Tau PET imaging and cognitive performance in Alzheimer's Disease: a biomarker of subthreshold neurodegeneration?

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Introduction

Recent literature suggests a significant association in Alzheimer's Disease (AD) between **tau burden** measured *in vivo* with positron emission tomography (PET), and **cognitive dysfunctions**. However, previous studies on this matter are marked by a high heterogeneity in patient characterization from a clinical (e.g., typical and atypical patients) and biomarker (e.g., amyloid positive and negative subjects) point of view. Besides, the link between tau-pathology and cognitive profile within the AT(N) framework is still unexplored. The aim of this study is to evaluate the association between tau burden, evaluated with 18F-flortaucipir PET and cognitive performances in a sample of patients in the AD continuum and to assess the effect of tau positivity (T) on cognitive performance in subjects classified as negative to structural neurodegeneration (N).

Methods

Fifty-seven subjects positive at amyloid PET, were prospectively recruited at Geneva University Hospitals (HUG). Subjects performed an in-depth neuropsychological evaluation, a 3T magnetic resonance imaging (MRI), and 18F-flortaucipir PET scan. Whole-brain analyses on 18F-flortaucipir PET images were performed to correlate the neuropsychological performance at specific cognitive tasks with 18F-flortaucipir retention. Clinical, cognitive and imaging features were compared in subjects classified as A+T+N- and A+T-N-.

Table 1. Demographic and clinical features of the sample

	Cognitively unimpaired	Cognitively impaired
Demographics		
F/M	5/3	23/26
Age in years	70.6±6.6	75.7±5.9
Years of education	15.7±4.1	13.9±3.6
Clinical		
CDR global score (median [IQ range])	0 [0-0]	0.5 [0.5-1]
Disease duration in months	30.2±38.9	33.7±31.9
MMSE score	28.6±0.9	25.6±3.1
Ten-point Clock test	9.8±0.4	8.3±2.1
FCSRT_ Immediate Free Recall	28.2±4.7	11.0±7.8
FCSRT_ Immediate Total Recall	44.5±2.7	28.1±13.8
FCSRT_ Delayed Free Recall	11.3±2.9	5.2±3.4
FCSRT_ Delayed Total Recall	15.4±1.1	11.5±2.9
Verbal fluency on semantic cue	19.0±4.6	14.5±5.9
Verbal fluency on phonemic cue	16.7±7.5	15.2±6.6
Trial Making Test – part A	48.1±10.7	58.9±33.1
Trial Making Test – part B	102.1±23.2	146.0±77.8
Trial Making Test – part B-A	54.0±20.4	95.8±70.2
Imaging biomarkers		
White-matter hyperintensities	3.5±1.4	7.0±7.0
Medial temporal atrophy scale Left (median [IQ range])	0.5 [0-1]	1 [1-2]
Medial temporal atrophy scale Right (median [IQ range])	1 [0-1]	1 [1-2]
18F-flutemetamol SUVR (cut-off 0.6, n = 22)	0.78±0.25	0.72±0.11
18F-florbetapir SUVR (cut-off 1.1, n = 35)	1.3±0.2	1.5±0.2
18F-flortaucipir SUVR (cut-off 1.24)	1.2±0.1	1.4±0.2

Results

Lower mnestic performance was found to be significantly associated to temporo-parietal regions, while visuo-constructive abilities to tau deposition in a left cluster extending from the superior temporal cortex, to the inferior parietal lobule. Tau deposits in these regions, as well as the inferior temporal gyrus, the fusiform gyrus and the precuneus, were also associated to low performance at the verbal fluency task on semantic cue. Finally, low performance in spatial exploration was significantly associated to 18F-AV1451 tracer binding in a right cluster including the inferior and middle frontal gyrus. A+T+N- patients showed lower performance on verbal memory compared to A+T-N-.

Conclusions

Our results confirm the regional specificity of the association between tau deposition and performance in different cognitive domains, supporting the direct association between 18F-Flortaucipir retention and cognition in the AD spectrum. In subjects without a detectable structural neurodegeneration, tau positivity might represent an early marker of **subthreshold neurodegeneration**.

Figure 1. Association between tau deposition and cognitive performance

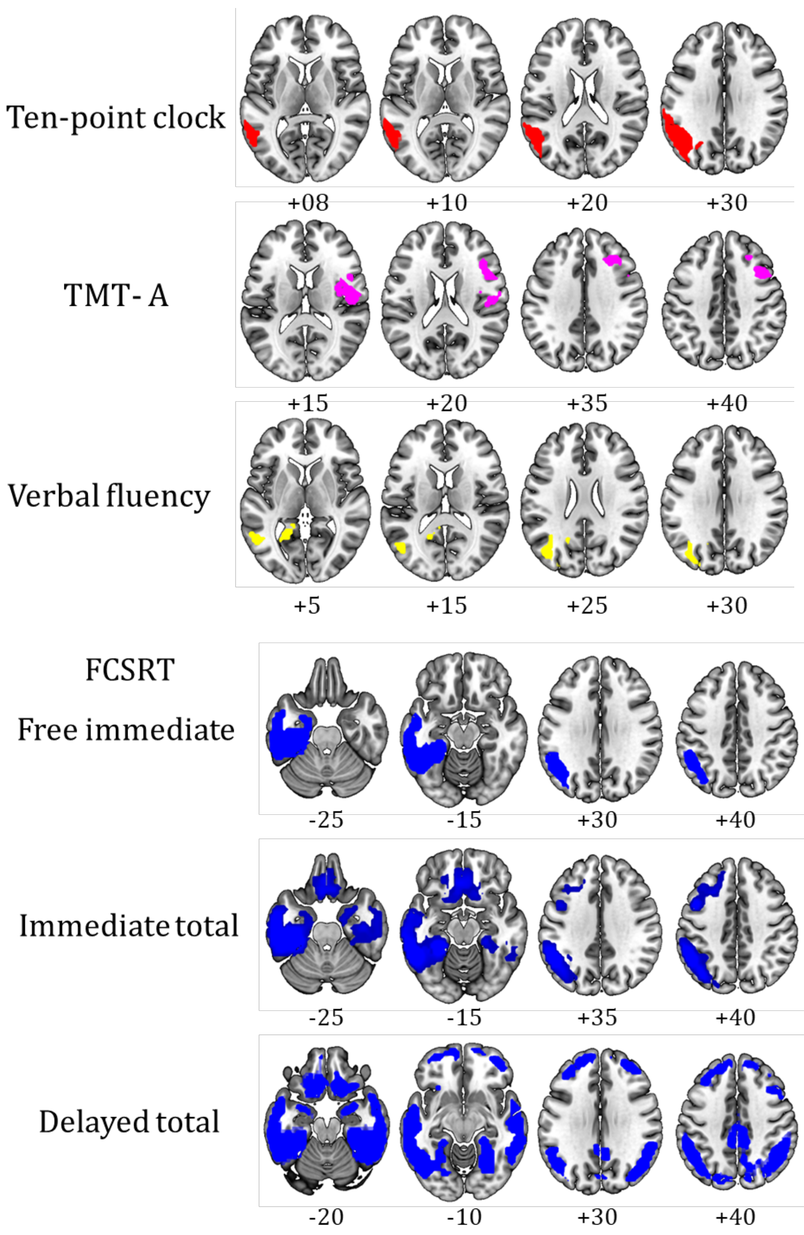

Table 2. Comparison between A+T+N- and A+T-N- subgroups

	T- (n=15)	T+ (n=25)	Statistics
F/M	7/8	16/9	n.s.
Age in years	75.0±7.2	75.9±5.2	n.s.
Years of education	13.1±4.6	13.7±3.4	n.s.
Clinical			
CDR global score (median [IQ range])	0.5 [0-0.5]	0.5 [0.5-0.5]	n.s.
Disease duration (months)	15 [6-39]	22 [12-36]	n.s.
MMSE score	28 [25-29]	27 [25-28]	n.s.
Ten-point Clock test	10 [8-10]	9 [8.25-10]	n.s.
FCSRT_ Immediate Free Recall	19 [11.5-28.25]	12 [5.5-20.5]	n.s.
FCSRT_ Immediate Total Recall	41 [36-43]	30 [23.75-44.25]	n.s.
FCSRT_ Delayed Free Recall	**9 [4.75-12.75]**	**6.5 [3-8]**	**p<0.05**
FCSRT_ Delayed Total Recall	**15 [14-16]**	**10 [9-15]**	**p<0.05**
Verbal fluency on semantic cue	16 [14.5-19]	14 [12-20]	n.s.
Verbal fluency on phonemic cue	16 [5.75-20.75]	19 [13-21]	n.s.
Trial Making Test – part A	49 [42.75-66.75]	49 [43-66]	n.s.
Trial Making Test – part B	127 [106-171]	107 [91-173]	n.s.
Trial Making Test – part B-A	74 [57-124.5]	68 [49-130]	n.s.
Imaging biomarkers			
White-matter hyperintensities	5 [2-11]	4 [3-5]	n.s.
Medial temporal atrophy scale Left	1 [0-1]	1 [0-1]	n.s.
Medial temporal atrophy scale Right	1 [0-1]	1 [0-1]	n.s.
Normalized angular gyrus GM	2.1±0.2	2.1±0.2	n.s.
Normalized superior parietal gyrus GM	1.7±0.2	1.7±0.1	n.s.
Normalized Precuneus GM	2.2±0.2	2.2±0.2	n.s.
Normalized Superior Temporal gyrus GM	2.1±0.2	2.1±0.2	n.s.
Normalized hippocampus GM	2.4±0.4	2.3±0.2	n.s.

Reference

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