, affective blunting, and social withdrawal. Moreover, the binding of these drugs to a wide range of dopaminergic receptors results in significant side effects, often forcing patients to refuse prolonged treatment. It is not surprising that there is a significant interest in developing new antipsychotic drugs with improved therapeutic properties and reduced side effects.

The research aimed at developing the new generation of antipsychotic drugs has been advancing in two major directions. The first direction is the investigation into possible therapeutic effects of drugs combining dopaminergic receptor-related activity with binding to selected nondopaminergic receptor sites in the hope of broadening the curative effects of antipsychotic medications. This direction is based on the observations that some antipsychotic drug-resistant symptoms of schizophrenia are similar to affective disorders responsive to drugs selective for serotonergic and adrenergic receptors. In addition, recent studies into the etiology of schizophrenia have suggested that this disease may be associated with abnormalities in the brain glutamatergic and GABAergic receptor sites which, therefore, should be the primary targets of antipsychotic medications. The second direction in the development of new antipsychotic drugs takes advantage of the discovery that dopaminergic receptors include five subtypes with distinct distribution and pharmacological properties. The researchers pursuing this direction study antipsychotic properties of chemicals targeting only selected dopaminergic receptor subtypes in the hope that, by limiting the scope of dopaminergic receptors bound by these drugs, it would be possible to eliminate the unpleasant side effects of the present medications while preserving their therapeutic activity.

To our knowledge, this is the first book fully devoted to the neurotransmitter receptors as targets of antipsychotic medications. We believe that it will be of great interest for researchers studying antipsychotic medications as well as for scientists involved in schizophrenia research in general. It will also be useful for physicians who want to understand the mechanisms of actions of antipsychotic drugs and to put the use of these drugs on a more scientific basis.

This book includes 15 chapters written by the leading specialists in the field of antipsychotic drug research. The first two chapters provide the basic knowledge of schizophrenic syndromes and give general descriptions of antipsychotic drugs available today. The next eight chapters describe the role of different receptors in action of antipsychotic drugs. The following four chapters will deal with special topics such as endogenous receptor occupation by antipsychotic drugs and the regulation of brain receptors by these drugs and others. The final chapter of this book discusses the perspectives of future antipsychotic drug design.
To two women in my life, Frida and Irina Lidow
Editor

Michael S. Lidow, Ph.D., is a Professor of Neuroscience at the University of Maryland, Baltimore. He received his doctoral degree in the Program in Neuroscience at Northwestern University in Evanston, IL in 1985. Upon graduation, he moved to Yale University in New Haven, CT as a post-doctoral associate at the Section of Neuroanatomy. In 1990 he became associate professor at the Section of Neurobiology at Yale University School of Medicine. In this capacity, he was invited to join the then newly organized Center in Cortical Mechanisms in Schizophrenia headed by Dr. Patricia Goldman-Rakic. Under her guidance, Dr. Lidow became interested in the role of neurotransmitter receptors in the etiology of schizophrenia, as well as in their role as targets of antipsychotic medications. While still being an active participant in the Yale Center in Cortical Mechanisms in Schizophrenia, Dr. Lidow now resides in Baltimore where he is a Professor of Neuroscience at the Departments of Oral and Craniofacial Biological Sciences and Anatomy and Neurobiology of the University of Maryland. He is a recipient of several grants from the National Institutes of Health and private foundations and is a member of the New York Academy of Science, the American Association for the Advancement of Science, and the American Society for Neuroscience. He has also published extensively in the areas of neuroscience and psychopharmacology.
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I. INTRODUCTION

The symptoms of schizophrenia embrace virtually the full range of abnormal mental phenomena that afflict the human mind. These symptoms span the domains of perception, thought, emotion, volition, and behavior. The symptoms most characteristic of schizophrenia include delusions, hallucinations, formal thought disorder, inappropriate affect, blunted affect, impoverished thought, and diminished volition. In addition, many other symptoms that are common in other disorders, such as depressed mood, agitation, and anxiety, also occur in schizophrenia.

The symptom profile differs markedly between cases and also varies over time within individual cases. Attempts to divide the illness into separate subtypes on the basis of clinical features have been unsuccessful because, whatever classification is proposed, there are a substantial number of cases with a mixture of the features of the proposed subtypes. In addition, some cases tend to shift between categories over time. The classic subdivision of schizophrenia into paranoid, hebephrenic, catatonic, and simple schizophrenia is inadequate because it is difficult to define clear boundaries between the different types. For example, Daniel Schreber, the intelligent and articulate appeals court judge from Leipzig, East Germany who exhibited the classic features of paranoid schizophrenia that he describes so clearly in his memoirs,1 also exhibited the bizarre, inappropriate patterns of thinking, emotion, and behavior more characteristic of hebephrenia and motor disturbances characteristic of catatonia during his most florid episodes of illness. He eventually regressed into a disorganized, inaccessible state before his death in Liepzig-Dösen asylum in 1911.2

Perhaps the most fruitful approach to understanding the heterogeneity of the clinical features of the illness has been the dimensional approach. In a dimensional model, the diverse clinical features are attributed to several underlying dimensions, each of which reflects a distinguishable pathological process that nonetheless might arise from a single primary cause.

In this chapter we begin by describing two quite different dimensional models of schizophrenia, each of which has attempted to link clusters of observable symptoms to postulated underlying neuropathological mechanisms. First, we consider Crow’s type 1/type 2 model3,4 which is based on the assumption that there are two distinguishable, but related pathological processes in schizophrenia: one that is manifest in overt structural damage to the brain, while the other entails potentially reversible biochemical imbalance. Then we consider Liddle’s three-syndrome model5–7 according to
which three different clusters of characteristic symptoms arise from a neuropathological process that can affect one or more of three distinguishable neural systems responsible for the initiation, selection, and monitoring of self-generated mental activity, respectively. Finally, we present an integrated model according to which subtle, diffuse dysplasia disrupts the coordination between diverse cerebral areas, leading to several clusters of persistent symptoms, and, in addition, disrupts the regulation of neuromodulatory neurotransmitters, predisposing to acute exacerbations of symptoms at times of stress. We will call this model the developmental dysplasia model.

II. THE TYPE 1/TYPe 2 HYPOTHESIS

Crow\(^3,4\) produced a formulation of the pathophysiology of schizophrenia which has had a seminal influence on subsequent attempts to link the phenomena of the illness to the diverse abnormalities of brain structure and function that are associated with schizophrenia. The foundation of this formulation was the observation that the positive symptoms of schizophrenia tend to be transient, while the negative symptoms tend to persist. Positive symptoms are clinical features that reflect aberrant mental activity not present in healthy individuals. They include delusions, hallucinations, and formal thought disorder. Negative symptoms are clinical features that reflect a diminution of mental activity normally present in healthy individuals and include blunted affect, poverty of speech, and decreased voluntary activity. Positive symptoms usually respond to treatment with dopamine blocking medication, whereas negative symptoms are less responsive.\(^8\) Indirect evidence linked negative symptoms with indicators of overt structural brain damage, such as ventricular enlargement.\(^9\)

On the basis of these observations, Crow proposed that two pathophysiological processes occur in schizophrenia: type 1 and type 2. The type 1 process entails dopaminergic overactivity and generates positive symptoms. The type 2 process involves structural brain damage and is responsible for negative symptoms. In its most strict formulation, this proposal implies that positive symptoms might be alleviated by blockade of dopamine, while negative symptoms are irreversible.

A substantial body of evidence provides at least partial support for Crow’s proposal. In particular, a review of X-ray computed tomography (CT) scan studies by Lewis\(^10\) revealed that approximately half of the studies that had investigated the issue had found that ventricular enlargement was correlated with negative symptoms. More recently, in a study employing single-photon emission tomography (SPET) to measure endogenous dopamine release in response to administration of amphetamine, Laruelle et al.\(^11\) obtained evidence suggesting that schizophrenic patients exhibit an abnormally large release of dopamine and, furthermore, the amount of dopamine released correlates with the severity of induced positive symptoms.

Despite the evidence supporting Crow’s type 1/type 2 formulation, there are several respects in which it does not provide an adequate account of the observable clinical features of schizophrenia.

1. The positive/negative dichotomy does not take into account the full range of symptoms of schizophrenia. In particular, it ignores the fact that excitation and depression are prevalent in schizophrenia.
2. While a minority of studies of the relationships between symptoms support the hypothesis that the characteristic symptoms of schizophrenia segregate into positive and negative groups,\(^12\) the majority of studies demonstrate that the characteristic symptoms segregate into at least three groups.\(^5,6,13–16\)
3. Negative symptoms vary in severity over time and, in particular, resolve at least partially as florid episodes of illness subside.\(^17\)
4. While negative symptoms are relatively resistant to treatment, there is evidence that they do respond at least partially to atypical antipsychotic medication.\(^18\)
5. In some cases, positive symptoms persist despite a high level of blockade of dopamine D2 receptors.\(^19\)

A more comprehensive formulation of the relationships between symptoms, mechanisms, and causes is necessary.
III. THE THREE-DIMENSIONAL MODEL OF SCHIZOPHRENIA

A. THE SEGREGATION OF SYMPTOMS

The type 1/type 2 model implies that the distinction between symptoms based on symptom type is inextricably related to a distinction between acute and chronic symptoms. It does not account for the existence of chronic positive symptoms or transient negative symptoms. It does not answer the question of whether or not chronic positive symptoms and chronic negative symptoms arise from distinct pathophysiological processes. To address this issue, Liddle\(^5,6\) examined the relationships between symptoms in a group of schizophrenic patients with relatively homogeneous chronicity of illness. He recruited subjects with persistent symptoms during a stable phase of illness to test the hypothesis that even in such a sample, symptoms would segregate into positive and negative symptoms, as would be expected if the different types of symptoms reflected different neuropathological processes. He found that in the stable phase of chronic illness, the characteristic symptoms of schizophrenia segregated into distinguishable groups, but instead of two, there were three syndromes: reality distortion, disorganization, and psychomotor poverty, as shown in Table 1.

This pattern of segregation of chronic symptoms has subsequently been reported by many other studies.\(^13–16\) It has also been reported in many studies that have examined patients who are heterogeneous with regard to chronicity of illness. It has been reported in patients with mixed psychotic diagnoses.\(^20\) Furthermore, it should be noted that the three syndromes embrace only the symptoms characteristic of schizophrenia; if the full gamut of symptoms that can occur in schizophrenia and other psychotic illnesses is examined, the number of distinguishable syndromes is at least five.\(^21\) In addition to the three characteristic schizophrenic syndromes, there are two syndromes, depression and psychomotor excitation, that are more characteristic of bipolar affective illness, but nonetheless are prevalent in schizophrenia.

B. NEUROPSYCHOLOGICAL IMPAIRMENTS ASSOCIATED WITH SYMPTOMS

In a study employing a neuropsychological battery that embraced a wide range of aspects of cognitive functioning, Liddle\(^7\) found that in patients with persistent illness, each of the three groups of characteristic schizophrenic symptoms was associated with a specific pattern of neuropsychological
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impairment, which he interpreted as evidence that each group of symptoms might reflect dysfunction of a discrete neural system. On the basis on the types of impairment associated with each syndrome, and also taking account of the nature of the symptoms themselves, Liddle proposed that psychomotor poverty might reflect underactivity of a neural system linked to the lateral frontal cortex that is normally engaged in the initiation of mental activity; disorganization might reflect aberrant activity in a neural system linked to orbito-medial frontal cortex that is normally engaged in the selection between competing mental activities; while the reality distortion syndrome might arise from aberrant temporal lobe activity.

In a subsequent study employing a battery of frontal lobe tasks, Liddle and Morris confirmed that chronic psychomotor poverty is associated with impaired performance in tasks that involve initiating a plan for mental action, while chronic disorganization is associated with impairments in tasks that demand the ability to select between competing responses. For example, psychomotor poverty was associated with diminished rate of word generation in a verbal fluency task. Such a task entails the execution of a self-directed generated strategy for search through an individual’s store of words. On the other hand, severity of disorganization was correlated with slower performance in the Stroop task, in which the participant is presented with a color name printed in ink that is incongruent with the color name and is required to specify the ink color. Successful performance entails suppression of the tendency to respond to word meaning. Disorganization was also associated with slower performance in the Trails B task, in which the participant is presented with a series of dots that are labeled with either a letter of the alphabet or a number and is instructed to join the dots in an order that alternates between letters and numbers. This demands repeated switching of search criterion. However, in that study, Liddle and Morris found no evidence that reality distortion is associated with impairment in frontal lobe tasks.

Several subsequent studies have confirmed these findings. For example, Frith et al. found that psychomotor poverty symptoms are associated with decreased rate of word generation, while disorganization symptoms are associated with impaired performance in the Trails B task and also with an increased rate of errors of commission in a continuous performance task. Allen et al. found that psychomotor poverty is associated with a slowed rate of word generation during a verbal fluency task, while disorganization is associated with a tendency to select inappropriate or unusual words. Norman et al. also found that psychomotor poverty was associated with a decreased rate of word generation. Paradoxically, they interpreted their finding as a disconfirmation of the hypothesis that psychomotor poverty reflects malfunction of the dorsolateral frontal cortex because they considered word generation to be a test of orbital frontal function. However, abundant evidence from studies of lesions and from functional imaging studies demonstrates that left lateral frontal cortex is involved in word generation.

Baxter and Liddle found that chronic psychomotor poverty was associated with slowed responses in a two-choice guessing task in which the patient was required to generate the strategy for choice, while also confirming that disorganization was associated with impaired performance in the Stroop task. Similarly, Ngan and Liddle found that in patients with persistent illness, psychomotor poverty symptoms were associated with slowed simple reaction time, while disorganization was associated with slowed choice reaction time and impaired Stroop performance. It is of interest to note that in the studies by Baxter and Liddle and also the study by Ngan and Liddle, the pattern of association between symptoms and neuropsychological impairment was different in patients with acute, remitting illness than in patients with persistent illness, an issue that we shall address in greater detail in Section IV.

Overall, a preponderance of evidence confirms that in patients with persistent illness, psychomotor poverty is associated with impaired ability to initiate a plan of action or simply with slow execution of simple responses, while disorganization is associated with impaired ability to select between competing responses.

The question of the neuropsychological correlates of reality distortion is less easily answered. In his initial study, Liddle had reported that the severity of reality distortion was weakly correlated...
with impaired ability to discriminate between the figure and ground. Subsequent studies that have focused mainly on frontal lobe tasks have reported that reality distortion is not associated with neuropsychological impairment. However, a substantial number of studies have reported that either delusions or hallucinations are associated with impaired ability to process information in its correct context. For example, Morrison and Haddock\(^{29}\) found that the severity of hallucinations was associated with the degree of impairment of the ability to monitor whether or not an idea had been self-generated in a word-association task. Other studies have reported an association between reality distortion symptoms and the ability to monitor the source of self-generated actions. For example, Frith and Done\(^{30}\) found that the severity of delusions of control was correlated with impaired error correction in a task in which the ability to correct errors depended on the internal monitoring of self-generated activity. Consistent with this observation, Mlakar et al.\(^{31}\) found that delusions of control were associated with impaired ability to draw figures in the absence of visual feedback.

Norman et al.\(^{25}\) reported that reality distortion was associated with memory impairments attributed to temporal lobe dysfunction. While the association of reality distortion with temporal lobe malfunction is plausible, the finding of a correlation between reality distortion and memory impairment should be regarded with caution until replicated. On balance, the evidence indicates that reality distortion is not associated with cognitive deficits that are as wide ranging as those associated with psychomotor poverty or disorganization. Nonetheless, it is associated with specific impairments in the domain of evaluation of information in context.

Overall, the evidence supports the hypothesis that each of the three syndromes of characteristic schizophrenic symptoms is associated with a specific pattern of cognitive deficit. Each of the three syndromes is associated with malfunction of a particular aspect of executive function; psychomotor poverty is associated with impaired planning and initiation of activity, disorganization with impaired selection between competing responses, and reality distortion with impaired evaluation of information in context.

### C. Patterns of Cerebral Activity Associated with Syndromes

The observation that each of the three syndromes is associated with a specific pattern of cognitive impairment suggests that each might be associated with a specific pattern of abnormal cerebral activity. This hypothesis might be tested employing a functional imaging technique such as positron emission tomography (PET), which provides images of regional cerebral blood flow (rCBF) or regional glucose metabolic rate (rCMRglu). Since rCBF and rCMRglu are tightly coupled to the level of local neuronal activity, these techniques provide images that reflect regional neural activity.

Using PET to examine the patterns of rCBF associated with each of the three syndromes in a group of patients with persistent, stable illness, Liddle et al.\(^{32}\) confirmed that each syndrome was associated with a particular pattern of aberrant cerebral activity. In accord with this prediction, they found that psychomotor poverty was associated with underactivity in left lateral frontal cortex. Furthermore, the region of underactivity coincided with the region that is engaged during word generation in healthy subjects. In addition, psychomotor poverty was correlated with decreased rCBF in the left inferior parietal lobule, a region of association cortex that has strong reciprocal connections with the lateral frontal cortex, and bilaterally with increased rCBF in the basal ganglia and thalamus. Subsequently, Ebmeier et al.\(^{33}\) confirmed the finding of an association between psychomotor poverty and left frontal underactivity in an group of acutely ill schizophrenic patients, half of whom had never been treated with antipsychotic medication. Yuasa et al.\(^{34}\) confirmed that psychomotor poverty is associated with decreased frontal rCBF and with increased rCBF in basal ganglia and thalamus.

Disorganization was associated with underactivity in the right ventro-lateral prefrontal cortex, contiguous insula cortex, and lateral parietal cortex bilaterally. It was also associated with over-activity in the anterior cingulate and medial frontal cortex and with overactivity in the thalamus. The site of overactivity in the anterior cingulate coincided with the site that is maximally active in...
healthy subjects during the performance of the Stroop task. The observation that disorganization is associated with overactivity of the right medial frontal cortex and anterior cingulate has been confirmed by Ebmeier et al.\textsuperscript{33} and Yuasa et al.\textsuperscript{34} One the other hand, in a study employing PET to measure CMRglu, Kaplan et al.\textsuperscript{35} did not observe a correlation with overactivity in the medial frontal cortex, though they did replicate the finding of an association between disorganization and underactivity of the lateral parietal cortex.

On balance, the evidence provides strong support for the conclusion that disorganization is associated with overactivity of the medial frontal cortex and anterior cingulate and moderate support for an association with overactivity of the thalamus and underactivity of the lateral parietal cortex and ventro-lateral prefrontal cortex. This evidence, together with the evidence from studies of monkeys\textsuperscript{36} that ventro-lateral prefrontal cortex plays an important part in the suppression of inappropriate responses, suggests the speculation that in patients suffering from the disorganization syndrome, deficient function of the ventral prefrontal cortex predisposes to a tendency for inappropriate mental events to intrude into current mental processing. This would be expected to lead to overactivity of the anterior cingulate and medial frontal cortex, areas that are actively engaged when dealing with potential interference in the Stroop task.

Liddle et al.\textsuperscript{32} found that the severity of reality distortion was correlated with increased rCBF in the left medial temporal lobe and in ventral striatum and with underactivity in the right posterior cingulate and left superior temporal gyrus. The finding that reality distortion is associated with overactivity in the left medial temporal lobe and ventral striatum received support from the observation by Silbersweig et al.\textsuperscript{37} that auditory hallucinations are associated with overactivity in the ventral striatum and in medial temporal structures including hippocampus and parahippocampal gyrus.

Perhaps as important as the similarities between the findings of Silbersweig and those of Liddle are the differences. Most notably, Silbersweig did not observe any areas in which hallucinations were associated with a reduction in rCBF, whereas Liddle observed reality distortion to be associated with decreased rCBF in the superior temporal gyrus on the lateral aspect of the temporal lobe and in the right posterior cingulate cortex. This difference might reflect an important difference in methodology. Silbersweig et al. employed a longitudinal design in which they compared cerebral activity during the presence of hallucinations with that during the absence of hallucinations within the same patients, whereas Liddle employed a cross-sectional design that examined differences between patients who differed in the severity of reality distortion.

Longitudinal designs can identify cerebral sites involved in the experience of a symptom, whereas cross-sectional designs might identify the loci involved in the experience of the symptom together with those loci associated with underlying predisposition to the symptom, though the two types of loci cannot be distinguished. It is noteworthy that several longitudinal studies\textsuperscript{37–39} of the cerebral activity associated with hallucinations have observed temporal lobe overactivity, but no evidence of temporal lobe underactivity. In contrast, the cross-sectional study by Liddle et al.\textsuperscript{32} found that reality distortion was associated with medial temporal overactivity and lateral temporal underactivity. The cross-sectional study by Ebmeier et al.\textsuperscript{33} found that reality distortion was associated with lateral temporal underactivity, but did not detect a relationship with medial temporal overactivity. These observations raise the possibility that underactivity in the lateral temporal cortex reflects a loss of neural function that creates a predisposition to the reality distortion, while overactivity in the medial temporal lobe reflects transient release of aberrant activity that is associated with the actual experience of the symptoms.

The area of overactivity in the left medial temporal lobe identified by Liddle et al.\textsuperscript{32} included the site in the parahippocampal gyrus activated in healthy subjects during a task that entailed internal monitoring of self-generated movements.\textsuperscript{40} This is consistent with the hypothesis that reality distortion is associated with aberrant monitoring of self-generated mental activity.

In summary, each of the three syndromes is associated with a distinct aberrant pattern of regional cerebral activity. Furthermore, for each syndrome the cerebral areas involved include the cardinal
sites that are engaged in healthy subjects while performing the type of mental activity implicated in that syndrome.

Studies of the psychotomimetic glutamatergic antagonist ketamine provide indirect evidence about the cerebral sites likely to be involved in the expression of psychotic symptoms. Ketamine produces schizophrenia-like symptoms in healthy individuals and transient exacerbations of psychosis in schizophrenic patients. These symptoms include symptoms of disorganization as well as reality distortion. Lahti et al. demonstrated that ketamine increased rCBF in the anterior cingulate and contiguous medial frontal cortex in schizophrenic patients and in healthy controls. Furthermore, changes in positive symptoms induced by ketamine correlated with rCBF changes in the left medial temporal lobe and left ventral striatum, consistent with the finding by Liddle et al. and Silbersweig et al. that increased rCBF at these two sites is associated with reality distortion symptoms.

D. Reversibility of Aberrant Cerebral Activity Associated with the Three Syndromes

Whether or not the aberrant cerebral activity associated with each of the three syndromes is reversible is a question of major clinical importance. For each syndrome the observed pattern of cerebral activity includes areas of underactivity and areas of overactivity. It is possible that the regions of overactivity represent disinhibition of neural activity which results from failure of inhibitory input from those regions that are underactive. For example, in reality distortion, it is plausible that the predisposition to symptoms is created by a deficit in neural function, while the actual experience of symptoms is associated with consequent disinhibited activity elsewhere in the brain. In such circumstances, it would be anticipated that the symptoms might be treated successfully by pharmacological means using drugs that have an inhibitory influence in the relevant brain area.

The available evidence from functional imaging studies that have examined the relationship between changes in regional cerebral metabolism and the reductions in symptom severity after antipsychotic treatment provides support for the hypothesis that antipsychotic medication acts by decreasing overactivity at the cerebral sites implicated in the reality distortion and disorganization syndromes. In a study of the effects of the novel antipsychotic risperidone on cerebral metabolism in previously unmedicated first episode schizophrenic patients, Liddle et al. found that the degree of reduction in metabolism in the left hippocampus observed 90 min after the first dose of risperidone was a significant predictor of the degree of alleviation of reality distortion during subsequent treatment. Furthermore, after 6 weeks of treatment, there was a more extensive region of reduced metabolism in the left temporal lobe. These findings indicate not only that temporal lobe metabolism decreases as symptoms resolve, but also that the reduction is discernable 90 min after the first dose before any substantial reduction in reality distortion symptoms would be expected. This suggests that the reduction in hippocampal metabolism is not merely a consequence of symptom resolution, but actually plays a causal role in the therapeutic effect.

Ngan et al. found that risperidone produces a reduction in metabolism in the right medial frontal cortex that is discernable after the first dose of risperidone and becomes more extensive after 6 weeks of treatment. The degree of reduction in the right medial frontal cortex showed a strong trend toward significant correlation with a magnitude of the reduction in severity of disorganization (Pearson’s correlation coefficient, r = 0.59). These findings support the hypothesis that reduction of the right medial frontal metabolism is a component of the mechanism by which risperidone alleviates disorganization, but this interpretation should be regarded with caution until the finding has been replicated.

Overall, for both the reality distortion syndrome and the disorganization syndrome, the evidence supports the hypothesis that predisposition to the symptoms comprising these syndromes is associated with underactivity at certain cerebral sites (see Table1), but the actual expression of symptoms is
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due to a weakening of inhibitory control that leads to overactivity at other cerebral locations (also shown in Table 1), and, furthermore, that antipsychotic medication acts by reducing this overactivity.

The pattern of cerebral activity associated with psychomotor poverty also includes sites of overactivity and underactivity. However, unlike the reality distortion and disorganization syndromes, in which there is overactivity at the sites normally engaged during the type of cognitive process implicated in the syndromes (see Table 1), in the psychomotor poverty syndrome there is underactivity at the site in the left lateral frontal cortex in the region that is normally engaged during word generation. Reduced speech is one aspect of psychomotor poverty. Hence, it likely that the psychomotor symptoms are a direct manifestation of the observed neural underactivity. The observed overactivity at other sites, such as in the basal ganglia, might simply be an incidental consequence of the primary deficit. In such circumstances, the potential for pharmacological alleviation of the symptoms would depend on whether or not the underactivity at the cardinal site in the lateral frontal cortex is reversible. In instances where the underactivity arises from irreversible neural damage, pharmacological treatment might have little effect.

The question of whether or not pharmacological treatment can alleviate the lateral frontal underactivity associated with psychomotor poverty remains unanswered. However, there is evidence that even in cases with severe persistent psychomotor poverty, the underactivity does not reflect irreversible loss of neural function. In a PET study of regional cerebral activity during paced word generation in a group of patients with severe persistent schizophrenia, Frith et al. observed that the magnitude of activation in the left lateral frontal cortex was similar to that observed in healthy subjects producing words at the same rate. Furthermore, left lateral frontal activation of normal magnitude was observed in the subgroup of six patients who had marked psychomotor poverty. Thus, even in cases of severe, persistent illness, the left lateral frontal cortex can be activated under circumstances where the task is relatively simple and performance is paced.

However, Frith et al. observed that the normal magnitude of left lateral frontal activation during word generation in schizophrenic patients was accompanied by an absence of the suppression of activity in the superior temporal lobe that is observed in healthy subjects. The normal suppression of temporal lobe activity during word generation (relative to a control condition in which subjects articulated a list of words provided by the investigator) probably reflects a mechanism for minimizing interference from external auditory stimuli while words are being generated internally. The absence of this suppression in schizophrenic subjects might make them vulnerable to distraction or even to misinterpretation of internally generated words as if it were externally generated speech.

In a reanalysis of Frith’s data, Liddle et al. examined the patterns of covariance over six scans (within each subject) between rCBF in the left lateral frontal cortex and rCBF in all other cerebral gray matter pixels. They found that the pattern of covariance differed from that in healthy controls not only for the relationship between the left frontal cortex and left lateral temporal lobe, but also for the relationship between the frontal cortex and thalamus and between the frontal cortex and medial parietal cortex. Patients differed from healthy controls insofar as patients showed a positive covariance between the frontal cortex and left lateral temporal cortex, while the corresponding covariance was negative in healthy controls. In both patients and controls the covariance between the left lateral frontal cortex and medial parietal cortex was negative, but significantly more negative in patients than in controls. In contrast, the covariance between the left lateral frontal cortex and thalamus was positive in both patients and controls, but significantly less so in the patients. Overall, these observations support the proposal that the cardinal functional abnormality in schizophrenia is a defect in the coordination of cerebral activity.

The findings that the left lateral frontal cortex can be activated even in schizophrenic patients with severe, persistent psychomotor poverty suggest that lateral frontal underactivity associated with the psychomotor poverty syndrome is not due to an irreversible focal loss of neural function. The observation that left lateral frontal activation is associated with aberrant coordination of activity between the frontal cortex and other sites such as the thalamus, temporal lobe, and medial parietal cortex implies that there is a dynamic imbalance between neural activity in different cerebral regions.
Since the strength of neurotransmission between cerebral regions is, at least in principle, subject to influence by modulatory monoamine neurotransmitters such as dopamine and serotonin, these findings suggest that the prospects for alleviation of negative symptoms is not as bleak as is implied by Crow’s concept of type 2 schizophrenia. This conclusion is consistent with the accumulating evidence that novel antipsychotics can alleviate negative symptoms, though the question of whether or not currently available antipsychotics can relieve persistent negative symptoms remains a subject of debate.

IV. THE DEVELOPMENTAL DISREGULATION MODEL

While the type 1/type 2 model of schizophrenia provides a plausible explanation for the variation in degree of persistence of symptoms, the three-syndrome model provides a more satisfactory account of the heterogeneity of symptom type. In particular, the evidence supports the hypothesis that the pathophysiology of schizophrenia disrupts the function of a diverse set of cerebral sites and that the type of symptoms is largely determined by the nature of function of the affected cerebral regions.

Any comprehensive account of the pathophysiology of schizophrenia must take account not only of the diverse types of symptoms that occur within the illness, but also of the time course of the illness. Several major longitudinal studies of childhood development, such as the study of the cohort born in Britain in March 1946 and the study of the cohort born in March 1958, have demonstrated that the earliest signs of illness can be detected, at least with hindsight, in early childhood development. For example, in the 1946 birth cohort, the odds ratio that a preschizophrenic child would fail to develop speech by age two was 4.8 compared with the remainder of the birth cohort. In both this birth cohort and in the 1958 birth cohort, the preschizophrenic children exhibited significant impairment in a range of cognitive and social functions. The cognitive deficits were most marked in the domains of language and arithmetical skills, while the behavioral development of the preschizophrenic children was characterized by social unease and inconsequential behaviors.

It is important to note that many preschizophrenic children perform in the normal range in cognitive tasks and some even achieve a superior level of function. However, the evidence from studies of identical twins discordant for schizophrenia indicates that even when both twins perform in the normal range, the affected twin usually performs less well than the unaffected co-twin, indicating that the illness has led to a relative impairment. Furthermore, despite the observation that the cognitive impairments in schizophrenia cover a wide range of aspects of cognition, there is great variability between cases, and the possibility that domains of high performance might co-exist with subtle defects in other areas remains to be excluded.

Typically, in adolescence a more discernible prodrome, characterized by social withdrawal and episodes of anxiety or depressive symptoms, develops. In many cases, this prodrome lasts for several years before the development of overt psychosis. The first psychotic episode is likely to include symptoms of reality distortion and/or marked disorganization and psychomotor excitation. Though psychomotor excitation is common, in some cases negative symptoms become worse, and in a substantial proportion of cases there is significant depression. In over half of the treated first episode cases, the initial florid episode abates within 3 months, and in about 85% of cases there is at least a partial remission within 1 year. Subsequently, the illness is characterized by further acute episodes superimposed on a state of enduring disability, cognitive impairment, and residual symptoms. The severity of the enduring residual symptoms and of social and occupational disability varies greatly between cases. In some cases, the person functions well, apart from an undue sensitivity to stress. In the most severe cases, the patient is unable to perform the essential functions of daily life.

The long-term prognosis is also variable, but in over 50% of cases there is a gradual resolution with full or partial recovery after several decades. In a minority of cases, the illness progresses to a state of profound cognitive impairment that resembles dementia, although in such cases there is no increase in the pathological features of Alzheimer’s disease.
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The characteristic time course of illness indicates that the underlying pathophysiological mechanism is neither a progressive dementia nor a static encephalopathy. In general, the time course reflects the characteristics of a developmental disorder, though unlike many developmental disorders the degree of disability in schizophrenia does not usually achieve a stable level even in adulthood. Instead, during the younger adult years there are episodic exacerbations and then in later adulthood a tendency toward resolution in many cases.

This time course suggests a disorder in which a neuronal deficit progresses during childhood development. The florid episodes in young adulthood, which are often precipitated by stressful events or by stimulant drug abuse, suggest that the putative developmental deficit has weakened the regulation of the modulatory monoamine neurotransmitters, especially dopamine. Dopamine modulates the function of the various cortical and subcortical areas implicated in the expression of the three syndromes. Consequently, poorly regulated changes in the levels of modulatory neurotransmitters in response to stresses of various kinds might be expected to exacerbate any preexisting impairment of coordination between these cerebral sites. This would increase the likelihood of overt symptoms in previously asymptomatic cases or exacerbate symptoms in those with preexisting symptoms. In later adult life, age-related diminution in activity of the modulatory neurotransmitters would result in a tendency toward resolution of the illness.

The excessive release of endogenous dopamine following amphetamine administration in schizophrenic patients demonstrated by Laruelle et al. provides evidence that disregulation of monoamine neurotransmission does, in fact, occur in schizophrenia. Furthermore, Laruelle et al. found that the magnitude of the release of dopamine correlated with the severity of the positive symptoms induced by amphetamine administration.

There is also evidence that the disregulation of dopamine might arise from subtle structural deficits. Breier et al. demonstrated that an increase in production of the dopamine metabolite, homovanillic acid, in response to the stress of transient glucose deprivation is abnormally large in schizophrenia. The magnitude of this effect is inversely correlated with frontal lobe volume. The molecular mechanism by which a structural deficit might produce disregulation of dopamine remains speculative. Pycock et al. were the first of many investigators to report that lesions of the frontal lobes produce changes in subcortical dopaminergic function in rats. While the details of these findings have remained controversial, subsequent studies show that frontal lobe lesions in animals lead to increased dopamine release in the nucleus accumbens (homologous to the ventral striatum in man).

It is likely that the structural defects in schizophrenia are due, at least in part, to abnormal brain development. Subtle developmental anomalies are prevalent in schizophrenia. In particular, there is evidence of disordered development of coordination between diverse brain areas. For example, Woodruff et al. reported that the normal correlation between frontal lobe volume and temporal lobe volume is decreased in schizophrenia. Since this correlation is thought to reflect the functional linkage between these brain areas, the lack of correlation in schizophrenia implies a lack of coordination during development.

In summary, the time course of the illness, together with the evidence regarding the nature of the cerebral abnormalities of schizophrenia that we have reviewed, suggests that schizophrenia might best be described as a disorder arising from developmental disregulation of cerebral function. According to this hypothesis, the primary pathological process is a subtle dysplasia that affects coordination between cerebral regions. Impaired coordination of function results in enduring cognitive deficits and also causes impaired regulation of monoaminergic neuromodulatory transmitters. At times of stress or following administration of stimulant drugs, there is a tendency for excessive monoamine release leading to florid psychosis. The proposed links between causal factors, pathophysiological processes, and symptom profiles are illustrated in Figure 1.

This developmental disregulation hypothesis predicts that cases in which the developmental dysplasia mainly affects the regulation of monoaminergic transmission will exhibit few residual symptoms, apart from oversensitivity to stress, and relatively minor cognitive impairments during stable phases of
the illness. In contrast, cases with extensive dysplasia affecting multiple cerebral areas would suffer substantial persistent symptoms and cognitive impairments. Nonetheless, in such cases, symptoms might be exacerbated by excessive monoaminergic neurotransmitter release at times of stress.

The proposed pathological mechanism leads to several predictions about the observable relationships between symptoms, cognitive deficits, and underlying neuronal abnormalities. In particular, in the stable phase of the illness, the profile of cognitive impairment, and also of persisting symptoms, will be determined largely by the location of cerebral regions that are affected by the primary dysplasia. Monoamine disregulation would be expected to play a relatively minor role in the stable phase. It would be predicted that in this phase of illness, symptom profile and pattern of cognitive impairment would show consistent relationships, as found in the studies reviewed in Section III.B. However, during episodes of acute florid disturbance, variation between subjects in the type and severity of symptoms will be determined not only by the location of the regions affected by the primary dysplasia, but also by variation in the severity of monoamine disregulation. In this phase of illness, the factors influencing the severity of symptoms and cognitive impairment would be much more complex.

The developmental disregulation hypothesis predicts that patients with persistent, severe illness will have relatively marked disruption of coordination between the cerebral sites implicated in one or more of the three syndromes at all phases of the illness. In such patients, a strong correlation between the severity of a particular group of symptoms and severity of impairment of the cognitive processes that engage the cerebral sites implicated in relevant syndrome would be expected. However, the hypothesis also predicts that patients with remitting illness will have a relatively minor disruption of coordination between the cerebral sites implicated in the syndromes at baseline. In these cases, the major abnormality is impaired regulation of the monoamine neurotransmitters. During florid episodes of illness, the severity of both symptoms and cognitive impairments will be determined mainly by the severity of monoamine disregulation. Because the effects of monoamine disregulation are not confined to the neural pathways linking cerebral sites implicated in the syndromes, the relationship between symptoms and cognitive impairment would be expected to be weaker. The studies by Baxter and Liddle\textsuperscript{27} and Ngan and Liddle\textsuperscript{28} that have compared patterns of correlations between symptoms and cognitive impairments in cases with severe persistent illness with those in patients with remitting illness have confirmed this prediction.

Baxter and Liddle\textsuperscript{27} demonstrated that in patients with persistent illness, the severity of psychomotor poverty was correlated with impairment in a two-choice guessing task that tested the ability to produce a response that was entirely self-generated. This correlation was absent in patients

![FIGURE 1](image-url) The pathophysiology of schizophrenia.
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with remitting illness. Ngan and Liddle demonstrated that in patients with persistent illness, psychomotor poverty was associated with slowed simple reaction time, while disorganization was correlated with impaired choice reaction time. In patients with remitting illness, these relationships were much weaker.

The developmental disregulation hypothesis predicts that florid symptoms will respond to treatment with medication that reduces monoaminergic neurotransmission, especially dopaminergic neurotransmission. The more enduring symptoms and cognitive deficits that are a direct consequence of the primary dysplasia would be expected to be less responsive to treatment. Nonetheless, insofar as the evidence indicates that the primary problem is impaired coordination of activity between cerebral areas rather than overt loss of neurons, there is potential for successful treatment by agents that modulate neurotransmission. Assuming that regularly active connections tend to be reinforced, the hypothesis predicts that symptoms that persist for prolonged periods will be reinforced. Conversely, alleviation of the baseline abnormalities of coordination between cerebral areas is likely to require prolonged treatment, whether using psychological strategies or pharmacological agents that promote healthy patterns of coordination between cerebral areas.

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FIGURE 12 Reduced D1-D2 link in psychosis, as measured in postmortem human brain striata. 100

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