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Brain Metabolic Correlates of Cerebrospinal Fluid Beta-Amyloid 42 and Tau in Alzheimer's Disease

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Key Words
Alzheimer's disease · Dementia · ^{18}F-FDG positron emission tomography · Glucose metabolism · Cerebrospinal fluid · Tau protein · Beta-amyloid · Statistical parametric mapping

Abstract
Background: The cerebrospinal fluid (CSF) proteins β-amyloid 42 (Aβ42) and Tau are believed to indirectly reflect some core pathological features of Alzheimer's disease (AD). Their topographic origin and their association with synaptic dysfunction are still not well understood. ***Aim:*** The present study aimed to explore possible associations between cerebral glucose metabolism and CSF Aβ42 as well as Tau protein levels in AD. ***Methods:*** CSF analyses and ^{18}F-FDG PET scans were conducted on 32 patients with mild-to-moderate AD. Voxel-based statistical parametric correlations were computed for CSF protein levels and cerebral glucose metabolism. ***Results:*** After correction for multiple comparisons, a strong positive association between CSF Aβ42 levels and glucose metabolism was identified for 2 extensive clusters located in the right temporal, prefrontal and anterior cingulate cortices. For CSF Tau protein, no association was observed for any brain region. ***Conclusions:*** These findings point to a significant association between synaptic dysfunction as measured with ^{18}F-FDG PET and CSF Aβ42 levels, but do not suggest a correlation between synaptic function and CSF Tau levels.

Introduction

Intracellular neurofibrillary tangles – formed by abnormally phosphorylated isoforms of the microtubule-associated Tau protein [1] and extracellular senile plaques, with a core consisting mainly of β-amyloid 42 (Aβ42) proteins [2] – are the histopathological hallmarks of Alzheimer's disease (AD). Cytosolic Tau proteins are released from degenerating neurons into the extracellular space [3], whereas the highly fibrillogenic Aβ42 proteins disturb synaptic function and are deposited in plaques [4]. Assays have been developed which reliably measure Tau and Aβ42 protein concentrations in the cerebrospinal fluid (CSF). Increased Tau and decreased Aβ42 levels are consistently found in patients with AD [5], even in predementia stages [6], in accordance with the assumptions of

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elevated Tau release and Aβ42 deposition. Despite the broad clinical application of these biomarkers and their recent consideration as research diagnostic criteria for AD [7], it is still not entirely clear whether these CSF protein alterations reflect neuronal or synaptic dysfunction in AD, or which brain regions are involved. So far, only a handful of studies have set out to explore the associations between CSF protein levels and synaptic dysfunction. The regional cerebral metabolic rate of glucose (rCMRglc) in ^{18}F-fluoro-2-deoxy-glucose positron emission tomography (^{18}F-FDG PET) reliably measures the metabolic activity of astrocytes, which is mainly driven by the energy demand at the postsynaptic level [8]. This technique provides maps of synaptic activity, and therefore indirect information on neural activity; these maps are usually used to display regional synaptic dysfunction in neurodegenerative disorders, such as AD, dementia with Lewy bodies and frontotemporal dementia [9]. Most previous studies that correlated CSF proteins with rCMRglc focussed on Tau [10–14]; only 1 study explored the correlations between rCMRglc and CSF Tau as well as Aβ42 levels [11]. With 1 exception [14], no or only weak correlations between rCMRglc and Tau levels were found. In contrast, Okamura et al. [11] reported a significant relationship between Aβ42 and global and temporal glucose metabolism.

The present study was designed to investigate and localize brain regions showing a significant association between the degree of synaptic dysfunction and CSF protein levels of Tau and Aβ42 using a global voxel-based approach. Since synaptic failure is a major component of AD [15] and Aβ42 is known to affect synaptic function [16], we hypothesized that CSF Aβ42 levels are associated with decreased rCMRglc in brain regions typically affected in AD, i.e. the temporoparietal, frontal and posterior cingulate cortices [9]. In contrast, we did not expect any correlations between rCMRglc and Tau protein levels, since elevations of CSF Tau are believed to reflect neuronal degeneration.

Methods

Recruitment and Selection of Participants

Thirty-two patients with AD were enrolled, all of whom had been diagnosed according to the National Institute of Neurological and Communicative Diseases and Stroke/AD and Related Disorders Association (NINCDS-ADRDA) criteria [17] between 1999 and 2003 at the Centre for Cognitive Disorders of the Department of Psychiatry and Psychotherapy, Technische Universität München. To compare regional glucose metabolism, a preexisting dataset of 16 age-matched healthy control subjects was used that had been collected in a collaborative effort of the Departments of Psychiatry and Nuclear Medicine of the Technische Universität München for clinical and research purposes (7 men, 9 women; mean age: 68 years; mean education: 12 years) [18]. The characteristics of the study sample are presented in table 1. The thorough diagnostic evaluation included neuropsychological testing, routine blood and CSF sampling, physical and neurological examination and structural (magnetic resonance) and functional (^{18}F-FDG PET) imaging of the brain. Brain scans were visually evaluated by experienced readers as part of the routine clinical protocol. The neuropsychological diagnostic set-up was based on the Consortium to Establish a Registry for AD (CERAD) Neuropsychological Assessment Battery [19], which incorporates the Mini-Mental-State Examination (MMSE) [20]. The clinical documentation also included information on age, gender, age at onset of dementia, duration of disease and years of school education. All consecutive patients who fulfilled the inclusion and exclusion criteria were entered into the study. The PET scans and lumbar punctures were part of the routine diagnostic procedure. Written informed consent according to the Declaration of Helsinki is available from all patients. The study protocol was approved by the Ethics Committee of the Medical Faculty of Technische Universität München.

Table 1. Patient characteristics

Characteristic	Values
Age, years	69.34 ± 10.29
Age at onset of dementia, years	62.37 ± 9.59
Duration of dementia, years	5.00 ± 3.86
Men:women, n	16:16
Schooling, years	10.53 ± 2.76
MMSE score	22.00 ± 4.13
CSF Aβ42, ng/l	476.81 ± 220.88
CSF Tau, ng/l	578.72 ± 342.85

Where indicated, data are presented as means ± SD.

CSF Analyses

CSF (5–8 ml) was collected in sterile polypropylene tubes, using atraumatic canulas placed in the L3/L4 or L4/L5 intervertebral space, and gently mixed. Serum and EDTA plasma samples for each subject were obtained by venous puncture. In the native CSF, determination of routine chemical parameters was performed. These parameters included leukocyte and erythrocyte cell counts, as well as glucose and lactate measurement, total protein content, CSF-serum ratios of albumin and immunoglobulin G, and a screening for oligoclonal bands. Total protein content was measured by turbidimetry after denaturation with trichloroacetic acid. The CSF was centrifuged for 10 min at 4,000 *g* and aliquots of the remaining CSF supernatants were immediately frozen at –80°C for later Tau and Aβ42 protein determination. The Tau and Aβ42 concentrations were measured in duplicate using an enzyme-linked immunosorbent assay (Innogenetics, Zwijndrecht, Belgium), as described previously in greater detail [21, 22].

Acquisition and Preprocessing of ^{18}F-FDG PET Scans

PET scans were acquired according to a standard protocol [23]. All patients were administered with an i.v. bolus of 185 MBq ^{18}F-FDG at rest 30 min prior to PET scanning. Scans were performed under standard resting conditions with the patient's eyes closed in dimmed ambient light. Exactly the same scanning protocol was applied to every study participant. Imaging was performed on a Siemens ECAT/EXACT HR+ PET scanner (CTI, Knoxville, Tenn., USA). A sequence of 3 frames (10 min; 5 min; 5 min) was started (3-dimensional mode, total axial field of view of 15.52 cm) and later combined into a single frame. Attenuation correction was performed using a transmission scan. Data were corrected for random, dead time and scatter; images were reconstructed by filtered back-projection with a Hamm filter (cut-off frequency 0.5 cycles/projection element) resulting in 63 slices in a 128 × 128 pixel matrix (pixel size 2.06 mm) and interplane separation of 2.425 mm. Images were realigned, transformed into standard stereotactic space and smoothed in the statistical parametric mapping software package SPM5 (Wellcome Functional Imaging Laboratory, London, UK), based on Matlab v7.4 (The Mathworks Inc., Natick, Mass., USA) running on a standard personal computer. Smoothing was performed with an isotropic Gaussian kernel with 12-mm full width at half-maximum. Individual global counts were normalized by proportional scaling to a mean value of 50 mg/100 ml/min.

Statistical Evaluation

Patient characteristics were analyzed in the Statistical Package for Social Sciences v16 (SPSS, Chicago, Ill., USA). Parametric correlations (Pearson product-moment correlation coefficients) were calculated in order to explore statistical dependencies between cognitive test performance (MMSE) and CSF protein levels. All p values of these calculations are 2-sided, and subject to a statistical threshold of $p < 0.05$.

The image analyses of the ^{18}F-FDG PET data were performed in SPM5 software. The statistical evaluation of the imaging data included 3 steps. First, a group comparison of the rCMRglc was conducted between patients and controls in order to identify brain regions with significantly reduced metabolism in patients. To minimize false-positive results, a significance threshold of $p < 0.05$ corrected for multiple comparisons according to random field theory (false discovery rate, FDR) was applied [24]. Second, statistical parametric correlations (Pearson product-moment correlation coefficient) were calculated in SPSS between the CSF Tau and Aβ42 levels and the rCMRglc of the significant areas of the first analytic step (volume-of-interest analysis, VOI). In order to obtain the rCMRglc at the cluster with the most significant group difference according to a previously published procedure [25], the raw mean rCMRglc of these clusters (table 2) was extracted in the SPM5 toolbox MarsBar (http://marsbar.sourceforge.net). This mean value was then normalized to the raw mean rCMRglc of each patient's pons metabolism, which was obtained by a probabilistic map from the BrainMap database (http://hendrix.imm.dtu.dk/services/jerne/ninf/voi.html) [26] in MarsBar. The pons was chosen as a reference region because its metabolism is known to be well preserved in neurodegenerative disorders [27]. In the third step, 2 independent voxel-based linear regression analyses were performed with the rCMRglc as the dependent and the CSF Aβ42 and the total Tau levels as the independent variables in order to identify brain regions with a significant correlation between the rCMRglc and the CSF protein levels. To account for individual differences in overall cognitive function, age and sex, each patient's MMSE score, age at examination and gender were entered in the regression analyses as variables of no interest along with the CSF parameters. Again, a significance level of $p < 0.05$, FDR-corrected for multiple comparisons, was applied. In the case of significant findings, a scatterplot between the rCMRglc and the CSF protein levels was generated at the cluster with the strongest statistical correlation, and a regression line was fitted into the plot. The correlation coefficient was calculated in Matlab *(corrcoef)*. The anatomical localization of the significant coordinates was determined in the SPM5 Anatomy Toolbox (www.fz-juelich.de/inb/inb-3//spm_anatomy_toolbox).

Table 2. Peak metabolic reductions in patients with AD compared with controls

Brain region	x	y	z	z-score	Extension
Right posterior cingulate gyrus	**6**	**–52**	**32**	**7.16**	**24,672**
Right inferior parietal lobule	54	–60	42	6.55	
Left inferior parietal lobule	–48	–56	46	6.27	
Left thalamus	**–2**	**–18**	**4**	**6.83**	**608**
Left putamen	–22	–4	2	4.99	
Right thalamus	10	–16	6	3.93	
Right caudate nucleus	**14**	**12**	**–2**	**5.59**	**532**
Right putamen	26	–4	2	4.69	
Right putamen	26	4	–6	3.43	
Left thalamus	**–8**	**–10**	**–2**	**4.62**	**59**
Left thalamus	–14	16	2	3.98	
Right superior frontal gyrus	**10**	**42**	**50**	**3.10**	**105**
Right superior frontal gyrus	6	36	54	2.62	
Right superior frontal gyrus	–4	32	56	2.51	
Right insula	**40**	**18**	**0**	**3.09**	**209**

Bold markings indicate the maximum within a cluster, subsequent non-bold markings delineate further sub-maxima within the same cluster; brain regions are indicated by Montreal Neurological Institute coordinates, x, y and z.

x = Medial-to-lateral distance relative to the midline (positive: right hemisphere); y = the anterior-to-posterior distance relative to the anterior commissure (positive: anterior); z = superior-to-inferior distance relative to the anterior commissure/posterior commissure line (positive: superior); extension = cluster of contiguous voxels.

Results

Clinical data

The MMSE score range of 11–26 was suggestive of mild-to-moderate dementia with an average score of 22 [28]. Men and women were equally represented in the sample. The visual inspection of the ^{18}F-FDG PET scans

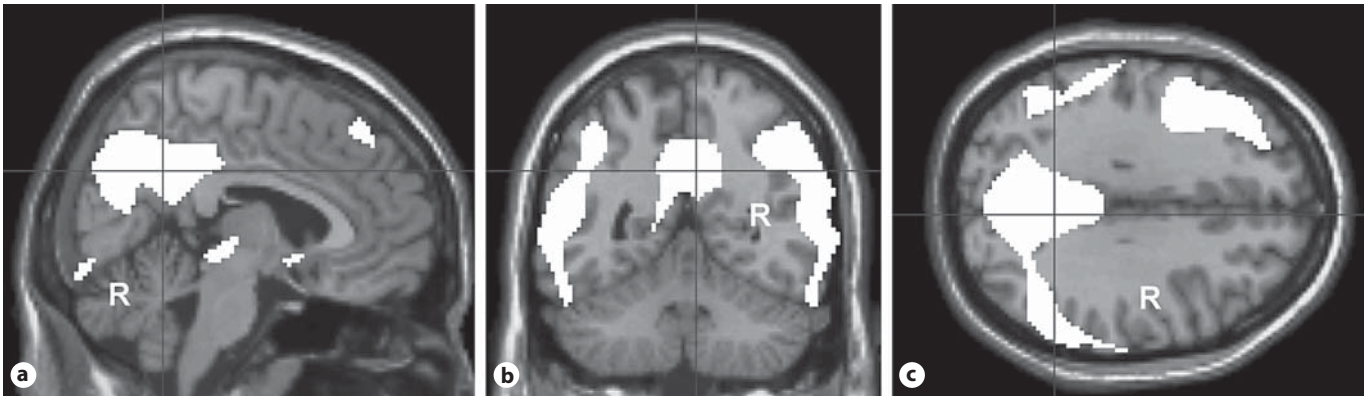

Fig. 1. Significant differences in glucose metabolism between the patient and healthy control groups. Anatomical localization as projected on sagittal (**a**), coronal (**b**) and axial (**c**) sections of a normal MRI, spatially normalized to the Montreal Neurological Institute (MNI) template [$p < 0.05$ FDR corrected for multiple comparisons, maximum at 6/–52/32 (x/y/z) in MNI space, right posterior cingulate gyrus], right side indicated (R), crossbars located at the global maximum.

Table 3. Peak positive correlations between glucose metabolism and CSF Aβ42 levels

Brain region	x	y	z	z-score	Extension
Right superior temporal gyrus	**60**	**–4**	**–12**	**5.02**	**7,959**
Right middle temporal gyrus	52	0	–26	4.43	
Right middle temporal gyrus	54	–8	–22	4.33	
Right medial frontal gyrus	**10**	**46**	**–38**	**4.14**	**2,489**
Left medial frontal gyrus	–2	36	36	3.79	
Right medial frontal gyrus	18	44	10	3.51	

Bold markings indicate the maximum within a cluster, subsequent non-bold markings delineate further sub-maxima within the same cluster; brain regions are indicated by Montreal Neurological Institute coordinates, x, y and z.

x = Medial-to-lateral distance relative to the midline (positive: right hemisphere); y = anterior-to-posterior distance relative to the anterior commissure (positive: anterior); z = superior-to-inferior distance relative to the anterior commissure/posterior commissure line (positive: superior); extension = cluster of contiguous voxels.

demonstrated a typical pattern for AD in all patients, i.e. a bilateral affection of the temporal and/or parietal and/or posterior cingulate cortices [9]. This typical pattern [9] was also confirmed by the voxel-wise group comparison between patients and controls, in which extensive bihemispheric hypometabolic areas in the temporoparietal, posterior cingulated and prefrontal cortices, the striatum, and the thalamus were detected (fig. 1). The CSF tau and Aβ42 levels were also in the expected range for this disease group [5] (table 1). There were no significant correlations between the overall cognitive test performance as measured by the MMSE and the CSF Aβ42 ($r = -0.24$, $p = 0.19$) and Tau ($r = 0.10$, $p = 0.60$) levels.

Association between Glucose Metabolism and CSF Aβ42 Levels

The voxel-by-voxel regression analysis with the rCMRglc as the dependent and the CSF Aβ42 levels as the independent variable revealed a significant positive association, FDR-corrected for multiple comparisons, in 2 extensive temporal and prefrontal, right hemispheric brain clusters. The first cluster included the middle as well as the superior temporal and inferior frontal gyri. The second cluster encompassed the medial frontal and the anterior cingulate gyri (table 3; fig. 2a–c). To exclude the possibility that the strict unilateral right hemispheric allocation is an artificial result due to the rigorous statistical correction procedure, we repeated exactly the same voxel-based regression analysis and applied a less stringent threshold of $p < 0.001$ without correction for multiple comparisons. Our initial findings, however, remained largely unchanged. The fitted curve for the linear regression analysis has a positive slope (fig. 2d). The additional correlation analysis between the adjusted rCMRglc and the CSF Aβ42 levels at the localization of the most significant cluster revealed a strong positive correlation of $r = 0.74$. This positive association was confirmed in the VOI analysis ($r = 0.41$, $p = 0.04$). There was

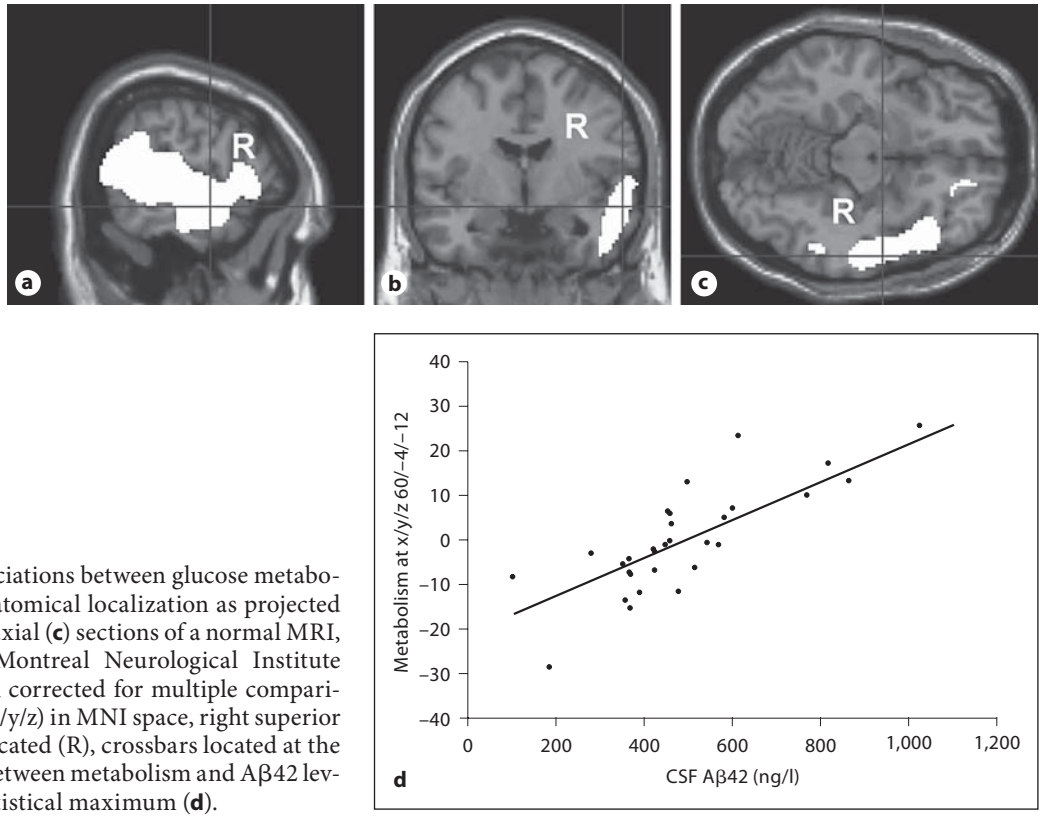

Fig. 2. Significant positive associations between glucose metabolism and CSF Aβ42 levels. Anatomical localization as projected on sagittal (**a**), coronal (**b**) and axial (**c**) sections of a normal MRI, spatially normalized to the Montreal Neurological Institute (MNI) template [$p < 0.05$ FDR corrected for multiple comparisons, maximum at 60/–4/–12 (x/y/z) in MNI space, right superior temporal gyrus], right side indicated (R), crossbars located at the global maximum. Scatterplot between metabolism and Aβ42 levels at the localization of the statistical maximum (**d**).

no inverse association between rCMRglc and CSF Aβ42 levels for any brain region.

Association between Glucose Metabolism and CSF Tau Levels

In the voxel-based regression analysis (FDR-corrected for multiple comparisons) between the rCMRglc and CSF Tau levels, neither positive nor negative associations were found for any brain region. In addition, raising the statistical threshold in an exploratory manner to $p < 0.001$ without correction for multiple comparisons also did not reveal significant results for any brain region. This lacking association was also confirmed in the VOI analysis ($r = 0.12$, $p = 0.56$).

Discussion

The present study was designed to localize brain areas showing an association between CSF Aβ42 and Tau protein levels and synaptic activity as measured by ^{18}F-FDG PET imaging in patients with mild-to-moderate AD. We identified a strong association of cerebral glucose metabolism and CSF Aβ42 concentrations in 2 extensive right-hemispheric brain clusters; in detail, decreased CSF Aβ42 protein levels were associated with lower rates of glucose consumption in the right temporal, prefrontal and anterior cingulate cortices. In contrast, however, we did not find any evidence for an association of CSF Tau levels and cerebral glucose metabolism, even after raising the statistical threshold to $p < 0.001$, uncorrected for multiple comparisons. In addition, no significant correlation between CSF Aβ42 and Tau protein levels and overall cognitive performance as assessed by the MMSE was observed in this collective.

Positive Association between Glucose Metabolism and CSF Aβ42 Levels

The major result of our study is a strong association between CSF Aβ42 levels and rCMRglc in brain regions typically showing hypometabolism in AD [9] that were also detected in a comparison between our patient sample and a group of age-matched healthy control subjects. Our findings strongly suggest that decreased CSF Aβ42 levels are associated with diminished synaptic function as reflected by reduced cerebral glucose metabolism us-

ing ^{18}F-FDG PET. This result is remarkable from a pathomechanistic perspective, as a number of cell-biological experiments have repeatedly demonstrated that soluble Aβ42 peptides and oligomers cause synaptic failure. In particular, glutamatergic synaptic transmission is disrupted by Aβ42 peptides, which subsequently leads to synaptic dysfunction and neuronal death [29]. Since numerous studies have shown that glutamatergic signaling is crucial for the occurrence of brain imaging signals [8], it is not surprising that brain areas with an association between synaptic dysfunction and CSF Aβ42 levels can be mapped with a technique such as ^{18}F-FDG PET. However, a further possible explanation of the strong association between CSF Aβ42 and rCMRglc is that Aβ42 levels may reflect more advanced plaque pathology [30], which in turn may be associated with impaired glucose metabolism.

A surprising finding of this study is the striking lateralization of the associated brain regions to the right hemisphere, although the visual inspection of all ^{18}F-FDG PET scans and their comparison with scans of a control group did not reveal any tendency for lateralization. Furthermore, a methodological artifact due to the strict correction procedure can be largely excluded, since raising the significance threshold without correction did not show major effects on the results. Although the probability of a false-positive result cannot be completely ruled out, this possibility appears rather unlikely as an established correction procedure was applied. Therefore, one can only speculate, but previously described asymmetric distributions of senile plaques in the early stages of AD [31] might at least partially explain this finding. Nevertheless, this finding of our study needs independent replication using patient samples with comparative disease stages. Interestingly, Kadir et al. [32] recently reported a positive association between CSF Aβ40 levels and rCMRglc, which was also lateralized to the right parietal cortex. However, the role of Aβ40 in AD and its association with Aβ42 are not well established, and the authors do not provide an explanation of their finding.

So far, only 1 study explored both the association between CSF Tau as well as Aβ42 levels and rCMRglc in patients with AD [11]. Corresponding to our study, Okamura et al. [11] reported that CSF Aβ42 was significantly correlated with the global and temporal rCMRglc in their AD sample, but no association was found for CSF Tau levels. Unfortunately, their statistical analysis was based on a combined assessment of right and left hemispheric regions of interest, and thus precludes further information regarding a potential asymmetry of their association. As methodological and statistical issues develop over the years, our study comprises, besides the larger sample size, some relevant improvements. As such, a non-hypothesis-driven voxel-based whole-brain approach was applied in contrast to the previous hypothesis-driven region-of-interest approach, which limits possible findings to a number of a-priori-defined brain regions. A further difference includes the consideration of MMSE scores as additional covariate to the logistic regression analysis to account for differences in disease severity as a possible confounding factor influencing the association result. Finally, due to the nature of the non-hypothesis-driven approach, this study included an established correction procedure.

No Association between Glucose Metabolism and CSF Tau Levels

In contrast to the strong association obtained for CSF Aβ42 and the regional glucose consumption, no significant association between CSF Tau levels and rCMRglc was observed. This finding is in line with most previous studies that either report no [10, 11, 13] or only weak associations [12]. The most likely explanation for this lack of association is that both measures indicate different, possibly unrelated pathological mechanisms. As mentioned before, elevations in CSF Tau protein levels indicate neuronal degeneration, whereas a reduction in cerebral glucose consumption reflects decreased synaptic activity.

To conclude, our study provides evidence that CSF Aβ42 levels are associated with the severity of synaptic dysfunction in AD. The results of the present study do not point to an association of synaptic activity with CSF Tau levels; furthermore, significant associations between overall cognitive impairment and CSF markers could not be established in this particular sample.

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