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Schizophrenia, "just the facts": What we know in 2008 Part 3: Neurobiology

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ABSTRACT

Investigating the neurobiological basis of schizophrenia is a critical step toward establishing its diagnostic validity, predicting outcome, delineating causative mechanisms and identifying objective targets for treatment research. Over the past two decades, there have been several advances in this field, principally related to developments in neuroimaging, electrophysiological and neuropathological approaches. Several neurobiological alterations in domains of brain structure, physiology and neurochemistry have been documented that may reflect diverse pathophysiological pathways from the "genome to the phenome". While none of the observed abnormalities are likely to qualify as diagnostic markers at this time, many can serve as potential intermediate phenotypes for elucidating etiological factors including susceptibility genes, and as therapeutic targets for novel drug discovery. Despite several challenges including the substantial phenotypic, pathophysiologic and etiological heterogeneity of schizophrenia, technological limitations, and the less than ideal animal models, considerable progress has been made in characterizing the neurobiological substrate of schizophrenia. The accumulating fact-base on the neurobiology of schizophrenia calls for novel integrative model(s) that may generate new, testable predictions.

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Just the Facts, Ma'am.
Attributed to Jack Webb in *Dragnet*

This phrase, familiar to anyone who experienced the television in the fifties and sixties in America, aptly captures the spirit behind much of schizophrenia research as we begin the 21st century. The reliability of psychiatric diagnoses has improved considerably over the past several decades and many theories of pathophysiology abound. The validity of the entities such as schizophrenia, however, still remains a matter of controversy. Investigating the neurobiological "facts" of the disorder is a critical step toward establishing validity. Our efforts to ameliorate the symptoms caused by schizophrenia also critically depend on a better understanding of the nature and causative mechanisms in this illness so that better, hypothesis-driven treatments may be developed.

While the neurobiological basis of schizophrenia has been suspected for over a century (Kraepelin, 1919–1971; Spielmeyer, 1930), precise understanding of its pathogenesis has remained elusive. In a seminal article summarizing the state of understanding of schizophrenia two decades ago, Richard Wyatt et al. (1988) opined that the facts available then generated more questions than answers. Over the past two decades, however, there have been impressive advances in this field, thanks to the emergence of sophisticated technological tools such as neuroimaging, electrophysiological and neuropathological methodologies. In this paper, we review

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Table 1
Biomarkers in schizophrenia

Abnormality	Effect in illness (ES where available)	Effect in relatives	Diagnostic specificity	Relation to illness course	Relation to medications	Relation to pathophysiology
Structural imaging measures						
Total brain volume reduced, and increased ventricular volume	Present; ES 0.25–0.49	Present	Also in BPD, MDD to a lesser extent	Persists and may progress during illness	Present in neuroleptic-naive patients	Raises possibility of progressive neural pathology during the illness
Gray matter volume reduction in hippocampus	Present	Present	Also seen in affective disorder	Present early and persists during illness	Present in neuroleptic-naive patients	Associated with genetic risk and may also be related to chronic stress
Structural alterations in white matter tracts	Present	Present	Also seen in relatives of bipolar disorder patients	NK	NK	Associated with neuregulin and myelin-related gene polymorphisms
Reduction or reversal of cerebral asymmetry	Present	Present, variable	Relatively specific to schizophrenia	Related to early age of onset	Unrelated to medications	May be related to genetic risk
Enlargements of the basal ganglia	Present	NK	Also seen in MDD	Seen in chronic, but not in first episode patients	Related to typical antipsychotics	Relation to pathophysiology unclear
Functional imaging abnormalities						
Decreased activity and increased "noise" of the prefrontal cortex both in resting and cognitive challenge studies ("hypofrontality")	Present; ES 0.42 (activation) and 0.55 (resting)	Present	Also in psychotic affective disorder to a lesser extent	Present early, and persists during course of illness	May change during antipsychotic treatment	Prefrontal DA and COMT polymorphisms implicated; reduced prefrontal activity may predict enhanced striatal DA
Abnormal activation patterns in temporal brain regions in functional imaging studies	Variable	NK	NK	NK	NK	Fronto–temporal interaction may be impaired
Neurophysiological abnormalities						
Abnormal P50 amplitudes	Present (ES 1.5) but varies widely	Present	Also seen in BPD	NK	Affected by clozapine	May be mediated by DA, ACh, NMDA, or 5-HT3 mechanisms
Abnormal pre-pulse inhibition	Present	Present	Also seen in BPD	Present in acute psychosis and may be reversed following treatment	Affected by clozapine and other atypical antipsychotics	May reflect gating deficit; DA, NMDA may be involved
Abnormal auditory P300 amplitudes	Present; ES=0.85	Present	Also seen in BPD, ADHD	May progress during the illness	Relatively unaffected by antipsychotics	DA, ACh, NMDA

Abnormal mismatch negativity (MMN)	Present; ES = ~1.0	Present	May be relatively specific to schizophrenia	May progress during the illness	Relatively unaffected by antipsychotics	NMDA, 5-HT2a
Pursuit eye movement abnormalities	Present	Present	Also seen in affective disorder	Persists during course of illness	Affected by antipsychotics	Ach, NMDA
Non-REM sleep deficits and shortening of REM sleep latency	Present, small ES (0.34–0.47)	NK	Also seen in affective disorder	Variable	Affected by antipsychotics	May be related to reduced neuropil and/or ACh
Neurochemical alterations						
Reduced *N*-acetyl aspartate (NAA) in the frontal and/or temporal cortex	Present	Present	Also seen in affective disorder	Variable	Affected by antipsychotics	Reduced prefrontal NAA may predict enhanced striatal DA
Reduced phosphomonoesters (PME) in prefrontal cortex	Present	Present	NK	NK	NK	Impaired membrane integrity
Increased D_2 receptor density in striatum	Present	NK	NK	NK	May be secondary to antipsychotics	Does not directly support the DA hypothesis, but observations of increased presynaptic DA are in support
Hypercortisolemia and hypothalamo–pituitary–adrenal axis dysregulation	Present	NK	Seen in several psychiatric disorders	Likely to be related to acute phases of the illness	Affected by antipsychotics	Points to the stress-diathesis model
Reduced expression of one or more subunits for NMDA receptors in the hippocampus	Present	NK	NK	NK	May be affected by antipsychotics	Supports the glutamatergic model
Neuropathological alterations						
Reductions in neuropil as evidenced by decreased dendrite density and normal/increased neuron density	Present	NK	NK	NK	Possibly affected by antipsychotics	May be related to either decreased proliferation and/or excessive pruning of synapses
Altered placement/disarray of neuronal elements in cortical and limbic structures	Variable across studies	NK	NK	NK	NK	Suggests abnormalities in neuronal migration
Absence of gliosis	Present	NK	NK	NK	NK	Makes classic neurodegenerative processes less likely

ES = effect size; BPD = bipolar disorder; MDD = major depressive disorder; NK = not known; DA = dopamine; COMT = catechol-*O*-methyltransferase; Ach = acetylcholine; NMDA = *N*-methyl D aspartate; 5HT = 5-hydroxytryptamine. NAA = *N*-acetyl aspartate.

our current status of understanding of the neurobiology of schizophrenia with a focus on the large body of literature accumulated over the past two decades.

The main focus of this paper is on pathophysiology; the questions of etiology are addressed elsewhere (Tandon et al., 2008a). We list a set of neurobiological "facts" on which a substantive body of literature has accumulated (Table 1), and critically discuss them; given the magnitude of the literature and the limited scope of the paper, we decided to cite either recent systematic reviews or meta-analyses; when other articles are cited, they represent examples of key areas of either early reports of findings where few systematic reviews or meta-analysis exist, or emerging new observations, and are not designed to be exhaustive. For a fuller list of these facts and our approach to derive them by consensus, the reader is referred to Tandon et al. (2008b). We address the following questions: (i) What are the neurobiological facts in schizophrenia? (ii) How can these facts be integrated toward unified models of what we call "schizophrenia", which may generate testable hypotheses? (iii) What are the implications of already known facts to improve further research diagnosis and management? and finally (iv) what are the major gaps in knowledge, challenges to hypothesis testing, and the key next steps?

1. From findings to "facts" of schizophrenia

We herein review major findings from the domains of brain structure, chemistry, physiology and neuropathology with a focus on the following questions: How robust are the observed alterations? How well replicated are they? Are they related to other core aspects of the illness, such as genetic factors, symptomatology and course of the illness? And finally, how specific are they to schizophrenia?

1.1. Neuroanatomical alterations

In vivo observation of brain volume reduction in schizophrenia relative to controls goes back to the 1920s using pneumoencephalographic studies (Jacobi and Winkler, 1927). Over the past three decades, advances in *in vivo* neuroimaging techniques such as magnetic resonance imaging (MRI) have led to the identification of a number of brain structural abnormalities in schizophrenia, and have in general confirmed earlier post-mortem findings. Systematic reviews and meta-analyses of structural MRI studies (mostly using region of interest, or ROI approaches) in schizophrenia indicate that the whole brain and gray matter volume is reduced and ventricular volume is increased (Daniel et al., 1991; Shenton et al., 2001; Steen et al., 2006; Ward et al., 1996; Wright et al., 2000). Small to moderate effect sizes such as 0.25 (brain volume) and 0.49 (ventricular volume) have been reported (Wright et al., 2000). Reductions are seen in temporal lobe structures, in particular the hippocampus, amygdala, and the superior temporal gyri (STG) (Lawrie and Abukmeil, 1998; Nelson et al., 1998), the prefrontal cortex and the thalamus (Konick and Friedman, 2001), anterior cingulate (Baiano et al., 2007), and corpus callosum (Woodruff et al., 1995).

Automated regional parcellation and voxel-based morphometry (VBM) techniques have helped to validate these ROI-based findings. VBM studies find gray matter density reductions in medial temporal lobes (MTL) and the superior temporal gyrus (STG) (Honea et al., 2005). STG volumes correlate with positive symptoms, while MTL reductions correlate with memory impairment (Antonova et al., 2004; Lawrie et al., 2004). In general, brain volume reductions are subtle and close to the detection thresholds of current MRI methods (~3%) while some regional changes are somewhat larger (~8% for the hippocampus) (Steen et al., 2006).

Some experts have suggested that disturbances in the development of cerebral asymmetry and anomalies in cerebral dominance are critical in the etiopathogenesis of schizophrenia and may be related to susceptibility genes (Crow et al., 1989; DeLisi et al., 1994). In support of this proposition, several studies have reported an excess of mixed-handedness and reductions in (and sometimes reversal) of the usual cerebral asymmetry in patients with schizophrenia and their unaffected relatives (Dragovic and Hammond, 2005; Flaum et al., 1995; Sharma et al., 1999). Leftward asymmetry of brain structures, especially those of the planum temporale (PT), is reduced in patients with schizophrenia as revealed in a meta-analysis (Shapleske et al., 1999); this is due to a relatively larger right PT than normal controls. Reduced hemispheric asymmetry appears to be relatively specific to schizophrenia (Falkai et al., 1995), and is related to younger age of onset (Maher et al., 1998).

Studies directly comparing structural differences between schizophrenia and other major psychiatric disorders such as bipolar disorder have been relatively few; structural brain changes in affective disorder appear to be less marked but are qualitatively similar to schizophrenia (Bearden et al., 2001; Hoge et al., 1999; McDonald et al., 2004; Strakowski et al., 2000, 2005). Meta-analyses (Elkis et al., 1995) have revealed statistically significant effect sizes for the mood disorders to have more ventricular enlargement (d=0.44) and sulcal prominence (d=0.42) than controls, and for schizophrenia patients to have somewhat greater ventricular enlargement than patients with mood disorders (d=−0.20). Thus, while brain structural alterations are robustly seen in schizophrenia, they may be diagnostically non-specific and structural alterations may be common to patients with psychotic features across diagnostic boundaries (Strasser et al., 2005).

At least some structural MRI alterations appear to be present at illness onset, and may be relatively independent of medication effects. Meta-analyses of first episode schizophrenia vs. controls (Steen et al., 2006; Vita et al., 2006) have shown whole brain and hippocampal volume reductions. Earlier onset of schizophrenia appears to be associated with similar, but more severe neuroanatomical alterations (Kyriakopoulos and Frangou, 2007). Some structural alterations such as basal ganglia volume increases may be related to treatment with typical antipsychotics (Chakos et al., 1994; Keshavan et al., 1994; Scherk and Falkai, 2006). Typical antipsychotics may increase, and atypical antipsychotics may decrease, basal ganglia volumes (Corson et al., 1999). In a recent multi-site longitudinal study of first episode schizophrenia patients, Lieberman et al. (2005) found that haloperidol was associated with significant reductions in gray matter volume, whereas olanzapine was not, during a two year follow-up. It was not clear whether the differential treatment effects on brain morphology could be due to haloperidol-

associated neurotoxicity or neuroprotective effects of olanzapine.

Brain structural changes appear to progress in a subgroup of patients during the course of schizophrenic illness (DeLisi, 2008; DeLisi et al., 2004). Such progression may not be confined to the early course of the illness alone, and may continue during the more chronic phases; more widespread cortical volume reductions may be seen in the latter (Ellison-Wright et al., 2008). Further, there is a large variability across studies, and progressive structural brain changes, if they occur, are not consistently related to clinical change (Weinberger and McClure, 2002). Woods et al. (2005) conducted a meta-analysis of the time course of brain volume reduction in schizophrenia using cross-sectional estimates of intra-cranial and extra-cerebral volumes. They noted that significant whole brain volume loss occurs in schizophrenia both before and after attainment of maximal brain volume, supporting the view that brain structural alterations in schizophrenia may stem from both early and late developmental derailments (Jarskog et al., 2007; Pantelis et al., 2005).

Brain structural measures are highly heritable (Baare et al., 2001; Bartley et al., 1997). A meta-analysis of region of interest (ROI) studies (Boos et al., 2006) as well as computational VBM studies (Job et al., 2003) of relatives at risk (genetic high risk) have shown regional as well as global brain volume reductions compared to controls. Studies of twins discordant for schizophrenia suggest partially overlapping, genetic—as well as disease specific gray matter deficits mainly in the heteromodal association cortex (Cannon et al., 2002). Follow-up studies of young genetic high risk relatives have shown progressive volume reductions in regions such as amygdala–hippocampi and thalami (Job et al., 2005). Ultra-High Risk (UHR) individuals, defined clinically based on subtle prodromal clinical symptoms, also show similar volume reductions during transition to psychosis (Pantelis et al., 2003). Recent data from this group using cortical pattern matching have shown greater reductions in right prefrontal volume in UHR subjects who developed psychoses vs. those who did not (Sun et al., 2008). This suggests that an active disease process may be taking place in the brain during the transition to early psychosis in those at genetic risk.

1.1.1. White matter pathology and disconnectivity

Reductions in white matter structures such as corpus callosum (Woodruff et al., 1995; Arnone et al., 2008) and other fiber tracts have been reported in schizophrenia. White matter abnormalities have also been reported in relatives of schizophrenia and bipolar patients (Cannon et al., 1998; McIntosh et al., 2006). White matter alterations appear to be correlated with cognitive impairments (Kubicki et al., 2007). The relation of white matter pathology to illness course has not been well studied. Studies of neural connectivity have been made possible by diffusion tensor imaging (DTI). DTI measures the orientation of water diffusion along the axis of tissue elements, such as axons. Fractional anisotropy (FA) measures such diffusion from 0 (random diffusion) to 1 (unidirectional diffusion); FA is a measure of the structural integrity of white matter tracts. Several DTI studies have documented reduced FA in white matter tracts in schizophrenia, including the corpus callosum, the cingulum, arcuate fasciculus, and the unicinate fascilulus (Kubicki et al., 2007). The findings have been somewhat inconsistent (Kanaan et al., 2005). There is a growing consensus in the literature that DTI is not sensitive to myelin integrity (Kubicki et al., 2005). Newer approaches such as magnetic transfer imaging (a form of imaging that detects changes in the properties of water protons and some other magnetic nuclei as they move from one physical state or chemical configuration to another) are thought to be a better reflection of myelin integrity (Konrad and Winterer, 2008; Segal et al., 2007).

White matter pathology may be one of the key etiopathological findings in schizophrenia and is consistent with dissociative thinking, and cognitive deficits observed in this illness; this aspect of pathophysiology is also consistent with the glutamatergic model of the illness, in view of the key role the glutamatergic system plays in glial integrity (Chang et al., 2007). The neuronal disconnectivity may be related to recent observations of dysregulated myelin-associated gene expression, reductions in oligodendrocyte numbers, and abnormalities in the ultrastructure of myelin sheaths (Haroutunian et al., 2007). Neuregulin (NRG1) a gene thought to be important for oligodendrocyte development and function, has been implicated in schizophrenia patients.

In summary, there is good evidence for global alterations in brain structure, more prominent reductions in regional brain volumes as well as connectivity, especially involving the medial and superior temporal and prefrontal cortices. These abnormalities are subtle with relatively small effect sizes by comparison to other dementing illnesses, diagnostically non-specific, appear to persist during the course of the illness, may be related to the genetic predisposition to the disorder, may evolve during the prodromal phase of the illness, may progress early during the illness, and may be more prominent in early onset forms of the disorder.

1.2. Alterations in in vivo brain function

Of the current *in vivo* structurally based neuroimaging techniques, positron emission tomography (PET) and blood oxygenation level dependent (BOLD)-based fMRI provide a good balance of spatial and temporal resolution to study regional brain function, though the latter has the major advantage of non-invasiveness. Unlike PET (positron emission tomography), fMRI does not require ionizing radiation, relying rather on the ferromagnetic properties of the brain's natural elements. PET, on the other hand, has advantages as well (e.g., better visualization of frontal lobe regions such as orbitofrontal cortex, ability to administer cognitive tasks in a quiet and controlled environment). Functional imaging studies have involved both examination of the physiological resting state as well as investigation of the effect of a behavioral or neuropharmacological challenge on regional brain function.

An oft-reported observation from functional brain imaging studies is the lack of activation of the dorsolateral prefrontal cortex (DLPFC) when challenged with cognitive tasks mediated by this brain structure (hypofrontality) (Berman and Meyer-Lindenberg, 2004). While the literature is widely variable, a meta-analysis showed moderate effect sizes for both “activated” (effect size = 0.42) and “resting” hypofrontality (effect size = 0.55) (Hill et al., 2004). Another meta-analysis of functional imaging studies also showed decreased

prefrontal activity as measured with PET and single photon emission computed tomography (SPECT) (Davidson and Heinrichs, 2003). At least in part the variability in the literature is related to the fact that neurocognitive paradigms across studies have varied, ranging from working memory tasks (such as the n-back), executive function tasks (such as the Wisconsin card sorting test), to verbal fluency being used to study both schizophrenia patients and their relatives. A meta-analysis of 12 fMRI studies of schizophrenia which examined only studies that used the n-back paradigm, also found reduced DLPFC activation but abnormal patterns were also seen in other brain regions such as increased cingulate activation (Glahn et al., 2005). However, this literature remains quite confusing, and other studies (Manoach et al., 1999) have suggested increased task-related prefrontal activity among patients than in controls. Performance differences between schizophrenia and control subjects may moderate DLPFC activation differences (Manoach, 2003; Van Snellenberg et al., 2006). Controlling for performance differences is therefore important and in general when this is done, it appears that patients may show more prefrontal activity than controls, suggesting an inefficient frontal response. It has been suggested that variability in prefrontal response in schizophrenia may reflect increased background "noise" leading to inefficient information processing (Winterer et al., 2004).

A recent meta-analysis of fMRI studies of relatives of patients affected with psychosis, and subjects defined to be in the prodromal phase of the illness showed qualitatively similar abnormalities in prefrontal cognitive functions but they were less severe than those observed in the first episode of illness (Fusar-Poli et al., 2007). Thus, it appears that impaired prefrontal function as seen in fMRI studies may be present in patients in the early phases of the illness and also in relatives at risk for developing the illness.

Altered prefrontal function may cut across diagnostic boundaries, and is observed in affective disorders as well (Stoll et al., 2000). However, prefrontal deficits related to context processing have been found only in schizophrenia patients early in the course of the illness; these dysfunctions were found to be related to symptoms of disorganization (MacDonald et al., 2005). Decreased prefrontal function and volume have been related to genetic factors in schizophrenia. Recent data suggest that genetic variations in the genes encoding catechol-*O*-methyltransferase (COMT) and the metabotropic glutamate receptor (GRM_3) and their interactions may influence prefrontal signal to noise ratio (Tan et al., 2007). Reduced prefrontal activity also predicts enhanced striatal dopaminergic activity as measured by F_{18}-DOPA uptake in the striatum in patients with schizophrenia (Meyer-Lindenberg et al., 2002).

Functional imaging literature in other brain regions reveals even less consistent findings. A systematic review of 13 SPECT studies and six PET studies found evidence of increased temporal activity in some studies, while many other studies showed decreased temporal activity in Zakzanis et al. (2000). Another large meta-analysis involving 155 studies failed to see clear patient–control differences in the temporal lobe function (Davidson and Heinrichs, 2003). Reviews of studies using the same methodology, however, reveal more consistent findings. Two independent studies (Kircher et al., 2004; Wible et al., 2001) have shown auditory cortex activation deficits in an MMN-type paradigm. Achim and Lepage Achim and Lepage (2005) observed group differences between schizophrenia and healthy controls in prefrontal and medial temporal activation in a meta-analysis of 18 studies examining neural correlates of episodic memory deficits.

Recent studies have emphasized inter-regional interaction rather than abnormality of any single region in the pathophysiology of schizophrenia (Friston, 1998). Several studies have investigated the interaction between the temporal lobe regions such as the hippocampus and the prefrontal cortex. Evidence for a regionally specific abnormality in the reciprocal modulatory interaction of frontal and hippocampal regions has been observed using functional MRI (Meyer-Lindenberg et al., 2005). Recent developments in imaging methodology such as resting state fMRI (Bluhm et al., 2007) as well as new image analysis procedures allow more refined assessment of these distributed network models (Ragland et al., 2007).

Taken together, functional imaging studies point to alterations in prefrontal, and less consistently temporal lobe function in schizophrenia. Functional connectivity between these regions may also be impaired, though more work is needed to confirm this interesting hypothesis. These alterations may be impacted by treatments (Davis et al., 2005). These alterations may be related to observed structural abnormalities and the underlying genetic liability to the illness, and may be more pronounced in schizophrenia than other psychiatric disorders. However, considerable variability exists in findings across studies, perhaps related to diverse and complex functional challenge paradigms; several factors such as non-uniform standardization of "resting" conditions, difficulty in interpreting activation differences in the context of performance differences, typically small samples and medication confounds limit confident interpretations. Overall, the observed alterations in functional neuroanatomy strongly point to altered physiology and neurochemistry, as will be detailed below.

1.3. Alterations in brain physiology

Neurophysiological techniques in general involve assessment of brain electrical activity using scalp electrodes at rest or while the subjects participate in one or other experimental paradigms. The major advantage of these approaches is the high temporal resolution, allowing the investigator to track the various stages of information processing from primary sensory to association brain regions (Javitt et al., 2008). A variety of approaches have been utilized, as briefly summarized here.

1.3.1. Mismatch negativity (MMN)

MMN is a negative voltage component of the *event-related potentials* (*ERP*), elicited when a train of uniform auditory stimuli are presented, interspersed with unique or deviant stimuli (such as an auditory oddball paradigm). It represents a pre-attentive stage of auditory information processing. Reduction in the amplitude of MMN has been consistently replicated in schizophrenia with a mean effect size of about 1 SD across studies in a meta-analysis of 32 studies (Umbricht and Krljes, 2005), and may be relatively selective for

schizophrenia (Umbricht et al., 2003). MMN may have a relation to prolonged illness duration suggesting progression during the illness (Umbricht and Krljes, 2005). The heritability of MMN is high (~68%), suggesting a significant genetic contribution (Hall et al., 2006). MMN deficits are related to impairments in sensory memory, and have been thought to reflect *N*-methyl D-aspartate (NMDA) receptor dysfunction, since they can be induced by NMDA antagonists in primates (Javitt et al., 2008). The brain generators of MMN are reasonably well localized to the primary and secondary auditory cortices (Naatanen and Alho, 1995). MMN sources have also been localized to the dorsolateral prefrontal cortices suggesting an important role of this region in mediating the generation of the MMN and possibly its dysfunction in schizophrenia (Sato et al., 2003). Mismatch negativity is lateralized and could inform the neurophysiologic basis of impaired language implicated in schizophrenia (Pulvermuller and Shtyrov, 2006).

1.3.2. P300 event-related potentials (ERP)

ERP involves averaging EEG epochs time locked to repeated presentations of specific stimuli or classes of stimuli (typically auditory or visual). Later components of this [ERP] response, such as the positive wave occurring about 300 ms after the delivery of a task-relevant or salient stimulus, are considered to reflect higher cognitive functions (P300). The auditory P300 is elicited using an auditory oddball paradigm. Subjects listen to a series of tones and respond (i.e. press a button, or silently count) to deviant ones. Schizophrenia is associated with blunted amplitude of the auditory P300 response to salient stimuli (Ford, 1999; Jeon and Polich, 2003). This observation is present early in the illness, and may progress during its course. The P300 latency is delayed in schizophrenia, although these differences are less consistent. In a meta-analysis involving 46 studies the effect size of the P300 amplitude difference between schizophrenia and patient groups was 0.85 (0.57 for latency) (Bramon et al., 2004). The same group also conducted a meta-analysis of the P300 data in non-psychotic relatives. Similar to patients, P300 amplitude was reduced, and latencies were delayed in relatives (Bramon et al., 2005). Many brain regions have been implicated in the generation of the P300 including the superior temporal gyrus, inferior parietal lobe, frontal lobe, as well as the hippocampus and thalamus (Smith et al., 1990). P300 amplitude reduction is relatively non-specific for schizophrenia, being seen in bipolar disorder and other psychiatric disorders (Hall et al., 2007).

1.3.3. P50 mid-latency auditory evoked response l

Another reported electrophysiological abnormality in schizophrenia is a deficit in the ability of the brain to attenuate the P50 response (a positive ERP component about 50 ms after each click) to the second stimulus when presented with two clicks separated by 500 ms (S1–S2). Some recent studies [e.g. (Blumenfeld and Clementz, 2001)] suggest that P50 deficits are not due to impaired inhibition of second stimulus, but to reduced amplitude of response to the first. This inhibitory effect is reduced in schizophrenia; this effect appears to be state-independent (though it may be affected by clozapine) and is present in unaffected relatives of schizophrenia patients. While an effect size of 1.28 was observed in one meta-analysis for patient–control comparisons, a wide variability between studies was also observed (de Wilde et al., 2007); another recent meta-analysis also found wide variability between studies (Patterson et al., 2008). These discrepancies might be related to methodological differences across studies. While the exact physiological basis of the P50 gating deficit remains unclear, the deficit has been linked to dopaminergic, cholinergic, GABAergic and serotonergic functions. Normal gating has been shown to be heritable in healthy individuals (Anokhin et al., 2003) and the deficit has been shown to be heritable in families of schizophrenia patients (Waldo et al., 1995). Recent data suggest a frontal lobe role for mediating this function (Korzyukov et al., 2007) and a larger body of data has implicated hippocampal dysfunction as underlying the gating deficit (Freedman et al., 1996). It is thus possible that gating deficit may reflect some form of frontal–hippocampal miscommunication as both regions have been implicated in schizophrenia. Nonetheless, more data are needed to ascertain the potential value of P50 non-suppression as an endophenotype for schizophrenia. Most importantly, methods to improve the test–retest reliability of the measure are needed (Fuerst et al., 2007).

1.3.4. Pre-pulse inhibition (PPI)

The startle response (such as a blink), typically elicited by a sudden auditory stimulus (such as a burst of loud white noise), is normally inhibited when the stimulus is preceded by a pre-pulse 60–120 ms earlier. This pre-pulse inhibition, thought to reflect the process of sensorimotor gating, is reduced in schizophrenia (Braff and Light, 2005). This abnormally is present in schizophrenia spectrum patients (Cadenhead et al., 2002), first episode patients (Bender et al., 1999) and in unaffected relatives (Cadenhead et al., 2002). A wealth of data exists from animal model studies, whereby abnormal PPI is induced by neonatal ventral hippocampal lesions or pharmacological manipulations such as dopamine agonists and NMDA antagonists (Braff, 2004). The neural circuitry mediating the PPI includes many of the structures implicated in the pathophysiology of schizophrenia (Geyer et al., 2001). The observation of a severe PPI deficit in Huntington's disease, strongly implicates the striatum (Valls-Sole et al., 2004). Functional neuroimaging studies suggest involvement of the striatum, hippocampus, thalamus, and frontal and parietal cortical regions in PPI (Kumari et al., 2003). PPI deficits are seen in a variety of psychiatric disorders suggesting a lack of specificity (Geyer, 2006; Turetsky et al., 2007). Heritability of PPI is about 70% (Anokhin et al., 2003), and PPI deficits are likely to be state-dependent (Meincke etal., 2004), being reversed following treatment, and can be reliably acquired across multiple testing sites (Swerdlow et al., 2007). PPI deficits are not influenced by conventional antipsychotics, but may be reversed by clozapine (Geyer, 2006; Levin et al., 2005). and other atypical antipsychotics (Kumari and Sharma, 2002). These deficits are therefore less robust later in the illness than when patients are initially seen. PPI deficits are induced by NMDA antagonists such as ketamine, and such deficits are reversed by clozapine, pointing to the value of this biomarker to investigate glutamatergic function in neuropharmacological challenge strategies (Geyer, 2006).

1.3.5. Eye movement (EM) abnormalities

There is considerable evidence that schizophrenia patients and their first degree relatives have oculomotor abnormalities. First, the normal smooth pursuit of the eyes to a moving target is impaired with abnormal "catch-up" saccades in schizophrenia (Holzman et al., 1988). Pursuit abnormality has a high heritability of around 91% as reported in a recent sibling-pair study (Hong et al., 2006). Pursuit deficits have been found to be related to reduced function in the extraretinal motion processing pathways (Hong et al., 2005). Second, schizophrenia patients and their first degree relatives also have an inability to suppress the automatic reflexive glances towards an object during the antisaccade task where the subject is asked to look away for the target (Levy et al., 2004). The antisaccade abnormality has been reported in a large number of studies of schizophrenia (Hutton and Ettinger, 2006; Turetsky et al., 2007). Pursuit and antisaccade abnormalities do not necessarily have same functional correlates.

However, the pursuit and antisaccade abnormalities are both correlated with measures of prefrontal abnormality, such as an abnormal Wisconsin Card Sorting test performance (Radant et al., 1997), suggesting a role for the PFC for mediating these deficits. Failure of a frontal–striatal saccade suppression mechanism has also been implicated in schizophrenia (Raemaekers et al., 2002). However, these abnormalities may not be diagnostically specific (Trillenberg et al., 2004) and there may be potential confounding effects of antipsychotic medication on these abnormalities for schizophrenia (Reilly et al., 2006).

1.3.6. Sleep abnormalities

A large body of literature exists showing that schizophrenia is associated with alterations in sleep architecture, with reductions in total as well as non-rapid eye movement sleep, and increased awake time (Monti and Monti, 2005). A meta-analysis revealed modest reductions in stage 2 (effect size=0.47) REM latency (effect size=0.58), and to a lesser extent, stage 4 sleep (effect size=0.34) in schizophrenia (Chouinard et al., 2004). The potential confounding effects of neuroleptic medications cannot be excluded. Reduced spindle density has also been observed (Ferrarelli et al., 2007). Sleep alterations in schizophrenia may differ from those in depression, which is characterized by REM latency reductions and increases in REM density (Benca et al., 1992). The longitudinal stability and heritability of sleep alterations in schizophrenia is not well studied.

1.3.7. Alterations in neural synchrony

Information on synchronous brain activity between and within brain regions can be extracted from ongoing EEG activity using techniques such as Fourier transform or wavelet analysis. Such oscillatory activity can be in different frequency ranges. Of particular interest to schizophrenia has been the gamma band (30–80 Hz), thought to be related to perceptual binding and to inter-brain region synchronization. Deficits in gamma power, and abnormalities in cross-site as well as phase synchrony in response to auditory stimuli (Spencer et al., 2004) have been observed in schizophrenia; abnormalities in slower frequencies (such as theta) have also been observed (Winterer et al., 2004). A gamma-band abnormality mediated by thalamocortical integration dysfunction has been recently invoked as a possible underlying mechanism for perceptual abnormalities in schizophrenia (Johannesen et al., 2008). The diagnostic specificity, heritability and state–trait distinctions with these measures are still a matter of ongoing research.

The neurochemical bases of the above physiological alterations are complex, though glutamatergic (P50, PPI, P300, MMN, Pursuit EM, and gamma synchrony), serotonergic (P50, MMN), cholinergic (P50, P300, and Pursuit EM), dopaminergic (P50, PPI, and P300), and GABA systems (gamma synchrony) have been variously implicated. The details are beyond the scope of this paper, and have been well summarized recently by Javitt et al. (2008).

1.4. Neurochemical alterations

The neurochemical basis of schizophrenia is being increasingly better understood with the advent of *in vivo* imaging as well as post-mortem techniques and includes changes in metabolic, neurotransmitter and neuroendocrine systems as summarized below.

1.4.1. In vivo metabolic studies

Magnetic resonance spectroscopy (MRS) offers a non-invasive technique to longitudinally evaluate neurochemistry. MRS generates a "spectrum" consisting of biochemical peaks of different radio frequencies (or chemical shifts) with intensities proportional to the biochemical concentration. *In vivo* MRS is capable of providing information on the functioning or viability of neurons, axons and astrocytes as well as on the energy status and membrane constituents. *In vivo* ^{1}H spectroscopy has been the most popular approach to MRS. *N*-acetyl aspartate (NAA), the most abundant signal, is considered as a marker of functioning neuroaxonal tissue that includes functional aspects of the formation and/or maintenance of myelin. *In vivo* ^{31}P spectroscopy offers information on metabolites that are part of the anabolic and catabolic pathway of membrane phospholipids (MPLs) by quantifying the phosphomonoester [freely mobile precursors of MPLs, PME] and phosphodiester [freely mobile breakdown products of MPLs, PDE] levels. Therefore, *in vivo* ^{31}P spectroscopy measures of MPL precursor levels reflect the integrity of dendrites and synaptic connections (i.e., the neuropil) in health and disease.

Following the observations by Nasrallah et al. (1994) a substantial body of literature has accumulated showing NAA reductions in several brain regions in schizophrenia (Abbott and Bustillo, 2006). A recent meta-analysis of *in vivo* ^{1}H spectroscopy studies in schizophrenia showed reduced NAA primarily in the prefrontal and hippocampus (Steen et al., 2005). Most studies are of small sample sizes, and underpowered to detect these subtle differences. NAA reductions are seen in relatives at genetic risk for schizophrenia (Callicott et al., 1998) and may predict conversion to psychosis in individuals who met criteria for the prodromal phase of schizophrenia (Jessen et al., 2006). It is unclear if NAA changes are state vs. trait related, and they may not be specific to schizophrenia, since they are seen in affective disorders as well (Soares, 2003).

A number of studies have observed decreased PME levels in the prefrontal region of schizophrenia subjects compared

with controls suggesting decreased synthesis of membrane phospholipids (Pettegrew et al., 1991; Smesny et al., 2007; Stanley et al., 1995; Williamson et al., 1991). Prefrontal PME reductions are also seen in adolescent offspring at genetic risk for schizophrenia suggesting that these alterations may precede the symptomatic manifestations of the illness (Keshavan, 2003). The longitudinal stability, heritability and diagnostic specificity of prefrontal PME reductions remain unclear.

In summary, MRS studies have revealed reductions in neuronal and membrane integrity in early schizophrenia and in those at risk for the disorder in brain regions where structural and functional alterations are also observed. Future prospective ^{31}P and ^{1}H spectroscopy studies at high-field of children and adolescents at risk for and those already presenting with schizophrenia are needed to identify the point in time regional deviations occur at the early stage of illness with respect to the normal course of development. Many questions remain in regard to the precise pathophysiological significance of NAA and PME alterations in schizophrenia.

1.4.2. Neurotransmitter abnormalities

Understanding the neurochemistry of schizophrenia has benefited from *in vivo* neuro-receptor PET and single photon emission computed tomography (SPECT) studies which were preceded by *in vitro* binding measurements of receptor density and affinity and neuro-receptor auto radiographic studies in post-mortem brains.

1.4.2.1. Dopamine. While dopamine excess is among the oldest and most widely held theories of the pathophysiology of schizophrenia (Carlsson, 1977; Carlsson and Carlsson, 2006; van Rossum, 1966), direct evidence of this has been sparse. Laruelle et al. (1996) showed that acute psychosis is associated with increased striatal dopamine release in response to amphetamine challenge. However, the bulk of evidence for the dopamine theory is still indirect, i.e. the antipsychotic effect of dopaminergic blockade, and the psychotomimetic effect of dopamine agonists such as amphetamine (Guillin et al., 2007). Post-mortem and PET data suggest increased D_2 receptor binding in the brains of patients with schizophrenia with a mean effect size of about 1.5, but the potential contribution of prior antipsychotic drug exposure is difficult to exclude (Zakzanis and Hansen, 1998). Two other reviews came to similar conclusions (Erritzoe et al., 2003; Laruelle, 1998).

The main limitation of the DA hypothesis, as originally formulated, was that its explanatory power was stronger for one aspect of the illness, i.e. positive symptoms. It has been suggested that cognitive impairment in schizophrenia may be related to prefrontal D_1 deficit (Weinberger, 1987). Increased D_1 receptor availability has been found to correlate with impaired working memory in schizophrenia (Abi-Dargham et al., 2002). Although this literature still remains controversial, a hypoactive mesocortical dopaminergic system (underlying negative and cognitive symptoms) and a hyperactive mesolimbic dopamine system (underlying positive symptoms) have been postulated (Weinberger, 1987; Davis et al., 1991). It has been suggested that tonic dopaminergic activity may actually be decreased whereas the phasic response to stimuli such as stress may be exaggerated (Grace, 1991). Hsiao et al. (2003) observed a lack of right > left asymmetry in dopamine transporter ligand uptake in neuroleptic-naive schizophrenia patients, suggesting that the disorder could be due to a disruption in brain neurochemical lateralization.

1.4.2.2. Glutamate. Observations of reduced glutamate in the cerebrospinal fluid of patients with schizophrenia (Kim et al., 1980) initially led to the glutamate hypothesis of schizophrenia, though this finding was not subsequently replicated (Perry, 1982). It was subsequently proposed that schizophrenia may be related to a deficient glutamate mediated excitatory neurotransmission via *N*-methyl D-aspartate (NMDA) receptors (Moghaddam, 2003; Olney and Farber, 1995). This theory is supported by clinical observations of psychotic symptoms triggered by the NMDA antagonists phencyclidine (PCP) and ketamine (Javitt and Zukin, 1991). Post-mortem studies of schizophrenia patients have reported reduced expression of glutamate receptors especially of the NMDA receptor subunit in a variety of brain regions, notably the prefrontal cortex and the hippocampus (Harrison et al., 2003). However, such findings have not been consistently replicated (Lewis and Gonzalez-Burgos, 2006). Glutamate is ubiquitously distributed in the nervous system, and an impairment in this system does not easily explain the relatively localized disturbances in schizophrenia (Crow, 1995).

1.4.2.3. Gamma amino butyric acid (GABA). Post-mortem studies of schizophrenia patients have consistently shown reduced levels of GABA expression in prefrontal cortex as measured by mRNA levels of glutamic acid decarboxylase, the major determinant of GABA synthesis (Lewis et al., 2005). Additionally, GABAa receptors may be upregulated possibly reflecting a compensatory response to reduced GABA levels (Jarskog et al., 2007). The affected neurons belong to the chandelier subtype of GABA neurons. These changes appear to be somewhat disease specific (Benes et al., 2007); and these intriguing observations may account for the alterations in neural synchrony and consequently to the working memory impairments in schizophrenia (Lewis and Gonzalez-Burgos, 2006).

1.4.2.4. Other neurotransmitters. A majority of schizophrenia patients tend to be cigarette smokers. It has been suggested that this may be related to their attempt to compensate for a deficit in nicotinic cholinergic receptors. Several post-mortem studies have shown regionally specific decreases in selective muscarinic receptors in the brains of subjects with schizophrenia. Diminished inhibition of the P50 evoked response to repeated auditory stimuli has been linked to the chromosome 15q14 locus of the alpha-7-nicotinic receptor gene (Freedman et al., 2003). Evidence from neuropathological, neuroimaging, and pharmacological studies suggest that schizophrenia is associated with a relative deficit in CNS muscarinic activity (Raedler et al., 2007). Therapeutic implications of this model are that agents with alpha-7-nicotinic agonistic activity and/or promuscarinic activity may have utility in treating certain symptoms of schizophrenia (Olincy and Stevens, 2007; Lieberman et al., 2008).

The therapeutic benefits of serotonin antagonists such as clozapine and risperidone generated attention on the

interaction between serotonin and dopamine systems as a pathogenetic mechanism in schizophrenia (Kapur and Remington, 1996). The role of serotonergic antagonism in mitigating the extrapyramidal effects of antipsychotics is well established. Although direct evidence of serotonergic dysfunction in the pathogenesis of schizophrenia is lacking, there continues to be a significant interest in exploring the role of different serotonin receptors (particularly 5HT-3 and 5HT-6) in schizophrenia (Abi-Dargham, 2007).

1.4.3. Neuroendocrine alterations

It is well known that stress is commonly associated with the onset of the initial psychotic episode and the subsequent relapses (Norman and Malla, 1993). The psychological experience of stress is closely related to the hypothalamic–pituitary–adrenal (HPA) axis. In an early study, Sachar et al. (1970) showed elevations of urinary cortisol immediately preceding psychotic episodes when compared with periods of recovery. Levels during episodes were intermediate between the pre-episode and recovery periods. A large number of studies have investigated the HPA axis in schizophrenia (Tandon et al., 1991). A systematic review revealed that the incidence of dexamethasone non-suppression, a measure of HPA axis overactivation, in schizophrenia patients is significantly higher than that in normal controls (Yergani, 1990); post-dexamethasone cortisol levels were dependent upon phase of illness and medication status. Among psychotic patients, elevated cortisol secretion has been linked with greater symptom severity, impaired cognition and ventricular enlargement (Walder et al., 2000; Tandon et al., 1991). Chronic stress is known to cause structural alterations in the hippocampus (Bremner, 1999; McEwen, 2002), a brain region reported to be altered in the early phases of psychotic disorders (Pantelis et al., 2003). Further studies of the stress cascade in schizophrenia have implications for novel pharmacologic and psychosocial treatments as well as for relapse prevention.

1.5. Neuropathological changes

Post-mortem studies of the brains of schizophrenia patients have been conducted for over a century. Neuropathological changes are subtle and no pathognomonic "lesions" have been reported. Neuropathological studies have been limited by the problems of post-mortem tissue being compromised by long post-mortem intervals and poor prescription, confounding effects of medications and substance abuse, and the difficulty in obtaining data on a representative sample of the population.

Nevertheless, several important observations have been made in the last two decades using advanced histochemical, receptor autoradiography, in situ hybridization, stereological computer imaging, as well as gene array techniques. There is macroscopic evidence of reduced brain weight (Harrison et al., 2003) and for volume reductions in a variety of brain regions, along with cerebral ventricular enlargement, and a loss of cerebral asymmetry. Structural changes in the hippocampus are also seen in post-mortem studies (Heckers, 2001) though not all studies find this (Walker et al., 2002). Neuropathological studies have particularly revealed changes in temporal lobe regions, as well as alterations in cerebral symmetry (Harrison, 1999; Iritani, 2007).

A notable consistent finding is the absence of glial proliferation (Arnold et al., 1998; Harrison, 1999; Roberts et al., 1986) and some report even of a decrease in cortical glial density (for review, see Jarskog et al., 2007). While the absence of gliosis has been taken as lack of support for neurodegeneration, gliosis does not always occur following neuronal injury or apoptosis.

The observed neuropathological changes are subtle, and there is little evidence of large scale neuronal loss, though some loss of inter-neurons in select brain regions has been reported (Benes et al., 1991). There is gray matter thinning, along with increases or no change in neuronal density (Cullen et al., 2006; Selemon et al., 1995) and decreases (Pierri et al., 2001) or no change (Highley et al., 2003) in pyramidal cell somal volume; Golgi studies show reduction in the number of dendritic spines on pyramidal neurons in the prefrontal cortex (Glantz and Lewis, 2000). There's also a reduction in markers of axon terminals, such as synaptophysin. Together, these findings suggest a reduction in the synapse-rich neuropil (Selemon and Goldman-Rakic, 1999). It has been suggested, based on these findings, that the primary defect in schizophrenia might be in the integrity of synapses, perhaps related to excessive synaptic apoptosis (Glantz et al., 2006). However, Cullen et al. (2006) did not find overall neuronal density differences between schizophrenia and control subjects, but observed a left > right asymmetry of pyramidal cell density in controls that was lost or even reversed in the patients, consistent with the lateral asymmetry theory of schizophrenia (Crow et al., 1989).

Early studies reported cyto-architectural abnormalities in the entorhinal cortex and the hippocampi. Abnormal density of cells was found in the sub-cortical white matter, thought to be remnants of sub-plate neurons, and therefore indicative of aberrant neuronal migration (Akbarian et al., 1993). However, this observation has not been replicated (Beasley et al., 2002). Overall, it appears that there might be neuronal disorganization in cortical and limbic brain regions in schizophrenia, but more data are needed to draw firm conclusions.

2. What the known facts can tell us

2.1. Endo (or intermediate) phenotypes as foot-holds for elucidating etiology

A key goal of characterizing biomarkers is to help in the search for etiological factors. Unfortunately, our search for candidate genes in schizophrenia have not led to evidence of any robust findings, though genes of small effect cannot be ruled out (Sanders et al., 2008; Tandon et al., 2008a). Endophenotypes (or intermediate phenotypes on the causal pathway from the genotype to the phenotype) (Gottesman and Shields, 1973) offer a valuable strategy in this effort. While closely related to the phenomenological manifestations, the endophenotypic traits are also likely to have simpler genetic architectures than the phenotypes (they may be determined by fewer genes than the more complex phenotype); they may therefore offer a better "foot-hold" for the researcher to move closer to understanding the underlying causes of mental illness. Gottesman and Gould (2003) offered a set of five conditions by which a biological marker can be defined. In order to be called an endophenotype, a biological marker should: a) be associated with the illness in the relevant population; b) be state-independent, i.e. present both

during periods of illness and wellness; c) be heritable; d) co-segregate with the illness within families; and e) be present in unaffected family members more frequently than in the general population. The above review suggests that several, though not all markers described in this paper approach meeting these criteria, though none is ideal (Braff et al., 2007; Keshavan et al., 2007; Turetsky et al., 2007). In general, more data are available for the candidature of physiological, as opposed to structural or neurochemical biomarkers (Table 1).

Several of the observed neurobiological alterations, which are apparently derived from different domains such as structure, physiology and neurochemistry, are likely to be inter-correlated and may be mechanistically related to each other (Fig. 1). Several endo (or intermediate) phenotypes may represent consecutive "nodes" on common pathophysiological pathways from the genome to the phenome; such related groups of endophenotypes may be usefully termed "extended endophenotypes" (Prasad and Keshavan, in press), and can help integrate the large and diverse set of facts we now have about the neurobiology of schizophrenia.

2.2. Value of biomarkers in diagnosis

Two decades ago, Wyatt et al. (1988) had pointed out that according to psychiatric nosology at that time (DSM-III R) a diagnosis of schizophrenia required that it cannot be established that an organic factor initiated and maintained the disturbance. If neurobiological alterations are shown to be important in pathophysiology, he argued, this criterion had to be changed. Fortunately, since then, that criterion was dropped from DSM-IV (APA, 1994). Thus, schizophrenia is now viewed as an idiopathic, or primary psychotic disorder rather than as a "non-organic" disorder as DSM-III implied. However, the diagnosis of schizophrenia is still made based on clinical features, and the wide array of biomarkers now available has not yet been incorporated into the diagnostic scheme. As seen from this review, many of the biomarkers in schizophrenia are of less than robust effect sizes, carry substantive overlaps with schizoaffective disorder (Malhi et al., 2008), and non-schizophrenia populations, and are either too expensive or too complex to serve as possible diagnostic measures currently. Further characterization of the available biomarkers is needed to identify robust measures that can be used cost-effectively in clinical settings. The next iterations of DSM also need to consider including one or more neurocognitive, neuroimaging or psychophysiological markers as dimensional measures to supplement the diagnosis of schizophrenia. In the coming years, this will facilitate more objective and neuroscientifically based approaches to diagnosis.

2.3. Value of biomarkers in prediction

Biomarkers in schizophrenia can also help us chart the phenotypic variation in the course, outcome and treatment

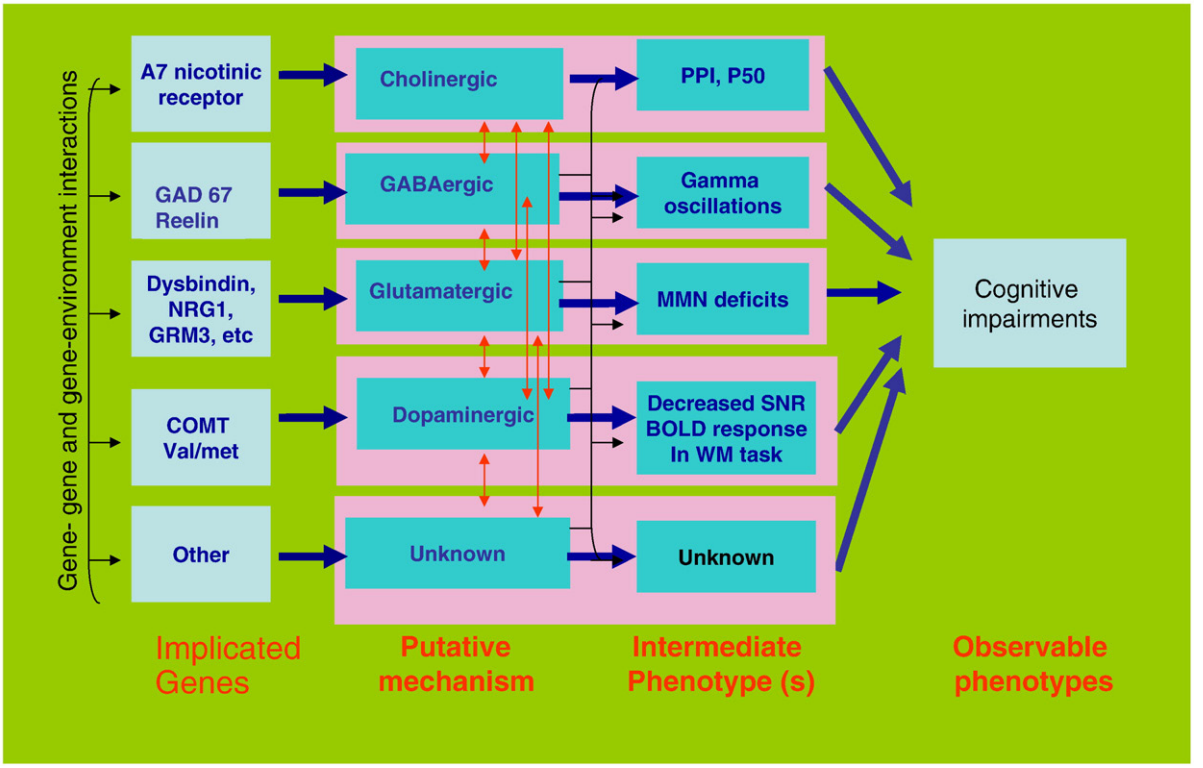


Fig. 1. Pathophysiological pathways from the genome to the phenome. Intermediate phenotypes may serve as nodes in this causal chain (see text). GABA = gamma amino butyric acid. NMDA: *N*-methyl D aspartate. GAD: glutamic acid decarboxylase. MMN: Mismatched negativity. PPI: pre-pulse inhibition. WM: working memory. PFC: prefrontal cortex. It is to be noted that the genes indicated in this figure have not been established to be linked to schizophrenia, but are known to mediate one or more functions involved in the proposed set of extended endophenotypes. Multiple arrows indicate the possibility of multiple causal mechanisms for each intermediate phenotype.

response of schizophrenia. Thus, some data suggest that structural alterations in the medial temporal cortex in the prodromal patients may help in the prediction of the emergence of psychotic symptoms at follow-up (Pantelis et al., 2003). Prefrontal structural (Prasad et al., 2005) and neurochemical alterations (Wood et al., 2006) are related to outcome after the first psychotic episode. Pharmacogenetic prediction of treatment response in psychosis is also an area of increasing interest, and of considerable clinical importance (Nnadi and Malhotra, 2007). While promising, none of the measures have yet been translated into clinical practice in the management of schizophrenia.

2.4. Treatment implications

An improved understanding of pathophysiology is critical for developing effective treatments with new mechanisms. Treatment in psychiatric disorders is currently limited both by under-utilization of available treatments and the fact that new drugs being discovered are mostly "me-too" compounds making at best modest improvements over current care (Insel and Scolnick, 2006). Identifying novel targets for treatment, using *in vivo* pathophysiological markers with known neurochemical bases, as well as developing valid animal models on which new compounds can be tested, will facilitate progress (Javitt et al., 2008). Examples of novel targets derived from such translational biomarkers include mGluR2/3 receptors (Patil et al., 2007) and second messenger systems such as phosphodiesterases (Menniti et al., 2006).

3. Towards integration: from facts to models

As may be seen from the above, the past two decades have led to a consolidation of several previous observations and the accumulation of some new knowledge about the neurobiological substrate of schizophrenia. Neurobiological research in schizophrenia has progressed from the study of crude measures such as 5-HIAA and HVA (metabolites of serotonin and dopamine, respectively) in various body fluids to elucidation of the role of specific circuits and receptors in the genesis of different manifestations of schizophrenic illness. But just as initially positive findings about alterations in 5-HIAA and HVA levels in schizophrenia were subsequently found to be less consistent (Tuckwell and Koziol, 1993, 1996), similar caution is necessary with reference to today's solid findings. The evolution of our understanding of the role of platelet monoamine oxidase (MAO) in the pathogenesis of schizophrenia also bears mention. Through the 1970s, reductions in platelet MAO were considered to be an established finding in schizophrenia, and in the early 1980s, a model of reduced MAO (related to dopamine excess and positive symptoms) contrasted with increased VBR (related to cortical atrophy and negative symptoms) was postulated (Jeste et al., 1985). This notion was challenged by observations of reductions in platelet MAO which were found related to neuroleptic treatment (DeLisi et al., 1981; Marcolin and Davis, 1992; Zureick and Meltzer, 1988). Earlier studies had also observed no platelet MAO changes in unmedicated patients (Owen et al., 1976).

Even as caution in ascertaining the veracity of findings is essential, it should be noted that the scientific process is not simply a random sequence of fact gathering; the facts assembled will need to generate explanatory models from which testable hypotheses may be derived (Popper, 1959; Tandon, 1999). Several attempts have therefore been made to "connect the dots" in understanding the neurobiological basis of schizophrenia. While comprehensive discussion of all these models are beyond the scope of this paper, we list them below and categorize the extant models of schizophrenia into those that pertain to pathophysiology, those that focus on pathogenesis and those that focus on etiology.

Pathophysiological models (which focus on the question of "what is wrong" with the neurobiology in the illness) stemmed from major observations that were topical at the time; thus, observations in the 1960s of the antipsychotic efficacy of dopamine blocking drugs led to *neurochemical theories* initially implicating the dopaminergic system; later theories included the glutamatergic, GABAergic, cholinergic and serotonergic systems, as discussed earlier. *Neuroanatomical theories*, which emerged as a result of imaging and neuropathological observations of brain structural and functional alterations, have referred variously to the postulated networks thought to underlie the symptoms. Examples include the heteromodal association cortex (Ross and Pearlson, 1996), aberrant inter-hemispheric connectivity as evident by loss or reversal of hemispheric asymmetry (Crow et al., 1989) or corpus callosal alterations (Nasrallah, 1985), cortico–thalamo–cerebellar circuitry dysfunction (Andreasen, 1999) and abnormal basal ganglia–thalamocortical networks (Williamson, 2007).

Theories of pathogenesis have focused on the nature and timing of pathology (the question of "when" the pathology is proposed to occur). These have included *early neurodevelopmental models* that posit an early disruption in neuronal migration or proliferation (Murray and Lewis, 1987; Weinberger, 1987), late developmental derailments of peri-adolescent processes of synaptic pruning (Feinberg, 1982; Keshavan et al., 1994; Murray and Lewis, 1987; Weinberger, 1987) and *neuroprogressive theories* that posit neuronal excitotoxicity or neurochemical sensitization as leading to post-illness onset deterioration (DeLisi, 1997; Lieberman et al., 1997).

Etiological models (which address the question of "why") variously posit the role(s) of genetic factors (Gottesman and Shields, 1967), abnormal gene expression, or epigenetic factors (Petronis, 2004) and a multitude of environmental factors (van Os et al., 2005).

Which of these is the right model may be a difficult (even futile) question to answer, since each theory may address a different aspect of the disease (s) we call schizophrenia, and clearly integration of theories is the need of the hour. Any "integrative" theory of schizophrenia, has to a) tie together the several clinical facts of schizophrenia such as the premorbid abnormalities, adolescent onset, phasic as well as persistent symptoms, response to antidopaminergic antipsychotics and deterioration in some patients; b) integrate known observations at structural, physiological, neurochemical and etiological levels; and c) allow us to develop falsifiable hypotheses, which will then lead to the accumulation of new knowledge about this complex disorder.

In an effort to offer an overarching hypothesis, Olney and Farber (1995) proposed that NMDA receptor hypofunction (NRH) may help tie together many features of schizophrenia

including premorbid impairments, adolescent onset, the role of dopamine and post-illness onset deterioration. As seen in this review, a primary glutamatergic dysfunction has a substantive explanatory power, is consistent with the structural, functional and electrophysiological abnormalities, as well as the early and late neurodevelopmental and neurodeteriorative aspects of the illness (Keshavan, 1999); an NRH hypofunction is also consistent with the dopaminergic (Grace, 1991; Weinberger, 1987) and GABAergic dysfunctions (Zhang et al., 2008). Several genes implicated in schizophrenia appear to affect the glutamatergic system (Arnold et al., 2005; Coyle, 2006). However, direct evidence for a primary glutamatergic abnormality is still lacking. If the NRH hypothesis is true, untreated patients in the earliest phases of schizophrenia and those at risk for the disorder should have *in vivo* evidence of reduced NMDA receptor sensitivity, and antipsychotic-naive patients with acute psychotic exacerbations should have evidence of excessive glutamate release. Definitive studies of this system in schizophrenia using *in vivo* MRS, PET imaging and electrophysiological studies are critically needed.

Crow (1995), having reviewed the NRH and other extant theories of schizophrenia, argued that no theory explained all key aspects of the illness, and proposed that many features of schizophrenia can be explained by a desynchrony of hemispheric development due to gene(s) involved in evolution of language and thus are selective to *Homo sapiens. While intriguing*, this hypothesis, like many others before it, also lacks direct evidence. It may well be that no one theory can explain all aspects of schizophrenia, just as no single model can be advanced to help understand all causes of cardiac failure. The resolution of the pathophysiologic and etiologic heterogeneity in schizophrenia may well obviate the need for a single unifying hypothesis.

To paraphrase the American poet John Godfrey Saxe (1816–1887), each of the extant pathophysiological theorists might be like one of the proverbial blind men of Indostan groping different parts of the same entity, and coming up with a different conclusion, and might thereby be missing the one big picture, the elephant. However, all these theorists might be assuming that there is one elephant that everyone could see, if only they were unblinded. However, we argue that even this assumption could well be wrong, and that there might be more than one elephant, or some other animals we do not know of.

4. From models toward new facts: challenges and opportunities

Several roadblocks to progress remain in our journey from model building to hypothesis testing toward further elucidation of the neurobiology of schizophrenia. First, heterogeneity of schizophrenia may account for the fact that the magnitude of the differences between SZ (as defined now) and controls may not be large enough to support any single neurobiological findings as a core deficit in the illness (see, Tandon et al., 2008b; Tsuang and Faraone, 1995). Similarly, any one pathophysiological model may be able to explain the disease entity in its entirety. There are three aspects of heterogeneity in schizophrenia: phenotypic, biological and etiological. However, effect sizes in discerning neurobiological differences might be stronger if clinically, pathophysiologically or etiologically meaningful subtypes of the illness are chosen for examination (e.g. subgroups with vs. without deficit symptoms, those with vs. without ventriculomegaly or those with vs. without histories of prior cannabis use). Second, our approaches to investigate neurobiology may still involve "blunt instruments". While *in vivo* imaging techniques have greatly enhanced our ability to investigate the living schizophrenia brain, the spatial, temporal and neurochemical resolution of these techniques is still limited by the state of technology. Post-mortem techniques, which allow us to investigate cellular and sub-cellular processes also have several limitations: difficulties in making ante-mortem diagnoses, confounding effects of post-mortem interval, variable tissue quality, typically small sample sizes and the difficulty in finding appropriate controls (Lewis, 2002). The third problem is one of not having an obvious "smoking gun", by comparison with neurodegenerative disorders such as Alzheimer's disease; schizophrenia does not have readily apparent neuropathological markers (e.g. plaques and tangles for Alzheimer's disease). Fourth is the fact that animal models, that represent the full phenotypic spectrum of a psychiatric disorder, such as schizophrenia, are very difficult to create. Given the phenotypic complexity of schizophrenia, it is difficult to model all aspects of the disease by any one model, and current approaches tend to create piecemeal components of the human disorder phenotype (Arguello and Gogos, 2006; Powell and Miyakawa, 2006). Further, the value of animal models may be limited if the disease involves human specific mechanisms such as those proposed by Crow et al. (1989). Finally, while well conducted meta-analysis and systematic reviews are considered to provide strong inferences in addressing many clinical questions, they are only as good as the studies included. Several sources of bias affect results such as choice of the study and patient exclusions (Tierney and Stewart, 2005). Publication bias is a roadblock to obtaining a clear picture, since positive results are more likely to be published, and negative results tend to remain in file drawers, the so-called file drawer effect. Meta-analyses that include such unpublished data (or "gray literature") are likely to reduce bias.

5. Neurobiology of schizophrenia: quo vadis?

Neurobiological research in the future is likely to expand because of both methodological and conceptual advances. Neurobiological research is likely to benefit from improvements in nosology, with the refinement of DSM criteria incorporating objective measures (such as the proposed inclusion of cognitive deficits) into the diagnostic criteria for schizophrenia (Keefe and Fenton, 2007). As neuroimaging and electrophysiological technology mature, dysfunctions are more likely to become readily apparent. Better integration of neuroimaging, neurochemical, and electrophysiological data, and the combined use of biomarkers may be more useful than individual markers used in isolation (Price et al., 2006). Multi-modal imaging (e.g. combining fMRI with ERP data) may be more useful than individual modalities alone. Neuropharmacological challenge strategies are more likely to elucidate dynamic alterations in neurotransmitter and receptor systems. Better delineation of endophenotypic markers and susceptibility genes is likely to

yield more valid animal models for further hypothesis testing. Larger, multi-site studies are also likely to improve statistical power to confirm/refute the tantalizing observations currently limited by small sample sizes.

The past two decades of research in neurobiology of schizophrenia have pointed to brain structural, functional and neurochemical alterations in an array of brain regions and their connecting circuitries. These alterations appear to begin early in development and evolve during the course of the illness suggesting a sequential derailment of developmental processes. Several conceptual and methodological challenges continue. Application of the accumulating knowledge base from *in vivo* neurobiological studies in schizophrenia for better diagnosis, prognostication and etiopathologic research is critically needed in the near future.

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Conflict of interest
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