Prefrontal Neurons and the Genetics of Schizophrenia

Daniel R. Weinberger, Michael F. Egan, Alessandro Bertolino, Joseph H. Callicott, Venkata S. Mattay, Barbara K. Lipska, Karen F. Berman, and Terry E. Goldberg

*This article reviews prefrontal cortical biology as it relates to pathophysiology and genetic risk for schizophrenia. Studies of prefrontal neurocognition and functional neuroimaging of prefrontal information processing consistently reveal abnormalities in patients with schizophrenia. Abnormalities of prefrontal information processing also are found in unaffected individuals who are genetically at risk for schizophrenia, suggesting that genetic polymorphisms affecting prefrontal function may be susceptibility alleles for schizophrenia. One such candidate is a functional polymorphism in the catechol-o-methyl transferase (COMT) gene that markedly affects enzyme activity and that appears to uniquely impact prefrontal dopamine. The COMT genotype predicts performance on prefrontal executive cognition and working memory tasks. Functional magnetic resonance imaging confirms that COMT genotype affects prefrontal physiology during working memory. Family-based association studies have revealed excessive transmission to schizophrenic offspring of the allele (*val*) related to poorer prefrontal function. These various data provide convergent evidence that the COMT* val *allele increases risk for schizophrenia by virtue of its effect on dopamine-mediated prefrontal information processing—the first plausible mechanism for a genetic effect on normal human cognition and risk for mental illness.*
Biol Psychiatry 2001;50:825–844 *© 2001 Society of Biological Psychiatry*

Key Words: Neurobiology, prefrontal cortex, schizophrenia, genetics, COMT

Introduction

Interest in the frontal lobe as a key to the origins of schizophrenia dates back to early in the 20th century. During the past two decades, studies of patients with schizophrenia have provided extensive evidence of disturbed function of prefrontal neuronal circuits, both local and distributed. These studies also provided a context for elucidating the first specific biological mechanism by which a gene increases susceptibility for schizophrenia. At the end of 2001, it can be argued that schizophrenia represents the expression of physiologic abnormalities in several prefrontocentric circuits, that prefrontal neurons are effector cells of these distributed physiologic abnormalities, and that a gene that affects the efficiency and tuning of the activity of these effector neurons is a susceptibility gene for schizophrenia. Data supporting these arguments will be reviewed in this article.

Cognitive Control and Prefrontal Pathophysiology

The evidence that prefrontal cortex is a site of abnormal brain function in schizophrenia is overwhelming. This includes data from many studies of neuropsychological and cognitive function (Barch and Carter, 1998; Gold et al 1997; Goldberg et al 1987, 1988; Goldberg and Weinberger, 1988; Keefe et al 1995; Mahurin et al 1998; Park and Holzman 1992; Stone et al 1998; Weickert et al 2000; Wexler et al 1998), neuroimaging (Andreasen et al 1996, 1997; Berman et al 1992; Callicott et al 1998a, 2000a; Carter et al 1998b; Catafu et al 1994; Curtis et al 1998; Ingvar and Franzen, 1974; Kawasaki et al 1993; Manoach et al 1999, 2000; Stevens et al 1998; Volz et al 1997; Weinberger et al 1986, 1988a, 1992), studies of eye movements (Cegalis and Sweeney 1979; Holzman et al 1974; Jacobsen et al 1996; Lieberman et al 1992; Litman et al 1997; Shagass et al 1974), and electrophysiologic studies (Abrams and Taylor, 1979; Guenther et al 1988; Hoffmann et al 1996; Karson et al 1987; Tauscher et al 1998). Results of this body of research have been summarized in several recent reviews (Bunney and Bunney, 2000; Callicott and Weinberger, 1999; Goldman-Rakic, 1999). Abnormal prefrontal function, however, is not a solitary finding or invariably found in every study, and physiologic abnormalities also are found in other areas that are anatomically connected to prefrontal cortex, especially in temporal and parietal cortices, cerebellum, striatum, and thalamus (Andreasen et al 1997, 1998; Buchsbaum et al 1996; Busatto et al 1994; Callicott et al 2000a; Catafau et al 1994; Deicken et al 1995; Fletcher et al 1998; Friston et al 1992; Gur et al 1995; Kawasaki et al 1997;

From the Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland. Address reprint requests to Daniel R. Weinberger, M.D., Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, 10 Center Drive (4S235), Bethesda, MD 20892.
Received April 10, 2001; revised July 12, 2001; accepted July 20, 2001.

© 2001 Society of Biological Psychiatry
0006-3223/01/$20.00
PII S0006-3223(01)01252-5

Mellers et al 1998; Reite et al 1988). Although we can shine the spotlight on any of these regions individually, it has become increasingly popular to view the abnormal findings in their totality, as expressions of malfunction of distributed circuits (Andreasen et al 1997; Bunney and Bunney, 2000; Bullmore et al 1997; Friston and Frith, 1995; Nestor et al 1998; Pearlson et al 1996; Weinberger 1991, 1993). This is consistent with the prevailing assumption of cognitive neuroscience that even relatively simple information is processed by distributed cortical networks of interconnected neurons (Herrmann et al 1993; McIntosh 1999; Mesulam 1990; Pastor et al 2000; van Lier and Wagemans 1998).

The physiologic and molecular mystery of the prefrontal deficit in patients with schizophrenia is beginning to unravel. Since the landmark report of Ingvar and Franzen (1974), which documented reduced frontal lobe regional cerebral blood flow (rCBF; "hypofrontality"), many studies of patients have reported reduced prefrontal physiologic activity (for review, see Callicott and Weinberger 1999). The results have been especially consistent when patients are studied during performance of tasks that normally are associated with prefrontal activation, particularly working memory tasks (Berman et al 1992; Carter et al 1998b; Callicott et al 1998a; Catafu et al 1994; Stevens et al 1998; Weinberger et al 1986, 1988a). Underactivation of a distributed network of interconnected cortical and subcortical sites, implicated in processing working memory, also has often been described; however, in most of these studies patients have tended to perform less accurately than control subjects, leaving unanswered the question of whether underactivation in the context of underperformance is necessarily a manifestation of a pathologic brain. If underactivation in the context of impaired performance is pathologic, then it might be predicted that normal subjects who are studied beyond their working memory capacity and who underperform would not appear hypofrontal. In fact, this assumption has not held. Functional neuroimaging studies of normal individuals who are required to process a working memory load beyond their capacities and in whom performance significantly deteriorates usually evince a reduction in dorsolateral prefrontal activity (Callicott et al 1999; Goldberg et al 1998a). These results are consistent with electrophysiologic studies of individual dorsolateral prefrontal neurons in nonhuman primates, which find decreased firing of working memory–specific neurons when capacity is exceeded and errors are made (Funahashi et al 1989, 1991). Interestingly, reduced dorsolateral prefrontal cortex (DLPFC) activation in normal subjects pushed beyond their working memory capacity is not seen throughout the working memory network; for example, in cingulate cortex in which activation probably reflects effort and error monitoring (Barch et al 1997; Carter et al 1998a; Pardo et al 1990), activation continues to increase (Callicott et al 1999). Thus, the hypofrontal response of patients with schizophrenia is at least partially consistent with a normal response to excessive working memory processing demands.

Despite these phenomenologic similarities, it is not clear whether patients and normal subjects become hypofrontal for the same reasons, and hypofrontality is not an inevitable correlate of poor working memory performance (Goldberg et al 1990; Schapiro et al 1999; Weinberger et al 1988b). Regardless of the mechanism of hypofrontality in schizophrenia, metaphorically speaking, patients appear to be especially prone to fall off the prefrontal information processing treadmill. In other words, as if unable to keep up with the processing demands, they seem to disengage working memory–related neuronal circuitry and become hypofrontal. This does not explain, however, why the capacity of patients with schizophrenia to stay on the "treadmill" is diminished. Although it is conceivable that the capacity limitations of patients are because of cellular pathology in DLPFC, the finding of hypofrontality does not, by itself, make this conclusion more or less likely.

Another approach is to study patients whose working memory performance is at or near normal. Five recent functional magnetic resonance imaging (fMRI) studies of patients who perform relatively well on tests of working memory have appeared, and the results are surprisingly consistent (Callicott et al 2000a; Curtis et al 1999; Manoach et al 1999, 2000; Stevens et al 1998). Under these circumstances, dorsolateral prefrontal cortical activity (Brodman's areas 9/46) is not reduced; rather it tends to be increased for either slightly impaired or equivalent cognitive output in comparison with control subjects. These results suggest that at least under certain conditions when patients are able to keep up with the processing demands, they do so less efficiently for a given level of performance accuracy. Metaphorically speaking, they have to run at a much faster pace to keep up with the track. Again, studies in normal subjects may provide perspective for understanding some aspects of this overactivation response. Rypma and Esposito (1999) have shown that in normal subjects performing a simple working memory task, reaction time—a measure of cognitive difficulty and efficiency of processing—varied directly with cortical activation of DLPFC. That is, the more difficulty normal subjects had in producing the correct response, the more they activated prefrontal cortex. The mechanism for this exaggerated response is unclear, in either normal subjects or in patients, and it is uncertain whether the mechanisms are the same. At a phenomenologic level, it seems as though

Table 1. Abnormalities of Prefrontal Function Associated with Schizophrenia

1. Abnormal performance on executive cognition and working memory tasks
2. Reduced physiologic activation of prefrontal cortex during certain tasks; probably a reflection of diminished capacity to stay focused on the task
3. Excessive physiologic activation of prefrontal cortex during certain tasks; probably a reflection of diminished efficiency and automaticity of information processing
4. Reduced N-acetyl aspartate measures

extraneous neural activity is recruited in subjects who do not process the information efficiently. This is analogous to the recruitment of extraneous neural activity that occurs in the early phases of a variety of learning paradigms; neural activation becomes more focused once a strategy for processing information has become more automatic and efficient (Andreasen et al 1995; Dinse et al 1997; Karni et al 1998; Mattay et al 1996; Petersen et al 1998; Shadmehr and Holcomb 1997; Van Horn et al 1998).

Regardless of the precise mechanisms, patients with schizophrenia have thus been found to manifest two abnormal phenomena related to the physiologic response of DLPFC during the performance of working memory tasks (Table 1): 1) their capacity to stay on task is reduced, which probably relates to findings of hypofrontality; and 2) while on task, they process the information with less efficiency and automaticity, which probably relates to the finding of hyperfrontality. The degree to which a patient or patient group will manifest either or both of these abnormalities will likely depend on the capacities of the patients and the characteristics of the task paradigm.

The overactivation response is particularly intriguing in several respects. It cannot be interpreted as a reflection of disengagement, or lack of effort, or poor performance—interpretations that have plagued the hypofrontality literature—because such explanations would not be associated with excessive activity. It is difficult to dismiss the conclusion that the overactivation response is a manifestation of a defective and inefficient neural strategy employed by patients in processing the working memory task. Thus, the physiologic response of the DLPFC to processing working memory information is abnormal in schizophrenia, but the physiologic texture of this abnormality (i.e., underactive or overactive) varies, reflecting how patients are managing the demands of the task. Moreover, both of these abnormal responses can be modeled to some degree in normal subjects by changing task demands. Still, why do patients with schizophrenia have diminished working memory capacity and efficiency?

Cellular Origins of Abnormal Prefrontal Function

Evidence is accumulating that the cellular architecture of DLPFC is abnormal in schizophrenia. Studies of postmortem tissue have found that although there is no obvious loss of neurons or other evidence of neurodegeneration, there is reduced volume of neuronal soma and neuropil and abnormalities of synaptic organization, probably in widespread regions of cortex (for review, see Lewis 1997; Selemon and Goldman-Rakic 1999). At the molecular level, abnormal expression of genes and proteins related to synaptic modifiability and maintenance ("plasticity") have been reported (Honer et al 1999; Karson et al 1999; Mirnics et al 2000; Shannon-Weickert et al 2000). These findings suggest that the organization of dorsolateral prefrontal cortical circuitry (i.e., its synaptic architecture) is anomalous. The postmortem data, however, do not elucidate whether and how such changes relate to the clinical and biological manifestations of schizophrenia or whether changes in prefrontal cortex are more germane to the clinical manifestations of the illness than similar changes reported in other cortical regions (e.g., hippocampus). Do the prefrontal cellular changes observed in the schizophrenic brain postmortem relate to the clinically manifest syndrome? This would be difficult, if not impossible, to answer without cellular and clinical data within the same subjects. Because cellular data in postmortem tissue tend to be from elderly individuals, very few of whom were participants in research, clinical data are often incomplete and complicated by chronic illness and other epiphenomena.

To a limited degree, it is possible to perform a direct cellular assay in vivo with proton magnetic resonance spectroscopy (MRS). This chemical assay technique provides the only clinically available method for direct measurement of chemical moieties in the living brain. Proton MRS can be used to interrogate specific neuronal populations in living subjects because of its capacity to assay N-acetyl aspartate (NAA), an intracellular neuronal marker that is found almost exclusively in mature neurons and their processes (Urenjak et al 1993), with highest concentrations in pyramidal glutamate neurons (Moffett and Namboodiri 1995). The exact implications of changes in NAA signals are uncertain because its cellular function is still unclear. N-acetyl aspartate is synthesized in mitochondria from glutamate and pyruvate or 3-hydroxybutyrate via L-aspartate-N-amino transferase and also is a byproduct of glutamate carboxypeptidase II catabolism of N-acetyl aspartyl glutamate (NAAG), which occurs within glia (Clark 1998). N-acetyl aspartate is a nonspecific, although highly sensitive, marker of neuronal pathology. Virtually all neurologic conditions involving neuronal

pathology that have been studied show changes in NAA signals. Moreover, NAA changes are sensitive measures of dynamic neuropathologic processes; for example, correlating over time with cognitive change in Alzheimer's disease (Doraiswamy et al 1998) and with the number of trinucleotide repeat expansions in Huntington's disease (Jenkins et al 1998). Whereas early studies interpreted NAA findings as indicative of cell loss, recent data have established that NAA reductions reverse following recovery from various forms of brain damage and correlate with clinical improvement and treatment (Bertolino et al 2001; De Stefano et al 1995; Hugg et al 1996; Moore et al 2000; Vion-Dury et al 1995). This has led to speculation that NAA reductions occur as a manifestation of changes in the overall integrity of neurons and their processes, perhaps reflecting reduced mitochondrial energy metabolism (Clark 1998; Jenkins et al 2000). It is interesting to note that in various conditions associated with tissue volume loss and reduced NAA signals (e.g., epilepsy, Alzheimer's disease, schizophrenia), these two parameters are only weakly correlated. Thus, NAA can serve as an indirect measure of the health and integrity of neurons beyond simply the question of neuronal loss.

Most studies of NAA concentrations in the brains of patients with schizophrenia have found reductions in hippocampal and dorsolateral prefrontal cortices (for review, see Bertolino and Weinberger 1999; Keshavan et al 2000). All of the studies that have used spectroscopic imaging, which affords higher resolution and more precise anatomic sampling than traditional single voxel approaches, report reductions of NAA measures in DLPFC and hippocampal formation (Bertolino et al 1996, 1998a, 1998b; Deicken et al 1997, 1998, 1999). These studies have included chronic patients, relatively acute patients, childhood-onset cases, as well as medication-free and medication-naïve patients, all of whom show similar regional abnormalities with similar effect sizes. These data are consistent with several findings in the postmortem literature implicating abnormalities of neuronal wiring in these cortical regions, including decreased neuronal soma size and neuropil volume, decreased expression of synaptic markers, and decreased expression of glutamate carboxypeptidase II in prefrontal and hippocampal cortices (Tsai et al 1995). Although NAA is present in highest concentration in glutamate neurons, it is present in GABA neurons as well, and NAA decreases might reflect abnormalities of this neuronal population, for which postmortem evidence also exists (Benes et al 1991; Pierri et al 1999).

Because NAA concentrations are measured with 1H-magnetic resonance spectroscopic imaging (1H-MSRI) in living subjects, it is possible to ask whether cellular abnormalities predict other clinical and biological phenomena associated with manifest illness. A series of studies aimed at this question have been performed. Bertolino et al (2000a) measured NAA in various brain regions in patients who had also undergone positron emission tomographic rCBF studies of cortical activation during two executive cognition paradigms. The capacity to activate the distributed working memory cortical network was predicted directly by NAA concentrations in DLPFC (i.e., the lower DLPFC NAA, the less activation of prefrontal, parietal, and cingulate cortices during tasks). No other region of brain showed these relationships, and they were not observed in normal control subjects. The results suggest that pathologic neurons specifically in DLPFC, presumably by virtue of their intracortical connectivities, affect the capacity of a functional neuronal network to stay active during executive cognition. The data further suggest that diminished working memory capacity, which is seen under some circumstances as hypofrontality (viz supra), is an emergent phenomenon related to cellular pathology of DLPFC. The results are also consistent with a growing basic cognitive neuroscience database showing that DLPFC neurons modulate the response of distributed systems of cortical neurons involved in various aspects of information processing and memory (Chafee and Goldman-Rakic 2000; Fuster et al 1985; Tomita et al 1999).

As noted previously, depending on the experimental circumstances, the response of the schizophrenic DLPFC to working memory demands also can be abnormally overactive (i.e., inefficient). Does this abnormal prefrontal response have a distinct cellular origin, or is it another functional manifestation of the same neuronal pathology implicated in the hypofrontality response? Callicott et al (2000b) measured NAA in patients who showed an abnormal prefrontal overactivation response. Notably, NAA concentrations in DLPFC predicted overactivation in patients, as well as their performance on the task (i.e., the lower DLPFC NAA, the greater DLPFC activation). Once again, such relationships were not observed in other brain regions or in normal subjects, presumably because the cellular pathology in DLPFC associated with schizophrenia drives the abnormal physiologic response. Together, the data of Bertolino et al (2000) and Callicott et al (2000) implicate a population of neurons in DLPFC as being "effectors" of abnormal physiologic activity of the working memory cortical network in schizophrenia, both its diminished capacity and efficiency. This represents the first direct evidence of a cellular origin for these abnormalities and implicates a candidate neuronal population as being effectors of these various phenomena.

Prefrontal cognitive deficits, especially involving working memory and executive functions, have been correlated in patients with so-called negative symptoms (e.g., Berman et al 1997), and it has been proposed that negative

symptoms also reflect impairment of prefrontal neuronal function (Weinberger 1987; Goldberg and Weinberger, 1988). Callicott et al (2000a) tested this hypothesis by measuring NAA concentrations with 1H-MRSI and negative symptoms in the same sample of patients ($n = 35$). N-acetyl aspartate in DLPFC, and again in no other brain region, correlated inversely with negative symptoms (i.e., the lower NAA, the more negative symptoms). In fact, NAA in DLPFC explained 25% of the variance in clinically rated negative symptoms. Interestingly, in this study NAA did not predict ratings of positive symptoms, perhaps because the symptoms are biologically unrelated; however, in contrast to negative symptoms and to NAA, which remain relatively stable over time within a patient, positive symptoms wax and wane, possibly making it difficult to find predictable relationships between these measures.

An alternative approach is to look for a relationship with a surrogate biological measure of positive symptoms. Although it is has been difficult to find robust biological predictors of positive symptoms, it is clear that drugs that block dopamine type-2 receptors reduce positive symptoms. Recently, three independent studies of patients with schizophrenia have shown that the response of dopamine terminals in the striatum to systemic amphetamine administration is excessive, and the magnitude of the response predicts induced positive symptoms (Abi-Dargham et al 1998; Breier et al 1997; Laruelle et al 1996). These studies have employed radionuclide imaging of striatal dopamine receptors before and after amphetamine administration, with the change in radioligand occupancy taken as a reflection of presynaptic release of endogenous dopamine.

Bertolino et al (1999a, 2000b) measured NAA concentrations with 1H-MRSI in patients who also underwent such radionuclide scanning experiments. Two findings emerged from these studies, both of which suggest that pathology of dorsolateral prefrontal projection neurons affects the activity of dopamine neurons in the brain stem and may explain why dopamine neurons respond abnormally to certain stimuli (e.g., amphetamine) in patients with schizophrenia. The first finding was that under unstimulated, steady-state conditions, NAA concentrations in DLPFC inversely predicted the availability of dopamine receptors in the striatum (i.e., the lower NAA, the greater availability of striatal DA receptors). This relationship likely reflects that low NAA, a measure of prefrontal neuronal integrity, predicts relatively less excitation of midbrain dopamine neurons and, thus, less terminal release of endogenous dopamine to occupy dopamine receptors. This finding is consistent with anatomic data in animals showing both direct and indirect projections from prefrontal pyramidal neurons to dopamine cell bodies in the mesencephalon (Carr and Sesack 2000; Sesack and Pickel 1992) and with physiologic data showing that the burst firing of these dopamine neurons (which accounts for most of the terminal release of dopamine) is regulated by this excitatory input from prefrontal cortex (Murase et al 1993; Shim et al 1996; Svensson and Tung 1989).

Table 2. Various Phenomena Predicted in Patients with Schizophrenia by an In Vivo Measure of Dorsolateral Prefrontal Neuronal Pathology (N-acetyl Aspartate Measures)

1. Negative symptoms
2. Working memory deficits
3. Reduced physiologic capacity of distributed working memory cortical network
4. Reduced physiologic efficiency of dorsolateral prefrontal cortex during working memory
5. Exaggerated response of dopamine neurons to amphetamine

The second finding was that the same NAA measure also predicted excessive response of dopamine terminals to amphetamine (Bertolino et al 2000b), that is, lower DLPFC NAA predicted greater decrease in dopamine receptor availability after amphetamine administration (i.e., greater apparent amphetamine effect). These results also are consistent with animal data showing that reduced prefrontal glutamatergic output produces an excessive dopamine response to amphetamine (Miller et al 1996; Roffman et al 2000). Again, these relationships were not seen with NAA measures in any other cortical region and were not found in normal subjects (Bertolino et al 2000b).

Taken together, these various clinical studies of the predictive relationships of NAA signals in DLPFC suggest that a population of neurons in DLPFC represent cellular effectors of several core phenomena associated with schizophrenia, including negative symptoms, abnormalities of cortical activation during working memory, and the activity of dopamine neurons both at steady state and after amphetamine challenge (Table 2). These relationships suggest that such clinical and biological phenomena represent emergent properties of prefrontal cellular pathology.

Modeling Prefrontal Cellular Abnormalities in Animals

The notion that functional abnormalities of distributed intracortical networks and dopamine neurons in the brain stem may reflect emergent properties of the biology of pathologic prefrontal neurons can be inferred from clinical studies but is nevertheless difficult to establish. Abnormalities of cortical physiology and of dopamine function associated with schizophrenia have been studied for decades as discrete entities unto themselves, not as potentially emergent phenomena linked to a core cellular

neuropathology. In experimental animals, this possibility can be tested further. Lipska and Weinberger (2000) created a model of developmental pathology of prefrontal cortex based on neonatal disconnection from ventral hippocampus. An excitotoxic injury to the ventral hippocampus of rat pups within the first week of life changes the development of the prefrontal cortex, as well as other brain regions, and many of the prefrontal cellular and behavioral changes, including social impairments (Sams-Dodd et al 1997) and working memory deficits (Moghaddam et al 1999) mimic those found in patients with schizophrenia. Analogous changes are not seen in animals with ventral hippocampal damage rendered in adults, indicating that the results in the neonatally lesioned animals do not reflect a simple loss of inputs, but rather a change in the developmental plasticity of prefrontal circuitry. Abnormalities of gene and protein expression in prefrontal neurons (e.g., decreased GAD 67 mRNA expression; Lipska and Weinberger 2000), decreased dendritic spine density and length of dendrites on pyramidal neurons (Lipska et al 2000), and decreased NAA concentrations (Bertolino et al 1999b), all of which are phenomenologically similar to findings in the schizophrenic brain, are also found, suggesting that the architecture of local prefrontal circuits is altered in these animals. The NAA changes are particularly intriguing because they do not emerge until early adulthood (Bertolino et al 1999b), again implying that the neonatal hippocampal lesion alters the plastic adaptations of intrinsic prefrontal neurons to developmental processes of early adult life.

Of greater interest to the question of emergent biological properties of the prefrontal cellular changes is evidence in these animals of altered regulation of dopamine neurons in brain stem. When animals with the neonatal lesion reach early adulthood (and not before), they are hyperactive when stressed and after amphetamine administration (Lipska et al 1993). When prefrontal cortical neurons are removed in the brains of these animals after they reach adulthood, these behavioral hypersensitivities are normalized (Lipska et al 1998). These results implicate intrinsic prefrontal neurons as effectors of abnormal dopaminergic-linked behaviors, analogous to the conclusions drawn from the clinical studies in patients. The changes in dopamine regulation and in dopamine-linked behaviors are emergent phenomena related, at least in part, to changes in prefrontal neuronal biology because the dopamine system is not directly damaged in this model.

A clue to the mechanism of dopamine dysregulation in these animals has come from a recent study by O'Donnell et al (1999). The study showed that the physiologic response of prefrontal pyramidal neurons to dopamine following stimulation of dopaminergic neurons in the brain stem is altered in the neonatally lesioned rats. Normally, ventral tegmental area (VTA) stimulation leads to partial depolarization and diminished spontaneous firing of action potentials of prefrontal pyramidal neurons. This may mimic the effect of certain stresses or rewards on priming prefrontal neurons to respond to critical inputs from other neurons. It is consistent with evidence from basic animal research that dopamine "tunes" prefrontal neurons to respond more precisely to stimuli with a particular contextual valence or saliency (Suri and Schulz 1999). This tuning or filtering function presumably reflects an integration of the effects of dopamine signaling at both glutamatergic and GABA-ergic neurons (see discussion below). Recent studies in the rat have shown that prefrontal dopamine activity is especially critical for gating hippocampal inputs during executive cognition and working memory (Gurden et al 1999; Seamans et al 1998). In the neonatally lesioned animals, VTA stimulation leads to normal partial depolarization of prefrontal pyramidal neurons, but instead of remaining quiet or "tuned," the prefrontal neurons begin to fire indiscriminately. Thus, the tuning function of dopaminergic input is disrupted on the background of putatively abnormal prefrontal circuitry. Interestingly, the abnormal physiologic activity of prefrontal neurons in the neonatal hippocampal lesion model appears to be specific for dopamine-related synaptic architecture. Stimulation of thalamic inputs to prefrontal cortex leads to the same changes in neuronal excitability in both neonatally lesioned and control animals (O'Donnell et al 1999).

Neurophysiologic data in rats suggest that with stress paradigms that increase dopaminergic stimulation of prefrontal cortex, abnormal firing of prefrontal pyramidal neurons could translate into abnormal recruitment of brain stem dopamine activity, perhaps leading to a vicious cycle of prefrontal malfunction and misregulated dopamine activity. This complex functional abnormality is related to the cellular biology of abnormal prefrontal neurons because excessive firing of pyramidal neurons following VTA stimulation is not seen in normal animals (O'Donnell et al 1999).

The relationship of prefrontal neuronal pathology and brain stem dopamine activity was further explored in a monkey model of dorsolateral prefrontal developmental pathology, induced by neonatal removal of mesial temporolimbic cortex (including hippocampus). Animals with neonatal removals were compared with normal animals and animals that had had similar surgical removals performed as adults (age 5 years). All animals were around 8 years of age when examined. The same pattern of NAA reductions as found in patients with schizophrenia are shown by 1H-MRSI. Specifically, NAA was reduced in DLPFC and not in other brain regions (although because

of the relatively small size of the monkey brain, fewer regions could be sampled; Bertolino et al 1997). The fact that NAA reductions were not found in adult lesioned animals indicates that the changes are not simply because of a loss of temporolimbic connections but, analogous to the data in the rat model, reflect more subtle plastic adaptations made in local circuitry as a result of its abnormal developmental history.

This study also explored whether the same measure of intrinsic neuronal pathology (i.e., NAA signals) that predicted availability of striatal dopamine receptors in patients might predict dopamine terminal activity in monkeys; however, instead of inferring dopamine terminal activity indirectly by measuring the availability of dopamine receptors, as was done using radioligand neuroimaging in patients, striatal dopamine release was sampled directly with in vivo cerebral microdialysis. Remarkable similarities between the relationships in the patients and in the monkeys were found. N-acetyl aspartate signals in DLPFC, and only in DLPFC, predicted both the steady-state and stimulus-induced release of dopamine in the striatum, and as in the patients, the directions of the relationships were inverted (i.e., under steady-state conditions lower NAA in DLPFC predicted less dopamine release, whereas after prefrontal stimulation with amphetamine, lower NAA predicted greater striatal dopamine release; Bertolino et al 1999). It should be noted, however, that amphetamine experiments in humans and monkeys may not be directly comparable. Although both measured the relationship between DLPFC NAA and a stimulus-induced response of dopamine terminals, in human subjects, amphetamine was administered systemically to awake individuals; in monkeys, it was administered under general anesthesia directly into the DLPFC. However, the results in monkeys are consistent with the electrophysiologic results in rats. When amphetamine was infused into DLPFC (i.e., a pharmacologic model of stress and VTA stimulation in that both lead to local increases in dopamine) of normal monkeys and monkeys with temporolimbic lesions produced in adulthood, dopamine release in striatum was downregulated (Saunders et al 1998). This is consistent with the data of O'Donnell et al (1999) in normal rats in that after dopamine stimulation of prefrontal cortex, pyramidal cell firing is reduced and excitatory drive from DLPFC on brain stem dopamine neurons should be diminished. In contrast, however, in the neonatally lesioned monkeys, dopamine release was increased in striatum under these conditions (Saunders et al 1998). Thus, analogous to the rat data, the effect of dopamine in DLPFC of monkeys with developmental cellular pathology of intrinsic prefrontal circuitry is dramatically altered and physiologically anomalous (Table 3).

Table 3. Evidence of Anomalous Prefrontal Circuitry in Animals with Neonatal Hippocampal Damage: Potential Parallels with Schizophrenia

1. Working memory cognitive deficits
2. Reduced prefrontal N-acetyl aspartate concentrations
3. Abnormal excitability and decreased signal-to-noise responses of pyramidal neurons to a physiological model of stress (VTA stimulation)
4. Abnormal prefrontal regulation of striatal dopamine activity

Results in experimental animals may model how, in the context of a specific developmental brain abnormality, stress can induce unexpected and anomalous responses in prefrontal function and related behavior. In prefrontal cortex that has developed normally, dopaminergic activation (e.g., during certain stresses) leads to focusing of prefrontal activity and downregulation of midbrain dopamine activity, perhaps helping to marshal cognitive resources toward an action strategy and accounting for the transient motor freezing of animals in certain stress paradigms, respectively. In contrast, dopaminergic activation of prefrontal cortex in our developmentally abnormal animals disorganizes prefrontal activity and leads to a paradoxical upregulation of midbrain dopamine function. Abnormal responses might translate into a loss of cognitive control and into symptoms related to excessive subcortical dopaminergic drive, both of which may characterize the acute psychotic state.

The animal data summarized here also indicate that many of the complex abnormalities of distributed neuronal functional systems implicated in schizophrenia can be modeled by developmental pathology of prefrontal cortical neurons. The pathology is subtle, as the prefrontal cortex is not targeted directly by the lesion. Clearly, however, the lesion changes the developmental history of prefrontal neuronal connectivity and biases these neurons to make abnormal molecular adaptations to the developmentally changing environment. The result is a set of complex emergent events that mimic biological phenomena associated with schizophrenia; however, simply because these phenomena can be modeled in animals does not mean that they reflect the same mechanisms in patients. There also are inconsistencies in the animal model that have yet to be explained. For example, whereas actively psychotic patients show excessive terminal release of dopamine following systemic amphetamine administration (e.g., Abi-Dargham et al 1998), developmentally lesioned rats do not (Lillrank et al 1999). These inconsistencies may reflect differences between the experimental contexts and between the impact of acute stimuli and chronic stress states (discussed in further detail in Lipska and Weinberger 2000), or perhaps limitations of the animal model. Nevertheless, various observations in animals at least lend credence to the possibility that similar

emergent events occur in schizophrenia. The validity of the comparisons stops there, however. Evidence that analogous developmental processes underlie the cellular biology of prefrontal neurons in schizophrenia is lacking, although there has been considerable speculation that such is the case.

Prefrontal Function and the Biology of Genetic Susceptibility

As a result of archival family, twin, and adoption studies of schizophrenia performed in the past century, it is accepted as fact that genes account for the lion's share of variation in liability for schizophrenia. In general, whereas neurobiological studies of schizophrenia have searched for evidence of how the brain has changed to account for symptoms, genetic studies have searched for relationships between genetic loci and clinical diagnosis in families ("genetic linkage") or between specific alleles and diagnosis in populations ("genetic association"). These complementary approaches to unraveling the mysteries of schizophrenia may dovetail in the prefrontal cortex.

The results of family-based linkage studies with noncoding markers spanning the genome have identified a few significant chromosomal loci that have been difficult to replicate (Gottesman and Moldin 1997; Pulver 2000). However, even if valid, these loci (and the genes that will likely emerge from some of them) probably do not account for the majority of genetic liability and do not segregate in many affected individuals (Brzustowicz et al 2000; Kendler et al 1996; Pulver et al 1994; Straub et al 1995). Considering that complex disorders such as schizophrenia probably involve locus and allelic heterogeneity, epistasis (i.e., nonadditive gene interactions), pleiotropy (i.e., diverse effects of an individual gene), and environmental modification, there is likely to be a weak relationship between clinical diagnosis and underlying genotype. This is why linkage analysis for polygenic, complex disorders, even with several thousand affected sib pairs, may be underpowered to find genes (Risch and Merikangas 1996). The weak predictive relationships between phenotype and genotype are probably further compounded by the likelihood that genes for mental disorders, as defined, are not specific for the diagnostic characteristics. Genes do not encode hallucinations, delusions, or thought disorganization; genes affect the basic biology of cells, and the relationship of such cellular effects to complex mental phenomena is not likely to be straightforward. As noted above, the path from cellular pathology to abnormalities of distributed physiologic phenomena associated with schizophrenia is a path that would not be obvious at the level of the putative emergent phenomena. Gottesman and Shields (1982) argued that qualitatively different genetic factors underlie different clinical subtypes or dimensions

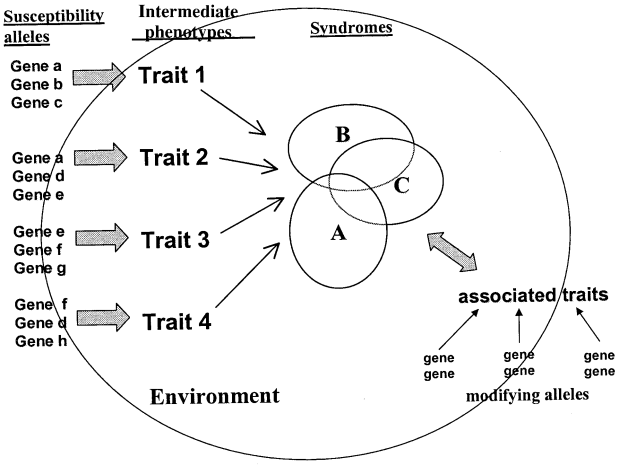

Figure 1. A complex genetic disorder: Simplified.

of schizophrenia and that the genetics of subtypes may be simpler than the genetics of the complex phenotype. Kendler et al (1997) proposed that evidence for familial heterogeneity in the schizophrenic syndrome is of potential significance in the search for susceptibility loci because it may allow a division of the sample before linkage analysis into etiologically distinct subgroups and thus increase power. Both of these approaches, however, seek to reduce genetic complexity by defining more clinically homogeneous subgroups based on arbitrary manifest phenomena that may not reflect discrete genetic effects.

The goal of reducing the genetic complexity of schizophrenia and of increasing the predictive relationship between phenotype and genotype also has encouraged speculation that the syndrome can be decomposed into heritable biological elements, each having a simpler genetic architecture. If the biological effects of genetic variations related to schizophrenia can be targeted, the apparent effect of a given gene might be greater at the level of such a biological phenotype. The conceptual basis of this approach is outlined in Figure 1. It is assumed that schizophrenia is a syndrome of overlapping constellations of symptoms or "syndromes." These symptoms are related ultimately to various susceptibility alleles, which can variably combine with each other and with environmental modifiers to produce variance in the syndromal picture. Modifying alleles (e.g., gender or temperament related) not related to susceptibility for schizophrenia also affect variability in the phenotype by modulating potentially interacting traits. Modifying alleles also may have protective effects. Susceptibility alleles are biased toward the expression of intermediate traits, which represent more direct gene effects, but which are not, in and of themselves, sufficient to account for the diagnosis. Some analogies include insulin receptor resistance as an intermediate phenotype related to risk for diabetes or colon

polyps as an intermediate phenotype related to genetic risk for colon cancer. Because the intermediate traits (i.e., endo or intermediate phenotypes) are more directly related to the biological effect of genes, they should have greater power as targets for identifying susceptibility genes in families. The work described in the earlier sections would support the hypothesis that the symptoms of schizophrenia are emergent properties of underlying abnormalities in brain information processing and that these may be the result of dissociable biological (and probably heritable) components, analogous to heart attack and stroke being the results of various discrete vascular and metabolic factors (Kremen et al 1994; Leboyer et al 1998; Tsuang 1993). The feasibility of this approach to schizophrenia has received preliminary support from a study of the P50 electroencephalographic (EEG) response (Freedman et al 1997) and from a study of eye-tracking dysfunction (Arolt et al 1996).

Selection of putative intermediate traits involves first identifying biological abnormalities in patients with schizophrenia that are quantifiable and enduring (i.e., "traitlike") and that preferably have a clear pathophysiologic basis. The next step is to demonstrate that such biological "traits" are segregating with increased frequency in genetically at risk, but not schizophrenic, family members. Because first-degree family members share on average 50% of their alleles, they will share 50% of the susceptibility alleles, and to the extent that such alleles produce intermediate phenotypes, they will share some of these phenotypes.

Several neurobiological abnormalities have been implicated in family and high-risk studies as promising intermediate phenotypes. Family studies have consistently observed attenuation in sustained attention, perceptual-motor speed, and concept formation in first-degree relatives of patients with schizophrenia (Cornblatt and Keilp 1994). Physiologic studies have also revealed deficits in family members in smooth pursuit eye movements (e.g., Holzman et al 1974) and in various EEG-evoked potentials (Freedman et al 1997; Siegel et al 1984). Cerebral ventricles have been found to be larger in siblings of patients with schizophrenia than in normal subjects (Weinberger et al 1981), and more recent studies have implicated structural changes in several cortical regions, as well (e.g., Seidman et al 1999; Sharma et al 1999). Considerable evidence also points to abnormal function of prefrontal cortex as a potential intermediate phenotype. In studies of monozygotic twins discordant for schizophrenia, Goldberg et al (1993, 1995) found deficits in unaffected twins in executive cognition/working memory and speed of processing, suggesting that such cognitive abnormalities may represent the phenotypic expression of genes related to risk for schizophrenia. In a recent study of monozygotic and dizygotic twins discordant for schizophrenia, Cannon et al (2000) extended these observations by showing that risk for working memory deficits was greater in monozygotic than dizygotic twins, supporting the conclusion that working memory deficits are related to genetic risk for schizophrenia. In a large sample of healthy siblings of patients with schizophrenia ($n = 183$), Egan et al (2001a) found that working memory and executive function deficits reflected in performance on the Wisconsin Card Sorting Test (WCST) were present up to 4 times more frequently in the siblings compared with the general population. Similar results also have been reported by other groups in smaller sibling samples (Cannon et al 1994; Faraone et al 1999; Yurgelun-Todd and Kinney 1993). Finally, using the N-back fMRI paradigm that has revealed evidence of inefficient prefrontal function in patients with schizophrenia (discussed above), it was recently shown that such physiologic deficits also are found in healthy siblings of patients with schizophrenia even if their accuracy and reaction time on the working memory task are indistinguishable from normal control subjects (Callicott et al 1998a). These various findings indicate that deficits in prefrontal cortical information processing are associated not only with schizophrenia, but also with increased genetic risk for schizophrenia and, thus, may be a reflection of the biological effects of susceptibility alleles. Therefore, a deficit in prefrontal information processing is an especially attractive intermediate phenotype for further genetic studies.

It should be noted that although studies have identified traits in patients that run in their families and may be inherited, it does not necessarily follow that the genes for these traits are susceptibility genes for schizophrenia. For example, cigarette smoking runs in families, has genetic determinants, and also is associated with risk for lung cancer; however, the susceptibility genes for nicotine dependence are probably not susceptibility genes for cancerous transformation of pulmonary epithelium; however, this argument is not compelling in the case of frontal lobe-related phenotypes and schizophrenia for several reasons: 1) frontal lobe cognitive deficits predict outcome and disability in ill individuals, possibly more so than diagnostic symptoms (Goldberg et al 1995; Green, 1996); and 2) the neurobiological basis of working memory and executive cognition-related traits involve neuronal populations and circuits that are implicated from many other research directions in the basic neuropathology of the disease.

A Gene for Frontal Cortical Information Processing and Susceptibility for Schizophrenia

A biological deficit in prefrontal information processing is an attractive intermediate phenotype related to genetic risk

for schizophrenia. The molecular biology of neuronal processing during working memory has been increasingly explicated in the experimental animal, making it possible to select potential candidate proteins that may explain variation in prefrontal function during executive cognition. Testing of candidate genes based on an understanding of the biological effect of a functional variant of the gene and on the relevance of such an effect to the biology of the illness is likely to be crucial for finding causative genes for common, polygenic diseases (Altshuler et al 2000; Weiss and Terwilliger 2000).

Although there are many cellular proteins involved in prefrontal neuronal function during working memory, a great deal of basic research has focused on the role of dopamine. As described earlier, dopamine modulates prefrontal activity by affecting the excitability of pyramidal (glutamatergic) and local circuit (GABA) neurons. Dopamine afferents to pyramidal neurons synapse on dendritic spines in close proximity to glutamate inputs from other cortical neurons, particularly inputs from hippocampal formation (Carr and Sesack 1996). Dopamine inputs to the dendritic shafts of local circuit (GABA) neurons also appear to be in close proximity to glutamate terminals (Sesack et al 1995). These anatomic observations suggest that dopamine gates the excitatory impact of associative cortical information mediated by intracortically projecting glutamate neurons and by locally recurrent collaterals of pyramidal neurons. Consistent with the anatomic data, physiologic experiments in behaving rats and monkeys have demonstrated that dopamine neurons tune the firing responses of pyramidal neurons in a variety of behavioral contexts, including stress, reward, working memory, and various learning paradigms (Gurden et al 1999; Schultz et al 1993; Schultz and Dickinson 2000; Williams and Goldman-Rakic 1995). These effects are mediated primarily at dopamine-1 receptors (Gurden et al 1999; Williams and Goldman-Rakic 1995), which potentiate NMDA-induced excitation postsynaptically (Seamans et al 2001) while reducing non-NMDA-induced excitation via a presynaptic mechanism (Seamans et al 2001; Gao et al 2001). These opposing effects on glutamate signals (i.e., enhancing NMDA currents, which are associated with sustained activation, while reducing non-NMDA currents, which are associated with transient activity) appear to provide a mechanistic account of the tuning function of dopamine during working memory, in that signals related to sustaining information are enhanced, whereas distracting noise is suppressed. Imaging studies in humans also have shown that pharmacologic manipulation of dopamine activity improves prefrontal physiologic signal to noise during executive cognition and working memory tasks (Daniel et al 1991; Mattay et al 1996, 2000). Overall, these experimental results are consistent with suggestions that dopamine inputs to the primate prefrontal cortex are critical for learning of goal-directed behaviors based on the attribution of meaning to environmental stimuli (Schultz et al 1993; Schultz and Dickinson 2000; Miller 2000).

If dopamine modulation of prefrontal cortical neuronal activity is an important factor in prefrontal information processing, it is reasonable to hypothesize that a genetic polymorphism that would impact the efficacy of dopamine in prefrontal cortex would affect prefrontal physiology and prefrontally mediated behavior. This hypothesis was tested in terms of the gene that encodes catechol-o-methyl transferase (COMT), the postsynaptic enzyme that methylates released dopamine as part of its catabolic cascade to homovanillic acid. Recent evidence suggests that COMT is an especially attractive genetic candidate to impact on prefrontal dopamine function. The COMT gene contains a highly functional and common variation in its coding sequence, a single nucleotide polymorphism at position 472 (guanine-to-adenine substitution), which translates into a valine-to-methionine change in the peptide sequence (Lachman et al 1996; Lotta et al 1995). This single amino acid substitution dramatically affects the temperature lability of the enzyme, such that at 37°C (i.e., body temperature) the met allele has one fourth the enzyme activity of the val allele (Lachman et al 1996; Lotta et al 1995). In peripheral blood and in the liver, most of the variance in COMT activity in human populations is explained by this genotype, and the alleles are codominant (Weinshilboum et al 1999). In the brain, individuals with the val/val genotype would presumably have more rapid inactivation of released dopamine relative to individuals with the met/met genotype, and heterozygous individuals should be intermediate. This putative genotype effect, however, is not likely to be biologically meaningful in terms of prefrontal function unless COMT is important in prefrontal synaptic dopamine inactivation. In the striatum, the synaptic action of dopamine is terminated primarily by transporter reuptake into presynaptic terminals (Giros et al 1996), and COMT does not appear to critically affect DA cycling in striatal synapses (Gainetdinov et al 1998; Jones et al 1998). Surprisingly, in the prefrontal cortex, the situation appears to be quite different. Pharmacologic studies in rats, which have explored directly the impact of COMT on catabolism of released dopamine (Karoum et al 1994), and studies of dopamine turnover in monkeys (Elsworth et al 1987) have implicated COMT in regulating extracellular dopamine concentrations in prefrontal cortex. COMT inhibitors have been shown to improve working memory in rats (Liljequist et al 1997) and in humans (Gasparini et al 1997). Moreover, COMT knockout mice show increases in dopamine tissue concentrations in prefrontal cortex and not in striatum (without changes in norepinephine), and heterozygote mice are intermediate

Table 4. Evidence of a Unique Role of the Catechol-O-Methyl Transferase (COMT) Gene on Prefrontal Function

1. Pharmacologic studies in animals reveal preferential dopamine metabolism by COMT pathway in prefrontal cortex
2. COMT inhibitors improve working memory in rodents and humans
3. COMT knockout mice have increased prefrontal cortical dopamine (and no change in norepinephrine)
4. COMT knockout mice have enhanced memory and response to stress

between homozygote knockouts and wild-type animals (Gogos et al 1998). Remarkably, COMT knockout mice also show superior performance on a memory task and under stress (Kneavel et al 2000) compared with wild-type mice. These various observations, implicating a unique role of COMT in prefrontal cortical dopamine inactivation, may be explained by recent evidence in monkeys and in rats that dopamine transporters are expressed in low density in prefrontal cortex and primarily not within synapses (Lewis et al 2001; Sesack et al 1998). Thus, although transporters on prefrontal dopamine (and also norepinephrine) afferents may play a role in removing dopamine that has diffused outside of the synapse, perhaps indirectly affecting synaptic activity by modifying extrasynaptic dopamine concentration gradients, COMT has a unique and direct impact on synaptic DA function in prefrontal cortex. To reiterate, the apparently selective effect of COMT on dopamine signaling in prefrontal cortex is not because of the distribution of COMT, which is expressed widely in brain in nondopaminergic neurons and glia, but because of the relative low abundance of synaptic DA transporters in prefrontal cortex (Table 4).

Based on these considerations, it was hypothesized that the COMT val allele, because it should result in relatively increased dopamine inactivation, would be associated with relatively compromised prefrontal function. Egan et al (2001b) found that COMT genotype predicted performance on a test of executive cognition, the WCST, in a sample 449 human subjects, with the val allele being associated, as predicted, with relatively poorer performance (i.e., more perseverative errors). Interestingly, the effect of genotype on WCST performance was found to be of similar effect size in normal subjects and patients with schizophrenia, indicating that the effect of this genetic variation on prefrontal executive cognition was not necessarily a schizophrenia-related phenomenon, but rather a generalizable human characteristic. Evidence for an allele load effect also was seen; heterozygote individuals tended to perform midway between homozygote val/val individuals, whose WCST performance was the poorest, and met/met individuals, whose performance was the best. Overall, the COMT genotype predicted 4% of the variance in WCST performance. Although this may seem like a small effect by itself, it is conceivable that in the context of other factors that affect prefrontal function (e.g., injury or aging), this 4% could have a substantial predictive impact on residual function. Interestingly, COMT genotype was not associated with IQ or with nonfrontal-type cognitive tasks. The relationship of COMT genotype to prefrontal executive function also may have evolutionary implications. The met allele appears to be a unique human mutation because it has not been found in great apes (Palmatier et al 1999), suggesting that it may be a factor in evolution of the human prefrontal cortex. Since the initial oral reports of these findings (Weinberger 2000a, 2000b), two independent groups have replicated the effect of COMT genotype on WCST performance (Malhotra et al in press; B.K. Lipska, personal communication). Moreover, T.E. Goldberg (unpublished data, 2001) recently reported similar genotype effects on the N-back working memory task.

It may be reasoned that if COMT genotype predicts performance on a test of executive cognition, presumably because of its underlying biological effect on prefrontal neuronal activity, it might also predict the physiologic activity of prefrontal cortex during the performance of a working memory task, even if task performance is held constant. To test this possibility, three cohorts of subjects, one group of patients with schizophrenia and two groups of unaffected siblings, were studied with the N-back working memory fMRI paradigm that revealed reduced efficiency of information processing in the patients and their unaffected siblings (Egan et al 2001b). The subjects in the unaffected sibling groups were chosen by matching for task performance so that the fMRI response could be compared based on genotype and not confounded by performance differences. Although earlier studies suggested that prefrontal dopamine activity modulated the physiologic response during the WCST (Daniel et al 1991; Mattay et al 1996), the impact of variations in dopamine on the working memory fMRI paradigm was uncertain. Mattay et al (in press), therefore, explored this question in a sample of patients with Parkinson's disease following 12 hours of L-dopa withdrawal and after L-dopa administration. Relative dopamine deficiency resulted in an exaggeration of the prefrontal cortical fMRI response during the working memory task (i.e., "inefficiency"), even though response accuracy was unchanged. Thus, in the study of Egan et al (2001b), it was hypothesized that COMT genotype would predict the efficiency of the cortical response and that the val allele, because it would be associated with relatively greater DA inactivation (i.e., relative dopamine "deficiency"), would be associated with lesser physiologic efficiency (analogous to the findings in the untreated patients with Parkinson's disease). The results were remarkably reproducible in each of the three

cohorts; similar locales primarily within the prefrontal and cingulate cortices showed precisely these predicted effects of COMT genotype. Moreover, as in the WCST data, an allele load effect was seen in that val/val individuals were less efficient than val/met individuals, who were less efficient than met/met individuals.

Because COMT genotype has an impact on the effectiveness and efficiency of information processing in prefrontal cortex, and because abnormal prefrontal cortical function is associated with schizophrenia and with genetic risk for schizophrenia, it follows that COMT genotype may be a factor contributing risk to manifest schizophrenia. Earlier studies testing for an association between the diagnosis of schizophrenia and COMT genotype have been inconclusive. Case-control association studies, which compare allele frequencies between ill and well populations, have produced some positive (de Chaldee et al 1999) but mostly negative results (Palmatier et al 1999). These studies, however, which have generally involved underpowered samples, are prone to artifacts related to population admixture or stratification. Palmatier et al (1999) reported that COMT allele frequencies vary across certain ethnic populations, suggesting that population stratification artifacts are potentially important confounders in case-control studies of this gene. To avoid this artifact, the proportion of alleles transmitted from heterozygote parents to ill offspring can be measured within families using the Transmission Disequilibrium Test (TDT; Spielman et al 1993). Although this test has reduced power compared with the case-control approach, it is immune to population stratification effects because the frequencies of transmitted alleles are determined within families. There are three earlier TDT reports of COMT alleles in schizophrenia in the literature, two involving completely independent samples, and all have been positive for the val allele (Kunugi et al 1997; Li et al 1996, 2000). These earlier reports have generally been regarded as inconclusive because of the negative case-control studies and because of uncertainty about how the val allele would increase biological susceptibility. Egan et al (2001b) studied 104 parent–offspring trios and also found that the val allele was transmitted significantly more frequently to the schizophrenic offspring than would be predicted by random assortment (60% transmission of val, $p < .04$), consistent in terms of allele frequencies and effect size with the earlier TDT reports. Moreover, excessive transmission to the healthy sibling was not greater than predicted by chance assortment.

Although our TDT results by themselves provide weak statistical evidence for the COMT val allele increasing risk for schizophrenia, the data are consistent with earlier TDT studies, which to date, have been uniformly positive for the val allele; however, in the case of polygenic disorders such as schizophrenia, even strong statistical evidence of association is not likely to be sufficient to validate that a causative gene has been found (Altshuler et al 2000; Weiss and Terwilliger 2000). Moreover, association data cannot rule out that another mutation in the same or a nearby gene is the causative allele and is in linkage dysequilibrium with the associated marker allele. As recently argued with respect to the weak effect of a susceptibility gene for Type II diabetes (Horikawa et al 2000), the endgame in identifying causative genes for complex, polygenic disorders will depend on clarification of the biology of the allele and how it relates to the biology of the illness. The following convergent evidence argues strongly that the val allele of the COMT gene is the causative mutation in a susceptibility gene for schizophrenia: 1) a defect in prefrontal information processing is a core biological feature of schizophrenia, 2) a defect in prefrontal function is associated with genetic risk for schizophrenia, 3) the COMT val/met polymorphism has an effect on protein structure and enzyme activity, 4) the val/met polymorphism has a predicted effect on prefrontal function, and 4) COMT inhibitor drugs and COMT gene knockouts change prefrontal function (Table 5).

Table 5. Evidence that Catechol-O-Methyl Transferase (COMT) val^{158} Is a Susceptibility Gene for Schizophrenia

1. 22q11 locus near "suggestive" positive linkage signal from genome scan studies
2. Functional polymorphism markedly affects the activity of an enzyme involved in prefrontal dopamine function
3. Predicted adverse effects on executive cognition and prefrontal cortical physiology relate to core biologic aspects of schizophrenia
4. Four positive transmission disequilibrium test studies

In many respects, the effect of the COMT val allele on risk for schizophrenia is analogous to the apolipoprotein (APO) E4 allele increasing risk for Alzheimer's disease, although the APO E4 effect is greater (Roses 1998). The APO E4 allele is not found in the majority of patients with Alzheimer's disease, nor is it a risk factor only for Alzheimer's disease. It is thought to increase risk for Alzheimer's disease by virtue of its biological effects on lipid trafficking in tissue, an effect that also increases risk for other medical conditions. The COMT val allele is certainly not a necessary, or sufficient, causative factor for schizophrenia, nor is it likely to increase risk only for schizophrenia; however, its biological effect on prefrontal function and the relevance of prefrontal function for schizophrenia implicate a mechanism by which it increases liability for this disorder. Metaphorically speaking, one might imagine the threshold of a cliff as representing a threshold of failure of critical prefrontal function. Patients with schizophrenia have fallen off the cliff. Healthy individuals are positioned far from the threshold, although

a variety of factors, genetic and environmental, will determine any individual's proximity to the precipice. Unaffected siblings of patients with schizophrenia, perhaps because of other shared alleles and environmental factors that also affect prefrontal function, tend to be closer to the edge than individuals without schizophrenia risk factors. The COMT val allele moves everyone a little closer to the precipice, including healthy subjects, unaffected siblings, and individuals destined to evince schizophrenia. Because some individuals might be teetering on the edge for reasons having nothing to do with COMT (e.g., other genes or developmental compromise, such as that modeled in the experimental animals with hippocampal disconnection or other putative brain defects associated with schizophrenia that may impact indirectly on prefrontal function, such as in hippocampus or thalamus), inheritance of the val allele will cause a few of them to lose their grip and fall off. This metaphor illustrates how there can be a population-attributable risk to the val allele, in that notwithstanding this allele, these few individuals would not have developed schizophrenia. In fact, the degree to which the val allele contributes to the overall schizophrenia prevalence in a population (i.e., its population attributable risk) can be estimated using a standard statistical genetic calculation from knowledge of the allele frequencies (see below), population frequency of schizophrenia (approximately 1%), and the odds ratio (see below) as detailed in Khoury et al (1993). Based on this calculation, in the United States, more than 100,000 cases of schizophrenia would not manifest the syndrome except for inheritance of the val allele.

Afterword

The data summarized in this review converge on the conclusions that 1) abnormalities of intrinsic prefrontal neuronal circuitry and information processing are core biological aspects of schizophrenia, 2) many of the clinical and biological features associated with schizophrenia are emergent phenomena related to this core biology, and 3) a genetic polymorphism that affects prefrontal information processing is a risk gene for schizophrenia because it interacts with this core biology. There are a number of caveats that should be kept in mind in considering these conclusions. First, schizophrenic deficits in information processing, in neuronal circuitry, and in physiologic activity are not unique to prefrontal cortex. Similar abnormalities have been described in other areas of brain in patients with schizophrenia, especially in the hippocampal formation (reviewed in Weinberger 1999). It is conceivable that independent environmental risk factors and genes contribute to abnormalities associated with other brain systems. It is also likely that risk factors other than COMT genotype contribute to prefrontal deficits; however, if the COMT effect interacts multiplicatively or even additively with these other factors, the COMT val allele in the context of these other factors (e.g., a defective "hippocampal" gene, a prenatal cortical injury) will have an exaggerated effect. Second, all patients with schizophrenia are not likely to have the same risk genes or be exposed to the same environmental factors. Thus, the COMT genotype may contribute risk differently across populations, perhaps because of protective or modifying alleles at other loci. Again, similar results have been reported for APO E4, which does not appear to consistently increase risk for Alzheimer's disease in individuals of recent African ancestry (Tang et al 1998). Third, the contribution of the COMT val/val genotype to risk is small; it increases the odds ratio of manifesting the illness only 1.5-fold. This may seem exceedingly weak, and perhaps even inconsequential, although the population attributable risk is not trivial; however, it is debatable whether a greater effect can be expected of any mental illness susceptibility gene in general populations. It is frequently stated in the literature that the genetic contributions to mental illness in unselected population samples are likely to involve common alleles, which will only account for small risk effects (Gershon 2000; Pulver 2000); COMT would seem to be one such gene. In our clinical sample (more than 300 patients and 600 control subjects) of Caucasian European ancestry, the val allele has a frequency in patients of approximately 60% and in control subjects of approximately 52% (significantly different at the .01 level). Thus, most healthy individuals have a val allele and many patients with schizophrenia do not; however, assumptions about the risk effects of a particular susceptibility gene pertain to risk for groups—an average effect of a common functional polymorphism across many individuals. The clinical impact of COMT genotype within any particular individual could be large or small, depending on a variety of other genetic and environmental background factors.

Efforts to put the magnitude of the COMT effect in perspective may be aided by considering again a susceptibility gene recently identified for adult-onset diabetes. Calpain-10 has been heralded as a gene that increases risk for this common form of diabetes (Alschuler et al 2000; Horikawa et al 2000). Yet the risk allele, which is found in 80% of diabetic patients, also is found in 75% of the healthy human population. Clearly, in general populations, this is a weak association and a small genetic effect, although the effect appears to be greater in selected subpopulations (Horikawa et al 2000). The population attributable risk of Type II diabetes for the high-risk Calpain-10 haplotype in Europeans is comparable with our calculations for the COMT val allele and schizophrenia; however, in contrast to the evidence for COMT and

schizophrenia, in the case of the putative diabetes gene, the biological effect of the mutation is unknown, as is how it contributes risk for diabetes. In the case of COMT and schizophrenia, the weight of the data provides convergent validity for the conclusion that this gene increases risk because of its biology (i.e., its effect on dopamine-mediated prefrontal information processing) and the importance of this biology for the pathophysiology of schizophrenia. This represents the first evidence of a plausible biological mechanism by which a specific allele affects variation in normal human cognition and risk for mental illness.

Aspects of this work were presented at the conference, "New Perspectives on the Neurobiology of Schizophrenia and the Role of Atypical Antipsychotics," held November 10–12, 2000, in Key West, Florida. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant provided by AstraZeneca.

References

Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, et al (1998): Increased striatal dopamine transmission in schizophrenia: Confirmation in a second cohort. *Am J Psychiatry* 155:761–767.

Abrams R, Taylor MA (1979): Differential EEG patterns in affective disorder and schizophrenia. *Arch Gen Psychiatry* 36:1355–1358.

Altshuler D, Daly M, Kruglyak L (2000): Guilt by association. *Nat Genet* 26:135–137.

Andreasen NC, O'Leary DS, Arndt S, Cizadlo T, Rezai K, Watkins GL, et al (1995): I. PET studies of memory: Novel and practiced free recall of complex narratives. *Neuroimage* 2:284–295.

Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Ponto LL, et al (1996): Schizophrenia and cognitive dysmetria: A positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proc Natl Acad Sci USA* 93:9985–9990.

Andreasen NC, O'Leary DS, Flaum M, Nopoulos P, Watkins GL, Boles Ponto LL, et al (1997): Hypofrontality in schizophrenia: Distributed dysfunctional circuits in neuroleptic-naive patients. *Lancet* 349:1730–1734.

Andreasen NC, Paradiso S, O'Leary DS (1998): "Cognitive dysmetria" as an integrative theory of schizophrenia: A dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull* 24:203–218.

Arolt V, Lencer R, Nolte A, Muller-Myhsok B, Purmann S, Schurmann M, et al (1996): Eye tracking dysfunction is a putative phenotypic susceptibility marker of schizophrenia and maps to a locus on chromosome 6p in families with multiple occurrence of the disease. *Am J Med Genet* 67:564–579.

Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD (1997): Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia* 35: 1373–1380.

Barch DM, Carter CS (1998): Selective attention in schizophrenia: Relationship to verbal working memory. *Schizophr Res* 33:53–61.

Benes FM, McSparren J, Bird ED, Vincent SL, SanGiovanni JP (1991): Deficits in small interneurons in prefrontal and anterior cingulate cortex of schizophrenic and schizoaffective patients. *Arch Gen Psychiatry* 48:996–1001.

Berman I, Viegner B, Merson A, Pappas D, Green AI (1997): Differential relationships between positive and negative symptoms and neuropsychological deficits in schizophrenia. *Schizophr Res* 25:1–10.

Berman KF, Torrey EF, Daniel DG, Weinberger DR (1992): Regional cerebral blood flow in monozygotic twins discordant and concordant for schizophrenia. *Arch Gen Psychiatry* 49:927–934.

Bertolino A, Breier A, Callicott JH, Adler C, Mattay VS, Shapiro M, et al (2000b): The relationship between dorsolateral prefrontal neuronal N-acetylaspartate and evoked release of striatal dopamine in schizophrenia. *Neuropsychopharmacology* 22:125–132.

Bertolino A, Callicott JH, Elman I, Mattay VS, Tedeschi G, Frank JA, et al (1998a): Regionally specific neuronal pathology in untreated patients with schizophrenia: A proton magnetic resonance spectroscopic imaging study. *Biol Psychiatry* 43:641–648.

Bertolino A, Callicott JH, Mattay VS, Weidenhammer KM, Rakow R, Egan MF, et al (2001): The effect of treatment with antipsychotic drugs on brain N-acetylaspartate measures in patients with schizophrenia. *Biol Psychiatry* 49:39–46.

Bertolino A, Esposito G, Callicott JH, Mattay VS, Van Horn JD, Frank JA, et al (2000): Specific relationship between prefrontal neuronal N-acetylaspartate and activation of the working memory cortical network in schizophrenia. *Am J Psychiatry* 157:26–33.

Bertolino A, Knable MB, Saunders RC, Callicott JH, Kolachana B, Mattay VS, et al (1999a): The relationship between dorsolateral prefrontal N-acetylaspartate measures and striatal dopamine activity in schizophrenia. *Biol Psychiatry* 45:660–667.

Bertolino A, Kumra S, Callicott JH, Mattay VS, Lestz RM, Jacobsen L, et al (1998b): Common pattern of cortical pathology in childhood-onset and adult-onset schizophrenia as identified by proton magnetic resonance spectroscopic imaging. *Am J Psychiatry* 155:1376–1383.

Bertolino A, Nawroz S, Mattay VS, Barnett AS, Duyn JH, Moonen CT, et al (1996): Regionally specific pattern of neurochemical pathology in schizophrenia as assessed by multislice proton magnetic resonance spectroscopic imaging. *Am J Psychiatry* 153:1554–1563.

Bertolino A, Roffman JL, Lipska BK, Van Gelderen P, Olson A, Weinberger DR (1999b): Postpubertal emergence of prefrontal neuronal deficits and altered dopaminergic behaviors in rats with neonatal hippocampal lesions. *Soc Neurosci Abstract* 25:1294.

Bertolino A, Saunders RC, Mattay VS, Bachevalier J, Frank JA, Weinberger DR (1997): Altered development of prefrontal neurons in rhesus monkeys with neonatal mesial temporolimbic lesions: A proton magnetic resonance spectroscopic imaging study. *Cereb Cortex* 7:740–748.

Bertolino A, Weinberger DR (1999b): Proton magnetic reso-

nance spectroscopy in schizophrenia. *Eur J Radiol* 30:132–141.

Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, et al (1997): Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: Evidence from a novel positron emission tomography method. *Proc Natl Acad Sci USA* 94:2569–2574.

Brzustowicz LM, Hodgkinson KA, Chow EW, Honer WG, Bassett AS (2000): Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21–q22. *Science* 288:678–682.

Buchsbaum MS, Someya T, Teng CY, Abel L, Chin S, Najafi A, et al (1996): PET and MRI of the thalamus in never-medicated patients with schizophrenia. *Am J Psychiatry* 153:191–199.

Bullmore ET, Frangou S, Murray RM (1997): The dysplastic net hypothesis: An integration of developmental and dysconnectivity theories of schizophrenia. *Schizophr Res* 28:143–156.

Bunney WE, Bunney BG (2000): Evidence for a compromised dorsolateral prefrontal cortical parallel circuit in schizophrenia. *Brain Res Brain Res Rev* 31:138–146.

Busatto GF, Costa DC, Ell PJ, Pilowsky LS, David AS, Kerwin RW (1994): Regional cerebral blood flow (rCBF) in schizophrenia during verbal memory activation: A 99 mTc-HM-PAO single photon emission tomography (SPET) study. *Psychol Med* 24:463–472.

Callicott JH, Bertolino A, Egan MF, Mattay VS, Langheim FJP, Weinberger DR (2000b): Selective relationship between prefrontal N-acetylaspartate measures and negative symptoms in schizophrenia. *Am J Psychiatry* 157:1646–1651.

Callicott JH, Bertolino A, Mattay VS, Langheim FJP, Duyn J, Coppola R, et al (2000a): Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb Cortex* 10:1078–1092.

Callicott JH, Egan M, Mattay V, et al (1998b): Altered prefrontal cortical function in unaffected siblings of patients with schizophrenia. *Neuroimage* 7:S895.

Callicott JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA, et al (1999): Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb Cortex* 9:20–26.

Callicott JH, Ramsey NF, Tallent K, Bertolino A, Knable MB, Coppola R, et al (1998a): Functional magnetic resonance imaging brain mapping in psychiatry: Methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology* 18:186–196.

Callicott JH, Weinberger DR (1999): Neuropsychiatric dynamics: The study of mental illness using functional magnetic resonance imaging. *Eur J Radiol* 30:95–104 .

Cannon TD, Huttunen MO, Lonnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, et al (2000): The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *Am J Hum Genet* 67:369–382.

Cannon TD, Zorrilla LE, Shtasel D, Gur RE, Gur RC, Marco EJ, et al (1994): Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. *Arch Gen Psychiatry* 51:651–661.

Carr DB, Sesack SR (1996): Hippocampal afferents to the rat prefrontal cortex: Synaptic targets and relation to dopamine terminals. *J Comp Neurol* 369:1–15.

Carr DB, Sesack SR (2000): Projections from the rat prefrontal cortex to the ventral tegmental area: Target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. *J Neurosci* 20:3864–3873.

Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998a): Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–749.

Carter CS, Perlstein W, Ganguli R, Brar J, Mintun M, Cohen JD (1998b): Functional hypofrontality and working memory dysfunction in schizophrenia. *Am J Psychiatry* 155:1285–1287.

Catafau AM, Parellada E, Lomena FJ, Bernardo M, Pavia J, Ros D, et al (1994): Prefrontal and temporal blood flow in schizophrenia: Resting and activation technetium-99 m-HM-PAO SPECT patterns in young neuroleptic-naive patients with acute disease. *J Nucl Med* 35:935–941.

Cegalis JA, Sweeney JA (1979): Eye movements in schizophrenia: A quantitative analysis. *Biol Psychiatry* 14:13–26.

Chafee MV, Goldman-Rakic PS (2000): Inactivation of parietal and prefrontal cortex reveals interdependence of neural activity during memory-guided saccades. *J Neurophysiol* 83: 1550–1566.

Clark JB (1998): N-acetyl aspartate: A marker for neuronal loss or mitochondrial dysfunction. *Dev Neurosci* 20:271–276.

Cornblatt BA, Keilp JG (1994): Impaired attention, genetics, and the pathophysiology of schizophrenia. *Schizophr Bull* 20:31–46.

Curtis VA, Bullmore ET, Brammer MJ, Wright IC, Williams SC, Morris RG, et al (1998): Attenuated frontal activation during a verbal fluency task in patients with schizophrenia. *Am J Psychiatry* 155:1056–1063.

Curtis VA, Bullmore ET, Morris RG, Brammer MJ, Williams SC, Simmons A, et al (1999): Attenuated frontal activation in schizophrenia may be task dependent. *Schizophr Res* 37:35–44.

Daniel DG, Weinberger DR, Jones DW, Zigun JR, Coppola R, Handel S, et al (1991): The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. *J Neurosci* 11:1907–1917.

de Chaldee M, Laurent C, Thibaut F, Martinez M, Samolyk D, Petit M, et al (1999): Linkage disequilibrium on the COMT gene in French schizophrenics and control subjects. *Am J Med Genet* 88:452–457.

Deicken RF, Pegues M, Amend D (1999): Reduced hippocampal N-acetylaspartate without volume loss in schizophrenia. *Schizophr Res* 37:217–223.

Deicken RF, Zhou L, Corwin F, Vinogradov S, Weiner MW (1997): Decreased left frontal lobe N-acetylaspartate in schizophrenia. *Am J Psychiatry* 154:688–690.

Deicken RF, Zhou L, Schuff N, Fein G, Weiner MW (1998): Hippocampal neuronal dysfunction in schizophrenia as measured by proton magnetic resonance spectroscopy. *Biol Psychiatry* 43:483–488.

De Stefano N, Matthews PM, Antel JP, Preul M, Francis G, Arnold DL (1995): Chemical pathology of acute demyelinating lesions and its correlation with disability. *Ann Neurol* 38:901–909.

Dinse HR, Godde B, Hilger T, Haupt SS, Spengler F, Zepka R (1997): Short-term functional plasticity of cortical and tha-

lamic sensory representations and its implication for information processing. *Adv Neurol* 73:159–178.

Doraiswamy PM, Charles HC, Krishnan KR (1998): Prediction of cognitive decline in early Alzheimer's disease. *Lancet* 352:1678.

Egan M, Goldberg TE, Gsheidle T, Bigelow LB, Weinberger DR (2001a): Relative risk for cognitive impairments in siblings of patients with schizophrenia. *Biol Psychiatry.* 50:98–107.

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al (2001b): Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci USA* 98:6917–6922.

Elsworth JD, Leahy DJ, Roth RH, Redmond DE Jr. (1987): Homovanillic acid concentrations in brain, CSF and plasma as indicators of central dopamine function in primates. *J Neural Transm* 68:51–62.

Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT (1999): Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: A 4-year follow-up study. *J Abnorm Psychol* 108:176–181.

Fletcher PC, McKenna PJ, Frith CD, Grasby PM, Friston KJ, Dolan RJ (1998): Brain activations in schizophrenia during a graded memory task studied with functional neuroimaging. *Arch Gen Psychiatry* 55:1001–1008.

Franke P, Maier W, Hain C, Klingler T (1992): Wisconsin Card Sorting Test: An indicator of vulnerability to schizophrenia? *Schizophr Res* 6:243–249.

Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, et al (1997): Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proc Natl Acad Sci USA* 94:587–592.

Friston KJ, Frith CD (1995): Schizophrenia: A disconnection syndrome? *Clin Neurosci* 3:89–97.

Friston KJ, Liddle PF, Frith CD, Hirsch SR, Frackowiak RS (1992): The left medial temporal region and schizophrenia: A PET study. *Brain* 115:367–382.

Funahashi S, Bruce CJ, Goldman-Rakic PS (1989): Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol* 61:331–349.

Funahashi S, Bruce CJ, Goldman-Rakic PS (1991): Neuronal activity related to saccadic eye movements in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol* 65:1464–1483.

Fuster JM, Bauer RH, Jervey JP (1985): Functional interactions between inferotemporal and prefrontal cortex in a cognitive task. *Brain Res* 330:299–307.

Gainetdinov RR, Jones SR, Fumagalli F, Wightman RM, Caron MG (1998): Re-evaluation of the role of the dopamine transporter in dopamine system homeostasis. *Brain Res Brain Res Rev* 26:148–153.

Gao W-J, Krimer LS, Goldman-Rakic PS (2001): Presynaptic regulation of recurrent excitation by D1 receptors in prefrontal circuits. *Proc Natl Acad Sci USA* 98:295–300.

Gasparini M, Fabrizio E, Bonifati E, Meco G (1997): Cognitive improvement during Tolcapone treatment in Parkinson's disease. *J Neural Transm* 104:887–894.

Gershon ES (2000): Bipolar illness and schizophrenia as oligogenic diseases: Implications for the future. *Biol Psychiatry* 47:240–244.

Giros B, Jaber M, Jones SR, Wightman RM, Caron MG (1996): Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature* 379:606–612.

Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, et al (1998): Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. *Proc Natl Acad Sci USA* 95:9991–9996.

Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR (1997): Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Arch Gen Psychiatry* 54:159–165.

Goldberg TE, Berman KF, Fleming K, Ostrem J, Van Horn JD, Esposito G, et al (1998a): Uncoupling cognitive workload and prefrontal cortical physiology: A PET rCBF study. *Neuroimage* 7:296–303.

Goldberg TE, Berman KF, Mohr E, Weinberger DR (1990): Regional cerebral blood flow and cognitive function in Huntington's disease and schizophrenia: A comparison of patients matched for performance on a prefrontal-type task. *Arch Neurol* 47:418–422.

Goldberg TE, Kelsoe JR, Weinberger DR, Pliskin NH, Kirwin PD, Berman KF (1988): Performance of schizophrenic patients on putative neuropsychological tests of frontal lobe function. *Int J Neurosci* 42:51–58.

Goldberg TE, Torrey EF, Gold JM, Bigelow LB, Ragland RD, Taylor E, et al (1995): Genetic risk of neuropsychological impairment in schizophrenia: A study of monozygotic twins discordant and concordant for the disorder. *Schizophr Res* 17:77–84.

Goldberg TE, Torrey EF, Gold JM, Ragland JD, Bigelow LB, Weinberger DR (1993): Learning and memory in monozygotic twins discordant for schizophrenia. *Psychol Med* 23:71–85.

Goldberg TE, Weinberger DR (1988): Probing prefrontal function in schizophrenia with neuropsychological paradigms. *Schizophr Bull* 14:179–183.

Goldberg TE, Weinberger DR, Berman KF, Pliskin NH, Podd MH (1987): Further evidence for dementia of the prefrontal type in schizophrenia? A controlled study of teaching the Wisconsin Card Sorting Test. *Arch Gen Psychiatry* 44:1008–1014.

Goldman-Rakic PS (1999): The physiological approach: Functional architecture of working memory and disordered cognition in schizophrenia. *Biol Psychiatry* 46:650–661.

Gottesman II, Moldin SO (1997): Schizophrenia genetics at the millennium: Cautious optimism. *Clin Genet* 52:404–407.

Gottesman II, Shields J (1982): *Schizophrenia: The Epigenetic Puzzle*. Cambridge: Cambridge University Press.

Green MF (1996): What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 153:321–330.

Guenther W, Davous P, Godet JL, Guillibert E, Breitling D, Rondot P (1988): Bilateral brain dysfunction during motor activation in type II schizophrenia measured by EEG mapping. *Biol Psychiatry* 23:295–311.

Gur RE, Mozley PD, Resnick SM, Mozley LH, Shtasel DL, Gallacher F, et al (1995): Resting cerebral glucose metabolism in first-episode and previously treated patients with schizophrenia relates to clinical features. *Arch Gen Psychiatry* 52:657–667.

Gurden H, Tassin JP, Jay TM (1999): Integrity of the mesocortical dopaminergic system is necessary for complete expression of in vivo hippocampal-prefrontal cortex long-term potentiation. *Neuroscience* 94:1019–1027.

Herrmann M, Ruppin E, Usher M (1993): A neural model of the dynamic activation of memory. *Biol Cybern* 68:455–463.

Hoffmann RE, Buchsbaum MS, Jensen RV, Guich SM, Tsai K, Nuechterlein KH (1996): Dimensional complexity of EEG waveforms in neuroleptic-free schizophrenic patients and normal control subjects. *J Neuropsychiatry Clin Neurosci* 8:436–441.

Holzman PS, Proctor LR, Levy DL, Yasillo NJ, Meltzer HY, Hurt SW (1974): Eye-tracking dysfunctions in schizophrenic patients and their relatives. *Arch Gen Psychiatry* 31:143–151.

Honer WG, Falkai P, Chen C, Arango V, Mann JJ, Dwork AJ, et al (1999): Synaptic and plasticity-associated proteins in anterior frontal cortex in severe mental illness. *Neuroscience* 91:1247–1255.

Horikawa Y, Oda N, Cox NJ, Orho-Melander M, Hara M, Hinokio Y, et al (2000): Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus. *Nat Genet* 26:163–175.

Hugg JW, Kuzniecky RI, Gilliam FG, Morawetz RB, Fraught RE, Hetherington HP (1996): Normalization of contralateral metabolic function following temporal lobectomy demonstrated by 1H magnetic resonance spectroscopic imaging. *Ann Neurol* 40:236–239.

Ingvar D, Franzen G (1974): Distribution of cerebral activity in chronic schizophrenia. *Lancet* 2:1484–1486.

Jacobsen LK, Hong WL, Hommer DW, Hamburger SD, Castellanos FX, Frazier JA, et al (1996): Smooth pursuit eye movements in childhood-onset schizophrenia: Comparison with attention-deficit hyperactivity disorder and normal control subjects. *Biol Psychiatry* 40:1144–1154.

Jenkins BG, Klivenyi P, Kustermann E, Andreassen OA, Ferrante RJ, Rosen BR, et al (2000): Nonlinear decrease over time in N-acetyl aspartate levels in the absence of neuronal loss and increases in glutamine and glucose in transgenic Huntington's disease mice. *J Neurochem* 74:2108–2119.

Jenkins BG, Rosas HD, Chen YC, Makabe T, Myers R, MacDonald M, et al (1998): 1H NMR spectroscopy studies of Huntington's disease: Correlations with CAG repeat numbers. *Neurology* 50:1357–1365.

Jones SR, Gainetdinov RR, Jaber M, Giros B, Wightman RM, Caron MG (1998): Profound neuronal plasticity in response to inactivation of the dopamine transporter. *Proc Natl Acad Sci USA* 95:4029–4034.

Karni A, Meyer G, Rey-Hipolito C, Jezzard P, Adams MM, Turner R, et al (1998): The acquisition of skilled motor performance: Fast and slow experience-driven changes in primary motor cortex. *Proc Natl Acad Sci USA* 95:861–868.

Karoum F, Chrapusta SJ, Egan MF (1994): 3-Methoxytyramine is the major metabolite of released dopamine in the rat frontal cortex: Reassessment of the effects of antipsychotics on the dynamics of dopamine release and metabolism in the frontal cortex, nucleus accumbens, and striatum by a simple two pool model. *J Neurochem* 63:972–979.

Karson CN, Coppola R, Morihisa JM, Weinberger DR (1987): Computed electroencephalographic activity mapping in schizophrenia: The resting state reconsidered. *Arch Gen Psychiatry* 44:514–517.

Karson CN, Mrak RE, Schluterman KO, Sturner WQ, Sheng JG, Griffin WS (1999): Alterations in synaptic proteins and their encoding mRNAs in prefrontal cortex in schizophenia: A possible neurochemical basis for 'hypofrontality.' *Mol Psychiatry* 4:39–45.

Kawasaki Y, Maeda Y, Higashima M, Nagasawa T, Koshino Y, Suzuki M, et al (1997): Reduced auditory P300 amplitude, medial temporal volume reduction and psychopathology in schizophrenia. *Schizophr Res* 26:107–115.

Kawasaki Y, Maeda Y, Suzuki M, Urata K, Higashima M, Kiba K, et al (1993): SPECT analysis of regional cerebral blood flow changes in patients with schizophrenia during the Wisconsin Card Sorting Test. *Schizophr Res* 10:109–116.

Keefe RS, Roitman SE, Harvey PD, Blum CS, Du Pre RL, Prieto DM, et al (1995): A pen-and-paper human analogue of a monkey prefrontal cortex activation task: Spatial working memory in patients with schizophrenia. *Schizophr Res* 17:25–33.

Kendler KS, Karkowski-Shuman L, O'Neill FA, Straub RE, MacLean CJ, Walsh D (1997): Resemblance of psychotic symptoms and syndromes in affected sibling pairs from the Irish Study of High-Density Schizophrenia Families: Evidence for possible etiologic heterogeneity. *Am J Psychiatry* 154:191–198.

Kendler KS, MacLean CJ, O'Neill FA, Burke J, Murphy B, Duke F (1996): Evidence for a schizophrenia vulnerability locus on chromosome 8p in the Irish Study of High-Density Schizophrenia Families. *Am J Psychiatry* 153:1534–1540.

Keshavan MS, Stanley JA, Pettegrew JW (2000): Magnetic resonance spectroscopy in schizophrenia: Methodological issues and findings—Part II. *Biol Psychiatry* 48:369–380.

Khoury MJ, Beaty TH, Cohen BH (1993): *Fundamentals of Genetic Epidemiology*. New York: Oxford University Press.

Kneavel M, Gogos J, Karayiorgou K, Luine V (2000): Interaction of COMT gene deletion and environment on cognition *Soc Neurosci Abstracts* 26:1–2.

Kremen WS, Seidman LJ, Pepple JR, Lyons MJ, Tsuang MT, Faraone SV (1994): Neuropsychological risk indicators for schizophrenia: A review of family studies. *Schizophr Bull* 20:103–119.

Kunugi H, Vallada HP, Sham PC, Hoda F, Arranz MJ, Li T, et al (1997): Catechol-O-methyltransferase polymorphisms and schizophrenia: A transmission disequilibrium study in multiply affected families. *Psychiatr Genet* 7:97–101.

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM (1996): Human catechol-O-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics* 6:243–250.

Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, et al (1996): Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci USA* 93:9235–9240.

Leboyer M, Bellivier F, Nosten-Bertrand M, Jouvent R, Pauls D, Mallet J (1998): Psychiatric genetics: Search for phenotypes. *Trends Neurosci* 21:102–105.

Lewis DA (1997): Development of the prefrontal cortex during adolescence: Insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology* 16:385–398.

Lewis DA, Melchitzky DS, Sesack SR, Whitehead RE, Sungyoung AUH, Sampson A (2001): Dopamine transporter immunoreactivity in monkey cerebral cortex. *J Comp Neurol* 432:119–136.

Li T, Ball D, Zhao J, Murray RM, Liu X, Sham PC, et al (2000): Family-based linkage disequilibrium mapping using SNP marker haplotypes: Application to a potential locus for schizophrenia at chromosome 22q11. *Mol Psychiatry* 5:77–84.

Li T, Sham PC, Vallada H, Xie T, Tang X, Murray RM, et al (1996): Preferential transmission of the high activity allele of COMT in schizophrenia. *Psychiatr Genet* 6:131–133.

Lieberman JA, Alvir JM, Woerner M, Degreef G, Bilder RM, Ashtari M, et al (1992): Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. *Schizophr Bull* 18:351–371.

Liljequist R, Haapalinna H, Ahlander M, Ying HL, Mannisto PT (1997): Catechol O-methyltransferase inhibitor tolcapone has minor influence on performance in experimental memory models in rats. *Behav Brain Res* 82:195–202.

Lillrank SM, Lipska BK, Kolachana BS, Weinberger DR (1999): Attenuated extracellular dopamine levels after stress and amphetamine in the nucleus accumbens of rats with neonatal ventral hippocampal damage. *J Neural Transm* 106:183–196.

Lipska BK, al-Amin HA, Weinberger DR (1998): Excitotoxic lesions of the rat medial prefrontal cortex: Effects on abnormal behaviors associated with neonatal hippocampal damage. *Neuropsychopharmacology* 19:451–464.

Lipska BK, Jaskiw GE, Weinberger DR (1993): Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: A potential animal model of schizophrenia. *Neuropsychopharmacology* 9:67–75.

Lipska BK, Weinberger DR (2000): To model a psychiatric disorder in animals: Schizophrenia as a reality test. *Neuropsychopharmacology* 23:223–239.

Lipska BK, Weinberger DR, Kolb B (2000, December): Synaptic pathology in prefrontal cortex and nucleus accumbens of adult rats with neonatal hippocampal damage. *Abs Am Coll Neuropsychopharmacol* 209.

Litman RE, Torrey EF, Hommer DW, Radant AR, Pickar D, Weinberger DR (1997): A quantitative analysis of smooth pursuit eye tracking in monozygotic twins discordant for schizophrenia. *Arch Gen Psychiatry* 54:417–426.

Lotta T, Vidgren J, Tilgmann C, Ulmanen I, Melen K, Julkunen I, et al (1995): Kinetics of human soluble and membrane-bound catechol O-methyltransferase: A revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry* 34:4202–4210.

Mahurin RK, Velligan DI, Miller AL (1998): Executive-frontal lobe cognitive dysfunction in schizophrenia: A symptom subtype analysis. *Psychiatry Res* 79:139–149.

Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg TE, Goldman D (in press): A functional polymorphism in the COMT gene and performance on the Wisconsin Card Sort Test. *Am J Psychiatry*.

Manoach DS, Gollub RL, Benson ES, Searl MM, Goff DC, Halpern E, et al (2000): Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biol Psychiatry* 48:99–109.

Manoach DS, Press DZ, Thangaraj V, Searl MM, Goff DC, Halpern E, et al (1999): Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biol Psychiatry* 45:1128–1137.

Mattay VS, Berman KF, Ostrem JL, Esposito G, Van Horn JD, Bigelow LB, et al (1996): Dextroamphetamine enhances "neural network-specific" physiological signals: A positron-emission tomography rCBF study. *J Neurosci* 16:4816–4822.

Mattay VS, Callicott JH, Bertolino A, Heaton I, Frank JA, Coppola R, et al (2000): Effects of dextroamphetamine on cognitive performance and cortical activation. *Neuroimage* 12:268–275.

Mattay VS, Tessitore A, Callicott JH, Bertolino A, Duyn J, Frank JA, et al (in press): Dopaminergic modulation of working memory circuitry in patients with Parkinson's disease. *Ann Neurol*.

McIntosh AR (1999): Mapping cognition to the brain through neural interactions. *Memory* 7:523–548.

Mellers JD, Adachi N, Takei N, Cluckie A, Toone BK, Lishman WA (1998): SPET study of verbal fluency in schizophrenia and epilepsy. *Br J Psychiatry* 173:69–74.

Mesulam MM (1990): Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol* 5:597–613.

Miller DW, Abercrombie ED (1996): Effects of MK-801 on spontaneous and amphetamine-stimulated dopamine release in striatum measured with in vivo microdialysis in awake rats. *Brain Res Bull* 40:57–62.

Miller EK (2000): The prefrontal cortex and cognitive control. *Nature Rev Neurosci* 1:59–65.

Mirnics K, Middleton FA, Marquez A, Lewis DA, Lewitt P (2000): Molecular characterization of schizophrenia viewed by microarray analysis of gene expression in prefrontal cortex. *Neuron* 28:53–67.

Moffett JR, Namboodiri MA (1995): Differential distribution of N-acetylaspartylglutamate and N-acetylaspartate immunoreactivities in rat forebrain. *J Neurocytol* 24:409–433.

Moghaddam B, Aultman J, Weinberger DR, Lipska BK (1999): Neonatal damage of the rat ventral hippocampus impairs acquisition of a working memory task. *Soc Neurosci Abstract* 25:1891.

Moore GJ, Bebchuk JM, Hasanat K, Chen G, Seraji-Bozorgzad N, Wilds IB, et al (2000): Lithium increases N-acetyl-aspartate in the human brain: In vivo evidence in support of bcl-2's neurotrophic effects? *Biol Psychiatry* 48:1–8.

Murase S, Grenhoff J, Chouvet G, Gonon FG, Svensson TH (1993): Prefrontal cortex regulates burst firing and transmitter release in rat mesolimbic dopamine neurons studied in vivo. *Neurosci Lett* 157:53–56.

Nestor PG, Akdag SJ, O'Donnell BF, Niznikiewicz M, Law S, et al (1998): Word recall in schizophrenia: A connectionist model. *Am J Psychiatry* 155:1685–1690.

O'Donnell P, Lewis BL, Lerman D, Weinberger DR, Lipska BK (1999): Effects of neonatal hippocampal lesions on prefrontal cortical pyramidal cell responses to VTA stimulation. *Soc Neurosci Abstract* 25:1659.

Palmatier MA, Kang AM, Kidd KK (1999): Global variation in the frequencies of functionally different catechol-O-methyltransferase alleles. *Biol Psychiatry* 46:557–567.

Pardo JV, Pardo PJ, Janer KW, Raichle ME (1990): The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proc Natl Acad Sci USA* 87:256–259.

Park S, Holzman PS (1992): Schizophrenics show spatial working memory deficits. *Arch Gen Psychiatry* 49:975–982.

Pastor J, Lafon M, Trave-Massuyes L, Demonet JF, Doyon B, Celsis P (2000): Information processing in large-scale cerebral networks: The causal connectivity approach. *Biol Cybern* 82:49–59.

Pearlson GD, Petty RG, Ross CA, Tien AY (1996): Schizophrenia: A disease of heteromodal association cortex? *Neuropsychopharmacology* 14:1–17.

Petersen SE, van Mier H, Fiez JA, Raichle ME (1998): The effects of practice on the functional anatomy of task performance. *Proc Natl Acad Sci USA* 95:853–860.

Pierri JN, Chaudry AS, Woo TU, Lewis DA (1999): Alterations in chandelier neuron axon terminals in the prefrontal cortex of schizophrenic subjects. *Am J Psychiatry* 156:1709–1719.

Pulver AE (2000): Search for schizophrenia susceptibility genes. *Biol Psychiatry* 47:221–230.

Pulver AE, Karayiorgou M, Wolyniec PS, Lasseter VK, Kasch L, Nestadt G, et al (1994): Sequential strategy to identify a susceptibility gene for schizophrenia: Report of potential linkage on chromosome 22qI. *Am J Med Genet* 54:36–43.

Reite M, Teale P, Zimmerman J, Davis K, Whalen J, Edrich J (1988): Source origin of a 50-msec latency auditory evoked field component in young schizophrenic men. *Biol Psychiatry* 24:495–506.

Risch N, Merikangas K (1996): The future of genetic studies of complex human diseases. *Science* 273:1516–1517.

Roffman JL, Lipska BK, Bertolino A, Van Gelderen P, Olson AW, Khaing ZZ, et al (2000): Local and downstream effects of excitotoxic lesions in the rat medial prefrontal cortex on in vivo 1H-MRS signals. *Neuropsychopharmacology* 22:430–439.

Roses AD (1998): Apolipoprotein E and Alzheimer's disease: The tip of the susceptibility iceberg. *Ann N Y Acad Sci* 855:738–743.

Rypma B, D'Esposito M (1999): The roles of prefrontal brain regions in components of working memory: Effects of memory load and individual differences. *Proc Natl Acad Sci USA* 96:6558–6563.

Sams-Dodd F, Lipska BK, Weinberger DR (1997): Neonatal lesions of the rat ventral hippocampus result in hyperlocomotion and deficits in social behaviour in adulthood. *Psychopharmacology* 132:303–310.

Saunders RC, Kolachana BS, Bachevalier J, Weinberger DR (1998): Neonatal lesions of the medial temporal lobe disrupt prefrontal cortical regulation of striatal dopamine. *Nature* 393:169–171.

Schapiro MB, Berman KF, Alexander GE, Weinberger DR, Rapoport SI (1999): Regional cerebral blood flow in Down syndrome adults during the Wisconsin Card Sorting Test: Exploring cognitive activation in the context of poor performance. *Biol Psychiatry* 45:1190–1196.

Schultz W, Apicella P, Ljungberg T (1993): Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *J Neurosci* 13:900–913.

Schultz W, Dickinson A (2000): Neuronal coding of prediction errors. *Annu Rev Neurosci* 23:473–500.

Seamans JK, Floresco SB, Phillips AG (1998): D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. *J Neurosci* 18:1613–1621.

Seamans JK, Durstewitz D, Christie BR, Stevens CF, Sejnowski TJ (2001): Dopamine D1/D5 receptor modulation of excitatory synaptic inputs to layer V prefrontal cortex neurons. *Proc Natl Acad Sci USA* 98:301–306.

Seidman LJ, Faraone SV, Goldstein JM, Goodman JM, Kremen WS, Tourville J, et al (1999): Thalamic and amygdala-hippocampal volume reductions in first degree relatives of patients with schizophrenia: An MRI-based morphometry analysis. *Biol Psychiatry* 46:941–954.

Selemon LD, Goldman-Rakic PS (1999): The reduced neuropil hypothesis: A circuit based model of schizophrenia. *Biol Psychiatry* 45:17–25.

Sesack SR, Hawrylak VA, Matus C, Guido MA, Levey AI (1998): Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter. *J Neurosci* 18:2697–2708.

Sesack SR, Pickel VM (1992): Prefrontal cortical efferents in the rat synpase on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. *J Comp Neurol* 320:145–160.

Sesack SR, Snyder CL, Lewis DA (1995): Axon terminals immunolabeled for dopamine or tyrosine hydroxylase synapse on GABA-immunoreactive dendrites in rat and monkey cortex. *J Comp Neurol* 363:264–280.

Shadmehr R, Holcomb HH (1997): Neural correlates of motor memory consolidation. *Science* 277:821–825.

Shagass C, Amadeo M, Overton DA (1974): Eye-tracking performance in psychiatric patients. *Biol Psychiatry* 9:245–260.

Shannon-Weickert C, Webster MJ, Hyde TM, Herman MW, Bachus SE, Bali G, Weinberger DR, Kleinman JE (2001): Reduced GAP-43 mRNA in dorsolateral prefrontal cortex of patients with schizophrenia. *Cereb Cortex* 11:36–147.

Sharma T, Lancaster E, Sigmundsson T, Lewis S, Takei N, Gurling H, Pearlson G, Murray R (1999): Lack of normal pattern of cerebral asymmetry in familial schizophrenic patients and their relatives—The Maudsley Family Study. *Schizophr Res* 40:111–120.

Shim SS, Bunney BS, Shi WX (1996): Effects of lesions in the medial prefrontal cortex on the activity of midbrain dopamine neurons. *Neuropsychopharmacology* 15:437–441.

Siegel C, Waldo M, Mizner G, Adler LE, Freedman R (1984): Deficits in sensory gating in schizophrenic patients and their relatives: Evidence obtained with auditory evoked responses. *Arch Gen Psychiatry* 41:607–612.

Spielman RS, McGinnis RE, Ewens WJ (1993): Transmission test for linkage disequilibrium: The insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am J Hum Genet* 52:506–516.

Stevens AA, Goldman-Rakic PS, Gore JC, Fulbright RK, Wexler BE (1998): Cortical dysfunction in schizophrenia during auditory word and tone working memory demonstrated by

functional magnetic resonance imaging. *Arch Gen Psychiatry* 55:1097–1103.

Stone M, Gabrieli JD, Stebbins GT, Sullivan EV (1998): Working and strategic memory deficits in schizophrenia. *Neuropsychology* 12:278–288.

Straub RE, MacLean CJ, O'Neill FA, Burke J, Murphy B, Duke F, et al (1995): A potential vulnerability locus for schizophrenia on chromosome 6p24–22: Evidence for genetic heterogeneity. *Nat Genet* 11:287–293.

Suri RE, Schultz W (1999): A neural network model with dopamine-like reinforcement signal that learns a spatial delayed response task. *Neuroscience* 91:871–890.

Svensson TH, Tung CS (1989): Local cooling of pre-frontal cortex induces pacemaker-like firing of dopamine neurons in rat ventral tegmental area in vivo. *Acta Physiol Scand* 136:135–136.

Tang MX, Stern Y, Marder K, Bell K, Gurland B, Lantigua R, et al (1998): The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. *JAMA* 279:751–755.

Tauscher J, Fischer P, Neumeister A, Rappelsberger P, Kasper S (1998): Low frontal electroencephalographic coherence in neuroleptic-free schizophrenic patients. *Biol Psychiatry* 44: 438–447.

Tomita H, Ohbayashi M, Nakahara K, Hasegawa I, Miyashita Y (1999): Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature* 401:699–703.

Tsai G, Passani LA, Slusher BS, Carter R, Baer L, Kleinman JE, et al (1995): Abnormal excitatory neurotransmitter metabolism in schizophrenic brains. *Arch Gen Psychiatry* 52:829–836.

Tsuang MT (1993): Genotypes, phenotypes, and the brain: A search for connections in schizophrenia. *Br J Psychiatry* 163:299–307.

Urenjak J, Williams SR, Gadian DG, Noble M (1993): Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. *J Neurosci* 13:981–989.

Van Horn JD, Gold JM, Esposito G, Ostrem JL, Mattay V, Weinberger DR, et al (1998): Changing patterns of brain activation during maze learning. *Brain Res* 793:29–38.

van Lier R, Wagemans J (1998): Effects of physical connectivity on the representational unity of multi-part configurations. *Cognition* 69:B1–9.

Vion-Dury J, Nicoli F, Salvan AM, Confort-Gouny S, Dhiver C, Cozzone PJ (1995): Reversal of brain metabolic alterations with zidovudine detected by proton localised magnetic resonance spectroscopy. *Lancet* 345:60–61.

Volz HP, Gaser C, Hager F, Rzanny R, Mentzel HJ, Kreitschmann-Andermahr I, et al (1997): Brain activation during cognitive stimulation with the Wisconsin Card Sorting Test: A functional MRI study on healthy volunteers and schizophrenics. *Psychiatry Res* 75:145–157.

Weickert TW, Goldberg TE, Gold JM, Bigelow LB, Egan MF, Weinberger DR (2000): Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. *Arch Gen Psychiatry* 57:907–913.

Weinberger DR (1987): Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44:660–669.

Weinberger DR (1991): Anteromedial temporal-prefrontal connectivity: A functional neuroanatomical system implicated in schizophrenia. In Carroll BJ, Barrett JE, editors. *Psychopathology and the Brain.* Philadelphia: Lippincott-William & Wilkins, 25–43.

Weinberger DR (1993): A connectionist approach to the prefrontal cortex. *J Neuropsychiatry Clin Neurosci* 5:241–253.

Weinberger DR (1999): Cell biology of the hippocampal formation in schizophrenia. *Biol Psychiatry* 45:395–402.

Weinberger DR (2000a): Neuroimaging in the postgenome era. *Biol Psychiatry* (suppl):1.

Weinberger DR (2000b): The Adolf E. Meyer Lecture, American Psychiatric Association, Chicago, May 15.

Weinberger DR, Berman KF, Iadarola M, Driesen N, Zec RF (1988b): Prefrontal cortical blood flow and cognitive function in Huntington's disease. *J Neurol Neurosurg Psychiatry* 51:94–104.

Weinberger DR, Berman KF, Illowsky BP (1988a): Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: III. a new cohort and evidence for a monoaminergic mechanism. *Arch Gen Psychiatry* 45:609–615.

Weinberger DR, Berman KF, Suddath R, Torrey EF (1992): Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: A magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. *Am J Psychiatry* 149:890–897.

Weinberger DR, Berman KF, Zec RF (1986): Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. regional cerebral blood flow evidence. *Arch Gen Psychiatry* 43:114–124.

Weinberger DR, DeLisi LE, Neophytides AN, Wyatt RJ (1981): Familial aspects of CT scan abnormalities in chronic schizophrenic patients. *Psychiatry Res* 4:65–71.

Weinshilboum RM, Otterness DM, Szumlanski CL (1999): Methylation pharmacogenetics: Catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Annu Rev Pharmacol Toxicol* 39:19–52.

Weiss KM, Terwilliger JD (2000): How many diseases does it take to map a gene with SNPs? *Nat Genet* 26:151–157.

Wexler BE, Stevens AA, Bowers AA, Sernyak MJ, Goldman-Rakic PS (1998): Word and tone working memory deficits in schizophrenia. *Arch Gen Psychiatry* 55:1093–1096.

Williams GV, Goldman-Rakic PS (1995): Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* 376:572–575.

Yurgelun-Todd DA, Kinney DK (1993): Patterns of neuropsychological deficits that discriminate schizophrenic individuals from siblings and control subjects. *J Neuropsychiatry Clin Neurosci* 5:294–300.