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Molecular Substrates of Schizophrenia: Homeostatic Signaling to Connectivity

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Abstract

Schizophrenia (SZ) is a devastating psychiatric condition affecting numerous brain systems. Recent studies have identified genetic factors that confer an increased risk of SZ and participate in the disease etiopathogenesis. In parallel to such bottom-up approaches, other studies have extensively reported biological changes in patients by brain imaging, neurochemical and pharmacological approaches. This review highlights the molecular substrates identified through studies with SZ patients, namely those using top-down approaches, while also referring to the fruitful outcomes of recent genetic studies. We have sub-classified the molecular substrates by system, focusing on elements of neurotransmission, targets in white matter-associated connectivity, immune/inflammatory and oxidative stress-related substrates, and molecules in endocrine and metabolic cascades. We further touch on crosstalk among these systems and comment on the utility of animal models in charting the developmental progression and interaction of these substrates. Based on this comprehensive information, we propose a framework for SZ research based on the hypothesis of an imbalance in homeostatic signaling from immune/inflammatory, oxidative stress, endocrine and metabolic cascades that, at least in part, underlies deficits in neural connectivity relevant to SZ. Thus, this review aims to provide information that is translationally useful and complementary to pathogenic hypotheses that have emerged from genetic studies. Based on such advances in SZ research, it is highly expected that we will discover biomarkers that may help in the early intervention, diagnosis or treatment of SZ.

Keywords

Schizophrenia; neurotransmission; white matter; inflammation; oxidative stress; endocrine and metabolism

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Introduction

Schizophrenia (SZ) is one of the most devastating mental conditions with a lifetime prevalence of about 0.7-1%.[1] If we include the prevalence of subclinical psychotic experiences and symptoms, which are likely to share similar biological mechanisms with SZ, the prevalence increases to about 8%.[2] The cross-sectional clinical manifestations and course of SZ are heterogeneous with a complex phenomenology. However, even among clinical psychiatrists, a more simplified sub-classification of clinical symptoms is frequently used to facilitate biological and translational studies[3]: positive symptoms (e.g., hallucinations, delusions, and disorganized thoughts and speech), negative symptoms (e.g., apathy, affective flattening, social withdrawal), and cognitive dysfunction (e.g., deficits in working memory, verbal memory). Although SZ typically manifests in the second decade of life, abnormal neurodevelopmental processes are thought to begin during prenatal and perinatal stages.[4]

Several 'biological' hypotheses of SZ were originally proposed because of the effects of drugs. The dopamine hypothesis of SZ evolved from multiple observations and studies including findings that antipsychotic drugs used for SZ block dopamine D2 receptors.[5–7] Years later the glutamatergic hypothesis of SZ was proposed based on observations that phencyclidine or ketamine mimic SZ-like manifestations, even including some aspects of negative symptoms and cognitive dysfunction, by blocking N-methyl-D-aspartate receptors (NMDAR).[8, 9]

SZ is now considered a polygenic condition;[10–12] many candidate susceptibility genes have been identified, however, individual effect sizes are modest in sporadic cases. Single nucleotide polymorphisms (SNP), copy number variations, and *de novo* mutations have been implicated in conferring risk of SZ.[13, 14] In addition, in the contexts of both common and rare variants, susceptibility factors that have been suggested for SZ confer risk for other mental conditions, such as bipolar disorder and autism.[10, 15–18] This is reasonable given that the current diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM), emphasize clinical reliability and utility rather than etiological validity.[19]

In addition to genetic studies (bottom-up approach), years of research with clinical subjects and biospecimens have implicated multiple molecular targets of SZ. In this review, we discuss the different 'molecular' substrates of SZ that have been identified primarily through human (patient) studies, namely those using top-down approaches, and sub-classify them by biological system (**Table 1**): neurotransmission, white matter-associated connectivity, immune/inflammatory response and oxidative stress, endocrine system, and metabolic cascades. For each system, we focus on evidence from brain imaging, neurochemical, postmortem, genetic, and clinicopharmacological studies (**Table 2**). Lastly, we describe the possible integration of these systems and additional evidence from animal models of SZ under an overall perspective of an in-depth understanding of the disease pathology and translational application.

The goal of this review article is to provide comprehensive information that is translationally useful and complementary to pathogenic hypotheses that have recently emerged from

genetic studies. To address this goal, we propose a framework for SZ research based on the hypothesis of an imbalance in homeostatic signaling that, at least in part, underlies deficits in neural connectivity relevant to SZ. More concretely, we describe how inflammatory, oxidative stress, endocrine, and metabolic homeostatic signaling processes mediate and pathologically modulate neurotransmission and myelinated tracks. Given that many comprehensive review articles on psychiatric genetics and animal models have been published recently,[20–24] we only touch on the critical conceptual viewpoints in these areas.

By referring to the information from genetic studies, we can address the question of whether molecular substrates identified through human patient studies are primary or secondary. In particular, molecular studies in first episode psychosis and individuals with high genetic risk of SZ combined with convergent evidence from genetic and animal models can help determine the central disease processes. The successful integration of pathogenic-oriented (bottom-up) and patient phenotype-oriented (top-down) research has precedence in many other diseases, such as cancer, metabolic syndrome and Alzheimer's disease.[25–29]

Neurotransmission

Dopamine

Molecular brain imaging studies have provided useful insights into dopamine, glutamate, and γ-aminobutyric acid (GABA) neurotransmission in SZ. The majority of the molecular imaging studies using positron emission tomography (PET) and single photon emission computerized tomography (SPECT) have suggested that presynaptic striatal dopamine is elevated and dopamine release is increased in subjects with SZ. PET studies have found that striatal L-[β-^{11}C]DOPA or [^{18}F]DOPA uptake is elevated in subjects with SZ as well as subjects showing prodromal symptoms of SZ, suggesting an elevation in presynaptic striatal dopamine in SZ (**Figure 1**).[30–34] A PET study using [^{11}C]raclopride and SPECT studies using [^{123}I]IBZM found significantly greater amphetamine-induced reductions in the binding potential of the radiotracers in the striatum of subjects with SZ compared to controls, suggesting that there is enhanced dopamine release in SZ.[35–37] However, it has been suggested that the elevated dopamine observed in SZ is linked to psychosis rather than the disease itself.[38]

It has been further shown that subjects with SZ have a significant increase in dopamine D2 receptor (D2R) availability in the associative striatum, specifically in the precommissural dorsal caudate, but not in the ventral or the sensorimotor striatum, after dopamine depletion.[39] A meta-analysis of 13 studies using PET and SPECT found a significant, but small, elevation in striatal D2R density in subjects with SZ.[40] Studies analyzing D2R availability in the thalamus, anterior cingulate cortex and temporal cortex have found both decreased and unaltered D2R availability in SZ.[41] Additionally, a recent genome-wide association study (GWAS) found that the *D2R* gene is within a SZ-associated locus.[42]

Results of PET studies using [^{11}C]SCH23390 and [^{11}C]NNC112 to image prefrontal cortex dopamine D1 receptor (D1R) binding are contradictory, reporting reduced, unaltered and increased receptor binding in SZ patients.[43–45] A meta-analysis of seven postmortem studies and one PET study did not find an elevation in D1R in SZ.[46] Studies measuring levels of

homovanillic acid, a metabolite of dopamine, in the cerebrospinal fluid (CSF) of subjects with SZ are inconsistent; some report no difference between SZ and control subjects but others report lower levels in SZ.[47, 48]

Abnormalities in dopamine neurotransmission have also been suggested by postmortem studies. Changes in the density and mRNA levels of some classes of dopamine receptors have been suggested in the prefrontal cortex, striatum, and hippocampus of SZ subjects.[49–51] Reductions in the density of tyrosine hydroxylase, an enzyme involved in dopamine synthesis, and the density of dopamine membrane transporter immunoreactive axons in the prefrontal cortex have been reported in SZ.[52] A reduced density of tyrosine hydroxylase immunoreactive axons in the entorhinal cortex has also been reported.[53]

In summary, the main finding on dopaminergic neurotransmission is that a state of overstimulation of D2R in the associative striatum exists in SZ starting early in the prodromal phase and corresponds with psychosis as well as with the therapeutic response to antipsychotics.[31, 39, 54] Other symptom domains are thought to relate to deficits in dopamine transmission in cortical and extrastriatal regions, but conclusive evidence for this has not emerged yet.[55]

Serotonin

Most typical antipsychotics are D2R antagonists, whereas several atypical antipsychotic drugs also target serotonin receptors, in particular the $5HT_{2A}$ receptor, for antipsychotic efficacy.[56] Furthermore, indoleamine hallucinogens such as psilocybin, can elicit SZ-like symptoms that can be blocked by $5HT_2$ antagonists.[57] Postmortem studies have shown a reduction in the density of $5HT_{2A}$ receptors in the prefrontal and frontal cortex in SZ.[58] These results suggest involvement of serotonin in the pathophysiology of SZ, or at least in psychotic manifestations.

Glutamate

Pharmacological evidence has also implicated glutamate neurotransmission in SZ. Acute administration of NMDAR antagonists, such as phencyclidine (PCP) or ketamine, transiently induces symptoms typically associated with psychosis, including positive, negative and cognitive deficits.[59, 60] This observation led to a hypothesis for NMDAR glutamate dysregulation as a prominent pathophysiological feature of SZ. Studies using autopsied brains have shown reduced numbers of dendritic spines on pyramidal neurons in SZ.[61, 62] Furthermore, analysis of GWAS and genetic and gene expression studies have indicated the significance of genes involved in glutamate receptor signaling.[12, 14, 42, 63] These include the NMDAR subunit gene *GRIN2A*, glutamate receptor, ionotropic, AMPA 1 (GRIA1), and genes involved in the activity-regulated cytoskeleton-associated protein (ARC) signaling complex.

Many ^1H magnetic resonance spectroscopy (MRS) studies have measured glutamate, glutamine or the sum of glutamate and glutamine (Glx) in subjects with SZ; some studies also include GABA in the measurement.[64] Several reports have indicated that glutamatergic levels in the medial prefrontal cortex and anterior cingulate cortex are elevated in medication-naïve and unmedicated SZ subjects; however, studies also report that

glutamatergic levels tend to decrease during the disease course, possibly reflecting treatment response and/or disease progression (**Table 3**).[8, 64–68] A recent review summarizes the findings of many MRS studies with an emphasis on regional specificity: medication-naïve and unmedicated SZ subjects have elevated glutamatergic levels in the medial prefrontal cortex, but not in the dorsolateral prefrontal cortex and hippocampus, while studies on the thalamus report more variable effects with unaltered, increased or decreased glutamatergic levels (**Table 3**).[64, 69] Meanwhile, studies with CSF have shown that the levels of glutamate are similar between control and medicationnaïve or unmedicated SZ subjects.[70–72] Lastly, some studies have explored a role for glutamate in SZ pathophysiology:[73, 74] ketamine administration to rodents elicited hypermetabolism in the CA1 sub-region of the hippocampus, while repeated exposure shifted the hippocampus to a hypermetabolic basal state with concurrent atrophy. Similarly, hypermetabolism of the hippocampus, in particular the CA1 sub-region, has also been seen in SZ patients, which may be a predictive factor of hippocampal atrophy.[73, 74]

In addition, reports of patients who have autoantibodies to the NMDAR (anti-NMDAR encephalitis) and show psychotic symptoms including visual or auditory hallucinations and paranoid thoughts have supported the involvement of glutamate and NMDAR in the pathophysiology of SZ and psychosis.[75–78] The causality of the autoantibody to psychosis, at least in this specific disease condition, has been demonstrated in cases where an ovarian teratoma is present: tumor removal and intravenous immunoglobulin or intravenous steroids can reverse the psychiatric symptoms within weeks.[79, 80] Collectively, these pharmacological, clinical, genetic, and autoimmune studies have repeatedly implicated glutamate dysfunction in SZ.

GABA

There is still a technical debate about measuring GABA consistently in different scanners and institutions. However, one group found reduced GABA concentrations in the basal ganglia, but not in the frontal lobe, in early stage SZ subjects.[81] In contrast, another group has reported that GABA levels were elevated in the medial prefrontal cortex in unmedicated SZ subjects.[66] As for chronic SZ, studies have reported unaltered GABA concentrations in the basal ganglia, reduced concentrations in the visual cortex, and elevated levels in the parieto-occipital cortex.[82–84] Unaltered and elevated GABA concentrations in the anterior cingulate cortex have been reported in chronic SZ, while a more recent study found reduced GABA concentrations in the anterior cingulate of older subjects with chronic SZ (**Table 3**).[82, 84, 85] Recently, a study using MRS and magnetoencephalography (MEG) to measure resting GABA and glutamate concentrations and stimulus-induced gamma oscillations in the occipital cortex of healthy subjects, reported that there was no correlation between GABA, glutamate, or the GABA/glutamate ratio and gamma peak frequency or gamma amplitude.[86] In addition, several studies have measured GABA levels in the plasma and CSF of unmedicated SZ patients and reported no major differences between SZ and controls, however, one report found a significant decrease in mean CSF GABA levels after neuroleptic treatment.[87–89] One study reported significantly lower CSF GABA levels in patients whose duration of illness was 4 years or less compared to subjects whose duration of illness was greater than 4 years.[90] However, another study reported similar GABA levels

between acute SZ subjects and controls but increased CSF GABA levels in chronic SZ subjects.[91] In general, MRS studies on GABA in SZ are scarce and show inconclusive results at this time.

Postmortem studies have provided convincing evidence of GABAergic changes in SZ.[92, 93] These studies have consistently reported alterations in GABAergic interneurons in the prefrontal cortex. These alterations include decreased glutamic acid decarboxylase 67 (GAD67) and parvalbumin (PV).[94–98] Additionally, some potassium channels (Kv3.1 and KCNS3) that are predominately expressed in PV positive neurons, are decreased in the prefrontal cortex in SZ.[99, 100] PV positive neurons are fast spiking, synchronize pyramidal neuron firing and play a role in the generation of gamma oscillations.[101] Thus, deficits in this population of neurons may contribute to the cognitive deficits observed in SZ.[101] Decreased somatostatin and cholecystokinin mRNA levels have also been reported in SZ.[102]

α7-nicotinic receptor

A high percentage of SZ patients smoke cigarettes. It has been shown that cigarette smoking improves sensory gating, P50 inhibition, and prepulse inhibition in SZ.[103–105] The P50 sensory deficit observed in SZ might be genetically linked to the locus of the α7-nicotinic acetylcholine receptor gene, *CHRNA7*, on chromosome 15q14.[106] Multiple linkage studies have also supported this evidence.[107, 108] Postmortem studies using [^{125}I]alpha-bungarotoxin have shown fewer nicotinic receptors in the hippocampus, the reticular nucleus of the thalamus, and the cingulate cortex of subjects with SZ.[109–111] Brain imaging studies to validate this hypothesis using [^{123}I]5-IA-85380 and 2-[^{18}F]FA, radiotracers for high affinity nicotinic acetylcholine receptors, are under way.[112, 113]

Synaptic assembly

As described above in the context of glutamate, some genetic susceptibility factors for SZ have distinct synaptic functions in a broader sense.[12, 14, 42, 114] Some of the genes involved in synaptic function and plasticity that have been identified within SZ-associated loci include potassium channel tetramerization domain containing 13 (KCTD13), contactin 4 (CNTN4), p21 protein-activated kinase 6 (PAK6), neuroligin 4, X-linked (NLGN4X), and genes related to the postsynaptic ARC complex.[12, 42] Functional studies of such candidates, including disrupted in schizophrenia 1 (DISC1) and p21 protein-activated kinase 7 (PAK7), also support synaptic roles.[115–117] Microarray analysis of the prefrontal cortex found that the expression of genes related to the presynaptic secretory machinery [for example, N-thylmaleimide sensitive factor (*NSF)* and synapsin II (*SYN2)*] were decreased in SZ.[118] Although brain imaging studies of synaptic changes in SZ are lacking, the field awaits the development of new techniques to assess synaptic changes in SZ.

As described, multiple lines of evidence suggest that multiple types of neurotransmission, in particular dopaminergic, glutamatergic, and GABAergic neurotransmission, are altered in the brains of SZ patients. However, at this time it is unclear if the reported changes are causal or secondary, but in either case, the changes are critical for the pathophysiology.

White matter-associated connectivity

Neurotransmitters play a role in cell-cell communication in the brain, but distant communication is also dependent on proper transduction of action potentials along axon tracts. White matter regions contain long-range axonal connections insulated by myelin, a lipid-dense material produced by oligodendrocytes. Signaling between oligodendroyctes and axons mediates the formation of nodes of Ranvier (NoR) and internodal myelin sheathes.[119] The myelin sheathes increase electrical resistance, allowing for faster propagation of electrical signals along axons. Dysmyelination can affect neuronal connectivity; decreased white matter integrity has been correlated with functional deficits in demyelinating diseases.[120] Although there is no robust demyelination in the brain in SZ, many reports have indicated a deficit in white matter associated connectivity.[121]

Diffusion tensor imaging (DTI) with MRI can measure the diffusion of water molecules along white matter bundles. Fractional anisotropy (FA), a metric of the rate of diffusion along axons and a measure of myelin integrity, is reduced in SZ patients.[121-123] Deep white matter tracts in the frontal and temporal lobes interconnecting to the thalamus, cingulate gyrus, amygdala, insula, hippocampus, and occipital lobe are reportedly those most affected in SZ.[124] Changes are observed in chronic, first episode, and adolescents with early onset SZ as well as subjects in prodromal stages and adolescents at high clinical risk for developing SZ.[125, 126] A longitudinal study in SZ patients also found heterogeneous decreases in white matter volume (total cerebral, frontal, temporal, parietal) over the disease course, primarily at the onset of the disorder.[127] Notably, the regions that are prominently affected are those still undergoing myelination during late adolescence. Furthermore, functional MRI (fMRI) studies now suggest altered connectivity in SZ patients. Recently, it was reported that the global brain signal (the average signal across all voxels in the brain derived from fMRI) is altered in SZ subjects, but not in subjects with bipolar disorder.[128] Time series of resting-state fMRI suggest that patients with SZ have reduced functional network strength and altered brain network topology.[129-131] Also, recent investigations have documented robust and replicable dysconnectivity in thalamocortical systems in chronic SZ.[132, 133] Patients with SZ also show impaired task-dependent communication between brain regions including reduced suppression of default network activity and weaker activation of task-associated regions.[134-136] Several recent studies combining functional and structural imaging have found correlations between reduced FA and altered brain activity in specific neural circuits.[137] Collectively, these structural and functional investigations repeatedly point to profound alterations in major neural systems related to executive control.[138, 139]

Postmortem tissue analyses of SZ brains have found abnormalities in oligodendrocytes, the brain's source of myelin.[140] For example, a report indicated a decrease in the number and density of oligodendrocytes in the grey and white matter of Brodmann area 9.[141] Additionally, microarray and real-time quantitative polymerase chain reaction (qPCR) studies identified changes in the expression of oligodendrocyte and myelin-related genes such as proteolipid protein 1 (PLP1), myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), and oligodendrocyte transcription factor 2 (OLIG2) in the prefrontal cortex.[142, 143] Similar studies have noted expression changes in myelination-

related genes in additional brain areas including the temporal cortex, cingulate cortex, and the hippocampus.[144–146]

Furthermore, a number of myelin-related genes have been genetically linked to an increased risk of SZ.[147] These include genes encoding neuregulin-1 (NRG1), receptor tyrosine-protein kinase erbB-4 (ERBB4), reticulon 4 (RTN4/NOGO), PLP1, MAG, MOG, OLIG2, 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP1) and ankyrin-3 (ANK3).[147–156] Several of the molecules that are genetically associated with SZ also have altered expression in the SZ brain, such as PLP1, MAG, MOG and OLIG2. While no myelin-related genes reached significance in a large GWAS set for SZ,[11] a few (*NRG1, ERBB4, ANK3*) had sub-threshold associations (p-value $< 5 \times 10^{-5}$), and broader pathway analysis revealed a significant association for genes in myelination-related pathways and those with specific glial cell-type functions.[157, 158] NRG1 and its erbB receptors are important signaling molecules for axon guidance and myelination.[150] Unaffected subjects carrying a risk allele for NRG1 have reduced white matter density.[159] ANK3 is an axonal protein that helps form the scaffolding for NoR and has also been identified as one of the most significant genetic risk factors shared between SZ and bipolar disorder.[156] Another recent study identified several NoR proteins affected in SZ, including ANK3 and its interactors.[160] These results highlight the importance of neuron-glia interactions at the NoR in psychiatric illness.[161] In addition, while not traditionally identified as myelin/oligodendrocyte-associated genes, several susceptibility genes for SZ that encode the zinc finger binding protein 804A (ZNF804A), L-type voltage-dependent calcium channel CAV1.2 (CACNA1C), DISC1, and microRNA-137 (MIR137) have been associated with white matter phenotypes in SZ patients, as well as, control subjects that carry risk alleles.[161, 162]

Lastly, we refer to some interesting aspects of clinicopharmacology. Studies have suggested that treatment with antipsychotics, lithium, antidepressants, and electroconvulsive therapy may share common myelin-protective signaling mechanisms.[163] One study found that higher white matter integrity in first episode SZ was predictive of responsiveness to antipsychotics.[164]

In summary, data from imaging and postmortem studies have suggested the presence of abnormal myelination in SZ. Genetic studies have suggested the importance of neuron-oligodendrocyte interactions. Given that the typical onset of SZ coincides with the final stages of myelination in the frontal and temporal cortices, aberrant myelin development may contribute to the presentation of symptoms in patients.

Immune/inflammatory response and oxidative stress

Epidemiological studies have suggested that prenatal infections with viruses, bacteria, or parasites increases the risk of their offspring developing SZ in adulthood.[165] Given that the full onset of SZ is frequently in late adolescence and young adulthood, addressing mechanisms and mediators of the long pathological trajectory from initial predisposition to disease onset remains a central question of SZ research.[4, 166]

Cytokines

An imbalance in the cytokine/chemokine network may be an explanation for why multiple infections can increase the risk of SZ; the disturbance of this network during the neonatal period may alter fetal brain development.[165] In accordance with this hypothesis, studies on serum levels of cytokines in SZ suggest that IL-1β, IL-6, TNF-α and IL-2 are increased in SZ.[167,171] However, it should be noted that there are also studies that report unaltered serum levels of IL-1β, IL-6, TNF-α and IL-2 in SZ.[167, 169, 172, 173] A recent meta-analysis also found that serum levels of IL-1β, the soluble IL-2 receptor (sIL-2R), IL-6 and TNF-α were increased in drug-naïve first episode psychosis (SZ, schizophreniform disorder, delusional disorder and brief reactive psychosis), however, IL-2, IL-4 and IFN-γ levels were not altered.[174] A meta-analysis of antipsychotic-induced cytokine changes in SZ found that antipsychotic treatment increased IL-12 and sIL-2R and reduced IL-1β and IFN-γ plasma levels, with treatment duration having no effect.[175] Additionally, two studies found an association between maternal cytokine levels (TNF-α and IL-8) and increased risk of SZ in the offspring.[176, 177] Studies that compare such inflammatory mediators in the CSF of controls and SZ subjects (and prodromal subjects) are also available. In particular, a recent study that purely utilized unmedicated first onset SZ and prodromal subjects supports alterations of inflammatory mediators in psychotic subjects, including the IL-6 cascade and IL-8.[178]

Microglia

Chronically activated T cells, macrophages and microglia produce cytokines that may impact brain development.[167, 179, 180] The potential involvement of microglia is of particular interest from a mechanistic viewpoint since recent studies have indicated a role for microglia in synaptic pruning and maintenance.[181,183] Aberrant synaptic pruning in adolescence is one of the important working hypotheses in SZ pathology.[184] Furthermore, a study using *in vivo* two-photon imaging has shown that blockade of excess synaptic pruning in late adolescence ameliorates deficits in prepulse inhibition, at least in an animal model that may model some SZ manifestations.[116] Taken together, reactivation during adolescence of microglia pathologically primed in early development may be a likely scenario to account for the mechanism. Some postmortem studies have found an increase in the density or activation of microglia in SZ: however, other studies found no difference between controls and subjects with SZ.[179, 185,189] A more recent study that used next generation sequencing and Western blotting has shown that microglial markers are upregulated in the dorsolateral prefrontal cortex of SZ.[190] Furthermore, immunohistochemistry for the human leukocyte antigen (HLA) class II molecules (HLA-DP, -DQ and –DR), which are expressed on antigen-presenting cells, revealed more positive cells in the white matter of subjects with SZ; the authors also indicated that these positive cells morphologically resembled microglia.[190, 191]

Although these studies provide promising evidence for the involvement of microglia and the inflammatory cascade in SZ, we also need to be prudent in interpreting data from the autopsied brain because confounding factors exist and the plausibility of detecting adolescent pathology from typically aged autopsied brains is unknown. Validation of ‘brain’ inflammation in SZ at the time of psychosis has recently been pursued using PET imaging with tracers that target molecules changed in neuroinflammation. In particular, radioligands

that target the translocator protein (TSPO) (previously known as the peripheral benzodiazepine receptor) have been frequently used.[192] Activation of microglia results in an increase in the number of mitochondria per cell and an increase in the density of the peripheral benzodiazepine receptor in the outer mitochondrial membrane.[193, 194] Two PET studies found an increase in the regional binding potential of [^{11}C]PK11195, a classic TSPO tracer, in subjects with a psychotic disorder or SZ.[195, 196] Given the limitations in the [^{11}C]PK11195 tracer, such as high nonspecific binding, high lipophilicity and poor signal-to-noise ratio, recently new PET tracers (e.g., [^{11}C]PBR28 and [^{11}C]DPA713) have been developed and are beginning to be used.[197, 198] A general limitation of TSPO brain imaging to test neuroinflammation is that this protein can also be influenced by mitochondrial deficits and oxidative stress that may also occur in SZ.[199] Assessment of brain inflammation in SZ using radioligands that target other inflammatory markers will shed further light on the role of inflammation in this disease.

Autoimmunity

Multiple combinations of environmental stressors and genetic factors contribute to SZ pathology.[165, 200–202] Aberrant activation and an imbalance of immune/inflammatory cascades are likely due to both environmental influences and host susceptibility. Epidemiological data linking autoimmune diseases and SZ has recently been reviewed: celiac disease, autoimmune thyroiditis, Graves' disease, type 1 diabetes, multiple sclerosis, autoimmune hepatitis, psoriasis, and Sjögren's syndrome are all associated with SZ, whereas, there is a very unique and negative association with rheumatoid arthritis.[203, 204] The increased co-morbidity of SZ with many autoimmune diseases supports the idea that SZ has an intrinsic susceptibility to the immune/inflammatory response. This notion is further supported by GWAS, which found an association of SZ with the major histocompatibility complex (MHC) region.[11, 42, 205, 206] Additionally, as discussed in the neurotransmission section, in some cases of anti-NMDAR encephalitis the presence of the autoantibody appears to be related to the psychiatric symptoms.[79, 80]

Oxidative Stress

The inflammatory response is interconnected with oxidative stress.[207] The significance of oxidative stress in SZ pathology is that the stress can lead to synaptic deterioration, abnormal myelination and interneuron deficits.[207, 208] Oxidative stress occurs when antioxidant defense mechanisms fail to counterbalance reactive oxygen species (hydrogen peroxide, superoxide radicals, and hydroxyl radicals). Imbalances in the oxidative and antioxidant defense systems have been reported in SZ.[208, 209] Studies with biospecimens (autopsied brain, olfactory cells, CSF and blood) have indicated changes in glutathione (GSH), microsomal glutathione *S*-transferase 1 (MGST1), superoxide dismutase (SOD), and catalase.[209–214] A recent report indicates a significant reduction in CSF SOD-1 from recent onset SZ compared with matched controls, however, there was no difference in the level of SOD-1 in chronic SZ.[212] The most reproducible evidence may be a reduction of GSH in the blood. Because access to biospecimens from unmedicated first onset SZ and prodromal subjects have become more frequently available, the validation of peripheral signs of oxidative stress with such subjects is awaited.

Several studies have investigated 'brain' oxidative stress by directly measuring GSH in the brain of living SZ patients. Although the measurement of GSH via MRS is a promising approach, the data thus far are inconsistent.[208] An initial study found a 52% reduction in the GSH level in the medial prefrontal cortex of drug-free subjects with SZ.[215] Two subsequent studies, focusing on the anterior cingulate and the posterior medial frontal cortex, did not find a difference in the GSH level in medicated subjects with SZ.[216, 217] Finally, another study reported an increase in GSH levels in the medial temporal lobe of subjects with first episode psychosis.[218]

In summary, many clinical and epidemiological studies have supported immunological deficits in SZ, which are mediated, at least in part, by microglia. Such immuno-inflammatory changes are interconnected with deficits in antioxidant cascades and may affect neural connectivity.

Endocrine system

Although there are contradictory reports, multiple types of studies have suggested that the hypothalamic-pituitary-adrenal (HPA) axis is affected in first episode psychosis and SZ.[219] An MRI study comparing first episode and chronic SZ subjects to controls found increased and reduced pituitary volumes in first episode and chronic SZ, respectively.[220] Additional MRI studies support the finding of an increased pituitary volume in first episode SZ, as well as, an increased pituitary volume in subjects at high risk for developing psychosis (i.e., at-risk mental state).[221, 222] However, other studies have not found a change in pituitary volume in first episode or chronic SZ.[223–225] A smaller pituitary volume in unmedicated SZ has also been reported.[226] Findings from studies analyzing the volume of the hypothalamus in SZ are inconsistent and report both an increased volume as well as no change.[227–230]

Consistent with some brain imaging reports, a fraction of unmedicated, medicated, or chronic SZ patients have displayed elevated baseline adrenocorticotropic hormone (ACTH) and cortisol levels.[231–234] ACTH is secreted from the anterior pituitary gland in response to the hypothalamus releasing corticotropin-releasing hormone (CRH). Higher mean ACTH and cortisol levels have also been shown in first episode unmedicated SZ.[219, 235] Furthermore, the North American prodrome longitudinal study reported higher baseline cortisol levels in prodromal (i.e., at-risk mental state) subjects and found that baseline cortisol levels correlated with symptom progression: prodromal subjects who transitioned to psychotic level symptoms had significantly higher baseline cortisol levels compared to controls and prodromal subjects in remission.[236] However, other studies have not found elevated baseline cortisol levels in first episode psychosis and first episode SZ.[219, 237] Interestingly, antipsychotics (risperidone, haloperidol, olanzapine or flupenthixol) have been shown to significantly reduce cortisol levels.[168, 238] Consistent with some peripheral measures of ACTH, a postmortem analysis of pituitary glands found that the level of proACTH was elevated in pituitaries from subjects with SZ compared to controls.[239] Postmortem studies have also suggested a reduction in glucocorticoid receptors: glucocorticoid receptor mRNA expression was reduced in the basolateral/lateral nuclei of the amygdala, the frontal and temporal cortex and hippocampus.[240, 241] Overall, the data are

promising, however, additional studies assessing the relation of ACTH and cortisol with other biomarkers will improve our understanding of the role of the HPA axis in SZ.

Psychosis can occur as a result of elevated endogenous steroid levels (e.g., Cushing syndrome) or with exposure to exogenous steroids.[242] Steroid psychosis, a potential side effect of exogenous glucocorticoids, can present with sensory flooding, delusions, depression, and auditory and visual hallucinations.[243] Delusions and hallucinations, primarily auditory, can also occur in subjects with psychotic depression; some studies have shown that glucocorticoid antagonists, such as mifepristone, can have therapeutic effects on psychotic depression.[244, 245] Given that the effects of glucocorticoids on the brain include synaptic regulation and epigenetic control of key molecules for dopamine neurons (e.g., tyrosine hydroxylase),[246, 247] involvement of the HPA axis in SZ and psychosis is an important subject that should be studied to a greater extent. However, it may be important to sub-classify these conditions to increase the homogeneity of the study subjects.

SZ typically manifests later in life in females than men. This difference in age at onset might be partially attributed to the protective effect of estrogen. Estradiol has been found to be lower in subjects with SZ, males and females, compared to controls.[248, 249] Furthermore, an association study found that a polymorphism in an intron of the estrogen receptor alpha gene occurred more frequently in subjects with SZ and was related to lower mRNA levels in the prefrontal cortex.[250] The molecular targets of estrogen are diverse, but animal studies have shown that it can modulate the dopaminergic, serotonergic and glutamatergic pathways: for example, estrogen has been shown to alter D2R density, decrease monoamine oxidase activity, increase tryptophan hydroxylase activity, downregulate $5HT_{1A}$ receptors, upregulate $5HT_{2A}$ receptors, and alter NMDA receptor density.[251–253]

Taken together, hormonal measurements and studies with patient tissue suggest that the endocrine system is altered in SZ.

Metabolic cascades

Metabolic disturbances are highly prevalent in SZ patients. Obesity and diabetes are twice as common in SZ compared to the general population.[254, 255] These disturbances create an increased metabolic load, eventually leading to cardiovascular issues and other physical conditions that possibly account for the higher mortality rate and shorter life span in SZ.[256] It has also been shown that diabetic SZ patients have worse overall cognitive performance compared to SZ patients without diabetes mellitus. Furthermore, patients with untreated diabetes mellitus showed poorer overall cognitive performance compared to SZ patients without diabetes mellitus.[257] Major metabolic disturbance in SZ patients is likely elicited by neuroleptic medication,[258–260] however, first onset SZ patients, including unmedicated patients, also show higher fasting blood insulin levels, insulin resistance, and impaired glucose tolerance.[261–264] While lifestyle and dietary habits may contribute to this difference, it is also likely that an inherent metabolic dysregulation underlies the pathology of SZ. Although this concept may not have a scientific consensus yet, we discuss observed changes in several peripheral factors and their effects on the brain in SZ.

Studies using blood samples indicate functional deficits in insulin signaling in SZ,[261–264] while a separate study reported elevated glucose levels in the CSF, but not in serum, of first onset drug naïve SZ subjects.[265] In unmedicated SZ subjects, PET studies have shown that glucose metabolism is reduced in several brain areas, in particular the frontal cortex.[266, 267] A recent review has summarized microarray studies and found that several genes associated with metabolic cascades are differentially expressed in postmortem brains from SZ patients.[268] Postmortem studies have also found disturbances in the insulin-Akt pathway, a signaling pathway linked with several types of cognitive deficits.[269–272] Although data derived from postmortem brain tissue may be confounded by medication-induced metabolic changes, further analysis is warranted.[273] Some genetic studies have provided suggestive support for the involvement of glucose metabolism cascades in the genetic risk of SZ.[274, 275] The gene coding for Akt is also a putative risk factor for SZ, at least in part disturbing the signaling cascade involving the insulin-Akt pathway.[276]

In addition to glucose and insulin, other metabolic mediators (e.g., leptin and ghrelin) may play key roles in SZ pathology. Weight gain is associated with increased leptin and leptin resistance.[277, 278] Leptin inhibits the effects of cortisol signaling in the hypothalamus and predisposes to mental manifestations, in particular depression.[279, 280] The ghrelin receptor GHS-R1a forms functional heterodimers with the D2R.[281] Antipsychotics have differential effects on these two molecules: fasting morning leptin levels are increased by atypical antipsychotics (e.g., olanzapine and clozapine) but are unaffected by conventional antipsychotics (e.g., haloperidol).[282] On the other hand, fasting morning ghrelin levels are decreased in the first 2 weeks after atypical antipsychotic treatment but increase in the long-term.[282] Neurochemical studies suggest lipid metabolism may also be altered in SZ. Both chronic and unmedicated first onset SZ have significantly decreased apolipoprotein A1 (apoA1) in the brain, liver, red blood cells, sera, and CSF.[283, 284] However, another group found that apoA1 was increased in the CSF of medicated first onset SZ.[285] Vitamin D deficiency is commonly observed in SZ patients and is associated with clinical features of the disease.[286] Vitamin D deficiency is also observed in first-episode psychosis patients and developmental vitamin D deficiency has been shown to contribute to the risk of SZ, suggesting that neurodevelopment may be affected by vitamin D deficiency.[287, 288]

Pharmacogenetic studies, primarily focusing on olanzapine and clozapine, have identified SNP in several genes associated with antipsychotic-induced weight gain in SZ patients.[289] SNP within the genes encoding the serotonin 2C receptor (5-HT2CR), melanocortin 4 receptor (MC4R), and leptin are those with the most consistently strong evidence, implicating serotonergic and feeding-regulation systems in antipsychotic-induced weight gain.[290–293] Although these molecules have been identified as genetic modifiers of adverse metabolic effects in SZ patients, elicited by medication, the question remains whether the cascades involving these factors play roles in the intrinsic abnormalities of both metabolic and mental dysfunction found in SZ patients.

In summary, metabolic cascades are altered in SZ patients, which include changes in the levels of glucose, insulin, leptin, ghrelin, and apoA1. Antipsychotics affect these metabolic cascades, yet there is also evidence that some metabolic disturbances precede antipsychotic exposure. Genetic factors are known to modulate these changes, but it remains elusive

whether and how a genetic predisposition to metabolic disturbance plays a primary role in SZ pathology.

Modeling and future perspectives: towards understanding integrative systems

For this review article we chose to organize the molecular targets of SZ by biological system. However, there is obviously tremendous crosstalk among these biological systems (**Figure 2**). Oxidative stress, inflammation, the HPA axis, and metabolic signaling are tightly interconnected as homeostatic and stress cascades.[294_296] Neural networks, the foundation of brain function and dysfunction, are finely regulated by neurotransmitters and white matter-associated connectivity (**Figure 3**): recently, the significance of neuron-glia interactions in these fine regulations has been particularly recognized.[297] As described above, deviations in homeostatic and stress cascades affect key elements of neuronal circuitry, such as synaptic maintenance, interneuron functions, and myelination. Thus, the molecular changes described in the neurotransmission and white matter-associated connectivity subsections may be outcomes of the molecular disturbances in stress signaling described in the second half of this article. Alternately, disturbances in neural connectivity may also activate stress signaling, which in turn further alters the connectivity. While integration of evidence across biological systems remains elusive, this promising working hypothesis suggests a potential framework through which they could be linked.

Although human studies with patients and matched controls are essential to identify molecular substrates of SZ, there are many barriers to extending an in-depth understanding of the disease mechanisms exclusively through human studies. For example, the current spatial resolution of human brain imaging at both structural and functional levels cannot depict direct entities such as synapses and NoR where we can directly observe the functional outcome of the molecular substrates described above. In addition, while it is very important to grasp the overall molecular changes in the disease trajectory over 20 years, longitudinal human studies on this time scale are challenging and time-consuming.

Given the limitations of human studies, many people have supported the use of animal models. One of the major historical debates in regard to SZ animal models is whether we can reconstruct models for ‘human’ disease. It is impossible to recapitulate the human condition *per se* in animals. However, by targeting a particular system(s) and/or clinical endophenotype(s) in SZ, animal models can become very useful for understanding biological mechanisms. In addition to analyzing cross-sectional phenotypes in adult animals, it is even more crucial to analyze the disease trajectory from early development to disease onset in preclinical studies.[4] Given the diversity of SZ molecular substrates, ranging from homeostatic and stress cascades to neural circuitry components, a major working question in the field of animal models is whether and how stress cascades may affect neural connectivity along a neurodevelopmental trajectory leading to SZ.

The selection of animal models and their validity in SZ research is very important to consider. After the recent introduction of new genetic manipulation technologies,[298_300] simultaneous modulation of multiple genes is now technically feasible, but only a few

studies have been successful thus far. Thus, instead of reconstructing genetic validity from multiple common variants with mild biological impact on the pathology, we propose that models stemming from the modulation of rare genetic variants with a stronger biological impact (e.g., chromosomal micro-deletion or duplication, and genetic modulation identified from cytogenetic approaches) may be more widely used in SZ research.[4, 18, 301] To test the functional outcome of multiple common variants for SZ, human stem cell biology can be used as a complementary approach to animal models.[302] For example, CRISPR/Cas9 genetic manipulation of induced pluripotent stem cells (iPSCs) originally derived from patients carrying multiple disease-associated common genetic variants and subsequently differentiated into neurons and glia can be used to assess the contribution of each individual genetic variant.

Gene environment interaction plays a key role in the etiology of SZ;[165, 200–202] therefore, consideration of proper environmental stressors, possibly in combination with a genetic factor(s), is crucial when building animal models. Some successful examples include combining adolescent social isolation or prenatal immune activation with a genetic risk factor.[202, 247, 303–305] Although an advantage of animal models includes their potential to trace the possible developmental trajectory to full onset of disease,[306–308] it is also useful to build models by administering relevant drugs to recapitulate specific pathophysiologies and phenotypes associated with SZ.

Taken together, several animal models have been proposed to understand the biology relevant to SZ. Regardless of whether these animal models are genetic or non-genetic, many of them are generated by perturbing biological processes of neurotransmission, white matter-associated connectivity, inflammatory and oxidative stress, or endocrinology/metabolisms (see in **Table 4** where representative models are introduced).[304, 309–370] Most of the models were studied from the viewpoints of neurotransmission, neuropsychopharmacology, and behavioral neuroscience.[371, 372] However, recent studies have revisited these models beyond these classic paradigms and also elucidated deficits in white matter and stress-associated cascades, such as inflammation, oxidative stress, and the HPA axis.[323, 324, 328, 333, 359, 366, 373] Furthermore, models in which stress-associated cascades are primarily perturbed have also displayed abnormalities in neurotransmission and behavior: for example, mice with glutathione deficiency show impairments in parvalbumin-positive interneurons, myelination, and behavior.[340, 341, 343, 344, 374, 375] Several animal models have been designed to test the effect of stress cascades on neurodevelopment, including both prenatal and juvenile models of stress and immune activation.[322, 376, 377] These developmental stressors have been shown to affect neurotransmission, myelination, and even metabolism. The integrative biological concept of “disturbed homeostatic signaling to connectivity deficits” can be tested, at least in part, with such animal models.

In summary, this review highlights the molecular substrates discovered through studies with SZ patients that are implicated in SZ pathophysiology. We sub-classify the substrates by system, focusing on neurotransmission, targets in white matter-associated connectivity, immune/inflammatory and oxidative stress-related substrates, and molecules in endocrine and metabolic cascades, taking special note where there is convergence with genetic data. Crosstalk among these systems may be important in understanding disease progression and

animal models should prove important in charting the developmental progression and interaction of these substrates. As a working hypothesis, we propose the molecular changes in neurotransmission and white matter-associated connectivity may be outcomes of molecular disturbances in stress signaling. Alternately, disturbances in neural connectivity may also activate stress signaling, in turn further altering the connectivity. We optimistically propose that the identified molecular markers, together with further continuous efforts, will aid in discovering biomarkers that may help in the diagnosis, treatment, or early intervention of SZ.

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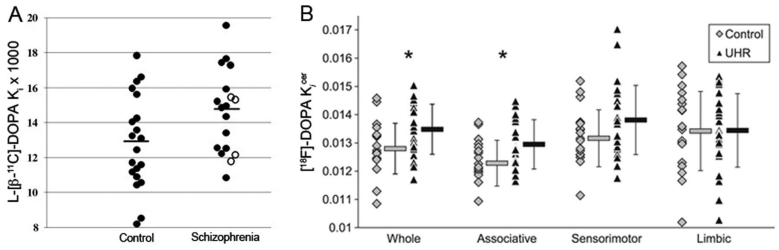

Figure 1.

L-[β-^{11}C]-DOPA and [^{18}F]-DOPA positron emission tomography (PET) imaging. (A) Individual k_i values in the left caudate nucleus. Horizontal lines represent mean values of the groups. In the schizophrenia group, closed circles indicate antipsychotic drug-naïve patients while open circles indicate drug-free patients. There was a significant group difference in k_i values for the left caudate nucleus. (reproduced with permission from Nozaki *et al.*[33]) (B) Individual and group mean±SD [^{18}F]-DOPA uptake (k_i^{cer}) (min–1) values in the whole, associative, sensorimotor, and limbic striatum. Data in the healthy control group are represented by grey diamonds and data in the ultra-high risk group (UHR) by black triangles. k_i^{cer} values were significantly higher in the UHR than control group in the whole and associative striatum (*p<.05), indicating elevated dopamine synthesis capacity. (reproduced with permission from Egerton *et al.*[34])

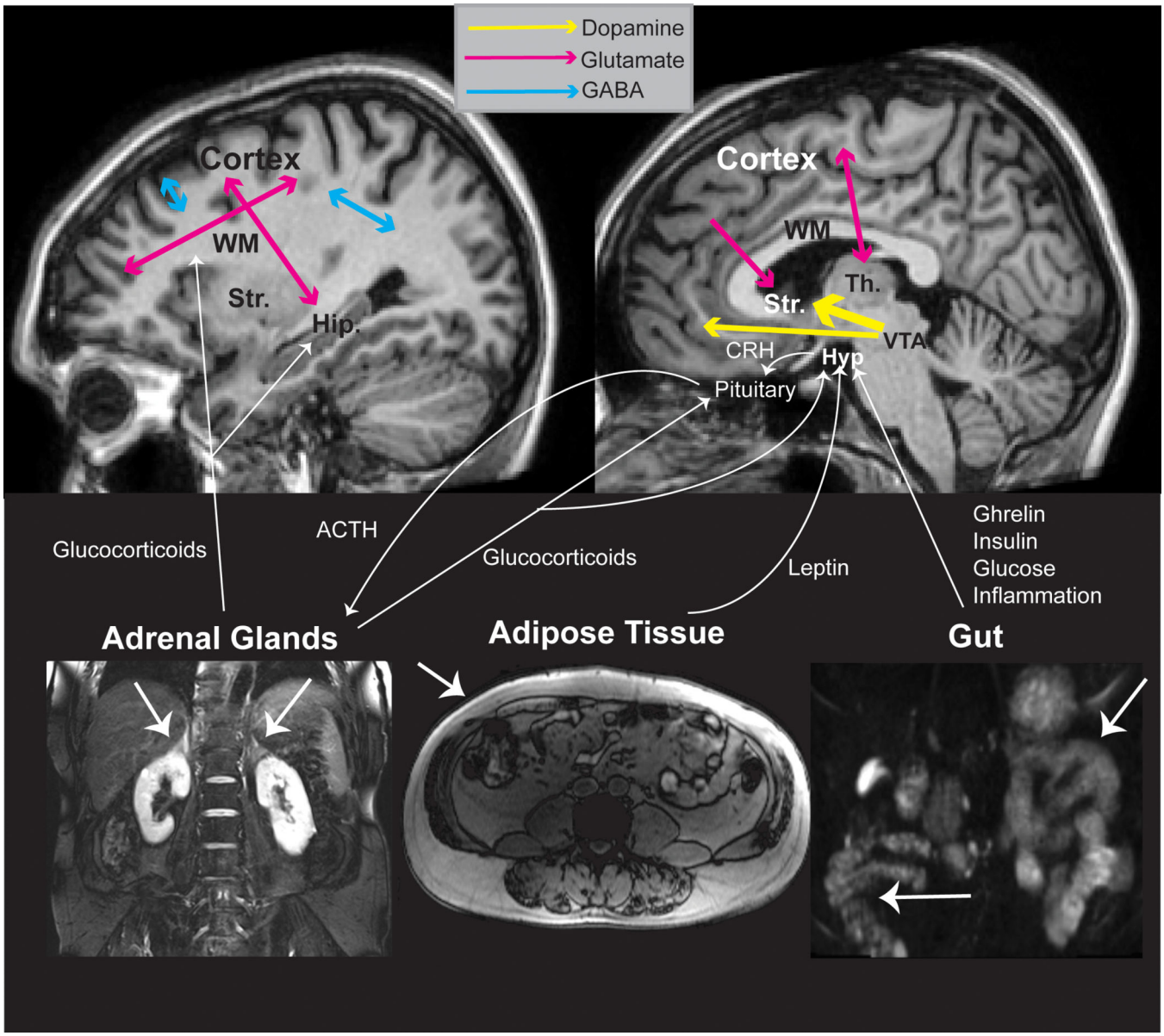

Figure 2.

Molecular crosstalk between the biological systems in schizophrenia. Mesolimbic dopaminergic projections (yellow) between the ventral tegmental area (VTA) and striatum (Str.) are significantly increased. The dopaminergic mesocortical pathway is also affected. Multiple glutamatergic (pink) pathways are affected. GABAergic (blue) pathways are also affected. Glucocorticoids released from the adrenal glands affect numerous brain targets including the cortex, hippocampus (Hip.), hypothalamus (Hyp) and pituitary gland. Molecular substrates of adipose tissue and the gut interact with the hypothalamic-pituitary-adrenal axis via the hypothalamus. Th, thalamus; WM, white matter; CRH, corticotropin releasing hormone; ACTH, adrenocorticotropic hormone.

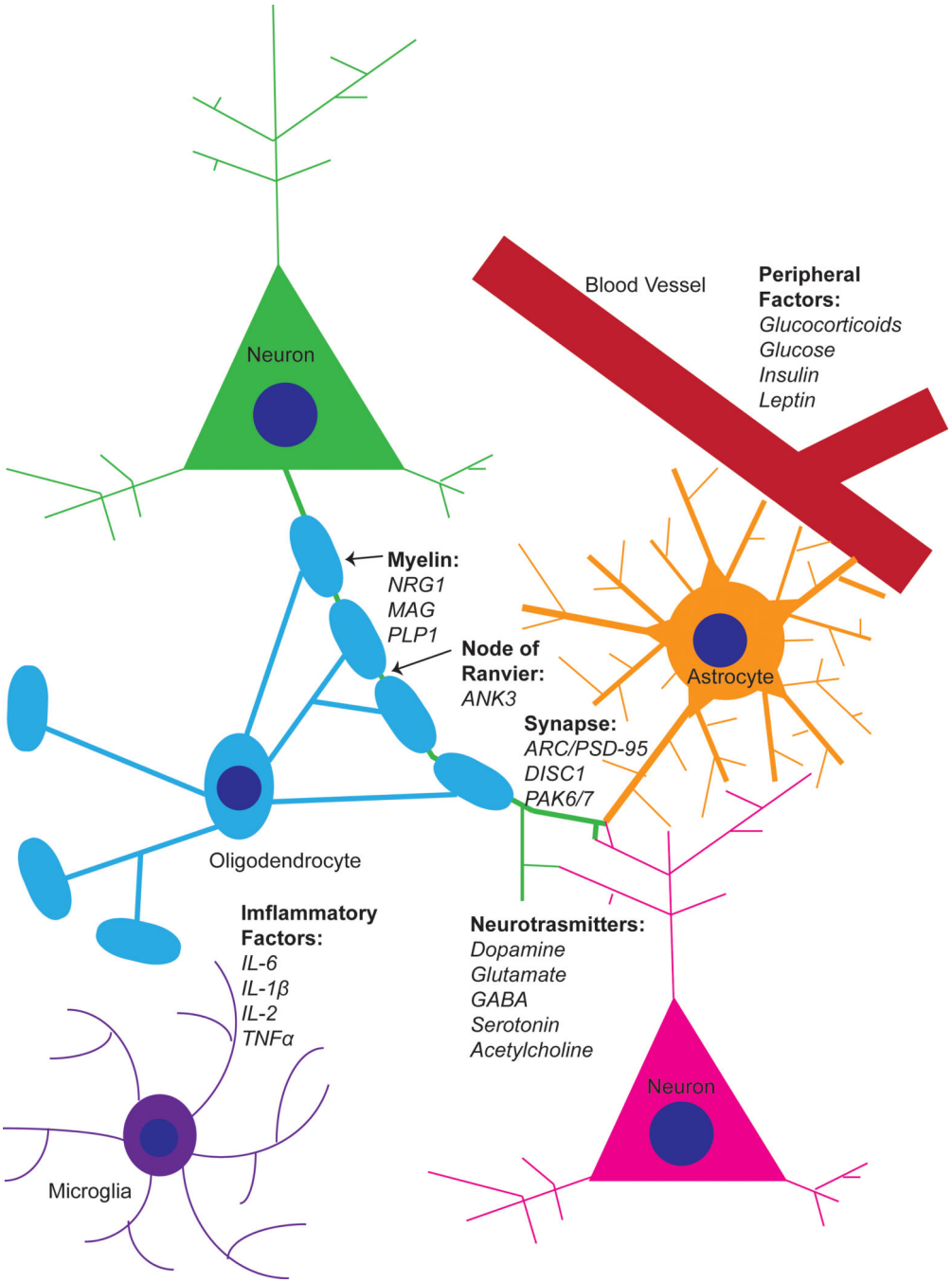

Figure 3.

Inter-cellular interactions of some important molecular substrates affected in schizophrenia. A glutamatergic synapse with contact from a nearby astrocyte represents changes in neuronal signaling. Changes in myelination and formation of nodes of Ranvier along the axon are represented by a single oligodendrocyte. Peripheral factors enter the brain through the blood-brain barrier formed between blood vessels and astrocyte end feet. Inflammatory factors are released by microglia and astrocytes. NRG1, neuregulin-1; MAG, myelin-associated glycoprotein; PLP1, proteolipid protein 1; ANK3, ankyrin-3; ARC, activity-

regulated cytoskeleton-associated protein; PSD-95, postsynaptic density protein 95; DISC1, disrupted in schizophrenia 1; PAK6, p21 protein-activated kinase 6; PAK7, p21 protein-activated kinase 7.

Table 1

Molecular and Cellular[1] Substrates of Schizophrenia, Organized by System

Neurotransmission
Dopamine
D2 Receptor
D1 Receptor
Homovanillic acid
Tyrosine hydroxylase
5HT2A receptor
Glutamate
NMDA Receptor
Glutamate receptor, ionotropic, NMDAR 2A (GRIN2A)
Glutamate receptor, ionotropic, AMPA 1 (GRIA1)
Activity-regulated cytoskeleton-associated protein (ARC) signaling complex
Glutamine
GABA
GAD67
Parvalbumin (PV)
Kv3.1
KCNS3
Somatostatin
Cholecystokinin
Nicotinic acetylcholine receptors (nAChRs)
Potassium channel tetramerization domain containing 13 (KCTD13)
Contactin 4 (CNTN4)
P21 protein-activated kinase 6 (PAK6)
Neuroligin 4, X-linked (NLGN4X)
Disrupted in schizophrenia 1 (DISCI)
P21 protein-activated kinase 7 (PAK7)
N-thylmaleimide sensitive factor (NSF)
Synapsin II (SYN2)
Dendritic Spines
White matter-associated connectivity
Proteolipid protein 1 (PLP1)
Myelin-associated glycoprotein (MAG)
Myelin oligodendrocyte glycoprotein (MOG)
oligodendrocyte transcription factor 2 (OLIG2)
Neuregulin-1 (NRG1)
Receptor tyrosine-protein kinase erbB4 (ERBB4)
reticulon 4 (RTN4/NOGO)
Cyclic-nucleotide-3′-phosphodiesterase (CNP1)
Akyrin-3 (ANK3)

Zinc finger binding protein 804A (ZNF804A)

L-type voltage-dependent calcium channel CAV1.2 (CACNA1C)

MicroRNA-137 (MIR137)

Disrupted in schizophrenia 1 (DISC1)

Myelin

Node of Ranvier

Oligodendrocytes

Immune/inflammatory response and oxidative stress

IL-1β

IL-2

IL-6

TNF-α

soluble IL-2 receptor

IL-12

IFN-γ

IL-8

Translocator protein (TSPO)

Major histocompability complex (MHC)

Glutathione (GSH)

Microsomal glutathione S -transferase 1 (MGST1)

Superoxide dismutase (SOD)

Catalase

Inflammation

Oxidative stress

Microglia

T Cells

Macrophages

Endocrine system

Adrenocorticotropic hormone (ACTH); proACTH

Corticosterone; Cortisol

Glucocorticoids; Glucocorticoid receptors

Estradiol

Hypothalamic-pituitary-adrenal (HPA) axis

Metabolic cascades

Glucose

Insulin; proinsulin

Akt

Leptin

Ghrelin

Apolipoprotein1

Melanocortin 4 receptor

5HT2C receptor

[1] Cellular substrates appear in italics

Table 2

Summary of Clinical Evidence by System

System	Brain Imaging	Neurochemical	Postmortem	Genetic	Clinicopharmacological
Neurotransmission	+++	+++	++	+++	++
White matter-associated connectivity	+++	+	++	++	++
Immune/Inflammatory response and oxidative stress	+	++	+	++	+
Endocrine system	++	+++	++	+/−	++
Metabolic cascades	++	++	++	++	++

+++, strong evidence; ++ sufficient evidence; + additional evidence needed; +/− some evidence

Table 3

Summary of glutamate and GABA ^{1}H MRS studies

Glutamatergic level (subject vs control)	Brain Region	Disease stage	Antipsychotic Status	References
↑	MPFC, ACC	E, C	-	Poels *et al.*[64]
↓	MPFC, ACC			Marsman et al.[65]
		ARMS	-	
		E	-	
		E	+	
		C	NR, +	
-	MPFC, ACC	C	+	Poels *et al.*[64]
-	DLPFC	E, C	-, +	Poels *et al.*[64]
-	Hippocampus			Poels *et al.*[64], Marsman et al.[65]
		ARMS	-	
		C	NR	
		E, C	+	
↓	Hippocampus	NR	-, +	Stan *et al.*[69]
↓	Thalamus	ARMS	-, +	Poels *et al.*[64]
↑	Thalamus	E	-	Poels *et al.*[64]
-	Thalamus			Poels *et al.*[64], Marsman et al.[65]
		ARMS	-	
		E	-	
		C	+	

GABA level (subject vs control)	Brain Region	Disease stage	Antipsychotic Status	References
-	Frontal Lobe	E	+	Goto *et al.*[81]
↑	ACC	C	+	Ongur *et al.*[84]
-	ACC	C	+	Tayoshi *et al.*[82]
↓	ACC	C, older age	+	Rowland *et al.*[85]
↑	MPFC	C	-	Kegeles *et al.*[66]
-	MPFC	C	+	Kegeles *et al.*[66]
-	DLPFC	C	-, +	Kegeles *et al.*[66]
↓	Basal Ganglia	E	+	Goto *et al.*[81]
-	Basal Ganglia	C	+	Tayoshi *et al.*[82]
↑	Parieto-Occipital Cortex	C	+	Ongur *et al.*[84]
↓	Visual Cortex	E, C	-, +	Yoon *et al.*[83]

Abbreviations: MPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; E, first-episode or early; C, chronic; ARMS, at-risk mental state; -, unmedicated; +, medicated; NR, not reported

Table 4

Animal models relevant to schizophrenia classified by molecular system

	Molecular Substrates Affected					
Target System	***Animal Model*[1]**	***Neurotransmission*[2]**	***White Matter*[3]**	***Immune/Oxidative Stress*[4]**	***Endocrine/Metabolic*[5]**	***Misc.***
NT	NMDAR antagonists (PCP, MK-801, ketamine)	Glu, GABA, DA, 5HT, spines	WM tracts	cytokines, nitrosative/oxidative stress	HPA, glucose/insulin	BDNF
NT	NR1 haplomorph	Glu, DA				
White Matter	NRG1 and ErbB4 knockout	Glu, GABA, DA, 5HT, spines,	WM tracts, oligodendrocytes		HPA	
Immune/Oxidative Stress	Maternal immune activation	Glu, GABA, DA, 5HT, spines,	WM tracts	cytokines, oxidative stress	HPA, glucose/insulin	
Immune/Oxidative Stress	Short-term cuprizone	Glu, DA,	WM tracts	cytokines		
Immune/Oxidative Stress	Genetic glutathione depletion (GCLM knockout)	Glu, GABA, DA	WM tracts, oligodendrocytes	GSH		
Endocrine/Metabolic	Vitamin D deficiency	Glu, GABA, DA,		redox		
Endocrine/Metabolic	AKT1 knockout	Spines				
Misc.	Social isolation	Glu, GABA, DA, 5HT, CB1, spines	oligodendrocytes	cytokines	HPA, metabolic	BDNF
Misc.	Neonatal ventral hippocampal lesion	Glu, GABA, DA, ACh, spines,	WM tracts	oxidative stress	HPA, glucose/insulin	
Misc.	MAM	Glu, GABA, DA, spines	WM tracts	GSH	HPA	BDNF, NGF

Abbreviations: NT, neurotransmission; PCP, phencyclidine; Glu, glutamate; GABA, γ-aminobutyric acid; DA, Dopamine; 5HT, serotonin; WM, white matter; HPA, hypothalamus-pituitary-adrenal axis; BDNF, brain-derived neurotrophic factor; NR1, NMDA receptor subunit NR1; NRG1, neuregulin-1; ErbB4, receptor tyrosine kinase erbB4; GCLM, glutamate-cysteine ligase modulatory subunit; GSH, glutathione; AKT1, RAC-alpha serine/threonine-protein kinase; CB1, cannabinoid receptor type 1; ACh, Acetylcholine; MAM, methylazoxymethanol; NGF, nerve

[1] A selection of representative genetic and non-genetic animal models targeting particular systems discussed in the text are listed. These animal models have already been validated from behavioral viewpoints.

[2] Molecular substrates affecting neurotransmission are grouped into glutamate (Glu), GABA, dopamine (DA), serotonin (5HT), acetylcholine (Ach), and dendritic spine (spines) systems.

[3] White matter is divided between tissue level analysis (WM tracts) and cellular-level studies (oligodendrocytes).

[4] Molecular substrates affecting inflammation (cytokines) and oxidative stress cascades (oxidative stress) are grouped. We make special note of redox and glutathione abnormalities (GSH).

[5] Molecular substrates affecting the hypothalamic-pituitary-adrenal axis (HPA) and glucose/insulin pathways (glucose/insulin) are broadly grouped. Broader metabolic abnormalities including lipid metabolism are labeled “metabolic.”