European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:1796–1805
https://doi.org/10.1007/s00259-019-04379-4

ORIGINAL ARTICLE

Brain metabolic patterns in patients with suspected non-Alzheimer's pathophysiology (SNAP) and Alzheimer's disease (AD): is [^{18}F] FDG a specific biomarker in these patients?

Agostino Chiaravalloti[1,2] · Gaetano Barbagallo[3] · Alessandro Martorana[4] · Anna Elisa Castellano[2] · Francesco Ursini[5] · Orazio Schillaci[1,2]

Received: 13 January 2019 / Accepted: 28 May 2019 / Published online: 14 June 2019

Abstract

Purpose The present study was conducted to compare the pattern of brain [^{18}F] FDG uptake in suspected non-Alzheimer's pathophysiology (SNAP), AD, and healthy controls using 2-deoxy-2-[^{18}F]fluoroglucose ([^{18}F] FDG) positron emission tomography imaging. Cerebrospinal fluid (CSF) biomarkers amyloid-β1-42 peptide (Aβ1-42) and tau were used in order to differentiate AD from SNAP.

Methods The study included 43 newly diagnosed AD patients (female = 23; male = 20) according to the NINCDS-ADRDA criteria, 15 SNAP patients (female = 12; male =3), and a group of 34 healthy subjects that served as the control group (CG), who were found to be normal at neurological evaluation (male = 20; female = 14). A battery of neuropsychological tests was administrated in AD and SNAP subjects; cerebrospinal fluid assay was conducted in both AD and SNAP as well. Brain PET/CT acquisition was started 30 ± 5 min after [^{18}F] FDG injection in all subjects. SPM12 [statistical parametric mapping] implemented in MATLAB 2018a was used for the analysis of PET scans in this study.

Results As compared to SNAP, AD subjects showed significant hypometabolism in a wide cortical area involving the right frontal, parietal, and temporal lobes. As compared to CG, AD subjects showed a significant reduction in [^{18}F] FDG uptake in the parietal, limbic, and frontal cortex, while a more limited reduction in [^{18}F] FDG uptake in the same areas was found when comparing SNAP to CG.

Conclusions SNAP subjects show milder impairment of brain [^{18}F] FDG uptake as compared to AD. The partial overlap of the metabolic pattern between SNAP and AD limits the use of [^{18}F] FDG PET/CT in effectively discriminating these clinical entities.

Keywords [^{18}F] FDG · Alzheimer, SNAP · PET/CT · Biomarkers

Abbreviations

[^{18}F] FDG	2-Deoxy-2-[^{18}F]fluoroglucose
PET	Positron emission tomography
CT	Computed tomography
CSF	Cerebrospinal fluid
T-tau	Total tau
P-tau	Phosphorylated tau

Introduction

Suspected non-Alzheimer's pathophysiology (SNAP) describes a clinical entity where older adults with or without subtle cognitive decline show one of the markers of neurodegeneration (e.g. neuronal injury markers), but test negative for brain amyloid (Aβ) pathology [i.e. cerebrospinal fluid (CSF) assay and positron emission tomography (PET)] and have not been diagnosed with a specific neurodegenerative disorder

---

This article is part of the Topical Collection on Neurology

✉ Agostino Chiaravalloti
agostino.chiaravalloti@uniroma2.it

[1] Department of Biomedicine and Prevention, University Tor Vergata, Viale Oxford 81, 00133 Rome, Italy

[2] IRCCS Neuromed, Pozzilli, Italy

[3] Institute of Neurology, University Magna Graecia of Catanzaro, Catanzaro, Italy

[4] UOSD Centro Demenze, Department of Systems Medicine, University of Roma Tor Vergata, Rome, Italy

[5] Department of Medical Sciences, University of Ferrara, Ferrara, Italy

[1]. The correct identification of SNAP is crucial, since it has been reported to affect up to 23% of cognitively healthy adult individuals [1, 2] and is characterized by a benign clinical course, with only a minor proportion of patients progressing to mild cognitive impairment (MCI) or clinical AD [2].

In the era of Aβ imaging, the exclusion of one of the pathological hallmarks of Alzheimer's disease (AD) is feasible. Several radiolabeled compounds have been developed for the in vivo visualization of the Aβ burden in brain tissue by means of PET [3]. On one hand, Aβ imaging with PET enables the correct classification of AD and the identification of those patients with MCI that will progress to AD [4]; on the other hand, it represents a suboptimal biomarker in the assessment of dementia severity [5]. Interestingly, cognitive decline is only weakly related to change in Aβ burden and, most importantly, Aβ deposition increases slowly from cognitive normality to moderate severity [5]. On the other side, PET with 2-deoxy-2-[^{18}F]fluoroglucose ([^{18}F] FDG) can efficiently demonstrate significant differences in the brain [^{18}F] FDG uptake when comparing AD with other types of dementia (e.g. frontotemporal dementia, FTD); in subjects affected by MCI, the pattern is less specific and reflects the neuropsychological profile, but an involvement of the cingulate cortex and hippocampus is usually observed [6]. Although extensively studied in AD, less is known about the role of PET imaging in SNAP individuals. To date, most of the studies in SNAP patients have been carried out using amyloid PET tracers, with the main purpose of excluding AD as a cause of cognitive impairment in these subjects [1, 2, 7]. To the best of our knowledge, the [^{18}F] FDG pattern has been evaluated only in one previous study, on a limited number of SNAP subjects [8].

The aim of the present study was to compare the pattern of the brain [^{18}F] FDG uptake in SNAP, AD, and healthy controls using [^{18}F] FDG PET imaging. CSF amyloid-β1-42 (Aβ1-42) was used as a marker of amyloid and CSF tau was used as a marker of neuronal injury, in order to differentiate AD from SNAP.

Materials and methods

Cognitive evaluation

A neuropsychological assessment battery (Table 1) was administrated in AD and SNAP subjects and included the following: Mini-Mental State Examination (MMSE) [10]; verbal episodic long-term memory (Rey Auditory Verbal Learning Test, long-term memory, 15-word list immediate and 15-min delayed recall) [11]; visuospatial ability and visuospatial episodic long-term memory (Rey Complex Figure Test, copy and 10-min delayed recall) [12]; executive function (Phonological Word Fluency Test) [13]; and analogical reasoning (Raven's Colored Progressive Matrices) [13]. Italian normative data were used in all tests both for score adjustment (gender, age, and education) and to define the cutoff score for normality, determined as the lower limit of the 95% tolerance interval (normative data are reported in the corresponding references).

CSF sampling

CSF sampling in AD and SNAP was conducted with the same modalities reported previously in another study by our group [14]. After lumbar puncture, the first 12 ml of CSF was collected in a polypropylene tube and directly transported to the local laboratory for centrifugation at 2000 *g* at +4 °C for 10 min. The supernatant was pipetted off, gently stirred and mixed to avoid potential gradient effects, and aliquoted in 1-ml portions in polypropylene tubes that were stored at −80 °C pending biochemical analyses, without being thawed and refrozen. In the AD patients, CSF t-tau and phosphorylated tau (p-tau, Thr181) concentrations were determined using a sandwich enzyme-linked immunosorbent assay (ELISA; Innotest® hTAU Ag, Innogenetics, Gent, Belgium). CSF AB1-42 levels were determined using a sandwich ELISA [Innotest β-amyloid(1-42), Innogenetics] specifically constructed to measure AB containing both the first and 42nd amino acid.

PET/CT scanning protocol

The study was conducted in the Nuclear Medicine facility of Policlinico Tor Vergata of Rome. The system used was the GE Healthcare VCT PET/CT scanner. All subjects were injected intravenously with [^{18}F] FDG (dose range 185–295 MBq) and hydrated with 500 ml of saline (0.9% sodium chloride). PET/CT acquisition was started 30 ± 5 min after [^{18}F] FDG injection and lasted 10 min in all subjects. Reconstructions parameters were as follows: ordered subset expectation maximization, 4 subsets and 14 iterations; matrix 256 × 256; full width at half maximum (FWHM), 5 mm [14, 15]. The PICASO system (www.picaso-project.eu) was used for the share of medical data.

AD and SNAP patients

The present study was conducted in 43 newly diagnosed AD patients according to the NINCDS-ADRDA criteria [16] and 15 SNAP patients. A general overview of the study population is provided in Table 1.

AD patients were recruited after a detailed clinical assessment including a thorough medical history, neurological examination, and laboratory testing according to a standardized protocol as described in other studies by our group [15, 17].

Selection of SNAP subjects was performed on the basis of CSF parameters as reported in previous studies, among clinically normal participants aged >65 years [18–20]. The SNAP group was defined by the absence of CSF amyloid marker and

Table 1 General overview of the AD and SNAP population examined including cerebrospinal fluid analysis results and neuropsychological evaluation

	AD	SNAP	FDR-corrected *P* value	CG	Spearman r; *P* value (AD subjects)	Spearman r; *P* value (SNAP subjects)
Population	43: f = 23; m = 20	15: f = 12; m = 3	0.10	34: f = 20; m = 14		
Age	70 ± 7 years	75 ± 4 years	0.06	71 ± 8 years		
Aβ1-42 (ng/ml)	347.8 ± 117.52	657.7 ± 125.87	<0.01	818 ± 202.71[a]		
T-tau (ng/ml)	789.6 ± 248.55	578.3 ± 163.36	0.01	272 ± 84.23[a]		
p-tau (ng/ml)	99.7 ± 50.52	79.3 ± 20.03	0.19	40.3 ± 10.93[a]		
MMSE score	20.0 ± 4.84	21.8 ± 4.55	0.23	28.7 ± 0.84		
Rey Auditory Verbal Learning Test, immediate recall	20.7 ± 7.65	30.7 ± 8.46	0.006	33.2 ± 7.57	T-tau: −0.11; 0.47 P-tau: 028; 0.06 Aβ1-42: −0.03;0.81	T-tau: −0.07; 0.57 P-tau: 0.12;0.66 Aβ1-42: 0.05;0.85
Rey Auditory Verbal Learning Test, delayed recall	1.9 ± 2.44	4.3 ± 3.74	<0.01	6.6 ± 2.12	T-tau: −0.02; 0.86 P-tau: 0.43;<0.01 Aβ1-42: −0.21;0.16	T-tau: −0.06; 0.82 P-tau: 0.30;0.26 Aβ1-42: 0.38;0.15
Rey Complex Figure Test, copy	16.6 ± 9.23	19.4 ± 10.02	0.36	25.3 ± 11.35	T-tau: −0.08; 0.58 P-tau: 0.13;0.37 Aβ1-42: −0.18;0.23	T-tau: 0.51; >0.05 P-tau: 0.65;0.01 Aβ1-42: <0.01;0.98
Rey Complex Figure Test, delayed recall	6.9 ± 4.34	9.8 ± 5.75	0.07	9.1 ± 5.24	T-tau: −0.02; 0.86 P-tau: −0.08;0.59 Aβ1-42: −0.21;0.16	T-tau: 0.17; 0.53 P-tau: 0.30;0.26 Aβ1-42: 0.10;0.72
Raven's Colored Progressive Matrices	18.9 ± 7.93	20.0 ± 6.89	0.65	24.4 ± 3.62	T-tau: −0.10; 0.52 P-tau: −0.17;0.29 Aβ1-42: −0.11;0.48	T-tau: 0.35; 0.20 P-tau: 0.56;0.03 Aβ1-42: <0.01;0.99
Phonological Word Fluency Test	20.8 ± 8.32	26.8 ± 11.22	0.06	26.9 ± 10.38	T-tau: −0.20; 0.18 P-tau: 0.15;0.30 Aβ1-42: <0.00;0.93	T-tau: 0.27; 0.31 P-tau: 0.21;0.43 Aβ1-42: −0.11;0.67

AD Alzheimer's disease, *SNAP* suspected non-AD pathology

[a] Data available from 13 subjects (see Chiaravalloti et al. [9])

presence of CSF neuronal injury marker, with or without subtle cognitive decline. The cutoffs for abnormality were less than 450 pg/mL for Aβ1-42, greater than 350 pg/mL for t-tau, and greater than 50 pg/mL for p-tau [21]. All SNAP patients had abnormal t-tau or p-tau in the presence of normal Aβ1-42, regardless of episodic memory ability.

All subjects examined underwent structural magnetic resonance imaging (MRI) performed within 1 month prior to [^{18}F] FDG PET/CT brain scan. Co-registration of PET and MRI data was carried out in doubtful cases. As for AD, subjects with the isolated deficit and/or unmodified Mini-Mental State Examination (MMSE) = 25/30 during follow-up visits, with Hachinski score and radiological evidence of subcortical lesions were excluded from this study. Other exclusion criteria were predefined as follows: patients with other neurological symptoms such as dysfunction in the hypothalamus and/or appendices suprasphenoidalis disease; the presence of pyramidal and/or extrapyramidal signs at the neurological examination; patients with thyroid disease, diabetes, cancer, HIV, or previous brain injury. Table 1 summarizes the main demographic and neuropsychological features of AD and SNAP subjects, as well as CSF amyloid and neuronal injury markers. Groups were matched for sex and age. AD patients did not differ from SNAP patients on neuropsychological tests investigation of global cognitive function (i.e. MMSE), visuospatial ability, executive functioning, or analogical reasoning. However, AD patients displayed statistically significantly lower mean scores in verbal episodic long-term memory than SNAP patients. Finally, as expected on the basis of predefined inclusion and exclusion criteria, significant differences between groups were found in CSF amyloid and neuronal injury markers. AD patients showed higher levels of Aβ1-42 and lower levels of t-tau and p-tau in the CSF than SNAP patients.

CG subjects

Thirty-four chemotherapy-naïve subjects (20 male, 14 female; mean age, 71 ± 8 years) undergoing an [^{18}F] FDG PET/CT and found to be completely negative for various diseases were enrolled in the study and served as the control group (CG). The population used as the CG was selected from a population that had already been evaluated in another report from our group [9], representing an optimal match for AD and SNAP patients. Data for amyloid and neuro injury biomarkers among

Table 2 Numerical results of SPM comparisons between [^{18}F] FDG uptake in SNAP and. AD

Analysis	Cluster level					Voxel level		
	Cluster p(FWE-corr)	Cluster p(FDR-corr)	Cluster extent	Cortical region	*Z* score of maximum	Talairach coordinates	Cortical region	BA
SNAP – AD (areas of reduced glucose metabolism in AD as compared to SNAP)	0.000	0.000	5077	R Temporal	3.61	48, −60, 30	Superior temporal gyrus	39
				R Frontal	3.57	26, 20, 50	Middle frontal gyrus	8
				R Parietal	3.48	36, −30, 62	Postcentral gyrus	3

In the 'cluster level' section on the 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 cortical region, and BA are reported for each significant cluster. In the case that the maximum correlation is achieved outside the gray matter, the nearest gray matter (within a range of 5 mm) is indicated with the corresponding BA

SNAP suspected non-Alzheimer's pathophysiology, *AD* Alzheimer's disease, *L* left, *R* right, *BA* Brodmann's area

the CG were available for some of them (13 subjects, 38%, see Table 1). Before their inclusion in our study, they had all been previously evaluated for the absence of clinical signs of AD by an experienced neurologist (A.M.), and the MRI, performed 7 ± 2 days before PET/CT examination, was negative for brain injury in all of them. Participants with a previous history of neurological or psychiatric disorders, use of typical or atypical antipsychotics, sensorial or motor impairments, or other clinical conditions that might influence cognitive performance (such as hypothyroidism or B12 vitamin depletion), or history of alcohol or other substance abuse were excluded from the present study.

Informed consent was obtained from all of the patients and CG subjects, and procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013 [22]. The study protocol was deemed observational by the internal review board of the Local Ethical Committee of Policlinico Tor Vergata that gave the approval.

Statistical analysis

SPM12 [statistical parametric mapping] implemented in MATLAB 2018a was used for the analysis of PET scans in this study (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). PET data were converted from DICOM to NIfTI format using MRIcron software (https://www.nitrc.org/projects/mricron) and were then subjected to a normalization process. A bias regularization was applied (0.0001) in order to limit bias due to smooth, spatially varying artifacts that modulate the intensity of the image and that can impede the automated processing of the images. The FWHM of Gaussian smoothness of bias (to prevent the algorithm from trying to model out intensity variation due to different tissue types) was set at a cutoff of 60 mm; a tissue probability map implemented in SPM12 was used (TPM.nii). A mutual information affine registration with the tissue probability maps [23] was used to achieve approximate alignment with the International Consortium of Brain Mapping (ICBM) space template–European brains [24, 25]. Warp regularization was set with

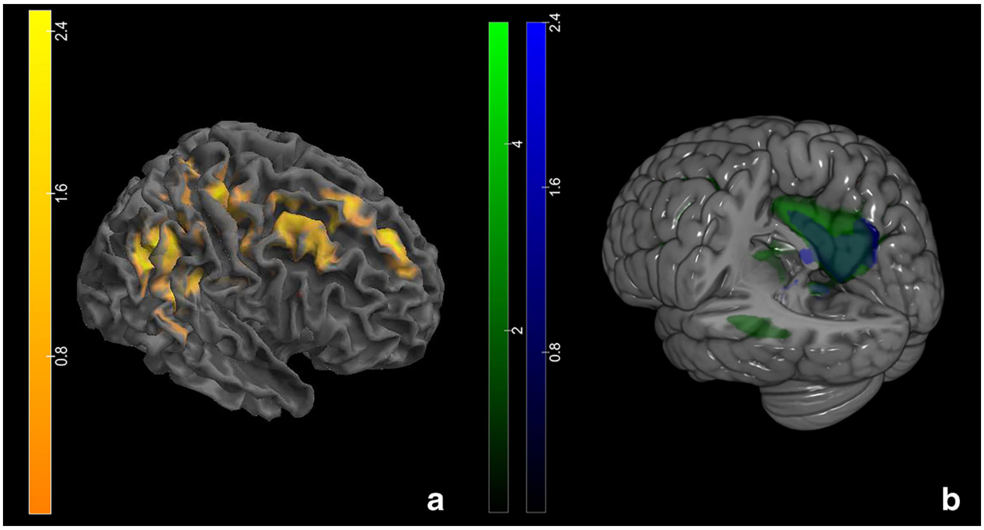

Fig. 1 3D rendering of data presented in Table 2 in **a** showing the results of SPM comparisons between [^{18}F] FDG uptake in SNAP vs. AD; significant hypometabolism in a wide cortical area that involves the right frontal, parietal, and temporal lobes. In **b** the 3D rendering shows the overlap of the metabolic pattern observed in CG-SNAP (blue) and CG-AD (green) comparisons in the right limbic cortex. Coordinate and other regional details are presented in Tables 2 and 3, respectively

Table 3 Numerical results of SPM comparisons between [^{18}F] FDG uptake in AD and SNAP vs. CG

Analysis	Cluster level					Voxel level		
	Cluster p(FWE-corr)	Cluster p(FDR-corr)	Cluster extent	Cortical Region	*Z* score of maximum	Talairach coordinates	Cortical region	BA
CG – AD (areas of reduced glucose metabolism in AD as compared to CG)	0.000	0.000	25,545	R parietal	6.98	44, −62, 36	Angular gyrus	39
				R parietal	6.90	50, −48, 38	Inferior parietal lobule	40
				R limbic	6.43	2, −40, 34	R cingulate gyrus	31
	0.000	0.000	10,762	R frontal	6.38	34, 8, 54	Middle frontal gyrus	6
				L frontal	5.67	−28, 30, 44	Middle frontal gyrus	8
				L frontal	5.54	−24, 24, 52	Superior frontal gyrus	8
CG – SNAP (areas of reduced glucose metabolism in SNAP as compared to CG)	0.011	0.008	3124	R limbic	4.31	6, −52, 20	Posterior cingulate	23
				R parietal	3.90	−6, −64, 24	Precuneus	31
				R limbic	3.70	4, −42, 34	Cingulate gyrus	31

In the ‘cluster level’ section on the 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 cortical region, and BA are reported for each significant cluster. In the case that the maximum correlation is achieved outside the gray matter, the nearest gray matter (within a range of 5 mm) is indicated with the corresponding BA

SNAP suspected non-Alzheimer’s pathophysiology, *AD* Alzheimer’s disease, *L* left, *R* right, *BA* Brodmann’s area

the following 1 × 5 array (0, 0.001, 0.5, 0.05, 0.2); smoothness (to cope with functional anatomical variability that is not compensated for by spatial normalization and to improve the signal-to-noise ratio) was set at 5 mm; sampling distance (that encodes the approximate distance between sampled points when estimating the model parameters) was set at 3.

We applied an 8-mm isotropic Gaussian filter to blur the individual variations (especially gyral variations) and to increase the signal-to-noise ratio. We used the following parameters and post-processing tools before regression analysis was applied: global normalization (that escalates images to a global value) = 50 (using proportional scaling); masking threshold (that helps to identify voxels with an acceptable signal in them) was set to 0.8; transformation tool of statistical parametric maps into normal distribution; correction of SPM coordinates to match the Talairach coordinates, subroutine implemented by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging). Brodmann areas (BA) were identified at a range of 0 to 3 mm from the corrected Talairach coordinates of the SPM output isocenter using the Talairach Client (http://www.talairach.org/index.html). As proposed by Bennett et al. [26], SPM t-maps were corrected for multiple comparisons with the false discovery rate ($P \leq 0.05$) and corrected for multiple comparisons at the cluster level ($P \leq 0.001$). The level of significance was set at 100 (5 × 5 × 5 voxels, i.e., 11 × 11 × 11 mm) contiguous voxels. The following voxel-based comparisons were assessed: AD vs. SNAP and vice versa; AD vs. CG and vice versa; SNAP vs. CG and vice versa. All comparisons were performed using a two-sample *t* test design model available in SPM12 [17]. We used sex, MMSE, and CSF as covariates in the analyses between AD and SNAP, and age, sex, and MMSE in the comparisons among AD, SNAP, and CG.

In order to investigate any hemispheric asymmetry of [^{18}F] FDG brain uptake in SNAP subjects, a selected ROI was placed on the cortical gray matter of both hemispheres by means of the WFU PickAtlas tool implemented in SPM 12, and further analyzed after a normalization process [27]. The mean signal intensities computed for the whole cluster were normalized within each subject to the average intensities of the cerebellar volume of interest (VOI) as defined in other reports published previously [28, 29]. Data are reported in Table 4.

For the comparison between AD and CG, voxel-based analysis was performed using a modality-adjusted paired *t* test (two conditions, one scan/condition), and the following

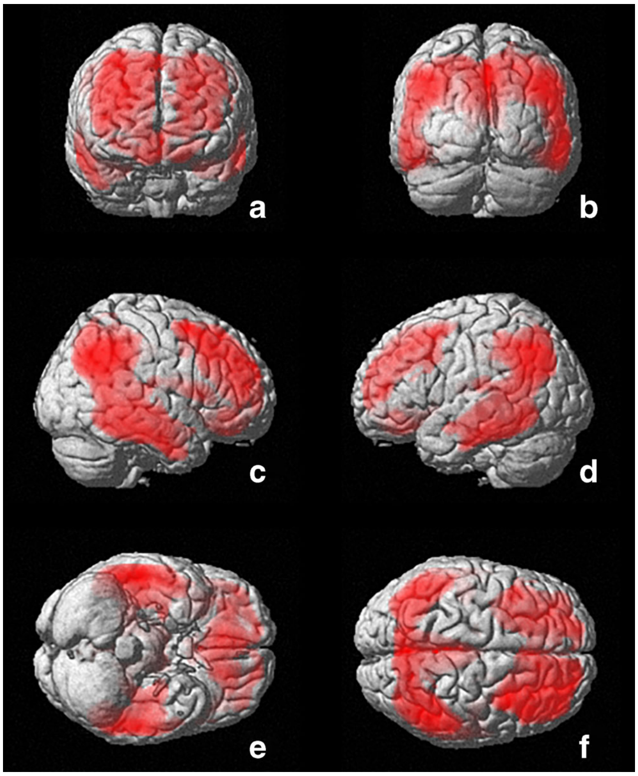

Fig. 2 3D rendering of data presented in Table 3 (CG-AD) showing the wide area of reduced glucose metabolism in AD as compared to CG (red). The reduction in [^{18}F] FDG uptake involved temporal, parietal, limbic, and frontal cortex. **a** Frontal view; **b** posterior view; **c** view of the right hemisphere; **d** view of the left hemisphere; **e** bottom view () and **f** upper view

comparison was assessed: AD vs. CG using gender and age as nuisance variables.

Comparisons of [^{18}F] FDG uptake values in different brain regions in SNAP subjects were analyzed with the Mann-Whitney *U* test (nonparametric test).

Correlation analyses of CSF values with neuropsychological tests results were performed using the nonparametric Spearman correlation.

Results

As compared to SNAP, AD subjects showed significant hypometabolism in a wide cortical area involving the right frontal, parietal, and temporal lobes (Table 2). We did not find any area of increased [^{18}F] FDG uptake when comparing SNAP to AD subjects. 3D rendering of data presented in Table 2 is shown in Fig. 1a.

As compared to CG, AD subjects showed a significant reduction in [^{18}F] FDG uptake in several cortical areas, as reported in Table 3, which included parietal, limbic, temporal, and frontal cortex (Fig. 2). A more limited reduction in [^{18}F] FDG uptake was obtained when comparing SNAP to CG (Table 3). For each comparison (Tables 2 and 3) we reported the *z* score. This value is used in statistics of a value's relationship to the mean (average) of a group of values, measured in terms of standard deviations from the mean.

We did not find any significant difference when comparing [^{18}F] FDG uptake in a selected cortical lobe as compared to an opposite lobe in SNAP subjects (i.e. [^{18}F] FDG uptake in left frontal lobe vs. right frontal lobe, etc.). Results are shown in Table 4. Moreover, we found no differences in [^{18}F] FDG uptake among different lobes of the same hemisphere (i.e. left frontal lobe vs. left temporal lobe), with the exception of the comparisons with the occipital lobe where, as expected, higher values of [^{18}F] FDG uptake were detected (Fig. 3).

We found no significant relationship between t-tau values and the results of neuropsychological tests in AD and SNAP subjects. As for p-tau, we found a significant relationship with the Rey Auditory Verbal Learning Test, delayed recall in AD subjects (negative correlation) and the Rey Complex Figure Test, copy and Raven's Colored Progressive Matrices in SNAP subjects (negative correlation). We did not find any significant relationship between Aβ1-42 CSF values and neuropsychological assessment in AD and SNAP groups (Table 1).

Discussion

SNAP is a biomarker-based concept that describes the presence of AD-like neurodegeneration in individuals without excessive amyloid-β (Aβ) deposition. SNAP was first described in 2012 in a study aimed at evaluating the criteria for preclinical AD proposed by the National Institute on Aging–Alzheimer's Association (NIA–AA) [1]. However, it is still a matter of debate whether SNAP should be considered an independent clinical entity with a different biological basis

Table 4 Region-by-region analysis of [^{18}F] FDG uptake in the cortex of SNAP subjects. Data reported show the presence/absence of asymmetries of [^{18}F] FDG uptake in SNAP patients

Cortical region	[^{18}F] FDG uptake[a] (mean ± SD)	*P* value
Left frontal lobe	1.27 ± 0.10	>0.05
Right frontal lobe	1.30 ± 0.11	
Left limbic lobe	1.27 ± 0.14	>0.05
Right limbic lobe	1.30 ± 0.12	
Left occipital lobe	1.46 ± 0.21	>0.05
Right occipital lobe	1.43 ± 0.19	
Left parietal lobe	1.36 ± 0.12	>0.05
Right parietal lobe	1.37 ± 0.11	
Left temporal lobe	1.26 ± 0.12	>0.05
Right temporal lobe	1.28 ± 0.12	

[a] The values for [^{18} F] FDG uptake were obtained from the normalization of PET data using WFU PickAtlas (see "Materials and methods" section)

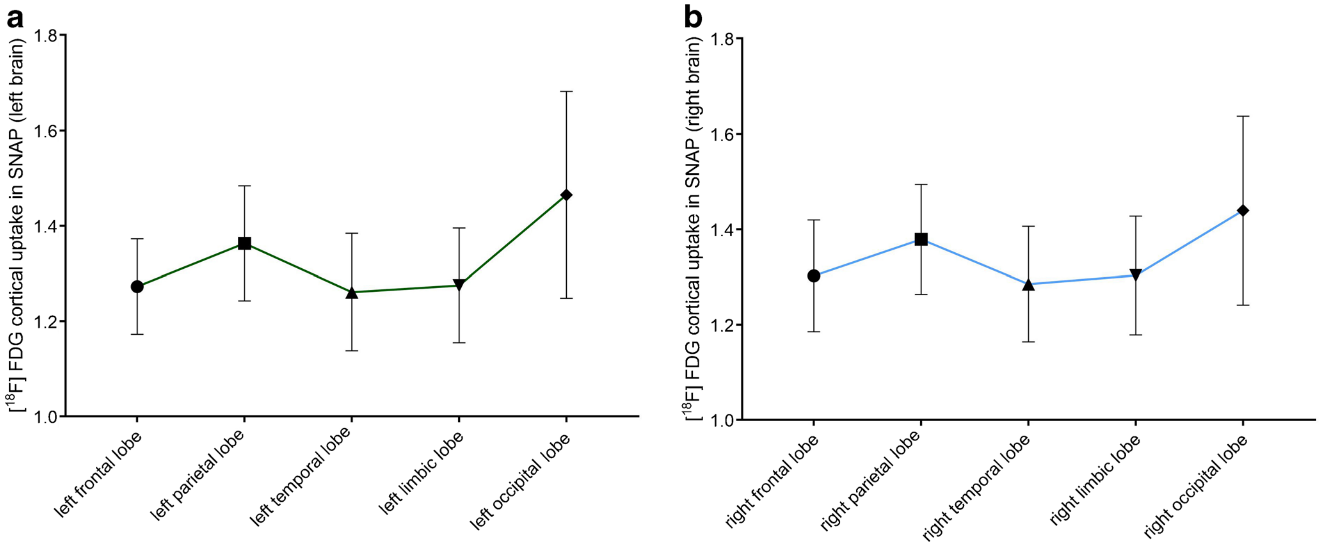

Fig. 3 Graphical overview of data reported in Table 4: **a** values of [^{18}F] FDG uptake in the left hemisphere, and **b** those in the right hemisphere. Although the [^{18}F] FDG uptake is lower in the temporal and frontal lobes bilaterally than in the parietal lobes (with a pattern similar to that of frontotemporal dementia), the difference was not statistically significant

from AD or, conversely, the result of measurement or classification errors [30]. Furthermore, SNAP classification is independent of any particular degree of cognitive impairment. In our cohort, indeed, SNAP individuals were classified regardless of episodic memory ability [15], although, as expected, they showed cognitive impairment. Interestingly, no significant differences were found between AD and SNAP regarding visuospatial ability, visuospatial episodic long-term memory, executive functioning, or analogical reasoning, whereas verbal episodic long-term memory function was more affected in AD than SNAP, suggesting a differential, although partially, in the pattern of impairment. In line with these neuropsychological findings, SNAP patients showed significant hypometabolism in parietal and limbic cortices versus CG subjects, with involvement of the cingulate gyrus and precuneus (Table 3 and Fig. 1). These results suggest that SNAP patients show a pattern of hypometabolism similar to that observed in AD patients [31], thus supporting the hypothesis that medial temporal and precuneus tau pathology without amyloidosis might be a major constituent of SNAP [32, 33]. In analogy with a common hypometabolic pattern in AD and SNAP that mainly involves the precuneus and cingulate cortex, the two conditions showed overlapping p-tau levels, suggesting that common tau pathology in these areas may account for the clinical similarities observed [30]. According to data reported in Table 1, the AD group had higher t-tau in the CSF and a nearly statistically significant difference in the Rey Complex Figure Test and the Phonological Word Fluency Test compared to the SNAP group. Hence, it could be hypothesized that the AD group could have more extensive cognitive impairment and neuronal injury than the SNAP; this could partially explain the higher extensive [^{18}F] FDG abnormalities in the AD group and the huge difference in the extent of the cluster reported in Table 3. In the SPM analysis, the potential effect of CSF biomarkers is mitigated by the use of Aβ1-42, t-tau, and p-tau values as covariates.

The regional analysis reported in Table 4 does not show hemispheric differences in [^{18}F] FDG uptake in SNAP patients, further suggesting that SNAP conditions may include heterogeneous non-AD pathologies. In Fig. 3, on the other hand, it is clearly discernible that [^{18}F] FDG uptake is lower in the temporal and frontal lobe bilaterally than in the parietal lobes (a pattern that may be consistent with frontotemporal dementia). Even if this difference suggests that SNAP patients may include the FTD variant, this finding did not reach statistical significance and, most importantly, was not confirmed in the comparison with CG (Table 3 and Fig. 1). In comparison with CG, the parietal lobe, in fact, is one of the cortical areas that shows a significant reduction in [^{18}F] FDG uptake, ruling out the FTD pattern. The exact pathological process leading to SNAP development remains to be elucidated. In this context, CSF analysis still plays a major role in differentiating SNAP from AD, but represents a highly invasive and costly diagnostic procedure. On the other side, according to our results, [^{18}F] FDG PET does not show major differences in the metabolic patterns observed in AD and SNAP sufficient to consider this diagnostic tool as a candidate for the differential diagnosis between AD and SNAP. Recent studies on amyloid imaging suggest that PET could be a determinant for a correct diagnosis in patients with persistent or progressive unexplained MCI, patients with progressive dementia and atypically early age of onset, and patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation [34]. In particular, in the study of by Bensaïdane et al. [35], the use of amyloid PET resulted in a diagnostic change in 32.1% (17.8% changed from AD to non-AD, 14.3% from non-AD to AD). If one considers the suboptimal performance of [^{18}F] FDG in discriminating SNAP from AD subjects in our study, it can be concluded that amyloid imaging should be considered instead of [^{18}F] FDG in doubtful cases.

A recent study using AD Neuroimaging Initiative (ADNI, http://www.adni-info.org) data demonstrated that the APOe genotype does not differ significantly between SNAP (negative for amyloid burden and positive for neurodegeneration in imaging biomarker) and subjects negative for both neurodegeneration and amyloid burden, suggesting that APOE and known genetic drivers of AD do not appear to contribute to the neurodegeneration observed in SNAP [36]. In another report from Schreiber et al. performed in a large population of normal subjects and patients with mild cognitive impairment, the SNAP group had a lower proportion of APOE ε4 carriers and less severe abnormalities on neurodegeneration biomarkers associated with AD, such as glucose metabolism [37]. Our results are in agreement with those of Schreiber et al., but data on the APOe genotype are available in a limited number of subjects in our study cohort (28 subjects with AD and 5 SNAP subjects). Twelve AD and two SNAP patients had the ε4 phenotype, and 15 AD and three SNAP had the ε3 phenotype; thus no conclusions can be drawn regarding the role of APOe genotype on our findings.

Despite providing an insightful comparison between AD and SNAP, our study has some limitations to be acknowledged. First, no postmortem pathological data were obtained in our patients; thus it is not possible to assume that all AD patients had clear amyloid-related pathology. However, biomarker-based validated criteria [13–15] were used. Second, our study was limited by the cross-sectional design, making it impossible to compare the rate and speed of progression of these two entities. SNAP remains an interesting model in which to study the pathophysiology of tau-related degeneration in the absence of detectable amyloid pathology; future longitudinal studies are needed to elucidate the course of metabolic changes in the parietal and limbic regions and their relationship to cognitive dysfunction. Lastly, also considering that the use of CSF biomarkers could improve the accuracy in patient selection in our study, a consensus on cutoff values for CSF in AD are still missing; it was recently suggested that each laboratory must use internally validated cutoff values and confirm longitudinal stability in their measurements [38]. The cutoff values used in our study are in line with those proposed by Forlenza et al., which have been reported to show acceptable values in terms of sensitivity and specificity for discriminating AD from controls [21]. Nevertheless, cutoff values must be carefully considered to guarantee optimal diagnostic performance of biomarkers.

Conclusions

SNAP subjects show milder impairment of brain [^{18}F] FDG uptake as compared to AD. The partial overlap of the metabolic pattern between SNAP and AD limits the use of [^{18}F] FDG PET/CT in effectively discriminating these clinical entities.

Acknowledgments The authors wish to thank Tiziana Martino (IRCCS Neuromed) for data collection. This work was funded in part by the European Commission Horizon 2020 programme, grant 689209: PICASO, A Personalised Integrated Care Approach for Service Organisations and Care Models for Patients with Multi-Morbidity and Chronic Conditions.

Compliance with ethical standards

Conflict of interest The authors report no financial disclosures/funding 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 the1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

References

1. Jack CR Jr, Knopman DS, Weigand SD, Wiste HJ, Vemuri P, Lowe V, et al. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. Ann Neurol. 2012;71:765–75. https://doi.org/10.1002/ana.22628.
2. Burnham SC, Bourgeat P, Dore V, Savage G, Brown B, Laws S, et al. Clinical and cognitive trajectories in cognitively healthy elderly individuals with suspected non-Alzheimer's disease pathophysiology (SNAP) or Alzheimer's disease pathology: a longitudinal study. Lancet Neurol. 2016;15:1044–53. https://doi.org/10.1016/s1474-4422(16)30125-9.
3. Filippi L, Chiaravalloti A, Bagni O, Schillaci O. (18)F-labeled radiopharmaceuticals for the molecular neuroimaging of amyloid plaques in Alzheimer's disease. Am J Nucl Med Mol Imaging. 2018;8:268–81
4. Villemagne VL, Rowe CC. Long night's journey into the day: amyloid-beta imaging in Alzheimer's disease. J Alzheimers Dis. 2013;33(Suppl 1):S349–59. https://doi.org/10.3233/jad-2012-129034.
5. Villemagne VL, Pike KE, Chetelat G, Ellis KA, Mulligan RS, Bourgeat P, et al. Longitudinal assessment of Aß and cognition in aging and Alzheimer disease. Ann Neurol. 2011;69:181–92. https://doi.org/10.1002/ana.22248.

6. Mosconi L, Tsui WH, Herholz K, Pupi A, Drzezga A, Lucignani G, et al. Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. J Nucl Med. 2008;49:390–8. https://doi.org/10.2967/jnumed.107.045385.
7. Duara R, Loewenstein DA, Shen Q, Barker W, Potter E, Varon D, et al. Amyloid positron emission tomography with (18)F-flutemetamol and structural magnetic resonance imaging in the classification of mild cognitive impairment and Alzheimer's disease. Alzheimers Dement. 2013;9:295–301. https://doi.org/10.1016/j.jalz.2012.01.006.
8. Wirth M, Villeneuve S, Haase CM, Madison CM, Oh H, Landau SM, et al. Associations between Alzheimer disease biomarkers, neurodegeneration, and cognition in cognitively normal older people. JAMA Neurol. 2013;70:1512–9. https://doi.org/10.1001/jamaneurol.2013.4013.
9. Chiaravalloti A, Ursini F, Fiorentini A, Barbagallo G, Martorana A, Koch G, et al. Functional correlates of TSH, fT3 and fT4 in Alzheimer disease: a F-18 FDG PET/CT study. Sci Rep. 2017;7:6220. https://doi.org/10.1038/s41598-017-06138-7.
10. Magni E, Binetti G, Padovani A, Cappa SF, Bianchetti A, Trabucchi M. The mini-mental state examination in Alzheimer's disease and multi-infarct dementia. Int Psychogeriatr. 1996;8:127–34.
11. Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A. Rey-Osterrieth complex figure: normative values in an Italian population sample. Neurol Sci. 2002;22:443–7. https://doi.org/10.1007/s100720200003.
12. Shin MS, Park SY, Park SR, Seol SH, Kwon JS. Clinical and empirical applications of the Rey-Osterrieth complex figure test. Nat Protoc. 2006;1:892–9. https://doi.org/10.1038/nprot.2006.115.
13. Carlesimo GA, Caltagirone C, Gainotti G. The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The group for the standardization of the mental deterioration battery. Eur Neurol. 1996;36:378–84.
14. Chiaravalloti A, Barbagallo G, Ricci M, Martorana A, Ursini F, Sannino P, et al. Brain metabolic correlates of CSF tau protein in a large cohort of Alzheimer's disease patients: a CSF and FDG PET study. Brain Res. 2018;1678:116–22. https://doi.org/10.1016/j.brainres.2017.10.016.
15. Chiaravalloti A, Castellano AE, Ricci M, Barbagallo G, Sannino P, Ursini F, et al. Coupled imaging with [(18)F]FBB and [(18)F]FDG in AD subjects show a selective association between amyloid burden and cortical dysfunction in the brain. Mol Imaging Biol. 2018;20:659–66. https://doi.org/10.1007/s11307-018-1167-1.
16. Varma AR, Snowden JS, Lloyd JJ, Talbot PR, Mann DM, Neary D. Evaluation of the NINCDS-ADRDA criteria in the differentiation of Alzheimer's disease and frontotemporal dementia. J Neurol Neurosurg Psychiatry. 1999;66:184–8.
17. Chiaravalloti A, Koch G, Toniolo S, Belli L, Lorenzo FD, Gaudenzi S, et al. Comparison between early-onset and late-onset Alzheimer's disease patients with amnestic presentation: CSF and (18)F-FDG PET study. Dement Geriatr Cogn Dis Extra. 2016;6:108–19. https://doi.org/10.1159/000441776.
18. Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurol. 2013;12:957–65. https://doi.org/10.1016/s1474-4422(13)70194-7.
19. Roe CM, Fagan AM, Grant EA, Hassenstab J, Moulder KL, Maue Dreyfus D, et al. Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. Neurology. 2013;80:1784–91. https://doi.org/10.1212/WNL.0b013e3182918ca6.
20. van Harten AC, Smits LL, Teunissen CE, Visser PJ, Koene T, Blankenstein MA, et al. Preclinical AD predicts decline in memory and executive functions in subjective complaints. Neurology. 2013;81:1409–16. https://doi.org/10.1212/WNL.0b013e3182a8418b.
21. Forlenza OV, Radanovic M, Talib LL, Aprahamian I, Diniz BS, Zetterberg H, et al. Cerebrospinal fluid biomarkers in Alzheimer's disease: diagnostic accuracy and prediction of dementia. Alzheimers Dement (Amst). 2015;1:455–63. https://doi.org/10.1016/j.dadm.2015.09.003.
22. World Medical Association (WMA). Declaration of Helsinki. Amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. WMA Archives, Ferney-Voltaire, France. https://web.archive.org/web/20140101202246/ http://www.wma.net/en/30publications/10policies/b3/. Accessed 24 Oct 2018
23. D'Agostino E, Maes F, Vandermeulen D, Suetens P. Atlas-to-image non-rigid registration by minimization of conditional local entropy. Information processing in medical imaging : proceedings of the conference. Inf Process Med Imaging. 2007;20:320–32.
24. Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J. A probabilistic atlas of the human brain: theory and rationale for its development. The international consortium for brain mapping (ICBM). NeuroImage. 1995;2:89–101..
25. Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, et al. A four-dimensional probabilistic atlas of the human brain. J Am Med Inform Assoc. 2001;8:401–30.
26. Bennett CM, Wolford GL, Miller MB. The principled control of false positives in neuroimaging. Soc Cogn Affect Neurosci. 2009;4:417–22. https://doi.org/10.1093/scan/nsp053.
27. Lancaster JL, Rainey LH, Summerlin JL, Freitas CS, Fox PT, Evans AC, et al. Automated labeling of the human brain: a preliminary report on the development and evaluation of a forward-transform method. Hum Brain Mapp. 1997;5:238–42. https://doi.org/10.1002/(sici)1097-0193(1997)5:4<238::aid-hbm6>3.0.co;2-4.
28. Soonawala D, Amin T, Ebmeier KP, Steele JD, Dougall NJ, Best J, et al. Statistical parametric mapping of (99m)Tc-HMPAO-SPECT images for the diagnosis of Alzheimer's disease: normalizing to cerebellar tracer uptake. NeuroImage. 2002;17:1193–202.
29. Schmahmann JD, Doyon J, McDonald D, Holmes C, Lavoie K, Hurwitz AS, et al. Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. NeuroImage. 1999;10:233–60. https://doi.org/10.1006/nimg.1999.0459.
30. Jack CR Jr, Knopman DS, Chetelat G, Dickson D, Fagan AM, Frisoni GB, et al. Suspected non-Alzheimer disease pathophysiology–concept and controversy. Nat Rev Neurol. 2016;12:117–24. https://doi.org/10.1038/nrneurol.2015.251.
31. Bailly M, Destrieux C, Hommet C, Mondon K, Cottier JP, Beaufils E, et al. Precuneus and cingulate cortex atrophy and Hypometabolism in patients with Alzheimer's disease and mild cognitive impairment: MRI and (18)F-FDG PET quantitative analysis using FreeSurfer. Biomed Res Int. 2015;2015:583931. https://doi.org/10.1155/2015/583931.
32. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol. 2011;70:960–9. https://doi.org/10.1097/NEN.0b013e318232a379.
33. Delacourte A, David JP, Sergeant N, Buee L, Wattez A, Vermersch P, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology. 1999;52:1158–65.
34. Booij J, Arbizu J, Darcourt J, Hesse S, Nobili F, Payoux P, et al. Appropriate use criteria for amyloid PET imaging cannot replace guidelines: on behalf of the European Association of Nuclear Medicine. Eur J Nucl Med Mol Imaging. 2013;40:1122–5. https://doi.org/10.1007/s00259-013-2415-x.

35. Bensaidane MR, Beauregard JM, Poulin S, Buteau FA, Guimond J, Bergeron D, et al. Clinical utility of amyloid PET imaging in the differential diagnosis of atypical dementias and its impact on caregivers. J Alzheimers Dis. 2016;52:1251–62. https://doi.org/10.3233/jad-151180.
36. Hohman TJ, Dumitrescu L, Oksol A, Wagener M, Gifford KA, Jefferson AL. APOE allele frequencies in suspected non-amyloid pathophysiology (SNAP) and the prodromal stages of Alzheimer's disease. PLoS One. 2017;12:e0188501. https://doi.org/10.1371/journal.pone.0188501.
37. Schreiber S, Schreiber F, Lockhart SN, Horng A, Bejanin A, Landau SM, et al. Alzheimer disease signature neurodegeneration and APOE genotype in mild cognitive impairment with suspected non-Alzheimer disease pathophysiology. JAMA Neurol. 2017;74:650–9. https://doi.org/10.1001/jamaneurol.2016.5349.
38. Mattsson N, Andreasson U, Persson S, Arai H, Batish SD, Bernardini S, et al. The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. Alzheimers Dement. 2011;7:386–95.e6. https://doi.org/10.1016/j.jalz.2011.05.2243.