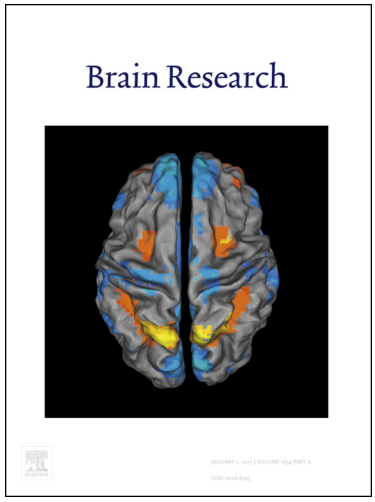

Research report

Brain metabolic correlates of CSF Tau protein in a large cohort of Alzheimer's disease patients: a CSF and FDG PET study

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Brain metabolic correlates of CSF Tau protein in a large cohort of Alzheimer's disease patients: a CSF and FDG PET study

Running title: CSF and brain ^{18}F FDG PET in AD

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Abstract

Aims: physiopathological mechanisms of Alzheimer's disease (AD) are still matter of debate. Especially the role of amyloid β and tau pathology in the development of the disease are still matter of debate. Changes in tau and amyloid β peptide concentration in cerebrospinal fluid (CSF) and hypometabolic patterns at fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET scanning are considered as biomarkers of AD. The present study was aimed to evaluate the relationships between the concentrations of CSF total Tau (t-Tau), phosphorilated Tau (p-Tau) and $A\beta_{1-42}$ amyloid peptide with ^{18}F-FDG brain distribution in a group of patients with AD.

Materials and methods: We examined 131 newly diagnosed AD patients according to the NINCDS-ADRDA criteria and 20 healthy controls. The mean (± SD) age of the patients was 70 (± 7) years; 57 were male and 74 were female. All patients and controls underwent a complete clinical investigation, including medical history, neurological examination, mini-mental state examination (MMSE), a complete blood screening (including routine exams, thyroid hormones and a complete neuropsychological evaluation). Structural MRI was performed not earlier than 1 month before the ^{18}F-FDG PET/CT. The following patients were excluded: those with isolated deficits and/or unmodified MMSE (=25/30) on revisit (period of follow-up: 6, 12 and 18 months); patients who had had a clinically manifest acute stroke in the last 6 months with a Hachinsky score greater than 4; and patients with radiological evidence of subcortical lesions. All AD patients were taken off cholinesterase inhibitor treatment throughout the study. We performed lumbar puncture and CSF sampling for diagnostic purposes 2 weeks (± 2 days) before the PET/CT scan. The relationship between brain F-FDG uptake and CSF biomarkers was analysed using statistical parametric mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab R2012b using the MMSE score, sex and age, and other CSF biomarkers as covariates.

Results: t-Tau, p-Tau and Aβ(1-42) in CSF resulted 774±345 pg/ml, 98±64 pg/ml and 348.8±111 pg/ml respectively. SPM analysis showed a significant negative correlation between CSF t-Tau and ^{18}F FDG uptake in right temporal, parietal and frontal lobe (Brodmann areas, BA, 20, 40 and 8; P

fdr and few corr < 0.001, ke 19534). We did not find any significant relationships with other CSF biomarkers.

Conclusions: t-Tau deposition in brain is related to temporal, parietal and frontal hypometabolism in AD.

Introduction

Alzheimer disease (AD) is an age-related neurodegenerative disorder and represents the most common cause of dementia in elderly patients. Clinical manifestations include impairment of memory and other cognitive skills and a gradual loss of the ability to perform activities of daily living; however these symptoms may occur in other dementias(Ballard et al., 2011). An accurate and early diagnosis is mandatory to be able to differentiate patients with AD from patients suffering from other forms of dementia and to ensure appropriate pharmacological treatment, counselling, and inclusion in clinical trials(Herukka et al., 2017). Pathophysiological mechanisms of AD are still matter of debate, especially the role of amyloid β- and Tau-mediated pathology in the development of the disease. Currently, the most promising approaches involve from one side the detection of soluble biomarkers in CSF and, from the other side, the molecular imaging of glucose metabolism and AD pathology (amyloid and Tau accumulation) in brain cortex with positron emission tomography (PET). Glucose metabolism shows typical alterations in AD, which significant difference (mainly involving temporal and parietal lobe) between patients with early onset as compared to those with late onset(Chiaravalloti et al., 2016).

Currently, the most validated biomarkers for early detection of AD in the clinical setting are represented by reduced levels of the 42-amino-acid form of amyloid-β (AB1-42) and elevated levels of total Tau (t-Tau) and phosphorylated Tau (p-Tau) in the cerebrospinal fluid (CSF); positive amyloid PET imaging; atrophy and microstructural damage of the medial temporal lobe (by magnetic resonance imaging); a characteristic pattern of glucose hypometabolism (by 2-deoxy-2-(^{18}F) fluoro-D-glucose (^{18}F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT)(Dubois et al., 2014; Herukka et al., 2017). A Tau/AB1-42 CSF evaluation shows acceptable sensitivity and specificity in distinguishing healthy from mild-to-moderate AD when compared to amyloid PET imaging(Mo et al., 2017).

To date, there are several conflicting reports regarding the cross correlation of various AD biomarkers. In a study published recently with PET for the imaging in vivo of the amyloid plaque,

Cairns et al. found that patient with clinically and CSF-positive AD was negative for plaque burden(Cairns et al., 2009) whereas in another study, normal individuals with cortical amyloid deposition had higher CSF levels of Tau and p-Tau(Fagan et al., 2009).

An autopsy performed in subjects with clinical diagnosis of AD found only neurofibrillary tangles, but no amyloid plaques(Crary et al., 2014).

Despite the exceptions mentioned above, the consensus view is that AD is characterized by a) increased amyloid and tau burden in brain; b) increased levels of cerebrospinal fluid (CSF) levels of t-Tau, p-Tau and reduced levels of amyloid-β (AB1-42) amyloid peptide; c) medial temporal atrophy in Magnetic Resonance Imaging (MRI), increased uptake of radiolabelled compounds for amyloid imaging and decreased ^{18}F-FDG uptake in PET(Khan and Alkon, 2015).

On the best of our knowledge, few studies have been carried out to date in order to investigate the relationships between different biomarkers in the same population of AD subjects. Hhence, the present study was aimed to investigate the relationships between CSF levels of t-Tau, p-Tau and amyloid-β (AB1-42) amyloid peptide and ^{18}F-FDG brain distribution in a large cohort of patients with AD.

Results

A general overview of the AD and HC population examined is provided in Table 1. The mean age (±SD) of the AD patients was 69 (±7) years. A neuropsychological evaluation, that included the MMSE and a standardized neuropsychological battery(Carlesimo et al., 1996), reported in all AD patients a cognitive profile consistent with mild dementia. On MMSE, AD patients scored a mean of 18.5 ± 6.4 and Clinical Dementia Rating score was 1.3 ± 1.21.

Relationships between ^{18}F-FDG-PET data and CSF biomarkers

In AD patients, we found a significant negative relationship between brain glucose consumption and T-Tau concentrations in CSF in a wide cluster that included the right temporal, frontal and parietal cortex [Brodmann Areas (BA) 20,8 and 40; Table 2). We did not find any significant relationships between ^{18}F-FDG distribution in brain and the other biomarkers p-Tau and AB1-42. In HC, we did

not find any significant relationships between ^{18}F-FDG distribution in brain and the CSF biomarkers.

Relationships between CSF biomarkers and neuropsychological data

In AD patients, T-Tau levels were correlated negatively with Raven matrix test ($r = –0.25$, $p = 0.02$), whereas AB_{1-42} levels were correlated negatively with Rey Auditory Verbal Learning Test-Delayed Recall ($r = –0.36$, $p < 0.001$. No further significant correlations between CSF markers and other cognitive scores (i.e. Mini Mental State Examination, Rey Complex Figure Test, Phonological Word Fluency Test).

Relationships between ^{18}F-FDG-PET data and neuropsychological data

In AD patients, FDG metabolism in BA-8 and BA-20 was positively correlated with Phonological Word Fluency Test ($r = 0.29$, $p = 0.008$) and Raven's Colored Progressive Matrices ($r = 0.23$, $p = 0.046$); whereas FDG metabolism in BA-40 was positively correlated not only with Phonological Word Fluency Test ($r = 0.32$, $p = 0.003$) and Raven's Colored Progressive Matrices ($r = 0.35$, $p = 0.002$), but also with Rey Auditory Verbal Learning Test-Immediate Recall ($r = 0.23$, $p = 0.037$), Rey Complex Figure Test-Copy ($r = 0.34$, $p = 0.002$) and Rey Complex Figure Test-Delayed recall ($r = 0.26$, $p = 0.019$).

AD vs. HC ^{18}F FDG PET comparison

Table 3 shows the results of the comparative analysis of ^{18}F-FDG-PET data. We found a significant cortical hypometabolism in a wide cluster that included temporal, limbic, parietal and frontal cortex bilaterally when comparing AD subjects vs. HC (BAs 39, 31, 40, 6, 8 and 9).

Discussion

In this work, we investigated the possible relationships between CSF biomarkers and brain ^{18}F-FDG distribution in a population with clinically diagnosed AD, in order to evaluate the possible modulatory effect of amyloid and Tau pathology on glucose metabolism. Our results show a relationship between ^{18}F-FDG PET imaging and levels of t-Tau protein, whereas CSF AB_{1-42} was not associated with specific alterations. A correction of PET data for brain atrophy by means of MR

data with the introduction of age into the multivariate analysis in SPM (see Materials and methods section) was performed in order to allow a better comparison of our results.

A significant negative relationship between t-Tau and ^{18}F-FDG uptake was found in a wide cluster that included in decreasing order the right temporal, right frontal and right parietal cortex (Fig 1). Notably, the Z-score of the maximum correlation point resulted located in inferior temporal gyrus in right temporal cortex, in medial and superior frontal gyrus in right frontal cortex. Interestingly, Giannakopoulos et al found that, in a large cohort of AD subjects, the occurrence of higher AD pathology (both amyloid plaques and neurofibrillary tangles) in the right hemisphere is associated with an increased score in clinical dementia rating scale(Giannakopoulos et al., 2009). According to other similar reports in this field, the predominant development of AD pathology in the left hemisphere may remain cognitively silent because of a functional compensation assumed at least partly by the right hemisphere. The invasion of the right hemisphere by AD lesions would disrupt this phenomenon leading to increased dementia severity(Reuter-Lorenz et al., 2000). According to results reported in Table 1, the clinical evaluation of our study cohort show a moderate to severe dementia that could justify a greater impairment of the right hemisphere ad compared to the left brain (see Table 3, AD vs. HC comparison). Future studies, possibly performed in subjects with a mild dementia could clarify this aspect.

The central role of Tau-pathology in AD physiopathology is supported by several studies with or without synergistic amyloid-pathology effects. Increased CSF T-Tau concentration and reduction in regional glucose metabolism is consistent with evidence that CSF concentration of this protein is increased in association with neuronal damage and loss of synapses. According Braak Tau-pathology may begin in medial temporal structures as transentorhinal cortex (transentorhinal stages I-II) and may extend in limbic regions (stages III-IV) of medial and inferior temporal lobe, until extensive isocortical involvement (stages V-VI)(Braak and Braak, 1991). Braak staging accuracy in describing Tau pathology seems to be confirmed by several studies that involved post-mortem evaluation of AD patients(Qian et al., 2017) and Tau tracers imaging(Jack et al., 2017; Scholl et al.,

2016; Schwarz et al., 2016). Tau pathology was reported by Tau PET imaging studies in the temporal lobe and temporoparietal junction, extended into parietal and frontal regions in clinical AD and in the medial temporal lobe in preclinical AD(Gordon et al., 2016), with a strong correlation to clinical and anatomical heterogeneity of AD(Ossenkoppele et al., 2016) and should be mainly responsible for the onset of early symptoms(Brier et al., 2016). Nowadays Tau pathology is one of the most promising study field in AD. The advent of the PET tracer ^{18}F-AV1451 or ^{18}F-T807 provides the opportunity to visualize the regional distribution of Tau pathology in the living human brain[6]. Post-mortem Braak staging of neurofibrillary Tau tangle topographical distribution is one of the core neuropathological criteria for the diagnosis of AD and in vivo ^{18}F-AV-1451 PET images across the AD spectrum could be classified into patterns similar to those prescribed by Braak neuropathological staging of Tau pathology; moreover Tau PET can be reported in stages specular to Braak stages(Jack et al., 2017; Scholl et al., 2016; Schwarz et al., 2016).

According Brier et al Tau deposition in the temporal lobe more closely tracks dementia status and is a better predictor of cognitive performance than Aβ deposition in any region of the brain, suggesting that Tau pathology closely tracks changes in brain function that are responsible for the onset of early symptoms. Furthermore, CSF Tau, mainly used to stage preclinical AD, correlated with Tau deposition in the temporal lobe(Brier et al., 2016). Symptomatic individuals demonstrated markedly increased levels of Tau tracer uptake in the temporal lobe and temporoparietal junction, extended into parietal and frontal cortices. In preclinical Alzheimer's disease, there is focal Tauopathy in the medial temporal lobes and adjacent cortices(Gordon et al., 2016). Accordingly, other authors found that Tau imaging-contrary to amyloid-β imaging showed a strong regional association with clinical and anatomical heterogeneity in Alzheimer's disease (Ossenkoppele et al., 2016). Tau ligands uptake in basal/ lateral temporal lobe, fusiform, inferior temporal, and middle temporal is associated with characteristics of AD. Temporal lobe Tau PET uptake also predicts elevated CSF Tau(Brier et al., 2016; Gordon et al., 2016).

^{18}F-AV-1451 PET retention is differentially associated with age and positive amyloid PET imaging;

but Tau retention pattern significantly explain the variance in cognitive performance and clinical outcome measures, independently of the associated/antecedent positive amyloid PET imaging(Tosun et al., 2017). These findings suggest that Tau tangles, but not amyloid-β plaques, correlate with cognition and clinical symptoms. According to others authors that related ^{18}F-AV-1451 PET to hippocampal volume loss and CSF changes, PET retention was associated with decline in global cognition but required the presence of cortical amyloid-β for the neurodegenerative process that leads to AD(Wang et al., 2016). A synergistic effect of amyloid and Tau deposits is also described in paper that compared Tau PET to amyloid PET and ^{18}F-FDG PET imaging and demonstrated in elderly its link to hypometabolism and memory decline in AD. Furthermore the amyloid effect was observed with Tau in neocortex, but not with Tau in entorhinal cortex(Hanseeuw et al., 2017).

This pattern of Tau-pathology distribution is in concordance with our hypometabolic pattern suggesting that Tau-pathology, evaluated by CSF measures, may influence glucose metabolism in brain tissues. Accordingly, temporal lobe Tau PET uptake also predicts elevated CSF Tau(Brier et al., 2016; Gordon et al., 2016; Ossenkoppele et al., 2016) confirming the effectiveness of CSF Tau as biomarker of Tau-pathology. Furthermore, in according with the strong relationship of the CSF T-Tau with frontal cortex hypometabolism, we found also a significant negative correlation between CSF T-Tau levels and analogic reasoning functions, measured by Raven matrix test. This finding further strengthens the link between Tau pathology and frontal impairment in AD.

Others authors described a significant agreement between the ^{18}F-FDG-PET imaging in AD and CSF Tau findings(Petrie et al., 2009) that, in some cases, appears to be related to a worse cognitive pattern (Yakushev et al., 2012) or to a different hypometabolic pattern (parietal, temporal and occipital lobe bilaterally)(Ceravolo et al., 2008). A weak correlation between t-Tau, not significant considering p-Tau, is also described(Haense et al., 2008). Furthermore a study on healthy individuals reports higher CSF t-Tau and p-Tau concentrations associated to hypometabolism in early affected regions in AD and lower AB_{1-42} concentrations in medial temporal lobe, supporting

the hypothesis that early Tau-pathology and amyloid-pathology may modulate metabolic changes in brain regions vulnerable to AD (Petrie et al., 2009). Similar findings are described also in clinical and pre-clinical AD patients, in which significant effects of CSF AB_{1-42} alterations on hypometabolism were observed in middle/inferior temporal gyrus, whereas ^{18}F-FDG-PET changes appeared to mediate t-Tau or t-Tau/ AB_{1-42} associated cognitive change across all brain regions examined(Dowling et al., 2015). Otherwise other findings suggest a correlation between CSF AB_{1-42} and ^{18}F-FDG-PET findings instead of CSF Tau proteins, that result not related(Petrie et al., 2009) or related to a more selective cortical metabolic pattern that mainly involve the cingulate cortex (Chiaravalloti et al., 2015a). Reasons for such discrepancies can be the different number of patients examined and/or the great heterogeneity among AD patients, but also the statistical analysis, carried out by SPM8 in this paper in order to improve data analysis.

In the current CSF-PET study we did not observe correlations between p-Tau phosphorylated at threonine 181 (p-Tau181) and brain ^{18}F-FDG uptake. This finding is in line with previous PET and pathological studies, in which p-Tau181 did not correlate with hypometabolism in ^{18}F-FDG-PET(Chiaravalloti et al., 2015a), neither with neocortical neurofibrillary pathology in AD(Buerger et al., 2007). An explanation for the lack of this correlation observed in our AD patients could be the fact that the isoform p-Tau181 is less sensitive than isoform p-Tau231 as an in vivo surrogate biomarker of neurofibrillary pathology in Alzheimer's disease.

Amyloid PET tracers and AB1-42 CSF are both considered as biomarkers of amyloid deposition in AD. Concordance between cerebrospinal fluid biomarkers and 11C PIB PET was described in a memory clinic cohort(Zwan et al., 2014). A correlation between 18F Florbetapir distribution and density of β-amyloid plaques was reported in post-mortem brain tissues of patients with a varying degree of neurodegenerative pathology(Choi et al., 2012). The overall diagnostic accuracies of AB1-42 CSF and amyloid PET with 18F Florbetapir were similar, but PET had greater specificity(Mattsson et al., 2014).

The correlation between FDG distribution and CSF biomarkers was described with not unanimous

results. These findings highlight the heterogeneous propagation of tau or amyloid pathology among patients with symptomatic AD, in contrast to the homogeneous changes seen in glucose metabolism, which better tracked clinical progression(Chiotis et al., 2017). Global cognition (measured with MMSE) declined significantly in patients with AD; this decline correlated with decreased FDG uptake but not with changes in tau tracers retention over time. In cross-sectional findings the association of FDG with global cognition was regionally more extensive than that of THK531(Saint-Aubert et al., 2016). These findings support the notion that while tau deposition in the temporal cortex may be related to the earliest memory impairment, global cognitive changes are more closely related with hypometabolism in the relevant areas than with measures of tau propagation. FDG uptake was significantly associated over time with both low global cognition and episodic memory encoding scores(Saint-Aubert et al., 2016). FDG PET, in fact, might be a better tool for monitoring symptom progression(Saint-Aubert et al., 2016). According other authors tauopathy effect on clinical aspects, as memory decline, was mediated by posterior cingulate metabolism that decreased when both amyloid and neocortical tau were high, predicting subsequent memory decline. In contrast, frontal hypometabolism related to the common age-related entorhinal tauopathy, but this dysfunction, independent of amyloid, did not predict clinical decline. Neocortical tauopathy was positively associated with metabolism in individuals with subthreshold amyloid, suggesting a subsequent metabolic model of preclinical AD in which glucose metabolism increases before decreasing(Hanseeuw et al., 2017). Therefore FDG uptake in AD can be considered as the mirror of effect of tau and/or amyloid deposition on glucose metabolism, an subsequently synaptic activity. Otherwise PET imaging with tau or amyloid tracers represent the distribution of tau and/oa amyloid-pathology.

Additional longitudinal studies are required to examine and validate hypothesized mediational relationships explaining the complex sequence of events leading to neurodegeneration in AD, but Tau-pathology is one of most promising study field. Therefore, future investigations should combine CSF markers with Tau-, and 18F-FDG-PET imaging to further investigate the relationships

between Tau pathology and metabolic abnormalities of patients with AD.

Our study has several limitations. First, the number of HC subject examined is small. This aspect severely limits the statistical analysis performed and in particular the comparison by means of SPM between AD and CG. The small HC group in fact could be one of the reasons for a lack of a significant hypometabolism in frontal regions in the group comparison, and explain the discrepancy with respect to the topography of the correlation with Tau values. Secondly, the basis for validating the diagnosis of AD, particularly early in its course, is notoriously inaccurate when subsequently validated with autopsies. Clinical diagnosis, therefore, may represent a sub optimal reference standard against which to compare the potential biomarkers evaluated in this study.

Materials and methods

Patients and healthy controls

A total of 131 patients with a diagnosis of probable AD according to the NINCDS-ADRDA criteria were enrolled in this study. The mean (± SD) age of the patients was 70 (± 7) years; 57 were male and 74 were female. 20 healthy subjects (HC, 9 men, 11 women; mean age 67±6 years old; age range 20-89 years) were enrolled in the study as a control group. Clinical examination was conducted by an experienced neurologist (A.M.) and Mini Mental State Examination (MMSE) did not reveal any cognitive deficit in all the subjects examined with a score greater than 28 being found in all of them, see below).

A complete clinical investigation was performed in each patient and healthy subject, including clinical aspects as medical history, a complete blood screening (including routine examinations, thyroid hormones, level of vitamin B12), and particularly neurological aspects as neurological examination, MMSE, a neuropsychological examination(Pierantozzi et al., 2004), a complete neuropsychiatric evaluation. Magnetic resonance neuroimaging (1.5-tesla MRI) was also performed in all patients. Patients with isolated deficits and/or unmodified MMSE (≥25/30) during follow-up (6, 12 and 18 months) and patients with clinically manifest acute stroke in the previous 6 months, Hachinski scale score >4 and radiological signs of subcortical lesions, were excluded.

Pyramidal and/or extrapyramidal signs were not found in this population. Antidepressants, neuroactive drugs (i.e. antiepileptic drugs, benzodiazepines, neuroleptics) and cholinesterase inhibitors were suspended in all patients 30 days before the enrolment, in order to avoid a possible modulation of cerebral cortex excitability.

The study was performed according to the Declaration of Helsinki and was approved by the Ethics Committee of the Tor Vergata University in Rome. All participants or their legal guardians gave their written informed consent after receiving extensive information on the study.

Cognitive evaluation

A neuropsychological battery (Table 1) was administrated in AD and HC subjects and included: Mini-Mental State Examination (MMSE)(Magni et al., 1996); verbal episodic long-term memory (Rey Auditory Verbal Learning Test, long-term memory, 15-word list immediate and 15-min delayed recall)(Caffarra et al., 2002); visuospatial abilities and visuospatial episodic long-term memory (Rey Complex Figure Test, copy and 10-min delayed recall)(Shin et al., 2006); executive functions (Phonological Word Fluency Test)(Carlesimo et al., 1996), and analogic reasoning (Raven's Colored Progressive Matrices)(Carlesimo et al., 1996). Italian normative data were used in all tests for both score adjustment (gender, age and education) and to define cut-off scores of normality, determined as the lower limit of the 95% tolerance interval (normative data are reported in the corresponding references).

CSF sampling

Lumbar puncture was performed and CSF biomarkers of AD were evaluated in all patients. The first 12 ml of CSF were collected in a polypropylene tubes and transported to the local laboratory. Samples underwent centrifugation at 2,000 *g* at +4°C for 10 min. The supernatant obtained was pipetted off, stirred and mixed to avoid potential gradient effects; then it was aliquoted in 1-ml portions that were stored at −80°C in polypropylene tubes until biochemical analyses, avoiding to thaw and re-freeze samples. In the AD patients, CSF t-Tau and phosphorylated Tau (p-Tau, Thr181) concentrations were determined using a sandwich ELISA (Innotest® hTau-Ag, Innogenetics, Gent,

Belgium), while CSF AB_{1-42} levels were determined using a sandwich ELISA [Innotest β-amyloid(1-42), Innogenetics] that specifically measure AB containing both the first and 42nd amino acid(Sancesario et al., 2010).

PET/CT scanning

PET/CT was performed in AD subjects and HC according to other similar reports of our group in this field(Alessandrini et al., 2014; Alessandrini et al., 2016; Chiaravalloti et al., 2015b). In particular, all the subjects fasted for at least 5 h before i.v. injection of FDG and serum glucose level was in the range according to European Association of Nuclear Medicine guidelines in all of them(Boellaard et al., 2015). All subjects were injected i.v. with 185-210 MBq of 18F-FDG and were hydrated with 500 ml of NaCl 0.9%. The PET/CT system Discovery VCT (GE Medical Systems, Tennessee, USA) has been used to assess ^{18}F-FDG brain distribution in all patients. For more details concerning PET acquisition parameters, please check the following references(Alessandrini et al., 2014; Alessandrini et al., 2016; Chiaravalloti et al., 2015a; Chiaravalloti et al., 2015b; Chiaravalloti et al., 2016).

Statistical analysis

The relationships between CSF biomarkers and brain ^{18}F-FDG uptake were analysed using statistical parametric mapping (SPM8) (Wellcome Department of Cognitive Neurology, London, UK) that was implemented in Matlab R2015a (Mathworks, Natick, Massachusetts, USA) for both HC and AD subjects. PET data were processed for statistical analysis as reported previously in other studies by our group in this field(Alessandrini et al., 2014; Alessandrini et al., 2016; Chiaravalloti et al., 2015a; Chiaravalloti et al., 2015b; Chiaravalloti et al., 2016). The voxel-based analyses were performed in AD and HC using a ‘regression analysis’ design model. The Aß1–42, p-Tau and t-Tau regression factors were assessed. Differences between AD and HC groups were assessed using a ‘two conditions: one scan/condition, paired t-test’ design model. The following comparisons were assessed: (i) HC versus AD and vice versa.

In SPM maps, we searched the brain areas with a significant correlation using a statistical threshold of P-value of 0.05, family-wise error corrected for the problem of multiple comparisons, with an extent threshold of 100 voxels.

The cluster obtained in the regression analysis was then exported by means of WFU Pickatlas tool implemented in SPM 8 and further analysed after a normalization process(Lancaster et al., 1997). In particular, the mean signal intensities computed by each cluster were normalized within each subject to the average intensities of the cerebellum volume of interest, as defined by other similar reports of our group in this field(Alessandrini et al., 2014; Liguori et al., 2016). The use of a normalization based upon activity in the cerebellum, instead of whole brain counts as in the reference region, was reported to result in a higher accuracy in distinguishing patients from controls in neurodegenerative diseases(Soonawala et al., 2002). As proposed previously by Pagani et al.(Pagani et al., 2015), a dataset including normalized ^{18}F-FDG values relevant to the examined cluster has been exported. To determine if cerebellum-normalized ^{18}F-FDG values for the cluster examined were of Gaussian distribution, the D'Agostino K squared normality test has been applied (where the null hypothesis is that the data are normally distributed).

Furthermore, in AD patients we calculated the Pearson's correlation coefficient to explore the relationships of CSF AB_{1-42}, p-Tau and t-Tau levels each other and with neuropsychological scores and normalized ^{18}F-FDG values.

Compliance with Ethical Standards

The authors report no financial discosures/fundings or conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Figure legends

Figure 1: 3D brain rendering showing in (a) the cluster obtained in SPM regression analysis of T-Tau in AD (red, Table 2).In (b) we show the clusted obtained from the comparison between HC and AD subjects (hypometabolism in AD, green, Table 3). In (c) both clusters are merged in the single image showing the overlap in temporal and parietal cortex (see text). AD: Alzheimer's disease; HC: healthy controls.

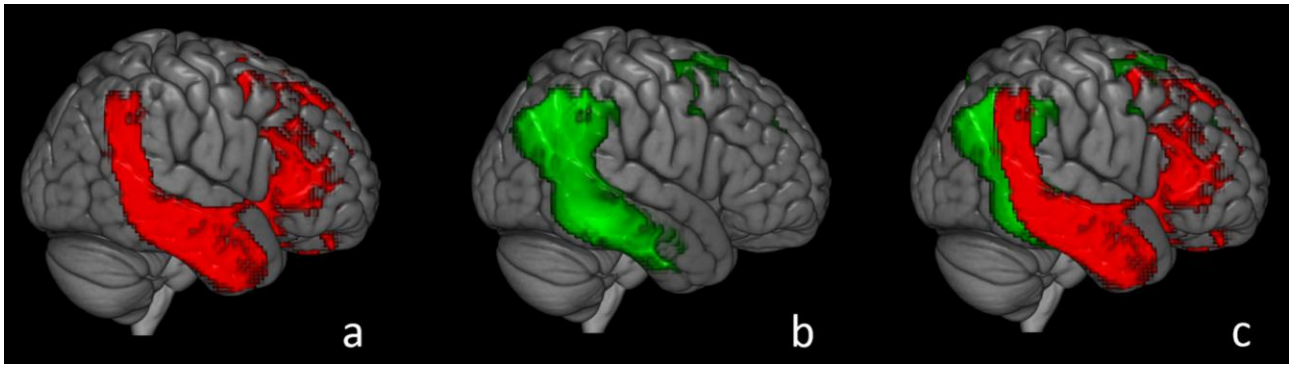

Table 1: General overview of the AD and HC population examined including cerebrospinal fluid analysis results and neuropsychological evaluation. AD= Alzheimer's disease; HC= healthy controls.

	AD	HC	P value
Population	131: f=74; m=57	20: f=11; m=9	ns
Age	70±6 years	67±6 years	ns
Aβ1-42 (ng/ml)	348.8±111.2	791.14±179.53	<0.05
T-Tau (ng/ml)	774.8±345.2	201±81.52	<0.05
p-tau (ng/ml)	98±64.7	37.4±11.7	<0.05
MMSE score	19.3±5.9	27.9±0.6	<0.05
Rey Auditory Verbal Learning Test, immediate recall	21.7 ±8.5	27.9±1	<0.05
Rey Auditory Verbal Learning Test, delayed recall	2.4±2.6	5.8±1.9	<0.05
Rey Complex Figure Test, copy	18.6±10	26.6±10.1	<0.05
Rey Complex Figure Test, delayed recall	7.6±5.9	9.8±5.5	<0.05
Raven's Colored Progressive Matrices	20.8±6.8	28.1±1.1	<0.05
Phonological Word Fluency Test	22.3±9.8	26.9±1	<0.05

Table 2: Multiple regression analysis showing the T-tau related areas of decreased ^{18}F FDG brain uptake (negative correlation).

Analysis	Cluster level					Voxel level	
Negative correlation	cluster p(FWE-corr)	cluster p(FDR-corr)	Cluster extent	Cortical Region	Z score of maximum	Talairach coordinates	Cortical region
	0.000	0.000	19534	R Temporal, Inferior Temporal Gyrus	5.42	62,-10,-22	BA 20
				R Frontal, Medial Frontal Gyrus	5.09	10,32,42	BA 8
				R Frontal, Superior Frontal Gyrus	4.93	24,38,44	BA 8
				R Parietal, Supramargynal Gyrus	4.89	53,-52,34	BA 40

In the ‘cluster level’ section on left, the number of voxels, the corrected P value of significance and the cortical region where the voxel is found, are all reported for each significant cluster. In the ‘voxel level’ section, all of the coordinates of the correlation sites (with the Z-score of the maximum correlation point), the corresponding sub cortical region is reported for each significant cluster. L, left; R, right; FWE, Familywise error; FDR, False discovery rate.

Table 3: Differences in cortical ^{18}F FDG brain in brain in AD vs. HC subjects (hypometabolism in AD).

Analysis	Cluster level					Voxel level	
HC-AD	cluster p(FWE-corr)	cluster p(FDR-corr)	Cluster extent	Cortical Region	Z score of maximum	Talairach coordinates	Cortical region
	0.000	0.000	21462	R Temporal, middle temporal gyrus	7.59	48,-62,24	BA 39
				R Limbic, cingulate gyrus	7.18	6,-46,40	BA 31
				R Limbic, cingulate gyrus	7.15	-2,-46,42	BA 31
				R Parietal, Supramargynal Gyrus	7.01	42, -48, 52	BA 40
				L Frontal, superior frontal gyrus	5.17	-26,-2,58	BA 6
			2775	L frontal, middle frontal gyrus	5.14	-28,30,46	BA 8
				L Frontal, superior frontal gyrus	5.06	-22,14,50	BA 6
				R frontal, middle frontal gyrus		30,16,50	BA 6
			2074	R frontal, middle frontal gyrus		40,8,48	BA 6
				R frontal, middle frontal gyrus		32,28,34	BA 9

In the ‘cluster level’ section on left, the number of voxels, the corrected P value of significance and the cortical region where the voxel is found, are all reported for each significant cluster. In the ‘voxel level’ section, all of the coordinates of the correlation sites (with the Z-score of the maximum correlation point), the corresponding sub cortical region is reported for each significant cluster. L, left; R, right; FWE, Familywise error; FDR, False discovery rate.

Highlights

- Cortical metabolism is related to Tau levels in CSF in AD subjects
- Phosphorylated Tau in CSF is not related to a peculiar metabolic pattern in AD
- There is a good relationship between levels of CSF Tau and neuropsychological performance in AD