REVIEW

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Dysfunctional Brain Networks and Genetic Risk for Schizophrenia: Specific Neurotransmitter Systems

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SUMMARY

Multiple neurotransmitter circuits are disturbed in schizophrenia, and the dopamine hypothesis of schizophrenia prevails as the hypothesis with most empirical support. On the other hand, schizophrenia is highly heritable with a pattern consistent with both common and rare allelic variants and gene × environment interaction. Advances in the field of neuroimaging have expanded our knowledge of intermediate phenotypes, the neurobiological processes that convey the risk from the genes to the complex phenotype. In this article, we review the recent and continuously accumulating evidence from *in vivo* imaging studies aiming at characterizing neurochemical intermediate phenotypes of schizophrenia. Dopaminergic alterations in schizophrenia are shared by individuals at genetic risk who do not express the illness, suggesting a "dopamine hypothesis of schizophrenia vulnerability." This hypothesis has the potential to help us better understand the dopaminergic dysfunction in the context of the complex pathophysiological process leading to schizophrenia. In the future, neurotransmitter imaging studies should investigate the gene × environment interaction in schizophrenia, and try to identify neurobiological correlates of heightened sensitivity to environmental stressors (e.g., cannabis, childhood trauma, and other psychosocial stress) in genetically vulnerable individuals.

Introduction

Schizophrenia is a severe and debilitating mental illness that affects approximately 1% of the population throughout the world. It is a multifactorial disease with strong genetic contributions along with prominent gene × environment interactions [1]. Schizophrenia manifests as a disease with subtle structural and functional abnormalities of various brain structures, such as the striatum, hippocampus, and prefrontal cortex [2,3]. At the molecular level, multiple neurotransmitter systems appear to be abnormal. Dopamine is traditionally associated with schizophrenia, owing to the propensity of dopamine D_2 receptor antagonists to alleviate and dopamine-releasing drugs to exacerbate positive symptoms of schizophrenia [4,5]. The dopamine hypothesis of schizophrenia suggests that subcortical dopamine overactivity is a common feature brought on by multiple contributing factors from genes and environment and by dysfunctions of many brain circuits [4,6]. Also, the cortical dopamine neurotransmission is suggested to be dysfunctional [7]. Dopamine abnormalities are tightly interwoven with glutamate and GABA deficits that are hypothesized to play a role in schizophrenia [3,8].

Schizophrenia is highly heritable, as indicated by epidemiological studies [9,10]. However, schizophrenia is neither a purely genetic disorder, nor caused by a single gene. Rather, it likely results from a combination of both rare and common genetic variants [11], environmental risk factors [12], and their interaction [1]. Research into intermediate phenotypes has become a popular strategy in the pursuit of identifying which factors convey the increased risk from the genes to the observed phenotype because intermediate phenotypes are more proximal to the underlying genes than complex clinical phenotypes. This strategy can be used to study the effects of previously identified genetic risk variants in the general population [13], or to study individuals who are at risk for developing the illness [14]. These studies have shown that risk variants for schizophrenia modulate neocortical and hippocampal structure, function, and connectivity in ways that resemble the pathophysiology of schizophrenia [13]—and that similar alterations are often found in individuals with genetic risk for schizophrenia but who do not express the illness [15–17]. The latter strategy is attractive since it allows the examination of inherited pathophysiology that is not confounded by antipsychotic medication or chronicity of illness.

The purpose of this review article is to summarize molecular imaging evidence for neurotransmitter abnormalities in individuals at genetic risk for schizophrenia. First, we briefly describe the most commonly used imaging strategies and discuss their potential. Next, we review the current literature on molecular imaging studies in schizophrenia, and discuss their consistency and implications for genetic studies. We then turn to actual evidence from imaging studies in high risk populations that target neurotransmitter systems relevant for schizophrenia. Finally, we attempt to form a synthesis of the emergent imaging data and suggest future directions.

Overview of Molecular Imaging Techniques

Molecular imaging techniques such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are based on the use of short-lived radioactive isotopes attached to a molecule of interest. These techniques have unsurpassed sensitivity and specificity to measure different proteins in the human body. To quantify receptor binding, the principles of *in vitro* receptor binding techniques are applied to the *in vivo* situation—with obvious limitations. For example, radioligands are typically given at very small doses, or "tracer" doses, which are assumed to occupy only a minimal proportion of the target molecules. This technique of using one small radiotracer concentration cannot measure receptor density and affinity separately—only their product, which is often referred to as the binding potential [18]. These imaging techniques are typically used to measure the availability of the target (e.g., receptor, transporter, or enzyme) in a baseline condition, and the result is inferred to reflect the density of the target in brain tissue. However, another technique is based on the principle that endogenous neurotransmitters compete with the radioligand in binding to the target; therefore, changes in synaptic neurotransmitter concentrations can be estimated by scanning the same subject before and after a pharmacological challenge. For example, binding of the dopamine D_2 receptor antagonist radioligands [^{11}C]raclopride and [^{123}I]IBZM has been shown to be sensitive to increases and decreases in endogenous dopamine [19], although factors other than competitive inhibition are likely to be involved [20]. These "challenge study" paradigms are able to provide a more comprehensive view of the neurotransmitter abnormalities.

Neurotransmitter Abnormalities in Schizophrenia Revealed by Molecular Imaging

This selective and brief overview will focus on two neurotransmitter systems with most evidence from imaging studies: dopamine and serotonin.

Striatal presynaptic dopamine system is dysregulated in schizophrenia. First, majority of studies show increased presynaptic dopamine synthesis capacity in schizophrenia, as measured by the uptake of either fluorine-18 or carbon-11 labeled fluorodopa (FDOPA), a precursor for dopamine [21–28]. Second, patients with schizophrenia have elevated amphetamine-induced striatal dopamine release [29–32]. This abnormality is also seen in schizotypal personality disorder [33], suggesting genetic contributions, since this condition is genetically related to schizophrenia [34]. Finally, patients with schizophrenia have increased baseline occupancy of D_2 receptors by dopamine in the associative striatum [35,36]. Thus, robust evidence suggest that schizophrenia is associated with increased presynaptic dopamine function, as implicated by increased synthesis capacity and higher tonic (baseline) and phasic (stimulated) dopamine release. The two latter phenomena appear to be correlated with each other in drug-naïve patients [37]. This increased dopamine function does not reflect increased number of dopamine terminals, since the density of dopamine transporters is unaltered in drug-naïve schizophrenia [38], but rather dysregulated function per existing dopaminergic neuron.

Early studies on striatal dopamine D_2 receptors found increased binding in patients with schizophrenia [39–41], but later studies conducted with a different class of radioligands failed to confirm this finding [42,43]. Nevertheless, a meta-analysis of all published studies [29–31,35,36,39–54] suggests a small but significant increase in striatal D_2 receptors in schizophrenia (Figure 1) [55], which may be partially masked by increased endogenous dopamine at baseline [35]. Although early theories emphasized striatal D_2 receptors in schizophrenia, cortical and thalamic dopamine D_2 receptors have later been recognized as important [56]. Although results from imaging studies have not all been consistent, most studies have shown decreased extrastriatal D_2 receptor binding in schizophrenia, especially in the thalamus [53,54,57–62]. Low thalamic D_2 receptor density may contribute to sensory gating abnormalities in schizophrenia.

Cortical dopamine D_1 receptors are crucial for working memory performance, which is disturbed in schizophrenia [7]. Decreased cortical D_1 receptor binding was initially reported [49], but was later not confirmed using the same radioligand, [^{11}C]SCH 23390 [63]. In contrast, using another radioligand, [^{11}C]NNC-112, increased D_1 receptor binding was reported [64], and high D_1 receptor binding was correlated with poor cognitive performance. Potential reasons for this discrepancy include differential responses to chronic dopamine alterations of the two radioligands used [65], binding of these radioligands to cortical 5-HT_{2A} receptors [66], antipsychotic medication [67], and genetics [68]. Recently, decreased binding of both D_1 receptor tracers was demonstrated in chronic and medicated schizophrenia [69], suggesting that choice of radioligand may not be relevant.

Studies on the serotonin system are far less abundant. Serotonin transporter density is unaltered in schizophrenia [70], whereas the stimulatory 5-HT_{2A} receptors are decreased in drug-naïve patients [71]. Although the involvement of the inhibitory 5-HT_{1A} receptors was supported by postmortem studies showing increased densities [72], subsequent PET studies found both increased [73] and decreased [74] binding—and the latest study with the most rigorous quantification showed no change [75].

In summary, molecular imaging studies in humans have established that schizophrenia is associated with increased presynaptic dopamine synthesis capacity; increased baseline (tonic) synaptic concentrations of dopamine, which likely mask a small increase in postsynaptic dopamine D_2 receptor binding; increased amphetamine-induced (phasic) dopamine release; decreased

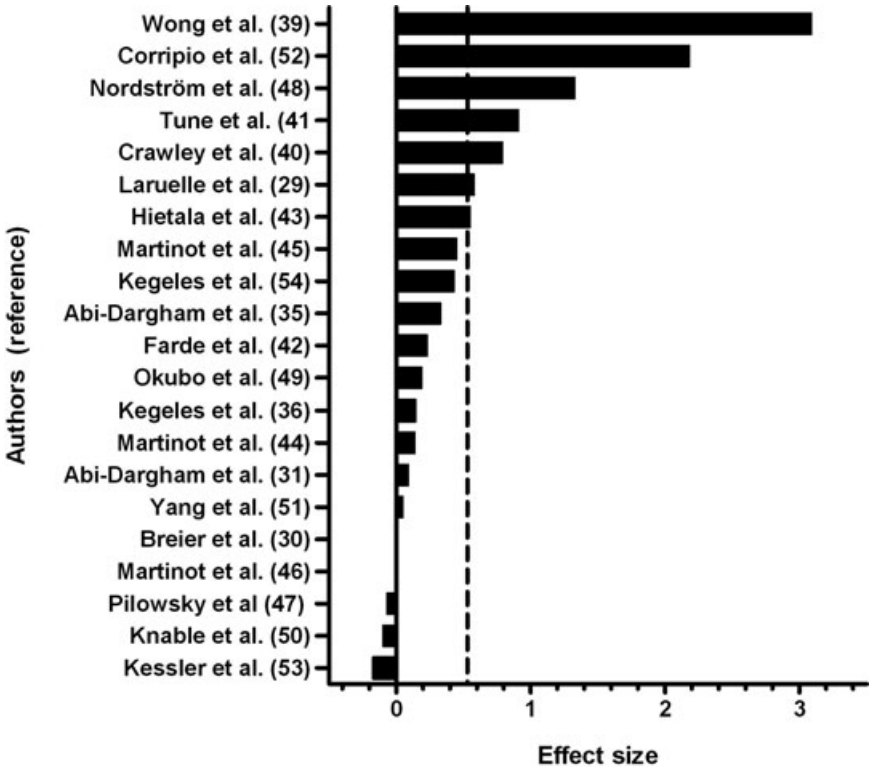

Figure 1 Meta-analysis of all published studies (N = 21) reporting striatal dopamine D_2 receptor binding in patients with schizophrenia (total of 294 patients) in comparisons with healthy subjects (total of 315 subjects). Effect size is calculated as the difference between the means of patients and controls, divided by the standard deviation in the control group. Dashed vertical line represents the average effect size 0.53 (standard deviation 0.80, 95% confidence interval 0.37–0.69), which corresponds to about 10% increase. The distribution of effect sizes is significantly different from that expected based on the null hypothesis of no overall differences between groups (one sample *t*-test, $P = 0.004$).

thalamic D_2 receptor binding; and possibly decreased cortical serotonin 5-HT_{2A} binding. However, brain imaging studies do not distinguish between state, trait or other phenomena, such as chronicity. Thus, it is possible that these abnormalities are associated with vulnerability to develop schizophrenia rather than the clinical phenotype of the illness; that is, are these abnormalities also present in the brains of individuals at risk of developing the illness.

Neurotransmitter Abnormalities and Genetic Risk for Schizophrenia

In general, *in vivo* molecular imaging studies looking at neurotransmitter abnormalities in individuals at genetic risk for schizophrenia are scarce, likely due to the challenging nature of both the imaging method and acquiring these individuals to participate in these studies. Nevertheless, the findings are beginning to show consistency in that some of the dopaminergic abnormalities are more likely due to vulnerability rather than expression of illness (Table 1). This section reviews the available literature from *in vivo* molecular imaging studies on two most commonly studied neurotransmitter systems: dopamine and serotonin.

To examine whether increased presynaptic dopamine function represents vulnerability or expression of schizophrenia, we recently examined [^{18}F]FDOPA uptake in 17 first-degree relatives of patients with schizophrenia (7 children and 10 siblings) in comparison with 17 healthy subjects [76]. These relatives were nonpsychotic as verified by structured psychiatric interviews and had mild (if any) and stable symptoms suggesting lack of any recent functional deterioration. The average age of these subjects was 34 years, meaning that they had predominantly passed the typical risk age for schizophrenia onset. We found about 20% higher striatal [^{18}F]FDOPA influx values in the first-degree relatives than in the healthy controls. This effect was more pronounced in the caudate than in the putamen. The effect size was roughly similar to that we previously found in patients with schizophrenia [21]. Curiously, one of the subjects who had two brothers and a father all diagnosed with schizophrenia had the highest [^{18}F]FDOPA influx values of all; he also presented with moderate symptoms. This finding suggests that increased striatal presynaptic dopamine function is a phenomenon shared by unaffected siblings of patients with schizophrenia, and is therefore likely related to vulnerability than clinical expression of the illness. Further support for this hypothesis comes from studies showing increased [^{18}F]FDOPA influx values in individuals at clinical risk

Table 1 Summary of evidence from molecular imaging studies of some of the neurotransmitter biomarkers in schizophrenia, high risk populations, and twins. See the text for details and references.

Imaging biomarker	Drug-naïve schizophrenia	Medicated schizophrenia	Genetic high risk	Clinical high risk	Heritability
Striatal D_2 receptor	↑	↑	↑	?	Yes
Thalamic D_2 receptor	↓	↓	?	?	Yes
Cortical D_1 receptor	↑	↓	↑	?	Yes
Presynaptic dopamine synthesis	↑	↑	↑	↑	?
Cortical 5-HT_{2A} receptor	↓	↓	?	↓	Yes

↑, higher than in healthy subjects; ↓, lower than in healthy subjects; ?, not enough data. Heritability refers to genetic contributions and is calculated as the intraclass correlation among identical twins.

for schizophrenia [4,77,78] and that [^{18}F]FDOPA uptake is only marginally affected by the clinical state of the patient [79]. Preferential involvement in our study of the caudate nucleus, which is part of the associative striatum as opposed to limbic or sensorimotor striatum [80], is supported by recent findings of increased tonic dopamine levels in schizophrenia specifically in this region [36]; together, these findings are compatible with the hypotheses linking prefrontal dysfunction with striatal hyperdopaminergia in schizophrenia.

To look more closely downstream in the dopamine signaling pathway, and also to acquire better sensitivity in terms of genetic loading, we recently studied striatal dopamine D_2 receptors as well as striatal and extrastriatal dopamine D_1 receptors in twins discordant for schizophrenia [81–83]. The twin paradigm has the advantage of gradually increasing the genetic similarity from about 50% in fraternal (i.e., nonidentical) twins to 100% in identical twins. Fraternal twins have about 10% risk and identical twins have about 50% risk of developing schizophrenia, which greatly exceeds the about 1% risk in the normal population. These middle-aged twins were recruited by cross-referencing the National Twin Registry in Finland [84] including all same-sex twin pairs born in Finland between 1940 and 1957 (N = 9692 pairs) with three national registers related to hospitalization, medications, and pensions [85]. This search identified 348 twin pairs with either or both cotwins having schizophrenia, and 9214 healthy twin pairs. We randomly sampled 11 discordant twin pairs (6 identical and 5 nonidentical) and 7 healthy twin (4 identical, 3 nonidentical) pairs for PET studies. D_2 and D_1 receptor binding was measured using PET and [^{11}C]raclopride and [^{11}C]SCH23390, respectively. We found that unaffected identical cotwins of patients with schizophrenia had higher D_2 receptor densities that did healthy twins, specifically in the caudate nucleus (effect size 0.75) (Figure 2) [82]. Increased caudate D_2 receptor density was negatively correlated with cognitive performance in the whole sample. Among identical healthy twins, we found high correlations in D_2 receptor densities specifically in the caudate, consistent with major genetic influences. However, two recent studies in unaffected relatives of patients with schizophrenia did not replicate increased caudate D_2 receptor binding at baseline [86,87], probably owing to only modest genetic loading and small sample sizes in these studies, given the large interindividual variability of D_2 measurements [88].

The pattern of results from dopamine D_1 receptor imaging in twins discordant for schizophrenia turned out to be more complex [81]. We found that unaffected identical cotwins had higher D_1 receptor densities in the prefrontal, temporal, and parietal cortex than did healthy twins (Figure 2), and that nonidentical cotwins were intermediate between identical cotwins and healthy twins in D_1 receptor binding. In these unaffected twins, high cortical D_1 receptor binding predicted poor spatial working memory performance. Surprisingly, patients with schizophrenia had much lower D_1 receptor binding in most regions in the brain than did their unaffected twins, and binding was negatively correlated with antipsychotic drug dose. Finally, cortical D_1 receptors were under tight genetic control among healthy identical twins as indicated by high intraclass correlations. Taken together, it seems that there are distinct vulnerability and disease-related contributions to cortical D_1 receptors: receptors are increased in individuals at genetic risk, but decreased in patients who express the illness, possibly due to chronic antipsychotic medications. This finding is consistent with a recent results published in abstract form by Abi-Dargham et al. [67] showing increased D_1 binding only in drug-naïve patients, but not in patients that had received prior antipsychotic drug treatment.

Unfortunately, there are no studies published to date on serotonergic markers in individuals at genetic risk for schizophrenia. However, there is preliminary evidence for abnormalities in these markers in people at clinical risk, and some of this evidence is compatible with theories on the role of these markers in the pathophysiology of schizophrenia. This evidence is for the involvement of the two major receptor subtypes: 5-HT_{2A} and 5-HT_{1A}.

As mentioned earlier, serotonin 5-HT_{2A} receptor is the major excitatory serotonin receptor in cortical pyramidal neurons [89] and is decreased in drug-naïve schizophrenia [71]. Hurlemann et al. [90] recently studied serotonin 5-HT_{2A} receptors with PET and [^{18}F]altanserin in 14 individuals at ultrahigh clinical risk for schizophrenia and in 21 healthy subjects. They found decreased 5-HT_{2A} receptor binding in individuals at risk for schizophrenia that was correlated with severity of the prodromal state. Binding was smallest in people who subsequently converted into first-episode psychosis. These findings suggest that decreased 5-HT_{2A} may predate the onset of schizophrenia [71], but they also clearly indicate that 5-HT_{2A} receptor expression is at least partly state-dependent in schizophrenia. Thus, the implications for the genetic mechanisms of schizophrenia remain unclear, but part of the decrease in 5-HT_{2A} receptors in the prodromal subjects may be attributable to genetic risk since some of the subjects had relatives with schizophrenia [90] and twin studies show that 5-HT_{2A} receptors are under strong genetic control [91].

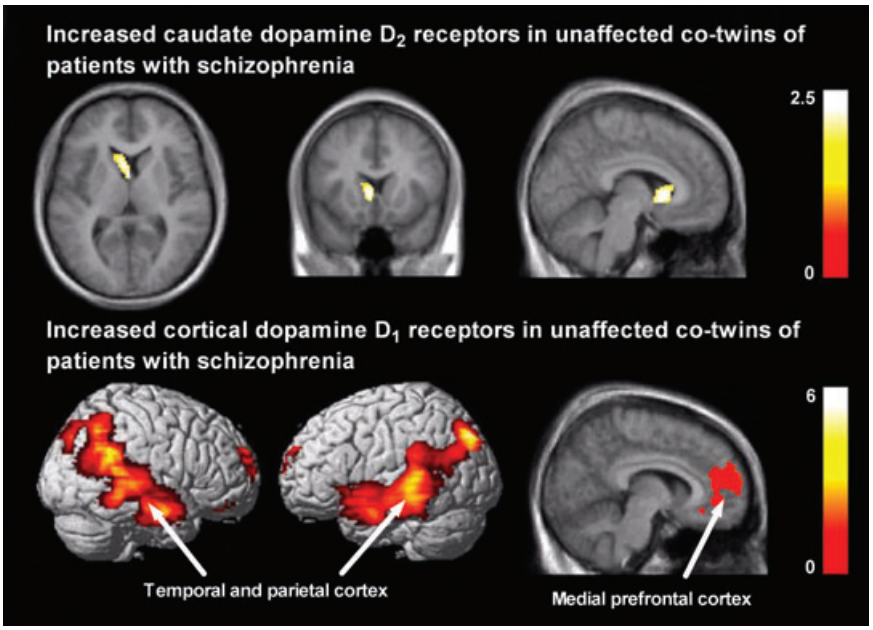

Figure 2 Increased caudate dopamine D_2 receptors (top row) and increased cortical dopamine D_1 receptors (bottom row) in unaffected cotwins of patients with schizophrenia. Results from a voxel-based receptor mapping analysis are visualized on a magnetic resonance imaging template. Color scales represent T-statistic values at voxel level. The right side of the brain appears on the right side of the images. See [82] and [81] for details.

The 5-HT_{1A} receptor, which occurs both pre- and postsynaptically and is the major inhibitory serotonin receptor, does not appear to be altered in patients with schizophrenia [75]. Despite widely studied in mood and anxiety disorders [92,93], there are no published imaging studies on the 5-HT_{1A} receptor in individuals at genetic risk for schizophrenia. However, we have recently observed decreased 5-HT_{1A} receptor binding in unaffected first-degree relatives of patients with schizophrenia compared with healthy subjects without such relatives (Huttunen, Hirvonen and Hietala, unpublished observations), using a similar study design as in our previous study on presynaptic dopamine function [76]. If confirmed, this preliminary finding suggests distinct vulnerability and disease-related contributions to 5-HT_{1A} receptors in schizophrenia, and encourages further examination of this biomarker in twin studies.

Discussion

Molecular imaging studies provide evidence that neurotransmitter abnormalities schizophrenia are shared by individuals at risk for developing the illness, most available evidence pointing toward alterations in the dopamine system. Studies both in individuals at genetic risk and in individuals at clinical risk point toward increased striatal presynaptic synthesis, increased striatal D_2 receptors, and increased cortical D_1 receptors are potential intermediate phenotypes that convey risk for schizophrenia.

Consistent with the modern version of the dopamine hypothesis of schizophrenia [4,5], it is likely that increased striatal D_2 receptor binding in unaffected cotwins of patients with schizophrenia is secondary to abnormal regulation of subcortical dopamine by cortical and hippocampal afferents, rather than being a primary pathological change. Reduced markers of pyramidal cell integrity in the prefrontal cortex predict increased dopamine D_2 receptors [94] and enhanced amphetamine-induced dopamine release [95] in patients with schizophrenia, while abnormal prefrontal activity is associated with increased presynaptic striatal dopamine in both patients [28] and individuals at clinical risk [77]. Glutamate NMDA receptor antagonism is associated with increased amphetamine-induced dopamine release in healthy humans [96], indicating the importance of glutamatergic control over subcortical dopamine. Regional specificity to the head of caudate is consistent with extensive connection of this striatal subregion with the prefrontal cortex [80]. Prefrontal pathology as a genetically mediated trait in schizophrenia is supported by findings of reduced gray matter volume [97] and deficits are frontally mediated cognitive functioning [98] in unaffected cotwins of patients with schizophrenia. Increased striatal D_2 receptors may be more readily detected in individuals at genetic risk, because they probably lack the higher synaptic dopamine concentration that occurs in schizophrenia [35,36] and that may occupy D_2 receptors [99]. This hypothesis predicts that striatal dopamine D_2 receptor may be a viable biomarker of vulnerability to schizophrenia. Whether this biomarker is useful for genetic association studies or clinical studies on early interventions remains to be seen.

If dopaminergic abnormalities in schizophrenia are genetically determined, which genes are involved? The gene for D_2 receptors has many polymorphisms, some of which affect receptor binding *in vivo*. A recent meta-analysis identified over-representation of the C allele of the C957T polymorphism in schizophrenia [100]

yet, this allele is associated with lower striatal D_2 receptor binding in healthy subjects [101]. Another variant is the cysteine allele of the Ser311Cys polymorphism, which is associated with schizophrenia [102] but does not affect binding *in vivo* [103]. Effects of variation in the gene coding for the D_1 receptor are less well understood [104]. On a larger scale, many schizophrenia risk genes, such as including dysbindin, neuregulin, and D-amino-acid oxidase and D-amino-acid oxidase activator, appear to converge onto dopaminergic or glutamatergic neurotransmission [3,6] and could thus be implicated in the dopaminergic abnormalities in individuals at genetic risk. One candidate gene relevant in this context is that coding for catechol-*O*-monoamine transporter (COMT), which degrades cortical dopamine. This gene variant is interesting since it provides a plausible mechanism for cortical dopaminergic dysfunction as a genetically mediated trait for schizophrenia. Valine allele of the valine-methionine polymorphism at amino acid 158 of this gene is putatively associated with lower cortical dopamine concentration and is largely implicated in prefrontal cortical pathology of schizophrenia [13,105], although overall association to the clinical phenotype is modest at best [106]. Interestingly, the valine allele has also been shown to be associated with increased dopamine turnover rate postmortem [107] and *in vivo* [108] as well as with higher cortical dopamine D_1 receptors *in vivo* [68]. Thus, the effects of the valine allele of the COMT gene would be consistent with higher striatal D_2 receptors [82] and higher cortical D_1 receptors [81] in unaffected cotwins of patients with schizophrenia. Although our results are consistent with the role of this genetic variant in the regulation of prefrontal function and subcortical dopamine, this variant is not associated with striatal or cortical D_2 receptors in the healthy population [109], suggesting interactions with other genes or the environment in the risk population.

Conclusions and Future Directions

In conclusion, molecular imaging studies have provided robust evidence for dopaminergic abnormalities in schizophrenia. Similar alterations are now seen in individuals who are at genetic risk but who do not express the illness, suggesting that dopaminergic mechanisms may serve as intermediate phenotypes, part of the neural substrate that conveys the risk from the genotype to the complex phenotype. Thus, we propose a novel hypothesis to be tested further, the "dopamine hypothesis of schizophrenia vulnerability." In addition to on-going efforts of developing and applying novel molecular imaging probes for other neurotransmitter systems, we should aim at further characterizing the role of dopamine disturbance in the genetic risk for schizophrenia. For example, it is not known whether the alterations in tonic [35] and phasic [29] dopamine systems are genetically determined. On the other hand, by combining multiple imaging techniques and strategies, these neurochemical alterations should be integrated with the structural and functional deficits that characterize schizophrenia [77,108]. Another avenue less frequently traveled is imaging the gene × environment interaction in schizophrenia, given that genetic and environmental factors (such as cannabis use, urbanicity, and childhood trauma) synergistically increase the risk of schizophrenia [1]. For example, individuals with preexisting genetically determined abnormalities may be at greater risk for triggering effects from the environment. Future neurotransmitter imaging studies should incorporate this design. The gene × environment interaction regarding cannabis is particularly interesting from the viewpoint of dopaminergic dysregulation in schizophrenia [110]. Cannabis is a risk factor for psychosis in the population [111], but those at genetic vulnerability to psychosis are at particular risk [112]. Interestingly, the COMT gene, which is closely associated with the sensitivity of the subcortical dopamine system (see above), modulates both short- and long-term effects of cannabis [113,114], and cannabis itself causes subcortical dopamine release [115]. Thus, neurotransmitter imaging might help unravel the intermediate phenotypes responsible for mediating the heightened sensitivity to this and other environmental stressors (e.g., childhood trauma and other psychosocial stress) in genetically vulnerable individuals. Ultimately, a comprehensive view of the intermediate phenotypes and how they interact with environmental factors could lead to discovery of novel pathophysiological mechanism and better treatment.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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