ORIGINAL ARTICLE

Increased Neocortical Neurofibrillary Tangle Density in Subjects With Alzheimer Disease and Psychosis

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Background: Psychosis is common in patients with Alzheimer disease. While the relationship between psychosis and clinical variables has been examined frequently, few studies have examined the relationship between psychosis and the 2 major neuropathological hallmarks of Alzheimer disease: neurofibrillary tangles and senile plaques. We characterized the occurrence of psychosis in relation to dementia severity and determined if subjects with Alzheimer disease and psychosis had a greater neurofibrillary tangle or senile plaque burden than subjects with Alzheimer disease and no psychosis.

Methods: One hundred nine subjects with Alzheimer disease were followed longitudinally with semistructured assessments in order to assign a Clinical Dementia Rating and determine whether psychosis was present. After the subjects died, their brains were obtained for histological examination. Analysis of variance was used to compare the densities of neurofibrillary tangles, total senile plaques, and cored senile plaques in subjects with psychosis vs subjects without psychosis, in several neocortical regions, the hippocampus, and the entorhinal cortex.

Results: Psychosis occured commonly in Alzheimer disease, affecting 63% of subjects. The frequency of psychosis increased with increasing dementia severity. More importantly, we found that subjects with psychosis had a 2.3-fold (95% confidence interval, 1.2-3.9) greater density of neocortical neurofibrillary tangles than did subjects without psychosis. The increase was independent of dementia severity. No similar relationship with psychosis was seen for total senile plaques or cored senile plaques.

Conclusions: The increase in psychosis frequency that occurs with the progression of dementia severity and the independent association between psychosis and neurofibrillary tangle density suggest the possibility that some common underlying process or processes specific to Alzheimer disease may regulate both phenomena.

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ALZHEIMER disease (AD) involves a gradual progressive deterioration in multiple aspects of brain function. Memory loss is common, but disturbances in other aspects of cognition (eg, language, reasoning, mathematical skills, and visuospatial abilities) also occur. While behavioral and neuropsychiatric disturbances such as major depression, personality changes, and psychosis are not required for the clinical diagnosis of AD, they occur frequently and are a common reason for medical intervention and nursing home placement.

Hallucinations and delusions—the hallmarks of psychosis—have been studied extensively in subjects with AD.[1-18] Longitudinal studies report psychosis occurring at rates of approximately 50%,[9,10,15] whereas those studies using cross-sectional evaluations tend to find psychosis occurring at a lower rate.[11,13] Psychosis has a fluctuating course and recurs at a high rate with few long-term spontaneous remissions.[10,12]

While several groups have examined the relationship of psychosis with other clinical variables (eg, course of illness and other behavioral and cognitive changes), few studies have examined the relationship of psychosis with the histological features of AD. Neurofibrillary tangles (NFTs) and senile plaques (SPs) are the major neuropathological hallmarks of AD, each one indicating different cellular processes. In this study, we set out to characterize the occurrence of psychosis in relation to dementia severity in subjects with AD, and to determine if AD subjects with psychosis had a greater NFT or SP burden than those who were not psychotic. The latter question was further refined based on evidence showing that psychosis generally does not appear until

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SUBJECTS AND METHODS

SAMPLE

Subjects were volunteers in longitudinal research studies at Washington University's Alzheimer's Disease Research Center, St Louis, Mo, and were drawn from 207 subjects with AD who underwent autopsy as described elsewhere.[23] Subjects and a responsible family member provided informed consent for all aspects of this study, including postmortem histological evaluation. The study was approved by Washington University's institutional review board. All subjects had been diagnosed clinically with AD or incipient AD during life in accordance with validated clinical diagnostic criteria.[24] For the present study, subjects at autopsy had to meet the neuropathological diagnostic criteria for AD reported by Khachaturian,[25] with the added requirement that the average SP density of 10 microscopic fields (1 mm^2) met the criteria in at least 1 of the 3 neocortical regions assessed, in addition to hippocampal area CA1 and the entorhinal cortex. The resulting 186 subjects eligible for this study met both clinical and neuropathological criteria for AD.[23] One hundred nine of these subjects had complete neuropsychiatric clinical assessments (see following section) that permitted their inclusion in the study.

CLINICAL ASSESSMENT

Diagnostic criteria and descriptions of the subject groups are given in detail elsewhere.[26] In brief, whenever possible the evaluation of subjects was carried out on an annual basis with a comprehensive semistructured interview of both the subject and an informed collateral source (usually a close relative) and a clinical examination of the subject administered by an Alzheimer's Disease Research Center clinician experienced in assessing subjects with dementia, resulting at each visit in the assignment of a Clinical Dementia Rating (CDR).[27,28] A CDR of 0 indicates no dementia, whereas CDRs of 0.5, 1, 2, and 3 represent questionable or very mild, mild, moderate, and severe dementia, respectively. The reliability of the CDR has been demonstrated previously.[29] On average, subjects died 15.5 months after their last clinical assessment (**Table 1**). After the death of a subject but before the results of the autopsy were known, a senior research physician reviewed all available longitudinal clinical data except cognitive testing results. This review included information obtained by a nurse specialist usually within 1 to 2 weeks of death. Based on this information, a final clinical diagnosis and an "expiration CDR" were assigned.[23] This expiration CDR was used as the indicator of dementia severity in this study.

In the mid 1980s, the clinical interview was modified to include specific assessments of psychosis (delusions [6 categories] and hallucinations [3 categories]) and other aspects of neuropsychiatric functioning (**Table 2**). Subjects were scored positively for an item based on clinical judgement and using agreed upon rules. Comprehensive reviews of clinical assessments were performed to abstract clinical information regarding neurologic and psychiatric signs and symptoms. Any subject who had hallucinations or delusions *at any point* in their course of illness was classified as psychotic. Because of the difficulty in determining disordered thinking in subjects with dementia, thought disorder was not used as a criterion for psychosis. Psychosis occurring in the setting of delirium was not counted as psychosis in this study.

NEUROPATHOLOGICAL ASSESSMENT

All neuropathological assessments were done on coded slides so that the investigator (D.W.M.) was blind to clinical data, including psychosis status. Sections from the subiculum and the CA1 portion of the hippocampus, the entorhinal cortex between the levels of the mamillary and lateral geniculate bodies from the left cerebral hemisphere, the middle frontal gyrus, the anterior third of the superior temporal gyrus, and the inferior parietal lobule were processed for microscopic morphometric analyses as previously described.[23,30]

For each of the 5 brain regions, 6-µm-thick sections were cut from paraffin-embedded blocks perpendicular to the pial surface. Sections were stained with 2 modifications of the Bielschowsky ammoniacal silver method, and the densities (expressed as average number per square millimeter) of NFTs, total SPs, and cored SPs were determined.[23,30] Cortical counts were obtained in 10 consecutive 1-mm^2 cortical fields per slide, 5 along the pial surface and 5 along the white matter–cortex junction. For CA1, 10 sequential 1-mm^2 microscopic fields were assessed proceeding from the medial to the lateral boundary with the

NFTs are beginning to emerge in the neocortex, after the appearance of cognitive abnormalities,[19,20] and when substantial nonneocortical temporal lobe abnormality is well established.[21,22] Based on these observations, we hypothesized that the development of neocortical rather than medial temporal lobe NFTs may be associated with the development of psychosis in subjects with AD.

RESULTS

SAMPLE DESCRIPTION AND PSYCHOSIS ANALYSIS

Of 109 subjects with AD, 69 (63%) manifested psychosis during the course of their illness (Table 1). Psychosis was uncommon in subjects (12%) who died during the CDR-0.5 stage of dementia. The frequency of psychosis increased dramatically after the CDR-0.5 stage, with 50% and 56% of subjects who died during the CDR-1 and CDR-2 stages, respectively, having experienced an episode of psychosis. The frequency increased again in the CDR-3 subjects, with the vast majority (79%) having been psychotic during the course of their illness.

Delusions occurred in almost all subjects with psychosis (94%). Hallucinations occurring in the absence of delusions were rare (6%). Suspiciousness was the most frequent delusion (**Table 3**), occurring in 62% of delusional subjects, followed by misidentifications, which occured in 49% of these subjects. Of the subjects who had misidentifications, 84% also had other psychotic symptoms. Visual hallucinations were more common than auditory (77% vs 40%). Two thirds of the subjects with

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subiculum. Both intracellular and extracellular tangles were included in the NFT counts. Total SPs included all varieties of argyrophilic diffuse and neuritic plaques. Diffuse plaques are amorphous or finely fibrillar deposits and lack abnormal argyrophilic neurites or central cores. Cored SPs have central compact cores and almost always contain neurites. Sections were also stained with hematoxylin and eosin, and cresyl echt violet (Nissl stain) to assess the presence of other neuropathological lesions. Their occurrence was noted but did not influence whether the subject received the histopathological diagnosis of AD.

Corticolimbic Lewy bodies (LBs) were assessed with an anti-ubiquitin–stained section of entorhinal cortex, chosen to be representative of the limbic system where cortical LBs (CLBs) tend to be prevalent.[31] Corticolimbic Lewy bodies were noted as present or absent after search through consecutive 1-mm^2 fields from the medial edge of the entorhinal cortex to the depth of the collateral sulcus. The presence of CLBs in any field resulted in the subject being scored as having CLBs. Corticolimbic Lewy bodies were distinguished from NFTs by being circular or oval, nonfibrillar, and usually associated with an eccentric nucleus. Classical haloed LBs were also noted to be present or absent on hematoxylin-eosin preparations of the substantia nigra.

Both Parkinson disease (PD) and LBs in the setting of AD have been linked to psychosis.[5,32-35] Because it is unclear whether this association with psychosis depends on the location of LBs (corticolimbic alone vs substantia nigral alone vs corticolimbic and substantia nigral combined), we divided subjects into 4 categories. Subjects with LBs restricted to the substantia nigra were categorized as having AD and PD (AD+PD). The presence of CLBs alone resulted in the diagnosis of AD and CLB (AD+CLB). Subjects with LBs in both the cortex and substantia nigra were categorized as having AD+PD+CLB.

DATA AND STATISTICAL ANALYSIS

Throughout the study, 2-tailed tests were used with an α level of .05. The Kendall τ-b was used to determine whether the frequency of psychosis was related to CDR stage. χ^2 Analyses and *t* tests were used to determine whether certain parameters (eg, duration of AD and sex) and LBs were related to the presence of psychosis. Since these variables had been previously associated with psychosis, no corrections for multiple comparisons were made on these tests. χ^2 Analyses were also used to determine whether certain comorbid medical conditions and neuropsychiatric behaviors were related to the presence of psychosis. Since these analyses were exploratory and unrelated to our study hypothesis, the α level needed for significance was Bonferroni adjusted by dividing .05 by the number of comparisons made.

The distributions of NFT, total SP, and cored SP densities in the 10 fields from each of the 5 regions for each subject showed substantial intrasubject variability with distributions skewed to larger values. In previous analyses of these data,[23] this variability was adjusted for by using the natural logarithm of each density (after adding 0.5 to each density to avoid logarithms of 0). For each lesion, region, and subject, a mean of these 10 logarithmic transformed density measurements was calculated. Analyses were done on these transformed density measures. Nontransformed mean densities are used in the figures and tables for clarity in data presentation.

Based on the knowledge that NFT density varies depending on CDR stage and brain region, the hypothesis that subjects with psychosis would have higher mean neocortical NFT densities was tested using an initial analysis of variance (ANOVA) model. The ANOVA model included the presence or absence of psychosis and CDR stage at death as between-subject factors, and brain region as a within-subject repeated measure term with 5 levels corresponding to the 5 regions sampled. The inclusion of CDR stage in the analysis addressed the concern that an association of psychosis with increased NFT density could be confounded by dementia severity. Similar ANOVA models were used for the total SP and cored SP analysis.

Significant interactions were subsequently decomposed using additional ANOVA models appropriate to these interactions. As indicated in the "Results" section, we also conducted additional analyses aimed at further clarifying whether psychosis was associated with neocortical NFT density independent of dementia severity. Finally, common disease parameters (ie, age of death and duration of illness) and pathological variables (ie, LBs), which were found to be associated with psychosis in this data sample, were added as covariates to subsequent runs of the ANOVA model to determine if there was any interaction with psychosis in predicting mean neocortical NFT density.

visual hallucinations had them in the absence of auditory hallucinations. Roughly two thirds (69%) of subjects with psychosis had signs and symptoms of psychosis from more than one category (mean, 2.3 categories; maximum, 4 categories).

Comorbid medical conditions (ie, head trauma, coronary artery disease, fall with fracture, stroke, and seizure) were not associated with the presence of psychosis ($P \geq .3$ in all instances; Fisher exact results and data not shown), indicating that in this study, the occurrence of psychosis was not confounded by delirium. Subjects were also assessed for the presence of several other neuropsychiatric behaviors. After correcting for multiple comparisons, only psychomotor agitation and withdrawn behavior were related to the presence of psychosis (Table 2).

QUALITATIVE NEUROPATHOLOGICAL ANALYSIS

To initially explore the relationship of psychosis to NFTs and SPs, we plotted the densities of these 2 neuropathological hallmarks as a function of CDR across all regions assessed. Ten-fold variations in the magnitude of total SP, cored SP, and NFT densities across regions[23] supported our plan to plot densities in these areas separately. Neocortical NFT density as a function of CDR showed a 2-phase increase (**Figure 1**A) that was similar to the pattern seen with psychosis frequency—a major increase in frequency between CDRs of 0.5 and 1 and another increase in frequency between CDRs of 2 and 3 (Table 1). Such a pattern was seen neither for total SPs (Figure 1) and cored SPs (data not shown), nor for NFTs

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Table 1. Sample Characteristics*

Characteristic	Without Psychosis (n = 40 [37])	With Psychosis (n = 69 [63])	Analysis Results
CDR			
0.5	15 (88)	2 (12)	Kendall τ–b = .45,
1	4 (50)	4 (50)	*df* = 107; *P*<.001
2	7 (44)	9 (56)	
3	14 (21)	54 (79)	
Women	24 (60)	40 (58)	Fisher exact *P*>.99
White	40 (100)	69 (100)	
Mean ± SD age at death, y	84.6 ± 8.2	80.9 ± 8.2	$F_{1,107}$ = 5.21, *P* = .02
Mean ± SD duration of AD, y†	6.7 ± 3.6	8.9 ± 3.8	$F_{1,96}$ = 7.09, *P* = .009
Mean ± SD No. of assessments	3.4 ± 3.0	3.3 ± 2.6	$F_{1,107}$ = 0.015, *P* = .9
Mean ± SD interval between last assessment and death, y	1.2 ± 1.1	1.4 ± 1.6	$F_{1,107}$ = 0.56, *P* = .4
No. of subjects positive for $apoE_4$‡	17 (47)	39 (67)	Fisher exact *P* = .08
Lewy bodies category			χ^2_3 = 10.29, *P* = .02
AD alone	30 (46)	35 (54)	
AD + PD	4 (44)	5 (56)	Fisher exact *P*>.99§
AD + CLB	2 (12)	15 (88)	Fisher exact *P* = .01§
AD + PD + CLB	2 (15)	11 (85)	Fisher exact *P* = .06§

*All values are presented as number (percentage) unless otherwise indicated. CDR indicates Clinical Dementia Rating; AD, Alzheimer disease; CLB, corticolimbic Lewy bodies; PD, Parkinson disease.

†Duration data were available on only 98 subjects.

‡For the $apoE_4$ analysis, a total of 36 individuals were without psychosis and 58 had psychosis. The specific procedures for determining the apoE genotype are detailed in a previous report.[24]

§Compared with Alzheimer disease alone.

Table 2. Association of Neuropsychiatric Behaviors With Psychosis

Neuropsychiatric Behaviors*	With Psychosis (n = 69)	Without Psychosis (n = 40)	*P*†
Physical assault	25 (36)	5 (12)	.008
Psychomotor agitation	46 (67)	13 (32)	<.001
Wandering without reason	31 (45)	9 (22)	.02
Leaving residence	3 (4)	2 (5)	.99
Hyperorality	3 (4)	1 (2)	.99
Jocularity	20 (29)	6 (15)	.11
Hypersexuality	4 (6)	1 (2)	.65
Other inappropriate disinhibited behaviors	8 (12)	0 (0)	.03
Irritability	41 (59)	14 (35)	.02
Emotional lability	8 (12)	0 (0)	.02
Pseudobulbar emotional lability	4 (6)	0 (0)	.29
Withdrawn	58 (84)	23 (58)	**.003**
Other behaviors	5 (7)	0 (0)	.16
Premorbid depressive symptoms	4 (6)	3 (8)	.70
Comorbid depressive symptoms	18 (26)	9 (22)	.82
Alcohol problems	1 (1)	1 (2)	.99

*Neuropsychiatric behaviors are based on semistructured clinical assessment. Criteria are available from the authors. "Other inappropriate disinhibited behaviors" indicates, for example, making gestures, touching people inappropriately, being hypertalkative, and exposing oneself in public. Pseudobulbar emotional liability indicates sudden, brief bursts of uncontrollable laughter or crying. "Other behaviors" indicates behaviors that could not be coded in another category (eg, executive dysfunction or mild personality changes). Premorbid and comorbid depressive symptoms indicate either medical intervention for a depressive episode or presence of clinically significant depressive symptoms. "Alcohol problems" is defined as alcohol use resulting in significant social, occupational, or medical impairment of function.

†P is obtained from Fisher exact analysis (df = 1; Bonferroni-corrected critical α = .05/15 = .003).

in the hippocampus and entorhinal cortex (Figure 1), an allocortical region. The similarity between the temporal pattern of psychosis frequency and neocortical NFT density is consistent with the hypothesis that neocortical NFT density might be related to the expression of psychosis. This hypothesis was, therefore, statistically tested.

PRIMARY QUANTITATIVE ANALYSES

We found a significant association between the occurrence of psychosis and neocortical NFT density. As described in the "Subjects and Methods" section, NFT density for all 5 brain regions was used as a within-subject repeated measure, while CDR and psychosis status were between-subject variables. Supporting the hypothesis that psychosis was associated with neocortical NFTs, a significant 2-way interaction was detected between brain region and psychosis ($F_{4,396}$=2.59, *P*=.04). An expected significant 2-way interaction between brain region and CDR ($F_{12,396}$=3.44, *P*<.001) also was detected, consistent with previous reports that NFTs predominate in nonneocortical temporal areas early in the illness.[21,23] There was no 3-way interaction between region, CDR, and psychosis status ($F_{12,396}$=0.75, *P*=.7), and no interaction between CDR and psychosis status ($F_{3,99}$=0.62, *P*=.6), suggesting that the association of psychosis with elevated NFT densities was not confounded by the severity of dementia. The interaction between the presence of psychosis and brain region was explained by subjects with psychosis having NFT densities 2.3-fold (95% CI, 1.2-3.9) greater than nonpsychotic subjects, taking the average difference across the 3 neocortical regions (**Table 4**). In contrast, psychosis-related differences in NFT densities in hippocampus and enthorhinal cortex were not statistically significant (Table 4). Confirming the selectivity of the relationship of psychosis to NFTs,

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Table 3. Frequency of Specific Delusions and Hallucinations

	No. of Subjects	Occurrence in Subjects With Psychosis, % (n = 69)	Occurrence in Subjects With Delusions, % (n = 65)	Occurrence in Hallucinating Subjects, % (n = 35)
Delusions	65	94	100	. . .
Suspiciousness	40	58	62	. . .
Total No. with misidentifications	32	46	49	. . .
Other people	25	36	38	. . .
Self	5	7.2	7.7	. . .
Television characters are real	2	2.9	3.1	. . .
Spousal infidelity	3	4.3	4.6	. . .
Other*	36	52	54	. . .
Hallucinations	35	51	. . .	100
Visual	27	39	. . .	77
Auditory	14	20	. . .	40
Other	6	8.7	. . .	17

*Examples of other delusions include people believing that deceased parents are still alive, that mature children still live at home, and that their living quarters are not considered "home" as they once were. Ellipses indicate not applicable.

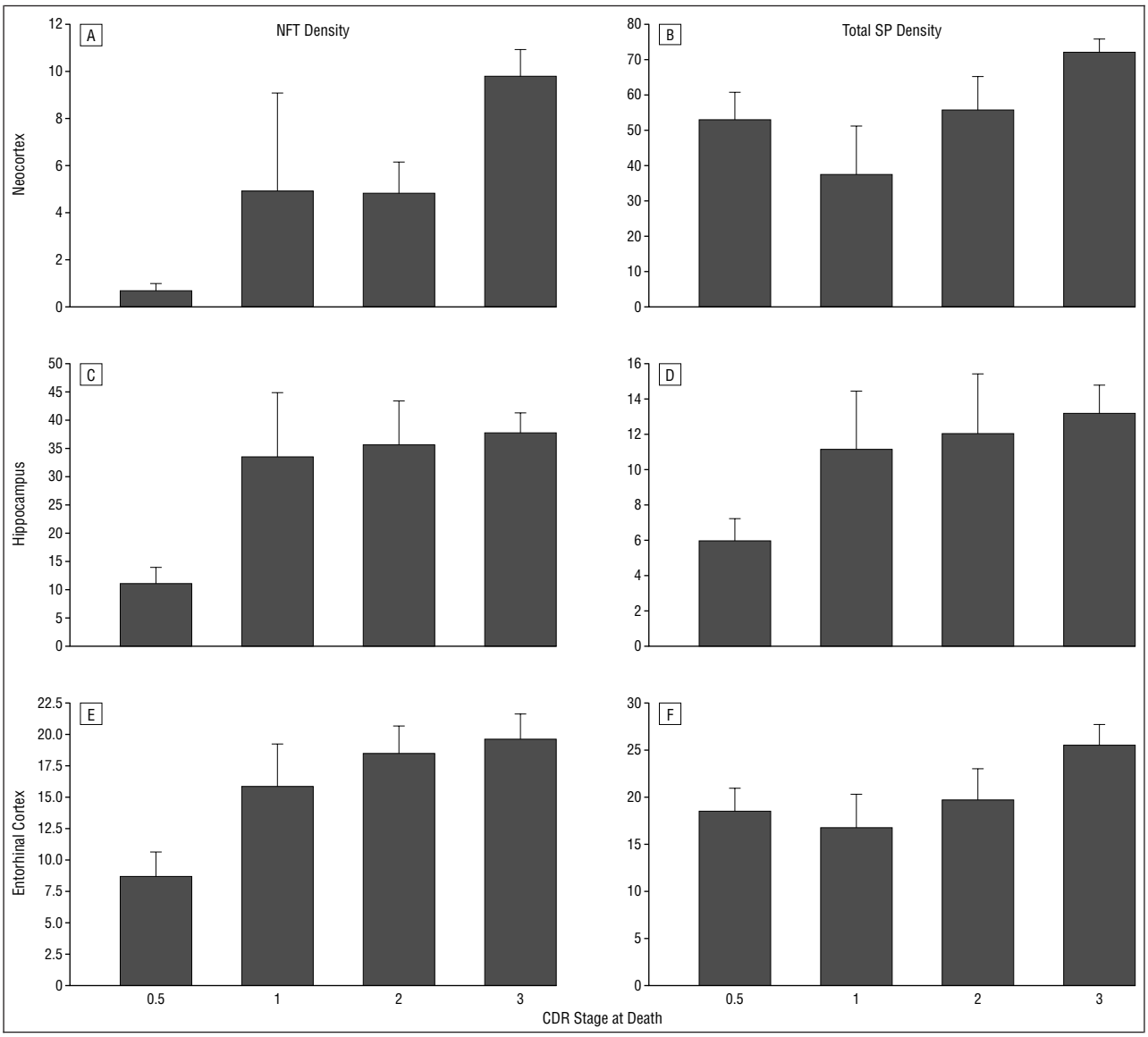

Figure 1. *Neurofibrillary tangle (NFT) and total senile plaque (SP) densities (number per square millimeter) in subjects grouped by Clinical Dementia Rating (CDR) stage at death (for CDRs of 0.5, n=17; 1, n=8; 2, n=16; and 3, n=68) in the neocortex (A and B), hippocampus (C and D), and entorhinal cortex (E and F). The pattern of increasing NFT density in the neocortex across CDR groups resembles the pattern of increasing psychosis observed across CDR groups (see Table 1). Densities are presented as means ± SEMs.*

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Table 4. Neurofibrillary Tangle Densities in Individuals With vs Without Psychosis by Brain Region

Brain Region	Density ± SD,* No./mm²		ANOVA†	
	With Psychosis	Without Psychosis	F Score	*P*
Middle frontal gyrus	7.9 ± 9.7	2.8 ± 5.5	$F_{1,107} = 6.98$	.01
Superior temporal cortex	11.9 ± 15.2	5.2 ± 7.9	$F_{1,107} = 7.28$	.008
Inferior parietal lobule	7.4 ± 10.0	4.0 ± 7.4	$F_{1,106} = 7.91$	.006
Hippocampus	36.0 ± 32.6	27.6 ± 28.7	$F_{1,106} = 0.51$	.5
Entorhinal cortex	19.3 ± 18.0	14.1 ± 10.1	$F_{1,106} = 1.11$	.3

*Density counts are actual density numbers (ie, not log transformed).
†Initial analysis found a significant 2-way interaction between psychosis and region in the prediction for neurofibrillary tangle density for the complete sample (see "Results" section). One-way analysis of variance (ANOVA) using psychosis as the between-subject factor and region-specific neurofibrillary tangle densities as dependent variables were used to decompose the interaction between psychosis and region. Statistical analyses were done on log-transformed data.

Table 5. Total and Cored SP Densities in Individuals With vs Without Psychosis*

Statistical Comparison	Statistical Result	
	F Score	*P*
Total SPs		
Psychosis × CDR × region	$F_{12,392} = 0.65$	.8
Psychosis × region	$F_{4,392} = 0.58$	.7
CDR × region	$F_{12,392} = 1.24$	.2
Psychosis × CDR	$F_{3,98} = 0.06$	.9
Region	$F_{4,392} = 69.3$	<.001
CDR	$F_{3,98} = 4.09$	.009
Psychosis	$F_{1,98} = 0.02$	.9
Cored SPs		
Psychosis × CDR × region	$F_{12,396} = 0.52$	.9
Psychosis × region	$F_{4,396} = 0.47$	.8
CDR × region	$F_{12,396} = 1.49$	.1
Psychosis × CDR	$F_{3,99} = 0.13$	.9
Region	$F_{4,396} = 36.1$	<.001
CDR	$F_{3,99} = 5.66$	.001
Psychosis	$F_{1,99} = 0.63$	.4

Region	Density ± SD, No./mm²	
	With Psychosis	Without Psychosis
Total SPs		
Middle frontal gyrus	90.4 ± 53.9	73.2 ± 35.9
Superior temporal cortex	58.0 ± 37.4	42.8 ± 21.7
Inferior parietal lobule	64.2 ± 42.4	57.9 ± 39.6
Hippocampus	12.3 ± 9.7	9.4 ± 9.0
Entorhinal cortex	25.8 ± 17.8	20.2 ± 18.4
Cored SPs		
Middle frontal gyrus	6.8 ± 5.1	4.7 ± 3.4
Superior temporal cortex	6.2 ± 5.3	4.2 ± 3.8
Inferior parietal lobule	7.8 ± 5.9	5.6 ± 4.6
Hippocampus	1.8 ± 2.1	1.2 ± 2.0
Entorhinal cortex	2.8 ± 2.8	2.0 ± 3.5

*Density counts are actual density numbers (ie, not log transformed). CDR indicates Clinical Dementia Rating. Because there was no significant interaction between psychosis and region in the prediction of total or cored SP (senile plaques) densities, no statistical analysis was done for each region. Mean ± SD density counts are given for completeness. There was also no main effect for psychosis.

there was no significant relationship between psychosis and either total SP or cored SP densities (**Table 5**).

To explore potential differences in the relationship of psychosis to NFT density across the 3 neocortical areas, we conducted a repeated measures ANOVA using density counts in each of the 3 neocortical regions as a within-subject repeated measure, and psychosis status as a between-subject factor. A main effect for psychosis ($F_{1,106}$=9.46, P=.003) was not confounded by a significant interaction between neocortical region and psychosis ($F_{2,212}$=0.10, P=.91). This result suggests that the presence of psychosis is associated with increased NFT density similarly across all neocortical regions assessed, suggesting in turn that psychosis may be associated with a more widespread neocortical process. Based on the lack of a significant interaction between neocortical region and psychosis in relation to NFT density, we used mean neocortical density for subsequent NFT analyses.

SUBSEQUENT QUANTITATIVE NFT ANALYSES

Although no significant interaction between psychosis and CDR in the prediction of neocortical NFT density was detected in the initial analysis, the possibility that the relationship between psychosis and NFT density might be confounded by dementia severity was further examined. Neocortical NFT density is strongly associated with CDR stage, primarily resulting from increased NFT density in CDR-3 subjects.[23] Because 60% of the current sample had a CDR of 3 at the time of death, it was possible that the greater neocortical NFT density in psychotic subjects could be the result of the higher frequency of psychosis in CDR-3 subjects. To exclude this possibility, another ANOVA model with mean neocortical NFT density as the dependent variable and psychosis as a between-subject factor was conducted, excluding CDR-3 subjects. For this subanalysis, the sample consisted of 41 subjects (15 subjects with psychosis and 26 subjects without psychosis). After the exclusion of CDR-3 subjects, subjects with psychosis still had greater than a 3-fold burden of mean neocortical NFTs ($F_{1,39}$=4.89, P=.03). We also plotted NFT density for each CDR stage (**Figure 2**). Subjects with psychosis had greater neocortical NFT densities than nonpsychotic subjects at every CDR stage, further indicating that the association between psychosis and increasing neocortical NFT density is not confounded by dementia severity. The biggest difference in mean neocortical NFT density between psychotic and nonpsychotic groups occurred at CDR-1 (Figure 2), coinciding with the biggest increase in the frequency of psychosis. However, the smaller sample size for these individual CDR comparisons limited power to detect statistically significant differences.

OTHER POTENTIAL CONFOUNDING FACTORS

Given the association between LBs and psychosis (Table 1), a between-subject factor for diagnostic category

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(4 levels) related to the presence of LBs was included in an ANOVA model to test the interaction of psychosis and diagnostic category in predicting mean neocortical NFT density. Diagnostic category was not associated with mean neocortical NFT density (main effect of diagnosis: $F_{3,96}=0.88$, $P=.4$). In addition, there was no interaction between psychosis and diagnostic category in predicting mean neocortical NFT density ($F_{3,96}=0.43$, $P=.7$), indicating that the association of psychosis with greater neocortical NFT density was not confounded by the presence or absence of LBs.

Finally, because age of death and duration of illness were significantly associated with psychosis (Table 1) we entered each as covariate terms in ANOVA models, using psychosis as the between-subjects factor and mean neocortical NFT density as the dependent variable, to determine if either interacted with psychosis in the prediction of mean neocortical NFT density. Both factors failed to show a significant interaction with psychosis ($F_{1,104}=2.65$, $P=.1$ and $F_{1,93}=0.50$, $P=.5$, respectively) although each demonstrated a significant main effect on mean neocortical NFT density ($F_{1,104}=4.81$, $P=.03$ and $F_{1,93}=9.04$, $P=.003$, respectively).

COMMENT

This study confirms previous reports[9,10,15] that psychosis is common in subjects with AD, and extends these reports with further evidence of an increase in psychosis frequency with dementia severity. The major finding of this study is that patients with AD who develop psychosis have a 2.3-fold greater density of neocortical NFTs than subjects without psychosis. This relationship between psychosis and NFT density was not observed in non-neocortical areas, and no similar relationship was seen for total SPs and cored SPs. This association between psychosis and NFTs may underlie reports that psychosis in AD is associated with a more rapid cognitive decline.[5,9,10,12,32]

Because both psychosis and NFT density increase with dementia severity, the association between psychosis and neocortical NFT density potentially could be a reflection of increasing dementia severity. However, there was no significant interaction between psychosis and dementia severity in our study. Moreover, a significant association between psychosis and neocortical NFT density remained evident when subjects with severe dementia (CDR-3) were excluded from the analysis.

Inspection of each CDR grouping revealed that subjects with psychosis had greater neocortical NFT densities than subjects without psychosis at each CDR stage and that the difference in NFT densities was particulary notable in mild AD. While the difference was not statistically significant, there were only 8 subjects and limited power, suggesting a possible type II error. Our study, a result of a decade and a half of subject accrual, is probably the largest study to date that examines neuropathological correlates of psychosis and to our knowledge, it is the only study of its kind to address the confound of dementia severity. Based on our results it will be important for future studies to include larger numbers of subjects in the earlier stages of AD.

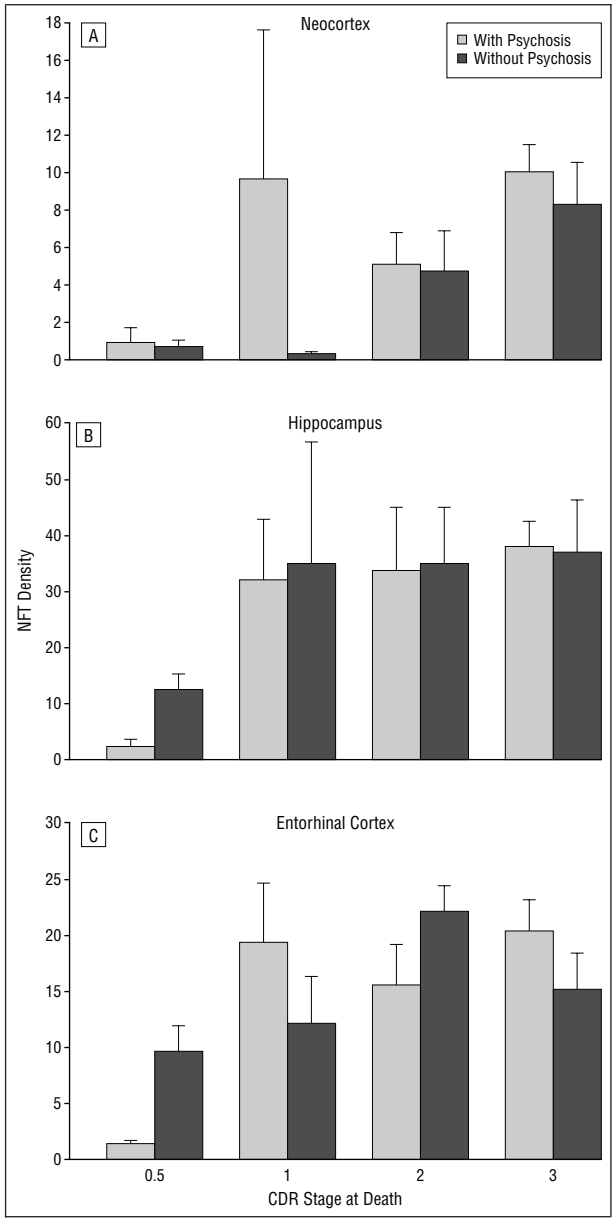

Figure 2. *Average neurofibrillary tangle (NFT) density (number per square millimeter) in the neocortex (A), hippocampus (B), and entorhinal cortex (C) for subjects grouped by Clinical Dementia Rating (CDR) and psychosis status. In the neocortex, subjects with psychosis have elevated NFT densities at every CDR stage but the differences were not statistically different (CDR of 0.5: $F_{1,15}=0.06$ and $P=.8$; CDR of 1: $F_{1,6}=2.12$ and $P=.2$; CDR of 2: $F_{1,14}=0.06$ and $P=.8$; CDR of 3: $F_{1,65}=0.004$ and $P=.9$) despite the overall analysis of variance being statistically significant ($F_{1,106}=9.46$, $P=.003$). The pattern in the hippocampus ($F_{1,106}=0.51$, $P=.5$) and entorhinal cortex ($F_{1,106}=1.11$, $P=.3$) was different with psychotic subjects not consistently having elevated NFT densities. Densities are presented as means ± SEMs.*

This analysis detected no relationship between psychosis and nonneocortical NFT densities, total SPs, or cored SPs. This result indicates that the selective association of neocortical NFT density and psychosis is probably not solely secondary to a general loss of brain parenchyma, but rather that it reflects an absolute increase in the number of NFTs. Few previous studies have examined the relationship of psychosis with histological measurements in AD. Forstl et al[36] reported that subjects with psychosis had changes in neuronal counts in

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the CA1 hippocampus and parahippocampal gyrus, but did not report on NFT or plaque measurements. Zubenko et al[37] found a relationship between NFTs and psychosis in the context of a broad analysis with approximately 70 comparisons. Reported findings included an increase in NFTs in the middle frontal cortex (uncorrected $P=.04$). Our results together with their finding support the association between psychosis and neocortical NFTs. It will be important to replicate this association in an independent sample of well-characterized subjects with AD. It would be of interest to determine whether subjects with cases of AD with minimal cortical NFTs[38] might have a lower risk of developing psychosis.

The association between psychosis and neocortical NFTs is consistent with previous reports that psychosis typically does not begin to occur until after the appearance of subtle cognitive abnormalities,[19,20] when NFTs are just becoming apparent in the neocortex but when they are already substantially present in the nonneocortical temporal lobe areas.[21,22] These findings suggest that dysfunction in the hippocampus and entorhinal cortex is probably not responsible for psychosis in people with AD, and instead that dysfunction in the neocortex or in some other brain region that develops dysfunction on a similar time course as that seen in the neocortex is responsible for psychosis in people with AD. Consistent with a role for the neocortex, abnormalities in cerebral blood flow and metabolism have been found in the cortex of AD subjects with psychosis compared with those without psychosis.[39-41] Highlighting the importance of neocortical NFTs for psychosis, a schizophrenia-like psychosis does characterize one multigenerational family with a presenile onset of an SP-lacking, non-AD dementia with NFTs present.[42,43]

The increase in neocortical NFTs in subjects with AD and psychosis suggests an interaction between mechanisms in the brain that regulate psychosis and disease mechanisms specific to AD. We do not conclude that the association between psychosis and neocortical NFT density indicates a close causal relationship between NFT production and psychosis (ie, that some mechanism produces NFTs, which subsequently cause psychosis, or that some mechanism directly produces both NFTs and psychosis). If this were the case, one might expect to observe prominent neocortical NFTs in other psychotic disorders such as schizophrenia, and this is not observed.[44-47] Instead, we suspect that a mechanism similar to that operative in other psychotic disorders also produces psychosis in people with AD, but that this mechanism may interact with disease processes specific to AD to up-regulate the production of NFTs. Additional research will be needed to clarify which area or areas of the brain and what underlying mechanisms are actually involved in the expression of psychosis, as well as the separate question of how these mechanisms responsible for psychosis production interact with those processes involved in the production of NFTs.

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