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Cortical Neuritic Plaques and Hippocampal Neurofibrillary Tangles are Related to Dementia Severity in Elderly Schizophrenia Patients

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Abstract

Cognitive decline has been described in elderly patients with schizophrenia, but the underlying pathology remains unknown. Some studies report increases in plaques and neurofibrillary tangles, but there is no evidence for an increased risk for Alzheimer's disease (AD) in elderly schizophrenics. Models of a decreased cerebral reserve suggest that increases in AD-related neuropathology below the threshold for a neuropathological diagnosis could be related to dementia severity in elderly schizophrenia patients. We tested this hypothesis in 110 autopsy specimens of schizophrenia patients , without a neuropatholgical diagnosis of AD or other neurdegenerative disorders. Furthermore, we assessed the effects of apolipoprotein E (ApoE) status, a known genetic risk factor for AD. Measures of density of neuritic plaques were obtained in five cortical regions, and the degree of hippocampal neurofibrillary tangles was rated. Dementia severity was measured prior to postmortem using the Clinical Dementia Rating (CDR) scale. In multivariate analyses of variance were conducted with the factors dementia severity, by ApoE4 carrier status. Hippocampal neurofibrillary tangles correlated with increased dementia severity ($p < .05$). Neuritic plaque density increased with greater dementia severity ($p < .005$), and ApoE4 carrier status ($p < .005$), and these differences were magnified by ApoE4 carrier status ($p < .01$). Even below the threshold for a

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neuropathological diagnosis of AD, neuritic plaques and hippocampal neurofibrillary tangles are associated with dementia severity in schizophrenia patients, even more so in the presence of genetic risk factors, suggesting that a decreased cerebral reserve in elderly schizophrenics may increase susceptibilty for dementia.

Keywords

Schizophrenia; Alzheimer's Disease; Neuropathology

1.1 Introduction

In line with Emil Kraepelin's concept of schizophrenia as a progressive deterioration of cognitive functioning (Kraepelin, 2002), several clinical studies (Buhrich et al., 1988; Davidson et al., 1995; Johnstone et al., 1981; Purohit et al., 1993; Taylor and Abrams, 1984) have shown severe cognitive impairment in elderly patients with schizophrenia. It has been suggested that the type of cognitive impairment seen can be progressive and is not attributable to a lack of cooperation, attention, nor motivation (Friedman et al., 2001; Harvey et al., 1999). Since Alzheimer's disease (AD) is the most common cause of dementia in the elderly, AD-related neuropathology (e.g., neurofibrillary tangles and neuritic plaques) has been implicated as a plausible candidate contributing to the dementia observed in elderly patients with schizophrenia (Powchik et al., 1998). In his classical study, Alzheimer (1897) showed that patients with dementia praecox exhibit increased neurofibrillary tangles and neuritic plaques, yet to a lesser degree, and that the amount of reactive gliosis surrounding these neuropathological changes may be reduced (see Bogerts, 1999, for a critical appraisal of these classical studies).

More recent postmortem neuropathologic investigations (Arnold et al., 1994; Buhl et al., 1988; Bruton et al., 1990; Dwork et al., 1998; Prohovnik et al., 1993; Purohit et al., 1998; Religa et al., 2003) have provided generally consistent results regarding the occurrence of Alzheimer's disease neuropathology in elderly patients with schizophrenia. Virtually all studies have employed group comparisons, in that they compared the extent of AD-related neuropathological changes (or the percentage of subjects with a neuropathological diagnosis of AD) in postmortem tissue from healthy elderly, elderly schizophrenia patients, and patients with AD. The general finding, summarized in 1997 in a review by Baldessarini et al. (1997), is that the proportion of cases with a neuropathological diagnosis of AD is comparable between elderly subjects with schizophrenia and healthy elderly (e.g., Buhl et al., 1988; Bruton et al., 1990; Prohovnik et al., 1993), or that the extent of AD-related pathology is considerably less in schizophrenia patients compared to patients with AD (Arnold et al., 1994; Religa et al., 2003). In an earlier report from this group (Purohit et al., 1998), we also found that AD-related neuropathology was not increased in schizophrenia patients compared to healthy controls.

Most studies do find some degree of AD-related neuropathology in elderly schizophrenia patients with severe cognitive and functional impairments (Arnold, 2001), and it is unclear if these neuropathological lesions contribute to the severity of dementia within elderly schizophrenia patients. There is some indication that dementia severity may be related to the amount of plaques and tangles in the brains of schizophrenia patients who do not meet neuropathological criteria for AD (Dwork et al., 1998).

On the other hand, Arnold (2001) suggested that the lack of a difference in neuropathological changes in demented patients with schizophrenia and cognitively intact controls could point to the possibility of a decreased cerebral reserve in elderly schizophrenia patients, in that "neurodevelopmental abnormalities in schizophrenia may represent a state of decreased

cerebral reserve with commensurately increased vulnerability to the effects of even small amounts of neural injury or neurodegenerative lesions." (Arnold, 2001, p. 73). Such a model would be consistent with findings of decreased cognitive abilities and reduced educational attainment (e.g., Reichenberg et al., 2002; Reichenberg et al., 2005) prior to the onset of schizophrenia. The decreased cerebral reserve hypothesis would imply, however, that neuropathological changes in demented elderly patients with schizophrenia are related to dementia severity, beyond the effects of age. Such a finding would not preclude other causes of cognitive impairment and we would hypothesize that some proportion of the variance would be accountable for by other factors in that young schizophrenia patients without degenerative changes still have substantial cognitive impairments.

Studies of cognitive reserve in Alzheimer's disease have often used genetic susceptibility as a marker of increased risk (Borenstein Graves et al., 2001; Kim et al., 2008), following the assumption that genetic susceptibilty affects cognitive function especially when cerebral reserve is low (Kim et al., 2008). Although there is mixed evidence with respect to an increased risk for schizophrenia (Sorbi et al., 1998) and psychosis in AD (Spaletta et al., 2006) conveyed by the apolipoprotein E allele, an increased association between AD-related neuropathology and dementia severity in geriatric schizophrenia patients with genetic susceptibility to AD would indicate an influence of genetic factors related to AD in the dementia seen in geriatric schizophrenia.

In the present study, we examined whether AD-related neuropathological changes, specifically, cortical neuritic plaques and hippocampal neurofibrillary tangles, are related to dementia severity within elderly patients with schizophrenia. Furthermore, we explored, within schizophrenia patients, whether a genetically defined risk for cognitive impairment and amyloid plaque deposition (specifically, ApoE4 carrier status) is related to the extent of AD-related neuropathological lesions.

1.2 Methods

1.2.1 Subjects

Analyses were based on the study of 196 consecutive brain donations to the Mount Sinai School of Medicine Department of Psychiatry Brain Bank of patients suffering from schizophrenia who had been hospitalized at the Pilgrim Psychiatric Center, Brentwood, NY. The diagnoses of schizophrenia were made in consensus conferences led by senior clinicians, and all cases in the study met DSM-III-R or DSM-IV (American Psychiatric Association, 1987) research criteria for schizophrenia. Because the objective of this study was to investigate the association between AD neuropathology and dementia severity in schizophrenia patients without co-morbid neurodegenerative disease, subjects with AD according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria were excluded (Gearing et al., 1995). This led to the exclusion of 57 cases from the sample (29 with a neuropathological diagnosis of definite AD, 16 with a neuropathological diagnosis of probable AD, and 12 with a neuropathological diagnosis of possible AD). Furthermore, we excluded cases with a neuropathological diagnosis of dementia with Lewy-Bodies (N= 21), cases with a neuropathological diagnosis of Parkinson's disease (N = 4), and cases with a neuropathological diagnosis of vascular dementia (N = 4). Therefore, the analysis was limited to the 110 subjects with a clinical diagnosis of schizophrenia without a neuropathological diagnosis of a neurodegenerative disorder. Of these, 60 were without significant pathology, 35 had a diagnosis of ischemic cerebrovascular disease, and 16 had a diagnosis of other pathologies (11 with frontal leucotomy, 3 with brain neoplasms, 1 with brainstem hemorrhage, and 1 with hemangioma). These subjects did not differ significantly from the excluded subjects in age at death, sex, or years of education. Postmortem donations were received by the Mount Sinai School of Medicine Department of Psychiatry Brain Bank, from the next of kin of deceased

patients of the Pilgrim Psychiatric Center and associated nursing homes. All assessments conducted prior to death were approved by the institutional review boards of both the Pilgrim Psychiatric Center and the Mount Sinai School of Medicine.

1.2.2 Clinical Assessments

All patients had been assessed in life prior to the collection of postmortem samples. The Clinical Dementia Rating (CDR; Berg, 1988) assesses cognitive and functional impairments associated with dementia and provides specific severity criteria for classifying subjects as nondemented (CDR = 0), questionably demented (CDR = 0.5), or increasing levels of severity of dementia from CDR = 1 to CDR = 5. A previously described (Purohit et al., 1998) multistep approach was applied to the assignment of postmortem CDR scale scores based on in person assessments of cognitive and functional status during the last 6 months of life. For our factorial design, CDR scores of 0 were classified as no dementia, CDR scores of 0.5 were classified as questionable dementia, CDR scores of 1 and 2 were classified as mild to moderate dementia, and CDR scores of 3 or greater were classified as severe dementia. In addition to CDR scores, the sum of box score rating was introduced since it has been shown to add information across other cognitive domains than memory alone (Lynch et al., 2005). Cognitive status was further assessed by the Mini-Mental Status Examination (MMSE; Folstein et al., 1975), administered at the last pre-mortem assessment. Psychopathologic symptoms of schizophrenia were measured with the Positive and Negative Syndrome Scales (PANSS). The original PANSS subscales: positive, negative, and general psychiatric symptoms were used (Kay et al., 1987).

1.2.3 Assessment of ApoE genotype

After DNA isolation from frozen, never-thawed, brain tissue specimens (50 mg) using Promega Wizard® Genomic DNA purification kit, ApoE genotyping was performed using a modification of published PCR techniques (Hixson and Vernier, 1990). Participants were categorized as ApoE4 carrier if they carried at least one copy of the E4 allele, and as a non-carrier if they carried none.

1.2.4 Neuropathologic Assessment

After the subject's death, consent for autopsy was obtained from the legal next of kin. Post-mortem interval time was noted. 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 after 4 to 6 weeks of fixation. Sections from paraffin-embedded blocks were stained using hematoxylin-eosin, modified Bielschowsky, modified thioflavine S, anti–β amyloid (4G8 [gift of N. Robakis, PhD, Mount Sinai School of Medicine]), and anti-tau (AD2 [gift of A. Delacourte, PhD, Unite INSERM 422, Lille, France]). Any subject showing evidence of Lewy body formation in the substantia nigra or locus ceruleus underwent antiubiquitin (Daka Corporation, Carpinteria, CA) staining. All neuropathological data regarding the extent and distribution of neuropathological lesions were collected by neuropathologists unaware of any of the clinical and psychometric data.

Every subject underwent evaluation for the extent of neuropathological lesions using the CERAD neuropathological battery (Gearing et al., 1995). Specifically, ratings of the extent of neurofibrillary tangles were performed on a four point scale (absent, sparse, moderate, and severe) by two experienced neuropathologists. Furthermore, quantitative data regarding the density of neuritic plaquess in the midfrontal gyrus (Brodmann area 9), orbital frontal cortex (Brodmann area 45–47), superior temporal gyrus (Brodmann area 21–22), inferior parietal cortex (Brodmann area 39), and calcarine cortex (Brodmann area 17) were collected. For these quantitative measures, 5 representative high-power fields (0.5 mm^2) were examined in each cortical region, and an average density score was calculated expressed as mean neuritic plaque density per square millimeter.

1.2.5 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 two-tailed with α set at 0.05. Parametric and nonparametric correlations were performed to describe the association between neuropathological lesions and overall cognitive performance as measured by the CDR sum of boxes score. To assess the overall relationship between dementia severity, ApoE carrier status, and neuropathological lesions, multivariate analyses of variance were conducted in a two-by-three between subjects factorial design (presence versus absence of ApoE4 by dementia severity, classified as absent versus questionable versus mild to moderate versus severe). Follow-up multivariate analyses of covariance were performed to control for confounds. Covariates were age at death in years, gender, race, education, post-mortem interval, positive and negative symptoms from the PANSS, and cognitive status as assessed by the MMSE. In cases where the variance-covariance matrix violated homogeneity assumptions, Wilk's λ is reported.

1.3 Results

1.3.1 Demographic and Clinical Characteristics

The overall study group (N = 110; Table 1) comprised 54 women (49.1%) and 56 men (51.9%), with a mean age at death of 79.25 years (SD = 11.38). 76.4% of the sample (N = 84) were caucasian, 19.1% (N = 21) were African-American, and 2.7% (3) were hispanic, with all other ethnicities accounting for less than 5% of the sample. 14.5% (N = 16) of the final sample were classified as having no dementia, 12.7% (N = 14) were classified as questionable dementia, while 23.6% (N = 26) were classified as mildly to moderately demented, and 49.1% (N = 54) were classified as severely demented. 26.4% (N = 29) were carriers of the ApoE4 allele, and 67.6% (N = 74) were not (data were missing in 7 cases). There were no statistically significant differences with respect to gender, race, education, post-mortem interval in hours, time from last assessment to death in months, and general psychiatric symptoms from the PANSS as a function of dementia severity (all ps > .14). However, there was a main effect of age ($F = 4.97$, $df = 3,109$, $p < .005$). Post-hoc tests showed that this effect was driven by the fact tha patients with questionable dementia were younger than all other groups (all ps > .001). Furthermore, patients with sever dementia exhibited less positive ($F = 2.93$, $df = 3,88$, $p < .05$) and more negative symptoms as assessed by the PANSS ($F = 5.21$, $df = 3,88$, $p < .005$), had lower MMSE scores ($F = 4.66$, $df = 3,95$, $p < .005$), and had worse CDR sum of boxes scores ($F = 8.79$, $df = 3,95$, $p < .001$). There were no statistically significant difference with respect to age at death in years, gender, race, education, post-mortem interval, positive and negative symptoms form the PANSS, and cognitive status as assessed by the MMSE as a function of ApoE carrier status (all ps > .17).

1.3.2 Differences in Neuritic Plaque Density

For neuritic plaque density measures in five cortical regions (Table 2), unadjusted analyses revealed a main effect for dementia severity ($F = 2.93$, $df = 6, 95$, $p < .05$, $\eta^2 = .11$), a main effect for ApoE4 carrier status ($F = 2.76$, $df = 6,94$, $p < .05$, $\eta^2 = .09$), and a significant interaction between these two factors ($F = 2.56$, $df = 7, 95$, $p < .05$, $\eta^2 = .08$). Post hoc analyses revealed that neuritic plaque density was larger in ApoE4 allele carriers in four cortical regions (for superior temporal gyrus, $t = 2.44$, $df = 102$, $p < .05$; for mediofrontal gyrus, $t = 3.30$, $df = 102$, $p < .001$; for orbitofrontal gyrus, $t = 2.79$, $df = 102$, $p < .005$; for inferior parietal cortex, $t = 2.59$, $df = 102$, $p < .05$), but not in occipital cortex ($t = 1.52$, $df = 102$, $p = .13$). Neuritic plaque density did not differ between non-demented, questionably demented, and mildly to moderately demented schizophrenia patients (all p's > .27). However, neuritic plaque density was larger in severely demented, compared to mildly to moderately demented schizophrenia

patients, in three cortical regions (for superior temporal gyrus, t = 2.03, df = 77, p < .05; for orbitofrontal gyrus, t = 2.46, df = 77, p < .05; for inferior parietal cortex, t = 2.29, df = 77, p < .05), but not in occipital cortex (t = 0.77, df = 77, p = .46) and mediofrontal gyrus (t = 1.37, df = 77, p =. 18).

Controlling for age at death, time from last assessment to death, post-mortem interval, gender, education, cognitive status, general psychiatric, positive and negative symptoms, and ischemic vascular change revealed that the effect of dementia severity (F =2.78, df = 15, 65, p < .001, η^2= .34), a main effect for ApoE4 carrier status (F = 6.53, df = 15,65, p < .001 , η^2= .34), and a significant interaction between these two factors (F = 2.34, df = 15,65, p < .05, η^2= .15) remained significant. In addition, the pattern of results remained essentially unchanged when we excluded the (overall younger) questionable dementia group from our analysis (data not shown).

1.3.3 Differences in Hippocampal Tangle Ratings

For hippocampal neurofibrillary tangles (Table 3), nonparametric analyses revealed a main effect for dementia severity (χ^2 = 7.73, df = 98, p < .005). However, there was no effect of ApoE4 carrier status (p = .17) or ischemic cerebrovascular disease (p = .11). These results did not change when stratifying for age at death in years, gender, race, education, post-mortem interval, positive and negative symptoms form the PANSS, and cognitive status as assessed by the MMSE.

1.1.4 Association between Overall Cognitive Function and Neuropathology

In order to substantiate that neuropathological changes correspond to cliunical dementia severity using the CDR sum of boxes score, we computed Person correlations between plaque density measures in all five cortical regions and overall cognitive performance as measured with the CDR sum of boxes. Unadjusted correlation coefficients ranged between r = .23 and r = .28 in all cortical regions (all ps < .05) except the occipital cortex (r = .14, p = .19). In addition, nonparametric correlation revealed a significant association between hippocampal tangle ratings and overall cognitive performance (Spearman's rho = .25, p < .05).

1.4 Discussion

This clinico-pathological study extends earlier studies to an analysis of the relationship between AD-related pathology and dementia severity within elderly schizophrenia patients. It further supports the idea that severe cognitive impairment is commonly observed in elderly patients with schizophrenia. In line with the predictions of a cerebral reserve capacity model of dementia in elderly schizophrenic patients, we found both neuritic plaques throughout the brain, as well as hippocampal neurofibrillary tangle, to be associated with dementia severity in elderly patients with schizophrenia.

However, it is central to note that the neuropathological alterations found in this study are well below the threshold for a neuropathological diagnosis of AD, and that schizophrenia patients suffering from neurodegenerative disorders were not included in this study. The amount of cortical neuritic plaques found in this sample is about half of that commonly seen in elderly patients with AD (see Haroutunian et al., 1998, for a numeric comparison using the same neuropathologic methods from the Mount Sinai Brain Bank), while the amount of neurofibrillary tangles in the hippocampus found in elderly schizophrenia patients with dementia is comparable to earlier studies on AD patients using similar methodology (Rapp et al., 2006). While we lack information on differences in the effect of AD-related neuropathology on reactive gliosis in geriatric schizophrenia, as was proposed originally by Alzheimer in 1897 (see Bogerts, 1999), our data do not rule out the possibility that AD-related neuropathology

may exert stronger effects on cognitive functioning in schizophrenia via a biological mechanism different from Alzheimer's disease. Yet, as was further substantiated by the association between dementia severity as measured with the CDR sum of boxes score, we did find an association between dementia severity and AD-related neuropathological changes in elderly schizophrenics who did not meet neuropathological criteria for AD.

In addition to these findings, ApoE carrier status had an effect on the amount of neuritic plaques in the cortex, but did not on the extent of hippocampal neurofibrillary tangles. These findings point to the possibility that cortical neuritic plaques are increased even in mild dementia and in at-risk cases (Haroutunian et al., 1998), whereas extensive hippocampal pathology reflects advanced dementia, possibly even in geriatric schizophrenia. On the other hand, however, the effect of AD-related neuropathology on dementia severity was magnified by ApoE carrier status, suggesting that genetic susceptibility for AD led to more severe dementia in the face of substhreshold AD-related neuropathological alterations.

Taken together, these findings suggest that dementia in elderly schizophrenics is related to relatively small amounts of AD-related neuropathological lesions, consistent with a decreased cerebral reserve in elderly schizophrenia patients. Specifically, our results show that dementia in geriatric schizophrenia is associated with increased "vulnerability to the effects of even small amounts of neural injury or neurodegenerative lesions." (Arnold, 2001, p. 73). In addition, the interaction effect with genetic susceptibility markers of AD suggests that AD-related changes may indeed play a role in the dementia of geriatric schizophrenia, albeit, due to a decreased cerebral reserve, even at below threshold levels of AD-related neuropathology.

Arnold (2001) suggested that a developmentally abnormal hippocampal region in patients with schizophrenia could become functionally defective even in the face of minor hippocampal pathology. However, more recent studies (Akbarian et al., 1996; Akbarian et al., 2003; Benes et al., 1991; Benes et al., 1992) have suggested that similar mechanisms could play a role in the prefrontal lobe and temporal lobe cortical circuitry. Such findings would be consistent with our finding of an increase in dementia severity with small increases in neuritic plaques throughout the cortex. Hence, it seems reasonable to argue that a decreased cerebral reserve in elderly schizophrenics may extend beyond the hippocampus and could affect cognitive functioning across different neuropsychological domains.

While this study shows an association between dementia severity and small amounts of AD-related neuropathology in the brains of geriatric schizophrenia patients with dementia, we do not know if AD-related pathology is triggering the dementia process in geriatric schizophrenia. Further, the amount of variance in cognitive impairment accounted for by neuritic plaques, neurofibrillary tangles, and ApoE4 status, while significant, is not extremely substantial. However, there is some evidence to indicate that AD-related pathology may play a direct role in the dementia seen in geriatric schizophrenia. For example, prior studies have reported a decrease in the level of acetylcholinesterase activity in schizophrenia patients (Holt et al., 2005), that may correlate with the severity of cognitive impairment observed in geriatric schizophrenia (Karson et al., 1996). This constellation suggest that AD-related pathological processes may play a role at lower overall levels than are usually observed in Alzheimer's disease. However, conclusive evidence is lacking.

The present study is limited by the fact that exact data on premorbid cognitive functioning are lacking. Such data would allow for a more direct test of the question whether AD-related pathology may lead to cognitive deterioration on the basis of a neurodevelopmental (Arnold, 2001) or premorbid cognitive impairment (Reichenberg et al., 2002; Reichenberg et al., 2005). We have earlier demonstrated that performance-based indices of academic achievement, word recognition reading scores, manifested a substantial relationship with

current cognitive impairment and negative symptoms, in elderly patients with schizophrenia (Harvey et al., 2006). It would be interesting to see whether such estimates of premorbid verbal intelligence moderate the relationship between neuropathological changes and dementia severity. However, the lack of data for word recognition reading in our brainbank dataset precludes us from this type of analysis.

In summary, the extent of AD related pathology found in geriatric schizophrenia seems significantly less than commonly observed in AD, but our study shows a significant association between AD-related neuropathology and dementia severity in geriatric schizophrenia. These results suggest that lower levels of AD-related pathology may be one of the causes of severe dementia in geriatric schizophrenia, possibly related to neurodevelopmental changes in the disease, consistent with a decreased cerebral reserve hypothesis. Further research is needed to establish causal relationships and delineate the differential impact of premorbid cognitive functioning, cognitive deterioration over time, and neuropathological changes in the dementia observed in geriatric schizophrenia.

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Table 1

Demographic characteristics of schizophrenia patients as a function of dementia severity

	No dementia (N=16)	Questionable dementia (N=14)	Mild/moderate dementia (N = 26)	Severe dementia (N=54)	Between-group differences (post-hoc tests)
Demographic Variable					
Age at death (years)	79.13 (7.12)	68.36 (19.49)	78.04 (7.17)	82.80 (10.08)	ND=MM=S>QU**
N female (%)	8 (50.0)	9 (64.3)	16 (61.5)	21 (38.89)	n.s.
Education (years)	10.16 (3.88)	9.46 (3.12)	10.58 (3.57)	9.09 (3.30)	n.s.
Postmortem Interval (h)	4.29 (3.04)	4.63 (2.68)	6.17 (5.07)	6.47 (5.03)	n.s.
Time from last assessment (months)	7.29 (2.84)	6.78 (3.49)	7.52 (3.48)	8.23 (4.03)	n.s.
MMSE[2] score	19.29 (9.11)	14.42 (10.81)	14.50 (8.96)	6.97 (8.74)	ND=QU=MM>S***
CDR sum of boxes score	0.43 (0.39)	1.71 (0.82)	4.10 (1.53)	11.31 (5.30)	ND<QU<MM<S***
PANSS general	40.92 (14.05)	40.20 (11.48)	45.59 (9.48)	47.59 (11.67)	n.s.
PANSS positive	18.28 (10.10)	18.90 (5.28)	20.68 (7.31)	16.96 (5.44)	ND=QU=MM>S*
PANSS negative	22.00 (8.59)	28.20 (9.34)	28.14 (7.31)	32.91 (9.98)	ND<QU=MM=S**
N ApoE4 carriers (%)	0 (0.0)	2 (6.7)	12 (46.2)	15 (27.8)	ND=QU<MM=S*

Note: "ND" denotes no dementia, "mild/moderate" denotes CDR scores of 1 or 2, "severe" denotes CDR scores greater than 2. MMSE denotes Mini-Mental State Examination. PANSS denotes Positive and Negative Syndrome Scale. Standard deviations in parentheses. ND denotes no dementia, QU denotes questionable, MM mild to moderate, and S secre dementia. Results from post hoc t-test.

*** $p < .001$

** $p < .01$

* $p < .05$.

Table 2

Mean density of neuritic plaques in five neocortical areas as a function of dementia severity and ApoE4 carrier status in schizophrenia patients.

	CDR <= 2, ApoE4 non-carrier (N=32)	CDR <= 2, ApoE4 carrier (N=24)	CDR > 2, ApoE4 non-carrier (N=39)	CDR > 2, ApoE4 carrier (N=15)
Neocortical area				
Superior temporal gyrus	0.85 (2.49)	2.27 (3.75)	2.37 (5.39)	6.26 (9.67)
Orbitofrontal gyrus	0.49 (1.74)	1.66 (2.53)	2.06 (4.28)	6.55 (10.22)
Mediofrontal gyrus	0.78 (2.57)	2.47 (4.30)	1.71 (3.53)	8.34 (13.32)
Inferior parietal lobule	0.68 (2.35)	2.01 (3.81)	1.77 (3.97)	4.91 (7.34)
Occipital cortex	0.80 (2.38)	2.28 (4.15)	1.27 (3.16)	2.37 (3.69)

Note: Means and standard deviations (in parentheses) for neuritic plaque density measures in five cortical regions. Unadjusted analyses revealed a main effect for dementia severity ($F = 2.93$, $df = 6, 95$, $p < .05$, $\eta^2 = .11$), a main effect for ApoE4 carrier status ($F = 2.76$, $df = 6,94$, $p < .05$, $\eta^2 = .09$), and a significant interaction between these two factors ($F = 2.56$, $df = 7, 95$, $p < .05$, $\eta^2 = .08$).

Table 3

Distribution of hippocampal tangle ratings as a function of dementia severity in schizophrenia patients

	CDR < 2 (N =46)	CDR > 2 (N =52)
Hippocampal tangle rating		
Absent	21 (37.5%)	11 (21.2%)
Sparse	25 (44.6%)	19 (36.5%)
Moderate	2 (3.6%)	5 (9.6%)
Severe	8 (14.3%)	17 (32.7%)

Note: Number of subjects within each tangle rating category (percentages of column total in parentheses). For hippocampal neurofibrillary tangles, nonparametric analyses revealed a main effect for dementia severity ($\chi^2 = 7.73$, df = 3, $p < .05$). There was no effect of ApoE4 carrier status ($p = .17$).