NEURODEGENERATION IN PEDIATRIC MOOD DISORDERS: SUPPORTING EVIDENCE AND THE CASE FOR NEUROPROTECTION

Kiki D. Chang

Summary

The role of neurodegeneration in mood disorders has come into increased scrutiny due to in vivo and postmortem brain studies finding direct or indirect evidence of decreased gray matter. In adults, these areas include prefrontal-limbic areas, such as dorsolateral prefrontal cortex, anterior cingulate, hippocampus, and amygdala. It is unclear whether these findings are due to the disorder itself or accompanying factors, such as the effects of medications, substance use, or medical comorbidities. Studies in children and adolescents with affective illness may decrease these confounds somewhat and generate data particular to illness effects. However, few longitudinal studies have been conducted in this population to definitively prove the presence of neurodegeneration. If neurodegeneration is occurring, then the possibility of early intervention to prevent this process should be explored. In this review, we highlight evidence for and against neurodegeneration in pediatric mood disorders and discuss the early, but important, potential for neuroprotective intervention.

Key Words: Neurodegeneration – Mood disorders – Dorsolateral Prefrontal Cortex – Anterior Cingulate – Hippocampus – Amygdala – Neuroprotective Intervention

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Kiki D. Chang, M.D. Director, Pediatric Bipolar Disorders Program. Stanford University School of Medicine 401, Quarry Road Stanford, CA 94306. Phone: 650-723-5511 – E-mail: kchang88@stanford.edu

I. Introduction

Pediatric onset neuropsychiatric disorders are particularly worrisome due to their appearance during highly active periods of brain development. Some degree of neurodegeneration is naturally expected during adulthood extending into older adulthood. Gray matter naturally decreases, external sulci and gyri become more pronounced and ventricles enlarge. While apoptosis is a natural event during brain development, gray matter loss during apoptosis is thought of as necessary, refining the circuits that will be used efficiently as adults. However, the possibility exists that useful neurons will be lost in children with neuropsychiatric disease. Neurodegeneration during childhood is difficult to detect – postmortem studies are thankfully near impossible, and in vivo studies are rarely longitudinal and again cannot distinguish normal pruning from unhealthy neuronal loss. However, by comparing healthy populations to those with neuropsychiatric disease, abnormalities in gray matter development may be detected. Findings of relatively decreased gray matter in patient populations may therefore point to either loss of healthy neurons or glia or a developmental abnormality in that those neurons were never present. Longitudinal studies before illness onset are necessary to distinguish between the two etiologies; nonetheless, we do have some evidence that neuronal densities are abnormal in certain cortical and subcortical areas in pediatric mood disorder patients. This evidence raises the possibility of interventions early in the course of affective illness that may reverse or slow the neudegenerative process. In this review, we will consider evidence for neurodegeneration in pediatric affective disorders and consider the current and future potential for such interventions.

II. Evidence for Neurodegeneration in Pediatric Mood Disorders

Neurodegeneration may be detected in vivo most reliably by MRI studies. First, morphometric studies may determine volumetric status of various brain areas, and automated programs that can fractionate gray, white, and CSF can be used to give these fractionated

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volumes (Reiss et al. 1998). Second, magnetic resonance spectroscopy (^{1}H-'MRS) can detect brain concentrations of N-acetylaspartate (NAA), a metabolite found largely in neurons. While the function of NAA is not exactly known, it may serve as an indirect marker of neuronal integrity and viability/density (Urenjak et al. 1993). Thus studies examining absolute NAA concentrations or NAA/Creatine (Cr) ratios may reveal possible areas of neuronal loss. Third, postmortem histological studies may be the most reliable method of detecting neuronal loss. However, fortunately this type of study is rare in children.

A. Depression

MRI studies of children with major depression have focused mostly on prefrontal cortex and subcortical structures, such as amygdala and hippocampus. Nolan et al. (Nolan et al. 2002) found pediatric patients with nonfamilial Major Depressive Disorder (MDD) to have larger left prefrontal volume than healthy controls, which does not speak to neurodegeneration. However, Botteron et al. (Botteron et al. 2002) reported on young women with adolescent onset MDD having smaller subgenual cingulate volumes than healthy controls. This prefrontal area has been proposed to be involved in the pathophysiology of both depression and Bipolar Disorder (BD). The findings regarding amygdala are mixed: one study reported on a trend to larger amygdalar volumes and smaller hippocampi in children with MDD (Rosso et al. 2005), while another reported reduced amygdalar and normal hippocampal volumes in MDD patients (MacMillan et al. 2003). MacMaster and Kusumakar (MacMaster and Kusumakar 2004) also reported smaller bilateral hippocampi in depressed children, but did not report on amygdalar volumes. These discrepancies in data may be due to differential tracing protocols of the structures, as the hippocampus is contiguous with the amygdala, or to other methodological differences between the studies, including gender differences (Rosso et al. 2005 studied mostly girls, while MacMillan et al. 2003 studied mostly boys). Furthermore, depression may be a more heterogeneous disorder, say, than BD, as some patients with MDD will go on to develop BD while others will not. Nonetheless, it is difficult to draw definitive conclusions or even generate hypotheses regarding neurodegeneration in pediatric MDD from these data.

MRS studies in pediatric depression also have not supported the possibility of neurodegeneration. Three studies have reported no differences in prefrontal (anterior cingulate cortex [ACC] and dorsolateral prefrontal cortex [DLPFC]) NAA between children with MDD and healthy controls (Caetano et al. 2005, Farchione et al. 2002, Rosenberg et al. 2004). Glx, which represents glutamate, glutamine, and GABA, can also be measured by ^{1}H-MRS and high levels may indicate potential neurogeneration, as high levels of glutamate may be neurotoxic. However, studies of depressed children indicate that prefrontal Glx levels may be *decreased* (Caetano et al. 2005, Mirza et al. 2004, Rosenberg et al. 2005) so the implications for this finding on possible neurodegeneration are unknown. Therefore, overall MRI and MRS data do not generally support the possibility of neurodegenerative processes occurring in children with depressive disorders. It appears that with longer duration of illness, children with MDD might experience hippocampal neurodegeneration, but the data are scarce. If this is proven, it might indicate that prolonged exposure to depressive episodes or stress might be directly neurotoxic to hippocampal neurons (Sapolsky 1985). Whether neurodegeneration may be occurring in prefrontal cortex (PFC) and amygdala in MDD is currently unclear.

B. Bipolar Disorder

Evidence for neurodegeneration has been more convincingly found in studies of adults with BD, primarily in prefrontal cortex. First, one study reported overall cerebral atrophy (Lewine et al. 1995) and another decreased gray matter volume (Lim et al. 1999) in patients with BD. However, other studies have found no differences in these morphometric measures between patients with BD and healthy controls (Dewan et al. 1988, Pearlson et al. 1997, Zipursky et al. 1997). One study also reported increased gray matter volume in adult patients with first-episode mania (Strakowski et al. 1993). While these differences in findings may be due to different patient populations (severity of BD, gender), MRI acquisition and data analysis protocols, and variability in medication exposure, overall neuronal loss in adults with BD is not universally found.

Prefrontal Cortex

Analyses of prefrontal cortex specifically have yielded more consistent results. Evidence of prefrontal neurodegeneration in adults with BD include decreased neuronal and glial density in the DLPFC (Rajkowska et al. 2001), decreased subgenual prefrontal gray matter (Drevets et al. 1997) and glial cells (Ongur et al. 1998), and decreased prefrontal gray matter volumes bilaterally (Lopez-Larson et al. 2002). With this convergence of histopathological and morphometric findings, it is likely that prefrontal gray matter is indeed decreased in adults with BD. However, as these data are from cross sectional studies, it is not certain that neurodegeneration is the etiology.

There have been fewer studies examining possible neurodegeneration in children with BD. Three studies (Blumberg et al. 2003a, DelBello et al. 2004, Frazier et al. 2005a) out of five (Botteron et al. 1992, Chang et al. 2005a)) examining total cerebral volume found decreased volume compared to controls. (One MRI study reported only a trend [$p = 0.09$] towards decreased gray matter in children with BD compared to healthy controls. In this study, there was no difference in gray matter volume in prefrontal cortex specifically). Voxel based morphometry (VBM) studies have reported decreased gray matter volume in ACC, orbitofrontal cortex, and left DLPFC (Wilke et al. 2004, Dickstein et al. 2005). One study did not find subgenual ACC decreases in children (Sanches et al. 2005) as had been reported for adults with BD (Drevets et al. 1997), although this group did find overall decreased left anterior cingulate vol-

umes in these subjects (Hajek et al. 2005). These morphometric studies suggest that if prefrontal neurodegeneration is occurring in children with BD, it is somewhat modest, but most likely in DLPFC and ACC.

Regarding spectroscopic findings, there have been five published ^{1}H-MRS studies in children with BD. The first study found no differences from controls in levels of NAA in frontal and temporal cortex (Castillo et al. 2000). Another ^{1}H-MRS study examining acutely manic children did not find differences in NAA in ACC (Davanzo et al. 2001). However, Chang et al. (Chang et al. 2003a) reported decreased NAA/Cr in right DLPFC in a cohort of 15 euthymic children and adolescents with familial bipolar disorder. Additionally, duration of illness tended ($p = 0.065$) to be negatively correlated with NAA/Cr levels. This finding suggests a neurodegenerative effect of time (possibly due to mood episodes or medication exposure) in prefrontal cortex.

In a follow up to this study, Gallelli et al. (Gallelli et al. 2005) studied 32 children with familial BD, 28 with subsyndromal symptoms of BD, and 26 controls. The researchers this time found no differences in left or right DLPFC NAA/Cr between all three groups. No correlation between mood stabilizer exposure and NAA/Cr could be found, decreasing the likelihood that lack of positive findings was due to medication confounds. In this study, subjects had a relatively short duration of illness (2.0 +/- 1.9 years). Findings of decreased NAA/Cr levels in studies of adults with BD [9% decrease in the left DLPFC and a 6.5% decrease in the right DLPFC, as compared to controls (Winsberg et al. 2000)] are more robust. Compared to the short illness duration in our young subjects with BD, adults in those studies likely had experienced their illness for much longer. However, these studies did not report illness duration of subjects. Nonetheless, it is possible that after greater illness duration we would begin to detect greater decreases in prefrontal NAA/Cr in children with BD, suggesting a neurodegenerative process.

Neurodegeneration as measured by NAA levels might still be occurring in other cortical regions. For example, Cecil et al. (2003) conducted a MRS study on 9 children with a mood disorder (MD) and at familial risk for BD. As compared to healthy controls, the MD group had an 8% decrease in NAA levels within the cerebellar vermis, and a 16% elevation of myoinositol levels in the frontal cortex. In summary, if neurodegeneration as indicated by decreased NAA levels is occurring in children with BD, it may be limited to specific regions, eg: (DLPFC, cerebellum), and may not occur until prolonged duration of illness (greater than 2 years). Spectroscopic studies of other cortical and subcortical regions of children before and after the onset of BD would help clarify this discussion.

It should also be noted that the role of NAA is not completely clear. Therefore, it may not be an entirely accurate marker of neuronal density. NAA is found in both white and gray matter and abnormalities in NAA have also been found in diseases of white matter, such as multiple sclerosis (Siger-Zajdel and Selmaj 2005). Nonetheless, current thinking still maintains that relatively low levels of NAA probably indicate neuronal loss.

Finally, later life prefrontal neurodegeneration in BD is supported by findings from fMRI studies of children and adults with BD. In a study of adults with BD, subjects had decreased DLPFC activation when viewing fearful faces as compared to healthy controls (Yurgelun-Todd et al. 2000). However, in another fMRI study, euthymic children and adolescents with BD performing both cognitive and affective tasks demonstrated *increased* activation in the DLPFC (Chang et al. 2004). This finding might be explained by relatively intact neuronal density in DLPFC of children with BD, allowing for overactivation of this area. Consistent with a prefrontal-subcortical model of mood regulation (Blumberg et al. 2002, Chang et al. 2004), increased prefrontal activation in euthymic children with BD might be in compensatory response to increased activation in subcortical limbic areas, in an effort to regulate mood. With longer duration of illness, it is possible that patients with BD would experience neurodegeneration in DLPFC (as reflected by decreased NAA and neuronal/glial density in adults with BD), eventually leading to under- (not over) activity of the DLPFC in response to emotion-related tasks. Other functional imaging studies in adults with BD support prefrontal underactivity: decreased activation in adults with BD was found in medial prefrontal cortex during a continuous performance task (Strakowski et al. 2004) and in ventral PFC independent of mood state during a color-word Stroop task (Blumberg et al. 2003b).

Overall, these findings suggest that there may be prefrontal neurodegenerative processes that occur sometime close to or after the development of full BD and then progress with increasing duration of the illness. Decreased prefrontal gray matter may be a phenomenon that begins to occur early in the course of BD and then continues throughout adulthood. This model is consistent with the course of BD into adulthood, with lack of treatment leading to closer episodes, more rapid cycling, and potential treatment resistance (Post 1992) as lack of prefrontal structures necessary to modulate mood would exacerbate affective symptoms. However, it is also possible that familial pediatric BD is neurobiologically distinct from adult-onset BD, and thus children with BD may not have significant neuronal loss in PFC. Longitudinal studies beginning at an early age in affected (BD) and unaffected children at high-risk for BD development would be necessary to determine if and when these children begin to differ in neurodevelopment, and if they continue to exhibit increasingly decreased gray matter into adulthood. These data also would support the concept that cross-sectional findings of decreased prefrontal gray matter reflect neuronal loss, rather than abnormal neuronal development.

Amygdala

Currently, six out of seven studies report decreased amygdalar volumes in pediatric BD (Blumberg et al. 2003a, Chang et al. 2005b, Chen et al. 2004, DelBello et al. 2004, Dickstein et al. 2005, Frazier et al. 2005b, Wilke et al. 2004). One of these studies reported on decreased gray matter volume in medial temporal lobe

structures as detected by VBM analysis (Wilke et al. 2004) and another study reported decreased fractionated gray matter amygdalar volumes as determined by manual tracings and automated tissue type fractionation (Chang et al. 2005b). Again, whether this was an inborn deficiency or developed over time remains unknown. However, adults with BD have been mostly found to have normal (Pearlson et al. 1997) or increased (Altshuler et al. 1998, Strakowski et al. 1999) amygdalar volumes. Explanations for this difference include duration of illness effects, medication effects, or again possible separate pathophysiology for children versus adults with BD. Regarding medications, Chang et al. (Chang et al. 2005b) reported that those children exposed to lithium or valproate tended to have normal amygdalar gray matter volumes compared to those who did not have such exposure. Therefore, prolonged exposure to mood stabilizers may also account for the findings of adults with larger than expected amygdalar volumes. We will discuss this possibility further under the neuroprotection section below.

Hippocampus

Two studies support smaller hippocampal volume in children with BD, although the contributions of gray versus white matter to this loss are unknown (Blumberg et al. 2003a, Frazier et al. 2005a). Other cortical and subcortical areas at this point do not appear to have decreased volumes in children with BD compared to healthy controls.

III. Discussion

Overall, the evidence for neurodegeneration that predates the onset of mood disorders in children is scarce. However, it does appear that after illness begins, the longer the duration the more likelihood of neuronal loss in certain areas: hippocampus in depression, and PFC in BD. The amygdalar story is less clear – children with mood disorders may have decreased amygdalar volumes, but whether this is due to inborn abnormalities or neurodegeneration is unknown. One longitudinal study (Blumberg et al. 2005) supports the idea that these are relatively inborn deficiencies since volumes do not change appreciably over time.

If neurodegeneration is truly occurring in areas such as hippocampus and PFC, then appropriate treatments would include an element of neuroprotection. The rest of this article will concentrate on the concept of neuroprotection and its potential utility in children and adolescents with or at high-risk for mood disorders.

IV. Neuroprotection

If neurodegeneration does indeed occur in pediatric mood disorders, then the issue of neuroprotection becomes paramount when considering treatment. Foremost to consider is the neuroprotective potential of psychotropic agents, given that they are effective in treating and preventing relapse of various neuropsychiatric disorders. However, while psychotropic medications have been studied for their acute therapeutic properties and adverse effects profile, less is known about their neuroprotective characteristics. Neuroprotection can be considered at four different levels: protection of brain tissue against injury or death (true neuroprotection), prevention of onset of a seizure disorder (anti-kindling properties), indirect promotion of neuronal survival or growth by activation of neurotrophic factors or inhibition of neurotoxic pathways at the cellular level, or detectable creation of new neurons (neurogenesis) (Chang et al., in press).

First, anticonvulsants have long been thought to have true neuroprotective qualities, as determined by animal studies in which animals given these medications have reduced areas of brain infarction following an induced stroke or other neurotoxic procedure. This type of neuroprotection has been found for topiramate (Kudin et al. 2004, Yang et al. 1998), lamotrigine (Calabresi et al. 2003, Shuaib et al. 1995), and tiagabine (Inglefield et al. 1995, Yang et al. 2000). Weaker evidence has been found for felbamate, leviteracetam, tiagabine, and zonisamide (Leker and Neufeld 2003). Barbituates, benzodiazepines, valproate, phenytoin, and carbamazepine may not be good candidates for ischemia prevention due to lack of efficacy or negating effects of cerebral blood flow reduction (Leker and Neufeld 2003). Of the atypical antipsychotics, which have been less studied for neuroprotection, olanzapine was found to protect neuronal cells from oxidation with hydrogen peroxide (Wei et al. 2003). While these findings are intriguing, this type of neuroprotection may be less relevant to diseases with non-ischemic models of neuronal insult, such as BD.

Anti-kindling properties of medications may be more relevant to the treatment of BD. Medications are typically tested for their anti-kindling potential by examining their efficacy in preventing amygdala-kindled seizures in rats. Anticonvulsants have not all been found to have the same anti-kindling potential, as they may differ by what stage they are most effective at. For example, if valproate and diazepam are administered early in the course of kindling before seizures appear, then the animal will not develop a seizure disorder (Loscher et al. 1989). However, phenytoin and carbamazepine do not have this effect and can only prevent recurrent seizures once the seizure disorder has begun (Findling et al. 2003). Similar anti-kindling properties also have been described for lamotrigine and leviteracetam (Stratton et al. 2003). Given the previous discussion of the amygdala's involvement in BD and the observed natural progression of the illness, the kindling model appears appropriate to apply to BD. However, whether anti-kindling agents can have neuroprotective effects in the context of treating BD remains to be seen.

The third type of neuroprotection involves direct or indirect cellular mechanisms leading to neuronal survival or growth. Valproate is one of the best-studied medications in regard to cellular mechanisms of neuroprotection. In animal studies, valproate has been shown to increase frontal cortex bcl-2 (Chen et al. 1999b, Manji et al. 2000a), a neurotrophic and neuroprotective protein that is a downstream agent of endogenous nerve growth factors. Valproate also activates protein kinases that mediate the effects of these neuro-

trophic factors to stimulate neural dendritic growth (Manji and Lenox 1999). Lithium has similar effects as valproate on protein kinase C, and bcl-2 (Manji and Lenox 1994, Manji et al. 2000b). Lithium also inhibits glycogen synthase kinase-3b (GSK-3b) (Gould et al. 2004), an enzyme that may be involved in activating proteins involved in neuronal death. Valproate may (Chen et al. 1999a) or may not (Jin et al. 2005) have similar effects on GSK-3b.

Neurogenesis may be the most interesting potential result of these neurotrophic processes. Both lithium and valproate have been found to have neurogenic effects in rat brains and neural stem cells (Hashimoto et al. 2003, Laeng et al. 2004). In another animal study, olanzapine had mitogenic effects on neurons through the MAP kinase pathway (Lu et al. 2004). Neurogenesis in humans, however, has only recently been discovered to occur (Eriksson et al. 1998), and remains controversial. Nonetheless, lithium has some data in support of neurogenesis in humans: in 8 out of 10 patients with BD, overall gray matter increased by 3% after 4 weeks of lithium monotherapy (Moore et al. 2000b). Lithium treatment in BD and healthy adults has also been found to increase cortical levels of NAA (Moore et al. 2000a). Other agents that have been reported to increase prefrontal levels of NAA include lamotrigine in adolescents with bipolar depression (Gallelli et al. 2006) and olanzapine in adolescents with BD whose mania had remitted during treatment (Delbello et al. 2006). Thus, agents already used to treat mood episodes of BD may have neuroprotective properties, and therefore be useful in preventing relapse or even preventing disorder development. While the implications from these findings are exciting to entertain, the question still remains whether or not such potential neurogenic effects of these medications are beneficial to the recipient. Furthermore, not all research concerning anticonvulsants and antipsychotics has supported these findings.

Antidepressants may also provide some degree of neuroprotection. Recent research has focused on the effects of stress and cortisol in decreasing hippocampal volumes in rats (Huang and Herbert 2005). Fluoxetine has been shown to reverse this process (Malberg and Duman 2003, Malberg et al. 2000), as, incidentally, has olanzapine (Kodama et al. 2004). Thus, antidepressants may have specific neuroprotective and pro-neurogenic effects on structures found to be affected in depression, such as the hippocampus. SSRIs might then be used more specifically to prevent the sequelae of chronic stress, such as depression or PTSD (Martenyi et al. 2002). They might not be suitable agents for preventing BD, however, given their propensity to trigger manic episodes in adults and children with or at high-risk for BD (Faedda et al. 2004, Goldberg and Truman 2003). Therefore, one might consider antidepressants to be used for preventing depression and mood stabilizers and atypical antipsychotics to be the class of medications to be used for prevention of BD. However, effects of medications on acute symptoms may differ from their potential effects in preventing worsening of pathology. Perhaps, then, medications proven useful in relapse prevention in depression the [SSRIs and venlafaxine, (Shelton 2004)] and BD [lithium, valproate, carbamazepine, lamotrigine, olanzapine, and aripiprazole; (Muzina and Calabrese 2005)] would be good candidates.

True intervention studies for neuroprotection are difficult to conduct. First, such a prospective study would require many years to follow subjects through years at risk for mood disorder. Second, how is neuroprotection measured? Therefore, no such prospective studies have yet been conducted, though perhaps some are ongoing. However, cross-sectional data may indicate that certain agents may be protective or delay onset of illness. Chang et al. (in review) found prior exposure to mood stabilizers to be correlated with a significantly later age at onset (by 2.2 years on average). Similarly, as mentioned earlier, children with BD who had lithium or valproate exposure had relatively normal amygdalar volumes (Chang 2005). Therefore, mood stabilizers early in the course of illness development may prevent or delay first manic episode.

Three studies have been published which attempted to address this possibility. Each of these were early intervention studies with eventual prevention in mind, but none followed subjects more than 12 weeks. First, Geller and colleagues (Geller et al. 1998) studied children with major depression and a family history of affective disorder. Forty-percent of subjects had a parent with BD, while the other 40% had a more distant relative (aunt, uncle, or cousin) with BD and 20% had a family history of major depression only (without mania). Subjects were randomized to receive six weeks of lithium or placebo in a double-blind fashion. No differences in improvement of depressive symptoms were found between the group taking lithium and the group taking placebo. The final Clinical Global Assessment of Severity scores in both groups, while improved, were still below 60, indicating continuing clinical problems. However, there appeared to be a fairly wide distribution of subjects who responded well and subjects who responded poorly, suggesting that some subjects may have had unique factors associated with response. Whether these factors were related to increased family history of BD is unknown, as the authors did not report such a subanalysis of data grouped by family history. Furthermore, no longitudinal follow up was done to investigate potential effects on bipolar outcome of these children, so the prophylactic benefit of lithium is still unknown.

In another early intervention study, Chang and colleagues (Chang et al. 2003c) investigated the use of divalproex (a form of valproate) in 24 offspring of parents with BD, who themselves had mood and/or disruptive behavioral disorders. None of the child and adolescent subjects had full bipolar I or II disorder, but all had at least some mild affective symptoms as manifested by a minimum score of 12 on the Young Mania Rating Scale (YMRS) or Hamilton Rating Scale for Depression (HAM-D). Thus, they fit criteria proposed for offspring at the highest risk for BD development (Chang et al. 2003b). Subjects were tapered off of any current medications, and then begun on divalproex monotherapy, eventually reaching a mean final dose of 821 mg/day (serum level = 79.0 +/- 26.8 μg/ml). After 12 weeks, 78% of subjects were considered responders, having general improvement in mood and functioning, with the majority showing improvement by week 3. While this study demonstrated the potential of

Table 1. *Studies supporting possible neurodegeneration in pediatric mood disorders*

Year	First Author	Disorder	Age Range,Years (mean)	Findings
2002	Botteron	MDD	17-23 (20.2) but onset mean 15.2	Decreased subgenual cingulatevolume
2003	MacMillan	MDD	8-17 (boys 13.8, girls 14.2)	Decreased amygdalar volume
2004	MacMaster	MDD	13-18 (16.7)	Decreased hippocampal volume
2005	Rosso	MDD	Adolescents (15.4)	Trend for decreased hippocampal volume
2003	Cecil	Offspring of parents with BD having mood disorders	8-12 (9.8)	Trend for decreased NAA in cerebellar vermis
2003a	Blumberg	BD	10 – 22 (15.7)	Decreased cerebral, amygdalar, hippocampal volume
2003a	Chang	BD	9-18 (12.6)	Decreased NAA/Cr in right DLPFC
2004	Chen	BD	10-21 (17)	Trend for decreased left amygdalar volume
2004	DelBello	BD	12-21 (16.3)	Decreased cerebral, amygdalar volume
2004	Wilke	BD	12-17 (14.5)	VBM found decreased gray matter in ACC, orbitofrontal, left DLPFC, medial temporal lobe
2005a	Chang	BD	9-18 (14.6)	Trend to decreased overall gray matter volume
2005b	Chang	BD	9-18 (14.6)	Decreased amygdalar gray volume
2005	Dickstein	BD	8-17 (13.4)	VBM found decreased gray matter in left DLPFC, accumbens, amygdala
2005a	Frazier	BD	6-16 (11.2)	Decreased cerebral, parietal, temporal lobe volume
2005b	Frazier	BD	6-16 (11.3)	Decreased total cerebral and hippocampal volume
2005	Kauer	BD	10-21 (15.5)	Decreased left ACC volume

MDD = major depressive disorder; BD = bipolar disorder, VBM = voxel-based morphometry study; DLPFC = dorsolateral prefrontal cortex; NAA = n-acetylaspartate; Cr = creatine

divalproex in treating acute symptoms of children with putative prodromal BD, another similar, but placebo-controlled, study found that both divalproex and placebo led to equal improvement of affective symptoms in adolescents with cyclothymia or bipolar disorder not otherwise specified who were bipolar offspring. Notably, though, divalproex was superior to placebo in a subset of patients who had very strong family histories of bipolar disorder (Findling 2002, Findling et al. 2000). Again, neither of these studies of divalproex followed children beyond three months, so it is unknown if these children developed full BD at lower rates than otherwise expected, which would indicate potential neuroprotection in prophylaxis of BD. Longitudinal controlled studies would be more definitive in elucidating the neuroprotective qualities of these medications in the prevention of BD development.

Finally, psychotherapeutic intervention may prove to be neuroprotective as well. For example, efforts have been made to intervene with group therapy for children at risk for depression by the genetic and environmental basis of having a parent with MDD (Beardslee and Gladstone 2001, Clarke et al. 2001). No such studies have been published for BD, but only recently have researchers begun to test the efficacy of adjunctive family interventions for children and adolescents with BD. Treatments such as Family Focused Therapy for Adolescents (FFT-A) (Miklowitz et al. 2004), Multi-Family Psycho-Education Groups (Fristad et al. 2003) and a combination of cognitive behavior therapy and FFT (Pavuluri et al. 2004) have shown initial success in decreasing symptom severity and preventing relapse in children with BD. Therefore, it is likely that modifications of these therapies may be useful for early intervention studies. For example, FFT-A is a modification of the adult version of FFT, addressing developmental issues and unique clinical presentations of adolescents with BD (Miklowitz et al. 2004). In an open trial of FFT-A, 21 family sessions plus standard pharmacotherapy were administered to 20 adolescents with BD who had an exacerbation of manic, depressed, or mixed symptoms within the previous 3 months. The first 9 sessions addressed psychoeducation, the next 5 sessions addressed communication enhancement, and the remaining 5 sessions taught problem-solving skills to the affected child and their family members. This open treatment trial found that FFT-A, in combination with standard pharmacotherapy, was associated with improvements in both depression and mania symptoms, as well as decreased parent-rated behavioral problems over the course of 1 year (Miklowitz et al. 2004).

FFT-A could therefore be modified for cohorts of children and adolescents at high-risk for BD, such as children with early symptoms of BD living in families in which a first-degree relative has fully developed BD. FFT-A consists of 3 phases: psychoeducation about mood dysregulation disorders and ways to enhance mood stability, communication, and problem-solving skills. All three topics should be addressed in high-risk samples as well, but a special emphasis could be placed on monitoring and prevention issues most salient to a high-risk population. Other helpful aspects of such interventions would be sessions designed to enhance mood stability in family members with BD in addition to the at-risk child. It is likely that the educational and skill-training focus of FFT would enhance the ability of other mood disordered family members (i.e., parents and siblings) to regulate their emotional states, and thus indirectly ameliorate factors thought to be involved in BD development, such as expressed emotion (Honig et al. 1997, Miklowitz and Hooley 1998) and family environment stressors (Post et al. 2001).

Clearly we are at the infancy of such targeted prevention studies. Furthermore, it is unclear precisely what areas of the brain we should be targeting and how this protection should be done. It should also be stated again that neuroanatomic abnormalities reported in children with mood disorders might be due to inborn deficiencies, developmental changes, or true neurodegeneration. Additionally, some studies have found *increased* volumes of certain areas, such as parahippocampal gyrus (Frazier et al. 2005a) and putamen (DelBello et al. 2004). Nonetheless, the possibility that mood disorders in children may have neurodegenerative components compels the investigation of the use of potentially neuroprotective agents (medications, therapies) in both children who already have mood disorders and those at high risk for developing them.Thus, the ideal ultimate outcome would be prevention or amelioration of the natural course of depression and bipolar disorders. Until then, more research targeting the understanding of neurodegenerative processes in childhood mood disorders would help spur on the search for suitable neuroprotective treatments.

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