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Neuroimaging and neurocognitive abnormalities associated with bipolar disorder in old age

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Abstract

Objectives—Cognitive dysfunction is prevalent in older adults with bipolar disorder (BD). High white matter hyperintensity (WMH) burden, a marker of white matter disease, detected on T2/fluid-attenuated inversion recovery brain magnetic resonance imaging (MRI) has been consistently reported in BD across all age ranges, including older adults. Yet, whether high WMH burden is related to the excess cognitive impairment present in older adults with BD is unknown. Therefore, we examine whether higher WMH burden is related to worse cognitive function in older adults with BD.

Methods—This is a cross-sectional study of 27 non-demented BD patients aged ≥50 years and 12 similarly aged mentally healthy comparators (controls). Subjects underwent both brain MRI and comprehensive neurocognitive assessment. We employed correlational analyses to evaluate the burden of WMH and the relationship between WMH and cognitive function.

Results—Although BD subjects had worse performance in all cognitive domains, BD subjects had less total WMH burden (t[13.4] = −3.57, p = 0.003). In control subjects, higher WMH was related to lower global cognitive function (ρ= −0.57, n= 12, p = 0.05). However, WMH did not correlate with neuropsychological performance in BD subjects. Further, BD and control subjects did not differ with respect to total gray and hippocampal volumes.

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Conflicts of interest: The following disclosures within the past 5 years are reported in connection with the manuscript:

1. Dr. Butters has received payment from the Northstar Neuroscience and Medtronic for providing NP assessment services to clinical trials and from Fox Learning Systems (via National Institutes of Health [NIH]-funded Small Business Innovation Research) for computerized test development. She is currently a consultant for GlaxoSmithKline, for whom she is interpreting the results of NP evaluations.
2. Dr. Gildengers has received research support from GlaxoSmithKline for an investigator-initiated study.
3. Dr. Mulsant has received research support in the form of pharmaceutical supplies for his NIH-sponsored research from Bristol-Myers Squibb, Eli Lilly and Company, Pfizer, and Wyeth.
4. Dr. Reynolds has received research support in the form of pharmaceutical supplies for his NIH-sponsored research from Bristol-Myers Squibb, Eli Lilly and Company, Forest, and Pfizer,
5. All other authors report no financial relationships with commercial interests.

Conclusions—Cognitive dysfunction in late-life BD does not appear to be due primarily to processes related to increased WMH or reduced gray matter volume. Future longitudinal studies should examine other potential neuroprogressive pathways such as inflammation, mitochondrial dysfunction, serum anticholinergic burden, and altered neurogenesis.

Keywords

bipolar disorder; cognition; aging; neuroimaging

Introduction

Bipolar disorder (BD) is an important cause of disability (Mathers et al. 2006). In older adults with BD, the disability experienced may largely be related to cognitive deficits that accumulated prior to old age (Gildengers et al. 2012). Cognitive dysfunction in older BD patients appears to involve multiple pathologic processes, including glutamatergic, dopaminergic, inflammatory, and oxidative stress that are inherent to BD (Berk et al. 2011). These various processes may act synergistically with the high rates of concurrent metabolic syndrome, cardiovascular disease, and other general medical problems highly comorbid with BD (Young *et al.* 2004; Gildengers *et al.*, 2008), worsening neuroprogression (Berk *et al.* 2011). We use the term *neuroprogression* rather than *neurodegeneration* to distinguish the cognitive and brain changes related to BD from disorders such as Alzheimer's disease or Huntington's disease (Andreasen 2010).

Geriatric BD patients are a unique population to study the *long-term* consequences of neuroprogression and their effect on cognitive function (Delaloye *et al.* 2011; Gildengers *et al.* 2012). Understanding the factors that lead to better (or worse) cognitive function in older age has important implications for the clinical management of cognitive dysfunction in patients with BD across the life span.

Emerging evidence suggests that cognitive deficits among older adults may also be moderated by cerebral vascular disease, as measured by white matter hyperintensity (WMH) burden detected on T2/fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). Greater WMH burden has been identified in children and adolescents with BD, suggesting that they may result from neuropathologic processes associated with BD itself (Beyer *et al.*, 2009). The WMHs appear to represent dilated perivascular spaces and oligemic or ischemic demyelination (Thomas *et al.* 2002). These abnormalities are not specific to BD and have been identified in other psychiatric disorders (e.g., schizophrenia and depression) and general medical illness (e.g., hypertension) (Kempton *et al.* 2008). Recently, regional parietal WMHs were found to be associated with increased incidence rates of Alzheimer's disease among community-dwelling older adults (Brickman *et al.* 2012). Similarly, a recent meta-analysis of structural imaging studies found that patients with BD had more WMHs than control subjects (Kempton *et al.* 2008). The WMH burden appears to be higher in late-onset BD patients than in those with early onset (Tamashiro *et al.* 2008), but it is unclear whether cere-brovascular pathology is a cause or a consequence of late-onset BD. Other studies have found that white matter tract coherence was reduced in BD patients (Haller *et al.* 2011). The BD patients appear to have white matter abnormalities in tracts connecting to the prefrontal cortex, such as the anterior thalamic radiation and uncinate fasciculus (Lin *et al.* 2011). These regions are highly involved in visuospatial ability, information processing, and executive dysfunction. A previous study by our group found that the association between vascular disease burden and both executive dysfunction and decreased information processing speed approached significance (Gildengers *et al.* 2007).

Other aspects of structural brain abnormalities in late-life BD are either unclear or have not been examined. Two studies have demonstrated that older adults with BD have lower total gray and hippocampal volumes than the control subjects (Beyer *et al.* 2004; Beyer *et al.*, 2009), although one study did not find this result (Delaloye *et al.* 2009). Exposure to mood stabilizing medications, such as lithium and valproate, has been found to be neurotrophic and neuroprotective in adults (Schloesser *et al.* 2012), yet, the use of higher doses has also been associated with cognitive deficits in older adults, especially on tasks involving executive function (Forester *et al.* 2009). The relationship between gray matter volume, cognitive function, and the medications used in late-life BD has not been well studied.

On the basis of the existing literature, our primary hypothesis was that in euthymic older adults with BD, higher WMH burden would be independently associated with worse performance on global and domain-specific cognitive abilities. In addition to the primary hypothesis, we had exploratory hypotheses regarding BD, cognitive function, and neuroimaging markers. First, we sought to determine whether BD patients had elevated WMH burden in tracts associated with the prefrontal cortex and whether WMH burden in this region was associated with worse cognitive function. Second, we wanted to assess whether WMH burden, cognitive function, and gray matter volume correlated with BD duration and severity, as determined by patient-report via the life chart method (Roy-Byrne *et al.* 1985) and the retrospective chart review.

Methods

We have previously described the study subjects, diagnosis and treatment, recruitment, and measures (Gildengers *et al.* 2012). The study involved non-demented individuals aged 50years and older who had comprehensive neuropsychological (NP) assessment. The NP assessment encompassed 21 well-established and well-validated individual tests measuring multiple cognitive domains that were organized into domain scores on the basis of a factor analysis. Domains included information processing speed/executive, language, memory, and visuospatial ability. A global cognitive function score was determined on the basis of all 21 individual tests. All subjects provided written informed consent, as required by the Institutional Review Board at the University of Pittsburgh. The current report focuses on the subset of participants (27 with BD and 12 mentally healthy comparators [control subjects]) who underwent neuroimaging. All subjects of the parent study were offered to participate in neuroimaging, but 20 subjects with BD and 9 control subjects refused because of contraindications (e.g., metallic implants) or reluctance to undergo neuroimaging MRI (e.g., claustrophobia). In the following section, we describe the neuroimaging methods and the statistical analyses specific to this report.

Neuroimaging

The MR Brain imaging was performed in the University of Pittsburgh MR Research Center by using a GE Signa 1.5 Tesla scanner (GE Healthcare, Waukesha, WI, USA). The MRI protocol included T1-weighted, T2-weighted, proton density-weighted, high contrast FLAIR imaging, and high-resolution volumetric spoiled gradient-recalled sequences. Imaging was then processed in the Geriatric Psychiatry Neuroimaging Laboratory (www.gpn.pitt.edu) under the supervision of Dr. Howard Aizenstein.

To determine the regional gray and white matter brain volumes, Dr. Aizenstein and colleagues developed a procedure referred to as the automated labeling pathway (ALP). The pathway combines a series of publicly available software packages (AFNI, BET, FLIRT, and ITK) as well as some custom programs to implement atlas-based segmentation of MRI images. Using ALP, anatomic regions of interest (ROIs), in this case, the bilateral hippocampus from the automated anatomic labeling atlas (Tzourio-Mazoyer *et al.* 2002)

defined on the reference brain (MNI, colin27) (Holmes *et al.* 1998) are transformed to fit each individual's anatomic image, which are then segmented into gray, white, and cerebrospinal fluid tissue types. After registration of the template to the individual subject space, the ROIs from the template are applied to label regions on the subject's MRI. The numbers of gray and white voxels in each of these regions, as well as the whole brain, are then counted to produce a table of ROI volumes for each region and each subject.

To image WMH, FLAIR images described previously were used for WMH quantification and localization. An automated method developed in Dr. Aizenstein's laboratory uses a fuzzy connected algorithm to segment the WMH (Wu *et al.*, 2006) and the ALP to localize the WMH into the anatomical space (Wu et al. 2007). A fully deformable registration (Wu *et al.*, 2006) combines the piecewise linear registration for coarse alignment with demons algorithm for voxel-level refinement. This method generates total WMH volumes, as well as WMH volumes for each frontal and subcortical white matter tracts defined in the Johns Hopkins white matter atlas (Mori and Crain 2005). Each normalized voxel measured $0.78 \times 0.78 \times 0.78$ mm^3. In our analyses, we have almost exclusively used total WMH volume, except for one instance in which we explored WMH volume bilaterally in the following prefrontal tracts (Lin *et al.* 2011): the anterior thalamic radiation, uncinate fasiculus, superior longitudinal fasciculus, cingulum, and inferior fronto-occipital fasciculus.

Statistical analysis

Descriptive statistics were generated to characterize BD and the control subjects. To determine how the groups differed with respect to basic demographic and clinical variables, Student's *t*-tests or Fisher's exact tests were used as appropriate. In BD and control subjects, we determined the relationship between NP scores and the total WMH burden by using Spearman's correlations. Correlational analyses were also used to assess associations between the following parameters: (i) prefrontal WMH burden and NP scores and (ii) the total WMH burden and NP scores with BD duration and severity. To assess statistical significance, a two-tailed α of 0.05 was used. All analyses were performed using SAS 9.3 statistical software (SAS Institute Inc., Cary, NC).

Results

Twenty-seven BD subjects and 12 control subjects underwent neuroimaging and NP testing. The BD and control groups of this study did not differ from each other with respect to age, sex, race, education, or body mass index. Compared with the control subjects, BD subjects had significantly higher Cumulative Illness Rating Scale for Geriatrics scores, as well as lower NP scores globally and in speed/executive and memory domains. The BD subjects had less total WMH burden but no difference in total or hippocampal gray matter volume (Table 1).

Among the BD subjects, overall WMH burden did not correlate with global cognitive function or function in any specific domain. However, in control subjects, higher overall WMH burden was significantly associated with lower global cognitive function (Table 2).

We also tested the exploratory hypotheses. When considering the white matter tracts associated with the prefrontal cortex (Lin *et al.* 2011), among the control subjects, higher WMH burden in these specific tracts correlated significantly with worse memory ability and global cognitive functioning, which was not the case in BD subjects (Table 3). The actual amount of prefrontal WMH burden was lower in BD subjects than in controls (0.0005 [SD = 0.0004] vs. 0.0011 [SD = 0.0006] normalized voxel counts, $t[37] = -3.41$, $p = 0.02$).

In the parent study, the Life Chart Method (Roy-Byrne *et al.* 1985) had been obtained on subjects with BD (n = 21) to quantify the potential effect of total duration and severity of illness. Neither the total duration of illness nor the number of psychiatric hospitalizations correlated with cognitive performance, WMH burden, total gray matter volume, or hippocampal gray matter volume. There was no difference in total and hippocampal gray matter volume between BD subjects and the control subjects. In both BD and control groups, neither the total gray nor the hippocampal volumes correlated with cognitive performance.

Discussion

In our study, among older individuals with BD, overall WMH burden was not related to global cognitive function or cognitive function in any specific domain. In contrast to individuals with BD, among mentally health comparators, higher total WMH burden was related to lower global cognitive function. Although BD patients had worse cognitive function (globally and among specific cognitive domains), they surprisingly had less total and prefrontal WMH burden than the mentally healthy comparators, which, may simply be a result of sampling bias or the relatively small control group. However, our findings, when taken together, suggest that overall WMH burden or lower gray matter volume may not be at the core of neurocognitive impairment in older adults with BD. Previous studies have identified a number of pathways that may be involved in BD-related neuroprogression including inflammation, mitochondrial dysfunction, serum anticholinergic burden, and altered neurogenesis (Mulsant *et al.* 2003; Berk *et al.* 2011).

Further, even though previous studies in younger adults with BD have shown an association between poorer cognitive function and both elevated serum amyloid levels (Piccinni *et al.* 2012) and presence of Apolipoprotein-ε4 (Soeira-de-Souza *et al.* 2010), our data suggest that cognitive impairment in late-life BD is not likely due to comorbid Alzheimer's disease or amnestic mild cognitive impairment. A recent study demonstrated that regional WMH burden, but not hippocampal volume, is associated with increased rates of Alzheimer's disease (Brickman *et al.* 2012). In our data, the control subjects with higher overall or prefrontal WMH had worse global and memory function, domains often affected in Alzheimer's pathology, but this was not the case for BD patients. Thus, the relationship between WMH burden and cognitive function may more purely reflect aging and vascular burden in control subjects. Even using alternative conceptual models of Alzheimer's-related cognitive deficits (Jack *et al.* 2010), BD and the control subjects in our study did not have different hippocampal or total brain volumes. This may also explain why cholinesterase inhibitors may not be effective in treating cognitive dysfunction in late-life BD (Gildengers *et al.*, 2008).

There are potential implications of our exploratory analyses. Even though BD patients had less WMH burden and worse NP scores, we did not find a correlation between WMH burden, neurocognitive function, and either BD duration or severity. This suggests that the Life Chart Method may not be well suited to *retrospectively* ascertain the past duration and severity of BD in older adults with BD because of the problems inherent in accurately recalling number, severity, and duration of mood episodes, especially in individuals who have experienced multiple episodes. This finding is consistent with other studies in adult mood disorder patients (Simon *et al.* 2012), adding to the evidence that patient recall may be inadequate in characterizing duration and severity of illness.

Limitations

Our neuroimaging study had a number of important limitations. Foremost was the small sample size. Further, despite our recruitment efforts, almost half of the patients in the parent

study did not participate because of the contraindications or reluctance to undergo MRI. The small sample size did not permit examination of medication effects on brain structure or cognitive function. Additionally, this was a tertiary care research sample, which may not be representative of older BD patients treated in the community. Also, recruiting control subject with comparable cardiovascular burden to BD subjects may have made the groups more similar in WMH burden. Had the control subjects had lower WMH burden, this would have arguably accentuated the cognitive differences between the groups. We note that there may be limitations to combining Cumulative Illness Rating Scale-Geriatrics heart and vascular items as a measure of vascular burden. However, we did not obtain the requisite information to use more widely accepted measures, such as the Framingham Stroke Risk Profile (Wolf *et al.* 1991). Further, when comparing cross-sectional brain volumes, intra-individual variability is so large that it may obscure potential effects of illness severity or medication exposure. Last, we were unable to examine microstructural white matter abnormalities with diffusion tensor imaging because these scanning sequences were not obtained in this study.

Conclusions

On the basis of our current data, the cognition dysfunction experienced in late-life BD does not appear to be primarily because of the processes related to increased WMH or reduced gray matter volume. Our results should be validated in larger, longitudinal studies including rigorous measurement of illness duration, severity, and pharmacotherapy with repeated neuroimaging in individuals across different age groups along with other measures of white matter disease (e.g., diffusion tensor imaging of white matter microstructural abnormalities). Future research should also examine other neuroprogressive pathways such as inflammation, mitochondrial dysfunction, serum anticholinergicity, and altered neurogenesis, especially in prefrontal brain regions. It is possible that these neuroprogressive mechanisms act synergistically to affect cognitive function on in late-life BD. A clinical implication of our data is that if cognitive dysfunction in older adults with BD is only partly related to vascular disease burden, then simply addressing vascular disease in these patients will likely not be adequate to treating cognitive dysfunction. Hence, interventions addressing alternate pathological pathways need to be investigated. Once the etiology of cognitive impairment in late-life BD is better understood, it may become possible to develop rational therapeutic strategies and prevent cognitive decline in this population.

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Key points

- In this group of older adults with BD –
- Cognitive dysfunction did not appear to be primarily related to overall white matter hyperintensity burden or reduced gray matter volume.
- White matter hyperintensity burden was not related to lifetime illness duration or severity.

Table 1

Demographics, clinical, neuroimaging, and neuropsychological measures

	Whole group	Bipolar Disorder	Controls	Statistics
	***N* = 39**	***N* = 27**	***N* = 12**	
Age (years)	68.2 (7.8) range = 52.6−83.2	68.6 (8.1)	67.1 (7.4)	$t(37) = 0.58$, $p = 0.57$
% female	66.7 (n = 26)	74.1 (n = 20)	50.0 (n = 6)	Fisher's exact $p = 0.16$
% Caucasian	87.2 (n = 34)	88.9 (n = 24)	83.3 (n = 10)	Fisher's exact $p = 0.63$
Education (years)	15.1 (3.2) range = 9−20	15.0 (3.4)	15.3(2.8)	$t(37) = -0.33$, $p = 0.74$
Body mass index	28.9 (4.7) range = 20.4−38.4	29.3 (4.9) range = 20.4−37.4	28.1 (4.2) range = 20.6−38.4	$t(37) = 0.78$, $p = 0.44$
% Bipolar type I (versus type II)	N/A	85.2% (n = 23)	N/A	N/A
Duration of bipolar illness (years)	N/A	44.8 (13.7) Median = 46 Range = 0.5−69	N/A	N/A
Number of past psychiatric hospitalizations	N/A	3.5 (4.2) Median = 2 Range = 0−15	N/A	N/A
CIRS-G				
Total	8.3 (4.7) range = 0−27	9.2 (5.3)	6.3 (2.3)	$t(37^a) = 2.37$, $p = 0.02$
Count	5.4 (2.4) range = 0−11	6.0 (2.5)	4.1 (1.2)	$t(36.5^a) = 3.11$, $p = 0.004$
Heart + vascular	1.9 (1.5) range = 0−6	1.8 (1.5)	1.9 (1.6)	$t(37) = -0.20$, $p = 0.85$
White matter hyperintensity[b]	0.0007 (0.0006) range = 0.00002-0.003	0.0004 (0.0004)	0.001 (0.001)	$t(13.4^a) = -3.57$, $p = 0.003$
Gray matter volume				
Total	0.31 (0.07) range = 0.12−0.46	0.31 (0.07)	0.31 (0.08)	$t(37) = -0.12$, $p = 0.90$
Hippocampal	0.006 (0.002) range = 0.003−0.009	0.006 (0.002)	0.006 (0.002)	$t(37) = 0.09$, $p = 0.93$
Neuropsychological Domains[c]				
Global	−0.60 (0.87) range = −3.13 to1.21	−0.88 (0.83)	0.04 (0.60)	$t(37) = -3.47$, $p = 0.001$
Speed/executive	−0.90 (1.24) range = −4.27 to 1.69	−1.35(1.14)	0.10(0.79)	$t(37) = -3.98$, $p < 0.001$
Visual	−0.82 (1.44) range = −5.55 to 1.36	−1.09(1.50)	−0.22(1.11)	$t(37) = -1.80$, $p = 0.08$
Language	−0.19 (0.86) range = −2.65 to 1.26	−0.34 (0.91)	0.14(0.65)	$t(37) = -1.64$, $p = 0.11$
Memory	−0.74 (1.13) range = −3.12 to 1.11	−1.16(1.06)	0.21 (0.58)	$t(35.1^a) = -5.23$, $p < 0.001$

N/A, not applicable; CIRS-G, Cumulative Illness Rating Scale for Geriatrics.

[a] Satterthwaite method reported because of unequal variances.

[b] Means and standard deviation reported in the original units. Square root transformation used in analyses.

[c] Neuropsychological domains same as in our group's previous paper (Gildengers et al. 2012)

Table 2

Spearman's correlation between white matter hyperintensity and neuropsychological scores

	Bipolar disorder	Controls
	N **=27**	***N*****=13**
Global	−0.23 (p = 0.24)	−0.57 (p = 0.05)
Speed/executive	−0.07 (p = 0.75)	−0.33 (p = 0.30)
Visual	−0.19 (p = 0.33)	−0.37 (p = 0.24)
Language	−0.30 (p = 0.13)	−0.25 (p = 0.43)
Memory	−0.34 (p = 0.08)	−0.53 (p = 0.08)

Table 3

Spearman's correlation between white matter hyperintensity in tracts related to prefrontal cortex (anterior thalamic radiation, uncinate fasciculus, superior longitudinal fasciculus, cingulate (upper and lower), and inferior longitudinal fasciculus) and neuropsychological scores

	Bipolar disorder (n = 27)	Controls (n = 12)
Global	−0.25 (p = 0.20)	−0.63 (p = 0.03)
Speed/executive	−0.11 (p = 0.58)	−0.38 (p = 0.22)
Visual	−0.23 (p = 0.26)	−0.31 (p = 0.33)
Language	−0.32 (p = 0.10)	−0.29 (p = 0.37)
Memory	−0.30 (p = 0.12)	−0.62 (p = 0.03)