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Neuritic pathology is lacking in the entorhinal cortex, subiculum and hippocampus in middle-aged adults with schizophrenia, bipolar disorder or unipolar depression

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Abstract Earlier reports have provided conflicting results regarding the association between Alzheimer's disease (AD) and mental disorders. Using a well-characterized postmortem series of 40 middle-aged human brains, we have performed quantitative analysis of neurofibrillary tangles and senile plaques in the entorhinal cortex, subiculum and rostral hippocampus in 9 subjects with schizophrenia, 8 with bipolar disorder, 12 with depression, and 11 age- and sex-matched controls. No significant differences were found among the four groups. Our study indicates that the Alzheimer-type changes, which might be related to the likelihood of AD development later in life, are not increased in middle-aged subjects with mental illness. The result also supports the more recent reports that have demonstrated no increased incidence of AD in mentally ill patients.

Keywords Neuritic pathology · Entorhinal cortex · Schizophrenia · Bipolar disease · Unipolar depression

Introduction

Several lines of evidence have suggested that the underlying pathology of neurodegenerative diseases such as Alzheimer's disease (AD), and mental illness such as schizophrenia, is different; significant neuronal loss with accompanying gliosis, while characteristic of a number of neurodegenerative disorders, is not observed in the latter [7, 8, 24]. Rather, reduction of glial cell density and neuronal size [7] and increased neuronal density [25, 28] in different brain regions have recently been noted in mental disorders. These two groups of diseases, however, do share some common clinical features and anatomical sites of involvement. Psychosis, the symptom dominating schizophrenia and some forms of depression, occurs not infrequently in subjects with neurodegenerative disorders [11, 13]. Conversely, cognitive impairment, the most debilitating manifestation of neurodegenerative diseases, is not uncommonly observed in elderly patients with schizophrenia (in 68–72% of the patients) [9, 23], depression [18], and in middle-aged subjects with bipolar disorder [26].

Studies have shown that psychosis in AD is related to increased neuritic pathology; Zubenko et al. [29] examined 27 subjects with AD (mean age 72 years) and found the symptoms to be associated with significantly increased densities of senile plaques (SP) and neurofibrillary tangles (NFT) in the prosubiculum and middle frontal cortex, respectively. A more recent report has demonstrated that 63% of 109 elderly AD subjects developed psychosis, and that there is a significant increase in NFT density in the neocortex of elderly AD patients with psychosis as compared to those without [11]. In the present study, a quantitative analysis of SP and NFT has been performed in the entorhinal cortex (ERC), subiculum and hippocampus in four groups of middle-aged subjects (schizophrenia, bipolar disorder, major depression and nonpsychiatric controls) to clarify whether AD-type pathology is significantly increased in patients with these forms of mental illness. The brain areas examined are well-known to be affected in AD [10] and, based on morphometric and imaging studies, are also involved in mental illnesses such as schizophrenia [2, 16] and major depression [4].

Methods and materials

Subjects

Forty postmortem human brains, including 9 subjects with schizophrenia, 8 with bipolar disorder, 12 with depression, and 11 age- and sex-matched non-psychiatric controls, were obtained from the Stanley Foundation Brain Collection. They were collected with the

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permission of the family from several medical examiner's offices. Brain sections including the ERC, subiculum and hippocampus from the four groups of subjects were examined; a few additional cases were excluded due to less than optimal anatomical matching of the available tissue sections or to inadequate samples. Matched sections were obtained from the rostral hippocampus to include the intermediate subarea of the ERC (Fig. 3D of [14]) and the subiculum. Macro- and microscopic examinations were performed to exclude other pathological changes, including Bielschowsky's silver stain of several cerebral cortical regions, the cerebellar vermis and the hippocampus. Autopsy records were also reviewed. Clinical records were reviewed independently by two psychiatrists (E. Fuller

Table 1 Demographics of cases (*Lat* laterality of brain side examined)

Case	Age (years)	Race	Sex	Cause of death	PMI (h)	Lat	Brain weight (g)	Onset/duration (age/years)	Formalin (months)
Schizophrenics									
1	44	W	M	Cardiac	50	R	1,640	17/27	7
2	44	W	M	Pulmonary disease	29	L	1,500	21/23	5
3	49	W	F	Cardiac	38	L	1,440	25/24	3
4	52	W	M	Cardiac	61	L	1,530	20/32	31
5	56	A	F	Suicide: overdose	12	R	1,420	24/32	9
6	58	W	F	Cardiac	26	R	1,410	42/16	9
7	60	W	F	Cardiac	40	L	1,395	15/45	13
8	60	W	M	Accidental drowning	31	R	1,340	27/33	9
9	62	A	F	Motor vehicle accident	26	L	1,270	38/24	7
Mean ± SD	54±7				35±14	4R/5L	1,438±108	25/28	10.33±8.25
Bipolar									
1	48	W	F	Pneumonia	22	L	1,260	16/32	8
2	48	W	M	Suicide: immolation	13	R	1,540	27/21	9
3	50	B	F	Malnutrition and dehydration	18	L	1,180	34/16	8
4	50	W	M	Suicide: jumped	19	L	1,380	17/23	4
5	50	W	F	Pulmonary emboli	62	L	1,320	25/25	2
6	54	W	M	Subdural hematoma	39	R	1,690	39/14	13
7	57	W	M	Cardiac	19	L	1,440	30/27	13
8	61	W	F	Suicide: overdose	60	L	1,415	18/43	9
Mean ± SD	52±5				32±20	2R/6L	1,403±160	26/25	8.25±3.85
Depressive									
1	42	W	F	Cardiac	25	R	1,340	39/3	9
2	42	W	M	Suicide: hanged	7	L	1,350	32/10	5
3	43	W	M	Cardiac	43	L	1,460	30/13	2
4	44	W	F	Suicide: overdose	32	L	1,410	27/17	18
5	46	W	M	Suicide: carbon monoxide	26	R	1,720	28/18	9
6	47	W	M	Cardiac	28	L	1,740	27/20	1
7	51	W	M	Suicide: gunshot	26	R	1,550	50/1	15
8	52	W	M	Cardiac	12	R	1,520	46/6	15
9	53	W	F	Acute alcohol intoxication	40	R	1,320	11/42	19
10	56	W	M	Cardiac	23	L	1,240	52/4	1
11	56	W	F	Pulmonary emboli	28	L	1,520	54/2	1
12	65	W	M	Cardiac	19	R	1,360	45/20	14
Mean ± SD	50±7				26±10	6R/6L	1,460±156	37/13	9.08±6.97
Controls									
1	41	B	M	Pulmonary embolus	11	R	1,305		2
2	42	W	M	Cardiac	27	R	1,500		2
3	44	W	F	Cardiac	25	R	1,490		10
4	44	W	M	Cardiac	10	L	1,510		2
5	52	W	M	Cardiac	22	R	1,330		2
6	52	W	M	Cardiac	8	L	1,840		8
7	53	W	M	Cardiac	28	L	1,400		2
8	57	W	F	Motor vehicle accident	26	R	1,400		2
9	58	W	M	Cardiac	27	L	1,780		1
10	59	W	M	Cardiac	26	R	1,560		10
11	68	W	F	Pulmonary embolus	13	L	1,360		5
Mean ± SD	52±8				20±8	6R/5L	1,497±174		4.18±3.49

Torrey, Llewellyn B. Bigelow) and it was agreed that patients met the DSM-IV diagnostic criteria for diagnoses.

Tissue processing

Brains were collected at autopsy over a period of 34 months. The left or right cerebral hemisphere was fixed by immersion in 10% phosphate-buffered formalin solution and stored at room temperature (RT) for a period of 1–31 months (one case), usually 10 months or less. The ERC and immediately adjacent temporal cortex were dissected into three blocks, each block 1 cm in thickness. The blocks were then embedded in paraffin and sectioned at a thickness of 10 μm. Each section was stained with Bielschowsky's silver stain (adapted for paraffin) for nerve fibers. Sections were matched at the level of the rostral hippocampus, with

Table 2 Summary of medications and substance abuse history (*Est*. estimated, *f mg eq* fluphenazine mg equivalents, *ECT* electroconvulsive thereapy)

Case	CNS medications at time of death	Est. lifetime antipsychotics (f mg eq)	Substance abuse history
Schizophrenics			
7	None; had ECT but probably never treated otherwise	0	No use of alcohol or drugs
4	None; untreated for over 20 years	9,000	No use of alcohol or drugs
6[a]	Haloperidol, diphenhydramine	35,000	Past alcohol abuse, no use of drugs
9[a]	None; untreated for several months	50,000	Moderate use of alcohol; no use of drugs
8[a]	Thioridazine, amitriptyline	80,000	No use of alcohol or drugs
1	Haloperidol, carbamazepine, fluoxetine, clonazepam, benzotropine	100,000	Moderate alcohol use, little or no use of drugs
2	Clozapine, chlorpromazine, lithium	130,000	Alcohol dependence
5	Haloperidol, lithium, diphenhydramine, chloral hydrate	150,000	No alcohol use, occas. past marihuana use
3	Haloperidol, clozapine, clonazepam	>200,000	No use of alcohol or drugs
Bipolar			
5[a]	Valproate, clomipramine	0	Light alcohol use; no use of drugs
2	Untreated for over 20 years	200 max.	Moderate alcohol use; marihuana use in college and again in months prior to death
6	Lithium, carbamazepine	2,500	Some alcohol abuse in 20s but abstinent thereafter; no use of drugs
3	None; untreated for several months	12,000	Marihuana and cocaine abuse
1	Valproate, sertraline, chlorprothixene, carbamazepine	32,000	Alcohol abuse; methadone abuse
8	Fluoxetine, valproate	40,000	Light alcohol use; no use of drugs
7[a]	Haloperidol, diphenhydramine	60,000	Abused alcohol in age 20's; no use of drugs
4[a]	Valproate, clozapine, flurazepam, benzotropine	60,000	Light alcohol use; no use of drugs
Depressive[b]			
1	Fluoxetine, lithium	0	Alcohol use light; no drug use
2	Temazepam but off medications for more than 2 weeks	0	Alcohol use light; occasional marihuana when young
3	Trimipramine	0	Alcohol dependence; some drug use: amphetamines, benzodiazepines, and opiods
4	Fluoxetine, imipramine, lorazepam	0	Alcohol use light; no drug use
5	Diphenhydramine, clonazepam	0	No use of alcohol or drugs
6	Fluoxetine, nefazadone	0	Alcohol use light; no drug use
7[a]	Nefazadone, hydroxyzine	0	Past alcohol dependence but abstinent for 14 years
8	No medication for 6 years	0	1–2 beers/day; no use of drugs
9[a]	Lithium, trazadone	0	Severe alcohol dependence
10	Sertraline	0	Alcohol use light; no drug use
11	Venlafaxine, buspirone, alprazolam	0	Alcohol use light; no drug use
12	Phenytoin for a single seizure; no other meds. for 5 years	0	Alcohol use light; no drug use

[a]Cases positive for neurofibrillary tangles

[b]Any depressive with antipsychotics was excluded. In the control group, no evidence of mental illness except for one case (saw counselor for weight control and had a family history of bipolar disorder in a 2° relative)

the adjacent intermediate subarea of the ERC and the subiculum. One matched section from each case was available for our study.

Method of counting

In the above 40 cases, we searched for NFT and mature neuritic plaques in the ERC, subiculum and hippocampus. Sections were obtained to include layers 2 through 6 of the intermediate subarea of ERC (applying the terminology of Krimer et al. (Fig. 3D of [14]) and of the subiculum and rostral hippocampus. Counts of the NFT and mature neuritic plaques were obtained at a magnification of ×200. Maps were drawn from the slides by projection from the Bielschowsky's-stained sections onto a surface at a total magnification of ×7.4. Two observers confirmed the boundaries of the maps. Positive neuritic plaques and NFT were counted from each case, in the total area of each of the three regions. This area ranged from 8 to 96 mm^2 with an average area of 34 mm^2. The number of NFT per unit area in these anatomic regions in different groups of subjects was compared (see Table 3).

Fig. 1A–D All sections are of a representative neurofibrillary tangle from the rostral intermediate subarea of the ERC at the level of the rostral hippocampus, stained with Bielschowsky's silver preparation adapted for paraffin sections. **A** Schizophrenic, age 60 years, cortical layer 3 of ERC. **B** Bipolar disorder, age 50 years, layer 3. **C** Depressive disorder, age 56 years, deep layer 3. **D** Non-psychiatric control, age 59 years, layer 6 (*ERC* entorhinal cortex). *Bar* 20 μm

Statistical analysis

Kruskal-Wallis ANOVA and/or Mann-Whitney U tests were applied to compare the demographic parameters [age, race, sex, post-mortem interval (PMI), laterality of brain side examined, brain weight and the duration of formalin fixation] and the density of NFT among the four groups. The correlation between the density of NFT and the age was tested using the Spearman rank order correlation.

Results

This study was designed to examine the occurrence of neuritic pathology in a relatively young population of patients with schizophrenia, bipolar disorder and major depression. Table 1 summarizes the demographics. Patients with schizophrenia ranged in age from 44 to 62 years (mean 54 years), with a mean PMI of 35 h. Bipolar cases ranged from 48 to 61 years of age (mean 52 years), and a PMI of 32 h. Depressive patients ranged between 42 and 65 years (mean 50 years), and a PMI of 26 h. Control subjects ranged from age 41 to 68 years (mean 52 years), and a mean PMI of 20 h. The primary cause of death for both groups was cardiac disease, suicide, pulmonary disease (emboli) or somatic diseases not affecting the brain. No history of dementia was found in the available clinical records of any of these subjects. Details of medications,

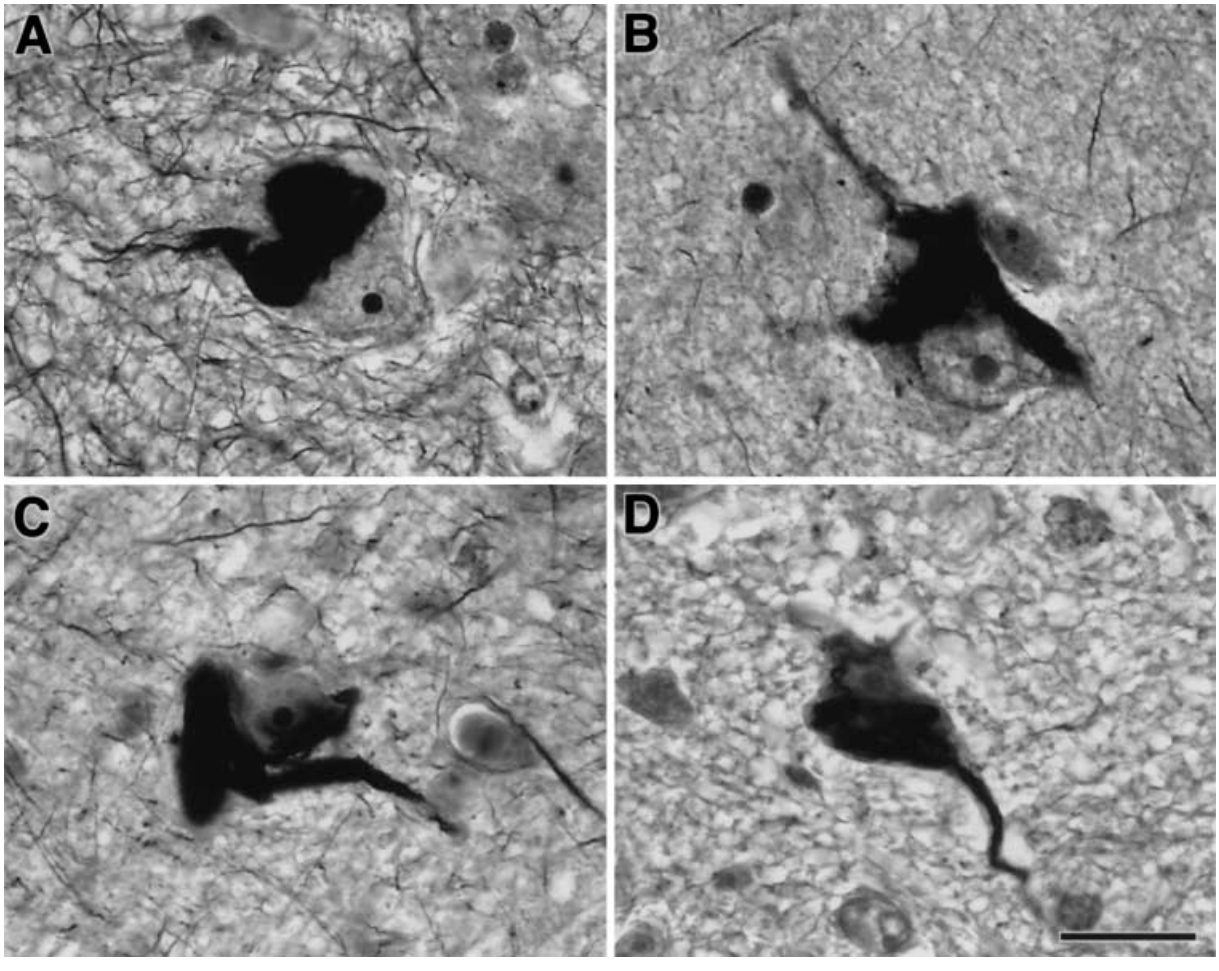

Table 3 Number and density of NFT in hippocampus, subiculum and intermediate subarea of the ERC for subject groups. The first number under each brain area represents the total number of NFT, and the second number is the density of NFT/mm^2. No significant differences are found in NFT density between the schizophrenic, bipolar disorder, major depressive and control subjects in any of these regions. No mature neuritic plaques were detected in any of the subjects (*Hipp*. hippocampus, *Sub*. subiculum, *ERC* entorhinal cortex, *NFT* neurofibrillary tangles)

Schizophrenic					Bipolar					Depressive					Control				
Case	Hipp.	Sub.	ERC	Age	Case	Hipp.	Sub.	ERC	Age	Case	Hipp.	Sub.	ERC	Age	Case	Hipp.	Sub.	ERC	Age
1	0/0	0/0	0/0	44	1	0/0	0/0	0/0	48	1	0/0	0/0	0/0	42	1	0/0	0/0	0/0	41
2	0/0	0/0	0/0	44	2	0/0	0/0	0/0	48	2	0/0	0/0	0/0	42	2	0/0	0/0	0/0	42
3	0/0	0/0	0/0	49	3	0/0	0/0	0/0	50	3	0/0	0/0	0/0	43	3	0/0	0/0	0/0	44
4	0/0	0/0	0/0	52	4	3/0.09	0/0	2/0.04	50	4	0/0	0/0	0/0	44	4	0/0	0/0	0/0	44
5	0/0	0/0	0/0	56	5	2/0.04	0/0	20/0.5	50	5	0/0	0/0	0/0	46	5	0/0	0/0	0/0	52
6	0/0	0/0	1/0.01	58	6	0/0	0/0	0/0	54	6	0/0	0/0	0/0	47	6	0/0	0/0	1/0.03	52
7	0/0	0/0	0/0	60	7	0/0	0/0	2/0.05	57	7	0/0	0/0	1/0.01	51	7	0/0	0/0	0/0	53
8	0/0	1/0.05	20/0.3	60	8	0/0	0/0	0/0	61	8	0/0	0/0	0/0	52	8	1/0.03	0/0	21/0.5	57
9	0/0	0/0	9/0.4	62						9	1/0.03	0/0	0/0	53	9	0/0	0/0	1/0.02	58
										10	1/0.04	0/0	0/0	56	10	0/0	0/0	5/0.2	59
										11	0/0	0/0	2/0.04	56	11	0/0	0/0	0/0	68
										12	0/0	0/0	4/0.2	65					

an estimation of lifetime anti-psychotic treatment and a summary of substance abuse history are summarized in Table 2. There were no statistically significant differences in any of the demographic parameters among the four cohorts using the Kruskal-Wallis ANOVA test. However, the PMI of the schizophrenic subjects was longer than that of controls and was statistically significant (U=16, P= 0.01) on the Mann-Whitney U test.

NFT were seen in some cases in all groups examined, most commonly in the ERC (Fig. 1), followed by the hippocampus and rarely in the subiculum (Table 3), but none of the cases demonstrated a higher NFT density than the previously published norms for age-matched normal subjects [19, 20]. Although there was a positive correlation between the increasing age of all subjects and the density of the NFT (P=0.002, Spearman rank order correlation), no significant difference in the NFT density was found among the four groups. Also, the number of cases with at least one NFT were similar between all the subject groups, i.e., in one-third to less than half the cases in each group. The above data suggest that the presence of NFT is correlated with age, but not with the type of mental illness. Lastly, no mature neuritic plaques were seen in any of the subjects.

Discussion

Earlier studies have provided conflicting results regarding the incidence of AD in patients with schizophrenia. An unexpectedly high percentage of neuritic pathology has been observed in some reports. For example, 8 of 23 (35%) elderly patients diagnosed clinically as having schizophrenia appeared to have AD at postmortem brain examination [5]. Another study showed that 28% of 544 elderly schizophrenics had neuropathological findings consistent with AD [21]. The results prompted the suspicion that elderly schizophrenic patients, especially those with a chronic course of illness, were prone to the development of AD [21]. However, other investigations, including the more recent ones, have failed to replicate this finding [6, 9, 12, 15, 17, 22, 23], and it has been estimated that the incidence of AD in elderly patients with schizophrenia is equal to or even less than that in the general population [12, 15, 17]. Our data, obtained from a study of middle-aged schizophrenics, have suggested that there is no increased neuritic pathology in this age group that may provide a substrate for the subsequent clinical appearance of AD in later life. This result is, therefore, in agreement with other studies [6, 9, 12, 15, 17, 22, 23], performed primarily in elderly schizophrenics. As suggested by several authors [1, 21, 22, 23], the initial observation of the increased susceptibility of elderly schizophrenics to develop AD might be due to several factors, including the small sample size examined, the absence of an age-matched nonpsychiatric control group, inaccuracies of psychiatric diagnosis or a lack of firm neuropathological diagnostic criteria for AD at the time the studies were performed.

In contrast to the large number of postmortem reports on schizophrenia, postmortem studies of affective disorders are scanty [3]. Some patients with mood disorders have been occasionally included in postmortem studies of neuritic pathology in schizophrenia, but these subjects are only recently beginning to receive attention. Additionally, probably due to the small sample size, different types of affective illnesses (depression and bipolar disorder) have been grouped together, making interpretation difficult. Nevertheless, the first postmortem neuropathology survey in patients with major depression has recently been carried out, and has not shown significant differences in neuritic plaques and NFT counts in various brain regions, including the hippocampus, between depressive subjects with and without cognitive impairment (mean ages 79 and 73 years, respectively), as compared to the published data on age-matched controls [18]. Our quantitative analysis of neuritic plaques and NFT in middle-aged patients thus

further supports the conclusion of O'Brien et al. [18] that the susceptibility for some patients with major depression to have a cognitive deficit is not related to increased AD-type pathology. On the contrary, unlike an earlier report that noted a substantial number of cases (4 out of 14 subjects) with neuritic pathology in patients with a mean age of 70 years, diagnosed clinically with manic-depressive psychosis [5], we have not been able to demonstrate increased neuritic plaques and/or NFT in our bipolar subjects in comparison to the controls.

The possible role of chronic neuroleptic administration and an increased frequency of NFT in elderly schizophrenics has been reported by Wisniewski et al. [27], who found a two times higher NFT concentration, with an earlier and more rapid occurrence of NFT, compared to those who did not receive these agents. Our data do not support this observation, although the number of subjects in our series is limited; two of the three schizophrenics with positive NFT had a considerably lower estimated lifetime treatment with anti-psychotics than did two of the three youngest subjects whose brains showed an absence of neuritic pathology.

Since the number of subjects in our series is limited, the potential for a type II error can not be excluded. As a consequence, small differences between the groups could be missed. However, such small differences would be of dubious clinical relevance.

To summarize, our present study has not demonstrated an increase in neuritic pathology in the ERC, subiculum and hippocampus in well-characterized middle-aged subjects with schizophrenia, bipolar disorder and depression as compared to controls. The finding is in keeping with recent reports that have shown no significant increase in AD in elderly patients with mental illness, and supports the view that the mechanism underlying cognitive dysfunction in mental disorders is different from that of AD.

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References

1. Arnold SE, Trojanowski JQ (1996) Cognitive impairment in elderly schizophrenia. A dementia (still) lacking distinctive histopathology. Schizophr Bull 22:5–9
2. Barta PE, Powers RE, Aylward EH, Chase GA, Harris GJ, Rabins PV, Tune EL, Pearlson GD (1997) Quantitative MRI volume changes in late onset schizophrenia and Alzheimer's disease compared to normal controls. Psychiatr Res 68:65–75
3. Baumann B, Bogerts B (1999) The pathomorphology of schizophrenia and mood disorders: similarities and differences. Schizophr Res 39:141–148
4. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS (2000) Hippocampal volume reduction in major depression. Am J Psychiatry 157:115–118
5. Buhl L, Bojsen-Møler M (1988) Frequency of Alzheimer's disease in a postmortem study of psychiatric patients. Dan Med Bull 35:288–290
6. Casanova MF, Carosella NW, Gold JM, Kleinman JE, Weinberger DR, Powers RE (1993) A topographical study of senile plaques and neurofibrillary tangles in the hippocampi of patients with Alzheimer's disease and cognitively impaired patients with schizophrenia. Psychiatry Res 49:41–62
7. Cotter D, Mackay D, Landau S, Kerwin R, Everall I (2001) Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. Arch Gen Psychiatry 58:545–553
8. Damadzic R, Bigelow LB, Krimer LS, Goldenson DA, Saunders RC, Kleinman JE, Herman MM (2001) A quantitative immunohistochemical study of astrocytes in the entorhinal cortex in schizophrenia, bipolar disorder and major depression: absence of significant astrocytosis. Brain Res Bull 55:611–618
9. Dwork AJ, Susser ES, Keilp J, Waniek C, Liu D, Kaufman M, Zemishlany Z, Prohovnik I (1998) Senile degeneration and cognitive impairment in chronic schizophrenia. Am J Psychiatry 155:1536–1543
10. Esiri MM, Hyman BT, Beyreuther K, Masters CL (1997) Ageing and dementia. In: Graham DI, Lantos PL (eds) Greenfield's neuropathology, vol 2, 6th edn. Arnold, London, pp 175–188
11. Farber NB, Rubin EH, Newcomer JW, Kinscherf DA, Miller JP, Morris JC, Olney JW, KcKeel DW (2000) Increased neocortical neurofibrillary tangle density in subjects with Alzheimer disease and psychosis. Arch Gen Psychiatry 57:1165–1173
12. Jellinger KA, Gabriel E (1999) No increased incidence of Alzheimer's disease in elderly schizophrenics. Acta Neuropathol 97:165–169
13. Klatka LA, Louis ED, Schiffer RB (1996) Psychiatric features in diffuse Lewy body disease: a clinicopathologic study using Alzheimer's disease and Parkinson's disease comparison groups. Neurology 47:1148–1152
14. Krimer LS, Hyde TM, Herman MM, Saunders RC (1997) The entorhinal cortex: an examination of cyto- and myeloarchitectonic organization in humans. Cereb Cortex 7:722–731
15. Murphy GM, Lim KO, Wieneke M, Ellis WG, Forno LS, Hoff AL, Nordahl T (1998) No neuropathologic evidence for an increased frequency of Alzheimer's disease among elderly schizophrenics. Biol Psychiatry 43:205–209
16. Nelson MD, Saykin AJ, Flashman LA, Riordan HJ (1998) Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry 55:433–440
17. Niizato K, Arai T, Kuroki N, Kase K, Iritani S, Ikeda K (1998) Autopsy study of Alzheimer's disease brain pathology in schizophrenia. Schizophr Res 31:177–184
18. O'Brien J, Thomas A, Ballard C, Brown A, Ferrier N, Jaros E, Perry R (2001) Cognitive impairment in depression is not associated with neuropathologic evidence of increased vascular or Alzheimer-type pathology. Biol Psychiatr 49:130–136
19. Price JL (1997) Diagnostic criteria for Alzheimer's disease. Neurobiol Aging 18:S67–S70
20. Price JL, Davis PB, Morris JC, White DL (1991) The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging 12:295–312
21. Prohovnik I, Dwork AJ, Kaufman MA, Willson N (1993) Alzheimer-type neuropathology in elderly schizophrenia patients. Schizophr Bull 19:805–816
22. Purohit DP, Davidson M, Perl DP, Powchik P, Haroutunian VH, Bierer LM, McCrystal J, Losonczy M, Davis KL (1993) Severe cognitive impairment in elderly schizophrenic patients: a clinicopathological study. Biol Psychiatry 33:255–260
23. Purohit DP, Perl DP, Powchik P, Haroutunian VH, Davidson M, Davis KL (1998) Alzheimer disease and related neurodegenerative diseases in elderly patients with schizophrenia– a postmortem neuropathologic study of 100 cases. Arch Gen Psychiatry 55:205–211

24. Roberts GW, Royston MC, Weinberger DR (1997) Schizophrenia. In: Graham DI, Lantos PL (eds) Greenfield's neuropathology, vol 1, 6th edn. Arnold, London, p 917
25. Selemon LD, Rajkowska G, Goldman-Rakic PS (1998) Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: application of a three-dimensional, stereologic counting method. J Comp Neurol 392:402–412
26. Van Gorp WG, Altshuler L, Theberge DC, Wilkins J, Dixon W (1998) Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence: a preliminary report. Arch Gen Psychiatry 55:41–46
27. Wisniewski HM, Constantinidis J, Wegiel J, Bobinski M, Tarnawski M (1994) Neurofibrillary pathology in brains of elderly schizophrenics treated with neuroleptics. Alzheimer Dis Assoc Disord 8:211–227
28. Zaidel DW, Esiri MM, Harrison PJ (1997) The hippocampus in schizophrenia: lateralized increased neuronal density and altered cytoarchitectural asymmetry. Psychol Med 27:703–713
29. Zubenko GS, Moossy J, Martinez AJ, Rao G, Claassen D, Rosen J, Kopp U (1991) Neuropathologic and neurochemical correlates of psychosis in primary dementia. Arch Neurol 48:619–624