ORIGINAL ARTICLE

Increased Hippocampal Plaques and Tangles in Patients With Alzheimer Disease With a Lifetime History of Major Depression

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Context: The hallmark pathological changes in Alzheimer disease (AD) are abundant plaque and tangle formation, especially in the temporal lobes and hippocampus. Although there is increasing evidence that major depression may interact with neuropathological processes in AD, there have been no studies of neuropathological changes in AD as a function of history of major depression.

Objective: To test the hypothesis that neuritic plaques and neurofibrillary tangles are more pronounced in the hippocampus of patients with AD with a lifetime history of major depressive disorder, as compared with patients with AD without depression history.

Design: Postmortem study.

Setting: Nursing home.

Participants: The brains of 52 patients with AD without a lifetime history of major depression were compared with the brains of 50 patients with AD with a lifetime history of major depression.

Main Outcome Measures: Neuropathological ratings from the Consortium to Establish a Registry in Alzheimer Disease battery.

Results: Brains of patients with AD with a lifetime history of depression showed higher levels of both plaque ($P<.005$) and tangle ($P<.002$) formation within the hippocampus than brains of patients with AD without a history of depression. Post hoc analyses showed that patients with AD who had a history of depression exhibited more rapid cognitive decline than patients without a history of depression ($P<.004$). Furthermore, within the group of patients with AD with a history of depression, patients who exhibited concurrent depression at the time of first diagnosis of AD exhibited more pronounced neuropathological changes in the hippocampus ($P<.006$).

Conclusions: In AD, the presence of a lifetime history of depression corresponds to increases in AD-related neuropathological changes within the hippocampus. These changes go along with more rapid cognitive decline in patients with AD with a history of depression, and are more pronounced in patients with AD suffering from depression early on in the disease process, suggesting an interaction between major depression and AD neuropathology.

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THE HALLMARK PATHOLOGICAL changes in Alzheimer disease (AD) are abundant plaque and tangle formation, especially in the temporal lobes and hippocampus.[1,2] Criteria for the histopathologic diagnosis of AD emphasize the presence of both neuritic plaques (NP) and neurofibrillary tangles (NFT) in the neocortex.[3] Clinicopathological studies indicate that the severe memory deficits of individuals with AD[4,5] derive from the accumulation of plaques and tangles in memory-related neural systems in the brain, and that temporal lobe areas show the greatest damage in end-stage AD.[2,6,7]

At the same time, there is evidence to show that recurrent episodes of major depressive disorder (MDD) over the lifespan are a risk factor for subsequent onset of dementia. A number of studies have found an association of lifetime history of MDD with an increased risk of clinically diagnosed AD.[8-16] There is further evidence to suggest that recurrent geriatric MDD, as opposed to new-onset (vascular) geriatric MDD,[17] is associated with deficits in episodic memory suggesting a selective dysfunction in the mesial temporal lobes in older adults with a number of episodes of MDD across the lifespan.[18,19]

Imaging studies suggest that both the duration and the number of past episodes of MDD are associated with significant volume loss in the hippocampus in geriatric patients with MDD.[20,21] One possible mechanism for such findings has been pro-

posed in models of decreased hippocampal neurogenesis in MDD, suggesting that depressive episodes may lead to persistent neuronal loss in the hippocampus,[22,23] possibly mediated by acute and chronic stress.[24-26] Human postmortem studies have indicated that abnormalities in neurotrophic signaling may play a major role in MDD, and decreased levels of signal transducers, such as brain-derived neurotrophic factor, have been reported in suicide victims.[27,28] In addition, findings from animal models suggest that neurogenesis may play an important role as a compensatory mechanism toward neurodegenerative change over time.[29] Taken together, these findings would suggest an effect of longstanding or recurrent MDD on the hippocampus through neuronal losses and impaired neuroplasticity. In patients with AD who have a history of MDD, such changes could lead to a decrease in cognitive reserve prior to the development of AD.

Alternatively, it has been suggested that concurrent MDD could directly interact with processes leading to the accumulation of AD neuropathology. Sweet et al[30] reported preliminary data from an ongoing clinicopathologic study of recurrent geriatric MDD in which AD was the predominant neuropathologic diagnosis in dementia patients with a lifetime history of MDD. One possible mechanism for such findings is that the activation of serotonin receptors[31] may be involved in shifting the processing of amyloid precursor protein from nonsecretory (amyloidogenic) to secretory pathways, resulting in a decrease of potentially amyloidogenic derivatives.[32] A decreased serotonergic activity in major depression could thus interact with the accumulation of amyloid early on in the process of AD, representing an effect of concurrent MDD on the progression of AD.

These findings point toward the possibility that the presence of a lifetime history of MDD may be an important factor in the progression of AD. To our knowledge, there have been no studies of neuropathological changes in AD as a function of history of major depression. In the present study, we examined whether the neuropathological presentation of AD is different in patients with a lifetime history of MDD compared with patients with no history of MDD. Specifically, we hypothesized that NP and NFT would be more pronounced in the hippocampus of patients with AD who have a lifetime history of MDD, as compared with patients without a history of depression. Planned post hoc analyses were included to establish the local specificity of such differences in the hippocampus and to assess differences in the rate of cognitive decline in patients with AD with and without a lifetime history of MDD. Furthermore, we contrasted patients (within the group of AD patients with a lifetime history of MDD) who either were or were not depressed at baseline to explore the effects of longstanding recurrent MDD on neuropathological changes vs the effects of concurrent MDD at the onset of AD.

METHODS

PARTICIPANTS

The study builds on the neuropathological portion of the Clinical and Biological Studies of Early AD Program project at the Department of Psychiatry of Mount Sinai School of Medicine, a prospective longitudinal study of cognition in old age. This cohort is part of a larger clinical and epidemiological study of AD in which all consenting residents and new admissions to the Jewish Home Nursing Home, Bronx, NY, were given a baseline screening using the Clinical Dementia Rating scale (CDR),[33] the Mini-Mental Status Examination (MMSE),[34] and an assessment of psychopathology including the Geriatric Depression Scale.[35] After the death of a participant, the last MMSE score obtained prior to death was recorded. Ethical approval was obtained from the institutional review boards of the Department of Veterans Affairs, Bronx, NY, and the Mount Sinai School of Medicine, New York, NY. Written informed consent to participate in the study was obtained from each participant or, in case the participant lacked capacity, from a caregiver.

For the present analyses of neuropathological differences, we used post-mortem data from 102 patients with AD (mean [SD] age at death=81.01 [7.78] years). These data represent all participants with a neuropathologically confirmed diagnosis of AD who completed baseline MMSE, CDR, and psychiatric assessment. For post hoc analyses of cognitive change as a function of lifetime history of MDD, we used MMSE scores at baseline, and at last assessment prior to death.

DIAGNOSIS OF AD

At baseline, dementia diagnosis was ascertained according to *DSM-III* or *DSM-IV* criteria,[36] respectively, and if present, clinical diagnosis of AD was further specified according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[37] research criteria in a consensus conference by attending psychiatrists at the Mount Sinai School of Medicine. Neuropathological diagnoses of AD were made according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathological protocol.[3]

HISTORY OF MDD

The MMSE and CDR scales were administered along with a standardized questionnaire assessing psychiatric history and current symptoms, and comprised assessment with the Geriatric Depression Scale. Trained research assistants administered all tasks. These research assistants completed a standardized questionnaire assessing the presence or absence of *DSM-III-R* or *DSM-IV* symptoms of MDD,[36] which was developed as a modified version of the mood disorders module from the Structured Clinical Interview for *DSM-IV* (SCID) Axis I disorders.[38] At baseline assessment, the presence or absence of a lifetime history of MDD was extracted from medical information, including charts and information obtained from the treating physician. Both the diagnosis of current major depressive disorder and the diagnosis of a lifetime history were reviewed and verified by a physician with specialty training in geriatric psychiatry.

Using the information from the psychiatric symptoms and history data, we defined a lifetime history of MDD as present in patients who had at least 1 prior episode of MDD before the onset of AD according to psychiatric history. Following this classification, 44 of the 102 brain bank patients were defined as having a lifetime history of MDD, whereas 51 did not have a history of MDD, and 7 could not be classified reliably. At the time of baseline assessment, 11 patients were suffering from MDD. In an earlier report,[18] the external validity of the lifetime history of MDD variable was assessed in comparison with scores on the Geriatric Depression Scale, and shown to be satisfactory (sensitivity=0.95, specificity=0.90).

NEUROPATHOLOGICAL ASSESSMENT

After the subject's death, consent for autopsy was obtained from his or her next of kin. A member of the Alzheimer disease brain bank team extracted and extensively photographed each brain. Any gross abnormalities were noted and the brain was divided in the midsagittal plane. The right hemisphere was then suspended from the basilar artery in 4% cold (4°C) buffered paraformaldehyde. All neuropathological studies were performed on the right hemisphere by 2 of us (D.P.P. and D.P.P.). Neuropathological assessments were performed after 4 to 6 weeks of fixation. The neuropathological assessment consisted of examining representative blocks from superior and midfrontal gyrus, orbital cortex, basal ganglia, amygdala, hippocampus (rostral and caudal levels with adjacent parahippocampal and inferior temporal cortex), superior temporal gyrus, parietal cortex, midbrain, pons, medulla, cerebellar vermis, and lateral cerebellar hemisphere. Sections from paraffin embedded blocks were stained using hematoxylin and eosin, modified Bielschowsky, modified thioflavin S, anti–β-amyloid and anti-τ. Any case showing evidence of Lewy body formation in the substantia nigra or locus ceruleus underwent anti-ubiquitin staining (Daka Corp, Carpinteria, Calif) of representative cerebral cortical sections for the identification of cortical Lewy bodies. Immunohistochemical procedures employed an avidin-biotin staining procedure with diaminobenzidine detection. All neuropathologic data were collected in a blinded fashion. After all of the previously mentioned data regarding the extent and distribution of relevant neuropathologic lesions were collected and entered into the research databases, individual cases underwent diagnostic neuropathology evaluation. For this process, all clinical, neuropsychological, and laboratory data were evaluated and a final neuropathological diagnosis was assigned.

Every case was evaluated for the extent of neuropathologic lesions using the CERAD neuropathologic battery.[3] Multiple high-power fields (5 in general) were examined in each slide and the density of NP (with and without amyloid cores) and NFT were rated on a 4-point scale of absent, sparse, moderate, or severe according to the scoring criteria established by the CERAD. When NP or NFT were unevenly distributed in each slide, plaques in the region with the highest density were counted. Assessments of NFT were based primarily on modified Bielschowsky staining.

STATISTICAL ANALYSES

Raw scores were used for all analyses. All analyses were performed using statistical software (SPSS Inc, Chicago, Ill). Between group *t* tests and χ^2 tests were used to assess group differences in descriptive variables and covariates. All tests of significance were 2-tailed with α set at .05. Effect sizes were calculated using Cohen's d.[39] To assess the overall relationship between lifetime history of MDD and neuropathological presentation in the hippocampus of patients with AD, CERAD scores of both NFT and NP were entered into a multivariate analysis of variance. Follow-up univariate F tests were then conducted to assess whether specific neuropathological changes (ie, NFT vs NP) differentiate between patients with AD with and without a history of MDD.

To control for confounds, multivariate analysis of covariance was used. Covariates were age at death in years, cause of death, time since baseline assessment (ie, time of admission to the nursing home) in years, sex, education, cognitive status as assessed by the MMSE, and dementia severity as measured with the CDR. In cases where the variance-covariance matrix violated homogeneity assumptions, Wilk's λ is reported.

To assess the local specificity of hippocampal changes as a function of lifetime history of depression, logistic regression analysis was performed to predict group membership (presence vs absence of a lifetime history of MDD) from the neuropathological scores of NFT and NP in the hippocampus over and above neuropathological scores in other brain areas that have been shown to be susceptible to structural change in the course of MDD.[40,41] To that end, NP and NFT scores in the entorhinal cortex, amygdala, and medial frontal cortex were entered at step1 in a logistic regression with group membership as the dependent variable. At step 2, NP and NFT scores in the hippocampus were entered. Using Nagelkerke statistics, this method allows for quantification of the amount of unique variance in group membership explained by hippocampal changes vs all other brain areas through the comparison of incremental model fits using likelihood ratio tests, and it reflects an indirect measure of local specificity.

Post hoc analyses were performed to determine differences in the rate of cognitive decline in patients with AD as a function of lifetime history of MDD. For descriptive purposes, annualized cognitive decline was estimated as the difference of scores between baseline assessment and last assessment prior to death, divided by the number of years from baseline to last assessment. Exploratory analyses were performed entering annualized decline into a multivariate analysis of covariance, controlling for age at death in years, cause of death, sex, and education.

Furthermore, we contrasted (within the group of AD patients with a lifetime history of MDD) patients who were or were not depressed at baseline to explore the effects of longstanding recurrent MDD on neuropathological changes vs the effects of concurrent MDD at the onset of AD. Neuropathological scores were entered in an analysis of covariance, controlling for covariates, and contrasting patients with AD with a lifetime history of MDD as a function of depression status at baseline (present vs absent).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The overall study group (N=95) was composed of 32 men (33.7%) and 63 women (66.3%), with a mean age at death of 81.36 years (SD, 7.79, range, 55-100), a mean education level of 11.74 years (SD, 3.57, range, 3-20). At baseline, the mean MMSE score was 21.48 (SD, 4.73, range, 8-30), and the mean CDR score was 2.02 (SD, 0.81, range, 0.5-3). The mean MMSE score at the last assessment prior to death was 12.37 (SD, 7.41, range, 0-30). At baseline, 68 patients received a clinical diagnosis of possible AD, and 33 patients received a diagnosis of probable AD according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria. Post-mortem neuropathological diagnoses were distributed in the following manner: 83 patients received a diagnosis of definite, 8 of probable, and 10 of possible AD. There was no difference between patients with AD with or without a lifetime diagnosis of MDD in the distribution of diagnoses (for clinical diagnoses, $\chi^2_2=7.30$; $P=.39$; for neuropathological diagnoses, $\chi^2_2=0.19$; $P=.99$).

There were no statistically significant differences between patients with AD with vs without a lifetime history of MDD with respect to sex and education. However, there was a statistically significant difference between

Table. Demographic Characteristics of Patients With AD Without and With a Lifetime History of MDD

Demographic Variable	Never MDD* (n = 51)	Past MDD* (n = 44)	t_{93}/χ^2_1	*P* Value
Age (SD) at death, y	80.03 (8.76)	82.89 (6.25)	1.80	.08
No. (%) of females	32 (62.7)	31 (70.5)	0.63	.52
Education (SD), y	11.43 (3.79)	12.09 (3.30)	0.90	.37
CDR score (SD) at baseline	1.93 (0.93)	2.14 (0.62)	1.24	.22
MMSE score (SD) at baseline	20.23 (5.48)	22.81 (3.33)	2.81	.01
Time (SD) since baseline, y	8.09 (3.11)	6.98 (2.34)	1.98	.05
Last MMSE score (SD) prior to death	12.70 (8.27)	11.98 (6.34)	0.47	.64
Time (SD) since last assessment, y	3.08 (2.01)	2.59 (1.32)	1.38	.17

Abbreviations: CDR, Clinical Dementia Rating scale; MDD, major depressive disorder; MMSE, Mini-Mental State Examination.
*Never MDD denotes participants without a lifetime history of major depression. Past MDD denotes participants with a lifetime history of major depression.

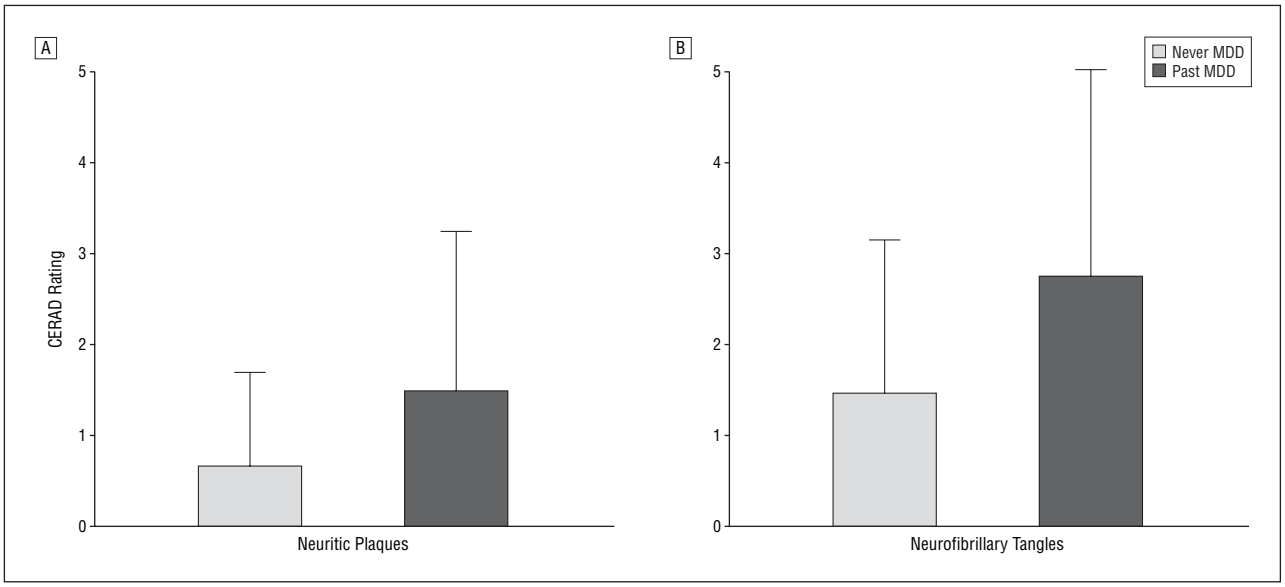

Figure. Neuropathological scores in patients with Alzheimer disease without a lifetime history of major depressive disorder (Never MDD) and with a lifetime history of major depressive disorder (Past MDD). A, Consortium to Establish a Registry in Alzheimer's Disease (CERAD) rating for neuritic plaques in the hippocampus. Significant main effect for lifetime history of major depressive disorder ($F_{1,95}$=8.28, d=0.58, P<.005). B, Consortium to Establish a Registry in Alzheimer Disease rating for neurofibrillary tangles in the hippocampus. Significant main effect for lifetime history of major depressive disorder ($F_{1,95}$=9.96, d=0.64, P<.002).

cognitive status at baseline as measured by the MMSE, in that patients with AD with a lifetime history of MDD slightly outperformed patients with AD without a lifetime history of MDD. There were no group differences in cognitive status at last assessment prior to death as measured by the MMSE. There was a trend difference in age at death. Time since last assessment prior to death did not differ between the lifetime history and non-MDD groups. However, there was a significant difference between time since baseline assessment (ie, time since admission to the nursing home), in that time from baseline to death was shorter in patients with AD with a lifetime history of MDD. Characteristics of the sample, alongside statistical indicators, are listed in the **Table**.

DIFFERENCES IN NEUROPATHOLOGY

An omnibus multivariate analysis of variance indicated a significant difference between patients with AD with and without a lifetime history of MDD in the ratings of NFT and NP in the hippocampus ($F_{2,94}$=5.33, P<.006). Neurofibrillary tangles and NP scores in both patients with and without a lifetime history of MDD are shown in the **Figure**.

Univariate analysis revealed that this effect was reliable in both NFT ($F_{1,95}$=9.96, d=0.64, P<.002), and NP ($F_{1,95}$=8.28, d=0.58, P<.005). Mean CERAD scores in both NFT and NP in the hippocampus were higher in patients with AD with a lifetime history of MDD, an effect which represented a medium effect size in the terminology of Cohen.[39]

POTENTIAL CONFOUNDS

Because age, sex, education, cognitive status and dementia severity have been related to volumetric and neuropathological changes in the hippocampus, age at death in years, time since baseline assessment in years (ie, time since admission to the nursing home), sex, education, cognitive status as assessed by the MMSE, and dementia severity as measured with the CDR scales were entered together in a multivariate analysis of covariance containing both NFT and NP. The main effect for group remained significant for the omnibus tests ($F_{2,87}$=4.68,

$P<.01$). Univariate analyses revealed that this effect was significant for NFT in the hippocampus ($F_{1,88}=8.86$, $d=0.59$, $P<.004$). Likewise, results remained stable for hippocampal NP ($F_{1,88}=6.90$, $d=0.46$, $P<.01$). Additional control analyses revealed that the cause of death did not differ between the 2 groups. Specifically, the most frequent causes of death in our sample, pneumonia (n=22), cardiovascular failure (n=21), renal failure (n=10), liver failure (n=6), and malignant disease (n=13), did not differ between patients with AD with and without a lifetime history of MDD ($\chi^2_4=3.19$; $P=.53$).

LOCAL SPECIFICITY OF NEUROPATHOLOGICAL CHANGES

Logistic regression for both NFT and NP revealed that CERAD scores in the entorhinal cortex, amygdala, and medial frontal cortex entered at step 1 accounted for 10% of the variance in group membership, a finding that did not reach statistical significance ($\chi^2_5=7.47$; $P=.19$). Entering hippocampal measures of NP and NFT at step 2 led to an increase of variance accounted for by 17.8%, a finding of statistical significance ($\chi^2_2=5.69$; $P<.05$).

Separate analyses for NFT and NP, respectively, revealed similar results. Logistic regression for NFT alone revealed that CERAD scores in the entorhinal cortex, amygdala, and medial frontal cortex entered at step 1 accounted for 9.2% of the variance in group membership, a finding that did not reach statistical significance ($\chi^2_3=6.77$; $P=.08$). Entering hippocampal NFT at step 2 led to an increase of variance accounted for by 14.8%, a finding of statistical significance ($\chi^2_2=4.35$; $P<.04$). Similar results were found for NP alone; at step 1, CERAD scores in the entorhinal cortex, amygdala, and medial frontal cortex accounted for 5.3% of the variance in group membership ($\chi^2_3=3.83$ $P=.15$). Entering hippocampal NP at step 2 led to an increase of variance accounted for by 11.3% ($\chi^2_1=4.48$; $P<.03$).

COGNITIVE DECLINE OVER TIME AS A FUNCTION OF HISTORY OF MDD

Mean annualized decline was 1.15 points (SD=1.13) in patients without MDD history, and 1.86 points (SD=1.16) on the MMSE in patients with AD with a lifetime history of MDD. An omnibus multivariate analysis of covariance, controlling for age at death in years, cause of death, sex, and education revealed that estimated annualized decline was larger in patients with AD with a lifetime history of MDD ($F_{1,94}=8.51$, $P<.004$).

NEUROPATHOLOGICAL DIFFERENCES IN PATIENTS WITH AD WITH A HISTORY OF MDD AS A FUNCTION OF DEPRESSION STATUS AT BASELINE

Of the 44 patients with a lifetime history of MDD, 11 were depressed at baseline assessment, whereas 33 were not depressed at baseline. The mean CERAD rating for patients with AD with a lifetime history of MDD who were depressed at baseline was numerically higher (for NP, M=3.00, SD=1.26; for NFT, M=4.82, SD=0.60) than in patients with AD with a lifetime history of MDD who were not depressed at baseline (for NP, M=1.24, SD=2.09, for NFT, M=2.20, SD=2.42). Controlling for age at death in years, time since baseline assessment in years, sex, education, cognitive status as assessed by the MMSE, and dementia severity as measured with the CDR scales, the omnibus multivariate analysis of variance indicated a significant difference ($F_{2,36}=5.84$, $P<.006$) in that patients with AD with a lifetime history of MDD who were depressed at baseline showed a larger proportion of NP and NFT in the hippocampus.

Univariate analysis revealed that this effect was reliable in both NFT ($F_{1,37}=11.99$, $P<.001$) and NP ($F_{1,37}=6.48$, $P<.02$). Mean CERAD scores in both NFT and NP in the hippocampus were higher in patients with AD with both a lifetime history of MDD and MDD at baseline, an effect which represented a medium effect size in the terminology of Cohen.[39]

COMMENT

In line with our hypotheses, we found distinct differences in both NP and NFT in the hippocampus of patients with AD as a function of depression history. To our knowledge, this is the first study to establish a larger number of NP and NFT in the hippocampus of patients with AD with a lifetime history of MDD. Specifically, we were able to show that patients with a neuropathologically confirmed diagnosis of AD who have a history of MDD (before the onset of dementia) exhibit a larger number of NP and NFT in the hippocampus than patients with AD who never had an episode of MDD in their life. Neuropathological changes in the hippocampus explained a small amount of variance in lifetime history of MDD over and above the effects of neuropathological changes in the entorhinal cortex, amygdala, and midfrontal gyrus, suggesting topographic specificity of the effect of lifetime history of MDD. Post hoc analyses suggest that patients with AD with a lifetime history of MDD exhibit more rapid cognitive decline than patients with AD without history of MDD. Within patients with AD with a lifetime history of MDD, those patients who at the time of first diagnosis of AD suffered from concurrent MDD exhibited an even larger number of hippocampal NP and NFT.

These results have great clinical significance in that the identification of potential mechanisms that link geriatric MDD as a treatable risk factor to neuropathological changes in AD may lead to the development of differential intervention and prevention strategies for AD. Such specific interventions would be especially needed since geriatric patients with MDD with cognitive impairment may have less favorable treatment outcomes.[42-44]

On a conceptual level, this study adds to earlier studies showing an increased risk for the development of AD in patients with recurrent geriatric MDD.[8-16] It is in line with a recent study showing an association between MDD and AD neuropathology in geriatric patients.[30] However, it also poses important questions toward the identification of potential mechanisms underlying the increase in AD neuropathology as a function of lifetime history of MDD. In that context, a limitation of this study

is the absence of volumetric data on hippocampal size in our sample. Consortium to Establish a Registry in Alzheimer Disease ratings of neuropathology in AD represent area-density of NP and NFT in the hippocampus.[3] In the absence of volumetric data, there remains some uncertainty as to whether the changes observed in our study reflect an increase in NFT or NP, respectively, or merely an increase in density of AD neuropathology in the face of volumetric losses that may have been caused by impaired neurogenesis through longstanding recurrent episodes of MDD,[22,23] as opposed to a direct interaction between concurrent MDD and beginning AD neuropathology, leading to a shift in amyloidogenic processing early in the AD process.[30-32] Thus, the final common pathway leading to increases in NFT and NP remains to be investigated. However, our study provides some preliminary evidence that allows us to formulate the hypothesis that a direct interaction model early on in the AD process may be valid. First, the effect sizes reported in studies of hippocampal volume loss related to recurrent MDD are usually smaller than the effect sizes seen in this study,[20,21] suggesting that volume loss alone cannot fully account for our findings. Second, additional post hoc analyses indicate that AD neuropathology is more pronounced in patients who, at the time of first diagnosis of AD, suffered from concurrent MDD, suggesting an interaction between concurrent MDD and AD progression. Third, cognitive status at baseline was better in patients with AD with a history of MDD, but crude annualized decline in these patients was larger than in patients with AD without MDD history, suggesting that indeed an accelerated process, rather than a reduced cognitive reserve at baseline, may correlate with the observed neuropathological changes.

Alternative to this explanation, the increased risk for AD in geriatric MDD could be mediated by other neuropathologic comorbidities, specifically vascular lesions[45-47] or Lewy body (DLB) pathology.[48,49] Prior studies have shown both cerebrovascular lesions[50] and DLB pathology[48,49] to be additive with AD pathology in generating cognitive symptoms. In some of our patients with AD, comorbid cerebrovascular lesions (n=23) or DLB pathology (n=9) were present but did not differ between patients with a history of MDD (for cerebrovascular lesions, n=5; for DLB pathology, n=11), and patients without a lifetime history of MDD (for cerebrovascular lesions, n=4; for DLB pathology, n=12). Thus, controlling for both the presence of vascular and DLB pathology did not essentially change the results (for the omnibus multivariate analysis of covariance, $P<.007$). A limitation in that context is the lack of systematic screening of amygdala and entorhinal cortex with α-synuclein, which may have led to an underestimation of cases with DLB pathology.

In terms of sampling bias, the prevalence rates of current MDD and lifetime history in our sample of patients with AD are comparable with representative samples. The reported point prevalence of MDD in older nursing home residents ranges from 6% to 32%,[51] and is thus comparable with the prevalence of about 11% in our sample. To our knowledge, there is only 1 study on the lifetime prevalence of MDD in adults aged 70 years and older, which in fact reports rates of 23% to 45%.[52] Clinical studies suggest that the prevalence of MDD in AD may be even higher, ranging from 30% to over 50%,[53] and is thus comparable with our finding of a lifetime prevalence of 44% in our sample.

Additional limitations of this study include the fact that because we studied participants of very old age in our sample, findings cannot be generalized to patients with AD who have onset in their fifth and sixth decades of life. Second, the retrospective assessment of a lifetime history of depression is characterized by intrinsic methodological limitations, and may, among other confounders, be biased by memory deficits. Prior studies showed that when informants and structured interviews are used, inter-rater reliability may not exceed 80%.[54] Thus, the specificity of our diagnosis of MDD may be limited. However, such an underestimation of lifetime history of depression would, for the case of this study, lead to an underestimation of the true effect size. Furthermore, our data are consistent with preliminary data from a longitudinal study on geriatric MDD that is currently under way.[27]

This study only establishes a cross-sectional association between lifetime history of depression and neuropathological changes in patients with AD. Further research is needed to establish whether these changes indeed reflect impaired neuroprotective mechanism processes owing to recurrent major depression throughout the life course, or whether they reflect an interaction between concurrent MDD and AD neuropathology at the onset of AD. Ideally, studies aimed at investigating the effects of lifetime history of MDD would follow older adults with mild cognitive impairment and a known presence or absence of past MDD longitudinally, to identify both age-related and disease-related change over time and possible underlying mechanisms.

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