Distinct amyloid and tau PET signatures are associated with diverging clinical and imaging trajectories in patients with amnestic syndrome of the hippocampal type

Julien Lagarde, Pauline Olivier, Matteo Tonietto, Philippe Gervais, Claude Comtat, Fabien Caillé, Michel Bottlaender and Marie Sarazin

INTRODUCTION

Progressive amnesia is the core feature of typical Alzheimer’s disease (AD) and can be assessed by different tests of episodic memory. A specific episodic memory disorder has been reported in AD, characterized by a low free recall not normalized with semantic cueing in tests controlling for a successful encoding. In early AD, this amnestic profile is correlated with hippocampal atrophy and gray matter loss in the medial temporal lobe, even at a prodromal stage [1], as well as with AD pathology determined by cerebrospinal fluid (CSF) AD-biomarkers [2]. It is supposed to reflect the hippocampal dysfunction, which underlies the so-called amnestic syndrome of the hippocampal type (ASHT) [3]. The presence of an ASHT was proposed as a core clinical marker of typical AD in the recommendations of the International Working Group (IWG), but it must be supported by AD pathophysiological markers to make a diagnosis, especially at an early stage. Whether the amnestic syndrome of the hippocampal type is a signature of AD pathology has been questioned in a recent neuropathological study, showing that free and cued memory assessment lack accuracy to predict AD pathology [4].

AD is indeed far from being the only cause of progressive amnesia [5, 6], and the biological heterogeneity of this clinical phenotype has been highlighted [7]. Neuropathological studies have also emphasized that different pathological lesions other than AD can lead to episodic memory deficits mimicking AD [4]. The term SNAP, or “suspected non-AD pathophysiology” [8–10] was proposed to identify these individuals, reflecting the notion that pathologies outside of AD (and particularly of amyloid) underlie their neurodegenerative change. The latest version of the National Institute on Aging and the Alzheimer’s Association (NIA-AA) criteria for AD diagnosis defined non-AD pathologic change as the absence of both amyloid and tau lesions [11]. Among non-AD pathologic changes, beyond Lewy body disease, frontotemporal lobar degeneration (FTLD) or vascular lesions, the focus has recently shifted to Hippocampal Sclerosis (HS) in advanced age and limbic-predominant age-related TDP-43 encephalopathy.
binding in order to capture possible neuropsychological-behavioural performances and brain atrophy patients with early AD according to PET imaging, (b) compare their ASHT. First, we aimed to (a) differentiate patients with SNAP from longitudinal imaging data, and did not use a strict de within the medial temporal lobes. They did not include both amyloid and tau PET imaging in order to identify SNAP knowledge, only two studies published by the same team used the combination of amyloid and tau PET imaging in amnestic patients permits the identification of the pathophysiological process and could limit the risk of misdiagnosis [4, 23, 24].

Very few studies confronted detailed cognitive characterization of patients with progressive amnesia to the in vivo assessment of both amyloid and tau pathologies. To our knowledge, only two studies published by the same team used both amyloid and tau PET imaging in order to identify SNAP [24, 25] in small groups of amnestic patients. None of them provided information about individual tau regional binding within the medial temporal lobes. They did not include longitudinal imaging data, and did not use a strict definition of progressive amnesia as defined above (ASHT).

In the present study, we aimed to determine the amyloid and tau PET signatures in a group of well-characterized patients with ASHT. First, we aimed to (a) differentiate patients with SNAP from patients with early AD according to PET imaging, (b) compare their neuropsychological-behavioural performances and brain atrophy patterns at baseline, (c) analyse individual tau PET regional binding in order to capture possible “PART” within the SNAP group. Second, we aimed at investigating the longitudinal progression of the cognitive deficit, the regional cortical atrophy (including the hippocampus, entorhinal cortex, amygdala and insula) and the tau PET tracer uptake after 2 years of follow-up in SNAP and AD patients. We hypothesized that we could identify a significant proportion of SNAP among these patients with ASHT, and that the distinct molecular signatures (AD vs SNAP) could be associated with diverging clinical and imaging trajectories during longitudinal follow-up, with a more pronounced cognitive decline and progression of temporoparietal atrophy in AD.

MATERIALS AND METHODS

Participants

We prospectively included 66 participants from the Shatau7-Imatau (NCT02576821) and Imabio3 (NCT01775696) studies. The Ethics Committee (Comité de Protection des Personnes Ile-de-France VI) approved the study. All subjects provided written informed consent.

Thirty-six patients with ASHT (age = 72.9 ± 7.8 years, MMSE = 24.5 ± 2.8) were enrolled according to the following criteria: (i) progressive episodic memory impairment characterized by a low free recall not normalized with semantic cueing (free recall score ≤ 17/48 and/or total recall score ≤ 42/48 at the Free and Cued Selective Reminding Test (FCSRT)) [26]; (ii) no other significant cognitive deficit than executive and social cognition impairments (preservation of language, praxis or visuo-spatial abilities); (iii) a Clinical Dementia Rating (CDR) scale ≤ 1; (iv) no depression (Montgomery-Asberg Depression Rating Scale (MADRS) score ≤ 15); (v) presence of a study partner who is willing to participate as a source of information and has at least weekly contact with the patient. We have chosen not to exclude patients with mild executive dysfunction and social cognition impairment in order to investigate the possible relationship of these clinical features with the underlying aetiology.

Thirty healthy elderly controls (age = 68.8 ± 5.6, MMSE = 29.2 ± 0.9) were recruited according to the following criteria: (i) Mini-Mental State Examination (MMSE) score ≥ 27/30; (ii) normal neuropsychological assessment; (iii) CDR = 0; (iv) no memory complaint; and (v) negative PiB-PET imaging.

Subjects were not included in the study if they had: (i) sleep apnea; (ii) extrapyramidal signs or neurological history suggestive of Parkinson’s disease with dementia, progressive supranuclear palsy, corticobasal degeneration or dementia with Lewy bodies; (iii) systemic illnesses that could interfere with cognitive functioning; (iv) structural abnormality on MRI (intra-parenchymal tumour or large cortical infarct).

Study design

At baseline, all participants underwent the same procedures including a complete clinical and neuropsychological assessment, 3 T brain MRL [(11C)-PiB and [(18F)]-Flortaucipir PET imaging. For controls, [(18F)]-Flortaucipir PET was performed in 13/30 subjects. Participants were then followed up annually with repeated standardized clinical and neuropsychological assessments for 2 years. Thirty-two patients and 30 controls were clinically followed up at one year, and 28 patients and 28 controls at 2 years. At the last visit, subjects were asked to undergo a second 3 T MRI (performed in 27/36 patients and 28/30 controls) and tau PET imaging (performed in 20/36 patients, n = 6 refused, n = 2 were lost to follow-up; n = 8 were outside the regulatory limits of the study). Blood samples were drawn to determine APOE and c9orf72 genotypes as well as plasma progranulin levels in patients.

Measures

Clinical, functional, and cognitive assessment. All subjects underwent a complete clinical and neuropsychological examination that included the Mini-Mental State Examination, the Clinical Dementia Rating scale, tests for assessing verbal (FCSRT) and visual (recall of the Rey complex figure) episodic memory, executive functions (digit spans forward and backward, Trail making test, letter fluency), Similarities subset of the WAIS III, social cognition (facial emotion recognition and faux-pas subtests of the Mini-SEA) [27], language (word naming task, category fluency), gestural praxis and visuo-spatial abilities (copy of the Rey complex figure). We defined a verbal episodic memory score as the sum of the scores obtained for the free and cued recalls of the FCSRT. Behavioural changes in daily living were assessed by the response provided by an informant to the revised version of the Cambridge Behavioural Inventory [28].

Magnetic resonance imaging. All subjects underwent magnetic resonance imaging performed at the Centre de Neuro-Imagery de Recherche (CENIR, ICM, Paris) using a 3 T whole-body PRISMA 64-channel system (for all patients and 14 controls) or TRIO 32 channels with a 12-channel head coil for signal reception (Siemens) (for the remaining 16 controls). A longitudinal MRI after two years was performed for 27 patients and 28 controls. The MRI examination included a three-dimensional (3D) T1-weighted volumetric magnetization-prepared rapid gradient echo (MP-RAGE) sequence (repetition time/echo time/flip angle: 2300 ms/3.43 ms/9°, inversion time = 900 ms, voxel size: 1 × 1 × 1 mm³). Before pooling our control subjects, we verified that the mean cortical thicknesses were not different between both subgroups of controls according to the scan. We used both VOI and vertex-wise complementary methods.

In a hypothesis-driven VOI analysis, we studied gray matter volumes in the following specific regions of interest: (1) the hippocampi and entorhinal cortices, whose atrophy is associated with amnestic syndromes (2) the amygdala, which are affected in non-AD pathologies, especially in LATE [13], (3) the insula, which has also been associated with non-AD progressive amnesia [29]. Volumetric segmentation of the hippocampi, amygdala, entorhinal cortices and insula was automatically performed on the 3D T1-weighted MP-RAGE scans using FreeSurfer 6.0.0 longitudinal processing stream (http://surfer.nmr.mgh.harvard.edu/) [30]. The volume measures were normalized to the individual intracranial volume (IV).

Mean cortical thickness indices for 68 VOIs were also obtained. We visually inspected the FreeSurfer parcellation results to identify global segmentation abnormalities and performed manual edits of the brainmask (pial surface errors) or of the white matter volume (segmentation errors) when necessary.

We also studied cortical thickness without any pre-specified VOI by using FreeSurfer’s built-in statistical tools for vertexwise generalized linear models on the individual surfaces previously resampled into the common

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Table 1. Main demographic, clinical, imaging, and biological data at baseline for the patient and control groups (mean (SD)).

| Demographic data | Whole ASHT group n = 36 | SNAP n = 15 | AD n = 21 | Controls n = 30 |
|------------------|--------------------------|-------------|-----------|-----------------|
| Age (years)      | 72.9 (6.8)               | 77.5* (5.5) | 69.5 (5.6) | 68.8 (5.6)      |
| Sex (M/F)        | 16/20                    | 6/9         | 10/11     | 20/10           |
| Education (years)| 14.3 (4.2)               | 13.6 (4.7)  | 14.7 (3.9) | 12.7 (4.1)      |
| Disease duration (years) | 4.8 (3.4) | 4.2 (2.7)  | 5.2 (3.8) | –               |
| Functional status|                          |             |           |                 |
| CDR 0            | 0                        | 0           | 0         | 30              |
| CDR 0.5          | 26                       | 17          | 10        | 0               |
| CDR 1            | 10                       | 6           | 4         | 0               |
| Neuropsychological assessment |            |             |           |                 |
| Global cognitive efficiency | MMSE       | 24.5 (2.8)  | 24.1 (2.6) | 24.8 (2.9) 29.2 (0.9)* |
| Short term/working memory | Digit spans | 9.7 (1.8)   | 9.9 (2.2)  | 9.5 (1.6) 10 (1.3) |
| Episodic memory verbal | FCSRT (Free + total recall) | 33.3 (17)  | 36 (16.2)  | 31.4 (17.7) 80.2 (4.5)* |
| Free recall (48) | 9.1 (6.3)                | 9 (5.6)     | 9.2 (6.8) 32.7 (4)* |
| Total recall (48) | 24.2 (11.4)              | 27 (11.2)   | 22.1 (11.4) 47.4 (0.9)* |
| Sensitivity index (%) | 41.1 (21.7) | 48.4 (22.2) | 35.9 (20.2) 96.7 (5.1)* |
| Episodic memory visual | Rey memory (36) | 7.25 (5.1)  | 7.3 (5.4) 7.2 (5.1) 18.7 (5.5)* |
| Instrumental functions | Naming (80) | 77.7 (2.8)  | 78.5 (1.6) 77.1 (3.4)# 79.8 (0.5) |
| Rey copy (36)   | 34.4 (2.2)               | 34.7 (2.6)  | 34.1 (1.9) 35 (1.7) |
| Praxis (72)     | 69.1 (2.9)               | 69.6 (1.8)  | 68.7 (3.4) 71 (1.3) |
| Executive functions | TMT A (seconds) | 53.7 (16.6) | 54.5 (17.1) 53.1 (16.6) 39.8 (14.1) |
| TMT B-A (seconds) | 104.9 (63.3) | 106.5 (60.6) 103.7 (66.6) 37.9 (23.6)* |
| Letter Fluency 2 min | 18.2 (5.8)  | 16.1 (5.1)# 19.7 (5.9) 24.6 (7.1) |
| Category Fluency 2 min | 20.4 (6.4) | 20.9 (7.8)  | 20 (5.4) 35.5 (9.6)* |
| Similarities (WAIS) | 19.6 (4.4) | 20.7 (3.9)  | 18.9 (4.7)# 22.3 (3.4) |
| Social cognition | Emotion recognition (35) | 28.5 (3.4)  | 27.8 (3.3) 29 (3.5) 29.6 (2.3) |
| Negative emotions (fear, sadness, anger, disgust) (20) | 14.8 (2.8)  | 14.3 (2.9) 15.1 (2.7) 15.6 (2) |
| Faux pas test (40) | 30.4 (5.2)  | 30.9 (4.7)  | 30 (5.7) 35.1 (2.9)* |
| Behavioral changes | CBI-R (180) | 38 (19.4)   | 42.1 (19.9) 35.4 (19.1) – |
| Genetic status | ApoE genotype (n with at least one E4 allele) | 18 | 2 | 16 | 2 |
| Progranulin plasma level (μg/l) | 108.5 (26)  | 114.6 (20.2) 104.1 (29.1) 127.3 (25.5) |
| c9orf72 mutation | None | None | None | – |
| Molecular PET imaging | PiB PET GCI | 2.28 (0.9)  | 1.35 (0.2) 2.93 (0.6)* 1.25 (0.1) |
| n with GCI > 1.45 | 24 | 3 | 21 | 0 |
| Tau PET GCI | 1.54 (0.65)  | 1.15 (0.1) 1.81 (0.7) 1.23 (0.11) |
| MRI | Fazekas score (0/1/2/3) | 20/12/3/1 | 7/5/2/1 | 13/7/1/0 | 20/8/2/0 |
| Left HV | 1.78 (0.3)  | 1.64 (0.27) 1.88 (0.29) 2.48 (0.2)* |
| Right HV | 1.85 (0.34) | 1.68 (0.3) 1.97 (0.32) 2.51 (0.23)* |
| Left EC | 0.92 (0.32) | 0.82 (0.26) 0.99 (0.34) 1.36 (0.23)* |
| Right EC | 0.93 (0.27) | 0.91 (0.3) 0.94 (0.26)# 1.25 (0.23) |
| Left Amygdala | 0.66 (0.14) | 0.64 (0.15) 0.67 (0.13) 0.93 (0.13)* |
| Right Amygdala | 0.8 (0.16) | 0.79 (0.18) 0.82 (0.14) 1.13 (0.15)* |
| Left Insula | 3.88 (0.42) | 3.76 (0.45) 3.97 (0.38) 4.4 (0.47)* |
| Right Insula | 3.84 (0.5)  | 3.74 (0.64) 3.92 (0.36) 4.3 (0.46)* |

*ASHT amnestic syndrome of the hippocampal type, CDR Clinical Dementia Rating scale, MMSE Mini-mental state examination, FCSRT Free and Cued Selective Reminding Test, TMT Trail Making Test, WAIS Wechsler Adult Intelligence Scale, CBI-R revised version of the Cambridge Behavioural Inventory, ApoE Apolipoprotein E, PiB-GCI Pittsburgh compound B global cortical index, HV hippocampal volume, EC entorhinal cortex. All volumes are normalized to the intracranial volume.

*p < 0.05 vs the other groups  #p < 0.05 vs controls.
also underwent [18F]-Flortaucipir PET. Twenty patients underwent an injection of [18F]-Flortaucipir. Standard Uptake Value ratio (SUVr) was computed in all VOIs. Moreover, amyloid imaging with [11C]-PiB (36) and 13 controls also underwent [18F]-Flortaucipir PET. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipir. Twenty patients underwent a second tau PET exam after 2 years. MRI and PET scans were performed at least 40 to 60 min after injection of [11C]-PiB, and 80 acquisitions were performed at least 40 to 60 min after injection of [18F]-Flortaucipip.
patients who did not fulfill these criteria were considered as having a non-AD pathology (SNAP).

**Statistical analysis**

The data were analysed using R version 3.6.1 (R Core Team, 2017). Differences between groups at baseline were assessed using analysis of covariance (ANCOVA), with age and education (for neuropsychological variables) and age and sex (for MRI variables) as covariates, after verifying that the residuals were normally distributed. Longitudinal clinical, MRI and tau PET data were analysed using mixed-effect models accounting for the repeated nature of the measures and for missing data. Subjects were included as a random intercept in the model, and age and education (for clinical data) or age and sex (for MRI data) were included as covariates.

Post-hoc pairwise t-tests, adjusted with a Bonferroni correction, were performed to test differences in baseline and longitudinal clinical and imaging parameters between groups. The level of statistical significance was set at \( p < 0.05 \).

**RESULTS**

**Baseline classification and clinical-neuropsychological features of the sample**

When combining amyloid and tau PET status as defined above, the 36 patients were divided into 2 subgroups: AD patients \((n = 21)\) and SNAP patients \((n = 15)\). The SNAP patients were significantly older than the AD patients and controls.

Significant differences were found between each patient subgroup and controls for the MMSE, episodic memory scores, category fluency, Trail Making Test and Faux pas test. There were no statistically significant differences between SNAP and AD patients’ subgroups (Table 1). The individual analysis of the data did not show a clear qualitative difference between SNAP and AD patients, apart from a slight tendency for more abnormal category fluency scores in AD patients \((6/21 vs 3/15)\), and more abnormal facial emotion recognition scores in SNAP patients \((6/15 vs 3/21)\) (Supplementary Table 1).

The number of subjects with at least one ε4 allele of the ApoE gene was higher in the AD subgroup (Table 1).

**Baseline imaging features of the sample**

Individual PiB GCI and tau PET SUVr in all VOIs are detailed in Fig. 1.

In AD patients, in addition to the positivity of PiB-PET, tau positivity extended beyond the medial temporal regions. In the SNAP group, PiB-PET was negative in 12/15 patients. The 3 SNAP patients with positive amyloid PET had negative tau PET, including no significant uptake in the entorhinal cortices, amygdala,
the left hemisphere, and SNAP patients (in red) and AD patients (in blue) when compared to each other (clusterwise correction for multiple comparisons, p < 0.05); and C SNAP patients (in red) and AD patients (in blue) when compared to each other (medial view of the left hemisphere and lateral view of the right hemisphere, p < 0.001, uncorrected).

Vertexwise comparison of the symmetrized percent change of cortical thickness controlled for age after 2 years showed a higher decrease in SNAP patients compared with controls (clusterwise correction for multiple comparisons, p < 0.05); and F SNAP patients (in red) and AD patients (in blue) when compared to each other (clusterwise correction for multiple comparisons, p < 0.05 in the left hemisphere, and p < 0.001, uncorrected in the right hemisphere).

parahippocampal or fusiform gyri. We found positive tau tracer binding restricted to the entorhinal cortices and/or amygdala in 5 (amyloid negative) SNAP patients (Figs. 1 and 2).

SNAP and AD groups had significantly lower hippocampal, entorhinal, amygdala, and insula volumes than the controls. There was no statistically significant difference between SNAP and AD subgroups (Table 1).

The vertexwise comparison of cortical thickness between patients and controls showed a significant decrease in the frontal lobes (superior and middle frontal gyri) in SNAP patients and in the temporo-parietal and frontal lobes in AD patients. The direct comparison between SNAP and AD patients showed lower (uncorrected) baseline cortical thickness in the frontal cortex in SNAP patients and in the posterior (temporal and occipital) cortex in AD patients (Fig. 3).

**Longitudinal clinical-neuropsychological analysis**

The decrease of the MMSE, verbal episodic memory, and naming scores was significantly higher in AD (n = 20 at one year and 18 at 2 years) than in SNAP (n = 12 at one year and 10 at 2 years) patients (p = 0.04, 0.01, and 0.03, respectively) (Fig. 4). There were no other significant differences. The individual analysis of the data also showed a higher number of patients whose naming score became abnormal during follow-up in the AD group (9/20 vs 2/12). We also found the same trend for letter fluency (6/20 vs 2/12) and the similarities subtest of the WAIS (5/20 vs 1/12). There was no difference regarding social cognition scores (Supplementary Table 1).

**Longitudinal MRI analysis**

The decrease of hippocampal volumes was higher in AD (n = 17) than in SNAP (n = 10) patients (p = 0.007 for the right hippocampus and p = 0.025 on the left side) (Fig. 4). There was no significant difference regarding the progression of entorhinal, amygdala or insula atrophy.

The vertexwise comparison of the symmetrized percent change of cortical thickness after 2 years showed a significant decrease in the temporal lobes for AD patients compared with controls (n = 28). The (uncorrected) comparison between SNAP patients and controls showed spots of decreased cortical thickness in the frontal lobes. The comparison between AD and SNAP patients showed a cluster of decreased cortical thickness in the left superior temporal gyrus in AD patients and (uncorrected) spots in the frontal lobes in SNAP patients (Fig. 3).

**Longitudinal tau PET imaging**

Eight SNAP patients and 12 AD patients underwent a second tau PET exam after 2 years. Tau tracer binding remained stable in all VOIs in SNAP patients, even in those with initially elevated binding in the entorhinal cortices and amygdala, while it globally increased in AD patients. We found a significantly higher increase of tracer binding in AD patients than in SNAP patients in the middle temporal gyri (p = 0.04) and in the parietal lobes (p = 0.025). We also found differences in the fusiform (p = 0.026), as well as inferior (p = 0.008), and superior (p = 0.01) temporal gyri and in the frontal lobes (p = 0.03), which did not persist after correction for multiple comparisons (Fig. 5, Supplementary Table 2).

**DISCUSSION**

By coupling amyloid and tau PET imaging in a clinically homogeneous cohort of 36 patients with ASHT, we aimed to identify AD and SNAP patients according to their molecular signatures and investigate their clinical and imaging trajectories after 2 years of follow-up.

We found that: (i) an important proportion of patients did not meet the molecular definition of AD and were thus classified as SNAP, with some of them having tau tracer binding limited to the entorhinal cortices and/or amygdala without amyloid deposition; (ii) SNAP patients were older and showed a lower ApoE ε4 allele frequency than AD patients but both groups had comparable isolated ASHT and a similar degree of medial temporal atrophy at baseline; (iii) disease progression differed in SNAP and AD patients regarding cognitive profile, brain atrophy and tau deposition patterns.

Only two studies with small sample sizes have so far explored the in vivo molecular signature of amnestic patients using both amyloid and tau PET imaging [24, 25]. Contrary to our work, the authors studied tau binding in a unique temporal meta-VOI, which includes entorhinal, parahippocampal, fusiform cortices and inferior and middle temporal gyri (defined by Jack et al. [39]). Using both amyloid (global cortical index) and tau positivity in the
temporal meta-VOI as a molecular definition of AD, 62% (15/24) of patients met the criteria for AD. As they were tau negative in the temporal meta-VOI, the other patients were considered as SNAP by the authors despite positive amyloid PET in some of them. Nevertheless, we cannot rule out a circumscribed tauopathy in the limbic regions suggestive of AD in these amyloid-positive amnestic patients. In addition, no longitudinal data were available.

In order to avoid any misinterpretation in the assessment of tau tracer uptake, we preferred to measure tau binding in selective regions corresponding to the earliest Braak stages within the medial temporal lobes rather than considering only one larger temporal meta-VOI. By doing this, we aim at identifying circumscribed tau deposits in areas involved in episodic memory both in amyloid-positive (early AD) and amyloid-negative (SNAP) patients.

In addition, we used strict inclusion criteria, i.e., ASHT without any other neurological or psychiatric signs, to avoid bias in the interpretation of the results. By investigating patients without an AD signature, we aimed to explore limbic predominant non-Alzheimer’s pathology, which is one major source of misdiagnosis in ASHT [9, 24].

We found that 42% of our patients with ASHT did not have an AD molecular signature and were therefore classified as SNAP. This result is consistent with neuropathological and previous imaging studies showing that an ASHT mimicking AD can be found without any amyloid or tau lesions [23, 24, 40]. In these conditions, the most frequent underlying pathologies are hippocampal sclerosis of ageing (most often associated with TDP-43 lesions), LATE neuropathological change (LATE-NC), and PART. The other possible aetiologies, such as Lewy body dementia, are less likely due to our strict clinical inclusion criteria.

LATE-NC is defined by a stereotypical TDP-43 pathology with or without hippocampal sclerosis [12, 13, 25]. The estimated prevalence reaches 30% among subjects autopsied past 80 years of age and increases with advanced old age [12, 13]. Interestingly, in our cohort, SNAP patients were indeed older than AD patients. Many subjects with LATE-NC have comorbid brain pathologies, often including amyloid plaques, which could be the case in our 3 amyloid-positive SNAP patients [13]. In general, the co-occurrence of different brain lesions, whether of the AD type, other proteinopathies (particularly TDP-43 or alpha-synuclein, which are often associated with AD), or vascular lesions, is a frequent finding in aged samples [41] and further complicates the in vivo characterization of the aetiology. In addition, the diagnosis of LATE is difficult to confirm in the absence of TDP-43-specific biomarkers [13].

In a subset of SNAP patients (n = 5/15), we observed a circumscribed tau tracer retention in the entorhinal cortices and amygdala, clearly distinct from the more extensive pattern of tau binding observed in AD. Even if the sensitivity of Flortaucipir for

Fig. 4 Evolution of the cognitive scores and hippocampal atrophy. Temporal diagrams representing the evolution of the verbal episodic memory score (sum of the free and cued recalls of the FCSRT) (A), MMSE score (B), and naming score (C) at baseline and after 1 and 2 years of follow-up and the evolution of the left (D) and right (E) hippocampal volumes at baseline and after 2 years of follow-up in each patients’ group and controls. The ribbons represent the 95% confidence interval. Boxplots with individual points for each group are shown. The black point represents the mean value for each group.
non-AD tauopathies has been questioned, elevated tracer retention compared to controls has been found in areas with non-Alzheimer tau pathology at autopsy [42]. This pattern of restricted tau tracer binding in the medial temporal cortex in the absence of amyloid pathology could therefore be suggestive of PART [43], a recently defined neuropathological category characterized by tau aggregates and neuronal loss in the medial temporal lobes without amyloid plaques [14]. In autopsy studies, PART occurs in 20–25% of individuals older than 90 years [16]. The cognitive presentation seems variable and remains under discussion [16]. Our results suggest that PART could be more frequent than previously thought before the age of 90 and could lead to ASHT.

The specificity of the tau PET radiopharmaceuticals has been discussed. Some Flortaucipir binding to the TDP-43 protein underlying FTD has been described in semantic dementia [44]. However, our amyloid-negative patients with increased tau binding had no semantic deficit, and binding to the TDP-43 protein underlying FTD would extend beyond the medial temporal lobes, which was not the case. Off-target binding, as observed in the basal ganglia or the hippocampi due to their close vicinity to the choroid plexus, is unlikely in the regions we have considered.

At baseline, SNAP and AD patients had identical cognitive profiles characterized by an isolated ASHT and a similar degree of medial temporal lobe atrophy, as previously described in HS and LATE with autopsy confirmation [12, 13]. We did not find any neuropsychological difference between both subgroups, apart from a qualitative trend towards more abnormal facial emotion recognition scores in the SNAP group, which was not confirmed for the faux-pas test and therefore does not clearly point to a characteristic social cognition deficit in these patients, as has been described recently [45]. Medial temporal lobe atrophy was slightly more pronounced in SNAP patients, in accordance with previous publications, perhaps due to their older age [5, 13]. This was not the case only in the hippocampi but also in the entorhinal cortices and amygdala, which has been thought to represent an “incubator” for misfolded proteins [46]. Nevertheless, we found differences in the cortical atrophy patterns between SNAP and AD, with predominant frontal involvement in SNAP, as has been reported in hippocampal sclerosis and TDP-43 proteinopathies [13, 47–50], and predominant temporoparietal involvement in AD, as expected.

After 2 years of follow-up, we observed distinct cognitive trajectories, with greater episodic memory and language decline in AD than in SNAP. Even if the cognitive trajectories in our SNAP patients were less homogeneous than in the AD group, probably due to heterogeneous underlying mechanisms, our results are in accordance with previous work on PART and HS [15–17, 49, 51]. We did not find a more pronounced decline in executive functions or social cognition in SNAP patients, contrary to what might have been expected [45].

The longitudinal MR imaging analysis showed a greater progression of hippocampal atrophy in AD than in SNAP, which was not reported in a previous work that found a similar atrophy progression [15]. However, in the latter study, the patient classification was performed without tau-PET imaging. In our cohort, the decline of cortical thickness also differed between AD and SNAP patients, with pronounced changes in the temporal lobes in AD patients and a more subtle decrease predominating in the frontal cortex in SNAP patients.

The longitudinal tau PET imaging after 2 years reinforces the distinction between the AD and SNAP groups by showing an increase of tau binding in AD patients, especially in the parietal and temporal cortices, which contrasts with the stability of tau binding in SNAP patients, including those with positive PiB-PET. Circumscribed medial temporal tau tracer binding was confirmed in the patients with suspected PART who underwent longitudinal tau-PET, without any cortical extension. This is in agreement with a non-AD diagnosis and with the slower disease progression observed [51].
Our study has several limitations, especially the relatively small sample size with missing data in the longitudinal analysis, and the lack of neuropathological confirmation. However, the longitudinal clinical and imaging data strengthen the distinction between AD and non-AD pathological processes. The small numbers of subjects in the different supposed SNAP subgroups make it difficult to account for subtle differences related to the clinical heterogeneity of this entity, which could help to tease apart the different aetiologies of SNAP. The presence and potential role of copathologies in AD patients is also difficult to determine in the present cohort, although this probably has important consequences on the clinical presentation and cognitive progression.

Following the description of HS of ageing, LATE-NC and PART, it appears necessary to increase our understanding of the pathological processes leading to ASHT in order to better target new disease modifying therapies. By coupling amyloid and tau-PET with longitudinal follow-up, we found distinct in vivo molecular signatures, which have consequences on clinical and atrophy progression. Longitudinal clinical and PET imaging data in larger cohorts will be important to improve our ability to determine the in vivo molecular diagnosis of this misleading cognitive profile, which is the only way to develop curative treatments.

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AUTHOR CONTRIBUTIONS
This study was conceived and designed by JL, MS, MB. Data were acquired by JL, PO, 
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MT, MB, and MS. Drafting of the manuscript was conducted by JL, MB, and MS. Critical 
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Correspondence and requests for materials should be addressed to Julien Lagarde 
or Marie Sarazin.

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