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Neuroprogressive effects of lifetime illness duration in older adults with bipolar disorder

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Abstract

Objective—The aim of the present study was to examine the long-term effects of bipolar disorder (BD) on brain structure (gray matter volumes).

Methods—Fifty-four adults with BD [mean (standard deviation) age = 64.4 (5.4) years] underwent brain MR imaging along with comprehensive clinical assessment. Total gray matter, hippocampal, and amygdala volumes were extracted using methods developed through the Geriatric Neuroimaging Laboratory at the University of Pittsburgh (Pittsburgh, PA, USA).

Results—Lower total gray matter volumes were related to longer duration of BD, even when controlling for current age and cerebrovascular accident (CVA) risk/burden. Additionally, longer exposure to antipsychotic medication was related to lower gray matter volumes. Lower hippocampal volumes were related to total years of antipsychotic agent exposure and CVA risk/burden scores. Older age was related to lower total gray matter, hippocampal, and amygdala volumes.

Conclusions—Our study of older adults with BD supports the understanding that BD is a neuroprogressive disorder with a longer duration of illness and more antipsychotic agent exposure related to lower gray matter volume.

Keywords

amygdala; bipolar disorder; brain; hippocampus; lithium; neuroimaging; neuroprogression

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Disclosures

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Bipolar disorder (BD) is a leading cause of worldwide disability (1). It is now conceptualized as a multi-system disorder that is chronic and progressive (2, 3). Studies have suggested neuroprogressive processes affecting brain health (4), such as dysregulated dopaminergic and glutamatergic systems, mitochondrial dysfunction and oxidative stress, and inflammation (5). We use the term *neuroprogressive* rather than *neurodegenerative* to distinguish the cognitive and brain changes related to BD from disorders such as Alzheimer's disease or Huntington's disease (6). These neuroprogressive findings have been identified in a comprehensive meta-analytic review of the structural neuroimaging literature that supports this conceptualization (7). Kempton and colleagues (7) identified neurostructural abnormalities consisting of increased lateral ventricle volume and increased burden of deep white matter hyperintensities in mixed-aged adults with BD. While lateral ventricle size could be a result of diffuse or focal gray/white matter reduction, their review did not find a relationship between ventricular enlargement and illness duration, suggesting that the ventricular enlargement may show up near the beginning of illness.

Studying older adults with BD would help identify the neuroprogressive changes that occur over longstanding illness. However, relatively few studies have focused on this segment of the BD population with neuroimaging.

- Delaloye and colleagues found impairments in cognitive function (primarily in processing speed and working and episodic memory) in older adults with BD (n = 15) mean (SD) age 67.9 (5.1) years old when compared to similarly aged controls (n = 15), yet they did not find evidence of volumetric or white matter differences between the groups at baseline or significant changes over two year follow-up (8, 9).
- Beyer and colleagues identified gray matter volume deficits in the inferior frontal lobe in BD (n = 36) mean (SD) age 58.2 (7.8) years compared with similarly aged mentally healthy comparators (n = 29) (10). Although they did not find any differences in total gray or white matter volumes between BD and comparators, they did find increased hippocampal volume associated with use of lithium. In a related analysis, using a similar set of older adults with BD with mean (SD) illness duration of 15.9 (16.5) years, they found that onset of BD after age 45 was associated with lower total gray matter volumes (11).
- Tamashiro and colleagues reported that relative to elderly controls and early-onset BD, late-onset BD subjects have increased hyperintense lesions on T2 images around the putamen, as well as in the deep white matter in frontal and parietal regions (12). Haller and colleagues performed an MRI study of elderly euthymic patients with BD (n = 19) mean age 68.5 (5.8) years along with 47 controls, mean age 69.7 (6.5) years and found presence of gray matter concentration decreases in the anterior limbic areas and reduced fiber tract coherence in the corpus callosum in patients with long-standing BD. Further, they found a trend relating longer illness duration to decreases in fractional anisotropy (FA). FA is an indicator of the myelination and coherence of white matter tracts (higher FA is better) (13).

- Most recently, using high resolution MRI, Wijeratne and colleagues compared hippocampal and amygdala volumes in 18 euthymic patients with BD I (mean [SD] age 57 years [9.9]) with 21 mentally healthy comparators (age 60.6 [8.5] years) and found that smaller hippocampal and amygdala volumes. Additionally, while amygdala volumes were not associated with duration of mood episodes, hippocampal volume was related (14).

Taken together these reports present a heterogeneous group of findings, suggesting that later onset of BD is associated with neuroimaging abnormalities consisting of increased WMHs burden along with generalized and regional atrophy, as well as suggesting longer illness duration related to lower brain integrity and possibly neuroprogression.

While there appear to be factors intrinsic to BD that are related to cognitive deterioration beyond normal aging effects, some of the cognitive deterioration may be offset by psychotropic medications commonly employed to treat BD (15, 16). Lithium, in particular, is related to upregulation of various neurotrophic factors, including BDNF and Bcl-2, which may enhance brain health and long-term cognitive function, as well as decreasing oxidative stress (5, 16–18). Additionally, lithium inhibits glycogen synthase kinase-3 (isoforms α and β), an enzyme critically involved in regulating neuronal myelination (19). Hence, on a long-term basis, patients may benefit not just from enhanced mood stability, but also from its impact on brain health. Studies have shown increased hippocampal and amygdala volumes in patients with BD treated with lithium compared to those not treated with it (7, 20–24).

Some of the brain benefits of lithium are not unique. Other psychotropic agents appear to have similar or overlapping biological effects (16). On the other hand, evidence also suggests detrimental effects *not borne by lithium* of some of these agents. Antipsychotic treatment can induce hyperglycemia, weight gain, and the metabolic syndrome (25), which are known risk factors for cognitive dysfunction and brain abnormalities (26).

To further investigate whether BD is a neuroprogressive disorder, we examined correlates of brain structure (total gray matter, hippocampal, and amygdala volumes) in a carefully characterized group of older Taiwanese adults with BD. The goal of these analyses was to examine whether clinical factors were related to overall measures of brain structure – in particular, standardized measures of total gray matter. Our primary hypothesis was that a longer duration of bipolar illness, controlling for current age, would be associated with decreased total gray matter, suggesting neuroprogression. Exploratory aims were to examine the putative neuroprotective effects of lithium treatment in relation to total gray matter, hippocampal, and amygdala volumes, as well as examine the effects of antipsychotic agent exposure. We chose to focus on the hippocampus and amygdala rather than other structures because of the literature supporting enlarged hippocampal and amygdala volumes related to long-term lithium treatment.

Methods

Subjects

Individuals were enrolled from Taipei Medical University Hospital (TMUH) and Taipei City Psychiatric Center (TCPC), Taiwan. Utilizing the computer data files of the two hospitals, we recruited those outpatients meeting the following criteria as potential subjects: (i) aged 60 years, (ii) having at least one psychiatric admission to TCPC or TMUH prior to the start of the study, and (iii) having a final diagnosis of bipolar I disorder (DSM-IV). The exclusion criteria were: (i) meeting criteria for any type of dementia (DSM-IV), (ii) mental disorders associated with general medical conditions, (iii) active substance abuse, or (iv) the inability to undergo brain imaging.

A total of 82 potential subjects gave written informed consent and received cognitive examination, along with a personal interview if they achieved symptomatic remission. Of these potential subjects, 28 were excluded due to the exclusion criteria and 54 went on to participate in the study. Two of the board-certified experienced psychiatrists involved in the present study interviewed participants and their reliable companions (mostly family members) using the Chinese version of the Structured Clinical Interview for the DSM-IV–patient edition to confirm the diagnosis of bipolar I disorder as well as any prior history of psychiatric disorders. The Institutional Review Board of TMUH and participating hospitals approved this protocol. Clinical data were obtained through a review of the medical records as well as the direct interviews with patients and their reliable companions. A cerebrovascular accident (CVA) risk/burden score (range: 0–7) was determined from a review by the authors of all consensus Axis III diagnoses, with each following the diagnoses receiving a score of one point: hypertension, diabetes, peripheral vascular disease, coronary artery disease, a history of transient ischemic attack or stroke, atrial fibrillation, and carotid bruit. We employed the same technique as previously described by our research group (27).

The psychotropic medication exposure for each patient was determined on an annual basis, from the year of the introduction until the year of the end of the observation period, based on medical record information and patient report. Lithium and antipsychotic medication exposure was quantified using a case-note form that has been in use at TMUH and TCPC since 1980. This form contains over 95 items structured to obtain information regarding patients admitted to TCPC or TMUH, including demographic data, clinical features, physical illness, and family history. All medical records were reviewed and all data were subsequently rechecked to rule out any potential individual errors. Demographic and clinical information were obtained from a review of the patients' medical records and direct interview with the participants and their reliable companions alike.

Neuroimaging

Brain images were obtained from each subject using the 1.5 T MR scanner (Signa contour, GE-Yokogawa Medical Systems, Tokyo, Japan) with three different pulse sequences: 124 contiguous, 1.2-mm thick axial planes of three dimensional T1-weighted images [spoiled gradient recalled acquisition in steady state: repetition time (TR) = 40 msec, echo time (TE) = 7 msec, flip angle = 90°, voxel size = 0.86 mm × 0.86 mm × 1.2 mm]; 58 contiguous, 3-

mm thick axial planes of proton density (PD) images spin echo (SE): TR = 2,860 msec, TE = 15 msec, voxel size = 0.86 mm × 0.86 mm × 3 mm); and 58 contiguous, 3-mm thick axial planes of T2-weighted images (SE: TR = 2,860 msec, TE = 120 msec, voxel size = 0.86 mm × 0.86 mm × 3 mm). Prior to further computational procedures, all MR images were converted into the ANALYZE format using MRIcro software. Imaging was then processed in the Geriatric Psychiatry Neuroimaging Laboratory (GPN, www.gpn.pitt.edu) under the supervision of one of the authors (HJA).

Automatic labeling pathway

To determine regional gray and white brain volumes, HJA and colleagues developed a procedure referred to as automatic labeling pathway (ALP). The pathway combines a series of publicly available software packages (AFNI, BET, FLIRT, and ITK), as well as some of the laboratory's custom-designed programs, to implement atlas-based segmentation of MR images. Using ALP, anatomic regions of interest (ROIs) defined on the reference brain (Montreal Neurological Institute, colin27) (28) are transformed to fit each individual's anatomic image, which are then segmented into gray, white, and cerebrospinal fluid tissue types. The anatomic ROIs are from the automated anatomical labeling atlas (90 manually traced regions) (29), the Brodmann atlas (82 regions, included with the MRIcro software package) (30), as well as from locally generated regions defined from functional MR imaging studies (31) and manual tracing (32). After registration of the template to the individual subject space, the ROIs from the template are applied to label regions on the subject's MR images. The number of gray and white voxels in each of these regions is then counted to produce a table of ROI volumes for each region and each subject. All volumes are corrected for intracranial volume to standardize the results across subjects.

Statistical analysis

Descriptive statistics were generated to characterize the BD sample on basic demographics and clinical variables, using means, SDs, medians, and ranges for continuous variables, and n (%) for categorical variables. Prior to analyses, distributions were examined and transformations were used if necessary. Pearson correlations were used to examine relationships of demographics and clinical variables with total gray matter, hippocampal, and amygdala volumes. Forward stepwise multiple linear regression models were examined. Prior to running the regressions, correlation among predictor variables were examined to identify multicollinearity issues. Any variables that were strongly correlated with other predictors, but not correlated with any of the outcomes, were dropped from consideration for the regressions. Regression models were repeated using the backward stepwise method to examine the stability of the models. As both methods gave identical results, the forward method is reported. Due to the exploratory nature of these analyses, we did not correct for multiple comparisons.

Results

Demographic and clinical data are presented in Table 1. Similar to other Western studies with older adult samples with BD, there were more female than male subjects (n = 39; 72%), with a comparable age at onset; however, given the mean of 10 years of education and the

reported high rates of overweight and obesity (2, 3), body mass index (BMI) and educational level were relatively low.

As expected, age at study interview was significantly correlated with total gray matter, hippocampal, and amygdala volumes ($p < 0.05$). Additionally, lifetime duration of BD and total years of antipsychotic agent exposure significantly correlated with total gray matter (Table 2). Due to multicollinearity among potential predictors, we removed years of lithium exposure, years of education, and BMI from the analyses because they were not correlated with any of the outcomes, but highly correlated with years of antipsychotic agent use (years of lithium exposure, BMI) or gender (years of education). We also removed age at first hypomanic or depressive episode because it was used to calculate lifetime duration of BD. In the multiple linear regression, we considered age, gender, duration of BD, years of antipsychotic agent exposure, and CVA risk/burden scores as predictors. We found that older age, longer lifetime duration of BD, higher total years of antipsychotic agent exposure (natural logarithm), and higher CVA risk/burden scores were all related to lower total gray matter (Table 3). When examining hippocampal volumes, lifetime duration of BD was not related to volume, although more years of antipsychotic agent use and higher CVA risk/burden scores were significantly related (Table 4). We found that only age remained significant for amygdala volumes (Table 5).

Discussion

In the present analysis of neuroimaging data in older adults with BD from Taiwan, we found correlational support for neuroprogression in older adults with BD. Longer lifetime illness duration was related to lower total gray matter, even when controlling for current age. Additional factors related to lower total gray matter included years of antipsychotic exposure and CVA risk/burden scores. Lower hippocampal volumes were related to total years of antipsychotic agent exposure and CVA risk/burden scores. We did not find clear evidence for a neuroprotective effect of lithium on total gray or hippocampal volumes. In relation to amygdala volumes, we found no effect of lifetime duration of illness, lithium, or antipsychotic agent exposure. The only significant effect for the amygdala was age, along with a trend-level effect for CVA risk/burden scores.

While our report is consistent with the current conceptualization of the chronic and progressive nature of BD, some limitations should be considered. First, our sample was of moderate size, underpowered to examine the neuroprotective effects of lithium or differences between early and late onset. Second, we employed cross-sectional analyses to address a question that is fundamentally longitudinal. Third, recall bias is more common in patients who are interviewed at a later age, which could have led to an underestimate of lifetime illness duration and length of psychotropic treatment, prior to study entry. Fourth, the CVA risk/burden score was not independently validated. Lastly, we did not have fluid-attenuated (flair) sequences to examine white matter hyperintensity burden or microstructural abnormalities using diffusion tensor imaging.

In spite of the limitations raised above, our analyses suggest that BD is not simply a *functional* disorder, but that the long-term effects involve progressive damage to the brain.

Research has recently focused on the neurotrophic and neuroprotective effects of lithium and other psychotropic agents (16). A compelling array of studies support that lithium, in particular, is neurotrophic and neuroprotective (15). Thus, some of the intrinsic damaging effects of BD may be offset by long-term treatment with lithium. By contrast, lower gray matter volumes have been shown with antipsychotic agent exposure in individuals with schizophrenia (33), and whether lower total gray matter is detrimental in schizophrenia remains a matter of debate (34, 35).

In summary, studying older adults with BD can clarify the long-term effects of having BD and the impact of medications. In particular, we can examine whether treatment with one medication versus another (lithium or divalproex versus atypical agents) is better in relation to brain health over the long term. Consequently, studying older adults with BD can inform treatment choices in younger and middle-aged adults. At the same time, we argue strongly for the necessity of conducting longitudinal studies examining neuroprogression that is combined with biomarker measurement of inflammation, oxidative stress, and other neuroprogressive pathways. In addition to the findings summarized above, our findings also argue for the value of conducting research in older adults with BD, who, until recently, have been a relatively neglected and under-studied segment of this population (36).

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Table 1

Demographic and clinical characteristics of 54 older adults with bipolar I disorder

Variable	N	Mean or %	SD	Minimum	Median	Maximum
Age at study interview, years	54	64.4	5.4	53.0	63.5	79.0
Gender, female	39	72.2	–	–	–	–
Education, years	53	7.0	5.1	0.0	6.0	16.0
BMI at study interview	46	26.5	3.9	17.6	26.9	33.5
BD lifetime onset	54	40.6	13.4	19.0	41.5	69.0
Minimum age of first mood episode, years	54	40.1	13.2	19.0	40.5	69.0
Lifetime duration of BD, years	54	24.3	13.4	0.0	25.5	48.0
Lifetime lithium use, years	54	4.6	6.1	0.0	1.5	23.0
Lifetime antipsychotic agent use, years	52	5.0	6.4	0.0	2.0	25.0
Number taking conventional antipsychotic agents	21	38.9	–	–	–	–
Number taking atypical antipsychotic agents	3	5.6	–	–	–	–
Total gray matter (standardized $\times 100$)	54	27.2	2.5	17.6	27.3	33.0
Hippocampal size (standardized $\times 100$)	54	0.5	0.1	0.3	0.5	0.7
CVA risk/burden scores	53	0.8	0.8	0.0	1.0	3.0

BD = bipolar disorder; BMI = body mass index; CVA = cerebrovascular accident; SD = standard deviation.

Table 2
Correlations of demographic and clinical variables with total gray and hippocampal volumes in 54 older adults with bipolar I disorder

Demographic and clinical variables	N	Gray		Hippocampal		Amygdala	
		PCC	p-value	PCC	p-value	PCC	p-value
Age at study interview, years	54	-0.43	0.001	-0.35	0.01	-0.29	0.03
Gender, male	54	-0.06	0.69	-0.13	0.35	0.05	0.69
Education, years	53	-0.07	0.63	0.07	0.62	-0.01	0.89
BMI at study interview	46	0.17	0.25	-0.04	0.79	0.06	0.66
Minimum age at first hypomanic, manic, or depressive episode	54	0.23	0.10	0.03	0.81	-0.004	0.97
Lifetime duration of bipolar disorder	54	-0.40	0.003	-0.17	0.21	-0.11	0.41
Lithium exposure ^a	54	-0.14	0.32	0.11	0.43	0.01	0.89
Antipsychotic agent exposure ^b	52	-0.30	0.03	-0.20	0.15	-0.02	0.85
CVA risk/burden scores	53	-0.19	0.18	-0.25	0.07	-0.26	0.055

BMI = body mass index; CVA = cerebrovascular accident; PCC = Pearson's correlation coefficient.

^aLN (total years of lithium in lifetime + 1).

^bLN (total years of antipsychotic agents in lifetime + 1).

Table 3
Regression model examining factors related to total gray matter volumes in 54 older adults with bipolar I disorder

Label	df	Parameter estimate	SE	t-value	Pr > t	Standardized estimate	Stepwise model R ²
Intercept	1	42.46	3.49	12.16	<0.001	0.00	
Lifetime duration of BD, years	1	-0.06	0.02	-2.37	0.02	-0.29	0.20
Age at study interview, years	1	-0.20	0.05	-3.60	<0.001	-0.41	0.34
Antipsychotic agent exposure ^a	1	-0.67	0.29	-2.28	0.03	-0.28	0.38
CVA risk/burden	1	-0.70	0.34	-2.04	0.05	-0.23	0.44

Model: $F(4,46) = 8.88$, $p < 0.001$, $R^2 = 0.44$. BD = bipolar disorder; CVA = cerebrovascular accident; df = degrees of freedom; SE = standard error.

^aLN (total years of antipsychotic agents in lifetime + 1).

Table 4

Regression model examining hippocampal volumes in 54 older adults with bipolar I disorder

Label	df	Parameter estimate	SE	t-value	Pr > t	Standardized estimate	Stepwise model R^2
Intercept	1	0.84	0.10	8.14	< 0.001	0.00	
Age at study interview, years	1	-0.01	0.002	-2.92	0.005	-0.37	0.12
Antipsychotic agent exposure ^a	1	-0.02	0.01	-2.15	0.04	-0.28	0.17
CVA risk/burden	1	-0.02	0.01	-2.13	0.04	-0.28	0.25

Model: $F(3,47) = 5.11$, $p < 0.004$, $R^2 = 0.25$. CVA = cerebrovascular accident; df = degrees of freedom; SE = standard error.

^aLN (total years of antipsychotic agents in lifetime + 1).

Table 5

Regression model examining amygdala volumes in 54 older adults with bipolar I disorder

Label	df	Parameter estimate	SE	t-value	Pr > t	Standardized estimate
Intercept	1	0.23	0.03	7.70	<0.0001	0
Age at study interview, years	1	-0.001	0.001	-2.23	0.03	-0.30

Model: $F(1,52) = 4.97$, $p = 0.03$, $R^2 = 0.09$, $df = \text{degrees of freedom}$; SE = standard error.