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 occurred 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. Longitudinal studies report psychosis occurring at rates of approximately 50%, whereas those studies using cross-sectional evaluations tend to find psychosis occurring at a lower rate. Psychosis has a fluctuating course and recurs at a high rate with few long-term spontaneous remissions.

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...
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. 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.

For the present study, subjects at autopsy had to meet the neuropathological diagnostic criteria for AD reported by Khachaturian, with the added requirement that the average SP density of 10 microscopic fields (1 mm²) 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.

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. 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). 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.

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 longitu-
dinal 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.

The reliability of the CDR has been demonstrated previously.

One hundred nine of these subjects had complete neuropsychiatric clinical assessments (see following section) that permitted their inclusion in the study.

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 occurred 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...
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≥.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 supported our plan to plot densities in these areas separately. Neocortical NFT density as a function of CDR showed a 2-phase increase (Figure 1A) 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 and SPs, which showed a 2-phase increase (Figure 1A and B) 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...
Assessment. Criteria are available from the authors. “Other inappropriate CLB, corticolimbic Lewy bodies; PD, Parkinson disease. 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.

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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 (F1,396 = 5.21, P = .02). An expected significant 2-way interaction between brain region and CDR (F1,396 = 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 (F1,396 = 0.75, P = .7), and no interaction between CDR and psychosis status (F3,99 = 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 entorhinal cortex were not statistically significant (Table 4). Confirming the selectivity of the relationship of psychosis to NFTs,
Table 3. Frequency of Specific Delusions and Hallucinations

<table>
<thead>
<tr>
<th></th>
<th>No. of Subjects</th>
<th>Occurrence in Subjects With Psychosis, % (n = 69)</th>
<th>Occurrence in Subjects With Delusions, % (n = 65)</th>
<th>Occurrence in Hallucinating Subjects, % (n = 35)</th>
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<tr>
<td>Delusions</td>
<td>65</td>
<td>94</td>
<td>100</td>
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<tr>
<td>Suspiciousness</td>
<td>40</td>
<td>58</td>
<td>62</td>
<td>...</td>
</tr>
<tr>
<td>Total No. with misidentifications</td>
<td>32</td>
<td>46</td>
<td>49</td>
<td>...</td>
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<td>Other people</td>
<td>25</td>
<td>36</td>
<td>38</td>
<td>...</td>
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<tr>
<td>Self</td>
<td>5</td>
<td>7.2</td>
<td>7.7</td>
<td>...</td>
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<td>Television characters are real</td>
<td>2</td>
<td>2.9</td>
<td>3.1</td>
<td>...</td>
</tr>
<tr>
<td>Spousal infidelity</td>
<td>3</td>
<td>4.3</td>
<td>4.6</td>
<td>...</td>
</tr>
<tr>
<td>Other*</td>
<td>36</td>
<td>52</td>
<td>54</td>
<td>...</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>35</td>
<td>51</td>
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<td>17</td>
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</tbody>
</table>

* 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.
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 (F1,198 = 4.96, P = .03) was not confounded by a significant interaction between neocortical region and psychosis (F2,212 = 0.10, P = 0.91). 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. 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 (F1,39 = 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 statistically significant differences.

### OTHER POTENTIAL CONFOUNDING FACTORS

Given the association between LBs and psychosis (Table 1), a between-subject factor for diagnostic category
(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: $F_{1,90}=0.88$, $P=.4$). In addition, there was no interaction between psychosis and diagnostic category in predicting mean neocortical NFT density ($F_{3,90}=0.43$, $P=.7$), 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).

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.\(^9,^{10,12,32}\)

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 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\(^{30}\) reported that subjects with psychosis had changes in neuronal counts in
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 NFTs38 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.23-25 Highlighting the importance of neocortical NFTs for psychosis, a schizophrenia-like psychosis does characterize one multigenerational family with some other brain region that develops dysfunction on a presenile onset of an SP-lacking, non-AD dementia with NFTs present.26,27

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 (i.e., 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.28-31 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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