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Insights into New Treatments for Early Psychosis from Genetic, Neurodevelopment, and Cognitive Neuroscience Research

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Abstract

Increasingly, schizophrenia research has emphasized the premorbid or prodromal periods of illness with a focus on identifying risk factors for later psychosis and understanding the mechanisms by which the neuropathological changes occur early in the course of illness. Genetic and epidemiological studies have begun to identify specific "vulnerability" genes and environmental risk factors which together may contribute to neurodevelopmental abnormalities and the emergence of psychosis. Neuroimaging and electrophysiological studies demonstrate altered developmental trajectories and evidence of compensatory changes in the early stages of psychotic illness, which perhaps reflects a period of neurotoxicity that coincides with the emergence of psychosis. These unique characteristics of early psychosis coincide with a time of increased brain plasticity, offering a window of opportunity to disrupt the neuropathological processes and remediate the neurocognitive and functional deficits. Insights from genetic, epigenetic, and biomarker studies in early psychosis have identified promising neuroprotective, disease-modifying, and cognitive remediation interventions that have the potential to alter the progressive trajectory of the illness. Adequately powered clinical trials that utilize information gained from biomarker studies are needed in early psychosis patients to determine the most effective individualized interventions. A synergistic treatment approach that offers precision pharmacologic intervention combined with remediation techniques is likely to have the greatest impact during the early course of illness.

Overview and Questions

Schizophrenia is a neurodevelopmental disorder that begins to develop most likely *in utero* and fully emerges during late adolescence or early adulthood. By identifying individuals in the prodromal phase of illness who are at risk for schizophrenia and following these cohorts into the first episode of psychosis, we have started to isolate the brain systems involved across multiple levels of analysis (behavioral, physiological, neurochemical, anatomical, genetic) during this critical pre-psychotic and early psychosis period. The use of multimodal techniques allows the assessment of the association of neurobiological markers to each other over time and provides further insight into the mechanism by which psychosis emerges. With increasing knowledge of the aberrant neurodevelopmental processes at the onset of psychosis, it may become possible to develop better treatment interventions to modify the disease outcome.

In this chapter, we review what is known about neurobiological predictors of psychotic illness, what they reveal about progressive neuropathological changes, and how this informs treatment in early psychosis. Evidence will be presented suggesting that neuropathological changes in the prodrome and first episode of illness, including compensatory changes that emerge at the onset of illness, differ from those found in more chronic forms of the illness. Therefore, specific treatments for prodromal and first-episode patients that target these aberrant processes have the potential to be more effective than the typical treatments used in more chronic forms of the illness, with a greater focus on neuroprotection, disease modification, and cognitive remediation.

The following questions guide our enquiry:

1. How do we best use psychosis risk biomarkers to inform treatment?
2. Is it possible to address the heterogeneity of early psychosis using neurobiological markers to individualize treatment?
3. Which neuroprotective strategies, disease-modifying agents, procognitive interventions, and remediation techniques show promise early in the course of illness?
4. Are there interventions that are unique to early psychosis and the hypothesized changes that occur at the onset of illness?

What Have We Learned about Risk of Psychosis, Mechanism of Disease, and Treatment from Genetic Studies?

With the heritability of schizophrenia estimated at 70–80% (for reviews, see Sullivan et al. 2003), a major proportion of disease risk can be explained by genes. Rapid progress has been made in the identification of genetic variants that confer risk of psychosis (Sebat et al. 2009; Purcell et al. 2009). Recent

findings that both rare mutations of large effect and common variants of modest effect contribute to genetic risk for schizophrenia suggest that the disease is characterized by much more genetic heterogeneity than was previously thought. The risk alleles that have been implicated include rare copy number variants (CNVs) and common haplotypes based on single nucleotide polymorphisms (SNPs). Of particular interest in predicting risk for psychosis are mutations with moderate to high penetrance and CNVs that increase risk for schizophrenia by fivefold or more. Genetic information can also be used to inform our understanding of the mechanisms of disease and perhaps subtype individuals to specify treatment.

Genetic Risk Score

One means of leveraging the heterogeneous genetic information is to develop a "genetic risk score" that quantifies the polygenic component of psychosis risk for each individual. Given that less than 40% of individuals who meet the prodromal syndrome criteria (Miller et al. 2003; Yung et al. 2002) are likely to develop schizophrenia or an affective disorder, additional risk factors (such as those provided by genetic information) may improve the positive predictive power of current psychosis prediction algorithms (Cannon et al. 2008), which are primarily based on clinical and family history data, and thus help to determine who would benefit most from preemptive intervention. By including information for the many (>1000) variants, including common putative risk alleles from genome-wide association (GWA) studies, SNPs and CNVs can be weighted proportional to their associated odds ratios to develop a single score that can be used in algorithms of psychosis risk (Mowry and Gratten 2013). First, however, it is essential to determine whether the genetic information provides any added value in identifying disease risk over and above the standardized clinical and demographic criteria currently used to characterize subjects at risk for psychosis.

Pharmacogenomics

The reproducible genetic findings in schizophrenia patients have also provided insight into the mechanism of disease (e.g., genes involved in glutamatergic neurotransmission and neurodevelopment) (Egerton et al. 2012b), supporting and informing translational models and treatment development. The goal is to individualize treatment based on which disease mechanism is present in a particular individual. To date, pharmacogenomic studies have focused primarily on prediction of antipsychotic response and adverse effects using a candidate gene approach based on dopamine and serotonin receptors (for reviews, see Malhotra et al. 2007, 2012; Burdick et al. 2011; Arranz and de Leon 2007). A recent meta-analysis by Zhang et al. (2010) determined that the most robust

pharmacogenetic findings are seen in the dopamine receptor D2 (DRD2) promoter region. Carriers of a functional polymorphism (–141C Ins/Del) are half as likely to show a clinical response to antipsychotic medication compared to noncarriers, and this effect was most prominent in first-episode psychosis patients. As noted by Malhotra et al. (2012), it is unlikely that we will attain perfect sensitivity and specificity using genetic data in the near future but it can help to clarify prognosis. We may identify a subgroup of patients who are less likely to respond to standard treatments and thus might benefit from a novel intervention.

Genetic Prediction of Adverse Treatment Effects

Although a number of studies have investigated antipsychotic-associated adverse effects such as clozapine-induced agranulocytosis and tardive dyskinesia, drug-induced weight gain may be the most powerful phenotype in pharmacogenetic studies (for a review, see Correll and Malhotra 2004). In a recent meta-analysis, Sicard et al. (2010) report that carriers of the T allele in a promoter region SNP (−759 T/C) in the 5-hydroxytrytamine 2C receptor (5-HT_{2C}) gene had less weight gain compared to those with the C allele. Similar results were recently reported in a study of patients in their first episode of psychosis, in which carriers of a functional promoter region variant (–141C Ins/Del) in DRD2 demonstrated more weight gain than noncarriers after six weeks of treatment, regardless of the antipsychotic. In terms of how this informs clinical practice, individuals at risk for increased weight gain or other adverse events might be given lower doses, adjunctive therapies (psychosocial or pharmacologic), and/or increased monitoring; however, this should be the standard of care for all patients on antipsychotic medication.

What Can Epigenetics Tell Us about Treatment of Early Psychosis?

Environmental risk factors associated with increased risk for psychosis in epidemiological studies include paternal age, hypoxia, urbanicity, migration, maternal infection, obstetric complications, nutritional deficiency, and cannabis use. While many of the environmental risk factors may affect the developing fetus, others appear to be "second hits" that occur in childhood or later adolescence, and may be more informative in determining which interventions are likely to be most effective in late adolescence. Theoretically, the second hits may act by epigenetic modulation of the genome in individuals who already have a genetic vulnerability, or they may potentiate biological pathways implicated in schizophrenia. Two specific environmental factors that illustrate the importance of understanding second hits are stress and drug abuse.

Stress and Psychosis Risk

The higher incidence of schizophrenia in urban areas, being a part of an ethnic minority, and migrant status may all be related to stress or social defeat and lack of social support (reviewed in van Os 2004; Rutten and Mill 2009). Although the link between childhood stress, epigenetic changes, and the onset of psychotic disorders has not been studied in humans, translational studies in animal models have shown that stress can mediate changes in gene expression during key developmental periods via epigenetic mechanisms (reviewed in Rutten and Mill 2009). For example, chronic psychosocial stress (e.g., defeat stress) alters gene expression, particularly of brain-derived neurotrophic factor (BDNF), via a range of epigenetic mechanisms, and this process can be reversed with *tricyclic antidepressant* treatment. Importantly, epigenetic moderation of *BDNF* transcription has been shown to be involved in neuroplasticity, suggesting the potential for preemptive intervention. Other recent advances in the understanding of the biological processes mediating stress have implicated the role of the hypothalamic-pituitary-adrenal (HPA) axis (Walker et al. 2008) as well as neuroinflammation (Meyer 2011).

HPA Axis and Stress Response

Increased HPA activity is associated with psychotic disorders and may increase the activity of dopamine pathways (Van Craenenbroeck et al. 2005; Tsukada et al. 2011; Wand et al. 2007). First-episode patients as well as individuals who meet the prodromal criteria for schizophrenia and later develop psychosis all have elevated cortisol levels relative to normal subjects (Walker et al. 2001, 2010; Guest et al. 2011). In addition, drugs associated with psychosis, including tetrahydrocannabinol (THC), amphetamine, and ketamine, all augment cortisol release in nonclinical and/or clinical populations (Oswald et al. 2005; van Berckel et al. 1998; Munro et al. 2006; D'Souza et al. 2005). Patients with schizophrenia who have the best response to antipsychotic medication show a higher pretreatment cortisol level, raising the possibility that one mechanism of action for antipsychotics may be to suppress the HPA axis.

Treatment implications: Early intervention research in schizophrenia patients has included both psychosocial means of reducing stress and salivary cortisol levels (e.g., yoga, exercise, relaxation) in vulnerable youth (Vancampfort et al. 2012; Cabral et al. 2011; Rocha et al. 2012) as well as pharmacologic interventions that can reduce stress. Antiglucocorticoid agents have been used in the treatment of depression to suppress the glucocorticoid response, but only one pilot study conducted on schizophrenia patients treated with ketoconazole reports improvement in observer-rated depression but no significant alteration of morning serum cortisol levels (Marco et al. 2002). Further studies of therapies such as yoga, exercise, or antiglucocorticoids are needed in prodromal or

first-episode subjects to determine whether it would be possible to alter the course of illness.

Neuroinflammation and Stress Response

It has been postulated that early-life exposure to infection and/or inflammation has the potential to induce latent neuroinflammatory abnormalities that can be unmasked by additional exposure to stressful stimuli (Meyer et al. 2011; Bilbo and Schwarz 2009), activating microglia and enhancing the production of proinflammatory cytokines in the central nervous system (Frank et al. 2007; Garcia-Bueno et al. 2008). Brown and Patterson (2011) propose that prophylactic treatments which target maternal infection and associated inflammatory processes could reduce the incidence of schizophrenia and related disorders by one-third. Animal models have demonstrated that the neurodevelopmental effects of prenatal infection/inflammation can be attenuated through interventions which target activated inflammatory response systems or associated physiological processes such as oxidative stress, hypoferremia, and zinc deficiency (Aguilar-Valles et al. 2010; Coyle et al. 2009; Girard et al. 2010; Lante et al. 2007; Pang et al. 2005; Robertson et al. 2007).

Treatment implications: Recent studies in early psychosis patients suggest that anti-inflammatory interventions may attenuate progressive brain changes (Meyer 2011). In an add-on study of *celecoxib* (a preferential cyclooxygenase-2 inhibitor, COX-2) given in conjunction with amisulpride, Muller et al. (2010) found that anti-inflammatory add-on therapy was more effective than antipsychotic treatment alone in treating negative symptoms when initiated in the early phase of schizophrenia. The broad spectrum antibiotic *minocycline*, when administered in conjunction with antipsychotic drugs, also has a significant effect on negative and cognitive symptoms compared with treatment outcomes using antipsychotic drugs alone in early psychosis (Levkovitz et al. 2010). Paralleling its known effects in reducing inflammation and preventing cell death when given after a traumatic brain injury, *aspirin* (COX-1, COX-2 inhibitor) has also been shown to have beneficial effects on symptoms of schizophrenia in patients with less than ten years of illness (Laan et al. 2010). The symptomatic improvement was most marked in patients with the lowest T_H1/T_H2 cytokine balance, suggesting that this treatment is most effective in individuals with relatively high anti-inflammatory cytokine production (Laan et al. 2010). In contrast, anti-inflammatory strategies are not effective in chronic schizophrenia (Rapaport et al. 2005), suggesting that neuroinflammatory processes are active primarily during the early phase of disease and are thus an important target for intervention. *Omega-3 fatty acids* such as eicosapentaenoic acid (EPA) and its derivative docosahexaenoic acid (DHA) have well-documented anti-inflammatory actions (Capper and Marshall 2001). In a randomized, double-blind, placebo-controlled trial conducted in 81 prodromal subjects, Amminger et al. (2010) found that after twelve weeks

of treatment, 2 out of 41 individuals (4.9%) in the omega-3 fatty acid group and 11 of 40 (27.5%) in the placebo group had transitioned to a psychotic disorder. Omega-3 fatty acids also significantly reduced positive, negative, and general symptoms and improved functioning compared with placebo. *Antipsychotic medication* has also been shown to affect the proinflammatory cytokine network and immune function in schizophrenia (for reviews, see Pollmacher et al. 2000; Drzyzga et al. 2006), perhaps providing an aspect of disease modification and prevention to the known therapeutic benefits on dopamine regulation.

Cannabis and Psychosis Risk

The epidemiological literature demonstrates an association between the early use of cannabis and later risk for psychotic illness (Andreasson et al. 1987; Arseneault et al. 2002; Weiser and Noy 2005; Moore et al. 2007). In a second-hit model of psychosis, Caspi et al. (2005) demonstrated that carriers of the catechol-O-methyl transferase (COMT) Met versus Val polymorphism (associated with rapid dopamine metabolism, low cortical, and high midbrain dopamine) were more likely to develop psychosis if they used cannabis. Translational studies have revealed the role of cannabinoid (CB) receptors and endocannabinoids in dopamine and glutamatergic regulation, immune function, energy metabolism, and the pathophysiology of schizophrenia (Koethe et al. 2009b; D'Souza 2007; Pacher et al. 2006; Hallak et al. 2011). In clinical studies, anandamide, an endogenous CB1 receptor agonist, has been shown to be elevated in antipsychotic and cannabis-naïve patients with schizophrenia (Leweke et al. 2007b; Giuffrida et al. 2004) and in the prodromal phase of illness (Koethe et al. 2009a). Koethe et al. (2009b) have proposed a model of psychosis in which the endogenous agonists like anandamide may rise in response to increased dopamine transmission and provide neuroprotection. Anandamide reuptake and hydrolysis is inhibited by cannabidiol (CBD), the second most abundant component of *Cannabis sativa* (besides THC), which has weak partial antagonistic properties at the CB1 receptor. Recent studies in animals, healthy humans, and patients with schizophrenia suggest that cannabinoids such as CBD and SR141716 have a pharmacologic profile similar to antipsychotic drugs (Roser et al. 2010).

Treatment implications: Because CBD can reverse many of the biochemical, physiological, and behavioral effects of CB1 receptor agonists, recent studies have explored the possible role of cannabinoids, including CBD, in the treatment of psychosis (Koethe et al. 2009b). While CBD and SR141716 monotherapy has not been found to be efficacious in chronic or treatment-resistant schizophrenia (Meltzer et al. 2004; Zuardi et al. 2006), Leweke et al. (2007a) found clinical benefits of CBD similar to amilsulpride in a preliminary study of 42 acutely ill patients with schizophrenia.

Neurodevelopmental Abnormalities: Can We Intervene?

Accelerated Gray Matter Volume Loss in Early Psychosis

Previous studies in schizophrenia, first-degree relatives, and at-risk subjects have shown reductions in multiple brain regions including prefrontal, superior, and medial temporal lobe gray matter volumes (Borgwardt et al. 2007; Pantelis et al. 2003; Koutsouleris et al. 2009; McCarley et al. 2002; Mechelli et al. 2011). Pantelis et al. (2003) examined gray matter changes over time in prodromal subjects and found that the converted group showed gray matter loss in left inferior frontal, left medial temporal, and cingulate regions at one-year follow-up. Moreover, prodromal subjects who later transition to psychosis have reduced gray matter volume in the left parahippocampal cortex at baseline compared to the nontransition at-risk group (Mechelli et al. 2011).

The neuroanatomical changes in schizophrenia appear to be progressive changes beyond those associated with normal development (Ho et al. 2003; Gur et al. 1998; Jacobsen et al. 1998; Keshavan et al. 1994). Cortical gray matter density declines normally during late adolescent development, resulting in decreased neuropil in the same brain regions implicated in the pathophysiology of schizophrenia (Huttenlocker 1979; Huttenlocker and Dabhokar 1997). As summarized by Pantelis et al. (2005), the available neuroimaging data provides evidence of early (pre- or perinatal) neurodevelopmental changes in schizophrenia which may lead to a vulnerability to postpubertal insults and contribute to the accelerated loss of gray matter and aberrant connectivity in the prefrontal regions. Factors such as substance abuse, stress, and HPA axis dysregulation may lead to neurodevelomental abnormalities which may be neurodegenerative, involving medial temporal and orbital prefrontal regions. Thus, while disturbances of brain structure early in life may be necessary for the future emergence of schizophrenia (Weinberger 1987), neurodevelopmental events during the late adolescent period may participate in psychotic symptom formation via a range of possible mechanisms, including inflammation, glutamatergic or dopaminergic transmission (Weinberger 1987; Feinberg 1982; Keshavan et al. 1994).

Treatment Implications: Pharmacologic and nonpharmacologic interventions have been shown to slow gray matter losses in schizophrenia and related disorders. Eack et al. (2010) used a computer-based *cognitive enhancement therapy* in patients during the early stages of schizophrenia. Compared to those who received supportive psychotherapy over a period of two years, there was greater preservation of gray matter in the left hippocampus, parahippocampal gyrus, fusiform gyrus, and left amygdala in patients who received the active treatment. In a study of treatment-naïve patients with obsessive compulsive disorder (OCD), Hoexter et al. (2012) found that after treatment with either fluoxetine or cognitive behavioral therapy (CBT), gray matter volume loss in the left putamen was no longer detectable relative to controls. Animal models

have demonstrated increased neurogenesis, dendritic arborization, and synaptogenesis with *serotonin reuptake inhibitors* (SSRI) (Richtand and McNamara 2008), supporting the notion that these agents may provide an element of neuroprotection. Preclinical and clinical studies also suggest that lithium may exert neurotrophic effects that counteract pathological processes, suggesting protective and potentially regenerative brain effects in the brains of patients with bipolar disorder (Manji et al. 2000; Bearden et al. 2007; Moore et al. 2009; Kempton et al. 2008; Lyoo et al. 2010). Moreover, a preliminary study by Berger et al. (2012) showed a reduction in T2 relaxation time (a nonspecific measure of neuropathological changes) in the hippocampus of putatively prodromal subjects treated with low doses of lithium compared to untreated prodromal subjects. Future early intervention studies using cognitive remediation, CBT, SSRIs, or lithium in the prodrome and first episode of psychosis should incorporate longitudinal analysis of gray matter volume to provide insight into the mechanism of these potential neuroprotective effects and clinical correlates.

Neurochemical Changes in Early Psychosis

While it is a matter of current debate as to whether the accelerated gray matter loss at the onset of psychosis involves (transient) neurodegenerative processes (Archer 2010; McGlashan 2006; McGlashan and Hoffman 2000) or perhaps a progressive excitotoxic process (Bustillo et al. 2010), recent reports using proton magnetic resonance spectroscopy (^{1}H-MRS) have identified neurometabolic changes which may be unique to the onset of psychosis and provide insight into the neuropathological changes (Bustillo et al. 2010; de la Fuente-Sandoval et al. 2011, 2013b; Kegeles et al. 2012; Stone et al. 2009). The dopamine hypothesis has been a useful model in our understanding and study of the psychotic state, but it does not explain the accelerated gray matter loss and deteriorating course in terms of cognition and function seen in the first few years of schizophrenia. Glutamate antagonists are well known to induce positive and negative psychotic symptoms more akin to schizophrenia than the positive symptoms induced by dopamine agonists alone (Javitt and Zukin 1991; Moghaddam and Javitt 2012), and it has been proposed that dopaminergic dysregulation is the final common pathway resulting from an altered glutamatergic neurotransmission early in the course of illness (Carlsson et al. 2001; Olney and Farber 1995a). According to glutamatergic theories, the abnormal developmental trajectory observed in neuroimaging studies could result from reduced elaboration of inhibitory (GABAergic) pathways and excessive pruning of excitatory (glutamatergic) pathways leading to altered excitatory-inhibitory balance in the prefrontal cortex (Lewis and Gonzalez-Burgos 2008). Glutamatergic theories of schizophrenia suggest that an increase in cortical glutamatergic activity, due to genetically or environmentally mediated hypofunction of *N*-methyl-D-aspartate (NMDA) receptors, may lead to a

time-limited neurotoxic process and dopaminergic dysregulation at the onset of psychosis (Carlsson and Carlsson 1990a; Javitt and Zukin 1991; Olney and Farber 1995b). The glutamatergic projections are thought to stimulate prefrontal dopamine release directly but inhibit midbrain dopamine neurons projecting to the striatum (via GABAergic interneurons) (Sesack et al. 2003; Sesack and Carr 2002). In support of this hypothesis, de la Fuente-Sandoval et al. (2011) report that antipsychotic-naïve first-episode and at-risk subjects have higher levels of glutamate in the dorsal caudate than normal subjects. In the cerebellum, no group differences were seen, suggesting that high levels of glutamate in the dorsal caudate, a region with prominent projections throughout the cortical mantle, could induce neuronal toxicity leading to a progressive functional and intellectual deterioration. Moreover, antipsychotic-naïve at-risk subjects who later converted to psychosis had higher glutamate levels than those who had not converted at two-year follow-up (de la Fuente-Sandoval et al. 2013b). In the treatment of schizophrenia with antipsychotic drugs, around 60% occupancy of brain DRD2 is required, on average, to produce a therapeutic response (Kapur et al. 2000). However, a substantial proportion of patients still show a poor response even when D2 occupancy is at this level (Pilowsky et al. 1993). This may reflect the importance of nondopaminergic neurochemical dysfunction in the pathophysiology of schizophrenia. A recent study demonstrated that clinically effective antipsychotic treatment normalized glutamate levels in antipsychotic-naïve first-episode psychosis patients (de la Fuente-Sandoval et al. 2013a). These results agree with a recent report (Egerton et al. 2012a) which found that clinically stable first-episode patients had lower glutamate levels compared to patients that were still symptomatic. While studies in medicated patients have shown the same or decreased levels of glutamate compounds compared to controls (Theberge et al. 2003; Tayoshi et al. 2009; Lutkenhoff et al. 2010; Reid et al. 2010; Rowland et al. 2012; Bustillo et al. 2011), patients experiencing psychotic state exacerbations demonstrate elevations of these compounds (Ongur et al. 2008; Ota et al. 2012), suggesting that an improvement in clinical symptoms might relate to decreases in glutamate levels.

Consistent with these findings, a recent ^{1}H-MRS study by Kegeles et al. (2012) found increased γ-aminobutyric acid (GABA) and glutamate+glutamine in the medial prefrontal cortex (mPFC) of primarily antipsychotic-naïve schizophrenia patients, adding support to the theory that dysfunction of fast-spiking parvalbumin-containing GABA interneurons may contribute to high levels of glutamate via pyramidal cell disinhibition (Lewis and Moghaddam 2006). Because there is also evidence that stable-medicated subjects either do not show a difference or demonstrate a decrease in glutamate levels compared with normal subjects (Marsman et al. 2011; Reid et al. 2010; Bustillo et al. 2010), it is tempting to hypothesize that a time-limited neurotoxic process may characterize the early stages of illness (McGlashan and Hoffman 2000; Archer 2010; Lahti and Reid 2011), primarily because excess synaptic glutamate levels are highly neurotoxic (Lau and Tymianski 2010). In addition, activated

microglia release substantial levels of glutamate (Barger and Basile 2001), and recent reports suggest that such microglia-mediated toxicity contributes to neuronal damage in the event of neuroinflammation (Block and Hong 2007; Perry 2007; Ransohoff and Perry 2009).

Treatment Implications: Glutamatergic theories of NMDA receptor hypofunction and resulting glutamate-mediated neurotoxicity suggest that glutamate and GABA-modulating agents may prove to be neuroprotective or even capable of modifying the disease early in the course of illness (Moghaddam and Javitt 2012). *LY404039* is a selective agonist for metabotropic glutamate 2/3 (mGlu2/3) receptors which regulate synaptic concentrations of glutamate and other neurotransmitters, including dopamine, GABA, and serotonin (Rorick-Kehn et al. 2007; Seeman and Guan 2009). Recent reports in chronic patients have found that LY404039 improves positive and negative symptoms of schizophrenia (Patil et al. 2007) or has no effect compared to placebo (Kinon et al. 2011). However, clinical trials using glutamate-modulating agents have not been performed in first-episode or at-risk subjects who may most likely benefit from the intervention. Since ^{1}H-MRS permits the *in vivo* study of regional concentrations of various brain metabolites (Di Costanzo et al. 2007), this noninvasive imaging technique may provide important clues into the mechanism of action of many interventions. Berger et al. (2008) assessed the effect of the omega-3 fatty acid, EPA (eicosapentaenoic acid), on brain metabolites with ^{1}H-MRS in the anterior hippocampus of both hemispheres in unmedicated first-episode psychosis patients. This study found that EPA treatment increased levels of glutamine+glutamate and glutathione, and this was associated with negative symptom improvement. Moreover, a study with EPA in depressed bipolar patients, using ^{1}H-MRS in the anterior cingulate cortex (ACC), found a significant increase in N-acetylaspartate levels, presumably induced by a neurotrophic role of EPA (Frangou et al. 2007). Omega-3 fatty acids are essential for normal brain function and development (Bazan 2005; Piomelli et al. 1991) and may also have neuroprotective properties (Lonergan et al. 2002; Lynch et al. 2007). There are also reports on the effects of omega-3 fatty acids on the glutamatergic system, such as modulation of glutamate transporters, glutamate release in hippocampi of aged rats (McGahon et al. 1999), and as a protective agent against neurotoxicity induced by NMDA antagonists (Ozyurt et al. 2007).

Cognitive Neuroscience Insights into Treatment Effects on Neurocognition and Perception

The structural and neurochemical brain changes early in the course of illness reflect changes in cells as well as fibers and extra-parenchymal elements. Abnormalities in the number and distribution of neurotransmitter receptors in these regions are likely secondary to loss of cells, fibers, or neurochemical

changes. These early neurochemical changes are hypothesized to lead to gray matter loss, reduced cortical connectivity, sensory, perceptual, cognitive, and global functioning abnormalities in chronic illness (Olney and Farber 1995b; Sharp et al. 2001). Thus, neural circuit dysfunction and associated information-processing abnormalities are likely downstream events that precede the onset of psychotic symptoms, and these may progress with illness onset and provide surrogate endpoints for treatment intervention studies.

Neurocognition in Early Psychosis

Neurocognitive deficits are prominent across the schizophrenia spectrum (Cadenhead et al. 1999b; Cannon et al. 1994; Hawkins et al. 2004; Heinrichs and Zakanis 1998). They are known to predict functional outcomes (Green 1996; Green and Nuechterlein 1999b) and to explain 20–60% of the variance in community functioning, social problem solving, and acquisition of psychosocial skills (Green et al. 2000). Neurocognitive deficits have been shown to be reliable (Faraone et al. 1999; Heaton et al. 2001; Rund 1998), heritable (Ando et al. 2001; Posthuma et al. 2002), and associated with genes linked to schizophrenia (e.g., glutamate signaling, COMT). Substantial cognitive deficits are already apparent in childhood for those individuals who go on to develop schizophrenia, and these tend to exacerbate before the onset of psychotic symptoms and worsen after the initial episode of the illness (Bilder et al. 2006). A number of recent reports (Keefe et al. 2006; Eastvold et al. 2007; Hambrecht et al. 2002; Seidman et al. 2010) have demonstrated that at-risk individuals have neurocognitive deficits across multiple domains that are intermediate to those observed in first-episode patients. In addition, at-risk subjects who later convert to psychosis have greater neurocognitive impairment at baseline compared to those individuals who remain "at risk" at follow-up (Hambrecht et al. 2002; Keefe et al. 2006; Seidman et al. 2010; Eastvold et al. 2007). Longitudinal neurocognitive studies of first-episode subjects show high stability (Addington et al. 2005). The few small longitudinal studies in at-risk subjects found a decline in verbal memory over time; this was most prominent in at-risk subjects who later converted to psychosis (Cosway et al. 2000; Brewer et al. 2005; Whyte et al. 2006; Pukrop et al. 2006; Jahshan et al. 2010).

Treatment Implications

Pharmacogenetic studies: Neurocognition has been used as an outcome measure to assess the cognitive enhancement effects of antipsychotics as well as other promising procognitive agents (reviewed in Burdick et al. 2011). Two studies (Need et al. 2009; McClay et al. 2011) using data from the CATIE (The Clinical Antipsychotic Trials of Intervention Effectiveness) trial have identified SNPs located close to specific genes (e.g., GRM8 [metabotropic

glutamate receptor 8], DRD2, and IL1A [interleukin-1-α]) that are associated with greater improvement in neurocognitive paradigms after treatment with antipsychotics. Three small published studies (Bertolino et al. 2004; Weickert et al. 2004; Woodward et al. 2007) have used a candidate gene approach focusing on COMT Val158Met genotype to predict neurocognitive performance after antipsychotic treatment. A Met versus Val homozygote predicted better neurocognitive response, suggesting that it may be possible to define which individuals are likely to show improvement in neurocognitive performance with antipsychotic treatment.

Cognitive enhancement: Given the limited response of neurocognitive deficits to antipsychotic treatments (Mishara and Goldberg 2004), there have been a number of efforts to develop targeted therapies for cognitive deficits in schizophrenia (Barak and Weiner 2011). For example, the *measurement of treatment effects on cognition in schizophrenia* (MATRICS) was developed as a means of identifying cognitive targets and promising molecular targets to enhance cognition (Marder and Fenton 2004). A detailed review by Keefe et al. (2013) found that the majority of cognitive enhancement double-blind add-on studies had been conducted on chronic patients and were underpowered to detect a significant effect. Agents acting at the NMDA receptor have been the most frequently studied compounds, including NMDA receptor modulation, glycine site agonism/partial agonism, and glycine site antagonism. Other trials have included agents that target various mechanisms, including H_3 antagonism, selective activation of hypothalamic regions associated with wakefulness, noradrenergic receptor reuptake inhibition, acetylcholine esterase inhibitors, α_7 receptors agonism/partial agonism, $\alpha 4\beta_2$ nicotinic receptors partial agonism, cannabinoid receptor antagonism, D_2 partial agonism + 5-HT_{2A} antagonism, and D_1/D_2 agonism. These important studies using promising procognitive agents have yet to provide robust results, perhaps because most studies are underpowered and use chronic rather than first-episode patients who would have greater potential for brain plasticity (Barch 2010). The sole exception noted by Keefe et al. (2013) was a six-month add-on treatment with minocycline versus placebo in young subjects in early phase schizophrenia (Levkovitz et al. 2010). In this study, minocycline (a tetracycline antibiotic with a distinct neuroprotective profile) was found to be superior to placebo in improving cognitive functioning as well as negative symptoms and general outcome. Little is known about the effects of omega-3 fatty acids on neurocognitive performance in schizophrenia, which has been studied more extensively in dementia (Kalmijn et al. 1997; Cole et al. 2009). Accelerated cognitive decline, mild cognitive impairment, and decreased brain volume correlate with lowered tissue levels of DHA/EPA (Tan et al. 2012). Supplementation improves cognitive function early in the course of illness (Mazereeuw et al. 2012). Omega-3 fatty acids as well as other potentially important procognitive agents need to be assessed in well-powered studies of early psychosis patients.

Cognitive remediation, cognitive training: Nonpharmacologic cognitive remediation trials have also shown promise in patients early in the course of illness (Wykes et al. 2007; Eack et al. 2010; Barlati et al. 2012; Breitborde et al. 2011), when intervention is likely to make the greatest impact on the developing brain. Cognitive remediation or training interventions include restorative (e.g., computer-based approaches; Fisher et al. 2009), compensatory (e.g., strategy-based approaches; Twamley et al. 2008, 2011), or environmental adaptation (Velligan et al. 2008). The most recent review and meta-analysis of cognitive remediation techniques (Wykes et al. 2011) found the largest effect sizes (mean effect size of .45 for cognitive improvement, .18 for symptom improvement, and .42 for functional improvement) for compensatory strategy-based approaches in the context of psychiatric rehabilitation. Compensatory strategies or cognitive prosthetics (which teach patients how to "work around" their deficits) can be helpful because they focus on application of appropriate cognitive strategies in the real world. Increasing patients' ability to remember appointments, sustain attention, encode important concepts, and think flexibly may well improve the success of concomitant treatments. Alterations in the environment to decrease cognitive demands and automatize everyday tasks may also be helpful. In essence, compensatory cognitive training provides an intervention which targets healthy neural circuitry to compensate for damaged circuit elements and may even protect this circuitry from future damage (Swerdlow 2011).

It is clear that larger studies are needed in early illness patients to determine whether it is possible to prevent or improve the cognitive deficits early in the course of illness. It is reasonable to expect that younger patients with greater potential neuroplasticity may be optimal candidates for a combined approach using pharmacological and nonpharmacologic intervention, but surprisingly, few data address this question empirically. Although cognitive remediation interventions have been added to augment antipsychotic medication, relatively little is known about the effectiveness of combining pharmacologic interventions (designed to enhance cognition, provide neuroprotection, or facilitate neuroplasticity) with cognitive remediation or CBT. In fact, reviews of the literature on cognitive remediation describe nonpharmacologic and pharmacologic interventions but they are all separate, rather than combined, trials (Goff et al. 2011). It is possible that the procognitive pharmacologic interventions will act synergistically with cognitive therapies to enhance clinical, neurocognitive, and functional outcome early in the course of illness. An analogy comes from anabolic steroids, which increase muscle mass only when used in concert with muscle-engaging activities (Swerdlow 2011). While reducing active psychosis with antipsychotics benefits any cognitive intervention, it is possible that drugs with procognitive effects might more specifically, and perhaps synergistically, enhance the clinical benefits of cognitive therapies.

Electrophysiology and Functional Imaging

Like the MATRICS initiative, Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) was developed to identify biomarkers derived from cognitive neuroscience as "surrogate endpoints" (Carter and Barch 2007). The U.S. National Institutes of Health website defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention." A number of potentially important paradigms have been identified which target specific cognitive or affective domains and can be studied in terms of the underlying neural system, animal models, and by using electrophysiological or neuroimaging paradigms. Importantly, for biomarkers to be useful in such models, it is essential that they demonstrate construct validity, reliability, and ease of use in treatment studies. Below, paradigms that hold particular promise, indicated by findings in early psychosis, are discussed as they may reveal neurodevelopmental abnormalities or compensatory processes which may differ from the more chronic forms of schizophrenia.

Prepulse Inhibition

Prepulse inhibition (PPI) is an index of sensorimotor gating in which weak lead stimuli are thought to inhibit the motor response to abrupt startling stimuli (Ison and Hoffman 1983; Graham 1975). PPI is deficient in schizophrenia, first-degree relatives, and schizotypal subjects (Braff et al. 1992; Cadenhead et al. 1993, 2000). In addition, PPI is stable with repeated testing (Cadenhead et al. 1999a; Cadenhead 2011) and is heritable (Greenwood et al. 2007), suggesting its utility as a neurobiological marker for psychosis risk. Genetic studies have identified SNPs that are strongly linked with PPI (Greenwood et al. 2007), including neuregulin-1 (activation of receptors, including glutamate), COMT, serotonin-2A, and DRD3. Translational studies demonstrate the emergence of PPI deficits after developmental manipulations in rodent models (Powell and Geyer 2002), suggesting that it may be useful in understanding a neurodevelopmental disorder such as schizophrenia. Animal studies have identified an extended forebrain/pontine circuit (limbic cortex, ventral striatum, ventral pallidum, pontine tegmentum) that modulates PPI (Swerdlow et al. 1992, 1999). The neurotransmitters active at several levels of this circuitry—dopamine, serotonin, glutamate—cause disruptions in PPI through the stimulation of DRD2s (amphetamine or apomorphine), activation of serotonergic systems, or blockade of NMDA receptors (phencyclidine or ketamine) (Geyer et al. 2001).

Few studies have reported PPI in first-episode psychosis (Aggernaes et al. 2001; Quednow et al. 2008; Kumari et al. 2007; Meincke et al. 2004; Ludewig et al. 2003; Mackeprang et al. 2002). Although the majority found PPI deficits in the first episode, they were not always robust (e.g., only in males,

antipsychotic specific). Three studies have assessed PPI in subjects at risk for psychosis: Quednow et al. (2008) and Ziermans et al. (2011) reported that at-risk subjects showed significant PPI deficits. However, Cadenhead (2011) found very different results in 75 first-episode, 89 at-risk, and 85 controls from the Cognitive Assessment and Risk Evaluation (CARE) sample. Unexpected findings included the fact that acutely ill, medication-naïve, first-episode subjects and at-risk subjects who later converted to psychosis had *greater* PPI than medicated first-episode subjects and at-risk subjects who did not convert to psychosis, respectively. This parallels findings from the visual perceptual organization literature (reviewed in Silverstein and Keane 2011; Parnas et al. 2001) that perceptual organization is intact or even superior at first episode. These findings introduce the possibility of early brain changes that diverge from findings in chronic patients early in the course of illness. Although the PPI findings from the CARE study differ from prior studies, it offers an intriguing possibility that there may be compensatory changes in inhibitory processes in response to early neurochemical changes, reflected by greater PPI, early in the course of psychotic illness. This finding may represent an initial change in the neural circuitry regulating PPI prior to the appearance of sensorimotor gating deficits in more chronic forms of the illness. Although preclinical studies show reduction in PPI in response to dopamine agonists and NMDA antagonists (Geyer et al. 2001), compounds such as N-acetylcysteine, which increase extracellular glutamate levels, enhance PPI (Chen et al. 2010). In addition, studies in control subjects have revealed evidence of enhanced PPI under certain conditions (high novelty seeking, specific doses) in response to dopamine agonists (amphetamine, pramipexole) (Talledo et al. 2009; Swerdlow et al. 2009a) and NMDA antagonists (ketamine, memantine, amantadine) (Swerdlow et al. 2002, 2009b; Abel et al. 2003; Duncan et al. 2001). This lends support to the idea of a period of acute glutamatergic dysregulation early in the course of illness leading to increases in PPI. It would then follow that more chronic hypoglutamatergic states would lead to reduced PPI in more chronic patients (Swerdlow et al. 2009b). The neurochemical mechanism by which PPI might be increased in the early stages of psychosis and the location in the modulatory circuitry (Swerdlow et al. 2008) where this occurs is unknown, but this work has implications for treatment development. Clearly, longitudinal studies of early psychosis patients are needed to follow the time course of PPI through the onset of disease to determine whether, for example, there is a window of compensatory changes that would benefit from interventions that reduce glutamate. When combined with other biomarkers (e.g., ^{1}H-MRS, fMRI), it should be possible to tease out the mechanism of disease and identify specific interventions likely to make an impact at this early stage.

Treatment implications: Although more work is needed to define the developmental neuropathology as indexed by PPI in the early stages of psychosis, important translational studies have been performed using the PPI paradigm. Atypical antipsychotics have been shown to reverse PPI deficits in

developmental animal models of psychosis and may "normalize" PPI in patients with chronic schizophrenia and clinically normal subjects (Swerdlow et al. 2006, 2008; Vollenweider et al. 2006; Wynn et al. 2007). Feifel and colleagues have demonstrated that *oxytocin* (a neurohypophyseal peptide known to regulate social cognition and affiliation) can modulate PPI deficits induced by NMDA receptor antagonists and dopamine agonists in rodent models (Feifel and Reza 1999; Feifel et al. 2010). Preliminary oxytocin studies in patients with schizophrenia have demonstrated improved positive and negative symptoms, social cognition, and emotional recognition (Feifel et al. 2010, 2012; Pedersen et al. 2011; Averbeck et al. 2011) but the effect of oxytocin on PPI has yet to be reported in schizophrenia patients.

Mismatch Negativity

One emerging view holds that the commonly observed clinical and neurocognitive deficits of schizophrenia patients may arise, at least in part, by dysfunction in the coordination of neural activity at the earliest stages of sensory and cognitive information processing (Green and Nuechterlein 1999a; Phillips and Silverstein 2003). Schizophrenia patients exhibit deficits in basic levels of sensory information processing that are present early in the course of the illness and even precede the emergence of psychotic symptoms. In a passive auditory oddball paradigm, a duration deviant stimulus elicits a mismatch negativity (MMN) response that peaks 100–200 ms after the onset of a stimulus deviance (Naatanen et al. 1978) and is assumed to reflect an automatic, sensory-based deviance detection process (Naatanen et al. 1978; Picton et al. 2000). Deficits in MMN generation using a variety of stimulation parameters (e.g., oddball stimuli that differ in pitch or duration) represent a remarkably robust finding in chronic schizophrenia (Shelley et al. 1991; Light and Braff 2005; Javitt et al. 2000), but the extant literature on MMN in the early stages of the disease is mixed, with some studies identifying abnormalities (Hermens et al. 2010; Umbricht et al. 2006; Devrim-Ucok et al. 2008) while others fail to detect any significant decrements in either duration or pitch of MMN in patients with a psychotic illness duration of less than three years (Valkonen-Korhonen et al. 2003; Salisbury et al. 2002). In a prospective study of first-hospitalized patients with schizophrenia (Salisbury et al. 2007), a strong relationship was found between the progressive reductions of MMN amplitude and left hemisphere Heschl gyrus gray matter volume. In chronic patients, Rasser et al. (2011) report that gray matter reductions are correlated with MMN amplitude. Several studies have now identified deficits in duration of MMN in not only the first episode of psychosis but also the prodromal period of illness (Bodatsch et al. 2011; Atkinson et al. 2012; Brockhaus-Dumke et al. 2005; Jahshan et al. 2012). These findings of MMN deficits in the prodrome contribute to the overall efforts to identify potential markers of vulnerability to schizophrenia

as well as to understand the underlying pathological processes leading to the development of the illness.

Treatment implications: Deficits in MMN generation may be associated with impaired NMDA receptor function because phencyclidine (PCP) and other NMDA antagonists inhibit MMN generation in primate models and normal volunteers. Consistent with the links between glutamatergic dysregulation and MMN, *N-acetylcysteine* (NAC, a glutathione precursor) has been shown to enhance MMN in patients with schizophrenia (Lavoie et al. 2008). Lavoie et al. (2008) report improved MMN in response to NAC versus placebo in patients with schizophrenia and suggest that increased levels of brain glutathione improve MMN and, by extension, NMDA function. *Memantine*, a noncompetitive NMDA receptor antagonist, enhanced the amplitude of MMN in normal subjects (Korostenskaja et al. 2007), but the effects have yet to be assessed in schizophrenia. Several studies report the ability to enhance MMN in healthy subjects using a variety of compounds including *serotonin reuptake inhibitors* (Kahkonen et al. 2005; Wienberg et al. 2010), *tryptophan depletion* (Ahveninen et al. 2002; Kahkonen et al. 2005), and *nicotinic receptor stimulation* (Baldeweg et al. 2006). A single case report (Higuchi et al. 2010) on the use of *tandospirone* (a 5-HT_{1A} partial agonist) in schizophrenia demonstrated an increase in MMN that preceded improvement in neurocognition. The effect of 5-HT_{1A} agonism on MMN may be mediated by its influence on glutamatergic and, possibly, GABAergic function (Huot and Brotchie 2011). With respect to antipsychotic agents, large MMN amplitudes predicted good treatment response to clozapine (Schall et al. 1999), although MMN appears to be insensitive to antipsychotic medication in schizophrenia (Umbricht et al. 1998, 1999; Korostenskaja et al. 2005). Event-related potentials (ERPs) could be especially useful in defining subgroups that might benefit from interventions other than dopamine-based treatments, but this requires going beyond group effects and reliably measuring individual differences. Methodological developments to improve the quantification of single-subject data are needed, along with more research which demonstrates that ERP measures can predict treatment response in schizophrenia patients.

Neural Synchrony

Abnormal gamma range (30–80 Hz) synchrony has proved to be an important biomarker for psychosis as it reflects core pathophysiological features of schizophrenia, including cognitive and perceptual abnormalities (reviewed in Gandal et al. 2012). Gamma oscillatory activity is thought to be the mechanism by which neural networks are integrated, facilitating coherent sensory registration. In schizophrenia, gamma abnormalities are evident in first-episode psychosis (Symond et al. 2005), in unmedicated patients (Gallinat et al. 2004), as well as in unaffected relatives (Leicht et al. 2011), suggesting that abnormal gamma synchrony is a heritable feature of schizophrenia. Gamma-band

responses have been associated with clinical symptoms, social cognition, neurocognitive performance, and loss of gray matter (Williams et al. 2009a, b), indicating that these measures are likely related to disease pathophysiology.

Treatment implications: Translational models of gamma-band responses have been used in preclinical studies, providing potential targets for treatment development. Several rodent studies have demonstrated that NMDA receptor antagonists (including ketamine, MK-801, and PCP) produce a dose-dependent increase in baseline gamma power (Ma and Leung 2007; Ehrlichman et al. 2009). Behaviorally, this increase in gamma power is associated with locomotor hyperactivity and deficits in PPI in animal models (Ma and Leung 2007; Hakami et al. 2009). Consistent with preclinical findings, ketamine increases baseline gamma power in healthy human subjects (Hong et al. 2010). Mechanistically, it has been proposed that the effect of NMDA receptor antagonists on gamma oscillations (and their psychomimetic properties) is due to reduced excitation of parvalbumin-containing GABA neurons (Lisman et al. 2008). Consistent with this hypothesis, Lewis et al. (2008) assessed MK-0777, a benzodiazepine-like agent with selective activity at $GABA_A$ receptors, versus placebo in 15 chronic patients with schizophrenia. MK-0777 was found to be associated with increased gamma-band power and improved performance on tests of working memory and cognitive control.

Mu Suppression

Mu rhythm suppression in response to biological motion is a relatively new candidate biomarker in schizophrenia research (Singh et al. 2011). Biological motion, as depicted in point light animations, is a well-studied construct in cognitive neuroscience. These displays provide sparse visual input that requires "filling-in" to recover object information to identify the kind of motion (e.g., walking, jumping, dancing) being produced (Keri and Benedek 2009; Blake and Shiffrar 2007). It has been suggested that neural processing of biological motion is an evolutionarily conserved mechanism and that it plays a fundamental role in social adaptation (Blake and Shiffrar 2007). Translational studies have associated biological motion with neural activity in the mu (8–13 Hz) range over the right sensorimotor cortex and are thought to index the activity of "mirror" neurons based on studies in primates (Bonini and Ferrari 2011; Keuken et al. 2011). Mu rhythms measured from this brain region show reliable, dose-dependent suppression when the subject perceives biological motion (but not nonbiological motion). Thus, mu wave suppression is an easily quantifiable operational measure of the neural processing of biological motion. In a recently published study, Singh et al. (2011) showed that neural mu wave suppression induced by biological motion is impaired in first-episode patients, and that the neural impairment is inversely correlated with negative symptoms and social adjustment, providing construct validity for the mu suppression paradigm as an operational measure of social cognition in patients

with psychosis. In a related study, McCormick et al. (2012) recorded and analyzed mu rhythm suppression over the sensorimotor cortex during observed and actual hand movement in actively psychotic patients and found evidence of increased suppression during observed movement that was correlated with positive symptoms.

Treatment implications: Keri and Benedek (2009) and Perry et al. (2010) have recently demonstrated that intranasal *oxytocin* significantly enhances detection of biological motion compared to intranasal placebo in normal subjects. Although oxytocin has been shown to improve social cognition and emotional recognition in patients with schizophrenia (Averbeck et al. 2012; Feifel et al. 2010; Pedersen et al. 2011), the effects of oxytocin on mu suppression in schizophrenia patients have yet to be reported. In an innovative study of *neurofeedback training* in high functioning autism, Pineda et al. (2008) report that individuals with autistic spectrum disorders who have mu suppression abnormalities can renormalize mu suppression and improve sustained attention after training to the mu frequency band. Like other cognitive remediation interventions, neurofeedback training offers a potential nonpharmacologic intervention which can target core information-processing abnormalities that contribute to social functioning deficits in patients with schizophrenia.

Functional Neuroimaging

The most robust fMRI findings associated with schizophrenia are altered PFC, ACC, and temporal lobe activation, particularly during the performance of tasks which engage executive functions, such as verbal fluency paradigms. Fusar-Poli et al. (2007) examined studies of first-episode psychosis and individuals at high risk (schizotypal, genetic high risk, at risk) for psychosis. First-episode patients showed significant PFC abnormalities with most studies reporting reduced activation in the dorsolateral prefrontal cortex (DLPFC) during cognitive tasks. Some authors have suggested that hypofrontality in the DLPFC may be a specific feature of schizophrenia at the time of the first psychotic episode. Only one study reports greater prefrontal activation in first-episode patients: Mendrek et al. (2005) found that first-episode patients had greater DLPFC activation during the easy level of a working memory task, but less activation when task demands were high.

In general, high-risk subjects display neurophysiological abnormalities in cortical regions that have also been observed to be dysfunctional in first-episode psychosis (Broome et al. 2010; Allen et al. 2012). In contrast to most first-episode studies, however, a number of genetic high-risk studies reported relatively greater prefrontal activation than in controls (Seidman et al. 2006; Callicott et al. 2003; Thermenos et al. 2004). Studies in prodromal subjects (Sabb et al. 2010; Allen et al. 2011, 2012) also found greater activation in specific brain regions: Sabb and colleagues found increased neural activity in the bilateral mPFC, left inferior frontal (LIFG) and middle temporal gyri, and

ACC in at-risk subjects compared to controls (Sabb et al. 2010; Allen et al. 2011). Further, increased activity in the superior temporal gyrus, caudate, and LIFG distinguished those at-risk subjects who subsequently developed psychosis from those who did not. Using a combined fMRI and PET study, Allen et al. (2011), reported that at-risk subjects who later develop a psychotic episode show increased activation in bilateral PFC, brainstem (midbrain/basilar pons), the left hippocampus, and greater midbrain-PFC connectivity during a verbal fluency task. Furthermore, exploratory analysis of [18F]-DOPA PET data showed that transition to psychosis was associated with elevated dopaminergic function in the brainstem region. These interesting findings of increased activation in genetic high risk and putatively prodromal subjects have been hypothesized to reflect a compensatory response to volumetric reductions in gray or white matter to maintain adequate performance (MacDonald et al. 2005a) or "cortical inefficiency"(Callicott et al. 2000).

Multimodal neuroimaging during the prodrome and first episode of psychosis offers the potential to delineate the causal relationship between key pathophysiological processes in the evolution of psychosis to determine if the unique findings of hyperactivation reflect compensatory changes related to the hypothesized window of neurotoxicity. For example, the combination of structural MRI, fMRI, PET, SPECT, or ^{1}H-MRS can address the relationship between glutamate or dopamine and changes in gray matter or cortical activation. In an elegant series of studies, Fusar-Poli and colleagues found that alteration in prefrontal activation in at-risk subjects in a verbal fluency task was related to elevated striatal dopamine using PET (Allen et al. 2011, 2012; Fusar-Poli et al. 2010, 2011a, b). In an fMRI study using a working memory paradigm, the same group found a positive correlation between frontal activation and fluorodopa uptake in the associative striatum in controls but a negative correlation in the at-risk group (Fusar-Poli et al. 2011a, b). The key finding from these studies is that, for individuals at very high risk of schizophrenia, altered prefrontal activation during a task of executive/working memory function was directly related to striatal hyperdopaminergia. This provides evidence of a link between dopamine dysfunction and the perturbed prefrontal function, which may underlie the deficits in cognitive processing evident in people with prodromal symptoms of psychosis and predate the first episode of frank psychosis.

Treatment Implications

Although a number of functional neuroimaging biomarkers are being developed as part of initiatives, such as the CNTRICS study, there is little consensus in the literature on treatment effects, such as antipsychotic effects, on the BOLD signal (Carter and Barch 2007). In a literature review on antipsychotic effects, Roder et al. (2010) report that there does not appear to be any common underlying mechanism of action of antipsychotic drugs that influence the BOLD signal in a systematic way in all areas of the brain in the same

direction. Some studies find differences in BOLD signal with treatment but others do not, and there is no clear difference between first- and second-generation antipsychotics on BOLD signal. The most consistent finding in the literature is that haloperidol decreases BOLD signal in cortical and subcortical structures.

In terms of nonpharmacologic interventions, both CBT and cognitive training have been found to improve working memory performance as well as brain connectivity (Kumari et al. 2009, 2011; Vinogradov et al. 2012). Kumari et al. (2009) examined changes in working memory performance in response to CBT using the N-Back and found stronger DLPFC activity. In addition, DLPFC-cerebellum connectivity during the highest memory load condition (2-back > 0-back) predicted post-CBT clinical improvement. Using a facial expression task, Kumari et al. (2011) found that the CBT group showed attenuation of fMRI BOLD response to fearful and angry expressions at follow-up relative to baseline. Preliminary cognitive training studies (Vinogradov et al. 2012) in schizophrenia patients have shown that computerized auditory training significantly improves verbal memory performance as well as early magnetoencephalographic responses in auditory and prefrontal cortices that are positively associated with quality of life six months later. Vinogradov et al. (pers. comm.) examined the association between computerized auditory training-induced behavioral improvements and changes in brain activation in an fMRI paradigm during a 2-back, verbal working memory task in patients with schizophrenia. At baseline, during the 2-back working memory task, patients showed impaired performance, reduced activation in bilateral DLPFC, and no significant associations between brain activation and 2-back performance. After cognitive training, patients significantly improved their performance on the task and showed increased DLPFC activation. These preliminary CBT and cognitive remediation studies demonstrate the importance of nonpharmacologic interventions in treating cognition deficits of schizophrenia. The functional brain measures provide an important tool to evaluate brain connectivity in response to psychosocial as well as cognitive enhancing drugs. Many important studies are needed to compare treatments as well as the potentially synergistic effect of combined treatment in early psychosis.

Given What We Know Now, Can We Alter the Pathological Processes in Early Psychosis?

As eloquently reviewed by Swerdlow (2011), an increasingly detailed image of neural- and molecular-level dysfunction in schizophrenia has emerged to reveal failures of early brain maturation, dysfunctional neural circuitry, and failure to develop appropriate connectivity across widely dispersed brain regions. These circuit abnormalities are complex, vary across individuals, and are hard wired, illustrating the challenge of developing treatment that can effectively

alter the course of the illness once it has reached the chronic or even acute phase. As knowledge of the mechanisms underlying the emergence of psychosis increases, the picture becomes even more complex with the identification of each new gene or epigenetic contribution and the resulting compensatory changes in hard-wired neural circuitry. Based on our current models of treatment for schizophrenia, it does not seem possible to reverse a process that has been developing for two decades; however, it may be possible to prevent or modify the identified neurobiological processes that occur at disease onset and improve outcome.

Clinical research has shown that the longer the duration of untreated psychosis, the poorer the treatment response (Addington et al. 2004; Melle et al. 2004), thus suggesting that earlier intervention may improve the outcome of the illness. In a comprehensive review, Berger et al. (2003) outline how altered regulatory mechanisms of progenitor cell generation and death could be targeted for neuroprotection or disease modification in early psychosis. Although researchers previously believed that stem and progenitor cell generation in mammals was only possible in early life, recent research suggests that the hippocampi (Kornack and Rakic 1999), periventricular zone, (Steindler and Pincus 2002) and olfactory bulbs (Byrd and Brunjes 2001) retain the capacity to generate progenitor cells which differentiate into neurons. A number of compounds reviewed in this chapter—which show potential in altering neurobiologically defined surrogate endpoints and also modulate apoptosis pathways (lithium, sodium valproate, BDNF, clozapine, quetiapine, lamotrogine, omega-3 fatty acids), block necrosis pathways (vitamin E)—increase synaptogenesis (SSRIs) or block the inflammatory response (COX-2 inhibitors, aspirin) (Jacobs et al. 2000; Malberg et al. 2000; Vaidya et al. 1997), and provide evidence of neuroprotective properties in preclinical and clinical studies.

Predicting Treatment Response

Ultimately, the goal of treatment in early psychosis patients is to modify active neuropathological changes and associated functional disability. With a greater understanding of aberrant neural systems in early psychosis, new treatments will be introduced. A number of psychosocial and pharmacologic interventions have great potential as neuroprotective, disease-modifying, or procognitive interventions in early psychosis (Tandon et al. 2011). Given the heterogeneity of the prodromal period and the first episode of psychosis, the importance of treatment "precision" is evident. If we can identify which type of treatment can best target the abnormal neural system of a particular individual, treatment is likely to be more effective (Vesell 1978; Foster et al. 2010; Wilke and Dolan 2011). Ideally, with the use of various risk factor and biomarker assessments it will be possible to develop a neurobiological profile to predict treatment response. In line with the Research Domain Criteria (Insel et al. 2010) proposed

by the National Institutes of Mental Health, it may be optimal to focus on neural systems to target treatment as opposed to diagnostic and statistical diagnosis (cf. Carpenter, this volume).

Where We Are and Where We Need to Go: Future Directions in Treating the Early Phase of Schizophrenia

It is astounding that the "dopamine hypothesis of schizophrenia" has been in the mainstream for over sixty years and that pharmacologic management of schizophrenia is still based on antagonists or partial agonists of the dopamine D2 receptors (for a review, see Howes et al. 2009). Despite extensive genetic, epigenetic, developmental, and cognitive neuroscience literature on schizophrenia, which reveals that many innovative ideas and directions are being pursued, it has been difficult to identify new pharmacologic interventions that take the treatment of schizophrenia much beyond first- or second-generation antipsychotic medication. The majority of treatment studies have been performed in chronic patients, and many are underpowered or plagued by methodological differences which complicate the reliable merging of data across studies.

It is clear that adequately powered studies of early psychosis patients are needed to assess the extensive armamentarium of neuroprotective, disease-modifying, and procognitive compounds already identified. The anti-inflammatory agents, including COX-2 inhibitors, omega-3 fatty acid, and minocycline, already offer promise in first-episode patients and may affect functional outcome by more effectively targeting negative symptoms and neurocognition. SSRIs and lithium may decelerate the loss of gray matter in the early stages of illness by promoting neurogenesis. Glutamate-modulating agents may be particularly important if the hypothesized window of neurotoxicity (revealed by possible compensatory changes in brain function, sensorimotor gating, and brain metabolism) proves to be present in early illness.

Psychosocial and cognitive remediation techniques have emerged as some of the most effective interventions to target neurocognition, functional capacity, and functional outcome. Empirically supported treatments for psychotic disorders now include a variety of psychosocial interventions, such as CBT, social skills training, vocational rehabilitation, and cognitive remediation. Substantial research indicates that CBT changes brain function in brain disorders such as OCD (Baxter et al. 1992; Schwartz et al. 1996; Saxena et al. 2009), and we now have preliminary evidence in schizophrenia (Vinogradov et al., pers. comm.; Kumari et al. 2011). CBT has been shown to reduce symptoms and improve long-term functioning in patients with chronic (Granholm et al. 2007) and first-episode schizophrenia (Power et al. 2003; Petersen et al. 2005) as well as those in the prodromal phase of illness (Morrison et al. 2004). Cognitive remediation offers the potential to reinforce healthy circuits

to compensate for areas of cognitive deficits and perhaps reduce gray matter loss and improve brain connectivity at the same time.

Although psychosocial treatment interventions have been added to augment antipsychotic medication, relatively little is known about the effectiveness of combining pharmacologic interventions designed to enhance cognition, provide neuroprotection, or facilitate neuroplasticity with CBT, cognitive remediation, or exercise. Future clinical trials in early psychosis patients should ideally compare nonpharmacologic and pharmacologic interventions as well as assess whether a combination of therapies is more effective than any one alone.

Clinical and functional outcomes are important in clinical trials but ongoing work to develop biomarkers linked to functional outcome, treatment response, and pathological circuitry as surrogate endpoints represents an innovative approach which should be pursued. Most importantly, if reliable neurobiological measures can be developed for the clinical setting to assist in the specification of treatments for a particular patient, it should be possible to truly individualize care based on brain function, risk factors, and prediction of response.

Acknowledgments

K. S. Cadenhead is supported by National Institutes of Health (NIH) grants R01 MH60720, U01 MH082022, and K24 MH76191

Schizophrenia

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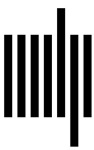
Citation:

Schizophrenia: Evolution and Synthesis
Edited by: Steven M. Silverstein, Bita Moghaddam, Til Wykes
DOI: 10.7551/mitpress/9780262019620.001.0001
ISBN (electronic): 9780262314602
Publisher: The MIT Press
Published: 2013



The MIT Press

This volume is the result of the 13th Ernst Strüngmann Forum,
held July 22–27, 2012, in Frankfurt am Main, Germany.

Series Editor: J. Lupp
Assistant Editor: M. Turner
Photographs: U. Dettmar
Design and realization: BerlinScienceWorks

The book was set in TimesNewRoman and Arial.
Printed and bound in the United States of America.

Library of Congress Cataloging-in-Publication Data

Schizophrenia : evolution and synthesis / edited by Steven M. Silverstein,
Bita Moghaddam, and Til Wykes.
pages cm. — (Strüngmann Forum reports)
Includes bibliographical references and index.
ISBN 978-0-262-01962-0 (hardcover : alk. paper)
1. Schizophrenia. 2. Schizophrenia—Etiology. 3. Clinical medicine—Decision making. I. Silverstein, Steven M. II. Moghaddam, Bita. III. Wykes, Til.
RC514.S3353 2013
616.89'8—dc23

2013013617

10 9 8 7 6 5 4 3 2 1