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Cerebrospinal Fluid Tau Protein Levels and ^{18}F-Fluorodeoxyglucose Positron Emission Tomography in the Differential Diagnosis of Alzheimer's Disease

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Key Words
Dementia · Mild cognitive impairment · Alzheimer's disease · Positron emission tomography, ^{18}F-fluorodeoxyglucose · Glucose metabolism · p-tau · Differential diagnosis

Abstract
Aims: In this study, we aimed to compare cerebrospinal fluid (CSF) levels of total tau (t-tau), phosphorylated tau (p-tau$_{181}$) and positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) in the differential diagnosis of Alzheimer's disease (AD) under clinical conditions. ***Method:*** In a cross-sectional, blinded, single-center study, we examined a sample of 75 unselected memory clinic patients with clinical diagnoses of dementia of Alzheimer type (DAT; n = 24), amnestic mild cognitive impairment (MCI; n = 16), other dementias (n = 13) and nondemented controls (n = 22). Discriminative accuracy, sensitivity and specificity were calculated and compared using ROC analyses. ***Results:*** p-tau$_{181}$ and FDG-PET were comparable in separating DAT from controls (sensitivity: 67 vs. 79%; specificity: 91% for both) and patients with other dementias (sensitivity: 71 vs. 79%; specificity: 100% for both). The sensitivity of p-tau$_{181}$ in differentiating MCI patients from controls was significantly ($p < 0.05$) superior to that of FDG-PET (75 vs. 44%) at a comparably high specificity (82 vs. 91%); t-tau measures were less accurate in all analyses. ***Conclusions:*** FDG-PET and CSF p-tau$_{181}$ levels are able to discriminate DAT in heterogeneous and unselected samples with a high accuracy. CSF p-tau$_{181}$ might be somewhat superior for a sensitive detection of patients with MCI.

Introduction

Tauopathy and loss of synaptic activity/density are major early events in the pathogenesis of Alzheimer's disease (AD). These characteristic AD lesions can be quantified in vivo using examination of cerebrospinal fluid (CSF) and positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) [1–4].

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Numerous studies have consistently shown that CSF levels of total tau (t-tau) and phosphorylated tau (p-tau) proteins are significantly elevated in patients with AD compared to healthy elderly controls [4]. A meta-analysis of over 30 studies indicated that both CSF biomarkers provided similar values of sensitivity and specificity (80 and 90%, respectively) in the discrimination of AD versus healthy aging [4]. Unlike t-tau, a marker of neuronal damage, p-tau specifically reflects tau hyperphosphorylation and, likely, the formation of tangles in AD. Accordingly, p-tau but not t-tau levels were found to be useful in discriminating between dementia of Alzheimer type (DAT) and other non-AD dementias [5–7]. Reduced CSF concentrations of amyloid beta peptides ($A\beta_{42}$ and $A\beta_{40}$) have also been used for differential classification of patients with AD, in most studies in combination with CSF tau proteins [8–10].

Like CSF examination, FDG-PET has been widely applied to assist the diagnosis of AD [11]. A reduced glucose metabolism in the posterior cingulate and parietotemporal association cortices with sparing of the primary sensorimotor areas and cerebellum is a well-established feature of DAT [12, 13]. Both visual reading and quantitative diagnostic approaches provide a similar sensitivity of 85–95% and specificity of 80–90% in differentiating probable AD from healthy aging [14–16]. Furthermore, FDG-PET was shown to possess a significant diagnostic potential in differentiating DAT from dementias of other causes such as dementia with Lewy bodies, frontotemporal, and vascular dementia [17–20].

The relatively high accuracy of the PET-derived hypometabolic pattern and abnormal levels of CSF proteins in discriminating manifest and even incipient AD [21, 22] has been reflected in recently proposed guidelines on AD, where both biomarkers were recommended as supportive but obligate diagnostic features [23]. For the use of biomarkers in routine diagnostic algorithms and differential diagnosis, however, the knowledge of the comparative diagnostic accuracy of different single markers is mandatory [24, 25]. So far, these biomarkers – of which one is costly but less invasive (FDG-PET), while the others are low priced but more invasive (CSF tau levels) – have not been compared regarding their discrimination properties. The objective of the present study was, therefore, to estimate the diagnostic accuracy of CSF t-tau, p-tau and FDG-PET in an unselected sample of patients with clinically diagnosed DAT, amnestic mild cognitive impairment (MCI) and other dementia disorders, and in nondemented controls.

Subjects and Methods

Subjects

The total sample (n = 75) consisted of subjects consecutively recruited from our memory clinic in the years 2001–2003. Most subjects had been referred to our clinic by general practitioners. The protocol including all assessments was part of the established clinical routine and accepted by the local ethics committee. All participants gave their written informed consent after the procedures had been fully explained.

Assessment

All subjects underwent interview, clinical psychiatric and neurological examinations, lumbar puncture, cranial magnetic resonance imaging (MRI), FDG-PET and laboratory tests including vitamin B_{12}, folate and thyroid hormone status. Neuropsychological assessment consisted of the Mini-Mental State Examination (MMSE) and delayed verbal recall test (DVRT) as part of the German version of the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) battery [26]. The costs of the diagnostics were covered by mandatory public health insurance.

On the basis of the clinical assessments and conventional cranial MRI scans, the following diagnostic categories were formed: (1) patients with probable AD, or DAT, (n = 24) according to NINCDS-ADRDA criteria [27]; (2) patients with amnestic MCI (n = 16) according to established criteria by Petersen [28]; (3) patients with other (non-AD) dementias (OD; n = 13) including vascular dementia according to NINDS-AIREN criteria [29] (n = 6), frontotemporal dementia according to Lund-Manchester criteria [30] (n = 2) and other dementias (n = 5), and (4) a nondemented control group (NOND; n = 22) that consisted of nondemented subjects with a psychiatric or neurological disorder (depression: n = 5; Parkinson's disease: n = 1), or healthy subjects complaining of memory deficits not verified by informants and not confirmed by neuropsychological tests who had a normal MRI finding on visual inspection and no clinical signs of dementia (n = 16). Clinical diagnoses were made without knowledge of the CSF tau protein levels and FDG-PET findings at the time of initial assessment.

CSF Analyses

CSF samples were obtained by a standard lumbar puncture procedure and immediately frozen at –20°C in polypropylene tubes until examination. All samples were analyzed within 3 weeks after lumbar puncture. CSF tau protein levels were determined by 2 sandwich ELISA: tau protein phosphorylated at threonine 181 ($p\text{-}tau_{181}$) was determined using the Innogenetics INNOTEST Phospho-Tau(181) kit, and t-tau by the INNOTEST-hTau-Ag kit (Innogenetics, Gent, Belgium) [31, 32]. For $p\text{-}tau_{181}$ and t-tau, the limits of detection were 15.6 ng/l and 60.0 ng/l, respectively. The standard ranges were 15.6–500 ng/l for $p\text{-}tau_{181}$, and 60.0–1,200 ng/l for t-tau, and the interassay reproducibility (coefficient of variation) of quality control samples was below 10%. At the time this study was conducted, assays for Aβ were not available at out institute, thus their levels could not be determined.

FDG-PET Data Acquisition and Analysis

Data acqusition has been reported in detail elsewhere [33]. Briefly, PET data were acquired under standard resting condi-

Table 1. Characteristics of study sample

Diagnostic group	Number	Female %	Age, years	MMSE score	DVRT score	AD-typical PET, %	CSF level[1], ng/l	
							$p\text{-}tau_{181}$	t-tau
NOND	22	41 (9)	61.8 ± 13.3 (43–82)	27.3 ± 3.1 (25–30)	6.8 ± 2.6 (1–10)	9 (2)	34 (16–46)	341 (176–435)
MCI	16	44 (7)	68.6 ± 7.9 (51–83)	26.1 ± 2.2 (22–30)	3.1 ± 1.8 (1–7)	44 (7)	62 (44–87)	336 (102–456)
DAT	24	79 (19)	70.3 ± 9.5 (51–89)	18.7 ± 5.8 (4–27)	2.0 ± 2.8 (0–8)	79 (19)	74 (48–105)	452 (248–701)
OD	13	39 (5)	68.1 ± 10.0 (51–80)	22.2 ± 6.5 (6–30)	3.3 ± 3.4 (0–9)	0 (0)	16 (7–35)	240 (44–425)
Total	75	53 (40)	67.0 ± 10.9 (43–89)	23.4 ± 5.9 (4–30)	3.8 ± 3.2 (0–10)	37 (28)	48 (17–76)	349 (181–459)

Values are means ± SD unless specified otherwise. Figures in parentheses denote numbers or ranges unless specified otherwise.
[1] Medians with 25th–75th percentiles in parentheses.

tions using a Siemens ECAT EXACT scanner (CTI, Knoxville, Tenn., USA) in 3-D mode. The PET camera has an axial field of view of 16.2 cm and axial resolution of approximately 6.0 mm full width at half maximum. Thirty minutes after injection of FDG, a sequence of three 5-min frames was started and later combined into a single frame. After correction for attenuation, scatter and dead time, images were reconstructed by filtered back projection using a 4-mm Hamming filter.

The PET scans were processed using Neurostat software (University of Washington; http://www.rad.washington.edu/research/Research/groups/nbl/neurostat-3d-ssp) [12]. After image realignment and spatial normalization, gray matter activities were extracted to predefined surface pixels using a 3-D stereotactic surface projection (3D-SSP) technique. This technique minimizes residual anatomic variances across subjects and partial volume effects [12]. Thereafter, each individual dataset was compared on a pixel-by-pixel basis with a normative reference database, resulting in parametric Z score images [34]. The AD-typical finding was defined as significant decrease (Z score < –2) in FDG uptake in at least 1 of the brain regions that were shown to be typically involved in early AD (posterior cingulate, lateral temporal, parietal regions) [12, 13]. This routine has been extensively evaluated in various disorders and has shown high external validity in both mono- [17, 35] and multicenter [20] studies. Based on this analysis and inspection of transversal FDG-PET image slices (TomoMagine software, http://tomomagine.de/index2.htm), the findings were finally rated as AD-typical or not AD-typical by 2 experienced physicians in nuclear medicine blinded to all other test results, including clinical diagnoses and CSF tau proteins. Disagreements were resolved by consensus. In an earlier study by our group using the identical rating protocol [34], the interobserver agreement was 94%.

Statistical Analysis

Descriptive statistics are shown as mean values, ranges and SD. For $p\text{-}tau_{181}$ and t-tau levels, group median and interquartile range (25th–75th percentile) are presented because the distributions differed statistically significantly from normal as determined by the D'Agostino-Pearson test ($p < 0.01$) [36]. Group differences in categorical data were analyzed by χ^2 tests; differences among all groups regarding continuous variables were assessed by nonparametric Kruskal-Wallis tests followed by Mann-Whitney U tests for single comparisons. Correlations were analyzed by Spearman's rank correlation coefficients.

To assess the predictive properties of FDG-PET, CSF $p\text{-}tau_{181}$ and t-tau, receiver operating characteristic (ROC) curve analysis was employed (MedCalc 9.3.6., 2007). The area under the ROC curve (AUC) with corresponding 95% confidence intervals (95% CI) was estimated; further, sensitivity, specificity, positive predictive value, negative predictive value and accuracy (percentage of correctly classified subjects) were calculated. Using clinical diagnoses as the criterion standard, the following ROC analyses were performed: comparison of patients with (1) DAT versus NOND, (2) DAT versus OD, (3) DAT versus MCI and (4) MCI versus NOND. Dichotomized binary FDG-PET findings, CSF t-tau and $p\text{-}tau_{181}$ levels were used as predictor variables. Additionally, age was used as the control predictor variable. Unbiased estimations of the AUC can be calculated in the same way for binary and continuously valued diagnostic tests [37].

Finally, the correspondence between CSF tau protein levels and FDG-PET findings was analyzed by ROC curves and group comparisons (Mann-Whitney U tests and χ^2 tests) in patients with or without AD-typical FDG-PET findings, irrespective of their clinical diagnoses. The level of statistical significance was set at a two-tailed α of 0.05. In case of multiple comparisons, Bonferroni adjustment was applied.

Results

Table 1 shows the characteristics of the 75 patients recruited for the study. Table 2 summarizes the results of overall group differences and Bonferroni-corrected single group comparisons.

Only minor differences emerged with respect to gender; age was not significantly different between the groups. Significant gender differences in CSF tau levels or the frequency of AD-typical FDG-PET findings were found neither between the 4 subgroups nor in the total group ($p > 0.10$). In the total sample, no significant correlation between age and CSF levels of t-tau ($r_s = 0.21$;

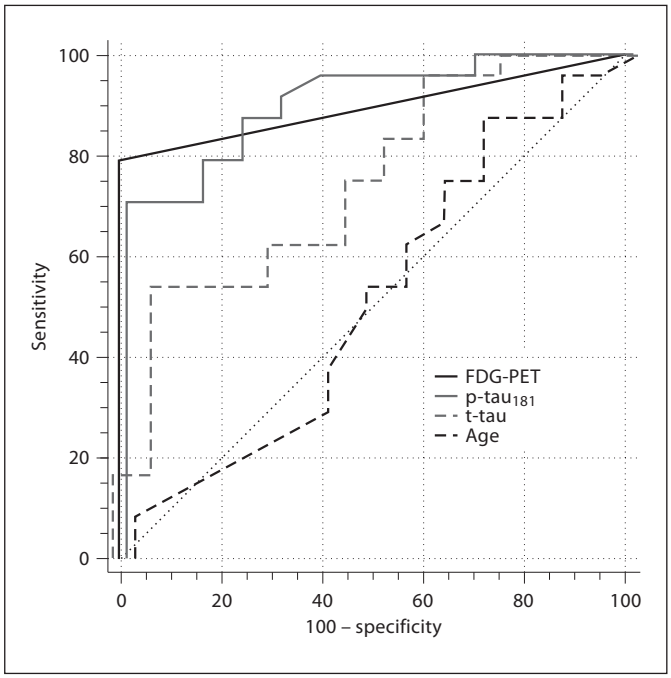

Fig. 1. ROC curves for discrimination of patients with DAT and non-AD dementias.

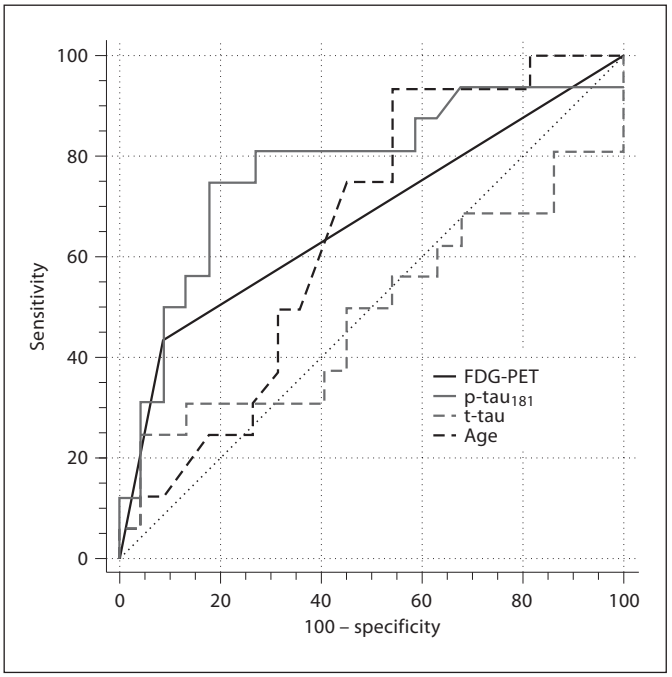

Fig. 2. ROC curves for discrimination of MCI patients from NOND individuals.

Table 2. Group differences (n = 75)

	Global test	Single comparisons*
Gender (% female)	$\chi^2 = 9.5$; d.f. = 3; $p = 0.023$[a]	NOND<DAT[a]
Age	$\chi^2 = 5.3$; d.f. = 3; $p = 0.151$[b]	–[c]
MMSE	$\chi^2 = 37.3$; d.f. = 3; $p < 0.0001$[b]	NOND>DAT, OD; MCI>DAT[c]
DVRT	$\chi^2 = 28.8$; d.f. = 3; $p < 0.0001$[b]	NOND>MCI, DAT, OD; MCI>DAT[c]
AD-typical PET	$\chi^2 = 33.5$; d.f. = 3; $p < 0.0001$[a]	NOND, OD<DAT[a]
p-tau$_{181}$	$\chi^2 = 28.3$; d.f. = 3; $p < 0.0001$[b]	NOND, OD<MCI, DAT[c]
t-tau	$\chi^2 = 7.2$; d.f. = 3; $p = 0.065$[b]	OD<DAT[c]

* $p < 0.05/6$ (= 0.0083) after Bonferroni correction.
[a] χ^2 test. [b] Kruskal-Wallis test. [c] Mann-Whitney U test.

d.f. = 73; p = 0.07) or p-tau$_{181}$ ($r_s = 0.16$; d.f. = 73; p = 0.18) was noted.

Global cognitive function as indicated by the MMSE score was significantly more impaired in DAT patients than in NOND and MCI subjects; patients with OD differed significantly from NOND but not from MCI or DAT patients regarding their MMSE scores. DVRT performance was significantly better in NOND subjects than in all other groups (MCI, DAT, OD) and was better in MCI than in DAT patients.

The t-tau protein levels differed significantly only between the groups of DAT and OD patients; p-tau$_{181}$ levels were significantly higher in MCI and DAT patients compared to NOND and patients with OD. AD-typical FDG-PET findings were noted more frequently in patients with DAT than in the NOND and OD groups. No significant difference in the frequency of AD-typical FDG-PET findings was found between MCI and DAT patients after Bonferroni correction (uncorrected p = 0.021) (table 2).

Table 3. Results of ROC curve analyses

Comparison:		(1) DAT vs. NOND	(2) DAT vs. OD	(3) DAT vs. MCI	(4) MCI vs. NOND
Number		46 (24/22)	37 (24/13)	40 (24/16)	38 (16/22)
AUC	FDG-PET	0.85[a, b] (0.71–0.94)	0.90[a, b] (0.75–0.97)	0.68 (0.51–0.82)	0.67 (0.50–0.82)
	p-tau$_{181}$	0.82[a, b] (0.68–0.92)	0.91[a, b] (0.77–0.98)	0.59 (0.42–0.74)	0.77[b] (0.61–0.89)
	t-tau	0.68 (0.53–0.81)	0.73[a] (0.56–0.87)	0.61 (0.44–0.76)	0.49 (0.32–0.66)
	age	0.68 (0.53–0.81)	0.54 (0.37–0.70)	0.57 (0.41–0.73)	0.65 (0.48–0.80)
Optimal cutoff values	FDG-PET	AD-typical	AD-typical	AD-typical	AD-typical
	p-tau$_{181}$	>65 ng/l	>65 ng/l		>50 ng/l
	t-tau	>520 ng/l	>440 ng/l		
	age	>67 years			
SENS/SPEC	FDG-PET	79/91	79[b]/100	79/56	44/91
	p-tau$_{181}$	67/91	71/100		75[c]/82
	t-tau	46/96	54/92		
	age	67/68			
PPV/NPV	FDG-PET	91/80	100/72	73/64	78/69
	p-tau$_{181}$	89/71	100/65		75/82
	t-tau	92/63	93/52		
	age	70/65			
Accuracy	FDG-PET	85% (39/46)	87% (32/37)	70% (28/40)	71% (27/38)
	p-tau$_{181}$	79% (36/46)	78% (29/37)		79% (30/38)
	t-tau	70% (33/46)	67% (25/37)		
	age	68% (31/46)			

SENS = Sensitivity; SPEC = specificity; PPV = positive predictive value; NPV = negative predictive value. Comparison of AUC and specificity/sensitivity: [a] $p < 0.05$ versus age; [b] $p < 0.05$ versus t-tau; [c] $p < 0.05$ versus FDG-PET; cutoff values and parameters of predictive power were only shown when AUC were significantly different from 0.50, i.e. the 95% CI did not include 0.50.

Table 3 shows the results of the ROC analyses of 4 parameters (FDG-PET, p-tau$_{181}$, t-tau and age) for the relevant group comparisons (DAT, MCI, OD and NOND).

The performance of FDG-PET findings and CSF p-tau$_{181}$ levels to separate DAT patients from patients with OD is illustrated in figure 1 (table 2).

The accuracy of the biomarkers for separating MCI patients from NOND individuals was, in general, relatively low. However, p-tau$_{181}$ levels performed most accurately when compared to FDG-PET findings, t-tau levels and age (fig. 2). The sensitivity of p-tau$_{181}$ to differentiate MCI from NOND individuals was significantly superior to that of FDG-PET ($p = 0.02$), whereas the specificity ($p = 0.42$), accuracy ($p = 0.59$) and AUC (table 3) of both markers were similar ($p = 0.28$). Compared to t-tau, the AUC for identifying MCI patients was significantly larger for p-tau$_{181}$ ($p = 0.001$), but not for FDG-PET patterns ($p = 0.11$).

The association of AD-typical FDG-PET patterns with CSF tau protein levels is shown in figure 3. p-Tau$_{181}$ and t-tau levels were significantly higher in subjects with AD-typical FDG-PET findings than in patients without such findings (Mann-Whitney U test, p-tau$_{181}$: $Z = -5.088$, $p < 0.0001$; Mann-Whitney U test, t-tau: $Z = -3.012$, $p = 0.003$). A cutoff value of p-tau$_{181}$ of >65 ng/l was found to separate patients with and without AD-typical FDG-PET (AUC = 0.85; 95% CI: 0.75–0.92; sensitivity: 71%; specificity: 89%), whereas CSF t-tau concentrations of >520 ng/l were identified as an optimal cutoff value (AUC = 0.71; 95% CI: 0.59–0.81; sensitivity: 39%; specificity: 92%). When the sensitivity was set at 85%, specificities of 70% (cutoff: 45 ng/l) for p-tau$_{181}$, and of 40% (cutoff: 220 ng/l) for t-tau concentrations were found. The AUC for t-tau and p-tau$_{181}$ were significantly different ($p = 0.003$). Twenty of 28 patients (71%) with AD-typical FDG-PET findings had p-tau$_{181}$ levels of >65 ng/l, compared to 5 of 47 patients (11%) without such findings ($\chi^2 = 26.5$; d.f. = 1; $p < 0.00001$).

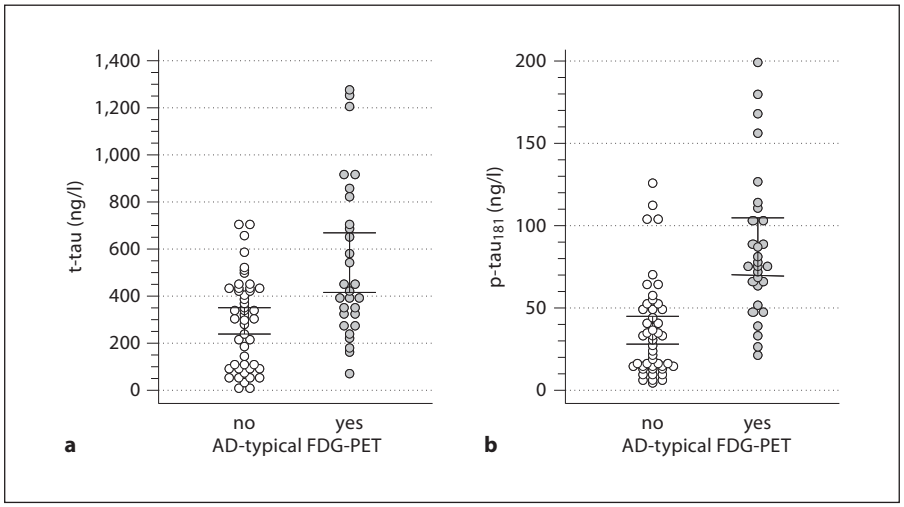

Fig. 3. CSF levels of t-tau (**a**) and p-tau$_{181}$ (**b**) in patients with AD-typical and AD-nontypical FDG-PET patterns. Error bars: 95% CI for means; **a** t-tau: Mann-Whitney U test, Z = 3.01, p = 0.0026; **b** p-tau$_{181}$: Mann-Whitney U test, Z = 5.09, p < 0.0001 (two-tailed).

Discussion

The main findings of the present study were that FDG-PET and CSF p-tau$_{181}$ levels performed well in differentiating DAT patients from NOND controls and patients with non-AD dementias, whereas CSF p-tau$_{181}$ was somewhat superior in the sensitive detection of patients with amnestic MCI who are considered to be at high risk for DAT. The findings were not related to age and gender, confirming that CSF p-tau$_{181}$ is a clinically valuable biomarker of early AD [6, 7]. Finally, and as expected, the accuracy of FDG-PET and CSF p-tau$_{181}$ levels was significantly superior to t-tau measures in all analyses.

A strength of the present study is its maximal proximity to routine clinical practice. To assess the utility of any biomarker, detailed elaboration of the setting in which the biomarker is efficient is highly important [38]. As a matter of fact, most PET and CSF studies are performed at academic centers with participating subjects being highly selected [39, 40]. Yet, as a likely application of any biomarker is to complement clinical diagnosis, one needs to know if or to what extent the existing data on the diagnostic accuracy of a biomarker might generalize to patients presenting to a clinician. Here, we studied a relatively large unselected sample representative of a university memory clinic. The patients and controls were somewhat younger than patients with AD in the community and than AD subjects who generally participate in clinical trials. Other aspects such as education and comorbidity, although important, were not addressed in the present study. Nonetheless, our approach to study a mixed collective of subjects with a broad variety of possible causes, relatively low age and partially preserved cognitive performance in all groups provides valuable insights into the diagnostic performance of the biomarkers, i.e. CSF tau proteins and FDG-PET, evaluated under clinical conditions.

In the literature, we found no study that had examined CSF p-tau levels in unselected patient collectives. As to FDG-PET, Scheltens et al. [41] and Jagust et al. [42] applied this neuroimaging tool to relatively unselected community samples; the issue of diagnostic accuracy was, however, not addressed in those studies. In view of that, the findings of the present study are of special interest. Overall, the accuracy of FDG-PET in discriminating DAT patients from both controls and OD patients was around 85%, thus well within the range typically reported in the literature (80–90%). Similarly, levels of CSF p-tau appeared to identify subjects with DAT with an accuracy of roughly 80%, also confirming findings from previous CSF studies (see Introduction). Of note, both biomarkers offered a high specificity of 90–100%. Thus, our data indicate that FDG-PET and CSF p-tau are able to detect DAT in heterogeneous and unselected samples with a high accuracy.

The clinical manifestation of AD begins insidiously, and now there is broad agreement that individuals with the amnestic subtype of MCI represent early clinical manifestations of AD with a high risk for transition to dementia within a few years [28]. In our study, the accuracy of FDG-PET in differentiating this clinical entity from nondemented controls was roughly 70% with a poor sensitivity (44%) but a high specificity (91%). While most of the (cross-sectional) studies used a quantitative region-

of-interest analysis, a few have examined the discriminative accuracy of the hypometabolic pattern in visual readings. Those studies reported rather variable results, with figures for accuracy ranging from 20 to 70% [43–45]. Notably, a better discrimination could be reached in studies that applied 3D-SSP [43, 45]. Thus, although the accuracy of FDG-PET in differentiating MCI from nondemented controls in the present study was relatively poor, its figures were still within the 'optimistic range' known from the literature. Indeed, metabolic deficits in MCI are, in general, milder and more variable than those found in DAT and are thought to agree with the heterogeneity of outcomes as well as with variations in the patterns of cognitive and behavioral alterations in individual subjects [46].

As to CSF markers in MCI, we found no study that had examined the discriminative performance of tau levels cross-sectionally. In the present study, CSF p-tau tended to perform better than FDG-PET in differentiating MCI from controls. Keeping in mind the above point about a relatively poor sensitivity of the AD-typical PET findings in MCI, this finding has rather been expected. In contrast to FDG-PET, CSF p-tau levels are not related to a particular brain region and may therefore be more robust in detecting early AD. Yet, as t-tau and p-tau levels stay relatively stable over significant periods of time despite the clinical progression of the disease [22], they do not seem to be superior to FDG-PET at the stage of DAT.

According to a recently proposed concept, both FDG-PET and p-tau levels reflect the same process, i.e. AD-specific neurodegeneration [47]. Our earlier as well the present data support this view. Previously, we have disclosed a strong relationship between elevated p-tau levels and AD-typical patterns of cerebral glucose metabolism in patients with amnestic MCI [34]. In line with this, a recent study reported a significant correlation between CSF p-tau$_{181}$, a marker of neurofibrillary pathology [1], and relative metabolic indices (as measured by FDG-PET) in the entorhinal/hippocampal and AD-typical regions in patients with probable AD [48]. A close neurobiological proximity of these two biomarkers has furthermore been highlighted in the present study, in which 71% of subjects with AD-typical FDG-PET findings, irrespective of their diagnostic classification, had pathological p-tau$_{181}$ levels.

There are several limitations to the present study. First, a follow-up examination was not available for many MCI patients (n = 7), precluding meaningful statistical analyses at a subgroup level. Although MCI is characterized by a high conversion rate to DAT, some individuals remain stable, revert, or develop other dementias [28]. Second, for technical reasons (unavailability of appropriate assays), we could not examine CSF Aβ levels. Although, in general, this parameter seems less specific for AD pathology as p-tau [49, 50], several studies demonstrated that a combination of tau proteins and Aβ or their ratio might have better diagnostic properties for detecting AD than each parameter on its own [22, 51]. Finally, there are many potential ways to analyze PET data. In the present study, we inspected 3D-SSP and transaxial images. Because of theoretical advantages [12] and a straightforward way of data presentation, the technique of 3D-SSP has been widely used in many clinics, in both single- and multicenter trials [20]. From our experience and the literature, at present, it is likely to be the most popular software for the visual interpretation of FDG-PET images in clinical practice. Nevertheless, there are several other software packages available that display images topographically, generate statistical maps and may provide similar, or in combination with 3D-SSP even superior, results.

In conclusion, our data suggest that under clinical conditions, FDG-PET and CSF p-tau$_{181}$ levels perform very accurately in differentiating DAT patients from nondemented controls and patients with non-AD dementias, whereas CSF p-tau$_{181}$ might be somewhat superior in the sensitive detection of patients with amnestic MCI.

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