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Are There Developmentally Limited Forms of Bipolar Disorder?

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Abstract

Bipolar spectrum disorders have traditionally been thought to be chronic in course. However, recent epidemiologic research suggests that there may be developmentally limited forms of bipolar disorder. Two large, nationally representative studies reveal a strikingly high prevalence of bipolar disorders in emerging adulthood (5.5%–6.2% among 18–24-year-olds) that appear to resolve substantially during the latter half of the 3rd decade of life (3.1%–3.4% among 25–29-year-olds). Although ascertainment bias due to early mortality, institutionalization, incarceration, and homelessness may account for some of this reduction, the prevalence distribution suggests a high incidence in late adolescence and emerging adulthood that appears to resolve spontaneously in most cases. There were very few differences across age groups in symptom endorsement and comorbid diagnoses, suggesting that 18–24-year-olds that meet criteria for bipolar diagnoses experience clinically significant impairment and associated consequences of the disorder. More fine-grained longitudinal research is needed to determine whether developmentally limited forms of bipolar disorder exist and, if so, what markers might distinguish these forms of the disorder from more chronic courses.

Keywords

bipolar disorder; developmental psychopathology; epidemiology

Community lifetime and 12-month prevalence estimates of bipolar (BP) disorder vary considerably from study to study. Traditionally, researchers have estimated that the lifetime prevalence of BP disorder is about one percent (e.g., Kessler, Akiskal, Ames, et al., 2006; Weissman et al., 1996). However, more recent research has suggested that psychopathologists have underestimated the prevalence of BP disorder (Merikangas et al., 2007; Merikangas et al., 2008). Estimates of lifetime prevalence rates from community samples range from 0.2% (Steffansson, Lindal, Bjornsson, & Guomundsdottir, 1991) to 3.3% (Grant, Stinson, et al., 2005) for Bipolar I disorder (BPI), from 0.2% (Faravelli & Incerpi, 1985) to 1.7% (Kessler, Akiskal, Ames, et al., 2006) for Bipolar II disorder (BPII), and from 1.4% (Kessler Akiskal, Ames, et al., 2006) to 5.1% (Judd & Akiskal, 2003) for subsyndromal BP symptoms. Twelve-month prevalence estimates are equally variable, ranging from 0.4% (Kessler, Rubinow, Holmes, Abelson, & Zhao, 1997) to 1.3% (Wittchen, Essau, von Zerssen, Krieg, & Zaudig, 1992) for BPI, from 0.4% (Wittchen et al., 1992) to 0.8% (Merikangas et al., 2007) for BPII,

and 1.2% (Grant, Hasin, et al., 2005) to 1.4% (Merikangas et al., 2007) for subsyndromal BP symptoms.

These prevalence statistics provide a context for characterizing the course of BP disorder over the lifespan. Traditionally, BP disorder is thought to be a chronic, relapsing condition that persists throughout a person's lifetime (e.g., McElroy et al., 1992). However, there is some evidence from previous research that there is an age gradient in BP disorder, such that the highest rates are between the ages of 18 and 29 (Grant, Stinson, et al., 2005) or 25 and 34 years (Kessler et al., 1994). The reason for this age gradient is unclear. One possible explanation is that the prevalence of BP disorder decreases with age because of increased risk for mortality associated with BP disorder (e.g., F. Angst, Stassen, Clayton, & Angst, 2002; Cipriani, Pretty, Hawton, & Geddes, 2005; Jamison, 2000; McIntyre et al., 2006), because of suicide (Jamison, 2000; Judd & Akiskal, 2003; Morgan, Mitchell, & Jablensky, 2005) and mortality due to unintentional injury, cardiovascular disease, and other physical conditions (F. Angst et al., 2002; Cipriani et al., 2005; McIntyre et al., 2006). BP-related mortality increases with age (Fenn et al., 2005), and hazard rates peak around age 25 (Osby, Brandt, Nestor, Ekblom, & Sparen, 2001). The percentage of people with BP disorder who die because of these risk factors is difficult to predict, but it has been estimated to be considerable (F. Angst et al., 2002) and could explain a part of the age gradient. Another possibility is that there is an ascertainment bias such that older people with BP are less likely to be included in population based surveys because they are incarcerated, hospitalized (Fisher, Packer, Simon, & Smith, 2000; Cassano, McElroy, Brady, Nolen, & Placidi, 2000), or homeless (Folsom et al., 2005). In addition, prospective studies of patients with serious mental illness indicate that those who are lost to follow-up or who refuse further participation typically have greater severity or related social deficits (e.g., Haapea et al., 2007). Assuming high chronicity, if age related rates of mortality and study nonparticipation exceed age related incidence of new cases of BP, we would expect to see decreased prevalence of BP as a function of age. At present, there are no population-based data of which we are aware that would allow us to estimate the extent to which mortality and ascertainment biases could cause an age gradient.

Despite the uncertainties surrounding possible mortality and ascertainment biases on a possible age gradient, another important possibility needs to be considered. Specifically, prior reports suggest that there may be one or more developmentally limited subtypes of BP that peak in the third decade of life. People with this type of BP disorder may meet criteria for BP in their 20s (or adolescence) but be symptom free or experience only subclinical symptoms later in life. Existing community data that follow adolescents with BP are limited (e.g., Lewinsohn, Klein, & Seeley, 1995, 2000) but suggest that many adolescents with BP remit by age 19 or 24 and that many of those who remit do not experience another episode by their mid 20s. Without further follow-up data, it is unclear if these participants have remitted from the disorder entirely or are in intermorbid periods. Moreover, the few longitudinal studies that have examined BP in childhood or adolescence in clinical samples have found that the majority "recovered" from the illness, and a significant minority of these recovered patients did not relapse by the end of the study (Birmaher et al., 2006; Geller, Tillman, Craney, & Bolhofner, 2004). The portrayal of BP as a life-course persistent, relapsing disorder is largely based on studies of adult, clinical samples who are known typically to have more severe forms of disorder than similarly affected, untreated community residents (Cohen & Cohen, 1984). This suggests that some children and adolescents (and likely adults) become free of symptoms and may not relapse, which is consistent with anecdotal reports of adolescents with BP maturing out of the disorder during "emerging adulthood" (e.g., Raeburn, 2004). However, the extent to which this might occur is presently unknown.

Of particular relevance to BP, individuals with disorders characterized by high levels of impulsivity and risk taking (e.g., substance use disorders, delinquency, borderline personality

disorder, and antisocial personality disorder [ASPD]; Costello, Foley, & Angold, 2006) often show peak hazards in adolescence and early adulthood followed by a “maturing out” in late adolescence and during the early 20s, a stage of development that Arnett and Taber (1994) refer to as “emerging adulthood.” Indeed, the frequency with which this occurs in delinquency/conduct disorder and alcohol use disorders has led some authorities to propose developmentally limited subtypes of both disorders (Moffitt, 1993; Zucker, Ellis, & Fitzgerald, 1994; Zucker & Noll, 1987). Possibly related, personality traits associated with negative emotionality and impulsivity also show large normative decreases during the third decade of life (Roberts, Walton, & Viechtbauer, 2006). Thus, the literatures on the developmental psychopathology of substance use disorder and other externalizing disorders and of normative personality change suggest that characteristics related to impulsivity and mood show large changes and suggest that it might be of considerable importance to examine age gradients in BP.

Because prior epidemiologic studies have tended to use coarse grouping in constructing age strata for analyses, the extent of the age gradient has not been examined with much resolution. When age-related variability in BP has been examined, most studies have focused on differing courses among people with an onset in childhood (less than 13 years old) as opposed to adolescence (13–18 years old) or adulthood (older than 18 years old), or they have presented prevalence rate differences between people aged 18–29 compared with older people (e.g., Grant, Hasin, et al., 2005). To characterize the age gradient for BP, in the current study, we examine the relation between age and prevalence of BP disorder in more detail. Specifically, the current study compares the prevalence of BP disorder in the age groups of 18–20, 21–24, and 25–29 years (and with older cohorts) to distinguish “emerging” and young adulthood. On the basis of the substance use disorder literature, as well as the literature on changes in normal personality traits, we might expect to see considerable change in prevalence over the third decade of life. Because it seems likely that BPI, BP II, and subsyndromal BP may have distinct courses, it is also important to examine these age gradients separately for each subtype of the BP spectrum. To this end, the current research examines how the lifetime and 12-month prevalence of BPI, BP II, and other BP vary with age in a large community-based sample, the National Epidemiological Survey of Alcohol and Related Conditions (NESARC; National Institute on Alcoholism and Alcohol Abuse, 2001–2005), with some supplementary analyses based on another community-based psychiatric survey, the National Comorbidity Survey—Replication (NCS–R; Kessler & Merikangas, 2004).

In the current study, we examined the 12-month and lifetime prevalence rates of BPI, BP II, and other BP diagnoses in people ages 18–20, 21–24, 25–29, 30–39, 40–49, 50–59, and >59 to determine if there was an age gradient in the prevalence of BP. Diagnoses were based on both the original NESARC diagnoses and revised criteria developed in the NCS–R. One possible explanation for an observed age gradient is age-related endorsement of specific symptoms or severity of illness. We tested age differences in the pattern of symptom endorsement to see if this varied by age. We also examined age differences in impairment and treatment experiences to see if there were differences in illness severity across age groups. In addition, we compared the comorbidity of younger participants with older participants. Finally, we tested the rate of offset in the recently released second wave of the NESARC dataset to see if younger participants who met criteria for BP at baseline were more likely to not meet criteria at follow-up (i.e., remit) than older participants, as would be predicted by the developmentally limited hypothesis.

Method

Data

Secondary data analyses were conducted on two nationally representative samples. A public-use version of the NCS–R, conducted in 2001 and 2002, was analyzed using an online interface

available through the Inter-university Consortium for Political and Social Research (http://www.hcp.med.harvard.edu/ncs/ncs_data.php) at the Harvard School of Medicine. The NCS–R sample includes 9,282 noninstitutionalized, English-speaking respondents aged 18 and over and is weighted to approximate the general US population.

Publicly available data from the NESARC, conducted during 2001 and 2002, and a follow-up sample collected in 2004 and 2005 by the National Institute of Alcohol Abuse and Alcoholism were obtained online (<http://www.nesarc.niaaa.nih.gov/>). The NESARC sample includes 43,093 noninstitutionalized, civilian respondents aged 18 and over and is weighted to approximate the general US population. Eighty percent of the original sample completed the follow-up survey ($N = 34,653$).

Measures

NCS–R—The NCS–R study used a slightly modified version of the Composite International Diagnostic Interview (CIDI; Kessler & Ustun, 2004) referred to as the University of Michigan CIDI (UM–CIDI). The UM–CIDI is a diagnostic interview that can be used to generate diagnoses of most major psychiatric disorders using either the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM–IV*; American Psychiatric Association, 1994) or the International Classification of Diseases (10th ed. World Health Organization, 1992) diagnostic system and is designed to be administered by nonclinician interviewers. Previous studies have shown that the UM–CIDI is valid and reliable for diagnosing mood disorders (Kessler, Akiskal, Angst, et al., 2006)

NESARC—Respondents in the NESARC study completed the Alcohol Use Disorders and Associated Disabilities Interview Schedule (*DSM–IV* Version; AUDADIS; see Grant, Dawson, & Hasin, 2001, for a detailed description of the instrument). Previous studies have shown that the AUDADIS is valid and reliable for diagnosing mood and anxiety disorders (Grant et al., 2004), selected personality disorders (Grant, Hasin, et al., 2005), as well as substance use disorders (Grant et al., 2004).

The follow-up assessment of the NESARC study used a modified version of the AUDADIS to reduce participant burden. Instead of asking about lifetime symptoms and experiences, the modified version asked only about the time “since the last interview,” which may have an impact, but has not been systematically studied to the best of our knowledge, on rates of lifetime symptom endorsement. However, this practice logically eliminates the phenomenon of “negative prevalence” (i.e., the well-documented finding that some [often large] proportion of individuals fail to receive a lifetime diagnosis for a given disorder at follow-up, despite having received such a diagnosis at an earlier time, a logical impossibility; e.g., Rice, Rochberg, Endicott, Lavori, & Miller, 1992; Vandiver & Sher, 1991). Further, information collected at the baseline interview was incorporated into the computerized version implemented at follow-up, but it is unclear how this “filling of variables” may have influenced prevalence rates of diagnoses. Limited information about revisions to the baseline assessment procedures for the follow-up survey are available online (<http://www.nesarc.niaaa.nih.gov/>) but suggest that it is probably best not to consider the two interviews strictly comparable, with the follow-up interview likely to yield higher lifetime (age-adjusted) prevalence rates than the baseline interview, because negative prevalence is preempted.

Variables

Diagnoses of bipolar spectrum disorders—To address issues regarding the extent that high prevalences have been reported in the literature to date, we considered alternative sets of BP diagnoses based on those used originally in the NESARC and those based on revised criteria developed in the NCS–R. Specifically, the NCS–R study used a recalibrated diagnostic

algorithm for BP spectrum disorders. For information on the validation of this algorithm, see Kessler, Akiskal, Angst, et al. (2006). For details about the recalibrations and specific criteria used in the algorithm, see the BP sections of the file available at <http://www.hcp.med.harvard.edu/ncs/diagnosis.php>. In addition to requiring participants to meet *DSM-IV* diagnostic criteria for BPI, the NCS-R recalibrated diagnosis required endorsement of at least 6 of 15 symptoms of mania with at least two of the following: having a lot more interest in sex than usual, being overly outgoing, getting involved in foolish schemes, getting into financial trouble, doing risky things, believing you were someone else or somehow connected to a famous person. Individuals who met criteria for *DSM-IV* BPI and these modified criteria in the past 12 months indicated a diagnosis of Strict-BPI. Diagnosis of BP-II was also modified. In addition to requiring that participants meet *DSM-IV* diagnostic criteria for BP-II, the diagnosis required a minimum duration of 14 days and at least two of the symptoms listed above for mania. Participants could also receive a diagnosis of Strict-BP-II if they met *DSM-IV* criteria for BPI (but not the recalibrated diagnosis of Strict-BPI), reported a depressive episode in their lifetime, and reported euphoria *and* racing thoughts. Finally, participants who met *DSM-IV* criteria for BPI or BP-II but did not meet the modified criteria for either disorder under the strict definition were diagnosed with “Other BP” disorder. It is important to note that the diagnostic label of “Other BP” that is used throughout this article (resulting from use of the NCS-R recalibrated diagnostic algorithm) is NOT equivalent to *DSM-IV* bipolar disorder not otherwise specified (BP-NOS) or cyclothymia diagnoses or to other definitions of subthreshold disorder used throughout the literature, typically defined as having significant symptoms and impairment but not meeting *DSM-IV* criteria. In fact, the diagnostic label of “Other BP” used in this study includes individuals who meet full criteria for *DSM-IV* BP I or II diagnoses as described in the manual but do not meet the more strict criteria defined by the NCS-R recalibrated algorithm. Therefore, our operationalization of “Other BP” is likely to result in more homogeneous and perhaps more severe cases than is typical in the broader literature. Diagnoses of BP-NOS and cyclothymia were not possible on the basis of the structured interview items contained in the NCS-R or NESARC surveys.

The NESARC study used standard *DSM-IV* diagnostic criteria to diagnose mania and hypomania. The presence of a manic episode ever and either a manic or depressive episode in the past 12 months indicated a diagnosis of past-12-month BPI, and the presence of a manic episode ever indicated a diagnosis of lifetime BPI. The presence of a hypomanic episode and a depressive episode ever indicated a diagnosis of lifetime BP-II, and the presence of either a hypomanic or depressive episode in the past 12 months and the lifetime presence of the other episode indicated diagnosis of past-12-month BP-II.

To compare diagnoses among the two samples, we created modified diagnosis (NESARC-Strict) of past-12-month mania among the NESARC participants intended to mimic the recalibrated diagnostic criteria used by the NCS-R study. In addition to requiring *DSM-IV* diagnostic criteria for BPI, we also required participants to endorse 5 of 13 symptoms of mania and either “increased sexual activity” or “doing things that could get you into trouble.” The presence of a BPI disorder meeting these enhanced criteria in the past 12 months indicated a diagnosis of past-12 month Strict-BPI. A modified diagnosis of past-12-month BP-II was also created. In addition to requiring that participants meet *DSM-IV* diagnostic criteria for BP-II, the diagnosis required minimum duration of 14 days and either “increased sexual activity” or “doing things that could get you into trouble.” Participants could also receive a diagnosis of Strict-BP-II if they met *DSM-IV* criteria for BPI (but NOT the recalibrated diagnosis of Strict-BPI), reported a depressive episode in their lifetime, and reported euphoria *and* racing thoughts. Finally, participants who met *DSM-IV* criteria for BPI or BP-II disorder, but who did not meet the modified criteria for either disorder, were diagnosed with “Other BP” disorder.

Analyses presented from the NESARC follow-up study use only the NCS–R recalibrated algorithm. Thus, all Wave 2 diagnoses are comparable to the “Strict” diagnoses as described above.

In addition to examining diagnostic categories, we examined individual responses to questions assessing BP features (elation, irritability, and past-12-month depression), *DSM–IV* criteria, and impairment (across five areas: personal, interpersonal, work or school, productivity, and legal) among NESARC participants at baseline. Four items assessing lifetime help-seeking for manic symptoms (provider help, hospitalization, emergency room visit, medication) were also included in descriptive analyses.

Diagnosis of comorbid disorders—To examine comorbidity of relevant psychiatric diagnoses with BP spectrum disorders in the NESARC sample, we used past-12-month diagnoses of anxiety disorders (panic disorder, generalized anxiety disorder, and social anxiety), substance use disorders, childhood conduct disorder, and lifetime diagnosis of ASPD as coded in the baseline NESARC public use dataset. The diagnoses of anxiety disorders used in this study excluded individuals who only experienced symptoms due to a medical condition or substance use (substance- and illness induced rule-out) but may include individuals whose anxiety symptoms were experienced as part of a mood disorder.

Results

Because of the complex sampling procedures used in both studies, we conducted analyses using SUDAAN software (Version 9; Research Triangle Institute, 2004). SUDAAN software is available as an adjunct to the SAS/STAT software package (Version 9.1; SAS Institute, 2003) and allows for the application of sampling weights, commonly used to adjust large epidemiologic data sets that employ complex sampling, to the data prior to computing common statistics. Specifically, a sample design is specified to allow the program to estimate standard errors. We specified a Taylor Linearization Method Without Replacement (Wolter, 1985) for the computation of standard errors in our analyses. Preliminary analyses using SUDAAN with this particular sample design specification resulted in replication of previously published prevalence estimates and corresponding standard errors for NESARC data.

Using *DSM–IV* diagnostic scoring, the overall prevalence of past-12-month BP disorder in the NESARC sample was 2.02% ($SE = 0.09$) for BPI and 0.82% ($SE = 0.06$) for BPPII, in contrast to a past-12-month prevalence of BPI of 0.6% ($SE = 0.10$) and 0.8% ($SE = 0.10$) for BPPII in the NCS–R using strict diagnostic scoring.

When the NESARC sample is stratified by age, the past-12-month prevalence using *DSM–IV* diagnoses was found to be higher among younger participants (see Figure 1) for BPI, $\chi^2(6, N = 43,093) = 22.38, p < .001$; BPPII, $\chi^2(6, N = 43,093) = 13.45, p < .001$; and BPI and BPPII combined, $\chi^2(6, N = 43,093) = 26.23, p < .001$, with similar age trends evident for lifetime diagnoses, $\chi^2(6, N = 43,093) = 22.36, 15.30, 26.14$ for BPI, BPPII and BPI/III, respectively (all $ps < .001$). In particular, the prevalence of past-12-month BPI for 18–20-year-olds (4.41%, $SE = 0.52$) and BPPII (2.87%, $SE = 0.46$) was significantly greater than among participants over 25 years old. Compared with the 18–20-year-old cohort, odds ratios (ORs) for the 25–29 cohort and all older cohorts are significant, with cohorts over 25 years old being at decreased odds of diagnosing compared with 18–20 year-olds (ORs ranging from 0.11 vs. the 60+ group to 0.80 vs. the 25–29 group; all $ps < .01$). Results in the NCS–R sample using strict scoring showed similar age trends for Strict-BPI, $\chi^2(6, N = 9,282) = 3.13, p = .013$; Strict-BPPII, $\chi^2(6, N = 9,282) = 5.01, p < .001$; Other BP, $\chi^2(6, N = 9,282) = 4.58, p = .001$; and BP spectrum, $\chi^2(6, N = 9,282) = 8.20, p < .001$. Although these age gradients are similar, it should be noted that the NESARC sample tended to have higher rates of bipolar disorders across all age groups.

Because the original scoring of the NESARC and the strict NCS–R samples yield different overall prevalences and different degrees of an age gradient, despite the fact that both are population-based, national samples, we explored the extent to which these large study differences could be attributable to different scoring algorithms. We therefore recoded NESARC diagnoses adapting the NCS–R Strict criteria and recalculated prevalence as a function of age. The resulting prevalence rates of BP disorder in the NESARC sample are more comparable to those in the NCS–R sample (see Figure 2). Specifically, the recoded Strict NESARC diagnoses yielded a reduction in both BPI (from 2.02% to 1.15%) and BPII (from 0.82% to 0.46%), although NESARC–Strict BPI diagnoses remained systematically more prevalent than NCS–R diagnoses (see Figure 3A). However, despite these changes in the overall rates of diagnoses, when NESARC was scored using the “strict” algorithm, the age gradient remained for Strict-BPI, $\chi^2(6, N = 43,093) = 18.35, p < .001$, and Strict-BPII, $\chi^2(6, N = 43,093) = 11.90, p < .001$ (see Figure 3B).

Rates of Strict-BPI in the NCS–R sample (see Figure 3A) are slightly lower than those for NESARC, with the decline in prevalence occurring after the third decade of life (30–39), slightly later than the decline in NESARC at 25–29. Despite this, the age gradient is still observed in NCS–R for Strict-BPI (see Figure 3A). Although the rates of Strict-BPII in the NCS–R sample appear to be relatively constant until after the sixth decade of life (>59), with the exception of 25–29-year-olds, we believe this may be due to a smaller sample size relative to the NESARC sample (note the large confidence intervals at younger age groups). It is also possible that there is greater inconsistency in Strict-BPII diagnoses generally, because of the impact of depressive episodes as required by the diagnostic criteria. When we examined rates of past-12-month hypomania regardless of major depressive episodes, the pattern across age groups was much more consistent (1.02%, $SE = 0.55$; 2.03%, $SE = 0.81$; 0.57%, $SE = 0.29$; 0.49%, $SE = 0.19$; 0.11%, $SE = 0.07$; 0.17%, $SE = 0.12$; and 0.00% among 18–20, 21–24, 25–29, 30–39, 40–49, 50–59, and >59 age groups, respectively). The prevalence of hypomania demonstrates a decline at age 25–29, similar to that in NESARC, $\chi^2(6, N = 9,282) = 2.90, p = .019$. Thus, at least in NCS–R, criteria for past-12-month Strict-BPII appear to be more heavily influenced by past-12-month major depression than by past-12-month hypomania in older cohorts. This suggests that the age gradient in Strict-BP diagnosis, especially Strict-BPII, is more specific to the mania/hypomania pole than to the depressive pole.

Age Differences in the Pattern of Symptom Endorsement

To understand better if the age gradient for NESARC Strict-BPI is attributable, in part, to age-related endorsement of specific symptoms, we examined the prevalence of criterion symptoms among those diagnosed with Strict-BPI. There were no significant differences across age groups in endorsement of elation, irritability, or past-12-month depression among participants with Strict-BPI, $\chi^2(6, N = 494) = 0.12, 1.24$, and 0.59 for elation, irritability, and depression, respectively (all $ps > .05$). However, participants diagnosed with Strict-BPI who were 18–20 years old were less likely to endorse racing thoughts than were age groups over 25, $\chi^2(6, N = 494) = 4.07, p = .002$. Compared with the 18–20-year-old cohort, ORs for the 25–29 cohort and older cohorts up to age 59 were significant (the ORs for >59 year-old cohort could not be computed because of small cell sizes), with cohorts over 25 years old being at increased odds of reporting racing thoughts when compared with 18–20 year olds (ORs ranging from 3.54 vs. the 30–39 group to 13.52 vs. the 25–29 group; all $ps < .05$). There were no other significant differences in criteria endorsement. These analyses do suggest, however, that the absence of racing thoughts could be a correlate of a developmentally limited form of BP.

Age Differences in Impairment and Treatment Experiences

NESARC measured impairment due to symptoms across five areas: personal discomfort, interpersonal, work or school, productivity, and legal. Participants who were diagnosed with

Strict-BPI and were 18–20 years old endorsed more legal impairment than did the 25–29 (OR = 4.69; 95% CI = 1.59, 13.85) and 50–59 (OR = 5.71; 95% CI = 2.03, 16.09) year-old age groups, $\chi^2(6, N = 494) = 2.58, p = .026$. No additional differences were found for impairment among participants with Strict-BPI. Differences across age groups in lifetime prevalence of help-seeking were found for participants diagnosed with Strict-BPI. Specifically, younger participants (age 18–39) were less likely to endorse seeing a health care provider for manic symptoms, $\chi^2(6, N = 494) = 2.34, p = .042$, than were older participants; and 18–29-year-olds were less likely to endorse using medications for manic symptoms, $\chi^2(6, N = 494) = 4.52, p < .001$, than were older participants.

On the basis of examination of age differences in symptoms and impairment, there appear to be relatively few differences between participants who diagnose between the ages of 18 and 20 and those who diagnose at older ages. However, the younger Strict-BPI participants reported fewer racing thoughts and more legal problems. Thus, with these two exceptions, at least internally, the diagnoses in NESARC appear to be generally consistent across age.

Comorbidity

If the apparent excess of BPI diagnoses in emerging adulthood represents Type I error in diagnosis, we might expect to see either greater or lesser comorbidity with conditions that frequently co-occur with BPI and BPII. If the age gradient is a result of disorder-specific misdiagnoses in the younger age groups (i.e., simple false positives), then we would expect to find that younger individuals have less comorbidity with other disorders that commonly co-occur with BP disorder. Conversely, relatively high levels of comorbidity could result from common reporting biases or relevant age-related criterial bias in BP and near neighbor diagnoses. Following this logic, rates of comorbidity that are statistically equivalent across age groups may suggest that the rates of Type I error in the NESARC study are random and not related to age. Thus, to assess age differences in the external validity of these diagnoses, we examined comorbidity with past-12-month anxiety disorders (5.73%, $SE = 0.19$ overall; 35.91%, $SE = 1.75$ among those with a BP spectrum diagnosis), lifetime ASPD (3.63%, $SE = 0.15$ overall; 20.97%, $SE = 1.49$ among those with a BP spectrum diagnosis), childhood conduct disorder (4.69%, $SE = 0.16$ overall; 23.51%, $SE = 1.54$ among those with a BP spectrum diagnosis), and past-12-month drug (2.00%, $SE = 0.10$ overall; 11.69%, $SE = 1.36$ among those with a BP spectrum diagnosis) and alcohol use disorders (8.46%, $SE = 0.24$ overall; 23.41%, $SE = 1.58$ among those with a BP spectrum diagnosis) across age strata. Overall, there is significant comorbidity with each of these conditions across all possible BP disorder diagnoses, with significant ORs for childhood conduct disorder, adult ASPD, substance use disorder diagnoses, and anxiety disorders (see Figures 4A, B, and C) across age groups.

Childhood conduct disorder (see Figure 4A, upper panel) and adult ASPD (see Figure 4A, lower panel) were consistently more likely across all age groups and all levels of BP spectrum disorder, with few exceptions (ORs ranged from 3.92 to 11.69 across all age groups for BP spectrum diagnosis; $ps < .05$).

Drug and alcohol use disorders were not as consistent as conduct disorder and ASPD but, nonetheless, appear to be more likely among those with a BP spectrum disorder in general. Drug use disorders were most likely to occur in participants with a Strict-BPI diagnosis (ORs ranged from 5.76 to 26.03 across age groups; all $ps < .05$; see Figure 4B, upper panel). Alcohol use disorders were also most consistently associated with Strict-BPI diagnoses (ORs ranged from 1.46 to 7.60; all $ps < .05$, except among participants 50 and older; see Figure 4B, lower panel).

Anxiety disorders were consistently more likely among all levels of BP spectrum disorders and age groups (ORs ranged from 3.16 for 25–29 year-olds with Strict-BPII to 30.98 for 60

and older with Strict-BPII; all $ps < .05$; see Figure 4C). Overall, results from these analyses suggest that a diagnosis of BP spectrum disorder at any age is associated with significant impairment and illness burden.

Other BP

As noted earlier, Merikangas et al. (2007) recently highlighted both the prevalence and clinical relevance of subthreshold BP symptomatology in the general population but failed to address the question of the age gradient of this type of symptomatology. To determine whether subthreshold symptomatology follows the same basic age gradient we observed for Strict-BPI, we estimated the prevalence of Other BP across age strata in both the NCS–R and NESARC, using the recalibrated criteria developed by NCS–R and used by Merikangas et al. (2007); these estimates are provided in Figure 5. Similar rates of past-12-month Other BP were obtained across the two samples with similar age gradients in both the NCS–R, $\chi^2(6, N = 9,282) = 4.58, p < .01$, and the NESARC, $\chi^2(6, N = 43,093) = 13.44, p < .001$ (see Figure 5A). Rates of Other BP disorder averaged across the 18–20- and 21–24-year-old cohorts are nearly twice as high (NESARC, 2.99%, $SE = 0.30$; NCS–R, 3.4%, $SE = 0.63$), as in the 25–29-year-old cohort (NESARC, 1.57%, $SE = 0.25$; NCS–R, 1.5%, $SE = 0.38$) for both samples. The rates of Other BP disorder in the 18–20 age group in NCS–R appear to be lower than expected, given the rates in the 21–24 age group. This is exacerbated by the small number of participants that comprise these small age intervals (3–5 years), resulting in bigger standard errors, compared with older age groups that contain larger age intervals (10 years) and, thus, relatively large numbers of participants. Further, the discrepancy between rates observed in the NCS–R and the NESARC data for this particular age group may be related to the sampling frame used by both studies to capture students residing in group housing units, such as residence halls and fraternity/sorority housing. Although both studies attempted to sample from such group housing units, their methods were different (for NCS–R procedures, see Kessler et al., 2004; for NESARC procedures, see online documentation at <http://www.nesarc.niaaa.nih.gov/>). When we examined the percentage of 18–20-year-olds who reported being students, it was significantly lower in NCS–R (13%) than in NESARC (44%), with rates in NESARC comparable to national statistics (39% of 18–24-year-olds in 2005; United States Department of Education, 2008). This discrepancy may explain some of the divergence in prevalence rates among this age group.

When combining all BP spectrum diagnoses (Strict-BPI, Strict-BPII, and Other BP), rates of any BP disorder are similar across samples, with the exception of 18–20-year-olds in NCS–R (see possible explanations above), and display similar age trends, NESARC $\chi^2(6, N = 43,093) = 26.23, p < .001$, and NCS–R $\chi^2(6, N = 9,282) = 8.20, p < .001$ (see Figure 5B). It is important to note that the Other BP category in the NESARC sample has relatively high levels of comorbidity, although they are somewhat lower than those for Strict-BPI and Strict-BPII (see Figures 4A, B, and C).

Examination of Offset in Prospective Data

On the basis of results from the baseline NESARC and NCS–R data, we anticipated that offset of BP disorder would be greatest among younger age groups, particularly for Other BP disorder. To determine whether the observed age gradient could be attributable to differential offset rates as a function of chronological age, we conducted a series of logistic regression analyses predicting the presence or absence of a 12-month BP diagnosis at follow-up among NESARC participants who were diagnosed at baseline and completed the follow-up survey ($n = 1,042$). Contrary to our expectation, offset at follow-up was not related to age (spectrum disorder $\beta = 0.00, p = .442$; Strict-BPI $\beta = 0.00, p = .603$; Strict-BPII $\beta = -0.02, p = .225$; Other BP $\beta = -0.01, p = .517$; controlling for sex in all models). In Figure 6, we illustrate these findings for Other BP, where we found the strongest age gradient and anticipated finding differential offset.

Figure 6 documents the various BP-related outcomes at follow-up among those with an Other BP diagnosis at baseline as a function of age. Although there is a drop in rate of offset from the 18–20- (70%) to the 21–24-year-old (54%) age groups, overall, the rate of offset from Other BP disorder is fairly constant across age groups ($M = 64\%$, with a range of 52% to 70%). This is also true for Strict-BPI and Strict-BPII ($M = 55\%$ for both disorders, with a range for Strict-BPI of 41% to 67% and for Strict-BPII of 40% to 69%; data not presented). These analyses are extremely informative in that they suggest that most of the age gradient is attributable to high hazard rates in late adolescence and early adulthood and not to differential remission or recovery rates.

Can the Gradient Be Explained by BP-Related Attrition From the Sample?

We conducted basic attrition analyses in the NESARC sample determine whether follow-up was related to BP diagnoses, age, sex. An overall diagnosis of BP spectrum disorder at baseline was associated with increased odds of completing the follow-up survey (OR = 1.37; 95% CI = 1.12, 1.66). Although follow-up was not significantly associated with a specific diagnosis of Strict-BPI Other BP at baseline, participants with a Strict-BPII diagnosis baseline were more likely to complete the follow-up survey (OR 1.61; 95% CI = 1.01, 2.58). In general, older age groups, Wald $F(6, N = 43,093) = 44.75, p < .001$, were more likely to complete the follow-up survey, as were women (OR = 1.61; 95% CI 1.11, 1.25). On the basis of these analyses, we do not believe that attrition in NESARC could explain the rates of offset observed at follow-up.

Discussion

The current study documents a striking age gradient in the prevalence of BP, with peak prevalences observed during emerging and, to a lesser extent, young adulthood. It is important to note that these findings were found in two large, informative data sets. Although we cannot address the extent that some of this gradient may be an artifact of early mortality and illness-related ascertainment bias in the NCS–R or baseline NESARC surveys, the NESARC follow-up suggests that these artifactual explanations are not likely to be major factors, because the presence of a past-year BP diagnosis at baseline did not predict nonparticipation at follow-up. If anything, those with a baseline BP past-year diagnosis were more likely to be followed up. Moreover, the sheer magnitude of the age gradient effect cannot be explained by early mortality, given that the decrease in prevalence exceeds what might be reasonably predicted on the basis of early mortality (F Angst et al., 2002). For example, in the baseline sample, the cross-sectional 35%–40% drop in past-year BP spectrum diagnoses from the 18–24 age groups to the 25–29 age group far exceeds the incidence of all cause mortality in BP on the basis of existing studies (e.g., the standardized mortality ratio for all cause mortality in patients with BP disorder was 2.5, which means that people with bipolar disorder are 2.5 times more likely to die than those without bipolar disorder; Osby et al., 2001). Second, the high and relatively comparable rates of comorbidity across all age strata suggest that there is rough comparability of total psychiatric burden across age. If the most severely affected individuals were not ascertained, we might expect this bias to manifest itself as lower comorbidity among the older cohorts.

One possible explanation for the observed age gradient in BP spectrum diagnoses is age-related ascertainment bias. The age gradient observed in the NESARC-Original *lifetime* diagnosis appears to support this hypothesis (see Figure 1). However, previous research has shown that lifetime diagnoses can be highly unreliable (Vandiver & Sher, 1991). Specifically, diagnoses are least sensitive (more unreliable) when the interval between an active episode and the time of report is greatest, that is, in older cohorts. For example, a 29-year-old who experienced a single manic episode at age 24 would be more likely to recall this episode than would a 58-year-old with the same history. Thus, the younger participant would be diagnosed with a

lifetime BP disorder, whereas the older participant would not. Still, some degree of early mortality and ascertainment bias (and perhaps even secular trends) could be responsible for some portion of the age gradients reported here. However the size and the abruptness of the decrease in past-year prevalence during the third decade of life are difficult to reconcile with the alternative hypothesis that this is primarily an artifactual relationship.

Another alternative explanation for the observed age gradient could be a secular trend in which younger cohorts are more likely to have BP disorder. Greater prevalence rates have been observed in younger cohorts, suggesting that age of onset of BP disorder may be decreasing (Chengappa et al., 2003), or rates of BP disorder may be increasing. Some possible mediators of this increase could be genetic anticipation (Lange & McInnis, 2002; Post, Leverich, Xing, & Weiss, 2001), changes in diet (Hibbeln et al., 2007), or increases in childhood adversity (Post et al. 2008). Another explanation for an increasing secular trend is improved detection; however, this cannot explain the results of the current study because all participants were assessed with the same diagnostic instrument. Moreover, it is not likely that cohort effect would emerge in a 3- or 5-year increment (i.e. only affect those 18–20 or 21–24 at baseline).

Similar to a developmentally limited form of BP disorder, there is mounting evidence that there is a developmental subtype of BP disorder based on age at onset, suggesting that earlier age of onset is associated with negative outcomes (e.g., Goldstein & Levitt, 2006). The mean age of onset of BP disorder is around 21–22 years old (Berk et al., 2007; Kessler, Akiskal, Ames, et al., 2006). In number of studies, earlier age of onset is associated with poorer general outcome, longer duration of illness, more severe and longer illness episodes, a more rapid cycling course, and a higher comorbidity with several other Axis I and Axis II disorders (Carter, Mundo, Parikh, & Kennedy, 2003; Ernst & Goldberg, 2004; Mick, Biederman, Faraone, Murray, & Wozniak, 2003; Schurhoff et al., 2000). Combining our findings with the existing literature on age-of-onset of BP disorder leads us to conclude that there are likely two variants of earlier onset BP disorder: a relatively severe form with poor prognosis and a developmentally limited form with (relatively) good prognosis. Indeed, the NESARC follow-up points to BP offsetting at a relatively constant and high rate, suggesting that nonchronic courses may be common throughout adulthood. This is contradictory to *DSM-IV* bipolar disorder, which is characterized as chronic, in which a history of mania is sufficient for a bipolar diagnosis. However, we remain cautious in drawing strong conclusions here, because a single follow-up after 3 years does not resolve the question of reoccurrence over the life course, and the lack of noncriterial symptoms included in the interview precludes more fine-grained analysis of residual symptomatology. Additional follow-up of the NESARC cohort and other prospective studies are needed to identify risk factors for both more chronic courses and more limited ones. Our finding that younger individuals with BP tend to have lower rates of racing thoughts points to one diagnostic feature that may tend to differentiate these two courses, but again, prospective study is indicated to evaluate this issue.

Our analyses with NESARC strongly confirm Merikangas et al.'s (2007) findings from the NCS-R that subthreshold BP (*Other BP* in our study) is prevalent and associated with significant comorbidity. It is important to note that our results extend these findings by suggesting that this form is especially likely to be evident in emerging adulthood.

Although the NESARC follow-up data suggest the BP excess in emerging adulthood is attributable primarily to onset processes in adolescence and emerging adulthood, and not offset processes particular to emerging adulthood, at this point, we believe that processes related to both onset and offset need to be considered, given the limited data currently available. With respect to onset processes, late adolescence and emerging adulthood are associated with increased risk for a range of internalizing (e.g., panic disorder; Eaton, Badawi, & Melton, 1995), externalizing (e.g., alcohol use disorders; Kessler et al., 2005), and psychotic (e.g.,

Riecher-Rossler & Hafner, 2000) disorders, and this increased risk can stem from a range of both developmental stressors (e.g., leaving home transition; Schulenberg, Sameroff, & Cicchetti, 2004) and neurodevelopment (Alloy, Abramson, Walshaw, Keyser, & Gerstei, 2006). Moreover, this period of life is associated with exposure to psychoactive drugs, which can presumably have relatively strong neurodevelopmental effects in vulnerable individuals during this sensitive period of brain development (e.g., Caspi et al., 2005). On the offset side, dramatic decreases in the prevalence of externalizing disorders, such as alcohol use disorders and Cluster B personality disorders (especially ASPD, see Hare, McPherson, & Forth, 1988; and borderline personality disorder, see Dulit, Marin, & Frances, 1993), during the third decade of life have been noted frequently by others. The maturing out of alcohol and other impulse-control disorders is increasingly being viewed as resulting from neuromaturation of the prefrontal cortex, which might be a potential common factor that could explain, in part, these age-graded trends in alcohol use disorders, impulse-control-related disorders (such as ASPD and borderline personality disorder), and the BP spectrum. Previous research has shown that people with BP disorder suffer from deficits in the same types of cognitive control and executive functioning that develop during late adolescence and early adulthood in normal people (Clark, Iverson, & Goodwin, 2001; Kronhaus et al., 2006; Martinez-Aran et al., 2004; Thompson et al., 2007; Torrent et al., 2006; Wilder-Willis et al., 2001). These processes mature along with the development of the pre-frontal cortex in childhood and adolescence and are virtually complete by the late 20s (Casey, Galvan, & Hare, 2005; Romine & Reynolds, 2005). In addition, several researchers have noted that the final maturation of these brain regions and associated cognitive skills coincides with the mean age for the development of BP disorder (Alloy et al., 2006), and problems in this phase of pre-frontal cortex development may play a causal role in the development of BP disorder (Alloy et al., 2006). Thus, the degree of maturation of the prefrontal cortex during the third decade of life might represent a key factor in resolving developmentally limited forms of BP and other disorders marked by disinhibition. Normative trends in personality structure show increases in emotional stability, self-control, and risk-avoidance as people reach adulthood (e.g., Johnson, Hicks, McGue, & Iacono, 2007; for review, see Roberts et al., 2006). These same personality traits have been related to putative affective temperaments underlying the vulnerability to BP disorders (e.g., Nowakowska, Strong, Santosa, Wang, & Ketter, 2005), although it seems likely that the broad trait of disinhibition is more closely linked to BPI and negative affectivity to BPII (Akiskal et al., 2006). Understanding the relations among neurocognitive changes associated with executive functioning and personality changes associated with disinhibition and negative affectivity may help to explain a significant portion of the apparent resolution or “spontaneous remission” of several related forms of adolescent and young adult psychopathology.

Limitations

There are a number of limitations that are primarily due to the nature of epidemiologic survey techniques and sampling procedures. For both samples, criteria were not assessed that would allow for diagnosis of cyclothymia. In addition, as mentioned in the Method section, our use of the term “Other BP” does not conform to that used in the previous literature, nor does our use of “spectrum” include the diagnoses of cyclothymia or BP-NOS, as is often done. Both studies used fully structured diagnostic interviews administered by laypersons. However, because results are comparable across the two studies, which used different diagnostic interviews and different types of interviewers (highly trained nonclinician interviewers in NCS-R vs. census workers in NESARC; for NCS-R, see Kessler et al., 2004; for NESARC, see online documentation at <http://www.nesarc.niaaa.nih.gov/>), and because there is evidence suggesting that both interviews have adequate reliability and validity in assessing mood disorders (Grant et al., 2004; Kessler, Akiskal, Angst, et al., 2006), as well as other disorders used in this study (Grant, Hasin, et al., 2005; Grant et al., 2004), we feel that this concern does not significantly compromise the implications of our major findings.

Although inclusion of follow-up data from the NESARC sample is a clear strength of the study, we acknowledge that the follow-up procedures are less than optimal. The single follow-up period of 3 years may be too short to observe recurrence for a disorder that is characterized by cyclicity; it is possible that some of the offsets observed at follow-up are intermorbid periods and not remissions. There are also several concerns regarding the NCS–R sample and protocol. Although the recalibrated diagnostic algorithm used in the NCS–R study results in rates of BP disorders that are more consistent with prior literature and lead to comparable rates in the NESARC study, the more strict requirements of this algorithm may not be the “best” because of conflict with the modal episode lengths described in the literature (J. Angst, Gamma, Sellaro, Lavori, & Zhang, 2003). Further, as described in the Results section, the NCS–R sampling protocol may not have ascertained a representative sample of 18–20-year-olds, only 13% of whom reported being students, compared with 44% in the NESARC baseline sample of 18–20-year-olds.

Although it is clear that our findings show a very strong age gradient in BP spectrum symptomatology, especially Other BP, the degree to which the fundamental nature of BP being assessed in these epidemiological studies is consistent with the prototypical patient seen by clinicians in emergency rooms, outpatient clinics, and inpatient facilities is difficult to determine. In ancillary analyses,¹ we found that those individuals who had sought treatment tended to have more persistent BP diagnoses, indicating that clinicians are likely to see more chronic cases than the much more prevalent cases found in the community. It is well established that epidemiological investigations provide more favorable impressions of the morbidity and course of various psychiatric disorders (Cohen & Cohen, 1984), perhaps in large part because of Berkson’s (1946) bias. Our analyses indicate substantial comorbidity between all forms of BP and other psychiatric conditions, indicating that reports of BP symptomatology occur in the context of other forms of psychopathology and the population-based species of BP identified in these studies are far from benign when active. However, what is unique about the findings here is the evidence for the extent of the dramatic excess during young adulthood and the high tendency toward remission. Clearly, more extensive longitudinal data are needed to resolve long-term course, as well as biological (including genetic), behavioral, and personality measures to establish concordance on endophenotypic indicators of disorder.

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¹To determine whether individuals who reported seeking treatment for manic symptoms were more likely to have a chronic form of bipolar disorder, we used logistic regression to predict offset from a dichotomous indicator of treatment seeking. We included age as a covariate in the model, because treatment seeking is related to age, despite the fact that age is not related to offset (we also tested for a possible interaction between age and treatment-seeking status but removed it from the final model because it was not significant). This supplemental analysis suggests that individuals with bipolar spectrum disorder who sought treatment for manic symptoms, prior to Wave 1, were less likely to offset at Wave 2 (OR = 0.49; 95% CI = 0.35, 0.70) and thus had a more chronic course.

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Figure 1.

Prevalence of past-12-month and lifetime-only Bipolar I, Bipolar II, and Bipolar I and II disorders using original *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994) criteria in the National Epidemiological Survey of Alcohol and Related Conditions (NESARC; National Institute on Alcohol Abuse and Alcoholism, 2001–2005) baseline sample ($N = 43,093$), presented by age group.

Figure 2.

Prevalence of past-12-month bipolar spectrum disorders using the strict criteria from National Comorbidity Survey—Replication (NCS-R; Kessler & Merikangas, 2004) in the NCS-R sample ($N = 9,278$) and the National Epidemiological Survey of Alcohol and Related Conditions (NESARC; National Institute on Alcohol Abuse and Alcoholism, 2001–2005) baseline sample ($N = 43,093$) and follow-up ($N = 34,653$), presented by age group.

Figure 3.

Comparison of prevalence rates across diagnostic algorithms and samples by age group. Includes prevalence of Bipolar I (A) and Bipolar II (B) in National Epidemiological Survey of Alcohol and Related Conditions (NESARC; National Institute on Alcohol Abuse and Alcoholism, 2001–2005) baseline ($N = 43,093$), using original *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994) criteria and using the strict criteria from National Comorbidity Survey—Replication (NCS-R; Kessler & Merikangas, 2004), and prevalence in NCS-R ($N = 9,278$) using strict criteria.

Figure 4.

Odds ratios across bipolar spectrum disorders and age groups using strict National Comorbidity Survey—Replication (Kessler & Merikangas, 2004) criteria in the National Epidemiological Survey of Alcohol and Related Conditions (National Institute on Alcohol Abuse and Alcoholism, 2001–2005) baseline sample ($N = 43,093$) of comorbid childhood conduct disorder (excluding adult ASPD; A, upper panel), lifetime adult antisocial personality disorder (A, lower panel), past-12-month drug use disorder (B, upper panel), past-12-month alcohol use disorder (B, lower panel), and past-12-month anxiety disorder (C). Note that missing odds ratios indicate that the statistic was not able to be estimated because of small cell counts.

Figure 5. Prevalence of past-12-month Other Bipolar disorder using strict criteria from National Comorbidity Survey—Replication (NCS-R; Kessler & Merikangas, 2004) in the NCS-R sample ($N = 9,278$) and the NESARC baseline sample ($N = 43,093$), presented by age group.

Figure 6.

Patterns of remission, stability, and progression among participants with past-12-month Other Bipolar disorder using strict National Comorbidity Survey—Replication (Kessler & Merikangas, 2004) criteria in the National Epidemiological Survey of Alcohol and Related Conditions (NESARC; National Institute on Alcohol Abuse and Alcoholism, 2001–2005) baseline sample (including only those who completed the follow-up; $N = 34,653$), presented by age group, with each bar divided by the diagnosis received at follow-up (3 years later). The percentage of each bar accounted for by a specific follow-up diagnosis is provided on the right-hand side of the bar.