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

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(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 in order to highlight the complexities of diagnostic overlap.

Similar to schizophrenia (Sowell *et al.*, 2000), unmedicated children and adolescents with ADHD (Castellanos *et al.*, 2002) have shown reductions in total brain volume. Consistent with reports of decreased prefrontal lobe activity (Andreasen *et al.*, 1992) and decreased striatal volumes (Keshavan *et al.*, 1998; Shihabuddin *et al.*, 1998) in schizophrenia, reduced prefrontal and striatal volumes and hypoactivation of the prefrontal cortex and striatum are seen in ADHD (for a review see Seidman *et al.*, 2005). Decreased levels of N-Acetyl Aspartate (NAA, a measure of neuronal integrity) have also been seen in the striatum in pediatric ADHD (Hesslinger *et al.*, 2001). NAA and gray matter volume reductions in frontal and anterior cingulate cortex are seen in childhood onset schizophrenia patients and unaffected offspring at increased risk for developing schizophrenia (Sowell *et al.*, 2000; Keshavan *et al.*, 1997). Finally, corpus callosum size reductions are seen in ADHD (Hill *et al.*, 2003), similar to those observed in schizophrenia (Shenton *et al.*, 2001); additionally, attentional problems appear to correlate with reductions in corpus callosal size (Kayl *et al.*, 2000).

By contrast with ADHD and schizophrenia, treatment-naïve pediatric OCD is not characterized by overall brain size reductions (Rosenberg *et al.*, 1997b; Rosenberg & Keshavan, 1998; Gilbert *et al.*, 2000). Anterior cingulate volume is increased in OCD patients compared to controls (Rosenberg & Keshavan, 1998; Szeszko *et al.*, 2004) while cingulate volume reductions are seen in schizophrenia (Noga *et al.*, 1995; Takahashi *et al.*, 2003). This observation is consistent with increased error related activation of rostral cingulate cortex in OCD using fMRI (Fitzgerald *et al.*, 2005). Unlike first episode neuroleptic-naïve patients with schizophrenia (Gilbert *et al.*, 2001), pediatric OCD patients show increased thalamic volumes compared to controls. However, similar to ADHD and schizophrenia, reduced striatal volumes are seen in child and adolescent OCD compared to controls in computerized tomography (Luxenberg *et al.*, 1988) and volumetric MRI studies(Rosenberg *et al.*, 1997a). Also, similar to ADHD, reductions in NAA are seen in the striatum in OCD patients compared to controls (Ebert *et al.*, 1997; Bartha *et al.*, 1998).

Total brain size is reduced in MDD in some studies (Steingard *et al.*, 2002; Brambilla *et al.*, 2001) but no significant differences have been observed in this measure between bipolar patients and controls. Thus, reduced total brain volumes may be similar between ADHD and MDD but not OCD and bipolar disorder. Reduced frontal white matter volumes have been reported in adult and pediatric patients with MDD (Steingard *et al.*, 2002). Both ADHD patients and MDD patients have reduced frontal white matter volumes compared to controls (Castellannos *et al.*, 2002), but ADHD patients also have reduced gray matter volumes compared to controls. The subgenual prefrontal cortex volume and cerebral blood flow reductions have been seen in familial adult MDD and BPD patients as compared to non-familial MDD and BPD patients (Drevets, 2000). Increased amygdala volume is consistently observed in volumetric neuroimaging studies of pediatric as well as adult patients with BPD (Frodl *et al.*, 2002; Altshuler *et al.*, 2000; Strakowski *et al.*, 1999).

fMRI studies show enhanced amygdala activation in response to fearful facial affect in BPD patients (Thomas *et al.*, 2001). Pediatric MDD frequently precedes bipolar disorder in adulthood (Geller *et al.*, 2001; Harrington *et al.*, 1990; Weissman *et al.*, 1999). Thus, increased amygdala and reduced hippocampal volumes are seen in pediatric patients with MDD and first episode adults with MDD (Frodl *et al.*, 2002). These findings contrast reports of decreased amygdala volumes in schizophrenia (see Shenton *et al.*, 2001 for review), and in those at risk for this disorder (Keshavan *et al.*, 2002b). The striatum appears larger in first episode bipolar patients (Strakowski *et al.*, 2002). On the other hand, basal ganglia volumes appear to be reduced in depression (for a review see Soares & Mann, 1997).

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 amygdalae 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 nonspecific 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 neurodeteriorative 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 responsivity 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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