Developmental biomarkers in schizophrenia and other psychiatric disorders: common origins, different trajectories?

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BIOMARKERS IN SCHIZOPHRENIA AND OTHER PSYCHIATRIC DISORDERS: COMMON ORIGINS, DIFFERENT TRAJECTORIES?

The biological bases of illnesses such as schizophrenia and bipolar disorder have been a subject of decades of research. However, the origins of these illnesses are largely unknown. The issue is important and timely because scientific understanding of the origins of these illnesses will permit earlier intervention, leading to better illness management and better outcome.

Understanding neurodevelopment during the adolescent period may be the key to understanding the emergence of psychiatric illness. Adolescence is marked by substantial cortical reorganization and change resulting from continuing processes of myelination and synaptic pruning (Durston et al., 2001; Huttenlocher, 1979). These concurrent processes may be crucial for the development of normal neural networks; myelination accelerates synaptic transfer of information, and normal pruning eliminates redundancies in metabolically expensive cortical gray matter (Keshavan et al., 1994; Laughlin & Sejnowski, 2003). Developmental changes in neurobiology also depend on patterns of gene- (Lesch, 2004) and behavior-environment interactions (Penn, 2001; Ramakers, 2005). This rapid cortical maturation during adolescence is associated with parallel increases in cognitive proficiency, particularly in basic cognitive systems such as attention and working memory, as well as affect perception and regulation. Pathologic processes including but not restricted to stress, obstetric complications, and alterations in gene expression (Nurnberger & Foroud, 2000) are likely to impact neurodevelopment and function during this critical period in unpredictable ways. As we discuss below, such pathological processes frequently co-exist across diagnostic boundaries (Walker et al., 2004) though more specific impairments in key neural networks may emerge during the period of adolescence (Pine, 2004).

The recently completed National comorbidity study (Kessler et al., 2005) has shown that about half of Americans meet the criteria for a DSM-IV disorder sometime in their life, with first onset usually in childhood or adolescence, comorbid conditions accruing later in life. Not surprisingly, there has been much debate recently about whether major psychiatric disorders such as schizophrenia and bipolar disorders are distinct clinical entities or whether an expanded psychiatric continuum exists between these disorders. The latter view is supported by co-occurrence of affective and schizophrenic symptoms (Adler & Strakowski, 2003), evidence of common susceptibility genes for the two disorders (Berrettini, 2003), similarities in neurotransmitter and neurophysiological dysfunction and in treatment response across these disorders (Moller, 2003). Neuroimaging studies show some overlapping findings in these two illnesses, in particular abnormalities in the fronto-striatal circuits that are associated with attention. Thus, attention deficit hyperactivity disorder (ADHD) frequently coexists with schizophrenia (Bellak et al., 1987), OCD (Sukhodolsky et al., 2005) and bipolar disorder (Kim & Miklowitz, 2002). Many children with ADHD have features of thought disorder similar to children with schizophrenia (Caplan et al., 2002). Individuals at genetic risk for schizophrenia (Keshavan et al., 2002a) and bipolar disorder...
(Chang et al., 2000) also show an increased frequency of attentional impairments. There is also evidence of overlap in other disorders. For example, comorbidities of schizophrenia and Obsessive Compulsive Disorder (OCD) are also frequent (Gross-Isseroff et al., 2003) suggesting some possibility of shared characteristics between them.

Such comorbidity and symptom commonality has made the search for distinct clinical phenotypes of illness expression often elusive. However, they also suggest fundamental commonalities in developmentally mediated dysfunction that may give rise to both common and unique biomarkers associated with these illnesses. Recent neuroimaging and genetic strategies are beginning to clarify biomarkers across childhood/adolescent onset neuropsychiatric disorders. We herein will emphasize the neurodevelopmental bases of diagnostic overlap and symptom commonality. In particular we will address similarities and differences in the neuroanatomical and functional basis of neuropsychiatric disorders that may have their genesis in childhood and development, specifically schizophrenia, attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), and mood disorders including major depressive disorder (MDD) and bipolar disorder (BPD). These disorders are marked by onset in adolescence or early adulthood, and may be preceded or accompanied by symptoms similar to developmental disorders such as ADHD.

COMMON VS. UNIQUE CHANGES IN NEURAL NETWORKS IN PSYCHIATRIC DISORDERS

Neuroimaging techniques have increasingly elucidated the intrinsic neural circuitry abnormalities underlying the pathophysiology of psychiatric disorders. We herein outline current findings in structural abnormalities inherent to several psychiatric disorders as they relate to schizophrenia, attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), and mood disorders including major depressive disorder (MDD) and bipolar disorder (BPD). These disorders are marked by onset in adolescence or early adulthood, and may be preceded or accompanied by symptoms similar to developmental disorders such as ADHD.

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ETIOLOGICAL COMMONALITIES AND DIFFERENCES ACROSS DISORDERS

There is a substantial genetic component to both schizophrenia and ADHD. Alterations in the gene encoding the dopamine D4 receptor have been reported in children with ADHD (LaHoste et al., 1996; Benjamin et al., 1996; Ebstein et al., 1996). An association between alterations in the gene encoding the dopamine transporter and ADHD has also been reported (Cook et al., 1995; Gill et al., 1997). Association with polymorphisms of the catechol-O-methyltransferase (COMT) gene which encodes an enzyme that degrades dopamine, has been reported in schizophrenia (Sawa & Snyder, 2002) as well as in BPD (Badner & Gershon, 2002). Targeted deletions of the COMT gene appears to decrease levels of dopamine only in the prefrontal cortex (Gogos et al., 1998). Prefrontal dopaminergic deficits have been thought to underlie attentional and executive function deficits seen in both schizophrenia and BPD.

By contrast with schizophrenia where replicable findings are beginning to emerge (O’Donovan et al., 2003), relatively few replicated genetic susceptibility loci have been identified for OCD and BPD. However, recent studies have suggested that there may be some susceptibility genes that are common to both schizophrenia; these include Neuregulin1 (NRG1) gene (Green et al., 2005), COMT and BDNF (Maier et al., 2005). Also of interest is the modest association observed between serotonin transporter gene and affective disorder (Lasky-Su et al., 2005). Recent fMRI studies have suggested that this association may be mediated by the effects of this gene on the response bias of the human amygdala to environmental threat (Hariri et al., 2005). Interestingly, a modest but significant association between this gene polymorphisms and affective disorders has been noted by metaanalyses (Lasky-Su et al., 2005).

While obstetric complications (OCs) are known to contribute to the vulnerability for schizophrenia, the diagnostic specificity and the cause effect relationship remain unclear; OCs are more frequent in other severe psychiatric disorders, such as ADHD (Sprich-Buckminster et al., 1993; Milberger et al., 1997). OCs may interact with genetic liability and later environmental risk factors (Verdoux & Sutter, 2002). OCs have been observed inconsistently in BPD (reviewed in Buka & Fan, 1999). Overall, the risk-enhancing effect of OCs has been better established in schizophrenia by comparison with bipolar disorder (Murray et al., 2004). OCs may contribute to volume losses in medial temporal structures such as amygdala, though genetic risk also contributes to this (Keshavan et al., 2002b).

TOWARD A SYNTHESIS

The observed pathophysiological similarities across psychiatric disorders are consistent with the observations of frequent comorbidity and diagnostic overlap discussed earlier. The similar reductions in ADHD and schizophrenia in overall brain volume, corpus callosum and frontostriatal circuits is consistent with evidence of attentional impairment as a core feature of schizophrenia as well as with observations of attentional problems being among the most robust premorbid predictors of later schizophrenia. Attentional impairment also predicts the later emergence of BPD (Kim & Miklowitz, 2002). Interestingly, an association has also been proposed between ADHD and childhood OCD (Geller et al., 2002). Thus, attentional impairments in childhood, perhaps related to frontostriatal pathology, may represent a common and non-specific precursor for diverse psychiatric presentations in adulthood such as OCD, BPD and schizophrenia. There are also some intriguing differences. Overall brain size reductions, seen in schizophrenia, are less prominent in BPD and OCD. Further, OCD patients, unlike schizophrenia patients, show increased and not decreased cingulate volumes. Similarly, BPD and depressive patients show larger amygdala volumes in contrast to the smaller amygdala volume observed in schizophrenia. BPD patients may also show larger basal ganglia unlike the schizophrenia patients. How do we make sense of these similarities and differences?

First, differential severity and trajectories of neurobiological disruptions may cause the varied phenotypic
expressions of psychiatric illnesses and disorders such as schizophrenia, bipolar disorder and obsessive compulsive disorder. Massive disruptions in circuitry may lead to extreme deficits in cognition and thought disorder that are observed in illnesses like schizophrenia (Lawrie et al. 2002). On the other hand, more selective disruptions in frontal, sub-genual and limbic circuitry may underlie disorders of mood regulation such as observed in disorders of mood like bipolar disorder and depression (Drevets 1999). Selective disruptions in frontal-striatal circuitry may lead to patterns of impaired inhibition that is observed in disorders such as obsessive-compulsive disorder (Maltby et al., 2005). Second, some of the differences in phenotypic manifestations may result from the consequences of continued illness, perhaps emerging from progressive neurodegenerative processes at least in some disorders such as schizophrenia (Keshavan, 1999). Finally, these distinct developmental trajectories may be related to differential compensatory pathoplastic responses of the subcortical brain structures such as the cingulate and amygdala and may mediate the emergence of distinct symptomatic presentations. It is well known that the amygdala and the cingulate, respectively, are critically involved in affect regulation and conflict monitoring (Ledoux, 2003). Thus, the amygdala enlargements in BPD might represent a pathological hyperplasia in that region related to repeated activation in the context of highly valenced emotional states, such as the manic and depressive episodes. Likewise, the cingulate enlargement in OCD might reflect a hyper-responsive error-monitoring system. On the other hand, the failure of optimal functioning of cingulate may underlie the deficits in self-monitoring leading to disorganized thinking in schizophrenia. Additionally, interactions between genetic predisposition and OCs such as hypoxia may result in smaller volumes of the amygdala and hippocampus, leading to diminished affective responsibility and blunted affect. The similarities and unique differences in pathophysiological trajectories may stem from differential combinations of genetic factors and environmental influences in each individual.

An integrated approach to longitudinal follow-up studies of children at risk for a variety of major psychiatric disorders using the non-invasive neuroimaging techniques can help us test such predictions. First, such studies enable us to further clarify the common and distinct neurodevelopmental alterations across diverse disorders and help us unravel the shared and distinct vulnerability factors of genetic or environmental origin. It would also help us understand whether changes in brain biology are related to the causes of, consequences of, or compensatory responses to these illnesses. Second, mapping the developmental trajectories of adult psychiatric disorders can help in designing prevention strategies. Of concern are recent observations that treatment is significantly delayed in such childhood disorders, leading to considerable cumulative morbidity (Kessler et al., 2005). Improved knowledge of the common developmental basis of psychiatric disorders will clearly promote a life-course developmental approach to psychopathology and eventually improve treatment and prevention. Emerging research suggests that apparently distinct clinical phenotypes associated with neuropsychiatric illness may have common origins in developmental derailment. The future to better understanding of psychiatric illnesses may involve understanding the trajectories and timing of developmental derailments and the relationship between these trajectories and the adopted classification of different disorders.

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