How Does Dementia Begin to Manifest in Bipolar Disorder? A Description of Prodromal Clinical and Cognitive Changes.

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Research

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Abstract

Background

This study aims to identify longitudinal cognitive changes that may signal early dementia in bipolar disorder.

Methods

Participants were 114 adults with bipolar disorder, all initially non-demented, who underwent annual neuropsychological assessment up to ten years (47.3 months average follow-up). A small subset (n=12) also had available structural neuroimaging data. Longitudinal features associated with future dementia status were examined with linear mixed-effects models, and yearly differences between incident dementia and controls cases were examined in the six years prior to diagnosis.

Results

Twenty-six participants (22.8%) developed dementia over the follow-up period ('incident cases'), and the remaining 88 (77.2%) remained dementia-free ('controls'). Alzheimer's disease was the most common presumed etiology in the incident cases, and this aligned with findings of smaller hippocampal volumes relative to controls. The incident cases showed clearly declining trajectories in episodic memory, verbal fluency and attention. Story recall and digit symbol substitution showed the earliest decline, four and five years before diagnosis respectively. Digit symbol substitution was most accurate at distinguishing cases from controls: impaired performance (<-1.5 SD) at any time during the follow-up period was associated with 54% sensitivity and 87% specificity of future dementia.

Conclusions

Prodromal dementia in bipolar disorder can be detected up to five years before onset using the same cognitive tests used in psychiatrically-healthy older adults. Cognition in the natural course of bipolar disorder is generally stable, and impairment or marked decline on measures of memory, fluency or attention may indicate an early neurodegenerative process.

Background

Cognitive deficits are a core feature of bipolar disorder (BD) (1). Executive functions and episodic memory are most commonly affected, although global cognition is also typically impaired (2,3). Cognitive impairments are present even in the absence of mood symptoms, as well as in first-degree relatives (4), suggesting that they might be endophenotypes of the disease. They are consistent and persistent in the natural course of BD, although generally mild (up to 1 standard deviation [SD] below normal) (3,5,6). In addition to deficits encompassed within the natural course of BD, considerable evidence from systematic reviews (7,8) suggests that BD increases risk for dementia later in life, most frequently Alzheimer's disease (AD) (1). This does not appear to be due to worsening of pre-existing

cognitive deficits (7). Overall, dementia prevalence in BD is generally around 20-25% (9,10), while the population prevalence of dementia is 7% in adults aged 60 or older (11).

Despite this apparent heightened risk, studies aiming to increase knowledge about dementia syndromes systematically exclude subjects with psychiatric conditions (12). In addition, the majority of published studies examining cognition in adult BD patients include only subjects younger than age 50 (13). Thus, relatively little is known about cognitive decline in BD later in life, or how clinicians should go about evaluating cognitive performance in the context of pre-existing deficits. Confusion between the 'core' deficits (i.e., deficits that are part of the natural history of BD) and those that signal a neurodegenerative process has been highlighted previously (14,15). Therefore, establishing features signaling the onset of neurodegenerative changes in BD would be helpful to inform the differential diagnosis at a critical period when early therapeutic intervention may be possible and important healthcare decisions must be made.

Previous studies have called for the identification of neuropsychological markers of prodromal dementia in individuals with BD (1,2). The few existing investigations of cognitive symptoms in older cohorts have focused on comparing elderly individuals with BD to age-matched controls *without* BD who are cognitively healthy (e.g., 16,17) or cognitively impaired (e.g., 18). Only one previous study has directly compared cognitive performance in BD patients with and without dementia (2); in this study, the authors assessed the use of the Cambridge Cognition Examination, Mini-Mental State Examination (MMSE), animal fluency, and clock drawing to distinguish BD with mild AD from BD alone, and reported good sensitivity and specificity for all tests. However, it remains unclear whether or not cognitive measures have value to identify BD subjects who are in the earliest stages of a neurocognitive disorder given that all participants in the aforementioned study already had dementia. Furthermore, participants with non-AD dementias were excluded.

Here, we used longitudinal neuropsychological data over a 10-year span to document the emergence of early features of dementia in BD, relative to those that constitute the natural course of cognitive changes in individuals with BD who do not develop dementia. The approach was exploratory and data-driven, and therefore did not include any *a priori* hypotheses.

Methods

Participants

This retrospective observational study used data from the National Alzheimer's Coordinating Center (NACC; www.alz.washington.edu). The database consists of participants recruited from several Alzheimer's Disease Centers (ADC) across the USA, and includes individuals with dementia, mild cognitive impairment (MCI) or normal cognition. Data for this study were for visits conducted between August 2005 and the September 2016 data freeze, and included any participant with self-reported or clinician-diagnosed BD.

Participants were 241 adults with BD seen at approximately yearly intervals. Individuals with no follow-up after their first visit (n=81) or those who were demented on admission (n=75) were excluded; 29 participants met both exclusion criteria. The remaining 114 participants were seen up to 112 months (4.3 total visits including baseline, or 42.8 months, on average). Sixty-four percent had self-reported BD, with the remaining 36% being clinician-diagnosed. Participants were classified as 'incident dementia cases' if they developed dementia at any point during the study. Dementia diagnoses were based on clinical judgement using DSM-IV criteria (19) (or similar/modified criteria; NACC acknowledges that diagnostic criteria may have varied between ADC sites). DSM-IV criteria include: 1) deficits in memory and at least one other cognitive domain; 2) significant impairment in social or occupational functioning due to cognitive impairments; 3) gradual onset and progressive course; 4) absence of contributing neurological or systemic conditions, delirium or other mental disorder. Twenty-six participants (22.8%) developed dementia during the follow-up period; the remaining 88 cases (77.2%) remained free of dementia for the duration of the study (up to nine years) and constituted the control group.

All contributing ADCs obtained participant consent and received approval from their individual Institutional Review Board prior to submitting data to NACC.

Risk factors for cognitive decline

The presence of neuropsychiatric symptoms (20) and vascular risk factors (21) has been associated with cognitive decline in non-BD populations. To determine the impact of these factors on dementia risk in this sample, data were used from the Neuropsychiatric Inventory (NPI) (22), which was completed by a knowledgeable informant. Vascular risk factors were assessed using the Hachinski scale (23). Information about tobacco use (total years smoked) and alcohol abuse (absent, recent/active, remote/inactive) was collected. Mood-stabilizing medications, such as lithium, are also known to impact cognition (24). Medication use within two weeks of assessment was documented in the present sample; unfortunately, lifetime exposure was not. All mood-stabilizing medications, as well as antipsychotics, benzodiazepines, and other antiepileptic drugs that can be used off-label as mood stabilizers, were considered.

Cognitive outcomes

All participants were administered the ADC Uniform Data Set (UDS) neuropsychological battery (25), which included the Wechsler Memory Scale Revised (WMS-R) forward and backward digit spans, WMS-R digit-symbol substitution (DSS), trails A and B, WMS-R Logical Memory Story A, semantic fluency (animals and vegetables) and confrontation naming. The MMSE was used as a brief measure of general cognition. Variables coded as 'missing due to a cognitive/behavior problem' were replaced with the lowest allowable score for that test. All other missing variables were left missing. Scores were then standardized to Z-scores using normative data derived from 3,268 cognitively normal participants from NACC published previously (26), where Z=0 provides a benchmark for expected performance in healthy older adults (with an associated standard deviation of 1), thus precluding the need for a non-psychiatric normal control group. In addition to formal cognitive testing, participants were asked about subjective

reports in memory decline relative to previous abilities (one subject had missing data for this question). They were also queried about the predominant cognitive symptom that was first recognized as a change from previous levels.

Structural neuroimaging

The NACC data repository included available structural magnetic resonance imaging (MRI) data on a small subset of 12 BD participants, including 5 incident dementia cases (4 males, 1 female) and 7 controls (4 males, 3 females). These images were analyzed to obtain supplementary insights into the possible neurological contributions to cognitive decline in BD. To this end, intracranial volumes were acquired using automatic segmentation in SPM12 (www.fil.ion.ucl.ac.uk/spm) which calculated white matter, grey matter, and cerebral spinal fluid volumes for each participant. These volumes were summed and corrected for voxel size to ensure consistency across participants. In addition, because AD is the most frequent type of dementia seen in BD (1) and is characterized by significant hippocampal atrophy, bilateral, manual segmentations of the hippocampi were traced for each participant using ITK-SNAP (27) (www.itksnap.org). A well-established protocol for manual segmentation of the hippocampus in T1-weighted images was used to train both the primary and secondary rater (28). Tracing reliability was assessed by having a second rater trace four of the 12 brains (two from each group). Volumes from the four tracings were highly correlated between raters ($r(2) = .926, p = .247$) suggesting a high degree of inter-rater reliability. Left and right hippocampal volumes were summed and corrected for voxel size to produce total hippocampal formation volumes for each participant.

Statistical analyses

All analyses were two-tailed, with alpha set at .05 except where stated otherwise. The incident dementia cases and dementia-free controls were first compared in terms of age and years of education using Mann-Whitney U, because the data were non-normally distributed (Shapiro-Wilk $p < .001$ for both variables). Sex was compared between groups using chi-square (χ^2).

Neuropsychiatric symptoms, vascular risk factors, tobacco, alcohol and medication use, and subjective impression of cognitive change at any time during the study (yes/no) were compared longitudinally using linear mixed models with Group (incident cases, controls) as a fixed effect. Because all medications ($n=29$) were considered independently in separate statistical analyses, the significance threshold was set at $p < .002$ using Bonferroni correction for multiple comparisons. A Group $\times$ Time interaction term was added to the model with neuropsychiatric symptoms in order to determine whether worsening neuropsychiatric symptoms were associated with incident dementia.

Cognitive change was examined as a function of the time interval (in months) between each assessment and 'Time0', ranging from -112 to 0. 'Time0' was always the date of dementia diagnosis for incident dementia cases, and last follow-up visit for controls. Of note, the earliest date of dementia diagnosis was always used, even if diagnosis subsequently reverted to MCI ($n=5$; two of these ultimately were re-diagnosed with dementia at a later visit). Linear mixed models were used to establish the relationship

between longitudinal performance on each cognitive test and dementia status. This statistical approach allows for correlated repeated measures within subjects, while permitting the inclusion of participants with missing data at certain time points (29). All longitudinal analyses included only data collected between Time-6 and Time0 because only two incident dementia cases had data prior to Time-6. Cognitive variables were entered individually into separate models with Time and Group as fixed effects, and covarying for sex as a fixed effect use due to a priori group differences (see Results, below). Group $\times$ Time interaction terms were added to all models and were the main outcome of interest. Six participants were excluded from these analyses because they lacked cognitive data at all time points, which were coded as 'Missing due to: Other problem' (i.e., not due to a physical, cognitive or behavioral problem, nor due to verbal refusal).

Hippocampal atrophy was examined using a one-way analysis of covariance (ANCOVA) accounting for age, intracranial volume, and the number of days between Time0 and the date of MRI acquisition. Additionally, a group effect was discovered in the number of days between Time0 and the date of MRI acquisition. Consequently, group means were removed from this variable by subtracting the group mean from the amount of days to Time0 for each participant. This was done to remove any inter-group variance while still maintaining a marginal amount of intra-group variance. Sex was not included as a covariate in these analyses because there were no sex differences in the neuroimaging sample ($\chi^2=0.686$, $p=0.408$).

Results

Participant characteristics

Participants' sociodemographic characteristics are summarized in **Table 1**. The 26 incident cases developed dementia after a mean of 33.96 months ($SD=25.71$), and the 88 controls remained free of dementia for a mean follow-up duration of 45.39 months ($SD=27.46$). Follow-up length was significantly longer in controls ($\chi^2=4.955$, $p=.026$). Age at Time0 ($\chi^2=2.970$, $p=.085$) and education ($\chi^2=3.325$, $p=.068$) were comparable between groups. The incident dementia group included a significantly greater proportion of males ($\chi^2=14.954$, $p<.001$). A significantly greater proportion of incident dementia cases reported concern about their memory compared to controls ($\chi^2=4.769$, $p=.029$).

Table 1. Mean (SD) characteristics of incident dementia cases and controls.

	Incident dementia cases (n=26)	Controls (n=88)	Statistic	<i>p</i>
Age at Time 0	75.50 (7.67)	71.61 (11.48)	2.798 ^a	.094
Years of education	15.38 (3.03)	16.61 (2.76)	3.325 ^a	.068
Sex (% males)	76.9%	34.1%	14.954 ^a	<.001
Mean follow-up length (years)	2.85 (2.22)	3.75 (2.29)	4.466 ^a	.035
Subjective sense of decline at any time (% yes)	69.2%	44.8%	4.769 ^a	.029
Baseline MMSE	27.42 (2.28)	28.57 (1.74)	15.758 ^b	<.001
Baseline NPI symptom severity	76.33 (13.78)	83.2 (13.93)	2.592 ^b	.110
Baseline NPI symptom distress	3.00 (2.15)	1.96 (2.16)	2.617 ^b	.108
Baseline Hachinski score	1.08 (1.53)	0.77 (1.03)	0.626 ^b	.430
Baseline smoking history (years)	11.54 (17.45)	13.64 (16.59)	0.228 ^b	.634
Baseline alcohol abuse (% never)	80.8%	76.1%	1.525 ^{a,b}	.219

Notes. SD=Standard deviation. NPI=Neuropsychiatric Inventory.

^a χ^2 was used because variables were non-normally distributed (Mann-Whitney U) or binary.

^b*F* statistic. Refers to longitudinal linear mixed models. Means refer to baseline only.

Risk factors for cognitive decline

The presence of neuropsychiatric symptom distress ($F= 6.952, p=.009$) and severity ($F= 6.686, p=.010$) was statistically different between groups, but the Group $\times$ Time interactions terms in the NPI distress model ($F=0.542, p=.462$) and the NPI severity model ($F=0.314, p=.576$) were not. Vascular risk factors were similar between incident cases and controls ($F=0.009, p=.925$), and there was no Group $\times$ Time interaction ($F=1.995, p=.159$). The groups did not differ on smoking (main effect: $F=0.380, p=.539$, interaction: $F=0.042, p=.838$) or alcohol abuse (main effect: $F=1.619, p=.206$, interaction: $F=1.062,$

$p=.304$) nor on two-week prior use of any psychotropic medication after correcting for multiple comparisons (all main and interactions effects $p>.002$).

Cognitive outcomes

Of the 26 incident dementia cases, 17 (65.4%) reported memory as the predominant symptom first recognized as a decline in cognition, five (19.2%) reported executive difficulties (judgment, planning, problem-solving), and three (11.5%) reported language symptoms. One participant observed no change. BD was determined to be the primary etiology contributing to cognitive impairment in two participants (7.7%), one of whom also had depression and Parkinson's disease as primary contributing factors. Fifteen participants (57.7%) had AD as a primary etiologic diagnosis, three (11.5%) had fronto-temporal lobar degeneration, two (7.7%) had Lewy body dementia. One participant had alcohol-related dementia, one had vascular dementia and one had normal-pressure hydrocephalus. In one participant, etiology was undetermined. These etiologic diagnoses were presumptive and determined by clinicians within individual ADCs based on clinical presentation.

Sex-adjusted linear mixed model results are illustrated in **Figure 1**. A main effect of Group was apparent in models involving immediate ($F=41.762, p=.000$) and delayed short story recall ($F=44.440, p<.001$), digit span forward ($F=12.193, p=.001$) and backward ($F=12.741, p<.001$), animal fluency ($F=23.582, p<.001$), vegetable fluency ($F=25.283, p<.000$), trails A ($F=22.214, p<.000$) and B ($F=13.245, p<.000$), DSS ($F=22.079, p<.001$) and confrontation naming ($F=26.180, p<.001$). A main effect of Time was apparent in models involving immediate ($F=4.662, p=.032$) and delayed story recall ($F=5.698, p=.018$), animal fluency ($F=18.701, p<.001$), vegetable fluency ($F=16.707, p<.001$) and trails A ($F=7.770, p=.006$) and B ($F=10.745, p=.001$), but not digit span forward ($F=1.440, p=.231$) or backward ($F=0.020, p=.887$), DSS ($F=1.531, p=.217$) or naming ($F=3.071, p=.081$). A significant Group $\times$ Time interaction was present in models involving immediate ($F=10.054, p=.002$) and delayed story recall ($F=11.096, p=.001$), animal fluency ($F=11.643, p=.001$), vegetable fluency ($F=5.625, p=.018$), trails A ($F=6.942, p=.009$) and DSS ($F=4.184, p=.042$). No interactions were significant in digit span forward ($F=3.092, p=.080$) or backward ($F=0.148, p=.700$), trails B ($F=1.888, p=.170$), or naming models ($F=3.071, p=.081$).

To determine the earliest point at which between-group differences appeared in models yielding a significant interaction term, yearly differences between incident cases and controls were examined using sex-adjusted ANCOVA. Only data from Time-6 to Time0 were included, due to insufficient data at prior time points. Effect sizes are reported as partial eta squared (η_p^2), where values .01, .06, and .14 are considered small, medium and large, respectively (30). Group differences in DSS were first apparent five years before the incident group's dementia diagnosis ($F=5.514, p=.027, \eta_p^2=.187$). Group differences in immediate ($F=7.519, p=.009, \eta_p^2=.165$) and delayed story recall ($F=4.297, p=.045, \eta_p^2=.102$) emerged four years before diagnosis. Animal fluency differences emerged three years prior to dementia diagnosis ($F=5.555, p=.023, \eta_p^2=.114$). Group differences in Trails A emerged two years before diagnosis ($F=8.978, p=.004, \eta_p^2=.112$). Vegetable naming group differences only became statistically significant at Time0 ($F=27.787, p<.001, \eta_p^2=.353$).

Because DSS and Logical Memory were the first to be affected in the incident dementia group, their usefulness as potential screening tools for dementia in BD was tested in exploratory post-hoc analyses. The presence of impairment (yes/no) on the DSS or Logical Memory immediate story recall at any time during the study (prior to their last visit) was first determined for each participant. Impairment was defined as performance below -1.5 SD based on published normative data(26). Sensitivity, specificity, accuracy, positive (PPV) and negative predictive value (NPV) were then calculated. Results indicated that DSS impairment at any time prior to dementia onset was associated with 0.54 sensitivity (95% CI [0.33–0.74]), 0.87 specificity (95% CI [0.77–0.93]), 0.80 accuracy (95% CI [0.71–0.87]) 0.54 PPV (95% CI [0.33–0.74]) and 0.87 NPV (95% CI [0.77–0.93]). Short story immediate recall impairment was associated with 0.46 sensitivity (95% CI [0.26–0.67]), 0.81 specificity (95% CI [0.71–0.88]), 0.73 accuracy (95% CI [0.64–0.81]), 0.41 PPV (95% CI [0.23–0.61]) and 0.84 NPV (95% CI [0.74–0.91]).

Neuroimaging

Intracranial volumes were compared across groups to ensure consistency of the automatic tracings. Intracranial volumes did not differ significantly between the incident dementia cases ($M=1,540\text{ cm}^3$, $SD=261\text{ cm}^3$) and controls ($M=1,476\text{ cm}^3$, $SD=211\text{ cm}^3$; $t(10)=.477$, $p=.644$). With the limited amount of imaging data provided for participants, hippocampal atrophy comparisons were largely underpowered. Therefore, hippocampal atrophy was only compared at the level of marginal means, providing a purely descriptive approach. A 7.4% reduction in hippocampal volume was found in the incident dementia cases ($M=3.255\text{ cm}^3$, $SE=.274\text{ cm}^3$) compared to controls ($M=3.516\text{ cm}^3$, $SE=.230\text{ cm}^3$) while controlling for age, intracranial volume, and number of days between Time0 and the date of MRI acquisition. This is on par with previous literature suggesting that mild to medium levels of dementia should result in a 5% to 10% reduction in hippocampal volume, respectively (31).

Discussion

To distinguish cognitive deficits inherent to BD from those signaling incident dementia, this study examined a large cohort of older adults with BD. Over the course of the study, nearly a quarter (22.8%) of the eligible sample eventually received a diagnosis of dementia, within the range of previously-reported dementia rates of 20-25% in BD (9,10) and higher than the 7% population prevalence in non-psychiatric samples (11). This group included predominantly males (76.9%), and most endorsed subjective concerns at some point during the study. Memory problems were the predominant symptoms first recognized as a change in cognition, and AD was the most commonly diagnosed etiology, consistent with prior reports in BD (1) and supported by between-group differences in hippocampal volumes in a small subset of participants with available structural neuroimaging data.

In this study, we showed for the first time that a standard neuropsychological assessment can be used to detect signs of dementia up to five years prior to dementia diagnosis in individuals with BD, and that neurodegenerative cognitive processes in this group of patients resemble that of the general population. Though this finding may appear self-evident, to our knowledge, it has not been documented empirically

by previous studies. We found that performance on all cognitive measures was associated with incident dementia, with short story immediate recall and DSS showing the earliest between-group differences, up to four and five years before diagnosis, respectively. Importantly, DSS and story recall were *not* impaired in BD controls who remained dementia-free throughout the study: at all time points, these patients' performance hovered around $Z=0$ (i.e., clinically normal) for both measures (**Figure 1**). Although this contrasts with reports of cognitive impairments being a core feature of BD (1), it is in line with other evidence suggesting that cognitive impairments within the natural course of BD are mostly mild (3,5,6).

Story recall has been identified in other studies as being sensitive to medial temporal lobe atrophy, the central neuroanatomical feature of AD (32). Regarding DSS, a measure of psychomotor speed that also taps sustained attention and set-shifting, other studies have similarly reported that it may be a particularly sensitive early measure of incident dementia (33,34), up to ten years before diagnosis (35), potentially reflecting its association with medial temporal lobe atrophy severity and cerebrovascular burden (36). In this sample, the value of these measures lay primarily in their negative predictive power, i.e., to rule out a possible dementing condition if performance is normal. If independent studies replicate our findings in broader BD samples, these measures may be worthwhile considering as potential cost-effective clinical screening tools for dementia risk in BD in memory clinics. It may also be worthwhile systematically investigating the use of these screening tools in other patient populations affected by memory disorders (e.g., schizophrenia: ,37).

Factors such as diminished cognitive reserve, vascular risk factors, and exposure to pharmacological treatments have been proposed to account for increased dementia risk in BD (7). Although the present study was not designed to specifically test these associations, its results do not appear to support this view. No differences were found between the incident cases and controls cases in terms of education (considered a cognitive reserve proxy: ,38), or Hachinski score (a measure of vascular risk: ,23). Psychotropic drug use was also not different between groups. Furthermore, statistical models revealed no interaction between group and time in terms of NPI symptom severity or distress measures, indicating that dementia onset was not associated with worsening neuropsychiatric symptoms over time. Three incident dementia cases (11.5%) reverted from 'dementia' to 'MCI' status during the study; this is in line with previous studies showing relatively less stability of dementia diagnoses in individuals with premorbid cognitive challenges (39).

Limitations

Data for this study were drawn from the NACC data repository, which inherently limits the generalizability of findings. AD is likely overrepresented in these data, and incident dementia cases within NACC may decline more significantly or at faster rates than incident dementia cases within the community. NACC included more than 35,000 participants enrolled as of the September 2016 data freeze, however only a small percentage of these had a diagnosis of BD, and even fewer eventually developed dementia. Average follow-up length was also relatively short in some cases. As such, the relatively small sample of individuals retained for analysis may be viewed as a limitation of this study.

Another important limitation concerns the reliability and validity of self-reported BD diagnoses. A considerable number of participants were cognitively impaired, which may have led to inaccurate reports of medical and psychiatric histories. Results should be replicated in more carefully characterized samples. Furthermore, a number of potentially important variables were also not collected in NACC, including lifetime exposure to different pharmacological treatments, number of previous affective episodes and hospitalizations, all of which are known to affect cognition in BD (3,40). Age of BD onset is also not available in the NACC dataset. This information would be helpful to confirm whether early-versus late-onset BD differ in their rates of cognitive impairment and dementia risk, as has been suggested previously (9).

Lastly, only a very small subsample of participants had available neuroimaging data, and these were obtained from a large collection of pooled scans from various centers with varying image acquisition protocols. Although the NACC protocol includes neuroimaging and cerebrospinal fluid (CSF) biomarker data collection to support the etiological diagnosis of dementia, these data were unfortunately not available for participants used in this study. Thus, it must be acknowledged that the etiological diagnosis of dementia was presumptive. Future work should characterize the structural and functional neurological changes that are associated with incident dementia in BD, as well as the presence and relevance of CSF biomarkers. Results from one recent study suggest that cognitively impaired BD patients do not display AD-specific CSF biomarkers (41), however additional work is necessary to corroborate this finding and its association with cognition longitudinally.

Conclusions

Although epidemiologic evidence suggests that adults with BD may have increased dementia risk, to date, little is known about what neuropsychological changes may be harbingers of early neurodegeneration in these patients due to cognitive deficits being a core feature of BD independent of dementia. Our study provides preliminary evidence that some specific cognitive deficits could be used as predictive measures for early diagnosis of dementia in patients with bipolar disorder. These findings are of significant relevance given that the planet's population will include growing numbers of seniors, many of whom will have BD and may be in the early stages of dementia and need appropriate clinical management. Indeed, it has been estimated that one in four BD is over age 60 (42), and thus at high risk for neurodegenerative disease (9). Future studies may rely on the findings provided in this study to further explore the issue of dementia in BD.

Abbreviations

AD = Alzheimer's disease

ACD = Alzheimer's Disease Center

ANCOVA = Analysis of covariance

BD = Bipolar disorder

CSF = Cerebrospinal fluid

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

DSS = Digit symbol substitution

MCI = Mild cognitive impairment

MMSE = Mini Mental State Examination

MRI = Magnetic resonance imaging

NACC = National Alzheimer's Coordinating Center

NPI = Neuropsychiatric Inventory

NPV = Negative predictive value

PPV = Positive predictive value

SD = Standard deviation

SE = Standard error

UDS = Uniform Data Set

WMS-R = Wechsler Memory Scale Revised

Declarations

Ethics approval and consent to participate: This work involves the use of secondary data collected from human participants at 39 Alzheimer's Disease Centers (ADC) across the United States. Each individual ADCs obtained participant consent and received approval from their respective Institutional Review Boards.

Consent for publication: Not applicable.

Availability of data and materials: The datasets analysed in the current study are available in the National Alzheimer's Coordinating Center data repository (<https://www.alz.washington.edu/>).

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: BLC conceptualized the study idea, obtained the dataset, analyzed and interpreted the psychiatric and neuropsychological data, and drafted the manuscript. MMG analyzed and interpreted the neuroimaging data, and drafted the manuscript. FB analyzed and interpreted the neuroimaging data, and drafted the manuscript. GI supervised the neuroimaging data analysis, and drafted the manuscript. All authors have contributed to and approved the final article.

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Figures

Figure 1

Cognitive change six years preceding a diagnosis of dementia (incident dementia cases, dotted line) or last follow-up (controls, solid line). Notes: $G \times T$ = Group by Time interaction results. *Earliest statistically significant group difference ($p < .05$) on tests with a significant $G \times T$ interaction, after controlling for sex differences.