Neural models of schizophrenia

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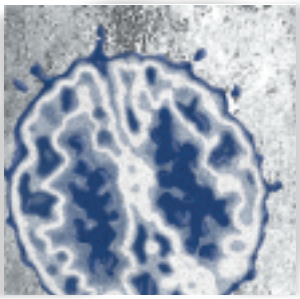

Hallucinations and delusions—two diagnostic features of psychosis shared across the spectrum of heterogeneous schizophrenia constructs—can be described in terms of the pathophysiology of sensory information processing: hallucination is the impaired ability to classify representations as internally or externally generated, while delusion is the immutable linking of representations with each other in the absence of external dependency. The key anatomical systems in higher-order information processing are the cortex, thalamus, basal ganglia, and medial temporal lobe, each of which is modulated by neurotransmitter projection systems. Preliminary evidence, concentrating to date on the dorsolateral prefontal cortex, thalamus, and hippocampal region of the medial temporal lobe, points to neural circuitry dysfunction within and between each system in psychosis. This may account for specific symptoms and associated cognitive deficits such as memory impairment, attention deficit, and language disturbance.

The psychiatric diagnoses **dementia praecox** (Kraepelin) and **group of schizophrenias** (Bleuler) were introduced to designate a group of psychiatric patients with similar clinical features, disease course, and outcome.[1-3] The diagnostic criteria used to define schizophrenia have varied over the last 100 years. They have included several forms of hallucinations and delusions, abnormalities of speech and motor activity, cognitive deficits such as poor attention and impaired memory, and affective disturbance.[2,4] Schizophrenia is now diagnosed in about 1% of the population worldwide.[5,6]

In the 4th edition of his psychiatry textbook, published in 1893, Kraepelin proposed that three groups of patients, diagnosed with catatonia (Kahlbaum),[7] hebephrenia (Hecker),[8] and dementia paranoides, represent different phenotypes of the same illness which he labeled dementia praecox.[3,9] We are still struggling to answer the two questions Kraepelin faced 100 years ago: How is schizophrenia different from other psychotic conditions? Is schizophrenia one illness or does it represent different diseases?

The heterogeneity of the schizophrenia construct poses a major hurdle for the study of disease mechanisms and etiology.[10] If the diagnosis covers a broad spectrum of patients who might not share the same symptoms, then the search for one etiology and pathogenesis that could predict treatment response and outcome may be futile. Therefore, schizophrenia researchers have attempted to reduce the complexity of schizophrenia by defining subtypes or dividing schizophrenia into one or more entities. Emil Kraepelin subdivided dementia praecox into subtypes based on the presence of one or more symptoms. His last attempt at subdividing dementia praecox/schizophrenia produced 10 different "clinical forms." The *Diagnostic and Statistical Manual of Mental Disorders (DSM)* has followed his tradition and the current version (*DSM-IV*) recognizes three of his subtypes (paranoid type, disorganized [ie, hebephrenic] type, and cata-

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Selected abbreviations and acronyms

BF	*basal forebrain*
CA	*cornu ammonis*
DG	*dentate gyrus*
DLPFC	*dorsolateral prefrontal cortex*
GABA	*gamma-aminobutyric acid*
GAD	*glutamic acid decarboxylase*
GAP	*growth-associated protein*
LC	*locus ceruleus*
MTL	*medial temporal lobe*
NADPH-d	*nicotinamide adenine dinucleotide phosphate-diaphorase*
PHG	*parahippocampal gyrus*
R	*raphe nuclei*
rCBF	*regional cerebral blood flow*
SN	*substantia nigra*
Sub	*subiculum*
VTA	*ventral tegmental area*

tonic type) and supplements them with two new ones (undifferentiated type and residual type). The Kraepelinian subtypes are defined by the presence, severity, and duration of symptoms, but their validity has been questioned.[11] For example, all subtypes, except the paranoid type, show poor temporal stability and might not represent a trait characteristic.[12-15]

Bleuler acknowledged the heterogeneity of the schizophrenia construct without providing a solution to this puzzle[16]:

> I call dementia praecox "schizophrenia" ... I use the word in the singular although it is apparent that the group includes several diseases ... so far we have been unable to discover any natural lines of division within the described clinical picture ... the subdivision of the group of schizophrenias is a task for the future.

A different approach to the complexity of schizophrenia can be traced back to the writings of John Russell Reynolds (1828-1896) and John Hughlings Jackson (1835-1911).[17] Jackson proposed a model of abnormal brain function in neurological and psychiatric disorders based on the evolutionary theory that the brain had developed to increasingly more complex levels. He suggested that higher levels of brain function (eg, cortex) control the function of lower levels (eg, subcortical structures, brain stem). Negative symptoms arise from the paralysis of a given hypothetical level of brain function. Positive symptoms arise when higher levels of brain function are impaired and, due to a lack of inhibition, lower levels become apparent, creating "symptoms" normally not observed. In Jackson's view, "where there is a positive symptom, a negative symptom must be."[17]

The positive/negative dichotomy resonated in the community of schizophrenia researchers. It seemed reasonable to divide the signs and symptoms of schizophrenia into those that are characterized by the production of abnormal behavior (positive symptoms) and those that represent a deficiency of normal behavior (negative symptoms) *(Table I)*.[18-20] It was thought that the two symptom dimensions could differentiate subtypes of schizophrenia. More recently, statistical methods have been applied to study the clustering of signs and symptoms in schizophrenia. If some features occur together with other symptoms more than is likely than by chance alone, then they might share etiology and/or disease mechanisms. Such studies have revealed two-, three-, four-, and five-factor models.[6,21-26]

Localizing schizophrenic symptoms

Once subtypes of schizophrenia had been defined, researchers attempted to localize the clinical features to distinct brain regions or neural networks. Southard published one of the first such models in the 1910s and proposed that temporal lesions (especially left superior temporal gyrus hypoplasia) are associated with auditory hallucinations, parietal atrophy and sclerosis are associated with catatonia, and frontal lobe aplasia or atrophy is associated with delusions.[27,28]

More recently, the positive and negative symptoms were associated with dysfunction of separate neural networks.[29-31] For example, the positive symptoms of schizo-

Positive	Negative
Hallucinations	Alogia
Delusions	Affective blunting
Formal thought disorder (language)	Avolition
Bizarre behavior	Anhedonia
	Attentional impairment

Table I. Signs and symptoms of schizophrenia.

phrenia have been correlated with temporal lobe abnormalities such as volume reduction and increased blood flow. Conversely, negative symptoms have been associated with decreased prefrontal blood flow.

Carpenter and colleagues have suggested that patients with schizophrenia can be classified as deficit syndrome patients (with enduring negative symptoms that are not due to medication and/or depression) and nondeficit patients.[32] They have proposed that deficit patients show more frontal lobe deficits than nondeficit patients, but that both subgroups show temporal lobe abnormalities.[33] So far, studies have reported differential impairment of cognitive function,[34-36] brain structure,[37] and brain function[38] in deficit and nondeficit schizophrenia.[39]

Localizing the signs and symptoms of schizophrenia to neural networks relies on neuroscientific models of how behavior is implemented in the brain. Here we will describe a basic outline of brain–behavior relationships. We will then use this framework to review studies of the neural basis of schizophrenia.

The neural basis of psychosis

In order to develop models of how the brain gives rise to psychosis, we need to define psychosis. Despite controversy about the relative weight given to positive and negative symptoms in the diagnosis of schizophrenia,[2,40] all classification schemes have included two features, hallucinations and delusions. These two symptoms provide the basis for the definition of psychosis as impaired reality testing. The underlying premise in the definition of psychosis is that the brain's processing of information, derived from the outside world, is perturbed in psychosis. The processing of sensory information involves three steps: the collection of sensory information through perceptual modules, the creation of a representation, and the production of a response.

Sensory organs provide information about physical attributes of incoming information. Details of physical attributes (eg, temperature, sound frequency, or color) are conveyed through multiple segregated channels within each perceptual module. Integration of the highly segregated sensory information occurs at three levels. The first integration occurs in unimodal association areas, where physical attributes of one sensory domain are linked together. A second level of integration is reached in multimodal association areas, which link physical attributes of different sensory qualities together; and a third level of integration is provided by the interpretation and evaluation of experience.[41] It is at this third level of integration that the brain creates a representation of experience that has the spatiotemporal resolution and full complexity of the outside world. Building on previous theoretical efforts,[42-46] we propose that the positive psychotic symptoms are due to an imbalance in the generation of representations: (1) the impaired ability to classify representations as internally or externally generated (hallucinations); and (2) the immutable linking of representations with each other in the absence of external dependency (delusions).

Following the evaluation and interpretation of the representation, the brain creates a response through a variety of channels, eg, language, affect, and motor behavior.[47,48] The diagnosis of psychosis is based on the analysis of these responses. For example, hallucinations, delusions, formal thought disorder, and flat affect are defined by abnormalities of the patient's language and motor behavior.

Neural circuitry in schizophrenia

Four anatomical systems (ie, the cortex, the thalamus, the basal ganglia, and the medial temporal lobe) are involved in higher order information processing. The function of these four systems is modulated by several groups of neurons that are characterized by their use of a specific neurotransmitter. First we will provide an overview of how these anatomical systems work together during normal brain function. We will then review, in detail, each of the four systems and how they are perturbed in psychosis.

The thalamus is the gateway to cortical processing for all incoming sensory information, here represented by the three major systems: somatosensory, auditory, and visual. The primary sensory cortex (S1, A1, V1) receives sensory information from the appropriate sensory modules (sensory organ and thalamus). The association cortex integrates information from primary cortices, from subcortical structures, and from brain areas affiliated with memory, to create the representation of experience. The medial temporal lobe serves two major functions in the brain: to integrate multimodal sensory information for storage into and retrieval from memory and to attach limbic valence to sensory information. The basal ganglia are primarily involved in the integration of input from cortical areas, particularly from the motor cortex. They modulate the activity of thalamocortical projections,

thereby creating a cortico-striato-pallido-thalamo-cortical loop.

Four groups of densely packed neurons provide widespread projections to many brain areas: cholinergic neurons in the basal forebrain (BF) and brain stem; dopaminergic neurons in the substantia nigra (SN) and ventral tegmental area (VTA); noradrenergic neurons in the locus ceruleus (LC); and serotonergic neurons in the raphe nuclei (R).

The anatomical organization of the human brain gives rise to several neural circuits, each affiliated with different aspects of brain function. Over the last 100 years of psychosis research, four major hypotheses have been put forward that propose abnormalities of these neural circuits in psychosis. (1) Beginning with Kraepelin, psychosis was thought to be a dysfunction of the association cortex in the frontal lobe, the dorsolateral prefrontal cortex (DLPFC). (2) Based in part on the observation that temporal lobe seizures often present with hallucinations and delusions, abnormalities of the medial temporal lobe (MTL) were proposed to explain the positive symptoms of psychosis. (3) The occurrence of psychotic symptoms after the use of amphetamine and cocaine, and the discovery that neuroleptic drugs block dopamine D_2 receptors, gave rise to the dopamine hypothesis. (4) More recently, the glutamatergic hypothesis, based in part on the fact that *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine and phencyclidine, can cause drug-induced psychotic states, has been put forward.

We will review here the evidence that the four anatomical systems (the cortex, the thalamus, the basal ganglia, and the medial temporal lobe) and their modulation by the neurotransmitter-specific projection systems are abnormal in schizophrenia. Although other brain regions, eg, the cerebellum, have also been implicated in the pathology of schizophrenia,[49] we will not review their role here.

Cortex

The association cortex of the human brain is a six-layered isocortex. Layers 2 and 4 are defined by a high density of small interneurons, ie, neurons that do not send long-ranging projections to other cortical or subcortical areas. In contrast, layers 3 and 5 are defined by a high density of pyramidal cells, which collect input through their dendrites and project to other cortical or subcortical areas. Interneurons are GABAergic cells (GABA: gamma-aminobutyric acid) and exert an inhibitory influence on their targets (via $GABA_A$ receptors) whereas pyramidal cells are glutamatergic and have an excitatory influence. Normal cortical function depends on an intricate balance between GABAergic inhibition and glutamatergic excitation.

Neuronal architecture

The anatomical and functional organization of the association cortex, especially the DLPFC, has been studied extensively in schizophrenia.[50] Volume reduction of the association cortex in schizophrenia has been reported in several postmortem and neuroimaging studies.[50,51] However, there is no marked loss of neurons or increased gliosis, a marker for the degeneration of neurons.[49]

Several subtle, yet significant, changes in the cortical architecture have been reported. First, a small subset of cortical neurons that express the enzyme nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) was found to be decreased in the frontal and temporal cortex and increased in number in the underlying white matter.[52-54] Similarly, the distribution of the Cajal-Retzius cells was shifted to lower parts of the first cortical layer.[55] Second, increased cell density in the frontal and occipital cortex has been described and attributed to changes in cortical neuropil.[56,57] Third, several abnormalities of GABAergic interneurons have been described: reduced release and uptake of GABA at synaptic terminals,[58] decreased expression of the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD),[59] altered expression of $GABA_A$ receptors,[60,61] and a reduction in axon cartridges of GABAergic chandelier neurons, terminating on the initial segment of pyramidal cell axons.[62] Fourth, the dendritic organization of frontal cortical areas has been found to be abnormal.[63] Fifth, the organization of synaptic connections, studied with the growth-associated protein GAP-43, was abnormal in frontal and visual association cortices.[64]

Neurotransmitter systems

Cortical neurons are targets for ascending fibers arising from the underlying white matter. Some of these inputs originate from other cortical areas or from the thalamus. Others arise from neurotransmitter-specific projection systems, such as the dopaminergic neurons of the VTA and the serotonergic neurons of the raphe

nuclei. Modulation of cortical function, via the D_1, D_4, D_5, and 5-HT_{2A} receptors, leads to the "fine tuning" of information processing, for example, by increasing the signal-to-noise ratio during corticocortical and thalamocortical neurotransmission.[65]

The effect of DA on cortical neurons is conveyed by three DA receptors, the D_1, D_4, and D_5 receptors. The D_1 and D_5 receptors are expressed primarily, but not exclusively,[66] on pyramidal cells, whereas the D_4 receptor is expressed primarily on GABAergic interneurons.[67,68] Compared to typical neuroleptics, which have a high D_2-blocking ability, the atypical neuroleptics are much more effective in blocking D_4 receptors. It is not clear whether some of the antipsychotic effects of atypical neuroleptics are conveyed through the D_4 receptors localized on GABAergic interneurons of the association cortex, especially the DLPFC.[69]

Alterations of the GABAergic system[59,60] and the D_1 receptors of the DLPFC have been reported in schizophrenia. The expression of cortical D_1 receptors is increased by the chronic treatment with typical neuroleptics.[70] Of interest, a recent positron emission tomography (PET) study found a reduction in cortical D_1 receptors, which was correlated with the severity of negative symptoms and poor performance on the Wisconsin Card Sorting Test.[71]

One serotonergic receptor, the 5-HT_{2A} subtype, is of relevance for the pathophysiology of psychosis.[72] Hallucinogens, eg, lysergic acid diethylamide (LSD), act as agonists at the 5-HT_{2A} receptor and several antipsychotic compounds, especially the atypical neuroleptics, block the activity of the 5-HT_{2A} receptor. Several postmortem studies have reported a decrease in 5-HT_2 receptors in schizophrenia, but others have not.[73,74] A recent PET study of neuroleptic-free patients with schizophrenia did not find any differences in the expression of cortical 5-HT_2 receptors in several cortical areas.[74]

Cortical function

Neuroimaging studies have revealed dysfunctional cortical networks in schizophrenia.[75-79] Regional cerebral blood flow (rCBF) and glucose metabolism were found to be abnormal in frontal cortex and temporal lobe structures at rest as well as during the performance of cognitive tasks. There is, however, no pattern that is diagnostic for schizophrenia. For example, frontal cortical activity at rest was found to be lower by some investigators[80-95] but not by others,[96-113] and temporal lobe activity at rest was found to be decreased,[91,104,109,114] normal,[95] or increased.[113,115] Similarly, frontal cortical recruitment during task performance was found to be decreased in some studies[80,84,85,106,112,116-122] but not in others.[123-125]

The clinical heterogeneity of schizophrenia might explain why schizophrenia as a whole is not associated with a pathognomonic abnormality of brain function. When the signs and symptoms of schizophrenia are used to categorize patients into two groups (positive and negative syndrome) or into distinct clusters, a more consistent pattern of neural dysfunction in schizophrenia emerges. Frontal cortex activity at rest correlates inversely with the degree of negative symptoms,[29,95,114,126-130] and left medial temporal lobe activity at rest correlates positively with the severity of psychopathology[115,131] or the degree of reality distortion.[29,130] Similarly, decreased frontal cortex recruitment during the performance of some cognitive tasks occurs primarily in patients with negative symptoms.[80,119]

Thalamus

The thalamus serves several important functions in information processing in the human brain.[132] First, the relay nuclei (ventral posterior lateral nucleus [VPL], medial geniculate nucleus [MGN], lateral geniculate nucleus [LGN]) relay sensory information from the sensory organs to the appropriate areas of the primary sensory cortex (S1, A1, and V1). Second, the association nuclei, especially the mediodorsal (MD) nucleus, establish reciprocal connections with the association cortex. Third, the motor nuclei (ventral) relay input from the basal ganglia to the motor and premotor cortex.

Two abnormalities of thalamic function have been proposed in schizophrenia. First, a breakdown of the sensory filter could lead to an increased stimulation of primary sensory cortical areas. Such a defective filter would implicate abnormalities in the thalamic relay nuclei. Second, dysfunction of the MD nucleus could lead to impairments of cortical association areas, especially the DLPFC.

Direct evidence for an involvement of the thalamus in the pathophysiology of schizophrenia is still limited. The most convincing evidence comes from morphometric studies, pointing to a volume reduction of the thalamus, especially the MD nucleus,[50,133] which has been attributed to cell loss.[133] A postmortem study reported a decrease in parvalbumin-positive neurons in the anteroventral nucleus, which would result in a loss of thalamocortical

projections to the prefrontal cortex.[134] Recently, some[135,136] but not all,[137,138] neuroimaging studies have revealed smaller thalamic volume. In addition, thalamic metabolism and blood flow were found to be impaired at rest and during the performance of cognitive tasks.[136,138,139] Of interest, the decrease in metabolism during the performance of a serial verbal learning test involved primarily the region of the mediodorsal thalamic nucleus.[138]

Basal ganglia

The basal ganglia include the ventral striatum, the dorsal striatum (caudate and putamen), and the globus pallidus. The dorsal striatum (caudate, putamen) receives input from motor cortex and projects to the globus pallidus. The globus pallidus relays the neostriatal input to the thalamus. The thalamus, in turn, projects back to the cortical areas that gave rise to the corticostriatal projections, thereby closing the cortico-striato-pallido-thalamo-cortical loop. This loop is involved in the generation and control of motor behavior. In contrast, the ventral striatum (the nucleus accumbens) is connected with the amygdala, hippocampus, and hypothalamus, and is therefore considered part of limbic system. Reward and expectancy behavior, and their derailment during drug addiction, involve the recruitment of the nucleus accumbens.

All basal ganglia structures are modulated by neurotransmitter-specific projection systems, in particular by dopaminergic neurons. Dopaminergic neurons of the SN project to the neostriatum (nigrostriatal fibers) and dopaminergic neurons of the VTA project to the nucleus accumbens (mesolimbic fibers) and cortex (mesocortical fibers). The two major DA receptors in the dorsal striatum are the D_1 and D_2 receptors. The nucleus accumbens expresses primarily the D_3 receptor.

The basal ganglia have been a focus of interest in psychosis research for three reasons: as potential sites of neuroleptic drug action at D_2 receptors, as a potential site for the generation of abnormal motor behavior during psychosis (eg, catatonia), and as a site for pathology in the limbic system.[140-143]

Dopaminergic afferents

The most extensive search has been at the level of dopamine receptors. Earlier studies reported an increased expression of D_2 receptors, but there is now good agreement by most studies that the D_2 receptor density is not abnormal in schizophrenia.[144] One recent study reported an increased expression of dopamine D_3 receptors in the nucleus accumbens.[145]

In addition to studies of dopamine receptors, there have been recent studies of dopamine release and intrasynaptic dopamine content in the striatum. Two groups have independently reported that the intrasynaptic content of dopamine after treatment with amphetamine is increased in schizophrenia.[146-148] Thus, not a tonic increase of dopamine release but an increased phasic release of dopamine could be involved in the pathophysiology of schizophrenia. In addition, the regulation of striatal dopamine activity via afferent fibers originating in the prefrontal cortex is impaired.[149]

Striatal structure

Several structural abnormalities of the basal ganglia in schizophrenia have been reported. First, the volume of basal ganglia structures was reported to be increased in medicated schizophrenic patients.[150-154] Striatal volume increase is closely related to the treatment with typical neuroleptics: basal ganglia volume is normal or even decreased in newly diagnosed neuroleptic-naive patients,[155] increases over time during treatment with typical neuroleptics, and decreases after patients have been switched to atypical neuroleptics.[156-158] The mechanism of this relationship is not clear. Second, recent postmortem studies have provided evidence for an overall increased number of striatal neurons[159,160] and for a change in the synaptic organization of the striatum, particularly the caudate nucleus.[161] Third, the number of nucleus accumbens neurons was found to be decreased.[133]

Medial temporal lobe

The medial temporal lobe contains the amygdala, the hippocampal region, and superficial cortical areas that cover the hippocampal region and form the parahippocampal gyrus (PHG). The hippocampal region can be subdivided into three subregions: the dentate gyrus (DG), the cornu ammonis (CA) sectors, and the subiculum (Sub). The neurons of the human hippocampal region are arranged in one cellular layer, the pyramidal cell layer. Most pyramidal cell layer neurons are glutamatergic whereas the small contingent of nonpyramidal cells are GABAergic. The serial circuitry of the glutamatergic neurons provide the structural basis for long-

term potentiation, a physiological phenomenon crucial for formation of memory.

The PHG receives many projections from multimodal cortical association areas and relays them to the hippocampal region.[162] Intrinsic connections within the hippocampal region allow further processing before the information is referred back to the association cortex. The hippocampus is also closely connected with the limbic system; Papez proposed that the hippocampal formation be recruited via these connections to regulate emotion or to modulate information processing by attaching limbic valence to sensory stimuli.[163,164]

In contrast to the 100-year-long search for cortical pathology in schizophrenia, studies of the medial temporal lobe in schizophrenia are more recent. However, in a short period of time, an extensive body of research has accumulated. Here we will review the evidence for abnormalities of the hippocampal formation in schizophrenia.

Hippocampal structure

Many studies have found a subtle (about 5%) hippocampal and parahippocampal volume reduction in schizophrenia.[51,165-168] Hippocampal volume reduction does not correlate with the duration of illness or correspond to schizophrenia subtypes such as deficit and nondeficit syndrome.[37,169-171] In addition to changes in volume, changes in hippocampal shape have recently been reported.[172] Furthermore, deficits of hippocampal structure (volume, *N*-acetylaspartate levels) are also found in healthy, first-degree relatives of schizophrenic patients.[173-175]

Most studies have found no change in the number of hippocampal pyramidal neurons[176-179] but nonpyramidal cells in the hippocampus (especially in CA2 subregion) seem to be reduced by 40%.[180] Studies of the orientation and position of pyramidal cells within the cornu ammonis subfields and of entorhinal cortex layer 2 cells are inconclusive.[181-185] There is evidence that the intrinsic hippocampal fiber systems and the reciprocal connections of the hippocampal formation are perturbed, leading to a loss of neuropil and an overall loss of white matter.[177,186-190] Synaptic organization is changed, possibly indicating altered plasticity of the hippocampus in schizophrenia.[191-195] In addition to these postmortem studies, magnetic resonance spectroscopy studies have provided evidence for abnormalities of membrane phospholipids and high-energy phosphate metabolism in the temporal lobe.[76,196-200]

Neurotransmitter systems

Glutamate receptors of the kainic acid/amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (KA/AMPA) subtype, primarily the GluR1 and GluR2 subunits, are decreased in the hippocampus in schizophrenia.[201-205] GABA-uptake sites are reduced and $GABA_A$ receptors are upregulated, possibly due to the loss of GABAergic hippocampal interneurons.[58,206-208] In addition, serotonergic 5-HT_{1A} and 5-HT_2 receptors are increased and 5-HT-uptake sites are unchanged in the hippocampus in schizophrenia.[209,210]

Hippocampal function

The metabolism and blood flow of the hippocampus are increased at baseline in schizophrenia.[115,211,212] Furthermore, hippocampal and parahippocampal rCBF is increased during the experience of psychotic symptoms and correlates with positive symptoms (delusions, hallucinations).[131,213] Recently, we have shown that hippocampal recruitment during the conscious recollection of semantically encoded words is impaired in schizophrenia.[214] Schizophrenic patients displayed increased levels of hippocampal blood flow at rest and lacked the normal modulation that predicts recall accuracy in control subjects. In addition, there is also indirect[215-217] evidence for the contribution of hippocampal abnormalities to cognitive impairments seen in schizophrenia.

Hippocampal lesion models of schizophrenia

Additional evidence for a contribution of hippocampal dysfunction to the pathogenesis of schizophrenia is provided by hippocampal lesions in rodents and primates. Hippocampal lesions produce behavioral states that share some resemblance with schizophrenia (attentional and memory deficits, stereotypic behavior, and hyperarousal) and behavioral changes are reversible by neuroleptic drugs.[218] Such lesion models have been established in adult rats,[219-221] in neonatal rats,[222-225] and in nonhuman primates.[226-229]

Conclusion

In summary, the neuropathology of schizophrenia remains elusive. However, postmortem and neuroimaging studies have provided evidence for the

involvement of several neural networks in schizophrenia. Impaired nodes include the dorsolateral prefrontal cortex, the thalamus, and the hippocampal formation. Abnormalities in these structures might explain some of the diagnostic features of schizophrenia as well as the cognitive deficits often seen in schizophrenia, eg, memory impairment, attentional deficits, and language disturbance. The two leading pharmacological models of schizophrenia, the dopamine and the glutamate model, and their implications for the study of pharmacological responses in schizophrenia, will be discussed in another article in this issue. ❑

Modelos neurales de la esquizofrenia

Las alucinaciones y los delirios -dos características diagnósticas de las psicosis presentes a través del espectro de los heterogéneos constructos de esquizofrenia- pueden ser descritos en términos de los procesos de información sensorial: la alucinación es el deterioro en la capacidad de clasificar representaciones generadas interna o externamente; en cambio, el delirio es la unión inmutable de representaciones con otras en ausencia de una dependencia externa. Los sistemas anatómicos clave en los procesos de información de orden superior son el córtex, el tálamo, los ganglios basales y el lóbulo temporal medial, cada uno de los cuales es modulado por sistemas de proyección de neurotransmisores. Existen evidencias preliminares que se concentran, a la fecha, en la corteza prefrontal dorsolateral, el tálamo y la región del hipocampo del lóbulo temporal medial y apuntan a disfunciones de los circuitos neurales dentro y entre cada sistema en la psicosis. Esto puede dar cuenta de síntomas específicos y déficits cognitivos asociados como deterioro de la memoria, déficit de la atención y trastornos del lenguaje.

Modèles neurologiques de la schizophrénie

Les idées délirantes et les hallucinations – deux symptômes de la schizophrénie, présents dans toutes les formes hétérogènes de cette maladie – peuvent être analysées sur le plan physiopathologique comme un dysfonctionnement du traitement des informations sensorielles : l'hallucination est l'incapacité de définir si une représentation est d'origine intérieure (mentale) ou d'origine externe et les idées délirantes sont dues à l'établissement par le sujet d'une relation immuable entre des représentations qui n'est pas justifiée par les éléments extérieurs. Les structures anatomiques essentielles impliquées dans les processus intellectuels sont le cortex, le thalamus, les ganglions de la base et le lobe temporal médian, chacune étant modulée par des systèmes de projections neuronales utilisant des neurotransmetteurs spécifiques. Les données que nous avions réunies antérieurement, impliquant jusqu'à présent le cortex dorsolatéral préfontal, le thalamus et la région hippocampale du lobe temporal moyen, soulignaient l'existence d'une dysfonction des circuits neuronaux au sein de ces structures et entre elles dans les psychoses. Ces anomalies pourraient expliquer les symptômes spécifiques et les déficits cognitifs associés tels que les troubles de la mémoire, les troubles de l'attention et les troubles du langage.

REFERENCES

1. Andreasen NC. The American concept of schizophrenia. *Schizophr Bull.* 1989;15:519-531.
2. Andreasen NC, Flaum M. Schizophrenia: the characteristic symptoms. *Schizophr Bull.* 1991;17:27-49.
3. Hoenig J. Schizophrenia. In: Berrios GE, Porter R, eds. *A History of Clinical Psychiatry.* New York, NY: New York University Press; 1995.
4. Alpert M. The signs and symptoms of schizophrenia. *Compr Psychiatry.* 1985;26:103-112.
5. Carpenter WT, Buchanan RW. Schizophrenia. *N Engl J Med.* 1994;330:681-690.
6. Andreasen NC. Symptoms, signs, and diagnosis of schizophrenia. *Lancet.* 1995;346:477-481.
7. Kahlbaum K. *Die Katatonie oder das Spannungsirresein.* Berlin, Germany: Hirschwald; 1874.
8. Hecker E. Die Hebephrenie. *Virchows Archiv.* 1871;52:394-429.
9. Palha AP, Esteves MF. The origin of dementia praecox. *Schizophr Res.* 1997;28:99-103.
10. Andreasen NC. Understanding schizophrenia: a silent spring? *Am J Psychiatry.* 1998;155:1657-1659.

11. Carpenter WT Jr, Stephens JH. An attempted integration of information relevant to schizophrenic subtypes. *Schizophr Bull.* 1979;5:490-506.
12. Pfohl B, Winokur G. The micropsychopathology of hebephrenic/catatonic schizophrenia. *J Nerv Ment Dis.* 1983;171:296-300.
13. Kendler KS, Gruenberg AM, Tsuang MT. Subtype stability in schizophrenia. *Am J Psychiatry.* 1985;142:827-832.
14. Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes. I. Longitudinal study of paranoid, hebephrenic, and undifferentiated schizophrenia. *Arch Gen Psychiatry.* 1991;48:969-977.
15. Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. *Arch Gen Psychiatry.* 1991;48:978-986.
16. Bleuler E. *Dementia Praecox or The Group of Schizophrenias.* 1950: 1, 8, 280.
17. Berrios GE. Positive and negative symptoms and Jackson. A conceptual history. *Arch Gen Psychiatry.* 1985;42:95-97.
18. Strauss JS, Carpenter WT, Bartko JJ. The diagnosis and understanding of schizophrenia, part 3: speculations on the processes that underlie schizophrenic symptoms and signs. *Schizophr Bull.* 1974;11:61-75.
19. Kay SR. *Positive and Negative Syndromes in Schizophrenia.* Vol 5. New York, NY: Brunner/Mazel; 1991.
20. Greden JF, Tandon R. *Negative Schizophrenic Symptoms: Pathophysiology and Implications.* Vol 28. Washington, DC: American Psychiatric Press; 1991.
21. Liddle PF, Barnes TR. Syndromes of chronic schizophrenia. *Br J Psychiatry.* 1990;157:558-561.
22. Klimidis S, Stuart GW, Minas IH, Copolov DL, Singh BS. Positive and negative symptoms in the psychoses. Re-analysis of published SAPS and SANS global ratings. *Schizophr Res.* 1993;9:11-18.
23. White L, Harvey PD, Opler L, Lindenmayer JP. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. *Psychopathology*. 1997;30:263-274.
24. Peralta V, Cuesta MJ, Farre C. Factor structure of symptoms in functional psychoses. *Biol Psychiatry.* 1997;42:806-815.
25. Dollfus S, Everitt B. Symptom structure in schizophrenia: two-, three- or four-factor models. *Psychopathology.* 1998;31:120-130.
26. Lancon C, Aghababian V, Llorca PM, Auquier P. Factorial structure of the positive and negative syndrome scale (PANSS): a forced five-dimensional factor analysis. *Acta Psychiatr Scand.* 1998;97:369-376.
27. Southard EE. On the topographical distribution of cortex lesions and anomalies in dementia praecox, with some account of their functional significance (part 1). *Am J Insanity.* 1914;71:383-403.
28. Southard EE. On the topographical distribution of cortex lesions and anomalies in dementia praecox, with some account of their functional significance (part 2). *Am J Insanity.* 1915;71:603-671.
29. Liddle PF, Friston KJ, Frith CD, Jones T, Hirsch SR, Frackowiak RSJ. Patterns of cerebral blood flow in schizophrenia. *Br J Psychiatry.* 1992;160:179-186.
30. Csernansky JG, Bardgett ME. Limbic-cortical neuronal damage and the pathophysiology of schizophrenia. *Schizophr Bull.* 1998;24:231-248.
31. Bogerts B. The temporolimbic system theory of positive schizophrenic symptoms. *Schizophr Bull.* 1997;23:423-435.
32. Carpenter WT Jr, Heinrichs DW, Wagman AM. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry.* 1988;145:578-583.
33. Carpenter WT Jr, Buchanan RW, Kirkpatrick B, Tamminga C, Wood F. Strong inference, theory testing, and the neuroanatomy of schizophrenia. *Arch Gen Psychiatry.* 1993;50:825-831.
34. Buchanan RW, Strauss ME, Breier A, Kirkpatrick B, Carpenter WT Jr. Attentional impairments in deficit and nondeficit forms of schizophrenia. *Am J Psychiatry.* 1997;154:363-370.
35. Bustillo JR, Thaker G, Buchanan RW, Moran M, Kirkpatrick B, Carpenter WT. Visual information processing impairments in deficit and nondeficit schizophrenia. *Am J Psychiatry.* 1997;154:647-654.
36. Buchanan RW, Strauss ME, Kirkpatrick B, Holstein C, Breier A, Carpenter WT Jr. Neuropsychological impairments in deficit vs nondeficit forms of schizophrenia. *Arch Gen Psychiatry.* 1994;51:804-811.
37. Buchanan RW, Breier A, Kirkpatrick B, et al. Structural abnormalities in deficit and nondeficit schizophrenia. *Am J Psychiatry.* 1993;150:59-65.
38. Tamminga CA, Thaker GK, Buchanan R, et al. Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Arch Gen Psychiatry.* 1992;49:522-530.
39. Thibaut F, Petit M. The deficit syndrome of schizophrenia: towards heterogeneity. *Psychopathology.* 1997;30:257-262.
40. David AS, Appleby L. Diagnostic criteria in schizophrenia: accentuate the positive. *Schizophr Bull.* 1992;18:551-557.
41. Mesulam MM. From sensation to cognition. *Brain.* 1998;121:1013-1052.
42. Goldman-Rakic PS. Circuitry of the prefrontal cortex and the regulation of behavior by representational knowledge. In: Plum F, Mountacstle V, eds. *Handbook of Physiology.* Vol 5. Bethesda, Md: American Physiological Society; 1987:373-417.
43. Gray JA, Feldon J, Rawlins JNP, Hemsley DR, Smith AD. The neuropsychology of schizophrenia. *Behav Brain Sci.* 1991;14:1-84.
44. Frith CD. *The Cognitive Neuropsychology of Schizophrenia.* Hove: Lawrence Erlbaum; 1992.
45. Hemsley DR. A simple (or simplistic?) cognitive model for schizophrenia. *Behav Res Ther.* 1993;31:633-645.
46. Hemsley DR. The disruption of the "sense of self" in schizophrenia: potential links with disturbances of information processing. *Br J Med Psychol.* 1998;71:115-124.
47. Houk JC, Wise SP. Distributed modular architectures linking basal ganglia, cerebellum, and cerebral cortex: their role in planning and controlling action. *Cerebral Cortex.* 1995;5:95-110.
48. Fuster JM. Linkage at the top. *Neuron*. 1998;21:1223-1229.
49. Andreasen NC, Paradiso S, O'Leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull.* 1998;24:203-218.
50. Heckers S. Neuropathology of schizophrenia: cortex, thalamus, basal ganglia, and neurotransmitter-specific projection systems. *Schizophr Bull.* 1997;23:403-421.
51. Lawrie SM, Abukmeil SS. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric resonance imaging studies. *Br J Psychiatry.* 1998;172:110-120.
52. Akbarian S, Vinuela A, Kim JJ, Potkin SG, Bunney WE Jr, Jones EG. Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. *Arch Gen Psychiatry.* 1993;50:178-187.
53. Akbarian S, Bunney WE Jr, Potkin SG, et al. Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. *Arch Gen Psychiatry.* 1993;50:169-177.
54. Akbarian S, Kim JJ, Potkin SG, Hetrick WP, Bunney WE Jr, Jones EG. Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. *Arch Gen Psychiatry.* 1996;53:425-436.
55. Kalus P, Senitz D, Beckmann H. Cortical layer I changes in schizophrenia: a marker for impaired brain development. *J Neural Transm.* 1997;104:549-559.
56. Selemon LD, Rajkowska G, Goldman-Rakic PS. Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. *Arch Gen Psychiatry.* 1995;52:805-818. Discussion: 819-820.
57. Selemon LD, Rajkowska G, Goldman-Rakic PS. Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: application of a three-dimensional stereologic counting method. *J Comp Neurol.* 1998;392:402-412.
58. Simpson MD, Slater P, Deakin JF, Royston MC, Skan WJ. Reduced GABA uptake sites in the temporal lobe in schizophrenia. *Neurosci Lett.* 1989;107:211-215.
59. Akbarian S, Kim JJ, Potkin SG, et al. Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics [see comments]. *Arch Gen Psychiatry.* 1995;52:258-266. Discussion: 267-278.
60. Benes FM, Vincent SL, Marie A, Khan Y. Up-regulation of $GABA_A$ receptor binding on neurons of the prefrontal cortex in schizophrenic subjects. *Neuroscience*. 1996;75:1021-1031.
61. Huntsman MM, Tran BV, Potkin SG, Bunney WE Jr, Jones EG. Altered ratios of alternatively spliced long and short gamma2 subunit mRNAs of the gamma-amino butyrate type A receptor in prefrontal cortex of schizophrenics. *Proc Natl Acad Sci U S A.* 1998;95:15066-15071.
62. Woo TU, Whitehead RE, Melchitzky DS, Lewis DA. A subclass of prefrontal gamma-aminobutyric acid axon terminals are selectively altered in schizophrenia. *Proc Natl Acad Sci U S A.* 1998;95:5341-5346.

63. Garey LJ, Ong WY, Patel TS, et al. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia [see comments]. *J Neurol Neurosurg Psychiatry.* 1998;65:446-453.
64. Perrone-Bizzozero NI, Sower AC, Bird ED, Benowitz LI, Ivins KJ, Neve RL. Levels of the growth-associated protein GAP-43 are selectively increased in association cortices in schizophrenia. *Proc Natl Acad Sci U S A.* 1996;93:14182-14187.
65. Goldman-Rakic PS. The cortical dopamine system: role in memory and cognition. *Adv Pharmacol.* 1998;42:707-711.
66. Muly EC III, Szigeti K, Godman-Rakic PS. D_1 receptor in interneurons of macaque prefrontal cortex: distribution and subcellular localization. *J Neurosci.* 1998;18:10553-10565.
67. Smiley JF, Levey AI, Ciliax BJ, Goldman-Rakic PS. D_1 dopamine receptor immunoreactivity in human and monkey cerebral cortex: predominant and extrasynaptic localization in dendritic spines. *Proc Natl Acad Sci U S A.* 1994;91:5720-5724.
68. Mrzljak L, Bergson C, Pappy M, Huff R, Levenson R, Goldman-Rakic PS. Localization of dopamine D_4 receptors in GABAergic neurons of the primate brain. *Nature.* 1996;381:245-248.
69. Lidow MS, Williams GV, Goldman-Rakic PS. The cerebral cortex: a case for a common site of action of antipsychotics. *Trends Pharmacol Sci.* 1998;19:136-140.
70. Knable MB, Hyde TM, Murray AM, Herman MM, Kleinman JE. A postmortem study of frontal cortical dopamine D_1 receptors in schizophrenics, psychiatric controls, and normal controls. *Biol Psychiatry.* 1996;40:1191-1199.
71. Okubo Y, Suhara T, Suzuki K, et al. Decreased prefrontal dopamine D_1 receptors in schizophrenia revealed by PET. *Nature.* 1997;385:634-636.
72. Jakab RL, Goldman-Rakic PS. 5-Hydroxytryptamine2A serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. *Proc Natl Acad Sci U S A.* 1998;95:735-740.
73. Gurevich EV, Joyce JN. Alterations in the cortical serotonergic system in schizophrenia: a postmortem study. *Biol Psychiatry.* 1997;42:529-545.
74. Lewis R, Kapur S, Jones C, et al. Serotonin 5-HT_2 receptors in schizophrenia: a PET study using [^{18}F]setoperone in neuroleptic-naive patients and normal subjects. *Am J Psychiatry.* 1999;156:72-78.
75. Gur RE. Functional brain imaging studies in schizophrenia. In: Watson SJ, ed. *Psychopharmacology. The Fourth Generation of Progress.* 1998 Edition CD-ROM. Lippincott-Raven; 1998.
76. McClure RJ, Keshavan MS, Pettegrew JW. Chemical and physiologic brain imaging in schizophrenia. *Psychiatr Clin North Am.* 1998;21:93-122.
77. Liddle PF. Functional imaging—schizophrenia. *Br Med Bull.* 1996;52:486-494.
78. Kotrla KJ, Weinberger DR. Brain imaging in schizophrenia. *Annu Rev Med.* 1995;46:113-122.
79. Buchsbaum MS. The frontal lobes, basal ganglia, and temporal lobes as sites for schizophrenia. *Schizophr Bull.* 1990;16:379-389.
80. Ingvar DH, Franzen G. Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatr Scand.* 1974;50:425-462.
81. Ariel RN, Golden CJ, Berg RA, et al. Regional cerebral blood flow in schizophrenics. Tests using the xenon Xe-133 inhalation method. *Arch Gen Psychiatry*. 1983;40:258-263.
82. Devous MDS, Raese JD, Herman JH, et al. Regional cerebral blood flow in schizophrenic patients at rest and during Wisconsin card sort task. *J Cereb Blood Flow Metab.* 1985;5(suppl 1):S201-S202.
83. Kurachi M, Kobayashi K, Matsubara R, et al. Regional cerebral blood flow in schizophrenic disorders. *Eur Neurol.* 1985;24:176-181.
84. Berman KF, Zec RF, Weinberger DR. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. II. Role of neuroleptic treatment, attention, and mental effort. *Arch Gen Psychiatry.* 1986;43:126-135.
85. Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence [see comments]. *Arch Gen Psychiatry.* 1986;43:114-124.
86. Geraud G, Arne-Bes MC, Guell A, Bes A. Reversibility of hemodynamic hypofrontality in schizophrenia. *J Cereb Blood Flow Metab.* 1987;7:9-12.
87. Mathew RJ, Wilson WH, Tant SR, Robinson L, Prakash R. Abnormal resting regional cerebral blood flow patterns and their correlates in schizophrenia. *Arch Gen Psychiatry.* 1988;45:542-549.
88. Erbas B, Kumbasar H, Erbengi G, Bekdik C. Tc-99m HMPAO/SPECT determination of regional cerebral blood flow changes in schizophrenics. *Clin Nucl Med.* 1990;15:904-907.
89. Paulman RG, Devous MD Sr, Gregory RR, et al. Hypofrontality and cognitive impairment in schizophrenia: dynamic single-photon tomography and neuropsychological assessment of schizophrenic brain function. *Biol Psychiatry.* 1990;27:377-399.
90. Sagawa K, Kawakatsu S, Shibuya I, et al. Correlation of regional cerebral blood flow with performance on neuropsychological tests in schizophrenic patients. *Schizophr Res.* 1990;3:241-246.
91. Buchsbaum MS, Ingvar DH, Kessler R, et al. Cerebral glucography with positron tomography. Use in normal subjects and in patients with schizophrenia. *Arch Gen Psychiatry.* 1982;39:251-259.
92. Farkas T, Wolf AP, Jaeger J, Brodie JD, Christman DR, Fowler JS. Regional brain glucose metabolism in chronic schizophrenia. A positron emission transaxial tomographic study. *Arch Gen Psychiatry.* 1984;41:293-300.
93. Wolkin A, Jaeger J, Brodie JD, et al. Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. *Am J Psychiatry.* 1985;142:564-571.
94. Wolkin A, Angrist B, Wolf A, et al. Low frontal glucose utilization in chronic schizophrenia: a replication study. *Am J Psychiatry.* 1988;145:251-253.
95. Volkow ND, Wolf AP, Van Gelder P, et al. Phenomenological correlates of metabolic activity in 18 patients with chronic schizophrenia. *Am J Psychiatry.* 1987;144:151-158.
96. Mathew RJ, Meyer JS, Francis DJ, Schoolar JC, Weinman M, Mortel KF. Regional cerebral blood flow in schizophrenia: a preliminary report. *Am J Psychiatry.* 1981;138:112-113.
97. Mathew RJ, Duncan GC, Weinman ML, Barr DL. Regional cerebral blood flow in schizophrenia. *Arch Gen Psychiatry.* 1982;39:1121-1124.
98. Gur RE, Skolnick BE, Gur RC, et al. Brain function in psychiatric disorders. I. Regional cerebral blood flow in medicated schizophrenics. *Arch Gen Psychiatry.* 1983;40:1250-1254.
99. Sheppard G, Gruzelier J, Manchanda R, et al. ^{15}O positron emission tomographic scanning in predominantly never-treated acute schizophrenic patients. *Lancet*. 1983;2:1448-1452.
100. Gur RE, Gur RC, Skolnick BE, et al. Brain function in psychiatric disorders. III. Regional cerebral blood flow in unmedicated schizophrenics. *Arch Gen Psychiatry.* 1985;42:329-334.
101. Kling AS, Metter EJ, Riege WH, Kuhl DE. Comparison of PET measurement of local brain glucose metabolism and CAT measurement of brain atrophy in chronic schizophrenia and depression. *Am J Psychiatry.* 1986;143:175-180.
102. Volkow ND, Brodie JD, Wolf AP, Angrist B, Russell J, Cancro R. Brain metabolism in patients with schizophrenia before and after acute neuroleptic administration. *J Neurol Neurosurg Psychiatry.* 1986;49:1199-1202.
103. Early TS, Reiman EM, Raichle ME, Spitznagel EL. Left globus pallidus abnormality in never-medicated patients with schizophrenia. *Proc Natl Acad Sci U S A.* 1987;84:561-563.
104. Gur RE, Resnick SM, Alavi A, et al. Regional brain function in schizophrenia. I. A positron emission tomography study. *Arch Gen Psychiatry.* 1987;44:119-125.
105. Wiesel FA, Wik G, Sjogren I, Blomqvist G, Greitz T. Altered relationships between metabolic rates of glucose in brain regions of schizophrenic patients. *Acta Psychiatr Scand.* 1987;76:642-647.
106. Szechtman H, Nahmias C, Garnett ES, et al. Effect of neuroleptics on altered cerebral glucose metabolism in schizophrenia. *Arch Gen Psychiatry.* 1988;45:523-532.
107. Berman KF, Illowsky BP, Weinberger DR. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. IV. Further evidence for regional and behavioral specificity [see comments]. *Arch Gen Psychiatry.* 1988;45:616-622.
108. Dousse M, Mamo H, Ponsin JC, Tran Dinh Y. Cerebral blood flow in schizophrenia. *Exp Neurol.* 1988;100:98-111.
109. Bajc M, Medved V, Basic M, Topuzovic N, Babic D. Cerebral perfusion inhomogeneities in schizophrenia demonstrated with single photon emission computed tomography and Tc99m-hexamethylpropyleneamineoxim. *Acta Psychiatr Scand.* 1989;80:427-433.
110. Cohen RM, Semple WE, Gross M, et al. Evidence for common alterations in cerebral glucose metabolism in major affective disorders and schizophrenia. *Neuropsychopharmacology.* 1989;2:241-254.
111. Cleghorn JM, Garnett ES, Nahmias C, et al. Increased frontal and reduced parietal glucose metabolism in acute untreated schizophrenia. *Psychiatry Res.* 1989;28:119-133.

112. Catafau AM, Parellada E, Lomena FJ, et al. Prefrontal and temporal blood flow in schizophrenia: resting and activation technetium-99m-HMPAO SPECT patterns in young neuroleptic-naive patients with acute disease. *J Nucl Med.* 1994;35:935-941.
113. Gur RE, Mozley PD, Resnick SM, et al. Resting cerebral glucose metabolism in first-episode and previously treated patients with schizophrenia relates to clinical features. *Arch Gen Psychiatry.* 1995;52:657-667.
114. Wiesel FA, Wik G, Sjogren I, Blomqvist G, Greitz T, Stone-Elander S. Regional brain glucose metabolism in drug-free schizophrenic patients and clinical correlates. *Acta Psychiatr Scand.* 1987;76:628-641.
115. DeLisi LE, Buchsbaum MS, Holcomb HH, et al. Increased temporal lobe glucose use in chronic schizophrenic patients. *Biol Psychiatry.* 1989;25:835-851.
116. Weinberger DR, Berman KF, Illowsky BP. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism [see comments]. *Arch Gen Psychiatry.* 1988;45:609-615.
117. Rubin P, Holm S, Friberg L, et al. Altered modulation of prefrontal and subcortical brain activity in newly diagnosed schizophrenia and schizophreniform disorder. A regional cerebral blood flow study. *Arch Gen Psychiatry.* 1991;48:987-995.
118. Berman KF, Torrey EF, Daniel DG, Weinberger DR. Regional cerebral blood flow in monozygotic twins discordant and concordant for schizophrenia. *Arch Gen Psychiatry.* 1992;49:927-934.
119. Andreasen NC, Rezai K, Alliger R, et al. Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. *Arch Gen Psychiatry.* 1992;49:943-958.
120. Volz HP, Gaser C, Häger F, et al. Brain activation during cognitive stimulation with the Wisconsin Card Sorting Test—a functional MRI study on healthy volunteers and schizophrenics. *Psychiatry Res: Neuroimaging.* 1997;75:145-157.
121. Parellada E, Catafau AM, Bernardo M, Lomena F, Catarineu S, Gonzalez-Monclus E. The resting and activation issue of hypofrontality: a single photon emission computed tomography study in neuroleptic-naive and neuroleptic-free schizophrenic female patients [In Process Citation]. *Biol Psychiatry.* 1998;44:787-790.
122. Stevens AA, Goldman-Rakic PS, Gore JC, Fulbright RK, Wexler BE. Cortical dysfunction in schizophrenia during auditory word and tone working memory demonstrated by functional resonance imaging. *Arch Gen Psychiatry.* 1998;55:1097-1103.
123. Frith CD, Friston KJ, Herold S, et al. Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *Br J Psychiatry.* 1995;167:343-349.
124. Fletcher PC, McKenna PJ, Frith CD, Grasby PM, Friston KJ, Dolan RJ. Brain activations in schizophrenia during a graded memory task studied with functional neuroimaging. *Arch Gen Psychiatry.* 1998;55:1001-1008.
125. Manoach DS, Press DZ, Thangaraj V, et al. Schizophrenia subjects activate dorsolateral prefrontal cortex during a working memory task as measured by fMRI. *Biol Psychiatry.* 1999;45:1128-1137.
126. Volkow ND, Wolf AP, Brodie JD, et al. Brain interactions in chronic schizophrenics under resting and activation conditions. *Schizophr Res.* 1988;1:47-53.
127. Wolkin A, Sanfilipo M, Wolf AP, Angrist B, Brodie JD, Rotrosen J. Negative symptoms and hypofrontality in chronic schizophrenia. *Arch Gen Psychiatry.* 1992;49:959-965.
128. Suzuki M, Kurachi M, Kawasaki Y, Kiba K, Yamaguchi N. Left hypofrontality correlates with blunted affect in schizophrenia. *Jpn J Psychiatry Neurol.* 1992;46:653-657.
129. Ebmeier KP, Blackwood DH, Murray C, et al. Single-photon emission computed tomography with ^{99m}Tc-exametazime in unmedicated schizophrenic patients. *Biol Psychiatry.* 1993;33:487-495.
130. Kaplan RD, Szechtman H, Franco S, et al. Three clinical syndromes of schizophrenia in untreated subjects: relation to brain glucose activity measured by positron emission tomography (PET). *Schizophr Res.* 1993;11:47-54.
131. Friston KJ, Liddle PF, Frith CD, Hirsch SR, Frackowiak RS. The left medial temporal region and schizophrenia. A PET study. *Brain.* 1992;115:367-382.
132. Scheibel AB. The thalamus and neuropsychiatric illness. *J Neuropsychiatry Clin Neurosci.* 1997;9:342-353.
133. Pakkenberg B. Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics. *Arch Gen Psychiatry.* 1990;47:1023-1028.
134. Danos P, Baumann B, Bernstein HG, et al. Schizophrenia and anteroventral thalamic nucleus: selective decrease of parvalbumin-immunoreactive thalamocortical projection neurons. *Psychiatry Res.* 1998;82:1-10.
135. Andreasen NC, Arndt S, Swayze VN, et al. Thalamic abnormalities in schizophrenia visualized through magnetic resonance image averaging. *Science.* 1994;266:294-298.
136. Buchsbaum MS, Someya T, Teng CY, et al. PET and MRI of the thalamus in never-medicated patients with schizophrenia. *Am J Psychiatry.* 1996;153:191-199.
137. Portas CM, Goldstein JM, Shenton ME, et al. Volumetric evaluation of the thalamus in schizophrenic male patients using magnetic resonance imaging. *Biol Psychiatry.* 1998;43:649-659.
138. Hazlett EA, Buchsbaum MS, Byne W, et al. Three-dimensional analysis with MRI and PET of the size, shape, and function of the thalamus in the schizophrenia spectrum. *Am J Psychiatry.* 1999;156:1190-1199.
139. Andreasen NC, O'Leary DS, Cizadlo T, et al. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proc Natl Acad Sci U S A.* 1996;93:9985-9990.
140. Mettler FA. Perceptual capacity, functions of the corpus striatum and schizophrenia. *Psychiatr Q.* 1955;29:89-111.
141. Klawans HL, Goetz C, Westheimer R. Pathophysiology of schizophrenia and the striatum. *Dis Nerv Syst.* 1972;33:711-719.
142. Schneider JS. Basal ganglia role in behavior: importance of sensory gating and its relevance to psychiatry. *Biol Psychiatry.* 1984;19:1693-1700.
143. Lidsky TI. Neuropsychiatric implications of basal ganglia dysfunction. *Biol Psychiatry.* 1997;41:383-385.
144. Sedvall G, Farde L. Chemical brain anatomy in schizophrenia. *Lancet.* 1995;346:743-749.
145. Gurevich EV, Bordelon Y, Shapiro RM, Arnold SE, Gur RE, Joyce JN. Mesolimbic dopamine D3 receptors and use of antipsychotics in patients with schizophrenia. A postmortem study. *Arch Gen Psychiatry.* 1997;54:225-232.
146. Laruelle M, Abi-Dargham A, van Dyck CH, et al. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci U S A.* 1996;93:9235-9240.
147. Breier A, Su TP, Saunders R, Carson RE, et al. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc Natl Acad Sci U S A.* 1997;94:2569-2574.
148. Abi-Dargham A, Gil R, Krystal J, et al. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry.* 1998;155:761-767.
149. Bertolino A, Knable MB, Saunders RC, et al. The relationship between dorsolateral prefrontal N-acetylaspartate measures and striatal dopamine activity in schizophrenia. *Biol Psychiatry.* 1999;45:660-667.
150. Heckers S, Heinsen H, Heinsen Y, Beckmann H. Cortex, white matter, and basal ganglia in schizophrenia: a volumetric postmortem study. *Biol Psychiatry.* 1991;29:556-566.
151. Jernigan TL, Zisook S, Heaton RK, Moranville JT, Hesselink JR, Braff DL. Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. *Arch Gen Psychiatry.* 1991;48:881-890.
152. Breier A, Buchanan RW, Elkashef A, Munson RC, Kirkpatrick B, Gellad F. Brain morphology and schizophrenia. A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures [see comments]. *Arch Gen Psychiatry.* 1992;49:921-926.
153. Swayze VWD, Andreasen NC, Alliger RJ, Yuh WT, Ehrhardt JC. Subcortical and temporal structures in affective disorder and schizophrenia: a magnetic resonance imaging study. *Biol Psychiatry.* 1992;31:221-240.
154. Elkashef AM, Buchanan RW, Gellad F, Munson RC, Breier A. Basal ganglia pathology in schizophrenia and tardive dyskinesia: an MRI quantitative study. *Am J Psychiatry.* 1994;151:752-755.
155. Keshavan MS, Rosenberg D, Sweeney JA, Pettegrew JW. Decreased caudate volume in neuroleptic-naive psychotic patients. *Am J Psychiatry.* 1998;155:774-778.

156. Chakos MH, Lieberman JA, Bilder RM, et al. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. *Am J Psychiatry.* 1994;151:1430-1436.
157. Keshavan MS, Bagwell WW, Haas GL, Sweeney JA, Schooler NR, Pettegrew JW. Changes in caudate volume with neuroleptic treatment [letter]. *Lancet.* 1994;344:1434.
158. Corson PW, Nopoulos P, Miller DD, Arndt S, Andreasen NC. Change in basal ganglia volume over 2 years in patients with schizophrenia: typical versus atypical neuroleptics. *Am J Psychiatry.* 1999;156:1200-1204.
159. Lauer M, Beckmann H. The human striatum in schizophrenia. I. Increase in overall relative striatal volume in schizophrenics. *Psychiatry Res.* 1997;68:87-98.
160. Beckmann H, Lauer M. The human striatum in schizophrenia. II. Increased number of striatal neurons in schizophrenics. *Psychiatry Res.* 1997;68:99-109.
161. Kung L, Conley R, Chute DJ, Smialek J, Roberts RC. Synaptic changes in the striatum of schizophrenic cases: a controlled postmortem ultrastructural study. *Synapse.* 1998;28:125-139.
162. Van Hoesen GW. The parahippocampal gyrus: new observations regarding its cortical connections in the monkey. *Trends Neurosci.* 1982;5:345-350.
163. Papez JW. A proposed mechanism of emotion. *Arch Neurol Psychiatry.* 1937;38:725-743.
164. Mesulam MM. *Principles of Behavioral Neurology.* Philadelphia, Penn: FA Davis; 1985.
165. Dwork AJ. Postmortem studies of the hippocampal formation in schizophrenia. *Schizophr Bull.* 1997;23:403-421.
166. Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging. *Arch Gen Psychiatry.* 1998;55:433-440.
167. Razi K, Greene KP, Sakuma M, Ge S, Kushner M, DeLisi LE. Reduction of the parahippocampal gyrus and the hippocampus in patients with chronic schizophrenia. *Br J Psychiatry.* 1999;174:512-519.
168. McCarley RW, Wible CG, Frumin M, et al. MRI anatomy of schizophrenia. *Biol Psychiatry.* 1999;45:1099-1119.
169. Marsh L, Suddath RL, Higgins N, Weinberger DR. Medial temporal lobe structures in schizophrenia: relationship of size to duration of illness. *Schizophr Res.* 1994;11:225-238.
170. Velakoulis D, Pantelis C, McGorry PD, et al. Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. *Arch Gen Psychiatry.* 1999;56:133-141.
171. Fukuzako H, Yamada K, Kodama S, et al. Hippocampal volume asymmetry and age at illness onset in males with schizophrenia. *Eur Arch Psychiatry Clin Neurosci.* 1997;247:248-251.
172. Csernansky JG, Joshi S, Wang L, et al. Hippocampal morphometry in schizophrenia by high dimensional brain mapping. *Proc Natl Acad Sci U S A.* 1998;95:11406-11411.
173. Callicott JH, Egan MF, Bertolino A, et al. Hippocampal *N*-acetyl aspartate in unaffected siblings of patients with schizophrenia: a possible intermediate neurobiological phenotype. *Biol Psychiatry.* 1998;44:941-950.
174. Seidman LJ, Faraone SV, Goldstein JG, et al. Reduced subcortical brain volumes in nonpsychotic siblings of schizophrenic patients: a pilot MRI study. Am J Med Genet, *Neuropsychiatr Genet.* 1997;74:507-514.
175. Lawrie SM, Whalley H, Kestelman JN, et al. Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. *Lancet*. 1999;353:30-33.
176. Benes FM, Sorensen I, Bird ED. Reduced neuronal size in posterior hippocampus of schizophrenic patients. *Schizophr Bull.* 1991;17:597-608.
177. Heckers S, Heinsen H, Geiger B, Beckmann H. Hippocampal neuron number in schizophrenia. A stereological study. *Arch Gen Psychiatry.* 1991;48:1002-1008.
178. Arnold SE, Franz BR, Gur RC, et al. Smaller neuron size in schizophrenia in hippocampal subfields that mediate cortical-hippocampal interactions. *Am J Psychiatry.* 1995;152:738-748.
179. Zaidel DW, Esiri MM, Harrison PJ. The hippocampus in schizophrenia: lateralized increase in neuronal density and altered cytoarchitectural asymmetry. *Psychol Med.* 1997;27:703-713.
180. Benes FM, Kwok EW, Vincent SL, Todtenkopf MS. A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. *Biol Psychiatry.* 1998;44:88-97.
181. Jakob H, Beckmann H. Prenatal developmental disturbances in the limbic allocortex in schizophrenics. *J Neural Transm.* 1986;65:303-326.
182. Arnold SE, Hyman BT, Van Hoesen GW, Damasio AR. Some cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia. *Arch Gen Psychiatry.* 1991;48:625-632.
183. Scheibel AB, Kovelman JA. Disorientation of the hippocampal pyramidal cell and its processes in the schizophrenic patient. *Biol Psychiatry.* 1981;16:101-102.
184. Kovelman JA, Scheibel AB. A neurohistological correlate of schizophrenia. *Biol Psychiatry.* 1984;19:1601-1621.
185. Conrad AJ, Abebe T, Austin R, Forsythe S, Scheibel AB. Hippocampal pyramidal cell disarray in schizophrenia as a bilateral phenomenon. *Arch Gen Psychiatry.* 1991;48:413-417.
186. Arnold SE, Lee VMY, Gur RE, Trojanowski JQ. Abnormal expression of two microtubule-associated proteins (MAP2 and MAP5) in specific subfields of the hippocampal formation in schizophrenia. *Proc Natl Acad Sci U S A.* 1991;88:10850-10854.
187. Goldsmith SK, Joyce JN. Alterations in hippocampal mossy fiber pathway in schizophrenia and Alzheimer's disease. *Biol Psychiatry.* 1995;37:122-126.
188. Colter N, Battal S, Crow TJ, Johnstone EC, Brown R, Bruton C. White matter reduction in the parahippocampal gyrus of patients with schizophrenia. *Arch Gen Psychiatry.* 1987;44:1023.
189. Longson D, Deakin JFW, Benes FM. Increased density of entorhinal glutamate-immunoreactive vertical fibers in schizophrenia. *J Neural Transm.* 1996;103:503-507.
190. Maier M, Ron MA. Hippocampal age-related changes in schizophrenia: a proton magnetic resonance spectroscopy study. *Schizophr Res.* 1996;22:5-17.
191. Eastwood SL, Harrison PJ. Decreased synaptophysin in the medial temporal lobe in schizophrenia demonstrated using immunoautoradiography. *Neuroscience.* 1995;69:339-343.
192. Eastwood SL, Burnet PWJ, Harrison PJ. Altered synaptophysin expression as a marker of synaptic pathology in schizophrenia. *Neuroscience*. 1995;66:309-319.
193. Browning MD, Dudek EM, Rapier JL, Leonard S, Freedman R. Significant reductions in synapsin but not synaptophysin specific activity in the brains of some schizophrenics. *Biol Psychiatry.* 1993;34:529-535.
194. Barbeau D, Liang JJ, Robitalille Y, Quirion R, Srivastava LK. Decreased expression of the embryonic form of the neural cell adhesion molecule in schizophrenic brains. *Proc Natl Acad Sci U S A.* 1995;92:2785-2789.
195. Harrison PJ, Eastwood SL. Preferential involvement of excitatory neurons in medial temporal lobe in schizophrenia. *Lancet*. 1998;352:1669-1673.
196. Fukuzako H, Takeuchi K, Hokazono Y, et al. Proton magnetic resonance spectroscopy of the left medial temporal and frontal lobes in chronic schizophrenia: preliminary report. *Psychiatry Res.* 1995;61:193-200.
197. Fukuzako H, Fukuzako T, Takeuchi K, et al. Phosphorus magnetic resonance spectroscopy in schizophrenia: correlation between membrane phospholipid metabolism in the temporal lobe and positive symptoms. *Prog Neuropsychopharmacol Biol Psychiatry.* 1996;20:629-640.
198. Kegeles LS, Humaran TJ, Mann JJ. In vivo neurochemistry of the brain in schizophrenia as revealed by magnetic resonance spectroscopy. *Biol Psychiatry.* 1998;44:382-398.
199. Deicken RF, Zhou L, Schuff N, Fein G, Weiner MW. Hippocampal neuronal dysfunction in schizophrenia as measured by proton magnetic resonance spectroscopy. *Biol Psychiatry.* 1998;43:483-488.
200. Fukuzako H, Fukuzako T, Hashiguchi T, Kodama S, Takigawa M, Fujimoto T. Changes in levels of phosphorus metabolites in temporal lobes of drug-naive schizophrenic patients. *Am J Psychiatry.* 1999;156:1205-1208.
201. Kerwin RW, Patel S, Meldrum BS, Czudek C, Reynolds GP. Asymmetrical loss of glutamate receptor subtype in left hippocampus in schizophrenia. *Lancet*. 1988;1:583-584.
202. Kerwin R, Patel S, Meldrum B. Quantitative autoradiographic analysis of glutamate binding sites in the hippocampal formation in normal and schizophrenic brain postmortem. *Neuroscience*. 1990;39:25-32.
203. Harrison PJ, McLaughlin D, Kerwin RW. Decreased hippocampal expression of a glutamate receptor gene in schizophrenia. *Lancet*. 1991;337:450-452.
204. Eastwod SL, McDonald B, Burnet PWJ, Beckwith JP, Kerwin RW, Harrison PJ. Decreased expression of mRNAs encoding non-NMDA glutamate receptors GluR1 and GluR2 in medial temporal lobe neurons in schizophrenia. *Mol Brain Res.* 1995;29:211-223.

205. Eastwood SL, Burnet PW, Harrison PJ. GluR2 glutamate receptor subunit flip and flop isoforms are decreased in the hippocampal formation in schizophrenia: a reverse transcriptase-polymerase chain reaction (RT-PCR) study. *Brain Res Mol Brain Res.* 1997;44:92-98.
206. Reynolds GP, Czudek C, Andrews HB. Deficit and hemispheric asymmetry of GABA uptake sites in the hippocampus in schizophrenia. *Biol Psychiatry.* 1990;27:1038-1044.
207. Benes FM, Wickramasinghe R, Vincent SL, Khan Y, Todtenkopf M. Uncoupling of GABA(A) and benzodiazepine receptor binding activity in the hippocampal formation of schizophrenic brain. *Brain Res.* 1997;755:121-129.
208. Benes FM, Khan Y, Vincent SL, Wickramasinghe R. Differences in the subregional and cellular distribution of $GABA_A$ receptor binding in the hippocampal formation of schizophrenic brain. Synapse. 1996;22:338-349.
209. Dean B, Opeskin K, Pavey G, et al. [^{3}H]Paroxetine binding is altered in the hippocampus but not the frontal cortex or caudate nucleus from subjects with schizophrenia. *J Neurochem.* 1995;64:1197-1202.
210. Joyce JN, Shane A, Lexow N, Winokur A, Casanova MF, Kleinman JE. Serotonin uptake sites and serotonin receptors are altered in the limbic system of schizophrenics [see comments]. *Neuropsychopharmacology*. 1993;8:315-336.
211. Kawasaki Y, Maeda Y, Suzuki M, et al. SPECT analysis of regional cerebral blood flow changes in patients with schizophrenia during the Wisconsin Card Sorting Test. *Schizophr Res.* 1993;10:109-116.
212. Kawasaki Y, Maeda Y, Sakai N, et al. Regional cerebral blood flow in patients with schizophrenia: relevance to symptom structures. *Psychiatry Res.* 1996;67:49-58.
213. Silbersweig DA, Stern E, Frith C, et al. A functional neuroanatomy of hallucinations in schizophrenia. *Nature*. 1995;378:176-179.
214. Heckers S, Rauch SL, Goff D, et al. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nature Neurosci.* 1998;1:318-323.
215. Weinberger DR, Berman KF, Suddath R, Torrey EF. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monzygotic twins. *Am J Psychiatry.* 1992;149:890-897.
216. Schroder J, Buchsbaum MS, Siegel BV, et al. Cerebral metabolic activity correlates of subsyndromes in chronic schizophrenia. *Schizophr Res.* 1996;19:41-53.
217. Bilder RM, Bogerts B, Ashtari M, et al. Anterior hippocampal volume reductions predict frontal lobe dysfunction in first episode schizophrenia. *Schizophr Res.* 1995;17:47-58.
218. Schmajuk NA. Animal models for schizophrenia: the hippocampally lesioned animal. *Schizophr Bull.* 1987;13:317-327.
219. Bardgett ME, Jackson JL, Taylor GT, Csernansky JG. Kainic acid decreases hippocampal neuronal number and increases dopamine receptor binding in the nucleus accumbens: an animal model of schizophrenia. *Behav Brain Res.* 1995;70:153-164.
220. Mittleman G, LeDuc PA, Whishaw IQ. The role of D_1 and D_2 receptors in the heightened locomotion induced by direct and indirect dopamine agonists in rats with hippocampal damage: an animal analogue of schizophrenia. *Behav Brain Res.* 1993;55:253-267.
221. Port RL, Sample JA, Seybold KS. Partial hippocampal pyramidal cell loss alters behavior in rats: implications for an animal model of schizophrenia. *Brain Res Bull.* 1991;26:993-996.
222. Lipska BK, Jaskiw GE, Weinberger DR. Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia. *Neuropsychopharmacology*. 1993;9:67-75.
223. Lipska BK, Swerdlow NR, Geyer MA, Jaskiw GE, Braff DL, Weinberger DR. Neonatal excitotoxic hippocampal damage in rats causes post-pubertal changes in prepulse inhibition of startle and its disruption by apomorphine. *Psychopharmacology (Berl).* 1995;122:35-43.
224. Chambers RA, Moore J, McEvoy JP, Levin ED. Cognitive effects of neonatal hippocampal lesions in a rat model of schizophrenia. *Neuropsychopharmacology*. 1996;15:587-594.
225. Flores G, Barbeau D, Quirion R, Srivastava LK. Decreased binding of dopamine D_3 receptors in limbic subregions after neonatal bilateral lesion of rat hippocampus. *J Neurosci.* 1996;16:2020-2026.
226. Beauregard M, Malkova L, Bachevalier J. Stereotypies and loss of social affiliation after early hippocampectomy in primates. *Neuroreport*. 1995;6:2521-2526.
227. Beauregard M, Bachevalier J. Neonatal insult to the hippocampal region and schizophrenia: a review and a putative animal model. *Can J Psychiatry.* 1996;41:446-456.
228. Saunders RC, Kolachana BS, Bachevalier J, Weinberger DR. Neonatal lesions of the medial temporal lobe disrupt prefrontal cortical regulation of striatal dopamine. *Nature*. 1998;393:169-171.
229. Bachevalier J, Alvarado MC, Malkova L. Memory and socioemotional behavior in monkeys after hippocampal damage incurred in infancy or in adulthood. *Biol Psychiatry.* 1999;46:329-339.