K. Chang[1]
D. J. Miklowitz[2]

Brain abnormalities prior to the development of bipolar disorder: clues to aid in eventual preventative interventions

[1] Pediatric Bipolar Disorders Program
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
California (USA)

[2] University of Colorado at Boulder
Colorado (USA)

INTRODUCTION

Bipolar disorder (BD) affects up to 4% of the US population[1] and leads to costs of over $45 billion per year. Between 15% and 28% of bipolar adults experience illness onset before the age of 13, and between 50% and 66% before the age of 19[2-4]. Understanding the etiology and pathophysiology of this disorder would aid greatly in more accurate and early diagnoses and in developing targeted interventions for symptom treatment and prevention. While currently there is no single biological finding that can serve as a marker for BD, neuroimaging studies have shown great promise in bringing us closer to understanding the neuropathophysiology of BD.

However, brain imaging studies in BD have concentrated on adults or children already with the fully expressed disorder, leading to questions regarding the role of the findings in BD. That is, it may be difficult 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[5]? Furthermore, adults with BD have usually been exposed to years of psychotropic medications and may have significant exposure to illicit substances that might directly affect brain morphometry and function. Therefore, neuroimaging studies conducted before the onset of BD would be essential to answer this issue. To do this, high-risk subjects would need to be studied before the onset of BD.

Correspondence:
Kiki Chang
Pediatric Bipolar Disorders Program
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
California (USA)
E-mail: kchang88@stanford.edu

IDENTIFICATION OF PRODROMAL BD

Due to the high heritability of BD, offspring of parents with BD are a good starting point for identifying children and adolescents at high-risk for BD development. Rates of BD spectrum disorders in these offspring range from 14%-50%, and rates of major depressive disorder (MDD) range from 7%-43%[6]. Offspring already with evidence of mood dysregulation may present the most logical cohort to study with neuroimaging. For example, the most reliable symptom complex predating mania has been depression. In a cohort of 642 adults with BD onset before age 18 years, approximately 60% reported depression as their initial mood episode[4]. ADHD in bipolar offspring also may be a harbinger of later BD development[4,6-10]. In recent cross-sectional studies, approximately 27% of bipolar offspring have met criteria for ADHD or significant behavioral or attention problems[6]. This finding, combined with the high comorbidity of ADHD and BD in childhood, 11 family studies[11,12], and retrospective histories of ADHD predating BD onset[13], 7 supports that ADHD in certain children with strong family histories of BD is a first sign of developing BD. Studying these high-risk children with neuroimaging would help elucidate brain abnormalities that lead to the development of full mania.

NEUROBIOLOGICAL MARKERS BEFORE FIRST MANIC EPISODE

Neuroimaging studies in adults and children with BD have implicated numerous regions of the brain in the pathophysiology of BD, namely regions serving prefrontal-limbic circuitry[14]. Prefrontal areas include dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (including anterior cingulate cortex), and ventrolateral (or orbitofrontal) cortex[15]. Subcortical areas include hippocampus, caudate, putamen, thalamus, and amygdala. The amygdala is particularly interesting due to its role in mood and emotion, and consistent findings of decreased amygdalar volume in children with BD[16-19]. We recently found children at-risk for BD, by nature of having a parent with BD and themselves early mood dysregulation, to have similarly decreased amygdalar volume. Therefore, this finding might be present

early on in the development of BD and reflect functional abnormalities within the limbic circuitry that predispose to emotion hyper-reactivity and eventually mood dysregulation.

Several H-MRS studies of adults and children with BD have found decreased NAA levels in dorsolateral prefrontal cortex (DLPFC)[20,21]. NAA reflects the level of neuronal integrity and density within a region, but decreased NAA may be more a sequelae of BD illness rather than an underlying cause. A follow-up study to the Chang et al. 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[5]. Thus, it is possible that decreases in NAA in DLPFC 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 till might be used to detect prodromal BD. A small MRS study of 9 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 ml concentration levels in the frontal cortex[22]. Thus, brain regions other than the DLPFC may show abnormal metabolite levels and potentially serve as an early marker of BD.

GENETIC INFLUENCE ON BRAIN STRUCTURE AND FUNCTION

The effects on brain structures and circuits thought to be involved in BD have been studied for some some gene polymorphisms that have been linked to BD development. For example, two potential BD gene candidates code for the serotonin transporter (5-HTT) and for brain-derived neurotrophic growth factor (BDNF). Polymorphisms of these genes have been associated with depression and BD (including early-onset and rapid-cycling varieties)[23-26,28]. Subjects with compared to those without the short allele of the 5-HTT gene have been found to have increased amygdalar and orbitofrontal activation when watching fearful faces or aversive pictures[29,30]. This finding is interesting in light of the amygdalar abnormalities found in BD, including amygdalar overactivity[31-33], and the association of the short allele with BD[26].

The val66met polymorphism of the BDNF gene may also affect brain structure and function. Healthy volunteers with the BDNF vall66met allele were found to have poorer episodic memory and decreased hippocampal activation on fMRI[34,35] and reduced hippocampal and prefrontal gray matter, especially bilateral DLPFC[36], compared to val/val carriers. This effect on prefrontal gray matter may be relevant to the course and severity of BD. For example, adults with BD who were carriers of the val66met allele had decreased performance on the Wisconsin card-sorting task compared to val/val carriers, implying reduced prefrontal cognitive function in BD patients with the val66met allele. Hippocampal effects of the BDNF polymorphism may also be relevant in BD. While our group did not find hippocampal volumetric differences in children with BD[16], one group did find decreased hippocampal volume in pediatric BD (Frazier JA, personal communication). Thus, it is likely that certain genes have effects on brain structure and function early on, predisposing the brain towards BD.

EARLY INTERVENTION

Intervention early in the development of BD might reverse or prevent further shaping of these brain circuits towards a bipolar course. Mood stabilizers, and to some degree antipsychotics, which are used to treat BD have been found to have neuroprotective and neurogenic properties and therefore may prove to be effective medications in early intervention/prevention schemas. In one[37] but not another[38] study, valproate was found effective in treating acute mood symptoms in children with subsyndromal BD, considered a group at high risk for BD development. Quetiapine was also effective in treating mood symptoms in a similar population, with some evidence of prefrontal NAA increase as well[39]. However, no longitudinal studies have been conducted to investigate prevention of the occurrence of full mania with these types of agents. Clearly, while difficult to conduct, this type of study is paramount for discovering valid options for BD prevention.

Psychotherapeutic interventions have now been proven to be essential as an adjunct treatment for individuals with BD and thus may also be useful for preventing or delaying BD onset. For example, family focused therapy (FFT) has been found effective for adolescents with BD[40], and a modified version may be useful for at-risk children (FFT-HR). This treatment, which is carried out with the high-risk child, his or her parents, and siblings is currently being evaluated in a treatment development study by the University of Colorado, Boulder and the Stanford University School of Medicine (D. Miklowitz [PI] and K. Chang [Co-PI]; NIMH grant R34-MH077856). The objectives of FFT-HR are to assist families to: *a)* recognize the symptoms of recurrent mood disorder, notably the prodromal symptoms of developing episodes; *b)* understand the child's potential vulnerability to future significant mood episodes or variability; *c)* accept the potential role of medications in managing mood states (where applicable); *d)* distinguish mood-dysregulated behavior from normative child or teen behavior; *f)* identify stress triggers for mood swings and develop plans to arrest mood escalations or deteriorations, and *g)* operate at a more effective level in family communication and problem-solving.

CONCLUSIONS

By understanding brain morphometry and function prior to the inset of the first manic episode, researchers may

eventually be able to better distinguish the effects of BD on the brain and vice versa. In this way, accurate information regarding the development of BD can be obtained, which would hopefully lead in turn to early diagnosis and preventative interventions. Including genetic effects on the brain will also increase this understanding. Promising areas for further exploration of brain markers for this purpose include prefrontal-limbic areas, especially the amygdala. Intervention studies should not wait until these markers are definitively established, as the burden of BD is too great[41]. The potential for neuroprotective medications and psychotherapies to prevent or delay the onset of BD is great and should be immediately explored in order to combat this devastating global illness.

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