RESEARCH ARTICLE

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Alzheimer's CSF markers in older schizophrenia patients

Giovanni B. Frisoni[1,2], Annapaola Prestia[1], Cristina Geroldi[1,2], Andrea Adorni[1,2], Roberta Ghidoni[3,4], Giovanni Amicucci[5], Matteo Bonetti[6], Andrea Soricelli[7], Paul E. Rasser[8,9], Paul M. Thompson[10] and Panteleimon Giannakopoulos[11,12]

[1]LENITEM—Laboratory of Epidemiology Neuroimaging and Telemedicine, Italy
[2]Psychogeriatric Ward, Italy
[3]Proteomics Unit, Italy
[4]NeuroBioGen Lab-Memory Clinic, IRCCS Centro San Giovanni di Dio FBF, Brescia, Italy
[5]Service of Anesthesiology, S.Orsola-Fatebenefratelli Hospital, Brescia, Italy
[6]Service of Neuroradiology, Istituto Clinico Città di Brescia, Brescia, Italy
[7]SDN Foundation and Institute of Diagnostic and Nuclear Development, and University of Naples Parthenope, Naples, Italy
[8]Schizophrenia Research Institute, Sydney, Australia
[9]Priority Centre for Brain and Mental Health Research, School of Design, Communication and IT, University of Newcastle, Newcastle, Australia
[10]Laboratory of Neuro Imaging, UCLA School of Medicine, Los Angeles, USA
[11]Division of Geriatric Psychiatry, University Hospitals of Geneva and Faculty of Medicine, University of Geneva, Switzerland
[12]Division of Old Age Psychiatry, Hospices-CHUV, University of Lausanne, Switzerland
Correspondence to: G. B. Frisoni, MD, E-mail: gfrisoni@fatebenefratelli.it

Objectives: Cognitive impairment is prevalent in older schizophrenia patients but its biological basis is unknown. Neuropathological studies have not revealed Alzheimer disease (AD) lesion burden but *in vivo* data are lacking.

Method: We investigated the concentrations of CSF biomarkers of brain amyloidosis (Abeta42) and neurodegeneration (total and p-tau) in a group of older schizophrenia patients and related them to cognitive and MRI measures. Older schizophrenia ($n = 11$), AD patients ($n = 20$) and elderly controls ($n = 6$) underwent cognitive testing, lumbar puncture, and MRI scanning. Abeta42 and total and p-tau concentrations were assayed in the CSF. MRI volumes were assessed using both voxel-based (cortical pattern matching) and region-of-interest analyses.

Results: CSF tau concentration in older schizophrenia patients was within normal limits (total tau 171 ± 51 pg/ml, p-tau 32 ± 8 pg/ml), while CSF Abeta42 (465 ± 112 pg/ml) levels were significantly lower compared to healthy elders (638 ± 130 pg/ml) but higher than in AD patients (352 ± 76 pg/ml). There was a strong positive relationship between CSF total or p-tau levels and MMSE scores in schizophrenia patients but not in AD, where higher concentrations of total tau were correlated with higher volumes in the occipital cortex ($r = 0.63$, $p = 0.036$), while in AD a significant correlation was found between lower Abeta42 concentrations and lower gray matter volume in the cingulate and lateral orbital cortices ($r > 0.46, p < 0.05$).

Conclusions: Older schizophrenia patients show a peculiar pattern of CSF Abeta42 and tau concentrations that relates to cognitive and structural markers but is not consistent with neurodegeneration and could be secondary to neurodevelopmental or drug treatment effects. Copyright © 2010 John Wiley & Sons, Ltd.

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Introduction

Cognitive deficits are prevalent in patients with schizophrenia and worsen with old age. Early studies showed an age-related increase in the prevalence of global intellectual impairment that mainly concerns chronically hospitalized patients over age 65 (Goldberg and Gold, 1995; Fucetola *et al*., 2000). The cognitive

impairment of older patients with schizophrenia is usually static or progresses slowly (Heaton *et al*., 1994). Neuropathological data suggested that this phenomenon is unrelated to Alzheimer's disease (AD) lesions (Casanova *et al*., 1993; Purohit et al., 1998; Dwork *et al*., 1998; Arnold *et al*., 1998; Religa *et al*., 2003; Dubois *et al*., 2007 and see Wisniewski and Konietzko, 2008 for a review). Patterns of cognitive impairment involving attention, memory, executive functions, sensory-visceromotor multimodal integration, motivation and decision-making have been repeatedly reported in elderly schizophrenia patients (Friedman *et al*., 2001) although neuropathological changes of AD and cerebrovascular lesions have been found remarkably rare (Religa *et al*., 2003). As those neuropsychological and morphostructural alterations are markers of the disease since the very early stage of the pathology (Jabben *et al*., 2010) or seem to be present even in patients at high risk of developing psychosis (Jahshan *et al*., 2010), commonly in interaction with environmental factors during early neurodevelopmental period (like pregnancy and delivery complications, such as intrauterine fetal hypoxia, infections, and malnutrition) or taking place later in life (like psychosocial stressors, such as residence in an urban area and dysfunctional family communication; see Tsuang, 2000 for a review) and smaller hippocampal and brain volumes have been found also in relatives of schizophrenia patients (Goldman *et al*., 2008), this evidence suggests a neurodevelopmental brain insult that persists throughout the entire life of a patient affected by schizophrenia different from that following the neurodegenerative process taking place in a brain affected by Alzheimer's disease pathology.

Recently, biological markers for *in vivo* diagnosis of AD have been developed that addresses the two pathophysiological features of the disease, i.e., disruption of the amyloid cascade resulting in amyloid deposition, and tangle formation, a result of hyperphosphorylation of tau, leading to neurodegeneration. The concentration of Abeta42 in the cerebrospinal fluid (CSF) is believed to mirror the deposition of toxic Abeta42 in the brain that, after being cut off by secretase, forms aggregations toxic to neurons (especially in its dimer form, Jagust *et al*., 2009) total tau is believed to reflect the neurons dying after tau hyperphosphorylation (Bertrand *et al*., 2010), and p-tau 181 (p-tau) may reflect neurodegeneration specific to AD. To our knowledge, only one study has so far assayed CSF tau in schizophrenia (Schönknecht *et al*., 2003a). Moreover, no study has yet studied CSF Abeta42 concentration *in vivo*, despite the interest in relating this marker to cognitive and brain structural changes in schizophrenia.

To address these issues, we investigated the concentrations of CSF biomarkers of brain amyloidosis (Abeta42) and neurodegeneration (total tau and p-tau) and related them to cognitive and structural magnetic resonance imaging (MRI) measures in 11 older schizophrenia patients. Control groups included 20 AD patients matched for age, sex, education, and cognitive performance, and six healthy elderly individuals. We hypothesized that concentrations of CSF total and p-tau and Abeta42 in elderly schizophrenia patients were significantly different from those observed in AD patients and more similar to normal elders, as the two pathologies should have different underlying mechanism (neurodevelopmental versus neurodegenerative); moreover, we expected to find positive correlations between gray matter density in brain areas known to be affected by the AD pathology and concentrations of tau and/or Abeta42 in Alzheimer's group whereas schizophrenia patients should display a different pattern of relationship.

Methods

Subjects and assessment

Patients with schizophrenia were selected from those staying at the Psychogeriatric Ward of the IRCCS Centro San Giovanni di Dio Fatebenefratelli in Brescia, Italy, from December 2006 to April 2008. They represent a sub-sample of those described in a previous study of the neuroanatomy of cortical changes in elderly schizophrenia patients (Frisoni *et al*., 2009a).

The ward is a 40-bed long-term unit where patients are referred from community services or, less frequently, from acute psychiatry units. The length of stay is typically 12–24 months but occasionally extends to 36 months. Selection criteria included old age (60 years and older) and a DSM-IV diagnosis of schizophrenia with onset before age 40. Exclusion criteria included history of substance dependence, other diseases of the central nervous system, or unstable medical conditions. Vascular risk factors such as hypertension, diabetes, and smoking were systematically ascertained. (Supporting information: For a full description of the disease-specific features of the schizophrenia patients, please refer to Supplementary Table 1 at: www.centroalzheimer.it/public/supplementary_csf_schizo.doc). Twenty patients with NINCDS-ADRDA probable AD were recruited from among those coming for observation at the Outpatient Memory Clinic from the same institution; they were matched with schizophrenia patients based on Mini-Mental State Examination (MMSE) score and age (Frisoni *et al*., 2009a).

All patients were assessed between October 2005 and October 2007 and underwent history taking with a structured interview from patients' relatives (typically spouses), laboratory exams (including genomic DNA extraction with APOE (apolipoprotein E) genotyping according to standard procedures), physical and neurological examinations. Neuropsychological assessment was performed and recorded by a psychologist after at least 4 weeks of observation in order to check stability of the psychiatric symptoms and included tests of language comprehension and production, long-term memory, constructional abilities, attention, and executive functions. The entire evaluation lasted around 1 h and 30 min and was administered in a dedicated room (Lezak *et al*., 2004).

Healthy controls were recruited among patients scheduled for surgery for hip replacement or other pelvic disease with spinal anaesthesia at the S. Orsola Fatebenefratelli General Hospital in Brescia. A few days before surgery, patients were asked permission to collect 4 cc of CSF for studies on brain disorders of old age and undergo a brief cognitive test, 12–18 weeks after surgery (Frisoni *et al*., 2009b, 2009c).

Written informed consent was obtained from all subjects and, in the case of schizophrenia and AD patients, from family relatives whenever possible. No compensation was provided for study participation. The study was approved by the local ethics committee, CEIOC (Comitato Etico delle Istituzioni Ospedaliere Cattoliche) and performed in accordance with the ethical standards developed in the 1975 and 1983 Declaration of Helsinki.

Biochemical analyses of CSF

CSF was obtained by lumbar puncture between L4 and L5 or L3 and L4 and collected in polypropylene tubes. CSF samples were centrifuged at $2000 \times g$ for 10 min to eliminate cells and other insoluble material, and immediately aliquoted and stored at $-80\,^{\circ}C$ before further analysis. Levels of Abeta1–42 and total and p-tau proteins were determined by commercially available enzyme linked immunosorbent assay (ELISA; Innogenetics, Belgium). Normative values used in this study were based on those of Sjögren *et al*. (2001) for total tau and Abeta1–42 and on those of Mattsson et al. (2009) for p-tau.

MR acquisition and post-processing

High-resolution gradient echo sagittal 3D MR scans were acquired with a Philips Gyroscan 1.0 T scanner (TR = 20 ms, TE = 5 ms, flip angle 30°, field of view = 220 mm, acquisition matrix = 256 × 256, slice thickness = 1.3 mm, no inter-slice gap). The gray matter was studied with the cortical pattern matching technique (Thompson *et al*., 2004) and results were analyzed with a voxel-based (CPM) and region-of-interest (ROI)-based approach, both performed by operators blind to diagnosis. The two approaches are complementary as the former offers an estimate of tissue density—and thus tissue volume—in each voxel, while the latter builds on CPM and provides an estimate of the average density of all the voxels in a given estimated Brodmann area (BA).

Cortical pattern matching

For a detailed description of the methods please refer to Thompson *et al*. (2003). Briefly, after re-orienting images along the AC-PC line, removing voxels below the cerebellum, setting the anterior commissure as the origin of the spatial coordinates, the images were normalized using a 12-parameter affine transformation to a customized template (Frisoni *et al*., 2007). For each individual brain, two 3D renderings were created, reconstructing the left and right hemispheres, using an intensity threshold that best differentiated gray matter from extracerebral CSF. After this, sulcal curves for each hemisphere were manually traced (17 sulci on the lateral and 12 on the medial surfaces, and 10 lines to outline interhemispheric gyral limits) by a single tracer (A.P.) following an extensive and validated protocol (http://users.loni.ucla.edu/∼khayashi/Public/medial_surface/; www.loni.ucla.edu/∼esowell/new_ sulcvar.html; Sowell *et al*., 2001).

Individual sulcal maps were averaged to create a common average sulcal map for all subjects in the study, then individual cortical surfaces were parameterized, flattened, and warped and image voxels were classified using a partial volume classifier algorithm (Shattuck and Leahy, 2001). The gray matter was extracted and mapped onto the corresponding parametric hemispheric model in exact spatial correspondence. Gray matter density was computed at each cortical point as the proportion of tissue classified as gray matter in a sphere centred at that point, with a radius of 15 mm, and then averaged within each group to obtain the mean gray matter density. A deformable Brodmann area (BA) atlas (Rasser *et al*., 2004) was applied to the left and right hemisphere average cortical surface models to extract the average densities of BAs in each subject.

Table 1 Descriptive features of the groups.

	Older schizophrenia patients	Alzheimer's patients	Healthy older controls
	($N = 11$)	($N = 20$)	($N = 6$)
Age, years	69.2 ± 6.5	71.1 ± 5.2	61.3 ± 7.0
[range]	[60–78]	[60–79]	[52–73]
Gender, female (%)	8 (73%)	15 (75%)	1 (17%)
Education, years	6.7 ± 3.2	6.8 ± 3.6	7.3 ± 3.1
Mini Mental State Exam	22.1 ± 4.0	21.3 ± 4.5	29.3 ± 0.8
[range]	[14–27]	[10–27]	[29–30]
ApoE ε4 carriers, *n* (%)	0/8 (0%)	7 (35%)	n.a.
Hypertension	3 (27%)	10 (50%)	3 (50%)
Diabetes	1 (9%)	3 (15%)	0 (0%)
Smoking	1 (9%)	0 (0%)	1 (17%)
Alcohol consumption	0 (0%)	3 (15%)	0 (0%)

Values denote mean ± SD; When the denominator is not shown, data are available for the whole group; n.a. = data not available

Statistical analysis

The non-parametric Mann–Whitney *U*-test was used to assess group differences for continuous variables. Chi-squared statistics were applied for dichotomous variables. Correlations were evaluated with the non-parametric Spearman's *r*. Differences between slopes were tested with analysis of covariance (ANCOVA).

Maps of Pearson's *r* correlations of CSF total, p-tau and Abeta42 concentrations with cortical gray matter density were computed as well as the associated *p*-value maps; correction for multiple comparisons was carried out by permutation testing. The *p*-value threshold for both significance maps and permutation tests was fixed at $p < 0.05$.

Results

AD and schizophrenia patients (Table 1) were well matched for age, gender, and education ($t < 0.89$, $p > 0.50$). However, the healthy elderly controls were younger than both patient groups ($t > 2.38$, $p < 0.031$) and many of them were males (Chi-squared < 4.9, $p < 0.0027$). As expected, healthy elderly controls achieved higher scores than both patient groups on all neuropsychological tests ($p < 0.022$).

Table 2 shows that despite comparable MMSE scores, schizophrenia patients displayed significantly poorer performances than AD patients in auditory verbal learning and Trail Making test A ($p < 0.007$). ApoE ε4 carriers were more prevalent among AD than schizophrenia patients (Chi-squared = 18.0, $p < 0.001$). The prevalence of cardiovascular risk factors was not significantly different among groups.

Table 3 and Figure 1 show that CSF total tau and p-tau concentration in schizophrenia patients was well within the normal range reported by Sjögren *et al.* (2001) (tau values <500 pg/ml) and Mattsson et al. (2009) (p-tau values <52 pg/ml).

These values were comparable to those of healthy controls ($p > 0.14$) and markedly lower (78% and

Table 2 Neuropsychological features of the groups. The performance of older schizophrenia patients was always significantly poorer than healthy older controls. Significant differences between schizophrenics and AD patients are denoted by (#). Significance was tested with the non-parametric Mann–Whitney *U*-test. Values indicate mean ± SD

		Older schizophrenia patients	Alzheimer's patients	Healthy older controls
		$N = 11$	$N = 20$	$N = 6$
Memory	Rey–Osterreith's complex figure—recall	2.0 ± 2.2	0.7 ± 1.5	17.5 ± 7.2
	Auditory verbal learning test—immediate recall	5.1 ± 10.9#	27.8 ± 7.3	39.7 ± 8.5
	Auditory verbal learning test—delayed recall	0.3 ± 1.0#	3.7 ± 3.1	8.7 ± 2.6
Language	Token test	24.5 ± 4.3	25.5 ± 4.9	34.7 ± 1.5
	Letter fluency	10.5 ± 8.4	17.2 ± 9.0	33.2 ± 9.8
	Category fluency	15.6 ± 13.0	20.1 ± 5.9	44.3 ± 6.6
Frontal-executive	Trial making test A	212 ± 104#	104 ± 55	35 ± 15
Visuospatial	Rey–Osterreith's complex figure—copy	12.6 ± 10.7	16.3 ± 11.3	33.5 ± 3.3

Table 3 CSF concentrations of Abeta42 and tau. Values denote mean ± SD. Δ denotes the percentage difference and *p* significance on Mann–Whitney *U*-test

	Older healthy ($N=6$)	Older schizophrenia patients ($N=11$)					Alzheimer's patients ($N=20$)		
			Δ vs. older healthy	*P*	Δ vs. AD	*p*		Δ vs. older healthy	*p*
Total tau, pg/ml	255 ± 133	171 ± 51	−33%	0.30	−78%	<0.0001	788 ± 335	+209%	<0.0001
P-tau, pg/ml	49 ± 28	32 ± 8	−34%	0.14	−67%	<0.0001	97 ± 43	+98%	<.0001
Abeta42, pg/ml	638 ± 130	465 ± 112	−27%	0.015	+32%	0.005	352 ± 76	−45%	<0.0001

67%) than those of AD patients ($p < 0.0001$). In this latter group, we observed the typically inverted ratio of total p-tau/Abeta42. In schizophrenia patients, the concentration of CSF Abeta42 values was, on average, 27% lower than that of healthy older persons ($p < 0.01$), but still significantly higher than that of AD patients ($p < 0.005$). Previous neuroleptic medication did not detectably alter these relationships.

There was no significant relationship between CSF markers and MMSE scores within each of our diagnostic groups (Figure 2). However, there were significant group differences in the regression slopes of CSF total tau and p-tau, but not Abeta42, with MMSE scores ($p < 0.0001$). The correlation between CSF markers and neuropsychological test scores was not significant ($r < 0.36$, $p > 0.30$). This was also true for the corresponding regression slopes.

The relationship of CSF biomarkers with gray matter volume in schizophrenia patients was examined with the voxel-based approach. This allowed us to define

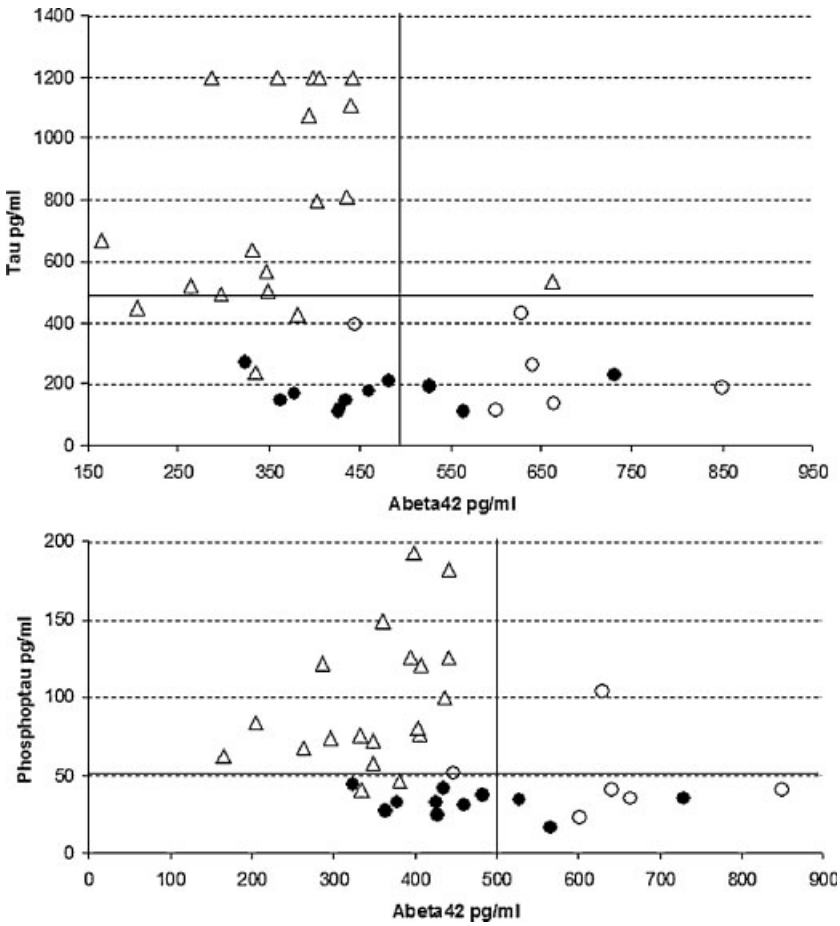
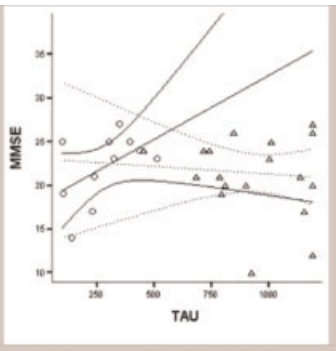
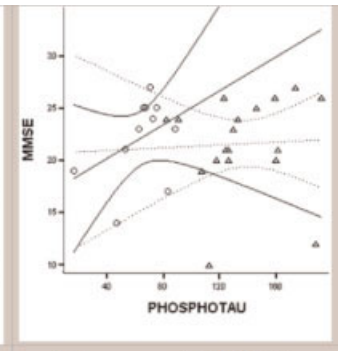
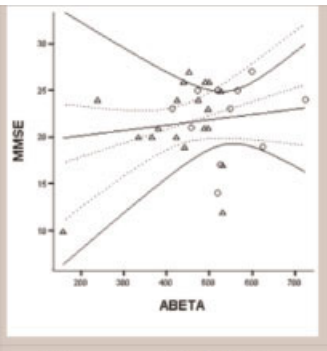


Figure 1 CSF total tau and p-tau concentrations. (△) Alzheimer's, (●) older schizophrenia patients and (○) healthy elderly.







	Beta	Standard Error	Beta	Standard Error	Beta	Standard Error
Schizophrenia	.037	.02	.18	.16	.0005	.012
Alzheimer's	-.001	.003	.003	.025	.015	.013
	Difference between slopes p<.0001		Difference between slopes p<.0001		Difference between slopes p=.98	

Figure 2 Correlations between CSF biomarkers and cognitive features in our groups. (△) Alzheimer's and (○) older schizophrenia patients (dashed and solid regression line and 95% confidence bounds around the slope).

areas where the relationship was significant on a voxel-by-voxel basis, and the overall significance of the maps, after correction for the multiple comparisons implicit in making the maps, was then confirmed with the ROI-based approach. Voxel-based measures indicated that we detected significant relationships between CSF total tau and volumes of the occipital cortex, superior frontal gyrus and orbitofrontal cortex (Figure 3A). ROI analyses revealed the strongest association between gray matter and CSF total tau in occipital BAs 17, 18, and 19, with higher tau concentrations being associated with greater cortical volume ($r = 0.63$, $p = 0.036$). The association between gray matter and CSF total tau in the superior frontal gyrus (BAs 6, 8, and 9), and orbitofrontal cortex (BA 11) approached significance ($r < -0.56$, $p = 0.07$). By contrast, the voxel-by-voxel correlation of gray matter volume with p-tau and Abeta42 failed to suggest significant correlations for any BAs.

In AD patients, no significant relationship was detected between CSF total and p-tau and gray matter volumes. In contrast, voxel-based analysis revealed positive associations between Abeta42 and right cingulate gyrus (BAs 23 and 24) and lateral orbital cortex (BA47) ($r > 0.46$, $p < 0.05$) volumes (Figure 3B). ROI analyses documented these correlations in the expected direction of lower CSF Abeta42 with lower gray matter volume of the cingulate gyrus and lateral orbital cortex.

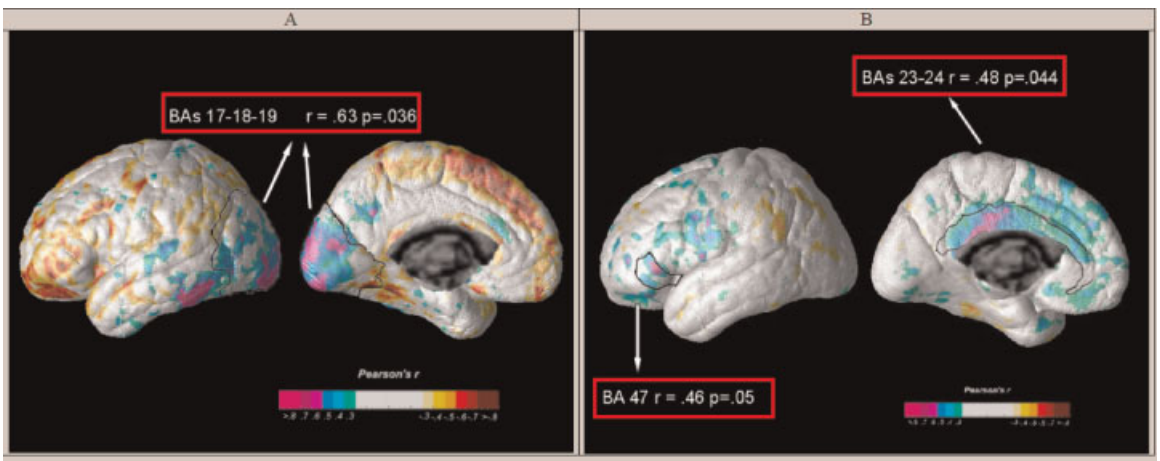


Figure 3 Voxel-based and ROI analysis of the correlations between CSF tau concentrations and gray matter volume in elderly schizophrenia patients (A) and between CSF Abeta42 concentration and gray matter volume in AD patients (B).

Discussion

Our findings revealed major differences in biochemical and structural alterations in schizophrenia versus typical AD. From a cognitive viewpoint and for similar MMSE scores, elderly schizophrenia patients displayed an increasing vulnerability of memory and executive functions compared to AD cases. Unlike the expected CSF pattern that was observed in AD, elderly schizophrenia patients had total tau and p-tau levels within the normal range whereas their Abeta42 levels were intermediate between AD cases and controls. In schizophrenia patients, higher levels of total tau were associated with greater gray matter volume in the cortical occipital regions and with higher MMSE scores. In AD cases, tau concentrations were not associated with MMSE scores while lower levels of Abeta42 correlated with lower gray matter volumes in the cingulate and orbitofrontal regions.

In a previous study on Alzheimer's CSF markers in adult and elderly schizophrenia patients, who were marginally younger (by 5 years) than our sample (Schönknecht *et al*., 2003a), total tau and p-tau 181 were studied. Interestingly, concentrations of CSF total tau and p-tau were remarkably similar to those of the present study (total tau 191 ± 109, p-tau 43 ± 18 pg/ml). Abeta42 has never been studied before in schizophrenia patients of any age and this is also the case for the relationship between CSF biomarkers, cognitive, and MRI volumetric findings.

Why is CSF tau normal in schizophrenia?

The normal CSF total tau and p-tau levels in our older schizophrenia patients contrasted with their marked elevation in our AD patients matched for MMSE scores. Tau protein is located in the axons of neurons and in AD is abnormally phosphorylated and aggregates into paired helical filaments (neurofibrillary tangles) (Preuss and Mandelkow, 1998) reflecting the degree of neurofibrillary pathology and neurodegeneration (Schönknecht *et al*., 2003b). The fraction of hyperphosphorylated tau has been found to be even more specific to AD than total tau levels (Blennow *et al*., 2001; Buerger *et al*., 2002). Neurofibrillary tangle burden is a good pathological correlate of clinical symptoms and its deposition maps to areas where atrophy is consistent with the neuropsychological deficits and their progression in AD (Thompson *et al*., 2003). The lack of detectable differences in CSF tau levels in older schizophrenia patients should be interpreted in the light of our recent observations in this field. We previously found that in the presence of cognitive impairment, cerebral atrophy in schizophrenia patients is remarkably less severe than in AD and maps to areas usually spared in AD such as the posterior part of the anterior cingulate gyrus and orbitofrontal cortex. The present results as well as previous neuropathological (Powchik *et al*., 1998) and biological (Schönknecht *et al*., 2003a) studies did not support the neurodegenerative theory in schizophrenia – they suggest that neurofibrillary pathology is not the biological basis of the cognitive impairment in this disorder (Frisoni *et al*., 2009a). This dissociation between the tau-related pathology in AD and schizophrenia was confirmed by the significant group differences in regression slopes for total tau and p-tau observed in the present series. While on average, MMSE scores were similar between AD and schizophrenia group, the relationship between this measure of cognitive performance and level of tau was different when analyzing the two groups of patients. In AD the trend was, as expected, of an increasing in tau concentration together with a decreasing in MMSE scores, whereas it was the opposite for the schizophrenia patients, clearly meaning different mechanisms undergoing those two diseases. The neurodegenerative hypothesis is also inconsistent with our present findings of higher levels of total tau associated with greater gray matter volume in the cortical occipital regions in elderly schizophrenia patients. Indeed, CSF tau is a marker of neurodegeneration (Lovestone and Reynolds, 1997) and, if anything, higher levels should be associated with lower gray matter volume and poorer cognitive performance. In a previous study on the occipital cortex (Pikkarainen *et al*., 2009) the findings of neurofibrillary tangles in aged nondemented subjects support the concept that the occipital association area may have enhanced vulnerability to neurodegeneration so that neuropathologic assessment of these areas should be recommended, particularly in subjects suspected or known to have had mild cognitive impairment. Our data on a positive relationship between CSF tau concentration and greater gray matter volume in those regions in elderly schizophrenia patients should not viewed in view of a neurodegenerative process. The role of neurodevelopmental factors believed to lie at the heart of the pathogenesis of schizophrenia (Jaaro-Peled *et al*., 2009) as well as the possible effect of neuroleptics on tau metabolism (Gong *et al*., 1996) remain matter of speculation that further studies with larger patient groups need to clarify. Interestingly, recent investigations proposed alternative substrates of the cognitive impairment in elderly patients with schizophrenia such as oxidative DNA damage

(Nishioka and Arnold, 2004) or pathology of the modulatory presynaptic proteins (Sawada *et al*., 2005).

Why is Abeta42 lower than normal?

Our elderly schizophrenia patients displayed intermediate Abeta42 values between those of controls and AD cases indicating the presence of altered amyloid metabolism. Unlike AD, this phenomenon was not related to neuropsychological performance. Furthermore, in our AD but not schizophrenia patients, there was a significant correlation between Abeta42 levels and volume deficits in cortical areas particularly vulnerable to the neurodegenerative process (Sheline *et* al., 2009; Jagust *et al*., 2009). Earlier observations also suggested that, although present, amyloid pathology in schizophrenia is not the main determinant of cognitive decline (Purohit et al., 1998; Dwork *et al*., 1998; Powchik *et al*., 1998). As postulated by Dwork *et al*. (1998)) deficits in functional and structural brain reserve rather than neurodegeneration may explain the increased cognitive sensitivity in elderly schizophrenia patients. One plausible scenario is that alterations of the Beta-Site APP-cleaving enzyme 1 (BACE1), which seems to play a key role in the pathogenesis of schizophrenia (Savonenko *et al*., 2008), may be partly responsible for the lower than normal concentration of CSF Abeta42 in our older schizophrenia patients. Another explanation may involve the effect of drugs on brain amyloid metabolism. Studies on cultured cells have shown that haloperidol, the most commonly prescribed neuroleptic, inhibits beta amyloid formation(Higaki *et al*., 1997) also, quetiapine, a well known second generation antipsychotic, seems to act similarly in transgenic mice (He *et al*., 2009). However, due to small sample sizes and markedly variable durations of pharmacological treatment exposure, this hypothesis could not be tested in our dataset.

Conclusion

Strengths of the present study include the combination of neuropsychological, MRI and biochemical analyses, assessment of all three CSF total tau, p-tau and Abeta42 levels as well as comparison of elderly schizophrenia patients with age-matched clinically overt AD cases. Since most prior hypotheses regarding the neurodegenerative aspect of schizophrenia concerned neocortical association regions, our MRI volumetric analysis mainly focused on these areas and did not take into account hippocampal subdivisions, for example. On the hand of limitations, we cannot therefore comment on possible relationships between CSF AD markers and neurodegenerative changes in these structures. Moreover, the CSF Abeta42 level differences between controls and schizophrenia patients may be influenced by the slightly younger age of the patients and caution should be used in considering just the MMSE scores as index of cognitive decline in schizophrenia patients. In conclusion, elderly schizophrenia patients show a peculiar pattern of CSF Abeta42 and tau concentrations and a relationship with cognitive and structural markers that is inconsistent with neurodegeneration. Future CSF/MRI analyses including assessment of Abeta42 oligomers and hippocampal volumetry paired with more accurate measures of cognitive performances and functional exploration of brain activation in larger cohorts of elderly schizophrenia patients are warranted to elucidate the origin of the cognitive deficits in this diagnostic group.

Key Points

- CSF Abeta42 and tau concentrations in schizophrenia are markedly different from AD.
- These concentrations are related to cognitive and structural markers.
- They might be not neurodegenerative but secondary to neurodevelopmental or drug treatment effects.

Conflict of interest

None declared.

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Supporting information

Supporting information may be found in the online version of this article.

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