Clinical phenomena

Schizophrenia is a chronic and often progressively deteriorating disorder of thought, affect, behavior and perception. The signs and symptoms of schizophrenia are characterized by the production of abnormal behavior (positive symptoms) and those that represent a deficiency of normal behavior (negative symptoms). Positive symptoms include hallucinations, delusions, formal thought disorder and bizarre behavior. Negative symptoms include alogia, affective blunting, avolition, anhedonia, and attentional impairment.

Neural circuitry in schizophrenia

Figure 1. Basic circuitry of information processing in the human brain. Straight arrows indicate glutamatergic pathways. The broken arrows indicate the widespread, neurotransmitter-specific projections arising from the basal forebrain (ACh) and brainstem (DA, NE, 5-HT). The basal ganglia-thalamus projection is GABAergic. M1 indicates primary motor cortex, S1 indicates primary sensory cortex, A1 indicates primary auditory cortex, V1 indicates primary visual cortex, BG indicates basal ganglia, MTL indicates medial temporal lobe, DA indicates dopamine, NE indicates norepinephrine, 5-HT indicates serotonin, and ACh indicates acetylcholine.

Cortex

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cortex receives sensory information from the appropriate sensory modules. 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 association cortex of the human brain is a six-layered isocortex. Cortical layers 2 and 4 are defined by a high density of small interneurons. 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 and exert an inhibitory influence on their targets (via GABAA receptors) whereas pyramidal cells are glutamatergic and have an excitatory influence. Normal cortical function depends on an intricate balance of GABAergic inhibition and glutamatergic excitation.

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 D1, D4, D5, and 5-HT2A receptors, leads to the “fine tuning” of information processing, for example by increasing the signal to noise ratio during cortico-cortical and thalamo-cortical neurotransmission.

Alterations of the GABAergic system and the D1 receptors of the DLPFC have been reported in schizophrenia. The expression of cortical D1 receptors is increased by the chronic treatment with typical neuroleptics. Of interest, a recent PET study found a reduction of cortical D1 receptors that correlated with the severity of negative symptoms and poor function in a frontal executive task. Also the serotonin 5-HT2A receptor is of relevance for the pathophysiology of psychosis. Hallucinogens, e.g. LSD,
act as agonists at the 5-HT2A receptor and several antipsychotic compounds, especially the atypical neuroleptics, block the activity of the 5-HT2A receptor. Several postmortem studies have reported a decrease of 5-HT2A receptors in schizophrenia, but others have not.

The anatomical and functional organization of the association cortex, especially the dorsolateral prefrontal cortex, has been studied extensively in schizophrenia. Volume reduction of association cortex in schizophrenia has been reported in several postmortem and neuroimaging studies. 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.

**Hippocampus**

There is evidence for the contribution of hippocampal dysfunction to the pathogenesis of schizophrenia. The serial circuitry of glutamatergic pyramidal and nonpyramidal neurons provides the structural basis for long-term potentiation, a physiological phenomenon crucial for formation of memory. The hippocampus is also closely connected with the limbic system. The hippocampal formation is recruited via these connections to regulate emotion or to modulate information processing by attaching limbic valence to sensory stimuli. Most studies have found no change in the number of hippocampal pyramidal neurons but nonpyramidal cells in the hippocampus (especially in CA2 subregion) seem to be reduced by nearly half. Synaptic organization is changed, possibly indicating altered plasticity of the hippocampus in schizophrenia. The metabolism and blood flow of the hippocampus are increased at baseline in schizophrenia. Furthermore, hippocampal and parahippocampal rCBF is increased during the experience of psychotic symptoms and correlates with positive symptoms (delusions, hallucinations).

**Thalamus**

The thalamus is the gateway to cortical processing for all incoming sensory information, here represented by the three major systems: somatosensory, auditory, and visual.
Primary sensory cortex (S1, A1, V1) receives sensory information from the appropriate sensory modules (sensory organ + 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 thalamo-cortical projections, thereby creating a cortico-striato-pallido-thalamo-cortical loop.

Two abnormalities of thalamic function have been proposed in schizophrenia. First, breakdown of the sensory filter leads 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 leads to impairments of cortical association areas, especially the DLPFC.

Figure 4. Figure 4- Three functional subdivisions of the human thalamus. Somatosensory information is relayed via the ventral posterior lateral nucleus (VPL), auditory information via the medial geniculate nucleus (MGN), and visual information via the lateral geniculate nucleus (LGN) to the appropriate primary cortices. Association areas of the cerebral cortex establish reciprocal connections with the mediodorsal nucleus (MD), and motor information travels from the striatum via the ventral anterior and ventral lateral (VL) nucleus to the motor cortex (MI).
**Basal Ganglia**

The basal ganglia include the ventral striatum, the dorsal striatum (caudate and putamen), and the globus pallidus. Dorsal striatal structures are 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 behaviors are derailed during drug addiction and this involves the recruitment of the nucleus accumbens. The two major DA receptors in the dorsal striatum are the D1 and D2 receptors. The nucleus accumbens expresses primarily the D3 receptor. The content of dopamine after treatment with amphetamine is increased in schizophrenia suggesting mesolimbic hyperactivity in this disorder. The volume of basal ganglia structures is increased in medicated schizophrenic patients. Post-mortem studies have provided evidence for an overall increased number of striatal neurons and for a change in the synaptic organization of the striatum along with a decreased number of nucleus accumbens neurons in schizophrenics.

**Figure 5.** Figure 5- Connectivity and dopaminergic innervation of neostriatum and limbic striatum.

The dopaminergic neurons of the substantia nigra (SN) project to neurons of the neostriatum, which mainly express D1 and D2 receptors. The dopaminergic neurons of the ventral tegmental area project to neurons in the nucleus accumbens; neurons in this projection area express a high density of D3 receptors. The dopaminergic neurons of the ventral tegmental area also project to the cortex, where pyramidal neurons and nonpyramidal neurons express primarily three dopamine receptors, the D1, D5, and D4 receptor.
Neurochemical models of schizophrenia

The dopamine model
Stimulant psychosis produces hyperactivity of mesolimbic dopaminergic neurons and is characterized by paranoid delusions, ideas of reference, hallucinations and agitation. Most normal subjects will develop psychotic symptoms if administered high doses of amphetamine over several days. Many patients with schizophrenia will demonstrate psychotic exacerbation following administration of relatively low doses of stimulant. Furthermore, hypoactivity of mesocortical dopamine neurons has been correlated with severity of negative symptoms and impairment in performance on tests of prefrontal cortical function. It is hypothesized that hyperactivity of mesolimbic dopamine neurons and hypoactivity of mesocortical dopamine neurons are responsible for positive and negative symptoms, respectively.

The glutamate model
Prolonged exposure to NMDA receptor antagonists, such as phencyclidine in abusers, has been associated with chronic, severe psychotic illness indistinguishable from schizophrenia. Ketamine, which is an NMDA antagonist drug, produces transient, mild psychotic symptoms, negative symptoms, and cognitive deficits in normal subjects, mimicking schizophrenia. When administered to patients with schizophrenia, ketamine produces transient exacerbations of psychotic symptoms.

Interactions between dopamine and glutamate systems
Chronic NMDA antagonist administration results in decreases in dopamine release in prefrontal cortex and persistent elevation of dopamine release in the nucleus accumbens. A lesion in hippocampal or frontal cortical glutamatergic circuits is hypothesized to develop in schizophrenia. It is hypothesized to produce dopaminergic hypoactivity in frontal cortex and hyperactivity in nucleus accumbens that is responsible for the symptoms of schizophrenia.

Pharmacology of schizophrenia
Current pharmacological treatments for schizophrenia share in common dopamine D2 receptor antagonism. Relatively selective D2 antagonists, such as haloperidol, are moderately effective for psychotic symptoms in approximately 70% of patients. While these drugs may produce modest improvement in negative symptoms, primary negative symptoms are generally unresponsive to D2 blockade. Cognitive deficits also exhibit minimal or no response to conventional antipsychotics. The link between dopamine D2 receptor blockade and antipsychotic efficacy is strengthened by the highly significant correlation between D2 receptor affinity and clinical potency of the
conventional antipsychotic agents. Similarly, striatal D2 receptor occupancy of 65% or greater has been associated with clinical response in vivo using PET ligand binding studies and extrapyramidal side effects are typically observed with occupancy greater than 80%.

Initially, dopamine antagonists increase firing rates of dopamine neurons in substantia nigra (A9) and ventral tegmental area (A10), presumably acting via presynaptic D2 autoreceptors. Two-to-four weeks after initiation of treatment with dopamine antagonists a substantial proportion of dopamine neurons become electrically silent. This “depolarization blockade” of A9 neurons may mediate extrapyramidal symptoms and depolarization blockade of mesolimbic A10 neurons may play a role in antipsychotic efficacy. In addition to altering firing patterns of dopamine neurons, subchronic treatment with D2 receptor antagonists increases postsynaptic D2 receptor density, which is associated with behavioral “supersensitivity” to dopamine agonists. Clozapine differs from classical dopamine antagonists in possessing greater efficacy for psychotic and negative symptoms while producing little or no neurological side effects. Clozapine was found to exert superior antipsychotic efficacy at doses producing only 20%-40% D2 receptor occupancy. Clozapine also acts at dopamine D1, D3, and D4 receptors as well as serotonin 5-HT2, 5-HT6 and 5-HT7 receptors, alpha-adrenergic receptors, histaminic receptors and muscarinic receptors. Of interest, preliminary studies suggest that clozapine, unlike conventional agents, blocks ketamine-induced exacerbation of psychotic symptoms mediated by blockade of the glutamatergic NMDA receptor complex.

The relative importance of these receptors for the unique therapeutic advantages of clozapine remains unclear. The relative importance of 5-HT2A blockade versus D2 blockade has been shown by these agents to reduce extrapyramidal side effects and contribute to increased efficacy for negative symptoms. This combination of relatively higher 5-HT2A over D2 affinity has been the cornerstone for development of the family of atypical antipsychotic agents, which have followed clozapine. In preliminary studies, addition of idazoxan, an alpha 2 adrenergic antagonist to a conventional antipsychotic improved psychotic symptoms. Several studies have also demonstrated that addition of agonists (glycine, D-cycloserine and D-serine) at the glutamatergic NMDA receptor complex improve negative symptoms and cognitive deficits. Therapeutic agents that block D2 receptors typically produce antipsychotic effects after a delay of 2-4 weeks. This suggests that secondary effects, such as depolarization blockade of A10 ventral tegmental dopamine neurons or pharmacodynamic alterations in glutamatergic receptor subunit composition, may play a more proximal role in antipsychotic effects. Addition of 5-HT2A antagonists and NMDA receptor agonists to D2 blockade improve negative symptoms. The locations of 5-HT2A and NMDA receptors responsible for these therapeutic effects remain unclear and could involve direct modulation of ventral tegmental dopamine neuronal firing or alterations in the
sensitivity of inhibitory GABAergic interneurons, which determine cortical pyramidal cell excitability.