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Effects of Age, Sex, and Independent Life Events on Amygdala and Nucleus Accumbens Volumes in Child Bipolar I Disorder

Barbara Geller, **Michael P. Harms**, **Lei Wang**, **Rebecca Tillman**, **Melissa P. DelBello**, **Kristine Bolhofner**, and **John G. Csernansky**
From the Department of Psychiatry (BG, MPH, LW, RT, KB), Washington University in St. Louis, St. Louis, Missouri; Division of Bipolar Disorder Research (MPD), University of Cincinnati College of Medicine, Cincinnati, Ohio; and the Department of Psychiatry and Behavioral Sciences (JGC), Northwestern University Feinberg School of Medicine, Chicago, Illinois

Abstract

Background—Relationships between environment and cortical-limbic-striatal pathways are not well-researched in child bipolar I disorder (BP-I).

Methods—This was a controlled, blindly rated magnetic resonance imaging study of children with DSM-IV BP-I, manic or mixed type, compared with matched typically developing children (TC).

Results—There were 47 subjects (21 BP-I, 26 TC) aged 14.0 ± 3.1 (BP-I onset age 8.8 ± 4.2). Total intracranial volume was greater in male subjects (n = 28) versus female subjects (n = 19) [$F(1,44)$ = 24.3, p <.001], controlling for age. Volumes were not significantly different in BP-I and TC groups, after accounting for multiple comparisons, in the medial orbital frontal cortex, rostral anterior cingulate cortex, hippocampus, amygdala (AMG), or nucleus accumbens (NAcc). Across subjects (n = 47), a greater number of independent life events (ILE) was associated with smaller AMG [$F(1,36)$ = 7.8, p = .009] and NAcc [$F(1,36)$ = 9.4, p = .004] volumes, controlling for total intracranial volume (TICV), group, age, sex, and family psychopathology. Use of stimulant medication at the time of the scan was associated with larger AMG volume [$F(1,41)$ = 9.0, p = .005], controlling for TICV, group, age, and sex. In male subjects, the age × group interaction was a significant predictor in general linear models of AMG (p = .028) and NAcc (p = .030) volumes. Effects of low maternal warmth were not significant.

Conclusions—Findings suggest that ILE affect AMG and NAcc volume, but further research is needed to examine specificity to child BP-I. Furthermore, differential age × group (child BP-I vs. TC) effects only in male subjects are consistent with differential brain development by sex.

Keywords

Adolescent; bipolar I disorder; child; independent life events; MRI

According to the 2000 U.S. census (1) there are 29,040,538 children ages 7–13 years old. Data from the largest ever National Institutes of Health-funded epidemiology study of bipolar I disorder (BP-I) (2), in which over 43,000 individuals were interviewed, found a 5% prevalence of BP-I in the youngest age group (12–29-year-olds). With these figures, there are an estimated 1,452,027 individuals ages 7–13 with BP-I in the United States. This number is expected to increase, because of data supporting that age of onset of BP-I is decreasing in more recently

Address reprint requests to Barbara Geller, M.D., Department of Psychiatry, Washington University in St. Louis, 660 South Euclid Avenue, St. Louis, MO 63110-1093; E-mail: gellerb@wustl.edu.

born cohorts (3). Even with the caveats of interpreting generational earlier age of onset (the so-called "anticipation" phenomenon) (4) and the lack of community prevalence data under the age of 12, these data forcefully argue for investigating the etiopathogenesis, including environmental effects on neuro-imaging in child BP-I.

However, to our knowledge, familial and environmental influences on cortical-limbic-striatal volumes, in a sample with child BP-I, has not previously been reported. To gain perspective on environmental and genetic factors, both family psychopathology and environmental factors should be examined within the same sample. These are especially cogent questions during childhood, because this is when peak brain growth occurs (5). In addition, recent work suggests a greater influence of environmental versus genetic factors during the early school-age years (6).

Prior work has shown that two measures of environmental adversity, low maternal warmth and greater number of independent life events (ILE), significantly differentiated child bipolar I disorder (BP-I) subjects from typically developing children (TC) (7,8). Recently published data found familial aggregation for child BP-I probands was 7–8 times higher than that for adult BP-I probands (3). Furthermore, even when accounting for familial psychopathology, low maternal warmth (which is akin to expressed emotion) remained a significant predictor of worse course of child BP-I over 8-year follow-up (9,10). On the basis of these findings, it was hypothesized that environmental adversity would affect cortical-limbic-striatal pathways that have been related to mood and substance use disorders (SUD) (11).

None of these magnetic resonance imaging (MRI) findings have been previously published.

Methods and Materials

Subject Ascertainment

Subjects were a subset of participants in the National Institute of Mental Health (NIMH)-funded "Phenomenology and Course of Pediatric Bipolar Disorders" study (10). Subjects with child BP-I were obtained between 1995 and 1998 from designated outpatient child psychiatric and pediatric facilities by consecutive new case ascertainment (12). Subjects in the TC group were obtained through a random survey that matched these subjects to the child BP-I subjects by age, sex, socioeconomic status (SES), ethnicity, and zip code (12).

Inclusion and Exclusion Criteria

Inclusion criteria common to both groups were 7–16 years old, male subjects and female subjects, and good physical health.

At baseline, subjects in the BP-I group had first episode DSM-IV BP-I, mixed or manic phase, for ≥ 2 weeks with at least one cardinal symptom (elation and/or grandiosity). The cardinal symptom criterion avoided diagnosing BP-I only by symptoms that overlapped with attention-deficit/hyperactivity disorder (12). To ensure clinical impairment, a Children's Global Assessment Scale (CGAS) (13) score ≤ 60 was needed (0 is worst, 100 is best, ≤ 60 is clinical impairment) (12). All DSM-IV severity and duration criteria were fulfilled. This child BP-I phenotype has been validated by unique symptoms (12), longitudinal stability (9,10,14), and familial aggregation (3).

At baseline, subjects in the TC group had no current or lifetime DSM-IV diagnoses and a CGAS score ≥ 70 (12).

Exclusion criteria for both groups were IQ < 70, adopted status, pervasive developmental disorders, schizophrenia, epilepsy or other major medical or neurological disorder, and baseline

substance dependency or pregnancy. Subjects who developed substance use disorders (SUD) or became pregnant during prospective follow-up were continued in the study. Subjects in the BP-I group could not exhibit manic symptoms only while receiving antidepressant, stimulant, or other mania-inducing medications. There were no family psychopathology exclusions in either group.

Rationales for the inclusion and exclusion criteria are described in detail elsewhere (12).

Assessment Instruments

Comprehensive assessment by blind research nurses included the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (15), given separately to mothers about their children and to children about themselves. The WASH-U-KSADS is a semi-structured interview with excellent reliability for mania symptoms, mood diagnoses, daily cycling, and time frames (κ values .82 – 1.00) (15). Different raters were used for the parent and child within each family to avoid bias from knowing what one informant reported when assessing the other (16).

The Psychosocial Schedule for School Age Children—Revised (PSS-R) (17) was administered separately to each informant (16). The PSS-R contains comprehensive measures of child interactions with parents, siblings, peers, and teachers and also assesses marital relationships. Measurements of maternal warmth are included in the PSS-R (17). Both continuous and categorical measures of maternal warmth were used in analyses. For the categorical analyses, a score of 1 (mutual concern and affection, close relationship) on maternal warmth indicated high warmth, and scores of 2–5 indicated low warmth (9,10).

The Life Events Checklist (LEC), which is embedded in the PSS-R, was used for assessment of life events. Like the WASH-U-KSADS and the PSS-R, the LEC was administered by experienced research nurses to parents about their children and children about themselves. The LEC consists of 57 items. Each of these items is grouped into one of the following categories: independent of the child (e.g., a parent died), dependent on the child (e.g., failed a school course), or uncertain (e.g., a sibling goes to boarding school, which might or might not be due to the subject's illness). It was previously shown that child BP-I subjects had significantly more independent, dependent, and uncertain life events than TC subjects (8). Although MRI scans were conducted a mean 2.7 years after baseline, the number of ILEs at the baseline assessment were used in the analyses.

MRI Methods

The MRI data were collected by aligning two three-dimensional T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequences (.94 × .94 × 1.5 mm^3 voxels) acquired on a 1.5-T Siemens Sonata scanner (Siemens Medical Solutions, Malvern, Pennsylvania). The MRI exclusions included SUD, loss of consciousness > 5 min, and certain braces, tattoos, and medical/neurological conditions (18). All scans were rated blind to whether subjects were in the BP-I or TC group.

MRI Data Processing

Cortical reconstruction and volumetric segmentation were performed with the imaging analysis suite FreeSurfer (https://surfer.nmr.mgh.harvard.edu). Details regarding the specific automated methods are presented in a series of articles (e.g., 19–22) but are described here in brief. First, variations in image intensities were normalized for each subject's three-dimensional image volume (23). Extra-cerebral voxels were then removed in a "skull-strip" of the brain with a hybrid watershed/surface deformation process (24). Remaining voxels were classified, with intensity and continuity information, into gray and white matter regions (20).

Subcortical white matter and deep gray matter structures were segmented with an automated approach (25,26). When compared with manual raters, this method demonstrated approximately 80% volume overlap for the right and left hippocampus and approximately 70% volume overlap with the left and right amygdala; volume overlap was not reported for the nucleus accumbens (25). The white matter segmentation was split into hemispheres, and the gray-white junction was tessellated. This surface was deformed and inflated outward to locate the approximate pial surface and subsequently refined to obtain a representation of the gray-cerebrospinal fluid boundary. Any geometric inaccuracies or topological defects were corrected with a combination of automatic and manual methods (22,27). Cortical volumes were derived from estimations of volume between the gray-white and pial surface. Parcellation of the cortex into gyral and sulcal structures was obtained through the overlaying of an atlas constructed by Bayesian algorithms, comparisons between this procedure and manual methods yielded intraclass correlations of .83 and .91 for the left and right medial orbital frontal cortices, and .81 and .84 for left and right rostral anterior cingulate cortices (28). Freesurfer morphometric procedures have demonstrated strong test-retest reliability across scanner manufacturers and field strengths (29).

This study was approved by the Human Studies Committee at Washington University in St. Louis. After complete description of the study, written informed consent was obtained from parents and written assent was obtained from children.

Statistical Analyses

Comparisons of demographic data in the BP-I and TC groups were made with *t* tests for continuous variables and χ^2 tests for categorical variables. Left and right region of interest (ROI) measurements were combined. Additional analyses of left and right regions were conducted if analysis of the combined volume was significant. Comparisons between BP-I and TC groups were made for gray matter medial orbital frontal cortex (mOFC), gray matter rostral anterior cingulate cortex (rACC), hippocampus (HC), amygdala (AMG), and nucleus accumbens (NAcc) volumes with general linear models. Comparisons of these brain structure volumes were also made for subjects by level of maternal warmth and by number of ILE. All models controlled for total intracranial volume (TICV), age at MRI scan, and sex. Comparisons of BP-I and TC groups also controlled for CGAS score, and the maternal warmth and ILE analyses also controlled for familial BP-I and/or recurrent major depressive disorder.

Because age at MRI scan varied widely in both the BP-I and TC groups, the interaction of age and group was analyzed in general linear models of ROI volumes that also covaried for age and group.

Significance levels were determined with the Bonferroni method of correcting for multiple comparisons. This resulted in a Bonferroni corrected significance level of $p < .01$ for comparisons of brain structure volumes by group, maternal warmth, ILE, and familial psychopathology.

Results

There were 21 BP-I and 26 TC subjects. Demography and severity characteristics of the two groups are presented in Table 1. At baseline, all BP-I subjects were in their first episode of DSM-IV BP-I, manic or mixed state.

Subjects were scanned a mean 2.7 years after baseline. At the time of scanning, 71.4% of BP-I subjects were in a mood episode. Mood states at the time of the scan were manic or hypomanic (38.1%), depressed (33.3%), and mixed manic (0.0%). No subject had post-traumatic stress

disorder at any rating time. Volumes were not significantly different between subjects with and subjects without a mood diagnosis at the time of the scan.

Subjects were assessed in the research unit, but all clinical care was given by their own community practitioners. At the time of the scan, 11 (52.4%) BP-I subjects were taking at least one psychotropic medication (33.3% stimulant, 28.6% neuroleptic, 23.8% anticonvulsant, 9.5% antidepressant, 0.0% lithium). No TC subjects were taking psychotropic medication. Use of stimulant medication at the time of the scan was associated with larger AMG volume [$F(1,41) = 9.0$, $p = .005$], controlling for TICV, group, age, and sex.

The TICV was significantly greater in male subjects compared with female subjects [$F(1,44) = 24.3$, $p < .001$], controlling for age.

The BP-I subjects had smaller mOFC volume compared with TC subjects [$F(1,41) = 5.7$, $p = .022$]. This difference, however, did not remain after Bonferroni correction. There were no significant differences in rACC, HC, AMG, or NAcc volumes in BP-I compared with TC subjects.

For all subjects ($n = 47$), a greater number of ILE was significantly associated with smaller AMG [$F(1,36) = 7.8$, $p = .009$] and NAcc [$F(1,36) = 9.4$, $p = .004$] volumes, controlling for TICV, group, age, gender, and familial BP-I and/or recurrent major depressive disorder. Separate analysis of left and right AMG showed no significant difference in volumes after Bonferroni correction [left: $F(1,36) = 5.7$, $p = .023$; right: $F(1,36) = 7.0$, $p = .012$]. A greater number of ILE was significantly associated with smaller left NAcc volume [$F(1,36) = 9.2$, $p = .005$] but was not significantly associated with right NAcc volume [$F(1,36) = 2.4$, $p = .128$]. Differences in AMG and NAcc volumes by number of ILE were more pronounced in male subjects (AMG: $p = .073$; NAcc: $p = .020$) compared with female subjects (AMG: $p= .153$; NAcc: $p = .400$), although no differences reached statistical significance, likely due to small sample size.

In the BP-I group (Figure 1), subjects with a greater number of ILE had significantly smaller NAcc volume [$F(1,14) = 11.3$, $p = .005$], controlling for TICV, age, sex, and familial BP-I and/or recurrent major depressive disorder. Separate analysis of left and right NAcc found that a greater number of ILE was significantly associated with smaller left NAcc volume [$F(1,14) = 11.1$, $p = .005$] but was not associated with smaller right NAcc volume [$F(1,14) = 1.9$, $p = .199$]. By contrast, there were no differences in mOFC, rACC, HC, AMG, or NAcc volumes by number of ILE in TC subjects. Of note, BP-I subjects had a significantly greater number of ILE than TC subjects ($t = 3.9$, $p < .001$). The maximum number of ILE in the TC group was 14. When BP-I subjects with >14 ILE were removed from the analysis, there was no longer a significant association between number of ILE and NAcc volume after Bonferroni correction [$F(1,6) = 6.8$, $p = .041$], although this might have been a result of small sample size ($n = 13$).

As shown in Figure 2 and Figure 3, there were significant age × group interactions in models of AMG [$F(1,27) = 5.5$, $p = .028$] and NAcc [$F(1,27) = 5.3$, $p = .030$] volumes in male subjects but not in female subjects. Age × group interactions in models of mOFC, rACC, and HC were not significant.

There were no significant differences in mOFC, rACC, HC, AMG, or NAcc volumes by maternal warmth.

All analyses detailed in the preceding text were also conducted on a subset of subjects that were matched by sex. The matched group consisted of $n = 20$ BP-I and $n = 20$ TC subjects, each group with 11 male subjects and 9 female subjects. Results of all analyses on this matched subset were consistent with the findings for the whole sample, with the following exceptions.

In the matched group, stimulant use was significantly associated with greater NAcc volume [$F(1,34) = 8.3$, $p = .007$], and the age × group interactions in the general linear models of AMG [$F(1,35) = 3.0$, $p = .092$] and NAcc [$F(1,35) = 3.0$, $p = .092$] volumes were not significant.

Discussion

These data, supporting environmental influences on limbic areas, are consistent with the significant effect of another environmental factor, low maternal warmth, on relapse rates in child BP-I, even when controlling for family psychopathology (9,10). Given the known high familial aggregation in relatives of child BP-I probands (3), these ILE data emphasize the need for examining gene–environment interactions in child BP-I populations. Furthermore, investigation of relationships among ILE, NAcc volume, and onset of SUD is warranted, given the high rate of SUD in child BP-I samples (10) and the significance of early adolescent environmental factors on later SUD (30).

Various volumetric differences between BP-I and TC have been reported for prepubertal and adolescent onset BP (31–38). Speculations on reasons for these differences across samples include sample size and MRI methods. In addition, different diagnostic methods and socioeconomic background might influence phenotypic and morphometric presentations. Given the relationship of AMG activation to fear, future studies of frightening ILE on AMG volume would be informative (39).

Sexually dimorphic findings presented in Figure 2 and Figure 3 are consistent with data on sex differences in normative developmental trajectories across this age group (5,40–43).

The increased NAcc volume in the matched sample in subjects receiving stimulants is consistent with an increase in NAcc volume for methamphetamine users (44).

There are, to our knowledge, no prior studies of the relationship between environmental adversity and MRI in child BP-I for comparison.

The meaning of volumetric differences between child BP-I and TC is not discernible from this study. But, these findings might inform avenues of future research.

Limitations include relatively small sample size and lack of a control group with a non-mood diagnosis, such as schizophrenia or conduct disorder, to examine specificity. In addition, at the time of scanning, this study was underpowered to fully examine medication exposures and variable mood states. Finally, manual tracing was not performed.

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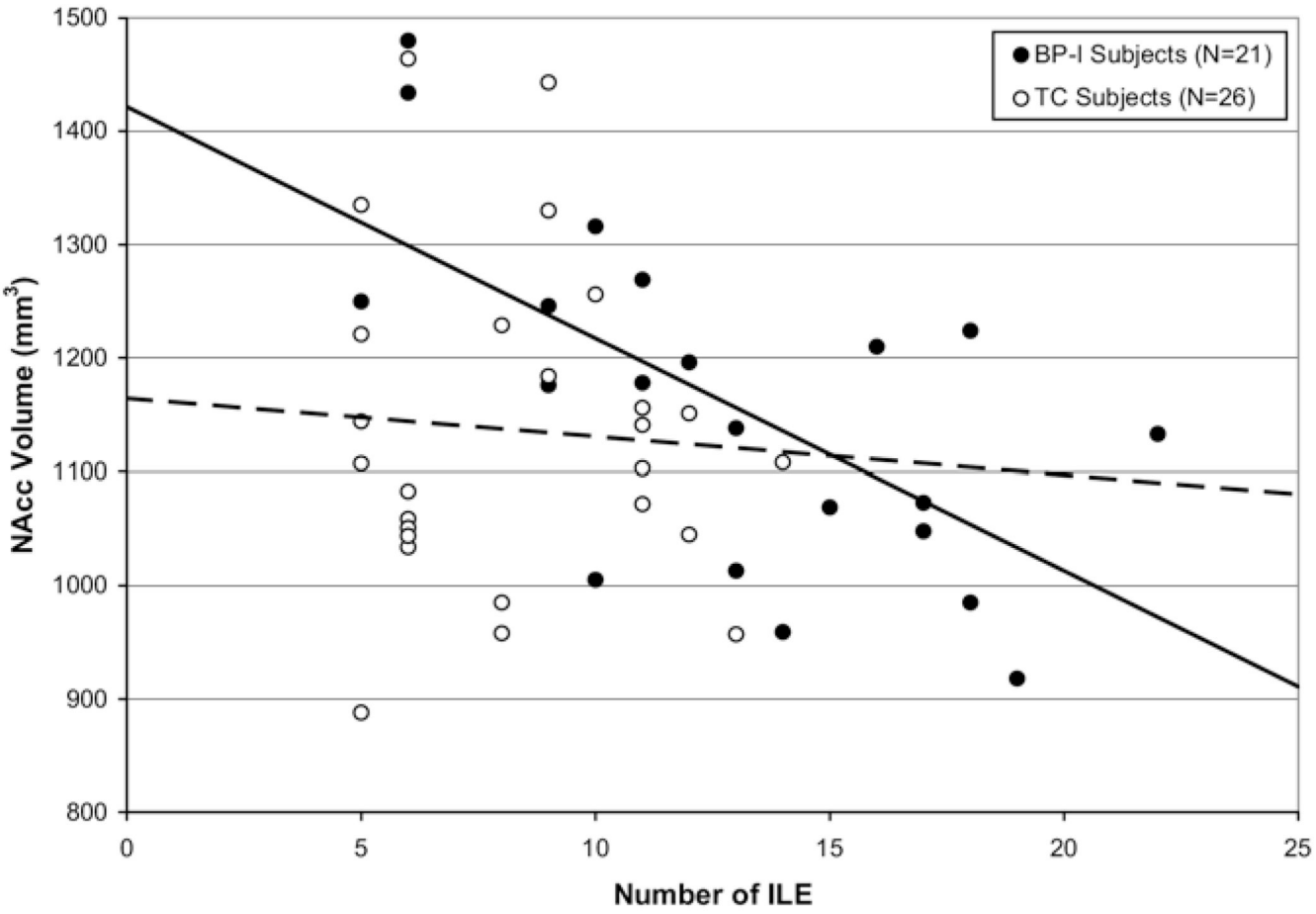

Figure 1.

Nucleus accumbens (NAcc) volumes by number of independent life events (ILE) in bipolar I disorder (BP-I) and typically developing control (TC) subjects. The solid line illustrates the relationship between number of ILE and NAcc volume in BP-I subjects, whereas the dashed line illustrates the relationship between number of ILE and NAcc volume in TC subjects. The BP-I subjects with a greater number of ILE had significantly smaller NAcc volume [$F(1,14) = 11.3$, $p = .005$], controlling for total intracranial volume, age, sex, and familial BP-I and/or recurrent major depressive disorder. The NAcc volume did not differ in TC subjects by number of ILE [$F(1,17) = .6$, $p = .45$].

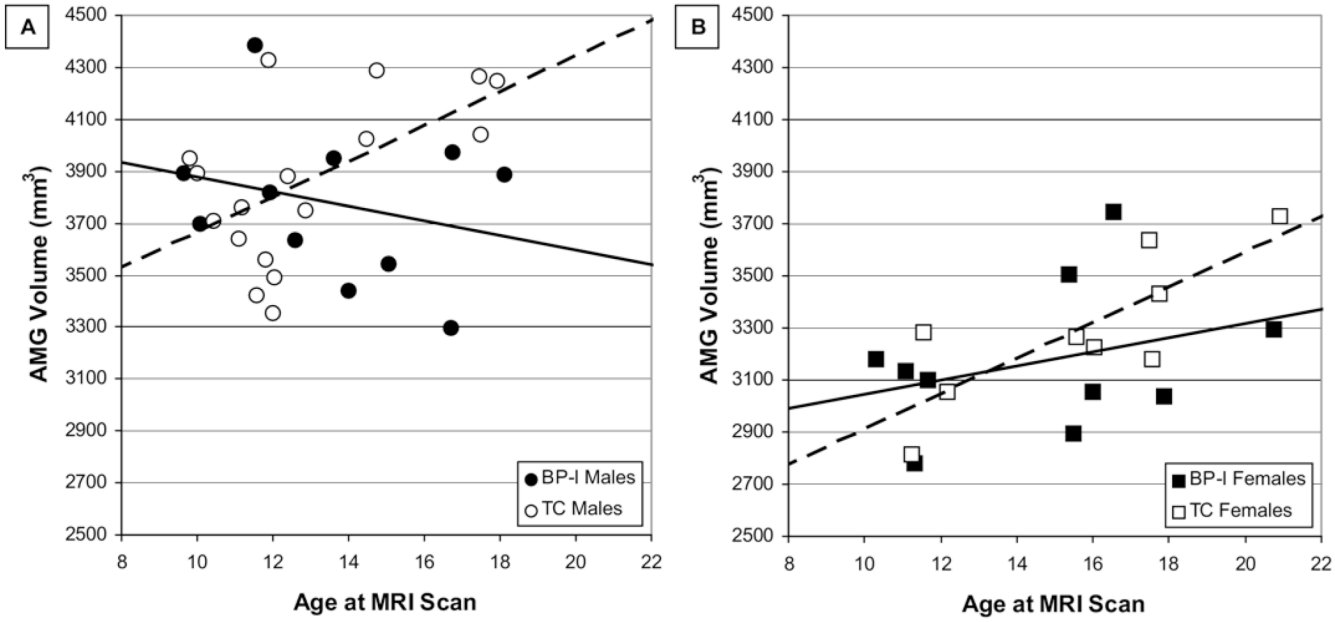

Figure 2.

Amygdala (AMG) volume by age and sex in bipolar I disorder (BP-I) and typically developing control (TC) subjects. **(A)** The solid line illustrates the relationship between age and AMG volume in male BP-I subjects, whereas the dashed line illustrates the relationship between age and AMG in male TC subjects. Significant predictors in a general linear model of AMG volume in male subjects were group ($p = .046$) and the age × group interaction ($p = .028$). **(B)** The solid line illustrates the relationship between age and AMG volume in female BP-I subjects, whereas the dashed line illustrates the relationship between age and AMG in female TC subjects. Age was a significant predictor in a general linear model of AMG volume in female subjects ($p = .016$). MRI, magnetic resonance imaging.

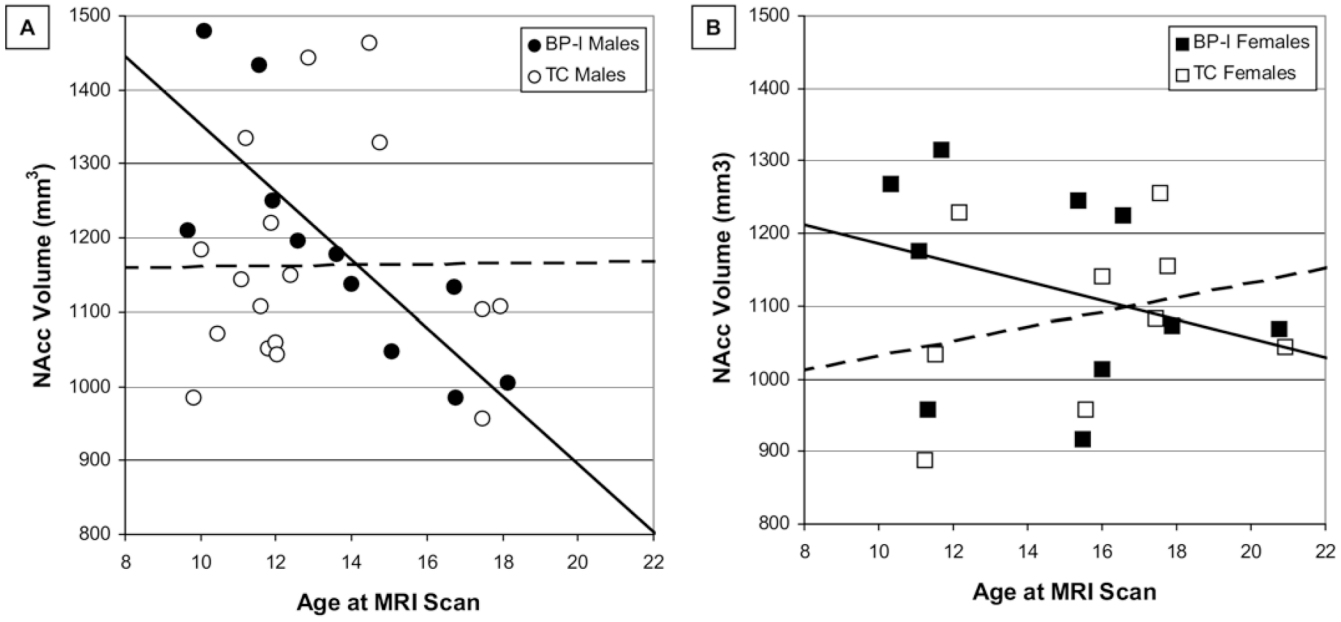

Figure 3.

Nucleus accumbens (NAcc) volume by age and sex in BP-I and TC subjects. **(A)** The solid line illustrates the relationship between age and NAcc volume in male BP-I subjects, whereas the dashed line illustrates the relationship between age and NAcc volume in male TC subjects. Significant predictors in a general linear model of NAcc volume in male subjects were age ($p = .034$), group ($p = .025$), and the age × group interaction ($p = .030$). **(B)** The solid line illustrates the relationship between age and NAcc volume in female BP-I subjects, whereas the dashed line illustrates the relationship between age and NAcc volume in female TC subjects. There were no significant predictors of NAcc volume in a general linear model that included age, group, and the age × group interaction. Abbreviations as in Figure 1 and Figure 2.

Table 1

Demography and Severity Characteristics in BP-I Versus TC Subjects

	BP-I (*n* = 21)		TC (*n* = 26)			
	Mean	**SD**	**Mean**	**SD**	***t***	***p***
Age at MRI Scan (yrs)	14.1	3.1	13.8	3.1	.3	NS
Age at Baseline (yrs)	11.3	3.2	11.3	2.8	.1	NS
Age of Mania Onset (yrs)	8.8	4.2	—	—	—	—
Duration of Baseline Mania Episode (yrs)	2.5	1.8	—	—	—	—
CGAS at MRI Scan	56.8	17.5	88.9	8.9	7.7	<.001[a]
	%	*n*	%	*n*	χ^2	*p*
Sex						
Male	52.4	11	65.4	17	.8	NS
Female	47.6	10	34.6	9		
Handedness						
Right	81.0	17	76.9	20	F.E.	NS
Left	19.0	4	23.1	6		
Race						
Caucasian	81.0	17	92.4	24	1.3	NS
African-American	9.5	2	3.8	1		
Other	9.5	2	3.8	1		

BP-I, bipolar I disorder; TC, typically developing control; MRI, magnetic resonance imaging; CGAS, Children's Global Assessment Scale; F.E., Fisher's Exact test.

[a]Severity was included as a covariate in analyses comparing BP-I and TC groups.