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By William R. McFarlane

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Please note that we have not reproduced the diagram or the endnote references.

THE BRAIN AND ITS ALTERATION IN SCHIZOPHRENIA

Alterations in brain function have consistently been shown to be associated with schizophrenia. By the end of this chapter, the reader will have a working knowledge of a multilevel, empirically derived model of brain function and dysfunction that can be highly useful in guiding family and patient education, adaptation to community life, and rehabilitation. This is termed the biosocial model, because it assumes reciprocal influences of both the social environment on the brain and the dysfunction of the brain on the social environment. Leaders of multifamily groups should be expert in the interaction of these seemingly distant spheres.

The Brain Stem, the Midbrain, and Their Activation Centers

We start with the brain stem and its upper portion, the midbrain. Over the course of evolution, more complex functions have generally been added by laying new structures on top of older structures. So, it is not an oversimpli- fication to say that the most basic, though primitive, functions are mediated by the brain stem, which lies at the base of the skull, just above the spinal cord, and that the most elegant and complex functions are mediated by the prefrontal cortex, which, as the name implies, lies just behind the forehead. Likewise, during fetal development, the lower centers are organized first, while higher order centers, especially the prefrontal cortex, arise last and involve the migration forward and upward of cell groups that start life directly adjacent to the brain stem. Migrating cells maintain important physical connections, mediated by electrical and chemical activity, with cells in the structures that gave rise to them. So prefrontal cells have important connections to cells in the brain stem and in the diencephalon, especially the principal sensory integration center, the thalamus. Their functions are interrelated as well. Schizophrenia affects parts of all these structures.

The brain stem regulates the level of activation of the nervous system, primarily through the action of three neurotransmitters—dopamine, serotonin, and noradrenaline. Four small structures, composed of groups of neurons and lying near each other in the midbrain (the upper portion of the brain stem), regulate the activity of other parts of the brain using these neurotransmitters. Those neuronal groups are the ventral tegmentum, the substantia nigra (both use dopamine), the raphe nuclei (serotonin), and the locus coeruleus (noradrenaline). They determine the level of consciousness as well as the varying levels of activity in almost all other higher brain structures.

The dopamine system controls the level of activity in both the prefrontal cortex and in the limbic cortex and other limbic structures, including the hippocampus and the amygdala, all of which are affected in schizophrenia (discussion follows). Dopamine was the first neurotransmitter to be linked directly to schizophrenia, because antipsychotic drugs decrease dopamine activity. These medications mimic the molecular shape of dopamine sufficiently to occupy the receptors, thus preventing the usual activation of this system.

Thus, it should be no surprise that schizophrenia is characterized by excess levels of dopamine activity during the acute episodes and periods of clinical instability, and by abnormally low levels when negative symptoms and extreme apathy predominate.[24-25] One effect is that the limbic system tends to be overstimulated during acute episodes. Dopamine activity normally also increases the activity of the prefrontal cortex, but this does *not* occur in schizophrenia. Usually, when the dopamine system is activated, so is the noradrenaline system, with the result that heart and respiratory rates, blood pressure, anxiety, and agitation are also increased.

It is too early in the progress of brain research to provide a clear understanding of the serotonin system and its role in schizophrenia. However, serotonin is widely distributed in the entire cortex and to many subcortical structures. It appears to inhibit the dopamine system, modulating its influence.[26] Also, in the schizophrenic dorsolateral prefrontal cortex, there are increased neurotransmitter receptors for some forms of serotonin and decreased receptors for others.[27] It is clear that drugs that block serotonin at the receptor, such as clozapine, have better negative symptom outcomes and fewer Parkinson's disease-like side effects, reflecting complex

effects on a variety of receptor subgroups and brain areas. The rest of the serotonin story is very complex and as yet far from clear.

It is now considered likely that other neurotransmitters are involved in the disorder, including gamma-aminobutyric acid (GABA), glutamate, and N-methyl-D-aspartate (NMDA), a subtype of glutamate. The last appears to be reduced in activity in the cortex in general, in some subcortical areas,[28] and in connections between the thalamus and the cingulate cortex, both of which are involved in processing more complex sensory information. [29, 30] Drugs that reduce activity in the glutamate system have been found in normal volunteers to induce thought disorder and negative symptoms that cannot be distinguished from those of patients on structured interviews of thinking.[31] Alterations of glutamate and/or NMDA have been found in the prefrontal and superior temporal cortex, and in the hippocampus, the areas most directly implicated in schizophrenia.[32-34] Remarkably, amino acids that regulate this neurotransmitter system, glycine and D-serine, have been found to improve positive and negative symptoms substantially for patients already taking antipsychotic medication.[35,36] GABA precursors (messenger RNA [mRNA]) and levels of GABA itself have been found to be markedly reduced in the prefrontal cortex, reflecting reduced neuronal activity in this important region. Recently integrated models for the interaction of some of these neurotransmitter systems have been proposed, explaining both biochemical findings and the differences in effects and efficacy among various antipsychotic drugs.

The key concept is that the midbrain is impaired in its ability to adjust the activation of the brain and nervous system in ways that are normal or appropriate to the situation at hand. Although the means by which this adjustment occurs are unclear, the brain under normal circumstances can very precisely change its activation to match the environmental, social, or internal demands imposed by exercise, infection, metabolic imbalance, and cognitive and emotional input. In schizophrenia, the dopamine and norepinephrine systems are both unstable, tending toward overactivity when stress is present. This abnormal activation then radiates its effects through at least three other neurotransmitter systems to the rest of the brain in ways that are complex but that nearly always undermine mental and emotional well-being. At the other extreme, negative symptoms tend to be associated with underactivity of dopamine-driven systems,[24] as well as reduced activity on the part of activating neurotransmitters, especially GABA and the glutamate/NMDA system. Studies of the excitatory neurotransmitters - glutamate, NMDA, and GABA - have great promise for development of new drug and perhaps nutritional treatments for this disorder.

The Limbic System and Thalamus

The next higher strata, above the brain stem, include the limbic cortex and the thalamus, as well as several other nearby structures. The limbic system is a way station among the prefrontal cortex, the thalamus, and the temporal lobe. Two of its components, the amygdala and the cingulate cortex, generate more primitive and life-sustaining affects and emotions, especially anger and fear, the classic fight-or-flight pattern of response. It is the limbic system that is most directly affected therapeutically by antipsychotic medications; that effect is mediated by dopamine blockade. The drugs alleviate labile emotions and delusional thinking, which are more extreme forms of fear and suspiciousness. The limbic system has consistently been found to be hyperactive during psychosis and underactive in conjunction with negative symptoms.

Another limbic structure of great importance is the hippocampus. This tiny, seashell-like structure mediates all short-term memory registration and many crucial components of attention, especially establishing and maintaining focus. In schizophrenic patients it has been found to be atrophied and its very cell structure disorganized.[41-42] The effect is a partial, but consistently confirmed, disability in directing attention appropriately, focusing attention, and ignoring distracting stimuli when necessary. Furthermore, this defect creates marked difficulties with storing information long enough to be transferred for longer-term retention, resulting in subtle and erratic memory deficits.

The thalamus, which serves as the central control system for integrating sensory input, has been found to be underactive in schizophrenia, resulting in an inability to screen out sensory stimuli and a tendency for all sensory information to be experienced as excessive, inappropriately generalized, and overwhelming.[43,44] One recent study has found that portions of the thalamus are reduced in size in schizophrenia, suggesting an anatomical basis for this impairment.[45] In schizophrenia, defects in the limbic and thalamic systems create a

state of sensory hypersensitivity, combined with a tendency toward excessive levels of fear, suspiciousness, and anger.[46-48]

Disorders of the limbic, thalamic, and midbrain systems are functionally linked in schizophrenia; that is, as arousal increases in response to outside or internal sources of stimulation, attention deteriorates. As attention deteriorates, arousal increases reactively, leading to a downward spiral that ends in hyperarousal in the entire limbic system, with resulting extreme states of primitive emotion, increasingly heightened sensory sensitivity, and severely limited attentional capacity. This cycle is termed the distraction - arousal hypothesis and is central to the psychoeducational approach.

Higher Cortical Areas Affected: Prefrontal, Superior Temporal Gyri, and Postcentral Areas

Modern imaging methods (CT [computed tomography], PET [positron emission tomography] , SPECT [single photon emission tomography] , and MRI [magnetic resonance imaging] scans) have demonstrated in schizophrenia an increase in the size of the ventricles, the usually small channels through which flows cerebrospinal fluid from brain to spinal cord to bloodstream.[50] Increased ventricular size usually indicates loss of cerebral tissue, though it says little about the site of loss; that is, in many people with schizophrenia, living brain tissue has been replaced by spaces filled with fluid. These studies show that in many persons with schizophrenia, the cerebral cortex is reduced in size and has less total volume. Indeed, some studies, though not all, show that the entire brain tends to be smaller on average. The changes are similar in type to dementias, though far less dramatic and less progressive over time. The most pronounced changes are concentrated in prefrontal, medial and superior temporal, and cingulate cortices. The differences noted do not seem to be acute, because there is only the weakest correlation with age or number of episodes. These changes are present even at the first episode in young adults. Studies of children with schizophrenia, followed into adolescence, show some enlargement of ventricles over a 2-year time span, suggesting that some degradation of brain structure may occur in the early years of adolescence in cases with a very early onset. Many studies have shown correlations of ventricular enlargement with negative symptomatology and cognitive impairment. *This indicates, perhaps more clearly than any other single set of findings, that functional disability in some persons with schizophrenia is secondary to structural defects in the brain itself.*

PET and functional MRI scans provide an increasingly coherent picture in several studies. Most important, the prefrontal cortex has been found to be less active than normal, especially when the subject is challenged to do complex and frustrating mental tasks, such as the Wisconsin Card Sort, a test of abstracting and problem-solving capacity under social duress. The dorsolateral prefrontal cortex appears to be the brain area that activates to accomplish the test. However, in schizophrenia, there is dramatically lower activation to the test and poor performance as well. Recent work has shown that the prefrontal area is less active in proportion to the degree of negative symptoms, verbal task demands, and cognitive impairments, and in the presence of delusions, hallucinations, and stereotyped ideas.

The left superior temporal area tends to be overactive in association with thought disorder, negative symptoms, and verbal tasks, even while having reduced physical volume. However, it is less active in the presence of delusions and hallucinations.[64-68] This last insight is particularly useful, suggesting that this area may be deficient in processing, inhibiting, and modulating auditory stimuli, predisposing patients to alterations and misperceptions in the auditory sphere. It is not clear how verbal hallucinations are formed, but given what is known, it may be that reduction in temporal brain tissue removes some key monitoring functions and leaves open the way to spontaneous verbal perceptions.

Another key finding is that activity is increased in the posterior portions of the cerebral cortex, in the parietal and occipital areas. These have long been known to be the processors of visual and other nonverbal sensory input, elaborating, correlating, and interpreting sensory data. A possible model is emerging: The thalamus is impaired and releases the parietal and occipital conical areas to overprocess, underinhibit, and overreact to sensory information, creating a tendency toward relative overactivity, in turn leading to the well-demonstrated heightened sensitivity to sensory stimuli so characteristic of this disorder.

To summarize, a picture is emerging from hundreds of studies, using scanning techniques, metabolic studies and the direct examination of brain tissue and cells. Physical and biochemical abnormalities correlate with symptoms and functional difficulties. Specifically, the functional axis comprising the midbrain, the thalamus, and the limbic, superior temporal, and prefrontal cortexes is disordered and in many patients is clearly but not

severely damaged, with secondary effects on the parietal-occipital/sensory cortical areas. The neurotransmitters involved in this axis—dopamine, serotonin, noradrenaline, glutamate, GABA, and some neuropeptides—tend to be deranged complexly: Dopamine in excess appears to mediate psychosis and, when decreased, mediates the deficit state, while excess serotonin that may be serving as an antipsychotic in reaction to excess dopamine activity may be deficient in some patients and in some receptor subsystems. The antipsychotic drugs act by down-regulating dopamine in the limbic cortex and perhaps serotonin in the prefrontal cortex. However, this is a partial and, in some areas of research, confusing picture. It is sure to be revised and expanded in the near future.

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