Genes, dopamine and cortical signal-to-noise ratio in schizophrenia

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There is general agreement that abnormal brain function in schizophrenia involves an extended network of brain structures including the frontal, temporal and parietal cortices, the basal ganglia, the cerebellum, the hippocampus and the thalamus [1]. Evidence for this conclusion has emerged from a generation of functional neuroimaging studies, from numerous studies of neurocognition, and from various electrophysiological approaches. Proper macrocircuit processing, however, depends on intact function within the microcircuits that comprise the nodes of the larger brain systems; the output of dysfunctional microcircuits can secondarily affect functional connectivity of macrocircuits [2]. In schizophrenia research, there has been a remarkable leap forward in elaborating mechanisms of microcircuit dysfunction based on recent discoveries of susceptibility genes that target the cortical synaptic signaling machinery [3]. These discoveries have not only elucidated potential causative mechanisms but also permitted a reformulation of classic observations about cortical function in schizophrenia and about the role of dopamine in psychosis and in antipsychotic drug therapy. This review summarizes recent progress in this rapidly evolving research arena.

Cortical microcircuit biology in schizophrenia

Evidence of cortical pathology in schizophrenia has emerged from many lines of investigation. Anatomical imaging studies have found gray matter volume deficits in first-episode [4] and chronic [1] schizophrenic patients, as well as before the outbreak of psychosis [5] and in non-psychotic family members [6] – the latter findings suggest a relationship to primary genetic susceptibility. Reductions of gray matter volume, however, appear to be accompanied not by a consistent change in total neuron number or signs of neurodegeneration, but possibly by an increase in cell packing density and a reduction in neuropil (i.e. neuronal processes and contacts) [7], although this is controversial.

Support for the notion of disturbed synaptic architecture of cortical gray matter neurons comes primarily from post-mortem investigations of synaptic proteins. Although inconsistencies characterize this literature, which is to be expected given the vagaries of measuring transcripts and proteins in post-mortem tissue of individuals who have been ill for decades, several trends have emerged. Reduced expression of presynaptic vesicle proteins such as the synapsins have been described [8,9], as have reduced levels of proteins of the SNARE vesicle-docking complex, including synaptosomal-associated protein-25 (SNAP-25) [10], complexin 1 and synapsin 2 [11]. Decreased densities of dendritic spines have also been reported [12], as has reduced expression of reelin [13], which is secreted by GABAergic neurons in association with dendritic post synaptic specializations. Additional synaptic proteins such as neuregulin1 (NRG1), dysbindin and regulator of G-protein signaling 4 (RGS4) have been implicated as susceptibility genes for schizophrenia [3,14,15] and preliminary evidence suggests that each of these proteins is abnormally expressed in schizophrenic prefrontal cortex [16–18].

Functional phenotypes of microcircuit dysfunction

Functional neuroimaging studies of patients with schizophrenia began in the 1970s and the ensuing enormous literature converges on the conclusion that abnormal cortical function is a characteristic of this illness and could underlie its clinical manifestations [1]. Classic symptoms such as auditory hallucinations have been correlated with abnormal activation patterns in sensory association cortices [19] and in prefrontal cortex [20]. Delusional states and negative symptoms (e.g. avolition and apathy)
also appear to involve primarily cortical, especially prefrontal, dysfunction [21]. Deficits of prefrontal-cortex-associated neuropsychological functions predict long-term disability, predate the emergence of the diagnostic syndrome, and show a strong association with genetic risk for the disease [22]. From the first functional neuroimaging studies of regional cerebral blood flow (rCBF) in schizophrenia [23], evidence of prefrontal dysfunction has been a consistent finding [1], usually correlating with cognitive deficits in prefrontal-type working memory tasks. Thus, the prefrontal cortex, although not the only cortical system implicated in schizophrenia, is an unavoidable research target for the investigation of local microcircuits simply because the evidence of abnormal prefrontal cortical function is so overwhelming.

Although neuroimaging techniques such as functional magnetic resonance imaging (fMRI) can isolate the locus of abnormal function, they cannot identify the mechanism of disturbed microcircuit behavior. Electrophysiological techniques that sample activity in the millisecond time frame have the potential to characterize cortical information processing better at the microcircuit level. A large electrophysiological literature also converges on the conclusion that cortical activation patterns are abnormal in schizophrenia [24]. Recent studies, moreover, have begun to elucidate the cellular physiology of the abnormal response and suggest that the problem is in the discrimination of signal from noise. Patients with schizophrenia and their healthy siblings appear to have increased noise in prefrontal cortical information processing circuits (Figure 1).

The electrophysiological findings could also shed light on one of the nagging mysteries in the schizophrenia neuroimaging literature. Although many functional neuroimaging investigations report cortical hypoactivation during cognitive tasks that patients perform poorly [1], studies conducted during successful performance of prefrontal cognitive tasks often do not find cortical hypoactivation, or even report the opposite (i.e. cortical hyperactivation) [25,26]. The electrophysiological findings suggest a common mechanism for both abnormal activation patterns – namely, greater cortical response variability (‘noise’) of schizophrenic patients (Figure 1). Thus, greater noise in the context of maintained cognition would be reflected as less focused activity or circuit inefficiency (i.e. hyperactivation); alternatively, greater noise might manifest as a loss of activation if the cortical network becomes too unstable and task performance degrades [1,27].

**Microcircuit stability and microcircuit dynamics**

Within the neocortex, two types of local microcircuits are of particular interest because they constitute the elementary basis of cortical information processing. These are: (i) reciprocal monosynaptic connections between two or more pyramidal cells, thought to be the basis for recurrent excitation that subserves persistent activity during the
delay connections of cortical and non-pyramidal neurons that are considered to mediate recurrent inhibition, which is believed to be essential for establishing neuronal specificity and temporal integration during cortical operations [29]. Neural network simulation studies support the importance of these basic connections by demonstrating that a structured network activity profile, which gives rise to increased signal-to-noise ratio (SNR) within a local cortical network, requires strong recurrent excitation between nearby neurons with a high spiking rate together with strong recurrent inhibition [30]. These models also suggest that a shift towards abnormal excitation (or lack of inhibition) leads to an uncontrolled spread of activation and an increase of the neuronal spontaneous discharge rate within the local cortical network and, hence, to decreased SNR or network specificity. Moreover, computational models of networks of spiking neurons have provided some insights into how synchrony emerges in networks characterized by prominent recurrent inhibition [31]. Although the complex mechanisms that lead to synchrony of neural assemblies are only beginning to be understood, it is currently believed that local recurrent inhibition is crucial not only for increasing the SNR or selectivity of neural activity but also for synchronization of synaptic activity of neural assemblies that gives rise to local field potentials (LFPs) [32]. These LFPs can be measured by means of electroencephalogram (EEG) scalp recordings. Moreover, blood-oxygenation-level-dependent (BOLD) responses obtained using fMRI also appear to reflect LFPs, at least in the visual cortex [33]. Accordingly, it is conceivable, although speculative, that the aforementioned increased prefrontal variance of scalp-recorded event-related activity (i.e. ‘noise’) and the unfocused BOLD response in schizophrenic patients are both related to a lack of synaptic LFP synchronization or ‘stability’ within cortical assemblies. Moreover, evidence indicates that this unstable physiological response predicts more global deficits in behavioral function (i.e. prefrontal cognition), suggesting that it could reflect the basic microcircuit mechanisms that are disrupted in schizophrenia [32].

Dopamine and cortical molecular biology in schizophrenia

The dopamine hypothesis revisited

The hypothesis of increased dopamine signaling in schizophrenia has served for over forty years as the major heuristic framework for understanding the impaired synaptic mechanisms in schizophrenia, and it remains the primary target of pharmacological treatment. As new information about dopamine pharmacology emerged during this period, the hypothesis underwent several revisions. Early versions focused on dopamine metabolism or receptor binding in striatum, primarily because of the dense striatal dopamine innervation, but subsequent variations stressed macrocircuit dysfunction implicating cortical regulatory inputs, albeit still focused on striatal dopamine as the effector of the psychotic state (Box 1). These newer models appeared to account for more of the basic and clinical data about the role of cortical–striatal circuits in schizophrenia.

As appealing as this macrocircuit formulation of schizophrenic symptoms might seem, it too is open to challenge. Prefrontal cortical function in animals and humans appears to have a predictable impact on regulation of striatal dopamine activity, but it is unclear whether this downstream affect relates to the psychotic symptoms of the illness or is an epiphenomenon not fundamental to these symptoms. A major problem with any account of psychosis based on striatal dopamine activity is that it has been difficult to establish the functional relevance of the striatum, even its ventral limbic part, with regard to the main target symptoms of antipsychotic D2 receptor blockade (i.e. hallucinations, paranoia and thought disorder). As already noted, imaging studies have suggested that such symptoms are more easily related to activity in the cerebral cortex, and that D2 receptors in the cortex – although perhaps two orders of magnitude less abundant than in the striatum – are occupied by antipsychotic drugs in vivo [34]. These considerations raise the intriguing possibility that the crucial role for abnormal dopamine signaling in the pathophysiology of schizophrenia might involve cortical, not striatal, microcircuits and that antipsychotic drugs could exert their principal therapeutic actions via D2 receptor blockade in cortex.

Dopamine and cortical microcircuitry in schizophrenia

A potential role for reduced cortical dopamine activity in schizophrenia first emerged when a direct relationship was found between cerebrospinal fluid concentrations of the principal dopamine metabolite (homovanillic acid) in schizophrenic patients and activation (measured as rCBF) of the dorsolateral prefrontal cortex (DLPFC) during an executive cognition task [35]. An anatomical basis for the apparent functional deficiency in prefrontal dopamine was later suggested by Akil et al. [36], who measured tyrosine hydroxylase protein immunostaining in post-mortem DLPFC and found decreases in patients with schizophrenia. Consistent with these findings, Abi-Dargham et al. [37] reported that using positron emission tomography (PET) and a specific dopamine D1 receptor radiotracer, schizophrenic patients tended to show higher receptor availability than controls, particularly in DLPFC. Moreover, prefrontal D1 receptor availability in the patients predicted poor working memory performance. Recent animal studies suggest that increased D1 receptor availability is related to decreased dopamine functional innervation, although there are negative studies of D1 receptor measurements in schizophrenic patients [38]. It is also interesting to note that in animals, diminished cortical dopamine innervation is associated with reduced spine density and dendritic arborization of target neurons [39], both of which are found in the post-mortem schizophrenic brain [12]. It is unclear whether decreased prefrontal dopamine innervation is an acute manifestation of illness, whether it develops before the expression of psychosis, or whether it emerges during the course of illness. In animal studies, sustained cortical dopamine stimulation (e.g. chronic stress) tends to ‘exhaust’ prefrontal dopamine terminals [40], perhaps because they lack dopamine recycling via dopamine transporters [1].
Findings that antipsychotic drugs increase presynaptic dopamine metabolism and block dopamine D2 receptors, and that dopamine-mimicking drugs are psychotogenic, are cornerstones of the classic dopamine hypothesis of schizophrenia [67]. Early versions of the dopamine hypothesis proposed that dopamine levels or receptor numbers were increased in patients with schizophrenia—a hypothesis that ultimately was not convincingly confirmed [34]. In part because of the failure to provide sufficient neurobiological explanation for the obvious therapeutic effects of antipsychotic drugs, another version of the dopamine hypothesis emerged in the mid-1980s, which proposed a macrocircuit model of a dysfunctional cortical–subcortical loop [68,69]. An anatomically updated version of this model is depicted here (Figure I). It is based on (i) evidence from animal studies that dopamine activity in the striatum is regulated by feedback from prefrontal cortex, and (ii) clinical and neuroimaging observations that emphasized the importance of prefrontal cortical dysfunction in schizophrenia [1]. These findings raise the possibility that striatal dopamine neuronal activity might be abnormal as a ‘downstream’ effect of a primary prefrontal abnormality. Anatomical evidence in rodents that prefrontal glutamate projections regulate subcortically projecting dopamine neurons through inhibitory neuronal intermediates (GABA neurons in Figure I) [70] further suggests that, in the context of abnormal prefrontal function, mesostriatal dopamine transmission would lack a normal tonic prefrontal inhibitory ‘brake’ and might be prone to a dysregulated response to stimuli [34,67]. Prefrontal dysfunctions (e.g. related to abnormal prefrontal dopamine signaling) would thus result in disinhibition of striatal dopamine activity [1]. In schizophrenia, there is evidence of reduced dopamine innervation of prefrontal cortex. Actively psychotic patients manifest increased responsiveness of striatal dopamine terminals to amphetamine administration when studied with D2 receptor radioligand receptor imaging [34]. In addition, there is also evidence of increased striatal uptake of the dopamine precursor fluoroor–dihydroxyphenylalanine (fluoro–dopa) in such patients [34,71]. As expected from the animal studies [1], and consistent with dopamine activity in striatum being tonically inhibited by prefrontal feedback, both of these striatal dopamine abnormalities (exaggerated amphetamine response and increased fluoroor–dopa accumulation) in patients are predicted by neuroimaging measures of abnormal prefrontal cortical neuronal function in the same subjects [71,72]. Prefrontal regulation of striatal dopamine also has been tested in humans with a genetic mechanism based on a common variation in the catechol-O-methyltransferase (COMT) gene that effects prefrontal cortical function, with valine alleles having relatively abnormal function. Akil et al. [73] examined expression of tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine biosynthesis, in nigral dopamine neurons of normal human brains grouped by COMT genotype. Consistent with predictions of the anatomical relationships in rodents [70] and findings in humans of prefrontal abnormalities predicting increased striatal dopamine activity [71,72], valine alleles were associated with significantly increased TH expression in neuron groups that project to the striatum.

The evidence of diminished prefrontal dopamine function and cortical ‘inefficiency’ in patients with schizophrenia also fits well with neuroimaging studies of pharmacological manipulations in healthy subjects and in patients with Parkinson’s disease. These studies have demonstrated that increasing dopamine activity ‘focuses’ the hemodynamic response of prefrontal cortex during frontal-lobe-related tasks (i.e. it enhances prefrontal efficiency) [41–43].

**COMT variation: a genetic test of dopamine effects on cortical processing**

The notion that effective prefrontal dopamine signaling is crucial for optimum SNR observed with neuroimaging has been tested in recent studies of functional variation in the gene encoding catechol-O-methyltransferase (COMT). As outlined elsewhere [1], because of the minimal role of dopamine transporters in cortical dopamine flux, COMT methylation plays a particularly important role in modulating prefrontal dopamine activity, at least in rodents. In humans, the COMT gene contains a common functional variation in the peptide sequence (a valine-to-methionine substitution at codon 158). The valine-containing alleles have significantly greater COMT activity than methionine alleles, suggesting that individuals with valine alleles would have relatively greater inactivation of prefrontal dopamine. If this matters in terms of prefrontal function, then these individuals should have poorer prefrontal function and signal-to-noise patterns. Consistent with these predictions, Egan et al. [44] reported that COMT genotype predicts 4% of the variance in performance on the frontal-lobe-associated Wisconsin card-sorting test, subjects with the valine allele showing relatively poorer cognitive performance, even if they were otherwise normal. Moreover, normal individuals with valine alleles showed a pattern of relatively inefficient prefrontal activity observed with fMRI. Several other independent studies have reported comparable effects of COMT genotype on prefrontal cognition [1,3]. One recent study compared performance of normal children in several memory tests, of which two tests involved prefrontal cortical function but only one was linked to prefrontal dopamine, based on earlier studies in dopamine-depleted monkeys and in children with phenylketonuria. Only the test linked to prefrontal dopamine showed COMT genotype effects, which were—as predicted—consistent with the likely relative levels of synaptic dopamine [45].
The effect of COMT valine alleles on dopamine flux in prefrontal cortex, particularly in the case of individuals at risk for schizophrenia, might be expected to interact with other factors related to abnormal prefrontal microcircuit stability and to bias towards instability and increased risk for manifesting schizophrenia. This scenario has been proposed as a neurobiological mechanism of genetic susceptibility for schizophrenia [1] and, indeed, in schizophrenic patients of European ancestry, association studies generally suggest that the valine allele could be a small risk factor for the illness [1,3]. Taken together, several lines of evidence from post-mortem, neuroimaging, pharmacological and genetic studies implicate reduced prefrontal dopamine activity as a component of the cortical abnormalities associated with schizophrenia. However, this evidence does not clarify the therapeutic effects of D2 receptor antagonist drugs, particularly whether these effects implicate cortical microcircuitry, because D2 blockade might be expected to diminish dopamine signals further and worsen the putative signal-to-noise problem.

D1/D2 activation ratio and cortical microcircuits in schizophrenia

The cellular and molecular mechanisms that influence a structured network activity profile or SNR are undoubtedly complex. Dopamine, however, appears to be crucial in maintaining the balance of excitatory and inhibitory synaptic interactions through modulation of the excitability of glutamate and GABA neurons. Network simulation studies suggest that locally sustained activity of prefrontal excitatory–inhibitory circuits, as required during the delay period of working memory tasks, are protected against distractors and instability by dopamine-mediated mechanisms in an inverted U-shaped manner [30,46]. This is in line with physiological studies in animals showing D1-receptor-mediated optimal levels of dopamine modulation during working memory performance [47] and of dopamine modulation of prefrontal neurons during ventral tegmental area stimulation [48]. How this stabilization and increased SNR of prefrontal networks are achieved is not yet clear. However, there is converging evidence that D1 signaling affects glutamate activity in part by enhancing NMDA-receptor-mediated postsynaptic currents in prefrontal pyramidal neurons [49,50]. In computational models [30,46], enhancement of NMDA currents via D1 stimulation leads to an input-specific increased firing rate of delay-active neurons (i.e. increased SNR during delay-type tasks), thereby increasing inhibitory feedback and thus indirectly reducing activity of ‘background’ neurons.

Dopamine also appears to affect prefrontal pyramidal neuron activity indirectly via modulation of GABA interneurons, although the precise receptor mechanisms and GABA cell types are uncertain. One interesting account of dopamine-mediated effects on GABA neurons has been proposed by Seamans and colleagues. Using whole-cell patch-clamp recordings in vitro, they reported that D2 receptor agonists induce an early and brief (i.e. phasic) decrease in GABA release probability and a reduction of the response to a GABA_A receptor agonist, whereas D1 agonists cause a delayed and long-lasting (i.e. tonic) increase of the intrinsic excitability of interneurons [51]. If these observations are confirmed, it might be concluded that postsynaptic D2 stimulation, by reducing inhibition selectivity, is alerting and orienting but not target-discriminating, whereas D1 stimulation is more important for response selection, target representation, network stability and, ultimately, goal-directed action. Further, too much D2 stimulation or a relative lack of D1-mediated signaling would be characterized by properties that are reminiscent of the neurophysiological, neuropsychological and clinical findings in schizophrenia already discussed (decreased SNR and poor differentiation of target from background), which could translate into local circuit stimulus overload, and over-alertness and unstable attention to contextually weak internal and external stimuli. It does not seem far-fetched to speculate that such a state, if prolonged, might ultimately gain the character of confusing sensory and ideational representations, perhaps emerging as hallucinations and paranoia, as well as poor performance on prefrontal cortex-associated neuropsychological tasks including working memory, planning ability, and focused thinking and behavior. Further, this corticocentric view suggests a secondary but still important role for striatal dopamine. The effect of altered cortical STN on the dysregulation of subcortical dopamine activity already described could lead to reinforcement and automation of striatum-mediated ideational and behavioral routines that appear contextually inappropriate, inflexible and bizarre.

Synaptic localization of D1 and D2 receptors might further interact with the dynamics of cortical dopamine signaling in schizophrenia. Constitutionally reduced prefrontal dopamine innervation (e.g. related to chronic stress, reduced anatomical innervation or COMT valine genotype) would tend to favor stimulation of intrasynaptic D2 receptors compared with extrasynaptic D1 receptors. D2 blockade with antipsychotic drugs might tend to restore a favorable balance of D1 stimulation, and thus improve cortical SNR. Recent evidence in animals suggests that some novel antipsychotic agents not only block D2 receptors but also increase presynaptic dopamine release in the prefrontal cortex, suggesting a novel mechanism for these agents [52]. Both of these actions would favor the D1-dominated state (Figure 2). Thus, if these assumptions about D1/D2 activation ratios in prefrontal cortex and in cognitive and physiological manifestations of schizophrenia are tenable, atypical antipsychotic drugs should improve prefrontal cognition and SNR of the physiological patterns. Indeed, improvements in cognition [53] and in fMRI response patterns have been reported in patients treated with these new agents [54]. Moreover, the beneficial effects of the pharmacological combination of D2 antagonism and D1 stimulation on cortical SNR have also been demonstrated in patients using rCBF techniques [55] and P300 electromagnetic source analyses [56]. Accordingly, the basic electrophysiological and computational studies on the balance between D1-mediated and D2-mediated effects within prefrontal microcircuits suggest that the therapeutic actions of antipsychotic drugs reflect changes in dopamine signaling within these circuits.
Cortical microcircuits and the broader molecular landscape

The prefrontal microcircuit model also relates, at least in principle, to other molecular hypotheses of schizophrenia, such as those of perturbed synaptic organization and abnormalities of GABA and glutamate signaling [57], and converges with emerging data about genetic mechanisms, all of which implicate disruption of multiple molecular mechanisms involved in cortical intercellular signaling [3]. In the past two years, several genes have emerged as compelling candidates for susceptibility factors in schizophrenia. In addition to COMT, these genes include DTNBP1 (which encodes dysbindin), NRG1, G72, RGS4 and CHRNA7 (which encodes the α7 neuronal nicotinic ACh receptor) [3]. The biology of these genes is still being elaborated but they are already known to affect aspects of glutamate and GABA signaling in the cortex. As such, they might be expected to converge with dopamine on the cellular physiology of microcircuit behavior and to affect both generation of asynchronous LFPs in cortical synapses and network stability. For example, reduced expression of glutamic acid decarboxylase 67 (GAD67) in post-mortem prefrontal cortex of schizophrenic patients has been reported by several groups [57,58], and involvement of a subset of inhibitory interneurons, so-called chandelier cells, has been highlighted [58]. Chandelier cells synapse at the initial segment of pyramidal axons and exert powerful inhibitory control over the excitatory output of pyramidal cells and, by inference, over recurrent excitation and inhibition. Of note, the aforementioned D1-mediated increase of interneuron excitability that results in increased inhibitory postsynaptic currents is seen primarily in this interneuron class [59].

NMDA receptor blockade, which is used as a pharmacological model of schizophrenia [57], reduces GAD67 expression in mice [60], as does lesion of glutamatergic projections to GABAergic interneurons [61]. Sustained NMDA receptor blockade also leads to reduced cortical D1 signaling, whereas NMDA stimulation recruits D1 receptors to the synaptic membrane [62]. These remarkably convergent relationships implicate a dopamine–glutamate–GABA loop of molecular risk factors, which have impacts on cortical microcircuit stability and SNR, and on drug treatment of schizophrenia.

Interestingly, current evidence from genetic and post-mortem studies suggest that reduced glutamate activity—if present in schizophrenia—does not appear to be mediated by gross abnormalities at the levels of NMDA receptor subunit structure, number or cellular localization [63]. Rather, several indirect mechanisms resulting in
diminished glutamate signaling have been implicated by recent genetic discoveries [3]. For example, NRG1 regulates the expression of glutamate receptor subunits and activates ErbB4 receptors, which are colocalized with NMDA receptors and regulate aspects of NMDA signaling [14]. Several other potential susceptibility genes, including DTNBP1, G72, RGS4 and CHRNA7, could also exert their effects indirectly on NMDA receptor function and glutamate-mediated synaptic plasticity [3,63]. Thus, these diverse molecular mechanisms of compromised NMDA signaling, by also potentially affecting trafficking of D1 receptors and the modulation of D1 signaling, might further degrade the D1/D2 activation balance and the tuning and stability of microcircuits.

Concluding remarks
Functional breakdown in microcircuit neuronal connectivity in schizophrenia might result from multiple molecular mechanisms involved in local circuit dynamics. Dopamine signaling, long considered relevant to symptomatic treatment, appears to be a key factor in mediating cortical SNR and serves as a heuristic model for understanding deficient functional connectivity of local cortical microcircuits. Abnormal decreases in the ratio of D1/D2 signaling – together with other molecular abnormalities involved in regulating local circuit SNR involving glutamate and GABA mechanisms – might unfavorably affect the stability of cortical representations of both internal and external stimuli. Available antipsychotic therapy, which targets D2 receptors, might restore more normal cortical SNR and thereby ameliorate symptoms, although the fundamental molecular pathogenesis of the disorder is not targeted by current treatments.

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