ORIGINAL ARTICLE

Lack of Association Between Depression and Loss of Neurons in the Locus Coeruleus in Alzheimer Disease

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Background: Depression, one of the most frequent psychiatric disturbances in Alzheimer disease (AD), is proposed to have its neurobiological basis in neuron loss in the noradrenergic locus coeruleus, although this is not the case in idiopathic depression.

Methods: We performed image analyzer–assisted morphometry of the locus coeruleus in 6 depressed, 6 transiently depressed, and 6 nondepressed patients with AD and in 8 control subjects, emphasizing longitudinal psychiatric evaluations and matching for the clinical and neuropathological severity of dementia.

Results: The mean (±SD) number of pigmented neurons in the locus coeruleus in controls (11 607±946) was higher than in patients with AD, regardless of being depressed (5165±928; *P*=.001), transiently depressed (5647±1163; *P*=.003), or nondepressed (3717±661; *P*=.001). No significant difference was found in the number of pigmented neurons between patients with AD who were depressed, transiently depressed, and nondepressed. Patients who had depression at the onset of AD had a higher pigmented neuron number than other patients with AD.

Conclusions: We confirmed the loss of pigmented neurons in the locus coeruleus of patients with AD; however, no supplementary loss of pigmented neurons in the locus coeruleus was found in patients with depression and AD. This finding resembles the situation in idiopathic depression, but is in contrast with earlier studies on depression in AD.

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ALZHEIMER DISEASE (AD) is generally considered a disturbance of cognition. Recently, however, depressive and other psychiatric symptoms have gained more interest, since these symptoms may seriously increase caregiver burden and are frequently the reason for hospitalization.[1] This is also of practical clinical relevance since depressive symptoms in patients with AD can be successfully treated with selective serotonin reuptake inhibitors.[2] These cause little postural hypotension[3] and can be used relatively safely in the elderly and for AD, whereas no effective treatment is, at present, available for AD itself.

The neurobiological basis of depression in AD is unclear, while that of idiopathic depression has been related to several monoaminergic systems, including the noradrenergic, system.[4,5] Neuropathological changes in the locus coeruleus (LC), which is the major source of central norepinephrine, however, have not been substantiated in patients with depression.[6,7] Over the past years, 3 groups hypothesized that depression in dementia[8] and especially in AD[9,10] may have a neurobiological basis in the LC. Their results suggest that the LC, which is known to be severely affected in AD, is even more affected in patients with depression and dementia.

Many methodological issues in these studies, however, may have given rise to false-positive results. We therefore studied the LC in patients with AD who were depressed, transiently depressed, and nondepressed and in control subjects, emphasizing longitudinal psychiatric evaluation at the symptom level, clinical matching for severity of dementia, and neuropathological matching for the severity of AD , neurological comorbidity, and image analyzer–assisted morphometry of the LC.

RESULTS

PSYCHOMETRY

Patients with AD and depression were notably more depressed on different

PATIENTS AND METHODS

DESIGN

Patients with dementia were studied at 6-month intervals in the framework of a prospective longitudinal study of depression in AD in 8 nursing homes. Informed consent for the interviews was provided by the patients' next of kin, and the patients' consent was provided at the time of each interview. Written, informed consent for brain autopsy was obtained before patients enrolled in the study, as part of the program of the Netherlands Brain Bank. All patients with major neuropathological comorbidity were excluded. The left LC of 22 patients fulfilling National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association[11] and the Consortium to Establish a Registry for Alzheimer Disease criteria[12] for definite AD and 8 controls could be obtained. While blind to the depression diagnosis, 4 of these 22 patients were excluded, since Lewy bodies were abundant in substantia nigra or cortex. The remaining 18 patients with AD (**Table 1**) were divided into 3 groups (depressed, transiently depressed, and nondepressed).

CLINICAL EVALUATION

Patients' next of kin and nursing home physicians were interviewed about medical history and the age at onset of AD. Possible and probable AD were diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association[11] and *DSM-III-R* criteria.[13] The *DSM-III-R* criteria (inclusive approach) were also used to diagnose a major depressive episode (except for the absence of an organic factor, ie, AD) or dysthymia (except for the 2-year duration criterion). The severity of the depressive symptoms was determined at 6-month intervals by the Hamilton Depression Rating Scale[14] and the Cornell Scale for the Assessment of Depression in Dementia.[15] To estimate the influence of symptom overlap, we interviewed our patients by using the standard (inclusive) method,[16] and by using the diagnostic–etiologic (exclusive) method[17] At 6-month intervals and immediately post mortem the Global Deterioration Scale[18] and Functional Assessment Staging[19] were used to determine the severity of clinical dementia. The mean (± SD) interval between the last clinical measurement and death was 4.3 ± 0.9 months and did not differ between the 3 AD groups ($P = .7$).

Six of the remaining 18 patients with AD suffered from a major depressive episode according to *DSM-II-R* at the time of death, with a minimum duration of 5 months and high scores on the Cornell Scale for the Assessment of Depression in Dementia (>13). This depressed AD group was matched for the duration of clinical dementia ($P = .5$) with 6 nondepressed AD patients having low scores on the Cornell Scale for the Assessment of Depression in Dementia (<9) (Table 1 and **Table 2**). Patients with AD and depression were also matched with 6 patients with AD and transient depression, who, in contrast to the depressed AD group, did not have a major depressive episode in the last 4 months of life. The patients with transient depression and AD had a transient major depressive episode or dysthymia during the course of AD (patients 7, 9, 10, and 11) or a history of depression requiring admission prior to AD with depressive symptoms during the course of AD (patients 6 and 12) (Table 1). Moreover, patients with AD and depression, transient depression, or no depression did not differ in severity of clinical dementia, age, age at onset, psychiatric comorbidity, medication used, and severity of AD (Table 1 and 2). Patients with AD and transient depression scales during the last measurement before death than patients with AD and either transient or no depression. Patients with AD and transient depression were more depressed than patients with AD and no depression. Patients with depression and AD who had also had a depression at the onset of AD (patients 2, 4, and 5) had the highest scores of all patients on the Hamilton Depression Rating Scale (26.3 ± 0.3), the Cornell Scale for the Assessment of Depression in Dementia (23.0 ± 2.5), and the exclusive Cornell Scale for the Assessment of Depression in Dementia (21.7 ± 2.3) (Table 1 and 2).

MORPHOMETRY

The intraobserver reliability (100% × SD per mean value) for the measurement of the number of pigmented neurons in the LC (8.2%), determined by measuring the same section 5 times in the course of the study, was good.

The volume of the LC in the control group was larger than in the AD groups, but no difference was found among AD groups (Table 2). The mean total number of pigmented neurons of the LC in patients in the control group was higher than in patients with AD, regardless of their being depressed, transiently depressed, or nondepressed (Tables 1 and 2). The control group had higher neuron numbers than the AD group in the rostral, middle, and caudal part of the LC, but no differences were found among the 3 AD groups in these areas (Table 2). The mean neuron number in the entire LC in the depressed and transiently depressed AD group was relatively high, but not statistically different from the nondepressed AD group. The 3 patients with AD and depression who had a depression at the onset of AD had a mean pigmented neuron number (6453 ± 1024) that was relatively high, but not statistically different from the other patients with AD (Table 1). Taking all patients with AD together (n = 18), no correlation was found between severity of depression (inclusive Cornell) and neuron number ($r = 0.14$, $P = .57$). In addition, no correlation was found between neuron number and the duration of depression ($r = -0.38$; $P = .46$).

COMMENT

The number of pigmented neurons in the LC in controls in our study, as well as the severity of neuronal loss in AD, is in agreement with the literature.[20,22] Our finding that the total number of pigmented neurons in

sion were all female, but this did not influence our data since sex differences in LC neuron counts have not been found in humans.[20] Finally, patients with AD were matched with 8 controls without any psychiatric or neurological diseases, except for patient 9, who had psychosis, and patient 21, who had used haloperidol for a transient delirium. Excluding these controls would only have intensified our results. All controls were free of neuropathologic changes, except for small or multiple infarctions. The mean (± SD) age of controls was lower ($P = .004$) than that of the entire AD group (84.6 ± 1.6 years), but this was not considered a relevant difference, since LC neuron number decreases by only 7% between the ages of 75 and 85 years.[21-23] Postmortem delay was longer in controls than in AD, but no difference was found between the 3 AD groups (Table 2).

NEUROPATHOLOGIC FINDINGS

After a standard fixation time of 4 weeks, a semiquantitative estimation of the severity of AD changes according to the classification of Braak et al[24] was performed by one of us (W.K.). A more differentiated semiquantitative sum-score of neurofibrillary tangles, neuritic plaques, and neuropil disruption was established in a Bodian staining of frontal, temporal, parietal, and occipital cortex and hippocampus. In each area all AD changes were separately scored as 0, absent; 1, absent to moderate; 2, moderate (ie, 2-3 neurofibrillary tangles, 2-3 neuritic plaques or 30%-60% of the normal network replaced by neuropil threads per 0.4 mm^2 area); and 3, more than moderate.

MORPHOMETRY

The left brainstem, containing the entire LC, was dissected and serial 6-µm paraffin sections were cut transversely. Every 100th section was stained with 0.1% hematoxylin and 0.2% eosin. Cell counts of the pigmented norepinephrine–producing[25] neurons and volume measurements of the LC were performed as described in detail elsewhere.[26] Briefly, the analyses were performed on an image analysis system (Imago Bild Analyse System; Kontron, Munich, Germany) connected to a television camera on a Zeiss microscope and equipped with a scanning stage; both were controlled by a joystick and the image analyzer. Reliability and calibration studies of the method are described elsewhere.[26] Counting neurons at high magnification (×500) was done in an area-weighed, nonselective sample taken by the image analysis system. The scanning stage moved automatically to the positions included in the sample. The total number of pigmented neurons was estimated using an unfolding procedure on the profiles of the pigmented neuron nucleus.[26] This procedure determines neuron density, precluding the double counting of neurons, multiplied by the LC volume. Since the rostral and middle part of the LC have projections to mood-related limbic structures, and the caudal part to the spinal cord, separate measurements were performed for the rostral, middle, and caudal part of the LC as defined by Chan-Palay and Asan.[25] During morphometry one of us (W.J.G.H.) was blind to clinical findings.

STATISTICAL ANALYSIS

For some variables the population variance in the AD and control groups was different. Differences among groups were therefore statistically evaluated by the nonparametric Kruskal-Wallis multiple comparisons test (2 tailed). Relationships between variables were assessed by Spearman rank correlation coefficients. P values less than .05 were considered to be statistically significant. All values are expressed as the mean ± SD.

patients with AD and depression is not different or lower than that of patients with AD and no depression is in contrast with earlier studies.[8-10] These studies suggested that the neuronal loss in the noradrenergic LC in AD was even more severe if the patient was also depressed, providing support for the noradrenergic hypothesis of depression and offering a theoretical rationale for noradrenergic antidepressant treatment of patients with AD and depression. In idiopathic depression, no neuron loss in the LC was found[6,7]; however, in AD 50% to 80% of the neurons are lost.[20,26] It is therefore difficult to detect a mild supplementary neuron loss due to depression, on top of the severe neuron loss that is already present in the LC of patients with AD. For the same reason, it is crucial that the patients with AD in the depressed group have the same degree of dementia as patients with AD in the nondepressed group, since a slightly more severe degree of AD in the depressed AD group would go together with a supplementary neuron loss in this group. Therefore, these previous studies[8-10] were susceptible to generating false-positive results due to a mismatch between the depressed and nondepressed dementia group regarding the clinically and neuropathologically established severity of AD.

Matching for covariables of severity of dementia is, however, complicated by many methodological issues. First, depression and dementia have some symptoms in common, including loss of interest, decreased energy, difficulty in thinking or concentrating, and psychomotor agitation or retardation.[27] To control for symptom overlap we used the Cornell scale, which was specifically developed for the assessment of depression in all stages of dementia. Furthermore, in our 6-month follow-ups we interviewed our patients using not only the standard (inclusive) method, but also the diagnostic–etiologic (exclusive) approach. The patients with high Cornell scores (>9) according to the exclusive approach had pigmented neuron numbers that were even among the highest of the AD group. The exclusive approach showed that an attempt to purify depression symptoms, thus diminishing symptom overlap, intensified our results. In most earlier studies, it was difficult to avoid symptom overlap, since retrospective interviews and medical chart reviews were used[10] and the severity of depression was not determined.[8,10]

The second methodological issue is that it may be difficult to clinically distinguish levels of severity of dementia in the final stages of AD (floor effect).[19] Therefore, we obtained Functional Assessment Staging

Table 1. Patient Characteristics*

NBB No./Sex	Depression Type and Course (Duration per Episode, mo)	Psychiatric Comorbidity	Somatic Disorders and Cause of Death	Medication (Last 3 mo)†	Neuropathologic Status
					Depressed AD
1/F	ND; dysthymia (10); MD (5)	None	Alcohol abuse	Folic acid	AD
2/M	D at onset and before AD; MD (36)	None	Type 1 diabetes, pneumonia	Haloperidol, promethazine, insulin	AD, small infarction
3/M	ND; dysthymia (5); MD (5)	Agitation, compulsive eating	Cardiac infarction	Haloperidol, temazepam	AD, small infarction
4/M	D at onset AD; ND; MD (36)	Hallucinations, anxiety	Anemia	None	AD
5/F	D at onset AD; ND; MD (27)	Agitation	Epilepsy, cardiac failure	Morphine sulfate	AD
6/F	ND; MD (24)	None	Hypertension, dehydration**	Diazepam, atenolol	AD, multiple infarction
					Transiently Depressed AD
7/F	ND; MD (6); dysthymia (18)	Delirium, anxiety	Cardiac failure, pneumonia	Digoxin, zuclopenthixol	AD
8/F	ND; recurrent D long before AD	Agitation	Rheumatoid arthritis	Morphine, diazepam	AD
9/F	ND; dysthymia (12); unknown (6); MD (6); ND (9)	Agitation	Cardiac infarction, dehydration#	Nitrazepam, spironolactone	AD
10/F	ND; MD (6); ND (4)	Hallucinations	Bradycardia, pneumonia	Diclofenac	AD
11/F	ND; dysthymia (24)	None	Hypertension, cardiac infarction	Oxazepam, ibuprofen	AD
12/F	ND; admission for D long before AD	None	None	Morphine, diazepam	AD
					Nondepressed AD
13/F	No mood disorder	Hallucinations, anxiety	Dehydration#	Haloperidol	AD
14/M	No mood disorder	Delirium	Fever of unknown origin	Haloperidol, oxazepam	AD
15/F	No mood disorder	None	Pneumonia, dehydration#	Morphine, clonazepam	AD, multiple infarction
16/M	No mood disorder	Apathy, agitation	Cerebrovascular accident, cardiac failure, pneumonia	Morphine, diazepam	AD
17/F	No mood disorder	None	Type 1 diabetes	Insulin	AD
18/F	No mood disorder	None	None	None	AD
					Control Subjects
19/F	. . .	Chronic psychosis	Hydronephrosis, sepsis	Penfluridol	Multiple infarction
20/F	. . .	. . .	Type 1 diabetes, hypertension, cerebrovascular accident	Phenytoin, insulin	Multiple infarction
21/F	. . .	. . .	Pneumonia, cardiac infarction	Haloperidol, digoxin	Normal
22/M	. . .	. . .	Hypertension, cardiac failure	Enalapril maleate	Normal
23/F	. . .	. . .	Asthma, cardiac failure	Nitrazepam, theophylline, prednisone	Normal
24/M	. . .	. . .	Cardiac infarction	Triamterene, isosorbide dinitrate	Normal
25/F	. . .	. . .	Cardiac failure, type 2 diabetes	Oxazepam, isosorbide dinitrate	Normal
26/F	. . .	. . .	Mamma carcinoma, dyspnea	Triamterene	Small infarction

**AD indicates Alzheimer disease; ND, no depression; MD, major depressive disorder; D, depressed mood; and NBB, Netherlands Bank.*
†*Patients with infections used antibiotics; patients were given morphine sulfate only in the last hour of life.*
‡*Parentheses indicate a more differentiated semiquantitative sum score of Alzheimer disease pathology in 4 cortex areas and the hippocampus.*
§*This is the total number of pigmented neurons in the locus coeruleus.*
‖*Indicates Cornell Scale for the Assessment of Depression in Dementia.*
¶*FAST indicates functional assessment staging.*
#*All patients with dehydration also showed some cachexia.*

scores every 6 months, and 1 additional Global Deterioration Scale score concerning the last 2 weeks of life was performed immediately post mortem. Since some floor effect of the clinical assessment may still be present, we also matched the depressed and nondepressed AD groups for the severity of neuropathological AD changes, according to Braak et al[24] and to a more differentiated semiquantitative analysis of AD changes (Tables 1 and 2). In 1 of the previous studies,[10] the patient groups were not exactly matched for AD severity, which may also have influenced their finding in the raphe nucleus.

Third, groups should be matched for neurological comorbidity.[28] To control for neurological comorbidity, we excluded all patients with dementia that showed neuropathological signs of major neurological comorbidity. This was done before the 3 AD groups were composed, thus precluding a selection bias concerning depression. Multiple cerebral infarctions were found in 1 patient with AD and depression and 1 patient with AD and no depression, while 2 more patients with AD and depression only showed 1 small infarction. One patient with AD suffered from alcoholism (Table 1), which may theoretically affect the LC,[29] but post hoc exclusion of these subjects would only have intensified our results. One of the earlier studies[8] included more patients with neuropatho-

Neuropathological Severity of AD‡	No. of LC Neurons§	Last Cornell Scale Score‖	Last FAST¶
6 (35)	2176	14	7d
4 (22)	8500	26	6e
4 (19)	6349	17	6e
6 (31)	5489	25	6e
6 (20)	5369	18	6
5 (22)	3110	14	7c
6 (28)	7559	12	7a
4 (25)	10 107	8	7f
4 (19)	4925	9	6e
5 (22)	4749	11	7c
5 (17)	4765	9	6c
6 (36)	1780	12	7c
4 (20)	5406	5	6d
5 (15)	2371	8	6e
6 (36)	2633	9	6e
4 (17)	6137	4	6
5 (19)	2787	5	7d
6 (31)	2967	9	7b
. . .	11 049	. . .	. . .
. . .	15 785	. . .	. . .
. . .	6515	. . .	. . .
. . .	11 883	. . .	. . .
. . .	13 399	. . .	. . .
. . .	10 973	. . .	. . .
. . .	12 807	. . .	. . .
. . .	10 448	. . .	. . .

logical signs of Parkinson disease in the depressed (n = 4) than in the nondepressed dementia group (n = 3), while a more severe LC neuron loss has been reported in patients with both parkinsonian and dementia signs.[30] According to this study[28] the increased number of Lewy bodies in the LC, as part of a composite score, shows that the LC is more affected in patients with dementia and depression than in patients with dementia and no depression. It may thus be that the LC in this study[8] is more affected by Parkinson disease than by depression. Groups should also be matched for the presence of vascular pathologic condition, since this may attribute to the severity of clinical dementia, although it has never been shown to affect the LC.[31] In the nondepressed dementia group of the latter study[8] 1 patient was included with both AD and multiple infarcts and 3 patients with vascular dementia. The depressed group in this study[8] may have been as clinically demented as the nondepressed group, even though having more neuropathologic AD changes. The more severe degree of neuropathologic AD changes in the depressed group may explain the supplementary number of tangles and neuron loss in the LC, rather than depression.

The fourth methodological issue is that the distribution of neurons in the LC is heavily dependent on the level in rostrocaudal direction where counting performed.[20] This may result in a large variability in neuron counts if the LC is delineated by hand[26] or if the number of sections in the sample is small or restricted to a certain portion of the LC as in most earlier studies.[8,9] To avoid biased outlining that might influence the results, we performed image analyzer–assisted morphometry[26] and counted the pigmented neurons in a large sample at all 3 levels of the LC (Tables 1 and 2). Moreover, since in our study mean values in patients with AD and depression were not lower than in patients with AD and no depression, it is hazardous to perform 1-tailed statistics, as was done in 1 previous study.[9]

It is unclear whether the subtle complaints of sadness of a patient with mild dementia signify the same depressive syndrome as the emotional incontinence of a patient with severe dementia. Therefore, we also studied patients with AD and transient depression in our study, who did not have a major depressive episode during the last stage of AD and who showed a mean neuron number that was not different or lower than that of patients with AD and no depression. Therefore, it is unlikely that our discrepant results are caused by a different (more severe) AD group, resulting in a floor effect in our study and precluding the detection of any additional neuron loss associated with depression. Moreover, the loss of LC neurons in AD in this study (59%) was not as extreme as in some other studies.[26] Finally, the duration and severity of dementia, the severity of neuropathological changes, and the percentage of LC neuron loss in AD resembled that of the other studies.[8-10] Although taking our patients with AD and depression or transient depression together (n = 12) only intensified our results, more studies in larger populations of patients with AD will be needed to confirm the absence of differences in locus coeruleus neuron counts.

In a recent editorial, Esiri[32] emphasized the difficulty and importance of postmortem brain research of the aminergic brainstem nuclei in patients with AD, who had behavioral symptoms that had been assessed over a longer period. The most frequent finding in the English-language literature on postmortem brain research in patients with AD and behavioral symptoms has been that the degenerated noradrenergic system in AD is even more affected if the patient is also depressed. In our study we could not confirm this. Even if LC neuron number was additionally decreased in patients with AD and depression, the pathogenetic relation to depres-

Table 2. Group Characteristics

Characteristics	Depressed AD, Mean ± SE*	Transiently Depressed AD, Mean ± SE*	Nondepressed AD, Mean ± SE*	*P* Value Between AD Groups†	Controls*	*P* Value Between AD and Control Group
Clinical						
GDS‡ at death	6.3 ± 0.2	6.5 ± 0.2	6.5 ± 0.2	.8	. . .	. . .
Last inclusive HDRS‡	22.5 ± 2.6	11.8 ± 1.4	8.3 ± 1.4	.009, .004, and .093	. . .	. . .
Last inclusive Cornell‡	19.0 ± 2.2	10.2 ± 0.7	6.7 ± 0.9	.002, .002, and .026	. . .	. . .
Last exclusive Cornell	15.5 ± 3.1	3.8 ± 1.7	3.7 ± 1.0	.009, .002, and 0.94	. . .	. . .
Age, y						
At onset of AD	75.5 ± 2.8	75.7 ± 1.5	74.7 ± 1.0	1.0	. . .	. . .
At death	83.2 ± 2.4	86.3 ± 0.7	84.2 ± 4.2	.3, .6, and .4	76.0 ± 2.0	.004
Postmortem						
Postmortem delay, min	274.2 ± 26.3	250.0 ± 31.8	256.7 ± 27.2	.7, .6, and, .8	542.1 ± 50.9	.002
Brain weight, g	1069.3 ± 56.2	1043.8 ± 20.3	1086.3 ± 66.1	.2	1191.5 ± 46.5	.2
LC‡ neuron, No.						
Rostral	678 ± 286	594 ± 143	369 ± 180	.6, .4, and .5	1786 ± 353	.01
Middle	1816 ± 406	2351 ± 470	1408 ± 278	.4, .6, and .2	4951 ± 397	.001
Caudal	2671 ± 521	2677 ± 638	1941 ± 349	.8, .2, and .2	4870 ± 740	.01
Total	5165 ± 928	5647 ± 1163	3717 ± 661	.9, .3, and .4	11 607 ± 946	.001
LC volume	16.0 ± 1.9	14.8 ± 4.4	13.4 ± 2.1	.7, .2, and .7	18.5 ± 2.8	.04
Severity of AD pathology§	5.2 ± 0.4 (24.8 ± 2.7)	5.0 ± 0.4 (24.5 ± 2.8)	5.0 ± 0.4 (23.0 ± 1.3)	.9 (.7)		

**Six patients had Alzheimer disease (AD) and depression; 6 patients had AD and transient depression; 6 patients had AD but no depression; and 8 patients were controls.*

†Kruskal-Wallis multiple comparisons test (2 tailed) was used to compute P *values. If differences between AD groups or between AD and control groups showed statistical significance, then* P *values are also given for depressed vs transiently depressed, depressed vs nondepressed, and transiently depressed vs nondepressed patients with AD.*

‡GDS indicates Global Deterioration Scale; HDRS, Hamilton Depression Rating Scale; Cornell, Cornell Scale for Assessment of Depression in dementia; and LC, locus coeruleus.

§See Table 1.

sion was unclear, since neuron loss in the LC may well be related to some overlapping symptoms of depression and dementia (eg, insomnia), while not being related to depressed mood. Our findings are in line with the normal LC neuron number found in idiopathic depression. In the same patient sample, we also found decreased postmortem norepinephrine concentrations in the cortex and increased activity of the remaining LC neurons, but no difference between patients with AD and depression and patients with AD and no depression (W.J.G.H., Matthijs G.P. Feenstra, Margriet H.A. Botterblom, et al, unpublished data, January 1, 1992-December 1, 1996). These findings confirm our morphometric results in the LC. Our data do not support the hypothesis that the comorbidity of depression in AD has a neuropathological substratum in the LC.

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