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Early Intervention in Bipolar Disorder, Part I:

Clinical and Imaging Findings

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Abstract

The concept of prevention is not new to psychiatry and has long been recognized in general medicine. Recent evidence has highlighted that early pharmacological and psychosocial treatment dramatically ameliorates poor prognosis and outcome for individuals with psychotic disorders, reducing conversion rates to full-blown illness and decreasing symptom severity. Nevertheless, despite the many recent advances in our thinking about early intervention, the need for early intervention in bipolar disorder (BPD) is an area that has been relatively neglected.

This review attempts to synthesize what is currently known about early intervention in BPD. We discuss methodological issues pertaining to this topic, review clinical studies that focus on high-risk subjects as well as first-episode patients, and review findings from brain imaging studies in the offspring of individuals with BPD as well as in first-episode patients.

A companion article discusses the cellular and molecular mechanisms of action of agents with neurotrophic and neuroplastic properties, with a particular emphasis on lithium and valproate.

Keywords

Early intervention; bipolar disorder (BPD); first-episode; high-risk; imaging

Introduction

The concept of prevention is not new to psychiatry (1) and has long been recognized in general medicine. In psychiatry, however, putting prevention into practice has proven difficult. Nevertheless, compelling recent evidence has highlighted that early pharmacological and psychosocial treatment dramatically ameliorates poor prognosis and outcome for individuals with psychotic disorders, reducing conversion rates to full-blown illness and decreasing symptom severity (2,3). Much of this work has investigated schizophrenic spectrum disorders and found that intervening early in the course of illness can both slow degenerative processes associated with the progression of the disease and ameliorate cognitive functioning (4-6).

The debate over whether to intervene early for patients who display subsyndromal symptoms or who appear to be at high risk for psychotic disorders has raised obvious ethical and methodological issues. Although there is now a general consensus that targeted early intervention is helpful, the question remains of how early is too early and, in addition, what

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constitutes the most appropriate treatment (7). Because the long-term effects of psychotropic drugs on brain development are still unknown, efforts have focused on detecting those individuals vulnerable to developing full-blown psychotic syndromes who display subthreshold symptoms, in order to avoid exposing subjects unnecessarily to the risks associated with the treatments themselves (5,8).

The term “early intervention” itself is one that is used to encompass several distinct efforts, including 1) early intervention with primarily psychotropic medications, but also with psychosocial methods, for individuals experiencing their first episode; 2) community-based screening to detect high-risk individuals or those experiencing prodromal symptoms (in a sense, earlier intervention); and 3) efforts to identify and prevent causal factors for a variety of psychiatric disorders. The first attempt is aimed at reducing morbidity and possibly mortality, the second at decreasing morbidity and perhaps the incidence of new cases of psychiatric disorders, and the third at preventing the occurrence of new cases of the disorders altogether.

Despite the many recent advances in our thinking about early intervention, the need for early intervention in bipolar disorder (BPD) is an area that has been relatively neglected (9). Thus, although BPD is associated with high overall morbidity (10,11), high suicide risk (12), residual symptoms (13), functional impairment, psychosocial disability (14), and medical (15) and psychiatric comorbidity (16), very little attention has been paid to studying the effects of early intervention in patients with either a genetic susceptibility to BPD or with attenuated symptoms of this disorder. Part of this dearth of research is due to the low specificity of prodromal symptoms for BPD, which may initially present in many different ways. Also, patients often experience several years of depressive symptoms or full-blown depressive episodes before their first episode of mania or hypomania. Thus, correctly recognizing patients with a strong bipolar diathesis at their earliest stage of illness is very challenging (7).

These two companion articles attempt to synthesize what is currently known about early intervention in BPD. In this paper we discuss methodological issues pertaining to this topic, review clinical studies that focus on high-risk subjects and first-episode patients, and review the findings from brain imaging studies in the offspring of individuals with BPD and in first-episode patients. Notably, evidence from brain imaging studies has shown that BPD is associated with morphological, functional, and metabolic abnormalities in brain areas involved in mood regulation (17); research on first-episode manic patients suggests that some of these abnormalities might be developmental in nature, appearing in the earliest stages of the illness or even in high-risk subjects, while other imaging findings may be related more directly to illness progression and cumulative relapses.

The susbsequent paper highlights the role of neuroprotective and neurotrophic agents in treating the early phases of BPD. Cumulative evidence from cognitive, neuroimaging, pharmacological, and community-based studies, supports the notion that symptom management before the onset of full-blown BPD is not only possible but warranted.

Why the need for early intervention?

BPD is a common, debilitating illness that affects 2.1% of the general U.S. population (18). Its diagnosis poses several problems, and epidemiological studies suggest that eight to 11 years usually elapse between an individual’s first clinical contact and a correct diagnosis of BPD (19,20). Patients with BPD are often misdiagnosed as suffering from schizophrenia, borderline personality disorder, or major depression; in fact, two thirds of patients with BPD have an onset that is initially depressive (21), and some of them may experience several depressive episodes before their first acute manic/hypomanic episode. This diagnostic lag

has obvious therapeutic and clinical implications that can dramatically affect outcome. First, though many individuals may have been ill before being correctly diagnosed, this does not mean that they have been untreated. Less than optimal treatments for these individuals may have included anxiolytics, antipsychotics, and antidepressants, depending on the nature of the misdiagnosis. Individuals afflicted with BPD who were treated with antidepressants in the earliest phases of their illness are at a particular disadvantage because of the possible risk of precipitating manic switches and cycle acceleration (22-24).

Second, some studies suggest that patients with a long-standing illness might be less responsive to lithium and have a more chronic course than patients who receive optimal early treatment (25,26); however this issue is still debated, as some researchers have shown that lithium responsiveness does not change over time in patients with BPD (19,27,28).

Third, there is substantial evidence that the number of previous affective episodes is a risk factor for episode recurrence, chronicity, and suicide; thus, appropriate early treatment would likely decrease the risk for these negative outcomes (29,30). Three independent studies have shown that both in major depression and BPD, the risk of episode recurrence increases as the number of previous and new illness episodes increase (31-33). However, these data do not necessarily imply a causal relationship, as greater number of past episodes might also be due to greater illness severity, or to an illness course marked by a higher tendency to cycle. Moreover, evidence from neuropsychological studies suggests that degree of cognitive impairment, which is likely to affect functioning, is significantly correlated with duration of illness and the number of previous episodes (31,34). The cognitive domains for which this association seems relatively consistent across studies include verbal memory, psychomotor speed, and some measures of executive function (see (35) for an extensive review). Furthermore, there is some evidence for correlation with verbal memory (35), psychomotor speed (36,37), and some executive functions. Interestingly, the number of past manic episodes, rather than past depressive or total episode count, shows stronger correlations with measures of neuropsychological impairment in patients with BPD (38,39).

Thus, one way that early intervention in subjects vulnerable to BPD might improve long-term outcome is by diminishing the number of affective recurrences and consequently ameliorate cognitive functioning and prognosis. However, there are alternative explanations for the correlations between duration of illness, number of past episodes, and neuropsychological impairment. For instance, patients with a more severe and recurrent form of the illness might receive more prolonged and aggressive treatment with medications, which might then cause the cognitive abnormalities associated with BPD. It is also possible that patients with more severe and recurrent forms of BPD might show more extensive cognitive deficits from illness onset, as a result of greater genetic and environmental loading.

Finally, early intervention in subjects susceptible to BPD could diminish the burden associated with the medical and psychiatric comorbidities that often co-occur with this disorder (15,16).

Early Stage BPD Research

Prodromal clinical studies—Clinically detecting the prodromal phase of BPD in the general population is very challenging; naturalistic studies have shown that full-blown bipolar symptoms that require medical care are usually preceded by subtle attenuated symptoms up to 10 years before acute onset of the illness (40,41).

As shown by a recent retrospective study, subthreshold symptoms usually represent attenuated forms of full-blown manic or depressive episodes (42). These include mood

lability, increased energy with lack of impulse control, hyperactivity, racing thoughts, and disinhibition (40,42-44). Other studies have suggested that, when patients present with a first episode of major depression, a personal history of labile mood, fluctuating symptoms, sleep inefficiency, and family history of BPD may help distinguish BPD patients from those with major depression (7). Other symptoms that might suggest the presence of an underlying bipolar diathesis are early age of onset, psychomotor retardation, and atypical symptoms (12,45). It remains unclear at this time whether exposing individuals with these attenuated and non-specific symptoms to pharmacological treatments would lead to benefits that outweigh the potential risks associated with drug treatment (8). More studies are needed to address this issue.

High-risk studies—Another informative approach to better understanding early BPD is studying the offspring of families in which one or both parents have BPD (46). Studies suggest that the offspring of a parent with BPD have a risk of developing any mood disorder that is increased four-fold compared to the general population (47), as well as increased risk for other psychiatric disorders such as ADHD, anxiety disorders, or disruptive disorders (46,48). The range of estimates for the risk of BPD in high-risk populations is wide (3-50%), but consistently much higher than in the general population (1.6-2.1%) (18,49), and varies depending on the length of observation and the operational criteria applied (for instance, whether or not to also consider bipolar spectrum diagnoses). Prospective studies also show that in this selected population, the polarity of onset for patients who develop a manic episode over a five-year observational period is usually depressive (50). Unfortunately, most studies of high-risk populations for BPD have small sample sizes and are descriptive; data are lacking about which symptoms are the most informative predictors for developing BPD in the follow-up period. In addition, most offspring of individuals with BPD do not themselves develop BPD, and the psychosocial and functional outcomes of subsyndromal symptoms are essentially unknown. Thus it is likely that recognizing patients at risk for developing BPD should be guided by different methodological paradigms.

First-episode patient studies—Patients experiencing their first episode of BPD provide a unique opportunity to identify clinical and biological predictors of psychosocial and functional outcome. Although their disorder is clearly manifest, at this stage they do not yet display the confounding effects of long-term mental illness and prolonged drug therapy. Despite the fact that some studies have shown that first-episode patients already have poor functional prognosis and, most often, a long-standing history of subsyndromal symptoms and comorbidities, evidence from brain imaging studies suggests that these patients show less morphological, functional, and metabolic brain abnormalities than multi-episode patients (51-55). This, in turn, suggests that early pharmacological intervention in first-episode patients may slow the progression of the illness, reverse some biological abnormalities, and improve the overall prognosis (51,52).

A number of limitations need to be considered in order to correctly interpret the data derived from first-episode studies. First-episode studies often present a significant heterogeneity in term of age at intake of the patients and the presence of previous psychiatric treatment for other diagnoses. First-episode BPD usually refers to a first manic episode, when BPD is clearly recognizable and the diagnosis is reliable; however, as noted above, for most patients with BPD the polarity of onset is depressive. Thus, patients at their first episode of mania may already have a long-standing history of depressive episodes, comorbidities, and, often, pharmacological treatment.

Also, a considerable amount of brain imaging data regarding first-episode BPD is drawn from studies focused on first-episode psychoses; these can include patients with either schizophrenia spectrum disorders or affective psychoses, with only a small sample size of

patients with BPD. Studies that enroll patients with a first psychotic episode make it difficult to tease apart which abnormalities are related to BPD itself and which are instead the result of psychosis. Moreover, because up to 50% of patients with bipolar I disorder (BPD-I) do not experience any psychotic symptoms over the course of their illness (12), studies that focus on first-episode affective psychoses are not representative of a considerable proportion of patients who suffer from BPD. Finally, all first-episode studies investigated patients with BPD-I disorder. Data about bipolar II disorder (BPD-II) patients are lacking.

Outcome studies in first-episode mania: recovery—Several prospective studies of first-episode mania suggest that most individuals, even in the early stages of illness, suffer from significant psychosocial disabilities and lingering subsyndromal symptoms (51,56-58). Strakowski and colleagues (1998) attempted to differentiate syndromic recovery from symptomatic and functional recovery in first-episode manic or mixed patients; syndromic recovery was defined as eight weeks without fulfilling DSM-III operational criteria for a manic or depressive episode, while symptomatic recovery was defined as eight contiguous weeks displaying only minimal affective symptoms as measured with standard rating scales. Functional recovery required returning to a basal premorbid level of functioning in their work and living situation. Although 56% of the patients achieved syndromic recovery during the 12-month follow-up period, only 35% of these patients achieved symptomatic recovery during this same 12-month interval, and, similarly, only 35% achieved functional recovery (57).

Other studies have used additional functional outcome criteria, including role function, interpersonal relationships, sexual activity, and recreational enjoyment (59). Tohen and colleagues (2000) showed that although 77% of the patients with a first-episode affective psychosis achieved syndromal or symptomatic recovery within six months of hospitalization, 79.8% failed to achieve a functional recovery in the same time span (58). A longer follow-up of the same cohort demonstrated very different trajectories for these three definitions of outcome: at two-year follow-up, 97.5% of the patients achieved syndromal recovery, while just 37.6% of them displayed functional recovery. Another study found that adolescent patients with first-episode mania displayed a similar pattern over 12 months, with the majority achieving syndromal (85%) but not functional recovery (39%) (56). Substance abuse, a positive family history of mood disorders, younger age at intake, comorbidity with ADHD, and lower premorbid functioning have all been identified as predictors of lower functional recovery (51,56,57).

Outcome studies in first-episode patients and high-risk subjects: cognitive impairment—Although cognitive impairment has long been believed to be an aspect of BPD, evidence for the precise nature of that impairment, as well as the timing of its appearance—before the first episode, after the first episode, or only after repeated episodes—has been conflicting. A recent neuropsychological study demonstrated long-lasting cognitive impairment in first-episode patients with BPD despite syndromic recovery; neuropsychological deficits encompassed different domains, including executive functions, sustained attention, and perceptuomotor function (60). Another study found an association between impaired cognitive performance and the presence of psychosis in a group of first-episode affective patients, while patients without psychotic symptoms had a cognitive profile similar to controls; first-episode bipolar patients and unipolar patients did not differ in terms of neuropsychological performance (61). Neuropsychological deficits in attentional measures and executive control functions among patients with BPD at their first hospitalization have also been recently reported by Gruber and colleagues (62). It should be noted, however, that the concomitant use of medications, whose impact on cognitive function is essentially unknown, may confound study findings (63). In fact, a recent study suggests that mood-stabilizing medications, such as lithium and valproate, may contribute to

cognitive deficits in affective processing and attention displayed by patients with BPD (64); however, the acute, potentially cognitive-impairing effects of these medications should not be confused with their long-term neurotrophic/neuroprotective effects.

Furthermore, subjects at high risk for developing BPD show widespread neuropsychological deficits in working memory (65,66), executive functions (67), executive control, declarative memory (65), psychomotor performance speed (68), and response inhibition (69), but not in sustained attention (70,71). In general, these deficits appear before a psychiatric diagnosis of any kind, but to a lesser degree than deficits displayed by patients with full-blown BPD compared to healthy controls (72). Taken together, this evidence suggests that both high-risk subjects and patients at the very early stages of BPD already experience significant long-lasting impairment in different cognitive domains. To what extent these impairments worsen following repeated episodes of BPD is uncertain. To our knowledge, only one study has compared cognitive performance between first- and multi-episode patients with BPD (60), and its results were inconclusive. First-episode patients performed better on some measures of executive function than multi-episode patients, but worse on measures of sustained attention, perceptuomotor function, and other measures of executive function. The impact of medication effects, social functioning, and other potential confounding factors could not be completely ruled out.

Regardless, because issues of recovery and cognitive impairment can significantly affect disability, quality of life, and outcome, early intervention for first-episode individuals with BPD is clearly important.

Future longitudinal studies will address whether the cognitive deficits commonly observed in the early phases of BPD worsen with illness progression. A rigorous analysis that controls for medication and practice effects is warranted to avoid possible confounding factors (73).

Neuroimaging and neuropathological findings in BPD

Neuroimaging and neuropathological studies are valuable methods to study the course of BPD. The number of structural neuroimaging studies in BPD has increased in recent years, expanding the literature on the nature of cerebral abnormalities underlying this disorder. Below, we summarize evidence from neuroimaging and neuropathological findings in BPD. Some of these abnormalities have been also reported in first-episode patients, while imaging data about high-risk subjects are lacking.

Brain imaging studies are particularly useful because they have the potential to help identify subjects at high risk for developing BPD in families with high genetic loading for affective disorders. Indeed, findings from morphological, metabolic, and functional studies in mood disorders are rather specific and point towards a dysfunction in the limbic-thalamic-cortical (LTC) circuits, involving the amygdala, medial thalamus, and orbital and medial PFC, and to the limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuits, involving components of the LTC circuit along with related parts of the striatum and pallidum (reviewed in (17)).

Several studies have demonstrated specific volumetric and neuropathological abnormalities in the prefrontal cortex, the amygdala, and the basal ganglia in patients with both major depression and BPD. Patients with familial mood disorders show a 20-40% reduction in the volume of the anterior cingulate cortex ventral to the corpus callosum (subgenual prefrontal cortex) compared to healthy subjects and to patients with non-familial mood disorders (54,74). Patients with familial mood disorders were defined as having a first-degree relative (74) or any relative (54) with mood disorders according to psychiatric family history. A reduced number of glial cells in the subgenual prefrontal cortex has also been found in familial mood disorders (75). Interestingly, there is evidence that neuroprotective and

neurotrophic treatments (reviewed in “Early Intervention in Bipolar Disorder, Part II: Therapeutics”) might prevent some of these morphometric abnormalities.

Volumetric abnormalities are paralleled by metabolic, functional, and neuropathological abnormalities shown by PET, fMRI, and post-mortem studies (reviewed in (17)). The most consistent finding reported in post-mortem studies in BPD and major depression is a reduction in the density and number of glial cells. Glial cell reductions have been reported in the anterior cingulate cortex, the dorsolateral prefrontal cortex, the orbitofrontal cortex, and the amygdala of patients with mood disorders (75-78). Increased glial cell size and abnormalities in cell shape have also been independently reported by different laboratories (reviewed in (79)). Whether astrocytes or oligodendrocytes are the glial cell involved in affective disorders is still being debated. In fact, early post-mortem studies used Nissl staining, a technique that did not allow researchers to distinguish between the three different kinds of glial cells. More recent post-mortem studies performed with appropriate methodologies have found decreased glial acid fibrillar protein (GFAP) mRNA levels—a marker specific to astrocytes—and reduction of key oligodendrocyte-related and myelin-related genes in patients with BPD compared to unaffected controls (80,81); this suggests that more than one kind of glial cell is likely to be involved in BPD pathophysiology.

Several studies have also shown more subtle abnormalities in neurons (see (82) for a review). The density of large-sized neuronal cells is reduced in layers II, III, and V of the prefrontal cortex; whether these changes are related to glutamatergic excitotoxicity, stress, and related hypothalamic-pituitary-adrenal (HPA)-axis hyperactivation, insufficient glial support, or some other factor, is essentially unknown. The prefrontal layers where most of these neuronal abnormalities have been detected are associated with areas where pyramidal glutamatergic neurons give rise to long projections to other cortical associational regions, such as the striatum and thalamus (79). These areas belong to the LTC and the LCSPT circuits.

In addition, immunohistochemical studies in patients with BPD have found decreased levels of calbindin and parvalbumin positive cells in the anterior cingulate cortex, the hippocampus, and the entorhinal cortex, thus suggesting a dysfunction of GABAergic interneurons in BPD patients (83-85).

A reduction of synaptic markers has been also extensively shown in post-mortem studies of BPD patients over the last decade. Fatemi and colleagues (2001) found that patients with BPD have reduced levels of the synaptosomal associated protein SNAP-25 in the hippocampus compared to healthy controls (86), although negative results about SNAP-25 have also been published (87). Recently, Scarr and colleagues (2006) showed an increase in SNAP-25 and synaptophysin in the dorsolateral prefrontal cortex in patients with BPD (88). However, heterogeneity of pre-mortem medication status and brain regions studied could explain the discrepancy of these findings. Abnormalities in synaptic proteins in patients with BPD have also been documented by Eastwood and Harrison (2001), who found a decrease of synaptophysin, complexin II, and GAP-43 in the anterior cingulate cortex (89). The reduction in these synaptic markers was positively correlated with duration of illness and was greater in subjects with a positive family history of mood disorders. The same group also demonstrated that patients with BPD have alterations of synaptic markers in the hippocampus (90). Finally, reduced dendritic spine density in the subiculum of BPD subjects (91) provides further evidence that the volumetric reductions seen in BPD are likely due to synaptic pathology and neuropil reduction.

Whether the neuropathological findings from post-mortem studies described above also apply to patients with first-episode BPD or to high-risk subjects is unknown at this time.

Treatment with medications that have neurotrophic and neuroprotective properties could benefit patients in the earliest stages of illness, as they might stop or reverse some of the core cellular pathophysiological causes of BPD (see “Early Intervention in Bipolar Disorder, Part II: Therapeutics”).

Brain imaging studies in the offspring and unaffected twins of probands with BPD—Few studies have investigated brain imaging abnormalities in the subsyndromal offspring of individuals with BPD and in the unaffected twins of patients with BPD. Gallelli and colleagues reported no difference in left and right dorsolateral prefrontal cortex NAA levels in the offspring of individuals with BPD compared with control subjects (92). However, decreased NAA concentrations have been found in the hippocampi (93,94), but not the dorsolateral prefrontal cortex (92) of first-episode manic subjects. NAA is particularly interesting because it might be a sensitive marker for studying the neurotrophic properties of mood stabilizers.

Brain imaging studies of subjects at high risk for BPD are very scarce and are often derived from studies whose focus was examining individuals at high-risk for psychosis in general. For example, Velakoulis and colleagues showed that high-risk subjects appear to have normal hippocampal and amygdala volumes, suggesting that limbic abnormalities might be the result of repeated episodes of illness rather than developmental in nature (95). An alternative explanation is that amygdala abnormalities apparent in the later phases of the illness might result from prolonged drug treatment. However, in that study only six subjects at ultra-high risk for psychotic BPD and seven patients at ultra-high risk for major depression were included in the sample of 135 ultra-high risk subjects. Thus, the generalizability of this finding to high-risk patients for BPD is questionable.

One twin study showed that unaffected twins appear to have larger caudate nuclei (96), a finding that is consistent with striatal abnormalities detected in first-episode subjects with BPD as well as patients with multi-episode BPD (55).

Further brain imaging studies in high-risk populations are needed to understand the subtle developmental abnormalities that may be present in subjects vulnerable to BPD. Newer brain imaging techniques might help clarify these issues. In particular, voxel based morphometry (VBM) is a promising approach used to investigate brain regions that are difficult to define anatomically, such as the striatum and the limbic structures. Diffusion tensor imaging (DTI) is another new MRI technique that measures aspects of water diffusion and has been shown to be sensitive for detecting axonal demyelinization and white matter (WM) pathology in general.

Brain imaging studies in first-episode mania—A promising strategy to investigate developmental neuroimaging abnormalities is studying subjects experiencing their first episode of mania when they are drug-naïve or have received medications for only a short period of time. Comparing these patients with multi-episode subjects may help clarify which abnormalities are developmental in nature and which are evident only in patients with prolonged illness. Such work can also highlight whether early intervention with neuroprotective agents can either slow or halt disease progression in affected individuals (97). However, issues such as heterogeneity in terms of age at intake and previous psychiatric contact (regardless of diagnosis) need to be considered for a correct interpretation of the findings (see “First-episode patient studies”, above).

Gray matter abnormalities—Adler and colleagues (2005) found gray matter volumetric increases in the ventral prefrontal cortex (VPC) and part of the anterior cingulate cortex in patients with BPD who had a relatively short duration of illness (illness duration: 8.7 years)

compared to healthy controls (98). A subsequent study by the same group comparing first-episode BPD patients to healthy controls found no evidence of morphological abnormalities in the VPC in the former group, suggesting that the increase in gray matter might be related to abnormal neuronal maturation later in the course of illness, perhaps due to impaired pruning mechanisms (99). First-episode patients with BPD had increased volume in left thalamus, fusiform gyrus, and cerebellum bilaterally; other areas with increased gray matter abnormalities included the anterior cingulate, the posterior parietal cortex and the middle/superior temporal and posterior cingulate gyri (99). Other studies of first-episode patients have found increased gray matter volume in the posterior cingulate cortex, an area that has been associated with metabolic abnormalities in patients with major depression (100) and with treatment response to antidepressants (101). Another study found an abnormal decrease in grey matter volume in the cingulate gyrus for first-episode patients with affective psychoses (21 patients with BPD and three patients with unipolar depression) (54). Specifically, patients with a first episode of affective psychosis who had a family history of mood disorders showed a reduction in left subgenual anterior cingulate cortex volume.

Interestingly, the anterior cingulate cortex shows progressive changes over time in patients with first-episode psychotic BPD; a follow-up longitudinal study showed gray matter volumetric loss in the anterior cingulate two years after onset, while no significant difference was found for healthy controls (53). The impact of medications on this finding is unknown, as patients underwent various treatment regimens during the follow-up period. Also, reduced anterior cingulate volume could be due to the presence of psychosis itself rather than being directly related to BPD.

First-episode patients with BPD also show larger putamen volumes compared to healthy subjects, although no significant difference was found when comparing first-episode to multi-episode subjects (55). The striatum is part of the circuit involved in mood regulation, and it also shows functional and metabolic abnormalities in pediatric BPD (102).

A recent study showed decreased amygdala volumes in first-episode subjects with psychosis, especially on the right side (103). The subjects had been medicated on average for less than three months at the time of the MRI acquisition. Interestingly, amygdala volume and WM volume showed a significant correlation, suggesting that they might share a common underlying pathophysiology. The authors speculated that loss of connectivity between limbic and prefrontal structures during cognitive maturation might lead to the eventual emergence of full-blown symptoms of BPD. Another study yielded conflicting results: first-episode subjects with affective psychoses showed enlarged right amygdala volumes compared to controls (95). Although the findings of amygdala volume are not unequivocal, converging results from morphometric, metabolic, and functional studies with adult patients all suggest that the amygdala is a key area in the pathophysiology of mood disorders (104). No volumetric differences between first-episode patients and controls were found in hippocampi (95) or cerebella (105). Enlarged third ventricular volume in patients with first-episode mania was reported by Strakowski and colleagues (1993), but was not confirmed in a subsequent study by the same group (55,106). Table 1 summarizes the findings regarding gray matter abnormalities in first-episode patients with BPD.

White matter (WM) abnormalities—One of the most consistently replicated neuroimaging findings is an increased number of white matter hyperintensities (WMH) in patients with BPD compared to healthy controls (107-111). Strakowski and colleagues (1993) showed that WMH were 1.7 times more prevalent in patients at their first hospitalization for mania compared to healthy controls, although this finding did not reach statistical significance (106). WMHs have been linked with cognitive disabilities, greater severity, and chronicity in patients with geriatric depression (112-114). The pathophysiology

of these lesions has yet to be fully elucidated, but recent neuropathological post-mortem findings suggest that WMHs are most likely determined by focal cerebral ischemia in patients with late-life depression (115). Intriguingly, recent evidence suggests that a significant portion of young patients with BPD (including children) exhibit WMH (116,117). These lesions have also been found to be increased in children with other psychiatric disorders, although were most frequent among those with BPD when compared to controls, particularly in the frontal lobes (116), and also early in the course of BPD in adolescents (117). These lesions appear to be associated with poor treatment response in patients with affective disorders (118), particularly when they are located in subcortical rather than periventricular areas (119). In addition, the prevalence of WMH in individuals with BPD and a history of suicide attempts appears to be higher than for those without such a history, suggesting that WMH may ultimately be a useful biological marker of suicidality (120,121).

Additional evidence for WM pathology in the early phases of BPD has been suggested by a recent study that used diffusion tensor imaging (DTI) in medication-free subjects experiencing their first episode of mania (122). Patients with BPD showed lower fractional anisotropy of the superior prefrontal region, suggesting a possible WM disorganization rather than axonal demyelinization (99). Similar findings have been shown by Atmaca and colleagues (2007) who found smaller areas in the corpus callosum in first-episode patients with BPD compared to healthy controls; the differences between groups were more pronounced in the anterior body, the posterior body, and the isthmus, but not in the genu or the splenium of the corpus callosum (123). Also, the degree of area reduction was correlated with the severity of the episode. A non-significant reduction in overall WM volume in first-episode patients with BPD was also recently reported by Rosso and colleagues (2007) (103). Some researchers (124) have hypothesized that WM disruption might determine decreased intrahemispheric and interhemispheric connectivity, leading to cognitive deficits. Evidence of WM pathology has also been suggested by studies of high-risk populations; for instance, twin studies have shown decreased left hemispheric WM volume in the unaffected twins of probands with BPD compared to healthy controls, but no change in gray matter volume (125).

Interestingly, some WM abnormalities might also be associated with illness progression. Farrow and colleagues (2005), in a study of first-episode patients with BPD who were rescanned two years after illness onset, found an increase in WM volume in the right posterior frontal/parietal cortex, left temporo-parietal junction, right parieto-occipital junction, left parietal lobe, and right cerebellum (53). This finding needs further replication, as the BPD group was small, and the effect of treatment between the first and second scans was not taken into account.

The meaning of WM volumetric differences between BPD patients and controls is still unclear; a recent VBM study suggested that differences in WM volume between patients with BPD and healthy controls might be due to secondary changes in gyral morphology in loci where decreased grey matter content is identified rather than reflecting WM pathology itself (126). Overall, however, these data suggest that further investigation of WM abnormalities in patients with BPD is needed to validate whether they might be a useful marker in subjects in the earliest phases of BPD. Table 2 summarizes the findings regarding WM abnormalities in first-episode patients with BPD.

Summary of brain imaging studies—The evidence from brain imaging studies in the early phases of BPD confirms abnormalities in brain areas belonging to the LTC and the LCSPT circuits; while high-risk subjects display subtle abnormalities, and further studies are needed to clarify the extension of morphological and functional abnormalities in areas

involved in BPD pathophysiology, first-episode subjects already show a broad involvement of subcortical and prefrontal structures, along with more pronounced WM involvement. Some brain regions, such as the anterior cingulate and the ventrolateral prefrontal cortex, show morphological abnormalities in later phases of the illness that are likely related to either illness progression or to the effects of drug treatment. Notably, recent evidence suggests that patients with BPD undergo progressive gray matter loss over time in the hippocampus, fusiform gyrus, and cerebellum, and that this decrease is related to the decline in cognitive performance commonly observed in patients with BPD (127). These findings highlight the importance of early intervention in patients at risk for BPD in order to slow the progression of brain abnormalities in key areas involved in mood regulation and BPD pathophysiology.

Pathophysiology of BPD: implications for early intervention

The evidence from brain imaging studies reviewed above suggests that patients with BPD show several structural and metabolic abnormalities in areas belonging to the LTC and LCSPT circuits. These findings are paralleled by neuropathological abnormalities involving neurons, glial cells, and the synapses. The volumetric reductions are likely to be due to decreased neuropil volume associated with smaller dendritic trees, and abnormal morphology of synaptic contacts. Stress, hyperactivation of the HPA axis, and dysregulation of glutamatergic transmission seem to play a prominent role in determining these changes (see (128) for a review). Besides directly determining hippocampal atrophy, stress and glucocorticoids also reduce cellular resilience, making cells more vulnerable to various insults, such as glutamatergic excitotoxicity (129). Stress also reduces hippocampal expression of brain-derived neutrophic factor (BDNF), which is critical for neuronal function and survival (130).

Stress also leads to the release of more glutamate in the hippocampus, creating the possibility of excitotoxic damage and dendritic remodeling (see (131) for a comprehensive review). In fact, abnormal activity of the glutamatergic system is likely a major contributor to the impairment in neuroplasticity and cellular resilience observed in patients with BPD (reviewed in (132)). Evidence from both animal and human studies of neuroprotective/neurotrophic agents in BPD (reviewed in the accompanying article) suggest that these agents increase cellular resilience in areas critical for BPD by decreasing the damage associated with stress and glutamatergic excitotoxicity and thus might be valuable therapeutic options in subjects at risk for BPD. Clinical drug studies in high-risk and first-episode patients, along with the cellular and molecular mechanisms of action of agents with neurotrophic and neuroplastic properties—and their potential use as early intervention strategies—are discussed in greater detail in the companion article, “Early Intervention in Bipolar Disorder, Part II: Therapeutics”. That article also provides a synthesis of the information highlighted in both papers.

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Table 1

Summary of brain imaging findings in first episode patients with BPD: gray matter abnormalities

Study	N First-episode bipolar patients M (F)	Comparison group	Age First-episode bipolar patients (±SD)	Medicated (%) at the time of the scan	Findings
Adler et al., 2007 (99)	33 (18)	HC (N=33)	19.9 (±7.9)	27 (82)	• Increased volume in left thalamus, fusiform, and cerebellum bilaterally in FE • Increased GM density in anterior cingulate and posterior parietal structures in FE • Increased GM density and volume in middle/superior temporal and posterior cingulate in FE
DelBello et al., 1999 (105)	16 (5)	Multi-episode BPD (N=14), HC (N=15)	24 (±4)	Not specified	• No difference in cerebellar volumes in FE vs. HC • Multi-episode patients had smaller cerebellar volumes
Farrow et al., 2005 (53)	8 (4)	HC (N=22)	17.5 (±2)	Not specified	• Decreased GM volumes in right inferior frontal/precentral gyrus, bilateral inferior temporal gyrus/uncus, left posterior inferior/middle temporal gyrus, left insula and left posterior cingulate gyrus in FE vs. HC • Decreased GM volumes over time (2-year follow-up) in the anterior cingulate bilaterally
Hirayasu et al., 1999 (54)	21	HC (N=20), SCZ (N=17), UP (N=3)	23.7 (±5.1) (BPD&UP together)	Not specified	• Decreased GM volumes in the left subgenual cingulate cortex in patients with affective psychoses and a positive family history of mood disorders
Rosso et al., 2007 (103)	20 (7)	HC (N=23)	23 (±2)	Most patients medicated	**1** Decreased amygdala volume in FE vs. HC (mostly on the right side)
Strakowski et al., 2002 (55)	18 (7)	Multi-episode BPD (N=17) HC (N=32)	22 (±6)	17 (94)	• Larger lateral ventricles in multi-episode patients vs. FE and HC • Larger putamen in FE vs. HC
Strakowski et al., 1993 (106)	17 (10)	HC (N=16)	28.4 (±6.8)	Not specified	• Enlarged third-ventricle volume in FE vs. HC
Velakoulis et al., 2006 (95)	22 (11) 12 UP (5)	HC (N=87)	21.7 (±2.4)	Not specified	**1** Enlarged right amygdala volume in FE with affective psychoses vs. HC. **2** No differences in hippocampal volumes

Abbreviations: HC: healthy control subjects; SCZ: patients with schizophrenia; UP: patients with unipolar depression; FE: first-episode patients; GM: gray matter.

Table 2

Summary of brain imaging findings in first-episode patients with BPD: white matter (WM) abnormalities

Study	N First-episode bipolar patients M (F)	Comparison group	Age First-episode bipolar patients	Medication status at the time of the scan	Findings
Strakowski et al., 1993 (106)	18 (10)	HC (N=15)	31.3 (±11.8)	Not specified	WMH were 1.7 times more prevalent in FE vs. HC (not statistically significant)
Adler et al., 2006 (122)	17 (6)	HC (N=17)	28.4 (±6.8)	All patients drug-naive	Lower fractional anisotropy in superior frontal cortex
Atmaca et al., 2007 (123)	12 (6)	HC (N=12)	28.2 (±6.5)	All patients drug-naive	Smaller areas in the corpus callosum in FE vs. HC (especially in anterior body, posterior body, and isthmus)
Rosso et al., 2007 (103)	20 (7)	HC (N=23)	23 (±2)	Most patients medicated	Decreased overall WM volume in FE vs. HC (not significant)
Farrow et al., 2005 (53)	8 (4)	HC (N=22)	17.5 (±2)	Not specified	Longitudinal increase in WM volume in the right posterior frontal/parietal cortex, left temporo-parietal junction, right parieto-occipital junction, left parietal lobe, and right cerebellum in FE (2-year follow-up)

Abbreviations: HC: healthy controls subjects; FE: first episode patients; WM: white matter; WMH: white matter hyperintensities.