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Will neuroimaging ever be used to diagnose pediatric bipolar disorder?

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Abstract

There is a great need for discovery of biological markers that could be used diagnostically for pediatric onset disorders, particularly those with potentially confusing phenomenology such as pediatric-onset bipolar disorder (BD). Obtaining these markers would help overcome current subjective diagnostic techniques of relying on parent and child interview and symptomatic history. Brain imaging may be the most logical choice for a diagnostic tool, and certain neurobiological abnormalities have already been found in pediatric BD. However, much work remains to be done before neuroimaging can be used reliably to diagnose this disorder, and because of the nature of BD and the limitations of imaging technology and technique, neuroimaging will likely at most be only a diagnostic aide in the near future. In this paper we discuss the characteristics of pediatric BD that complicate the use of biological markers as diagnostic tools, how neuroimaging techniques have been used to study pediatric BD so far, and the limitations and potential of such techniques for future diagnostic use.

There is a great need for discovery of biological markers that could be used diagnostically for pediatric onset disorders, particularly those with confusing phenomenology such as pediatric-onset bipolar disorder (BD). Obtaining these markers would help overcome current subjective diagnostic techniques of relying on parent and child interview and symptomatic history. This approach is problematic in the case of pediatric-onset BD, because it can be a complex and difficult disorder to diagnose (Pavuluri, Birmaher, & Naylor, 2005). There is ongoing controversy about whether euphoria and grandiosity should be necessary symptoms of pediatric mania (Carlson, 2005). Irritability appears to be a more dominant primary mood symptom of pediatric mania, but is certainly not specific to BD, as it is often seen in unipolar depression, attention-deficit/hyperactivity disorder (ADHD), and intermittent explosive disorder, among others (Leibenluft, Blair, Charney, & Pine, 2003). Next, rapid cycling, frequently ultradian, is commonly observed in pediatric BD, making episodic determinations necessary for a diagnosis of a manic episode difficult (Geller et al., 1998). Finally, comorbid psychiatric disorders, common in pediatric BD, may mask symptoms of mania (Pavuluri et al., 2005). Thus, an objective measure such as a biological marker specific to early-onset BD would be tremendously helpful in diagnosing this disorder.

Brain imaging may be the most logical choice for a diagnostic tool, because it is now clear that the symptoms of BD are related to dysfunction of brain circuitry, and certain neurobiological abnormalities have been found in patients with BD (for a review, see Adleman, Barnea-Goraly, & Chang, 2004; Frazier et al., 2005). However, neuroimaging research in pediatric BD is in its infancy, and

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currently neuroimaging *cannot* be used to diagnose this disorder. Indeed, other than possibly early Alzheimer disease dementia (Selkoe, 2005), there are no psychiatric disorders that can be diagnosed by neuroimaging alone to date. Why is this the case? Moreover, will neuroimaging ever be a useful diagnostic tool in pediatric onset BD? In this paper we attempt to elucidate this issue by first discussing the characteristics of pediatric BD that complicate the use of biological markers as diagnostic tools. Then, we will consider current neuroimaging techniques with the most potential, briefly review how they have been used to study pediatric BD so far, and discuss their limitations and potential for future diagnostic use.

Challenges in Studying Pediatric BD

Foremost, BD is a fairly heterogeneous disorder. The BD phenotype is probably a result of a number of different pathways affected by genetics, environment, development, and other factors. This concept, known as "equifinality," complicates efforts toward creating a truly homogenous biologically categorized group based on external behavior (Cicchetti & Rogosch, 1999; Gottlieb, 2001). Even in situations in which one could presume the most homogeneity of etiology, such as that of identical twins, the concordance of the disorder ranges from 40 to 97% (depending on the definition of BD; Hasler, Drevets, Gould, Gottesman, & Manji, 2006). Because it is likely that several different factors contribute to the phenotype of BD, even when it is most strictly defined, it may be difficult to find any single factor, or even many factors, that are uniformly present in all patients. If there were no factors uniformly present in all patients, then it would make biomarkers of BD particularly difficult to sort out.

Genetic studies have proposed a multitude of different candidate genes for BD (Schulze & McMahon, 2003), but several researchers have had trouble replicating the research using different subject populations (Baron et al., 1987; Egeland et al., 1987). It is almost certain that vulnerability to BD is polygenic (Berrettini, 1999), and likely unique to specific subsamples of patients. For example, one study has suggested that subjects with early onset of BD (age at onset $\leq$ 21 years) had a different pattern of genetic linkage than those with later onset (age at onset $>$ 21 years; Lin et al., 2005). Variations in gene expression can lead to within-group variations in brain structure and function. For example, healthy subjects with the short allele polymorphism of the serotonin transporter gene have been found to have overall decreased amygdalar volume (Pezawas et al., 2005) and increased amygdalar activation when watching fearful faces (Hariri et al., 2005). Thus, within a group of subjects with BD, there may be enough genetic heterogeneity to "wash out" positive findings, rendering diagnostic imaging difficult.

Development also may play a significant role in the outcome of BD in patients. Early-onset mood disorders affect a child's ability to function effectively during important developmental stages, and thus may cause a lifetime of poor psychosocial functioning. Adolescents with mood disorders have an increased risk of suicidal behavior (Perlis et al., 2004), illicit drug use and dependence (Ernst & Goldberg, 2004), high rates of psychiatric hospitalization (Biederman et al., 2005), psychotic features and mixed episodes (Schurhoff et al., 2000), and poor neuropsychological functions (Taylor & Abrams, 1981). Among patients with pediatric-onset BD, rates of remission over 1 year are low, while recurrence is common (Geller, Tillman, Craney, & Bolhofner, 2004). Childhood-onset BD may be more treatment-resistant and have a worse prognosis than adult-onset BD (Geller et al., 2000; Geller & Luby, 1997). There have been enough differences delineated for early-onset BD that Craney and Geller (2003) have defined a phenotype specific to pediatric BD.

These many differences between childhood-onset and adult-onset BD may be due to distinct etiologies for the disorders, to the increased length of exposure to the disease for patients with childhood onset, or simply because of the effects that BD may have on the brain at different stages of development. A brain insult that has a significant effect on the brain's ability to develop normally will cause

more difficulties than an insult that affects the brain after it has developed normally. For example, research suggests that development of the prefrontal cortex, both structurally (Giedd et al., 1999) and functionally (Adleman et al., 2002), continues throughout puberty and adolescence. Several studies have suggested that the prefrontal cortex may be a site of abnormality in BD (Adler, Levine, DelBello, & Strakowski, 2005; Blumberg, Leung, et al., 2003; Chang et al., 2004; Kronhaus et al., 2006). Interference with the normal development of prefrontal cortex in children with BD may contribute to future abnormalities in this area observed in adulthood (Blumberg et al., 2004). Blumberg et al. reported that normal age-related increases in ventral prefrontal cortex activation in healthy adolescents doing a Stroop task was not observed in adolescents with BD (Blumberg, Martin, et al., 2003), and further suggest that this may reflect a developmental disturbance in this region.

BD is also potentially a neurodegenerative disorder, as several studies have implied that longer illness duration may result in neuronal loss in specific regions. Mills, DelBello, Adler, and Strakowski (2005) found that cerebellar vermis regions were significantly smaller in bipolar patients who had experienced multiple episodes. Multiple-episode patients also demonstrate increased lateral ventricle size, and a higher number of previous manic episodes has been associated with increased ventriculomegaly (Strakowski et al., 2002). If brain structure or function continued to be affected over the course of the illness, then it would be quite difficult to isolate a specific biomarker of the disease itself, as this biomarker could be changing over time. Longitudinal studies of developmental trajectories would help to answer this question. For example, Sanches et al. (2005) reported a significant inverse relationship between age and volumes in the caudate and putamen in patients, but not controls, even after covarying for length of illness. Although abnormal trajectories might be detected in BD, one could not realistically expect a patient to wait 2 to 3 years between imaging studies for a diagnosis to be made.

Another confounding issue involves needing to separate the etiology of BD from the disorder's sequelae. With the lack of longitudinal studies that follow children through the onset of BD, it is often impossible to isolate whether a specific neural difference associated with BD is causal, or merely a symptom. For example, is neuronal loss in prefrontal regions a precipitant to the onset of BD, or is it a result of many neurotoxic mood episodes leading to degeneration of the prefrontal cortex (Gallelli et al., 2005)? In some respects, this issue may not be a significant one in answering the question of whether pediatric BD can ever be distinguished from other disorders by brain imaging. If prefrontal neuronal loss is always associated with BD, and our only goal is to differentiate pediatric BD from other disorders, then it may not be important to understand whether this loss is a cause or a result of the disorder. Yet, it will be important to know when a specific consequence of BD becomes evident, as such a consequence may not be useful as a biomarker if an overly long duration of illness is required before the marker becomes apparent.

BD, in its strictest definition, is characterized by severe mood swings between a manic or irritable episode and a depressive episode, often with intermittent periods of relative euthymia. Each state may, and likely does, influence brain chemistry and function. For example, in a functional magnetic resonance imaging (fMRI) study of facial affect recognition, bipolar manic patients showed significantly more activation in the fusiform gyrus in response to sad faces than did bipolar depressed patients or controls (who showed no group differences from each other). Alternatively, bipolar depressed patients showed greater responses in several regions in response to happy faces compared to bipolar manic or healthy subjects (Chen et al., 2006). Another fMRI study utilizing the Stroop task found that signal changes were associated with mood state in the ventral prefrontal cortex: increased signal on the left in the depressed and decreased signal on the right in the elevated mood group, compared to euthymic subjects (Blumberg, Leung, et al., 2003). Finally, adolescents with bipolar depression exhibit varying levels of amygdalar activation to negatively valenced affective pictures, which cor-

relates with degree of depressed mood (Chang et al., 2004). In the majority of bipolar spectrum illnesses, the mood states are not as clearly defined as those in the studies discussed above, and can include hypomania, cyclothymia, rapid cycling, mixed states, and dysphoria. It would seem difficult, therefore, to identify a specific biomarker associated with BD in all patients regardless of mood state.

Another concern when trying to elucidate biological differences between BD and other disorders or healthy controls, is that pediatric BD has high rates of comorbidity with other disorders such as ADHD (Biederman et al., 1996; Faraone et al., 1997; Wozniak et al., 1995), anxiety disorders (Perlis et al., 2004), panic disorder (Birmaher et al., 2002), and conduct disorder (Biederman, Faraone, Chu, & Wozniak, 1999). Each of these disorders will, of course, have its own effects on the brain and its circuitry, which may confound the examination of the effects of BD. Especially in the case of ADHD, for which up to 88% of patients with BD are presumed to be comorbid, it may be very difficult to isolate the effects of comorbid illness from core disorder. One group, however, did find that bipolar adolescents with ADHD, compared to those without, had decreased prefrontal and increased parietal/temporal activation when performing a continuous performance task (Adler et al., 2005). More studies such as this are needed to understand the effects of comorbidity on neuroimaging findings in BD. Meanwhile, the developmental concept of multifinality creates further heterogeneity in pediatric bipolar samples, given that individuals with this disorder are all affected to different degrees.

Treatment with medication is yet another confound of BD neuroimaging research. Many patients are already being treated with medication when they enter into a research study. For ethical reasons, it is usually not possible to discontinue medication regimens before scanning patients. Most mood stabilizers take at least 2 weeks to no longer be in a patient's system, and this amount of time off medication for research purposes is ethically unacceptable. It may also be difficult to discern what effects past medication exposure may have already had on a patient's brain, even if the patient is no longer on this medication. For example, lithium may increase gray matter (Moore, Bebchuk, Wilds, et al., 2000) and *N*-acetyl aspartate (NAA, a putative marker of neuronal viability; Moore, Bebchuk, Hasanat, et al., 2000) in several cortical regions. Other research suggests that valproate and carbamazepine are involved in cell cycle pathways and may have neurotrophic and neuroprotective effects (Bachmann, Schloesser, Gould, & Manji, 2005). Thus, psychiatric medications do affect the brain, at least in terms of chemistry and function, and potentially structure as well, so it is difficult to draw generalizable conclusions from a group of patients on heterogeneous types and amounts of medication. One relative benefit of studying pediatric BD is that children usually have had less exposure to medication than their adult counterparts. Although this decreases some of the potential confounds of medication, it does not negate them altogether.

Finally, current research in BDs in both children and adults indicate there is a large spectrum of the illness, with certain forms of the illness overlapping with other disorders, such as schizophrenia and unipolar depression. There are suggestions that the line between BD and associated disorders such as major depression (Angst & Cassano, 2005; Cassano et al., 2004) and schizophrenia (Ketter, Wang, Becker, Nowakowska, & Yang, 2004; Maziade et al., 2005) may not be as distinct as once thought. If BD and other similar disorders have similarly neural circuitry, then it might prove difficult to differentiate them using neuroimaging techniques.

Limitations of Neuroimaging Techniques

Along with the intrinsic research challenges that pediatric BD possesses, neuroimaging techniques themselves have serious limitations that impact their ability to be used as diagnostic tools (for a related review, see Peterson, 2003). Here, we will discuss primarily neuroimaging modalities that are based on MRI, as these modalities are currently the best suited for use in children and adolescents with psychiatric disorders.

MRI

MRI originally referred to three-dimensional volumetric imaging of the brain structure. The term has since expanded to cover a basic technology that is used by various imaging techniques, including fMRI, magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI). We first discuss the limitations of both volumetric MRI and MRI technologies in general.

The neuropathophysiology of BD likely involves many different brain structures, including prefrontal and subcortical regions, as well as several tracts between these structures, such as frontotemporal connections. MRI and fMRI may have susceptibility induced artifacts resulting in loss of signal in small regions near air–tissue interfaces (Deichmann, Josephs, Hutton, Corfield, & Turner, 2002; Wu, Lewin, & Duerk, 1997), such as the amygdala, which is located in the anterior temporal lobe. Often, in order to observe functional differences in such regions, region of interest (ROI) techniques must be employed. These techniques, although able to isolate differences in small structures between groups, may miss larger brain circuitry differences. In contrast, when utilizing a whole brain analysis to identify potential large-scale differences, it is quite easy to miss differences in small, but important, regions, such as the amygdala or nucleus accumbens, specifically if susceptibility gradients occur.

When using MRI technologies, it is of the utmost importance for subjects to hold still. Movement during a scan can complicate the signal, add noise, and lead to poor coregistration between structural and functional data. Motor hyperactivity is a problem in pediatric BD, both with and without comorbid ADHD (which obviously exacerbates the problem). With practice and effort using such valuable resources as scanner simulators and home training, it is possible to help these children remain still in the machine. However, the increased likelihood of movement in this patient group is an important consideration when performing analyses and group comparisons with control populations and other populations who might not move as much, such as patients with major depression (who may demonstrate motor hypoactivity).

Because MRI technologies utilize magnetic fields to ascertain images of the brain, ferrous metals can greatly affect the signal received by the machine, often leading to complete signal loss in regions in close proximity to metal. In addition, there is a potential burn risk to subjects with metal implants, as metal may heat up when exposed to the scanner's strong magnetic fields. For these reasons, orthodontia, such as braces or permanent retainers, are an exclusionary criteria for research imaging. This fact may lead to some subject selection bias, specifically excluding children in the early adolescent years when orthodontia is very common.

Finally, regarding within-group data from a single MRI study, it is important to note that interindividual variation is quite great. In any study in which differences between patients with BD and controls are identified, the differences are mean group differences, and within each group there is a range of values for the measurement. These ranges usually overlap between the groups, so it would be problematic to assign an individual measurement as definitively belonging to a particular group. This difficulty in determining a cutoff for a healthy, as opposed to disease, characteristic creates more difficulty in determining a biomarker for BD. Furthermore, results of MRI studies from different sites do not always agree, and so there is intrastudy variation in "normal" and "abnormal" values as well. These discrepancies may be due to the complexities of BD and the numerous differences in the technical aspects of MRI scanning and analysis between sites. For example, MRI studies in adults with BD have found normal (Swayze, Andreasen, Alliger, Yuh, & Ehrhardt, 1992), decreased (Blumberg, Kaufman, et al., 2003; Pearlson et al., 1997), and increased (Altshuler, Bartzokis, Grieder, Curran, & Mintz, 1998; Strakowski et al., 1999) amygdalar size compared to control subjects. Primary reasons for these different findings include heterogeneity of subjects in illness severity, duration, and medication and substance exposure, different MRI acquisition methods, and different amygdala tracing protocols. These are univer-

sal issues regarding MRI technology that affect studies using various MRI techniques, which will be specifically discussed next.

MRS

Proton MRS (^{1}H-MRS) is a noninvasive procedure using magnetic resonance technology to determine levels of neuronal substrates. ^{1}H-MRS is being used with increasing frequency to examine levels of specific neuronal substrates, such as NAA, choline, myoinositol (mI), glutamate and glutamine, GABA, and creatine plus phosphocreatine (Cr) in healthy adults and children as well as those with various neurological conditions (Miller, 1991). Relatively low NAA/Cr ratios have been suggested to indicate decreased neuronal integrity or functioning, and may be a possible risk marker or indicator of bipolar illness progression (Ross & Michaelis, 1994).

Although MRS represents a powerful method of detecting in vivo neurometabolite concentrations, its utility as a diagnostic tool is hampered by the general reasons discussed above, as well as reasons specific to this modality. Will abnormal levels of these metabolites be sufficient for diagnostic purposes? Several ^{1}H-MRS studies of adults and children with BD have found decreased NAA levels in dorsolateral prefrontal cortex (DLPFC; Chang et al., 2003; Winsberg et al., 2000). However, this finding has also been reported in patients with schizophrenia (Bertolino et al., 1998) and ADHD (Hesslinger, Thiel, Tebartz van Elst, Hennig, & Ebert, 2001). Furthermore, decreased NAA may be more a sequelae of BD illness rather than an underlying biomarker. A follow-up study to the Chang et al. (2003) study did not find any evidence of differences in DLPFC NAA/Cr ratios between different comparison groups of children and adolescents: bipolar offspring with BD, bipolar offspring at with subthreshold symptoms of BD, and healthy children with no family history of BD (Gallelli et al., 2005). Although at a quick glance, these studies appear to provide opposing views on the possibility of utilizing NAA as a biological marker for BD, it is likely that decreases in NAA in DLPFC simply do not occur before or shortly after the development of the first manic episode in pediatric-onset BD. The possibility remains that NAA levels in other cortical regions still might be used to detect prodromal BD. A small MRS study of nine children with a mood disorder and familial risk for BD found that compared with healthy controls, children with depression had an 8% decrease of NAA within the cerebellar vermis and a 16% elevation of mI concentration levels in the frontal cortex (Cecil, DelBello, Sellars, & Strakowski, 2003). This study supports the above hypothesis that brain regions other than the DLPFC may show abnormal metabolite levels and potentially serve as an early marker of BD.

Furthermore, NAA may not be the best neurometabolite to measure for early detection of BD. Utilizing NAA as a potential marker in children and adolescents may also be problematic due to some developmental confounds. There have been suggestions that in normal development, there are nonlinear age-related changes of NAA concentrations in frontal cortex gray matter. Recent research has shown that cortical NAA tends to increase through childhood, until about age 10 years, and then continues to decrease thereafter. It has been argued that these changes may be associated with dendritic and synaptic development and pruning (Horska et al., 2002). In general, the role of NAA is unclear, and may not only function as a marker of neuronal density. It is found in both white and gray matter, and abnormalities in NAA have also been found in diseases of the white matter, such as multiple sclerosis (Narayana, Wolinsky, Rao, He, & Mehta, 2004). The findings of Gallelli et al. (2005) suggest that DLPFC NAA/Cr levels should not be used as an early marker of BD. The authors instead suggest that efforts should be directed to investigating the possibility of prefrontal neurodegeneration only after BD development.

According to Silverstone, McGrath, and Kim (2005), mI is a primary component of the phosphatidylinositol second messenger system (PI cycle), which has been implicated in the pathophysiology of BD. Thus alterations in the PI cycle may be detected through abnormal mI levels, and can be measured through ^{1}H-MRS studies. It is interesting that ^{1}H-

MRS studies have found abnormalities mI concentrations in patients with BD, specifically in the frontal and temporal lobes, as well as the cingulate gyrus and basal ganglia (Davanzo et al., 2001; Gallelli, Howe, Wagner, Spielman, & Chang, 2006; Moore et al., 1999; Sharma, Venkatasubramanian, Barany, & Davis, 1992). Further ^{1}H-MRS studies examining alterations in the PI cycle should help us better understand the role of mI as a potential, effective marker/indicator of BD. However, it appears that mI levels in relevant brain areas may be mood dependent. Overall, studies have reported increased mI levels in patients during mania, and decreased levels during depression (Silverstone et al., 2005). Thus, the use of mI levels, as for NAA levels, for diagnosis of a trait (BD) is problematic due to the context of state variables (mood state).

In addition to limitations of measuring specific metabolites, there still exist several limitations in the use of MRS itself that hamper its potential as a reliable tool for diagnostic purposes. There still exists some debate in the field as to whether it is more informative to measure and report metabolite ratios versus absolute concentrations. Given that different researchers report either ratios or absolute values, it is difficult to collapse results from various studies. Similarly, our understanding of the relationship between specific neurometabolites and mood disorders has been complicated by incongruent findings of existing MRS studies. These often contradictory findings may result from specific technological confounds such as the use of different voxel acquisitions (in different brain regions) across studies, as well as the use of different magnet strengths and software used to analyze metabolite levels. MRS is still an evolving technology that may require further refinement before more definitive conclusions regarding specific neurometabolite markers may be made.

DTI

DTI uses the magnetic resonance signal to characterize the movement of water molecules, which helps characterize the vessel in which the water is contained. In neuroscience, DTI is most often used to investigate brain white matter structure. Water diffusion in white matter is highly anisotropic (i.e., not equal in all directions), as diffusion tends to be much higher parallel to the fiber axis than perpendicular to it. Anisotropy within a given white matter voxel is determined mostly by microstructural features of the tissue, including fiber diameter and density, degree of myelination (Basser & Jones, 2002), and macrostructural features such as intravoxel fiber-tract coherence (Basser & Pierpaoli, 1996). Changes in these features as a result of disease states can be detected as changes in water diffusion.

Two commonly used scalar measures of anisotropy in DTI research include fractional anisotropy (FA) and relative anisotropy (RA). FA is the ratio of the anisotropic component to the entire tensor, and RA is the ratio of the anisotropic component of the tensor to the isotropic component. Most DTI studies use FA values for their analyses because FA has been shown to have better contrast to noise ratio and signal to noise ratio compared to RA (Hasan, Alexander, & Narayana, 2004; Sorensen et al., 1999). Two additional measures often are used to assess overall intravoxel diffusion: trace apparent diffusion coefficient (TADC), a measure of mean intravoxel diffusivity derived from the diffusion tensor, and ADC, a measure of intravoxel diffusivity derived from diffusion weighted images.

An increased number of white matter hyperintensities is the most consistent structural finding in studies of adults with BD (Moore et al., 2001; Silverstone, McPherson, Li, & Doyle, 2003; Soares & Mann, 1997). Some (Botteron, Figiel, Wetzel, Hudziak, & VanEerdewegh, 1992; Lyoo, Lee, Jung, Noam, & Renshaw, 2002), but not all (Chang et al., 2005), studies in pediatric BD have found white matter hyperintensities to be more common in patients compared to controls. White matter hyperintensities are nonspecific findings associated with increased age, vascular risk factors, diabetes, and demyelinating disorders (Awad, Spetzler, Hodak, Awad, & Carey, 1986; Fazekas et al., 1988), and they provide potential evidence for white matter disruption in BD. It has been hypothesized that white matter connectivity is disrupted at the site of white

matter hyperintensities. DTI may then be used to investigate these white matter abnormalities in a quantitative fashion.

Four studies to date have used DTI to investigate white matter structure in BD. Three studies were done in adults and one in adolescents. All studies used ROI-based analyses. Two of the adult studies implicated abnormalities in prefrontal cortical white matter by reporting decreased FA values in subjects with BD in these regions (Adler et al., 2004; Beyer et al., 2005). The third adult study reported lower RA values in the posterior limb of the internal capsule in patients with bipolar spectrum disorders (Haznedar et al., 2005). Furthermore, a finding of lower RA values in patients with BD I compared with controls in the frontooccipital posterior fasciculus, but higher RA values in the anterior frontal white matter, suggests that bipolar patients may have a decrease in the proportion of "U" fibers with lower anisotropy and a greater proportion of fibers with vertical orientation or axial longitudinal fibers having higher anisotropy.

Finally, the fourth study, and the only DTI study to date in adolescents with BD, investigated 11 first-episode manic or mixed adolescents (6 females) and 17 typically developing control subjects (10 females; Adler et al., 2006). FA values and TADC were measured in white matter tracts adjacent to the prefrontal and posterior cortex. FA values were reduced in the bipolar group only in the superior prefrontal region, and TADC values did not differ between the two groups.

Taken together, the above studies suggest there may be white matter structural alteration in the internal capsule and in prefrontal regions in BD. Prefrontal white matter changes may be present early on in the development of BD. It is difficult to assess which white matter tracts are involved in the studies cited above as fiber-tracking techniques were not used in any study to date. Additional studies using additional ROIs or voxel by voxel analyses as well as fiber-tracking techniques would be helpful in further assessing white matter involvement in BD.

Although such DTI studies are important for pinpointing possible pathological processes involving white matter in BD, changes in FA can result from changes in fiber diameter, density, myelination, coherence, and changes in extracellular diffusion. At this point it is impossible to determine which of these changes occur when FA changes are observed in disease compared to nondisease states. Direct visualization of brain white matter can determine the histological underpinnings of the changes observed in DTI studies. For example, increased FA could result from increased myelination, fiber-density, or fiber-tract coherence, but also from decreases in these values in regions of crossing fibers. Regions of crossing fibers have lower FA values because of the overlap in fiber tracts with different orientations. This overlap would be reduced should there be, for example, reduced fiber-tract coherence within one of these overlapping tracts causing anisotropy and FA values to increase. In addition, beyond fiber-tract structure, coherence, and myelination, other factors may influence diffusion anisotropy (e.g., diffusion in extra-axonal space) and may affect measures obtained in DTI studies. Because the pathology in white matter in BD is unclear at this point, it is unlikely that DTI by itself will provide specific diagnostic clues in patients thought to have BD. However, DTI may eventually prove to be a useful neuroimaging modality along with fMRI to pinpoint disruptions in circuitry that may be specific to BD.

fMRI

fMRI utilizes MRI technology, but also provides data regarding brain activation as determined by the levels of oxygenated versus deoxygenated blood in a brain region. Thus, a commonly used measurement in fMRI is the blood oxygen level dependent (BOLD) signal. Few fMRI studies of children and adolescents with BD have been published to date. Blumberg, Martin, et al. (2003) observed significantly increased activation of the left putamen and thalamus in pediatric BD while subjects performed the color-naming Stroop task. This study also showed a positive correlation between depressive symptoms and activation in a ventral striatal ROI. The second study examined brain activation during a

visuospatial working memory task as well as an emotion processing task to assess the interaction of brain systems important for attention and mood (Chang et al., 2004). For both the working memory task and viewing negative pictures, the BD group showed greater activation in the dorsolateral prefrontal cortex and inferior frontal gyrus. The BD group also showed greater activation, compared to controls, in the anterior cingulate cortex, thalamus, and basal ganglia across both tasks. In addition, another unpublished study from our lab (Garrett, unpublished data) showed prefrontal (although medial) and ventral striatal hyperactivation in pediatric BD compared to control subjects during presentation of affective facial expressions. Thus, based on these initial studies, a circuit involving the prefrontal cortex and subcortical (possibly striatal) brain regions appears to function abnormally in pediatric BD.

These fMRI findings in pediatric BD are important in delineating the brain areas involved in the pathophysiology of BD, but do not yet provide a consistent biomarker specific to BD. Such an fMRI biomarker might come in the form of a difference in activation in one area, a set of areas, or relative activation change between different areas (Cox & Savoy, 2003; Haxby et al., 2001). As research hones in on particular affected brain regions, ROI analyses may be implemented. The activation of each ROI can be examined separately, as well as comparatively with correlations. Another analysis option is Multivariate Pattern Recognition, a whole-brain analysis technique that applies different weights to particular areas of greater interest. For example, greater weight in the model could be given to regions of higher interest, such as the DLPFC or amygdala, The statistical model would then be more sensitive to those neural areas of interest.

Unfortunately, present technology and methods may not detect an fMRI biomarker of BD. There are numerous limitations to fMRI technology that impair its likelihood to be used as a diagnostic tool. The large amount of variation between individuals creates problems. fMRI makes strong assumptions about the relation between brain activity and blood flow. It is possible for two individuals to have the same amount of activation in a particular area of the brain but have very different increases in blood flow (BOLD response) to that particular area in response to a stimulus. The inverse could also be true; BOLD responses might be similar, even though actual brain activations are not. Furthermore, differences in amplitude of the BOLD response may be identified using blocked design tasks, but the speed to peak response and the speed to return to baseline would not be taken into account. Event-related tasks would be able to identify this difference in speed of blood response.

Individuals also differ in their typical amplitude of BOLD response. Recently, Thomason, Burrows, Gabrieli, and Glover (2005) employed a breath-holding task to examine this phenomenon. This task determines an individual's particular vascular response so that this difference in response may be controlled for in further analyses of particular tasks or brain regions. Breath-holding measurements appear to reduce individual vasoreactivity differences by a factor of about 2.

fMRI also has relatively poor temporal resolution in relation to neuronal activity. The brain is sampled every 2 s and the hemodynamic response peaks at about 8 s, but even complex mental processes are performed in less time. Furthermore, activation maps can be misleading due to the structure of the brain's vascular system. Activation may be more prominent adjacent to large draining veins rather than directly at a capillary bed near the site of neuronal activation.

Another major limitation of fMRI is that activation patterns are determined only in the context of a contrast comparison, and potential group differences in resting activation level are not often accounted for or assessed. Therefore, differences may not be observed between two groups that exhibit similar increases in activation in response to a task, but have different resting baseline levels of activation.

Regardless of contrast condition, the question of what task will best elicit a BD biomarker remains. If the search for this holy grail is to be undertaken, then potential tasks should be run several times on each subject to account for intrasubject variation. Then, there

is the question of whether behavioral performance should be accounted for in the fMRI analysis. That is, how do we know that all subjects are giving equal exertion and concentration in performing the task? Moreover, would we not expect variations in exertion when studying patient populations who may have certain cognitive limitations?

Finally, there are numerous variables to consider when analyzing fMRI data that call into question the accuracy of the data and the ability to compare results across different sites. When doing any fMRI analysis there are several computations involved and decisions at each step that introduce experimenter variability. Techniques for movement correction, data smoothing, and other data processing steps may differ among labs and researchers. More choices can be made as to the threshold to use in the analysis, whether to statistically account for multiple comparisons, whether to employ a ROI analysis, which type of ROI to utilize, and how to measure activation within that ROI.

Finally, as with the other methodologies, results from fMRI studies are typically based on group averages, with groups of 10–25 subjects. Thus individual results might vary substantially and not resemble the group average. Taking an individual brain activation pattern and comparing it to a "diagnostic template" is therefore fraught with problems (Robinson, 2004).

However, fMRI technology continues to improve. Magnets continue to increase in power (1.5 to 3 to 7 T). The signal advantage of 3 over 1.5 T is estimated to be 35–85% better, depending on which part of the brain is being imaged (Krasnow et al., 2003). Reliability studies across sites are being conducted to perform multiple-site studies. Studies have also been conducted correlating the BOLD response with actual neuronal activation (Logothetis & Pfeuffer, 2004; Mukamel et al., 2005), assuring us that fMRI does give at least gross estimates of neuronal activation.

Conclusions

The field of pediatric BD research has come a long way, from the pre-1980 belief that early-onset BD was exceedingly rare, to current neuroimaging findings that are fairly consistent and reliable across studies. Clearly, MRI technology has allowed great scientific access to the child and adolescent brain, in a safe and detailed manner. However, the limitations discussed above with these technologies limit the use of MRI and other imaging modalities to being purely research pursuits for now. It is more likely that we will eventually be able to reliably diagnose pediatric BD by employing a combination of biomarkers from various sources, such as MRI, neuroendocrine markers, and genetic material, in addition to the clinical symptomatology and family history data we use today. Thus, an approach incorporating multiple levels of analysis, important in the field of developmental psychopathology (Cicchetti & Dawson, 2002), appears necessary for true understanding and meaningful categorization of BD. Until that time, it seems prudent to continue the push to find specific and reliable brain markers of this perplexing and diagnostically challenging disorder.

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