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DOPAMINERGIC HYPOTHESIS OF SCHIZOPHRENIA: A HISTORICAL PERSPECTIVE

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In search of evidence for the dopamine hypothesis of schizophrenia, this review focuses on studies of patients with schizophrenia. The review is composed of two parts: the first serves as a short reminder of the anatomy and function of the dopamine system, and the second guides the reader through the history of scientific discoveries and paradigms used to investigate the role of dopamine in the pathophysiology of schizophrenia.

1.1 DOPAMINE SYSTEM: NEUROANATOMY AND MODE OF ACTIVITY

Dopamine is a phylogenetically old neurotransmitter intrinsic to brain function and behavior. It is of central importance in movement, reward-associated behavior, and emotions. Abnormal patterns of dopamine neurotransmission have been suggested to underlie several neurological and psychiatric disorders, for example, Parkinson's and Huntington's diseases, schizophrenia, drug abuse, and attention-deficit/hyperactivity disorder (ADHD).

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1.1.1 Macroanatomy

Dopamine is synthesized in dopaminergic neurons from the amino acid tyrosine by the enzymes tyrosine hydroxylase (forming L-3,4-dihydroxylphenylalanine [L-DOPA]) and L-amino acid decarboxylase (AACD). Tyrosine hydroxylase is a rate-limiting enzyme in the synthesis of dopamine, and its mRNA expression is abundant in human mesencephalon.

Dopaminergic neurons showing the highest expression of tyrosine hydroxylase mRNA are aggregated in distinct clusters: the ventral midbrain (A8-9-10), diencephalon (A11-15), and telencephalon (A16-olfactory bulb, A17, and the retina). Dopaminergic neurons cluster into the three major nuclei in the brain that contain cell bodies: (1) the substantia nigra pars compacta (SN, A9), located in the ventral midbrain; (2) the ventral tegmental area (VTA) or A10, lying medial to SN; and (3) the arcuate nucleus of the hypothalamus, throughout the posterior and dorsomedial nuclei of hypothalamus (A11–15, in the diencephalon) [1, 2]. Smaller groups of dopaminergic neurons are located in the retina and the olfactory bulb, in the human cerebral cortex [3, 4], in the subcortical white matter, and in the striatum [5, 6].

The dopaminergic projections from these neurons are distributed throughout the anatomically segregated neuronal systems that control motor, limbic, and cognitive aspects of behavior (Fig. 1.1). The dopaminergic projections form three major long pathways:

1. The nigrostriatal pathway contains over 80% of all dopaminergic innervation, primarily targeting the striatal medium spiny projection neurons. Dopamine modulates cortical innervation to the striatum and is involved in the control of movement.

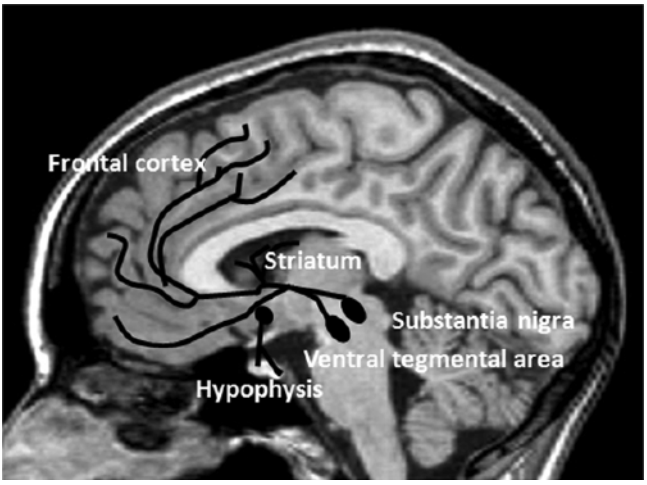

FIGURE 1.1 Dopamine projections in the human brain. A schema of the major dopamine projection systems is superimposed on an MR image of a human brain.

2. The mesolimbic pathway, with neurons from VTA synapsing in the nucleus accumbens and amygdala, is engaged in emotions, motivation, goal-directed behavior, pleasurable sensations, the euphoria of drug abuse, and the delusions and hallucinations of psychosis [7].
3. The mesocortical pathway originates in the VTA and terminates in the forebrain with its most abundant innervation in the prefrontal cortex, anterior cingulate, insula, entorhinal cortices. The majority of target neurons are excitatory pyramidal cells and minor target group are dendrites of local inhibitory neurons [8, 9] largely involved in cognitive functions.

There is a topographic organization of the SN/VTA innervation to the cortical regions (e.g., dorsal prefrontal and anterior cingulate cortices receive innervation from the dorsal group of cells of the SN and the retrobulbar area), while ventromedial limbic cortices receive input from the VTA [10]. In addition, several shorter pathways distinct from the major projections have been identified: the tubero-infundibular pathway, which projects from the hypothalamic nucleus to the anterior pituitary and contributes to the neurohumoral regulation of lactation; the mesohippocampal tract, which originates in the SN/VTA and terminates at the hippocampus and is involved in memory formation; and the mesofrontal tract, which traverses from the SN to the prefrontal cortex and is active in reward mechanisms. Ultrashort dopaminergic pathways connecting inner and outer layers of the retina (interplexiform amacrine-like neurons) and cells in the olfactory bulb (periglomerular dopamine cells) have also been reported [11], although their function is less well understood.

1.1.2 Microanatomy

Neurotransmission, including the synthesis–storage–release–receptor binding of the monoamine neurotransmitter as well as its uptake or degradation, is a highly controlled process. The complex balance of this cascade determines the intensity of dopaminergic signaling.

In 1979, Kebabian and Calne [12] found that dopamine exerts its effects by binding to two classes of receptors, dubbed as the dopamine D_1 and D_2 receptors (D1R and D2R). These receptors could be differentiated pharmacologically, biologically, physiologically, and by their anatomical distribution. All dopamine receptors are G-protein-coupled receptors (GPCRs). Heteromeric guanine nucleotide-binding proteins (G-proteins) are made up of alpha (α), beta (β), and gamma (γ) subunits, binding to which will influence effector recognition and can activate different signaling cascades. Therefore, based on the receptor coupling to GPCRs, activated subunits of G-proteins and further effects on second messengers, dopamine receptors are presently subdivided into the Gs-, Gq-, or Golf-coupled D_1 receptor family and Gi/o D_2 receptor family [13]. By their different G-protein coupling, D_1-family and D_2-family receptors have opposing effects on adenylyl cyclase activity (i.e., stimulatory

vs. inhibitory effect, respectively), on cyclic adenosine monophosphate (cAMP) concentration, as well as on phosphorylation processes [14]. Gene cloning revealed that DR2 family is further subdivided into dopamine D_2, D_3, and D_4 receptors (D2R, D3R, D4R) and their splice forms. A short splice version of D_2 (D_2Sh) and a long splice version of D_2 (D_2Lh) coexist in the brain as the most characterized dopamine receptor splice variants. The D_2Sh are predominantly presynaptic receptors (autoreceptors) and participate in the feedback mechanisms, or, when situated on the terminals, affect synthesis, storage, and release of dopamine into the synaptic cleft. The D_2Lh are viewed as the classical postsynaptic receptors. The D1R family includes dopamine D_1 and D_5 receptors (D1R, D5R).

1.1.2.1 Dopamine D_2/D_3/D_4 Receptors in the Human Brain (D_2-like receptors) The precise anatomical location of the dopamine receptors in the human brain has been most fully established for the dopamine D_2 receptors. In the adult human brain, D2R mRNA is markedly expressed in the striatum, neocortex, hippocampus, and amygdaloid complex, and differential expression is found in the thalamus as well as in most of the hypothalamic nuclei [15, 16]. D2R expression also follows a regional density pattern; there is a density gradient of D2R in decreasing order from the striatal structures, to the thalamus, to the midbrain, and finally, to the neocortex [17–19]. The dopamine D2R distribution in the neocortex is low, uneven, and varies between higher values in the temporal lobes (including hippocampus and amygdala) to minute receptor densities in the occipital lobes [20, 21]. Very heterogeneous D2R density is also found in the thalamus and in the striatum [22]. (Fig. 1.2a shows D2/D3R distribution as measured by molecular imaging in humans *in vivo*)

The D3R has a different anatomical distribution, being absent in the dorsal striatum, but abundant in the ventral striatum, thalamus, and hypothalamic nuclei (mainly mammillary bodies) and at low levels in the striatum and throughout the cortex. This is consistent with the mRNA expression pattern [19, 23]. However, so far there are no selective agonists available for D3Rs, and they are indistinguishable from D2Rs in *in vivo* measurements.

The D4R has eight polymorphic variants in humans [24]. The receptor is found at a high density in the limbic cortex and in the hippocampus and is absent from the motor regions of the brain. mRNA for D4R has low expression in human cortex and striatum [25]. D4Rs are preferentially co-expressed with enkephalin in GABAergic neurons, thus predominantly modulating inhibitory control in the cortex and projection pathways [26]. No compounds are yet available for *in vivo* visualization of D4R, nor are there any pharmacological tools to distinguish between the physiological or functional contributions of D_4 and D_2/D_3 receptors.

1.1.2.2 Dopamine D_1/D_5 Receptors in the Human Brain (D_1-like receptors) The cells expressing D1R mRNA are localized in the striatum, cerebral cortex, and bed nucleus of stria terminalis [16]. Dopamine D1R mRNA expression in

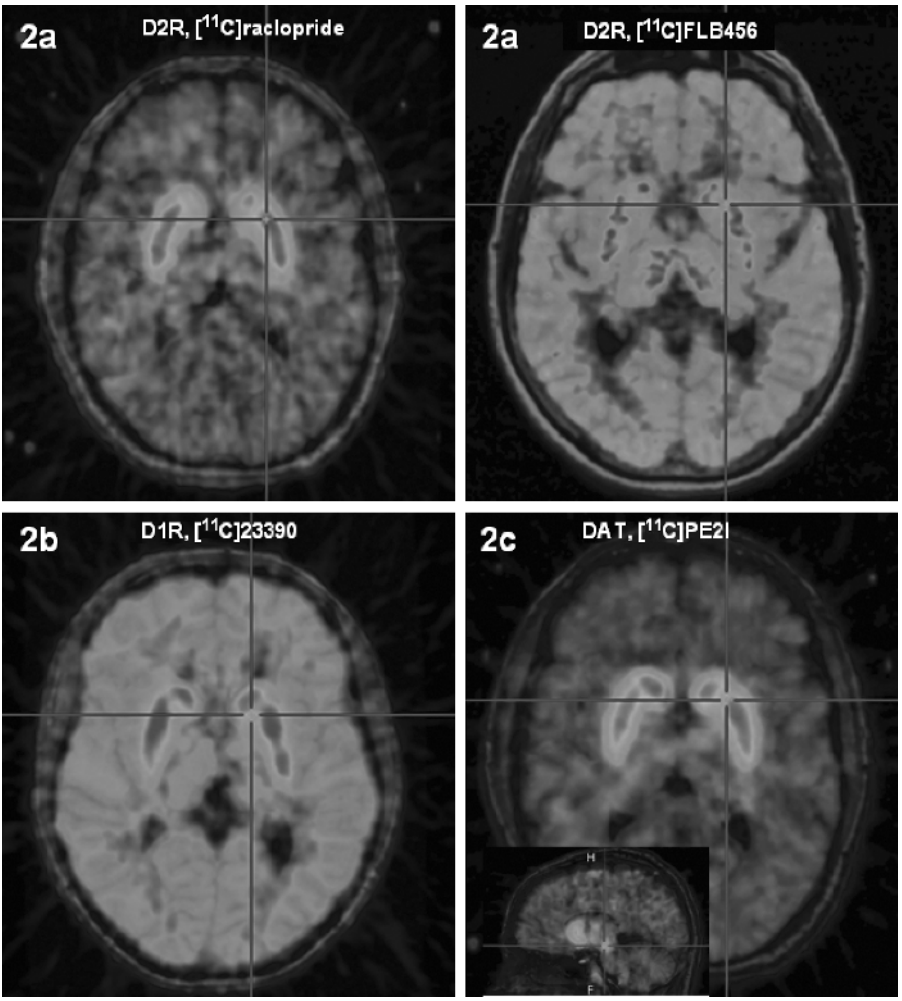

FIGURE 1.2 Dopamine receptor (D_1, D_2, D_3) and dopamine transporter distribution throughout the brain as measured by *in vivo* molecular imaging in humans by PET. (a) Regional radioactivity of [^{11}C]raclopride, representing binding to the striatal D2/D3DRs, and [^{11}C]FLB 456, representing binding to the extrastriatal D2/D3DRs. (b) Regional radioactivity of [^{11}C]SCH23390, representing binding to the D1/D5DRs. (c) Regional radioactivity of [^{11}C]PE2I, representing binding to the DAT. Summation PET images at transaxial and saggital planes. Substantia nigra indicated in saggital plane. (See color insert.)

the human cerebral cortex is the most abundant of all dopamine receptors. It is distributed in a laminar pattern and differs quantitatively between the cortical regions and subregions, with the highest expression in the medial orbital, insular, and parietal cortices [27]. Extremely low levels of D1R mRNA are found in the hippocampus, diencephalon, brainstem, and cerebellum, suggesting that neurons in those areas can mediate dopamine transmission via D1R, although mainly it would be mediated via D2/D3Rs. In the normal adult human brain, D1Rs show a widespread neocortical distribution, with D1R predominantly localized on spines and shafts of projection neurons [28]. D1Rs are found in high density in the basal ganglia, including regions of the caudate, putamen, globus pallidus, and SN [18, 29]. (D1R binding distribution *in vivo* is depicted in Fig. 1.2b). D1Rs in the globus pallidus and the SN are most likely localized on terminals, as there are no D1R mRNA expresssing cells in those regions. Within the basal ganglia, D1Rs are most abundant on GABAergic neurons expressing dynorphin/substance P [30].

D5R mRNA has predominant cortical expression and scattered low expression of mRNA is found in the subcortical structures, striatum, thalamus, and claustrum [31]. No radioligand selective for D5R is available. Immunochemistry studies suggest that D5Rs are concentrated in the hippocampus and entorrhinal cortex, but are also found in the thalamus and in the striatum [32].

The major functions of dopamine receptors are the recognition of the specific transmitter dopamine and the subsequent activation of effectors, leading to altered cell membrane potential and changes in the biochemical state of the postsynaptic cell. Neurotransmission via dopamine receptors is not sufficient to generate action potentials. Investigations into a possible neuromodulatory role of dopamine from the 1970s onward (i.e., electrophysiological experimental studies and microiontophoresis *in vivo*) have demonstrated that dopamine moderately depolarizes or hyperpolarizes neurons, usually by 5–7 mV [33]. Thus, dopamine acts as a neuromodulator, potentiating or attenuating cellular responses evoked by other neurotransmitters and thereby modulating neurotransmitter release, electrical excitability, and the neural firing properties of the target cell.

1.1.2.3 Regulation of Dopamine Neurotransmission (Synthesis, Reuptake, Storage, Degradation) Dopamine levels in the synaptic/extrasynaptic environment are controlled by a number of molecular mechanisms: dopamine reuptake involving the presynaptic dopamine transporter, storage by vesicular monoamine transporters, and metabolic degradation by the enzymes catechol-o-methyltransferase (COMT) and monoamine oxidase (MAO).

Dopamine Transporter (DAT) The topology of DAT shows that it is a plasma membrane protein, with 12 transmembrane domains. It is localized only on dopaminergic neurons and is considered the phenotypic marker of dopaminergic neurons. The DAT is encoded by a single gene [34]. The highest levels of DAT expression are found in the striatum and midbrain, and significantly less

is found in the frontal cortex and hypothalamus, with low levels in the olfactory bulb and the pituitary [35, 36]. The regional distribution of DAT in humans *in vivo* is shown in Figure 1.2C. Differential expression of DAT in various populations of dopamine neurons suggests regionally specific types of dopamine transmission regulation. The classical type of regulation via the uptake mechanisms exists in the striatum and the paracrine or volume transmission type of signaling is found in the midbrain and the neocortex [37]. DAT terminates neurotransmission by removing dopamine from the synaptic cleft via uptake back into presynaptic neurons. The end result of the reuptake system is maintenance of a narrow range of neurotransmitter at the synapse. Animal models have shown that genetic elimination of DAT leads to a considerably prolonged clearance time, elevated extracellular levels of dopamine, and altered neuronal firing properties [38]. Recently it has been suggested that the function of DAT may parallel the transmission type, in that it may have a reuptake function in the striatum and be involved in release in the midbrain [39].

Vesicular Monoamine Transporter (VMAT) VMATs transport cytoplasmic dopamine into storage vesicles and decrease levels of cytoplasmic dopamine, thereby modulating concentrations of free dopamine in the nerve terminals. Two VMATs localized to the membranes of the synaptic vesicles have been cloned, VMAT1 and VMAT2. The VMAT2 isoform is found in dopamine, norepinephrine, serotonin, and histamine releasing cells. In humans, the VMAT2 protein is encoded by the *VMAT2* gene.

Enzymes A major enzyme in synaptic dopamine catabolism in the cortical regions is COMT [40]. It is a relatively nonspecific enzyme, found in the cytoplasm of most tissues and in substantial amounts in the central nervous system (CNS). The precise cellular localization of COMT is not known. It is suggested that the enzyme functions extraneuronally. It plays a specific role in the regulation of synaptic dopamine levels in the cortical regions, but not in the mesolimbic or mesostriatal tracts. A functional genetic polymorphism for COMT involves a methionine-(Met)-to-valine (Val) substitution at codon 158. The Met allele has one quarter the enzyme activity of the Val allele. Therefore, the Met/Met individuals have significantly reduced enzyme activity and thereby higher dopamine levels in the prefrontal cortex [41].

Monoamine oxidase (MAO) is an enzyme that converts catecholamines to their aldehydes. It is a particle-bound protein localized in the outer membrane of mitochondria and also in the microsomes. MAO is considered an intraneuronal enzyme, but it is also found in abundance extraneuronally. It exists in two forms, MAO-A and MAO-B. The two are coded by different genes and expressed in different brain regions, MAO-A mRNA is found in noradrenergic neurons, while MAO-B is found in serotonergic and histaminergic neurons. Its presence in dopaminergic neurons is less known, however, and both MAO-B-positive dopaminergic neurons in SN and MAO-B positive glial cells near dopaminergic neurons have been documented [42].

1.1.3 Mechanistic Model of Activity of Dopaminergic Neuron

The firing characteristics of dopaminergic neurons have been described by electrophysiological techniques *in vitro* and *in vivo*. Spontaneously firing dopaminergic neurons have long action potential (2–5 ms) and *in vivo* display two different characteristic firing models, single spike firing, and burst firing [43, 44]. Single spike firing is a relatively regular, low frequency firing pattern, between 1 and 10 Hz. In contrast, burst firing is a transient high frequency discharge of multiple action potentials followed by an inactive period before spiking starts again. In general, it is thought that regular firing rates serve to induce tonic release of dopamine and thereby maintain a steady-state level of dopamine in the brain. Bursting neural activity gives rise to the phasic dopamine release and consequently induces high but transient increases in the dopamine levels, which convey discrete signals. Switching the firing pattern from regular to bursting and back is thought to be dependent on coinciding glutamatergic and cholinergic inputs from the subthalamic and pedunculopontine nuclei, respectively [45].

Electrophysiological activity of VTA and SN dopaminergic neurons is regulated by both autoinhibitory mechanisms and afferent inputs. The feedback regulation is largely executed by D_2-like autoreceptors located in the somatodendritic region of the dopaminergic neurons [43]. These receptors are activated by dopamine release from dendrites or axon collaterals. Activation of autoreceptors opens G protein-coupled inward rectifying potassium channels (GIRKs). Opening of the GIRK channels leads to increased membrane potassium conductance, which hyperpolarizes the cell membrane and consequently decreases the basal firing rate of the cell [46]. Thus, maintenance of a spontaneous, pace-maker-like firing pattern is mediated by auto-D2Rs. In addition to autoinhibitory mechanisms, the D_2-like autoreceptors may contribute to the regulation of dopamine transmission by modulating its synthesis and release. This function is brain region-dependent and is mediated by the autoreceptors localized on the cell terminals [47]; for example, the dopaminergic neuron terminals of mesocortical pathway have been shown to lack or have a reduced number of D_2 autoreceptors [48]. Autoreceptor stimulation in this pathway reduces the synthesis and release of dopamine.

Afferent inputs are of critical importance in the regulation of dopaminergic neuron firing rate. Glutamatergic innervation to the VTA, originating in the prefrontal cortex, sends an excitatory glutamatergic input to the dopaminergic neurons [49]. As a consequence, there is activation of glutamatergic N-methyl-D-aspartate (NMDA) receptors on dopaminergic cell bodies followed by a marked increase in cell burst firing [50]. The inhibitory γ-aminobutyric acid (GABA) input to dopaminergic cells in the VTA is mediated both by afferents from other brain regions and by GABAergic interneurons within the nucleus [51], which, in turn, receive glutamatergic input from the prefrontal cortex [52]. Experimental data indicate that noradrenaline also modulates dopamine neurotransmission in mesocortical dopamine systems. Activity of dopaminergic

neurons decreases following selective destruction of noradrenergic fibers while direct stimulation of the locus coeruleus strongly enhances the activity of dopaminegic neurons in the VTA, and drugs that increase central noradrenergic activity may enhance dopamine turnover [53].

1.1.4 Dopaminergic System in Brain Circuitry

The basal ganglia-thalamo-cortical system was hypothesized to be organized into multiple segregated circuits, which subserve different functions, including motor, oculomotor, prefrontal cognitive, and limbic functions [54]. Tract-tracing and physiological experiments have indicated a general topographic organization of the cortical-basal ganglia-thalamic loops and supported a model of basal ganglia function based on parallel and segregated pathways. Recent anatomical connectivity and neuroimaging studies reveal heterogenous neural activity patterns and show that the system is more complex. Cortico-striato-thalamo-cortical loops are not completely segregated. Pathways emanating from the cortical region and entering the striatum re-enter the initial cortical area that provides input to the striatum (close loops, serving segregated processes), but will also project back to other areas of the cortex, forming open circuits and by that serving integrative processes [55]. Furthermore, neuronal projections communicating between different loops (or functional domains) have also been discovered as well as nonreciprocal connections between the thalamus and the cortex. These terminals can influence different functional cortical areas that, in turn, will project to the striatum and back to the thalamus, where they can influence other circuits. So-called hot spots of convergence between terminals from different cortical regions may occur in the thalamus and in the striatum. Interloop connections in ventral striatum have also been shown by trans-synaptic neuronal tracing studies. Nonreciprocal connections are known to occur between striatum and SN [56].

In this complex neural circuitry, the dopamine system provides a bridge by which information circulating in the ventral limbic-cortico-striatal-thalamocortical loops connects to nigrostriatal loops (see Fig. 1.3, a connectivity diagram adapted after Reference [57]). The current understanding of the cortico-basal ganglia circuitry incorporates the model of two major pathways that transmit information through the basal ganglia, via the direct and indirect pathways. The direct pathway projects from the striatum to the internal segment of the globus pallidus and SN pars reticulata (the output structures of the basal ganglia). In the indirect pathway, information leaving the striatum flows through the external segment of globus pallidus and subthalamic nucleus before proceeding to the output structures. The function of these anatomical pathways is affected by the nature of the neurotransmitters they release. The direct pathway is purely inhibitory. The indirect pathway has both excitatory and inhibitory elements. Dopaminergic inputs to the basal ganglia arising from SN/VTA cell groups modulate the relative efficacy of these two opposing

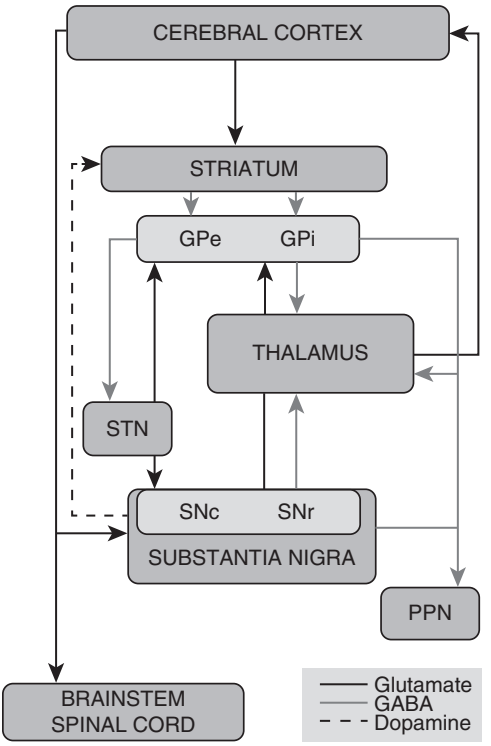

FIGURE 1.3 A connectivity diagram of the basal ganglia thalamocortical circuitry and major neurotransmitter systems. GPi, globus pallidus internus; GPe, globus pallidus externus; SNr, substantia nigra pars reticulate; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; PPN, pedunculopontine nucleus. Adapted from Reference [57].

streams of information transfer, enhancing stimulation via the direct pathway (mediated via D_1-like receptors) and enhancing inhibition via the indirect pathway (mediated predominantly via D_2-like receptors). The balance between these pathways determines whether the net relationship between the inputs and outputs of the basal ganglia will be inhibitory or excitatory. Finally, since the basal ganglia themselves inhibit the thalamus and the thalamus excites the cortex, increased outflow from the basal ganglia results in inhibition of the cortex. However, new anatomical and molecular biology studies suggest that these pathways are not so distinct. There are collaterals reaching out from the striatum to both GPe and GPi, direct striatal innervation to the cortex, without thalamic relay, direct excitatory input from the cerebral cortex to the subthalamic nucleus (hyperdirect pathway [58]), and there is evidence for co-expression of D_1- and D_2-like receptors on the same cells [59]. New models of cortico-striatal circuitry are under development.

1.2 DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

1.2.1 Emergence of the "Classical" Dopamine Hypothesis of Schizophrenia

The initial, "classical," dopamine hypothesis of schizophrenia was proposed over 50 years ago. In short, it suggested that schizophrenia may be related to an excessive activity of the dopaminergic system. Two main lines of research have contributed to the origins of this hypothesis: (1) discovery of neuroleptics and investigations of their mechanism of action and (2) investigations of the effects of psychostimulants, and observations that they may exacerbate psychosis or induce clinical symptoms mimicking positive symptoms of schizophrenia in healthy individuals.

Chlorpromazine was first synthesized in 1951 by P. Charpentier, S. Courvoisier, and colleagues at Rhône-Poulenc Laboratories (now Sanofi) [60–62]. Within half a year, chlorpromazine reached the patient clinics where it was first tested for its ability to potentiate anesthesia, as part of "lytic cocktail" [63]. Combination of contemporary clinical practice of the time (i.e., cooling of agitation with water) and the observed cooling effect of chlorpromazine led to the idea to test it in psychiatric clinics. The first administration of chlorpromazine to a patient with severe psychosis was successful [64]. Soon after, J. Delay and P. Deniker reported results of chlorpromazine application in a group of 38 manic and psychotic patients [65]. Numerous studies from all around the world facilitated the introduction of chlorpromazine into clinical practice both in Europe and the United States [66, 67]. However, side effects such as tardive dyskinesia were described from very early on. The beneficial effects of chlorpromazine (i.e., ameliorating the positive symptoms) generally occurred at doses that elicited neurologic side effects resembling Parkinson's disease. The symptoms gave rise to the term "neuroleptic" to describe these drugs (gr. *lēptos-seizing*, [68]).

Long before coming into Western medicine the sedative, calming features of the plant *Rauwolfia serpentina* had been used in India. Early scientific investigations were carried out as well. Rediscovery of *R. serpentina* and research into its sedative and antihypertensive properties at Ciba laboratories was followed by systematic clinical trials that documented the efficacy of its alkaloid, reserpine, in patients suffering from a variety of psychiatric disorders. Reserpine was introduced into clinical practice for the treatment of psychosis and research on its mechanism of action actively continued (for review, see [69]).

In parallel to the discoveries of chlorpromazine and reserpine, there were advancements in neuroscience that enabled the investigations of their mechanism of action. First, there was a shift in understanding of synaptic transmission, that is, from the idea that it is purely electrical to the concept of chemically mediated transmission. This further included the discovery of the first six neurotransmitters: acetylcholine, dopamine, GABA, norepinephrine, serotonin,

and substance P [70]. Second, the introduction of the spectrophotofluorometer offered the possibility to measure drugs and endogenous substances in different tissues (review Reference [71]). Consequently, the experimental studies with reserpine led to the discovery that it was depleting serotonin from tissue storage, blood platelets [72], and neural cell terminals in the brain [73]. Furthermore, the reserpine depletion in rabbits and mice leading to the akinesia and sedation could be reversed by the administration of L-DOPA, which restored dopamine levels in the brain [74]. A series of systematic studies in the 1970s eventually led to the discovery of dopamine receptors and the finding of the primary site of action of neuroleptics (i.e., interference of neurotransmission in the mesolimbic and nigrostriatal dopaminergic subsystems) [75–77]. In summary, this series of discoveries provided evidence that (1) neurochemical alterations in the brain lie behind the clinical symptoms and (2) interference of brain neurochemistry by pharmacological means could alleviate the symptoms of neurological and psychiatric disorders. These findings suggested the role of dopamine in the pathophysiology of neuropsychiatric disorders.

Amphetamine-induced psychosis was described in the early 1940s [78]. Initially it was thought that amphetamine directly stimulated peripheral adrenergic receptors, or that it acted at norepinephrine sites in the brain. Over several years, there was increasing evidence that the psychomotor effects of stimulants were induced *via* the central dopamine system and direct action on dopamine receptors was assumed [79, 80].

Based on the findings that (1) nonreserpine neuroleptics that induced extrapyramidal rigidity were dopamine receptor antagonists, (2) that psychostimulants that could exacerbate psychotic symptoms in schizophrenia patients acted on dopamine receptors, and (3) that dopamine found in high concentrations in the striatum was lacking in Parkinson's disease, J. van Rossum suggested that alterations in the dopamine system may play a role in the etiology of schizophrenia, be it overproduction of dopamine, overstimulation of receptors, or abnormal susceptibility of receptors [80] (review Reference [81]). Thus, schizophrenia was for the first time associated with changes in brain neurochemistry. The dopamine hypothesis of schizophrenia was formulated based on the indirect evidence coming from pharmacological sciences. This hypothesis opened a new line of investigations: a search for direct evidence of changes of dopamine biomarkers in patients with schizophrenia.

1.2.2 In Search of Evidence for the Dopamine Hypothesis of Schizophrenia

The 1980s and 1990s were marked by an extensive search for evidence to support the dopamine hypothesis of schizophrenia. Biochemical markers, such as levels of dopamine, its precursors and its metabolites were measured in patients' cerebrospinal fluid (CSF), blood, urine samples, skin fibroblasts, and postmortem brain. Initial measurements of the levels of dopamine in postmortem brain of patients with schizophrenia showed regional changes—higher

dopamine levels in caudate, nucleus accumbens, and amygdala [82, 83]. Those findings were not replicated and ultimately no clear alterations in the brain dopamine levels were confirmed. No clear changes in CSF levels of the dopamine metabolite homovanillic acid (HVA) were reported either. Thus, studies of schizophrenia patients using the peripheral biomarkers of dopamine system found no support for the hypothesis of increased dopamine metabolism [84].

Extensive development of molecular biology techniques and the cloning of five different dopamine receptors [85] stimulated the search for alterations in the dopamine receptor systems in patients with schizophrenia. Higher dopamine D2DR and D4DR binding in the striatum was found in the autoradiography studies [86, 87]. Meanwhile, developments in the area of molecular neuroimaging techniques provided new possibilities to visualize and quantify changes of dopamine receptors in the brain of living human individuals. Initial positron emission tomography (PET) studies using the nonselective radioligand [^{11}C]NMSP (which binds to the dopamine D_2, D_4 and 5-HT2 receptors) showed a two- to threefold elevated D2R density in the caudate nucleus of schizophrenia patients [88], a finding later attributed to the sensitizing effect of neuroleptics leading to receptor upregulation [82, 89]. No elevated D2Rs in the striatum were found in studies with drug-naïve patients and when using the more selective radioligand, [^{11}C]raclopride (which is selective for the D2R/D3Rs) [90–92]. High D4R density in the striatum of patients with schizophrenia seemed to suggest an explanation to the discrepant results of PET studies; however, these findings were also not replicated [93]. Thus, molecular brain imaging studies did not confirm postmortem findings of increased striatal D2Rs among patients with schizophrenia (review Reference [94]).

In summary, throughout the 1980s and 1990s, the most prevailing arguments supporting the dopamine hypothesis of schizophrenia still stemmed from an understanding of the mechanism of action of antipsychotic drugs, and in particular, the strong correlation between the antipsychotic potency of typical neuroleptics and the blockade of the D2Rs [75]. At the same time, the pharmacological evidence was questioned by the fact that clozapine, an effective atypical neuroleptic, was a weak D2R antagonist.

1.2.3 Dopamine Hypothesis Revisited

In the 1980s, the understanding of schizophrenia as a clinical entity was changing. Researchers began to focus attention on defining distinct dimensions of schizophrenia. Symptoms of schizophrenia were classified into separate categories such as positive (e.g., delusions, hallucinatory behavior, grandiosity) or negative (e.g., blunted affect, emotional withdrawal, motor retardation) and also the inclusion of anxiety/depression, disorganized thought, and hostility/excitement. Such questions as the change of certain symptom clusters over time, long-term outcomes, and the effect of antipsychotic treatment on different manifestations of illness were under investigation [95–97]. There was a subgroup of patients that did not respond to antipsychotics, and not all symptoms

of disorder could be treated equally efficiently. Accumulating observations on the use of neuroleptics and psychostimulants indicated that drugs that ameliorate positive symptoms of schizophrenia had no effect on negative symptoms or could even worsen them (e.g., amphethamine may worsen positive, but improve negative symptoms of schizophrenia) [98].

As the clinical understanding of schizophrenia and the history of its pharmacological treatment evolved, thinking of the disorder as simply a hyperdopaminergic state was becoming insufficient. Research was directed toward the investigation of a possible primary deficit within different dopamine subsystems.

1.2.3.1 The Theory of Regional Imbalance within Dopamine System In 1992, a hypothesis of "regional imbalance" in the dopamine system was suggested [99]. This hypothesis accepted dysfunction of the dopamine system in schizophrenia but did not implicate excessive dopamine transmission as the critical factor. It stated that both hypofunctional and hyperfunctional states in different brain regions may coexist in schizophrenia. Successors of this theory suggested that cognitive impairment and negative symptoms were related to the hypodopaminergic state in the cortical regions (i.e., mesocortical pathways), whereas positive symptoms of schizophrenia were associated with hyperdopaminergic activity in subcortical regions [100, 101].

Experimental studies supported the idea of regional differentiation in dopamine function. Neuroleptics were found to induce the selective effect on dopaminergic neuron firing; typical antipsychotics affected both A9 and A10 cells, while atypical antipsychotics affected only A10 cells [102]. Activation of the mesocortical dopamine system increased prefrontal glucose metabolism [103] and frontal glucose hypometabolism could be reversed by dopamine agonists [104].

In schizophrenia patients, it was the finding of reduced cerebral blood flow and glucose metabolism in the frontal cortices relative to other brain regions [105] and the "hypofrontality" concept that stimulated further search for the evidence of regional brain function differences in schizophrenia. However, a decade of neuroimaging studies yielded inconsistent results. Regional brain metabolism turned out to be dependent on a number of factors, such as medication effects, behavioral and emotional states during experiments (contextual variability), paradigms and methods of analysis used, and so on (review Reference [106]). Meta-analysis of neuroimaging studies added support for reduced frontal activation in schizophrenia, although the findings could also have been related to age or disease chronicity [107]. Studies using pharmacological functional magnetic resonance imaging (phMRI) techniques joined today in search for the link between regional brain metabolism and dopamine function in schizophrenia. It has been shown that atypical antipsychotics enhance prefrontal activity in patients with negative symptoms [101], findings that await replication.

The main controversies around this theory were and are related to the questions: (1) Are there indeed regional differences in brain activation pat-

terns in schizophrenia? (2) Is a pattern an artifact or epiphenomenon, or it reflects true, intrinsic differences in neuronal activity specific for schizophrenia, differences in activity of the dopamine subsystems? Dysfunction of frontal cortex seen in some patients with schizophrenia that has been thought to be primary and related to a decrease in "dopamine activity" has been recently challenged by animal research. Working memory and behavioral deficits attributed to the frontal cortex have been suggested to arise secondarily to excess striatal dopamine release, implying that each exacerbation of acute psychosis with excessive dopamine turnover increases the likelihood of frontal dysfunction [108]. Thus, there is still no direct evidence that the mesocortical dopamine system is disturbed in patients with schizophrenia.

1.2.3.2 Regional Imbalance between Dopamine and Other Neurotransmitter Systems What lies at the roots of the mesocortical–mesolimbic dysfunction in schizophrenia remains unknown. From the inception of the dopamine hypothesis of schizophrenia, most of the authors did not fully subscribe to it. A. Carlsson wrote in 1977: "while a primary disturbance in dopamine function in schizophrenia cannot be ruled out, the intimate relation between dopaminergic and other neuronal systems must be emphasized, the possible involvement of other amine, amino acid, or peptide transmitters in schizophrenia cannot be disregarded" [109]. Since then, several authors have proposed that dopamine levels in schizophrenia are normal but that they are elevated relative to other neurotransmitter levels. The emerging theories of schizophrenia suggest decreased levels of glutamate, NMDA receptor hypofunction [110–113], changes in serotonin system [114], and beyond (e.g., alterations among cytokines [115] or postsynaptic signal transmission system disturbances [116]). Loss of cholinergic interneurons in the striatum, hypoglutamatergia, or imbalance in glutamatergic and GABAergic projections from the prefrontal cortex have all been proposed as potential neurochemical alterations in schizophrenia. The grounds to these theories are in part built on the evidence of anatomical and functional interconnections between those neurochemical systems and dopaminergic subsystems, that is, the glutamatergic and GABAergic projections from prefrontal cortex synapse to the dopaminergic neurons of VTA and provide bidirectional control of dopaminergic neurons [100, 117].

1.2.4 Dopamine System in Schizophrenia: A Molecular Imaging Perspective

1.2.4.1 Postsynaptic Dopamine Receptors

Dopamine D_2/D_3 Receptors A recent meta-analysis of molecular imaging studies on striatal D2Rs in drug-naïve and drug-free patients with schizophrenia suggested that patients with schizophrenia have mildly elevated but more variable striatal D2R density compared with control subjects [118] (for a more detailed description of striatal D2R changes, see Section 1.2.2). Meanwhile,

measurements of the extrastriatal dopamine system in schizophrenia are less explored. This dopamine subsystem has long been of particular interest due to the findings of altered patterns of cortical activation, which were associated with psychotic symptoms and responded to antipsychotic treatment [118, 119]. The main questions asked were: Are the extrastriatal D2Rs changed in schizophrenia and can they be the primary target of antipsychotic medications? Development of high-affinity biomarkers for extrastriatal D2R enabled researchers to look for answers to these questions ([^{11}C]FLB457, [^{123}I]epidepride, [^{18}F]fallypride; [120–122]).

Thus far, a few extrastriatal regions with lower D2Rs in patients with schizophrenia have been suggested—the thalamus, the anterior cingulate cortex, the amygdala, and the temporal cortices—as well as increased D2Rs in SN [123–127]. Moreover, D2R binding in the cingulate cortex and the thalamus correlated negatively with the positive symptom score [123, 128]. Meta-analysis of pharmacological studies on the effect of antipsychotics on the extrastriatal D2Rs has shown that clinically effective doses of typical and atypical antipsychotics reach high receptor occupancy in the temporal cortex [129]. Slightly higher occupancy in cortical regions compared with the striatum have been reported for aripiprazole, clozapine, quetiapine, and ziprazidone ([^{18}F]fallypride,[130–133]. No prefrential cortical D2R occupancy has been reported for olanzapine or haloperidol ([^{18}F]fallypride, [134]), for clozapine ([^{11}C]raclopride and [^{11}C]FLB457, [135]), for risperidone ([^{11}C]FLB457, [136]), and for sertindole ([^{11}C]FLB457, [137]). Importantly, there was no relation between extrastriatal D2R occupancy and drug effect on the positive symptoms [130]. The best predictor of efficacy (i.e., response in positive symptoms) and of the propensity for extrapyramidal side effects still remains striatal D2R occupancy [138].

Dopamine D_1 Receptors Within experimental studies, there is ample evidence that dopamine plays an important role in modulating neurocognitive functions. Best established is its role in working memory. Dopamine levels rise at the beginning of a working memory task and stay elevated across many trials [139]. This suggests that a dopamine signal is present during encoding and use of information processing by the prefrontal neural circuitry. Furthermore, drug applications during working memory tasks have shown that increases in dopamine levels are mediated through D1Rs [140, 141]. Given the evidence for the decrease in working memory capacity in schizophrenia, changes in the D1R system have been predicted. PET studies have examined cortical D1Rs in neuroleptic-naïve or neuroleptic-free schizophrenic patients. Decreased ([^{11}C]SCH23390, [142]), increased ([^{11}C]NNC112, [143]), or no difference in D1R binding in the prefrontal cortex ([^{11}C]SCH23390, [144]) in patients relative to controls was found. Higher D1R in cortical subregions (i.e., medial prefrontal cortex, superior temporal gyrus, angular gyrus) have been associated with increased genetic risk for schizophrenia, and with impairments in working memory [144, 145]. Downregulation of cortical D1Rs by

clozapine, haloperidol, and remoxipride has been demonstrated in experimental studies [89] and in patients with schizophrenia using different antipsychotics [145].

In summary, blockade of the striatal D2R remains the main therapeutic target in the treatment of schizophrenia today just as it was 50 years ago. The role of the extrastriatal D2Rs in the pathophysiology of schizophrenia is still not established, although cortical D2Rs are likely to be involved in the action of antipsychotics. Experimental studies provide evidence for the role of D1Rs in cognitive functions. However, the link between cognitive dysfunctions in patients with schizophrenia and D1Rs is not yet fully understood.

1.2.4.2 Presynaptic Dopamine System Investigations of presynaptic markers of the dopamine system were largely driven by the hypothesis of regional dopamine imbalance and predictions of lower dopamine synthesis rates in prefrontal cortex. Initial studies in patients with schizophrenia showed increased [^{18}F]fluorodopa uptake, but primarily in the ventral striatum [146], Review of cross-sectional studies on [^{18}F]fluorodopa uptake in schizophrenia showed that results are rather inconsistent, with elevated, reduced, or unchanged presynaptic dopamine function in patients relative to comparison subjects [147]. Interestingly, a recent follow-up study of a single patient in remission (total/positive score on a Positive and Negative Syndrome Scale (PANSS) was 55/17), and an acute severe episode of psychosis (PANSS 119/40) demonstrated that [^{18}F]fluorodopa influx changes little, if at all, during the development of acute psychosis [148]. This case evaluation contradicts suggested excessive presynaptic dopamine synthesis in the striatum preceding the onset of schizophrenia [149, 150]. Thus, in summary, evaluation of dopamine synthesis rate in schizophrenia showed no clear changes but has raised an interesting question for further studies: whether "state" or "trait" related changes of dopamine levels occur during psychosis.

Two other presynaptic markers, the vesicular monoamine transporter, type 2 (VMAT2), and the DAT are thought to reflect density of dopaminergic projections in the striatum. There were no changes in the striatal binding of the radioligand [^{11}C]dihydrotetrabenazine (DTBZ), marking VMAT2, in the schizophrenia patients on medication [151] and no changes in DAT binding in the first-episode, drug-naïve patients with schizophrenia, relative to controls ([^{11}C]CFT [152], [99mTc]TRODAT-1, [152]). Higher variability in DAT levels, inverse interaction between striatal DAT and D2R, loss of right–left caudate DAT asymmetry [153, 154], as well as significant negative correlation between DAT availability in the striatum and PANSS scores have been reported [155]. Thus, the hypothesis that excessive dopamine activity in schizophrenia could be explained by increased density of striatal dopamine terminals has not been confirmed.

In summary, evaluation of the presynaptic markers of dopamine system in schizophrenia suggests that changes, if any, are minor and possibly are only within a subgroup of patients with schizophrenia.

1.2.5 Beyond Psychopharmacology: Cognitive Models and Genetic Links

Schizophrenia involves different aspects of cognition. Early work in the field concentrated on a reduction in intelligence and a slowness in reaction time. Recently, the research focus has shifted to other cognitive domains, such as working memory, episodic memory, attention, and linguistic processing. Advanced computational network models and functional brain imaging techniques provide the possibility to look at schizophrenia at both the molecular and system levels. It has been hypothesized that the abnormal cognitive functions found in schizophrenia are a consequence of disordered anatomical connectivity, primarily dominated by a disruption in higher levels of perception and hierarchical temporal processing by the brain [156–159]. The dominant understanding today is that there might be an interplay of dysfunctional and compensatory cortical regions or networks in schizophrenia and, thus, combinations of regions with increased and decreased activation or reduced functional connectivity, which in turn is likely to be critically dependent on D1Rs and their role in enhancing NMDA receptor-mediated postsynaptic currents in prefrontal pyramidal and GABAergic neurons [141, 160]

A major enzyme in synaptic dopamine catabolism in the cortical regions is COMT. A common polymorphism in the COMT gene resulting in two valine-to-methionine Val(108/158)Met substitutions gives rise to a significant reduction in its enzymatic activity in the prefrontal cortex [41, 161]. Higher synaptic dopamine in COMT Met-homozygotes is thought to be favorable for the function of frontoparietal networks, for improved working memory after antipsychotic treatment [162, 163]. Given that COMT regulates cortical dopamine levels and that prefrontal cortical dysfunction is seen in schizophrenia, it has been predicted that the gene coding for COMT may serve as a susceptibility gene for schizophrenia (review Reference [164]). However, most recent research suggests that the relationship between COMT function and brain dopamine levels is much more complex and present knowledge is not sufficient to suggest definitive conclusions on its role in the development of schizophrenia [165, 166].

The evidence that schizophrenia can be inherited is compelling with the worldwide risk of schizophrenia of about 1%. The risk increases to about 8–10% if the patient has a first-degree relative (sibling, parents) who suffers from schizophrenia, and in monozygotic twins the risk increases to as high as 50% [167]. Despite the overwhelming evidence that schizophrenia is an inherited illness, a particular defective gene responsible for it has not been found. Genetic loci that appear to confer susceptibility for schizophrenia have been mapped to several chromosomes, including 1q21-22, 1q32-43, 6p24, 8p21, 10p14, 13q32, 18p11, and 22q11-13. Mutations in genes coding for subtypes of dopamine receptors have been explored. A network of interacting genes within the dopamine system increases the risk of schizoprenia. Suggested susceptibility genes are those encoding dystrobrevin binding protein (DTNBP1), disrupted-in-schizophrenia-1 (DISC1), neuregulin 1 (NRG1),

dopamine receptors (D_1–D_4), COMT, and postsynaptic transduction mechanisms (via DARP32). There are numerous studies that support the presence of a link between gene polymorphisms and clinical symptoms, but an equal number of studies do not. Meta-analyses most often show no or only weak associations of single genes for the units of dopamine system and schizophrenia ([168]; for *D1DR* [169]; for *D2DR* [170–172] for *D3DR* [173]; for *D4DR* [174]; for *DAT* [175]; for *COMT* [176, 177]).

So far, no gene mutation that could be reliably related to schizophrenia has been found. The existence of multiple loci conferring susceptibility to schizophrenia suggests that the disease is caused by the interaction of many different genetic components. Thus, a polygene model, where multiple genes contribute to vulnerability to schizophrenia, is currently the most broadly accepted model.

1.3 SUMMARY AND CONCLUSIONS

Thus far, the most compelling evidence for the involvement of the dopamine system in the pathophysiology of schizophrenia remains the finding that clinical efficacy of antipsychotics is mediated via antagonism at striatal D2DRs. However, although blocking of D2DR ameliorates psychosis, this does not necessarily mean that the dopamine system is abnormal in schizophrenia. It is common in medicine that symptoms can be treated by mechanisms unrelated to disease etiopathogenesis. Vigorous search for abnormalities in the dopamine system in schizophrenia so far has yielded inconclusive results. The increasing understanding of the behavioral complexity of schizophrenia suggests that it is unlikely that a single neurotrasmitter system can explain such diverse symptoms, for example, inattention and hallucinations.

Thus, any simple, exclusive pathology of the dopamine system in schizophrenia was and is doubtful. Despite these doubts, continuing attempts to develop effective drugs for the treatment of different symptoms of schizophrenia by restoring the homeostasis of dopamine is warranted since many of the mental processes impaired in schizophrenia involve brain circuitry that is modulated by dopamine.

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