Early-phase ^{18}F-Florbetapir and ^{18}F-Flutemetamol images as proxies of brain metabolism in a memory clinic setting

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1. MRI acquisition

The following acquisition parameters were used: repetition time [TR] = 1930 ms, echo time [TE] = 2.36 msec, field of view = 256 x 256 mm, flip angle = 8°, slice thickness = 0.9 mm, matrix size = 288 x 288 pixels. Or a high-resolution anatomical 3D T1 was acquired on a 3 Tesla MR750w scanner (GE Healthcare, Milwaukee, Wisconsin) with the following parameters: matrix size = 254 x 254, slices = 178, 1mm isotropic, TR = 7.2 ms.

2. PET acquisition

All scanners were from the same vendor and of the same generation, harmonized regarding their performance and reconstructions, and cross-calibrated.

^{18}F-FDG-PET - ^{18}F-FDG-PET was performed according to the European Association of Nuclear Medicine (EANM) guidelines (*1*,*2*). Subjects fasted for at least 4 hours. Before radiopharmaceutical injection, blood glucose was checked and was 7mmol/L or less for all subjects. Subjects were injected with 203.89±15.62 MBq of 18F-FDG via a venous cannula, eyes open in a dimly lit room. The required minimum time interval between injection and scan start was 30 minutes. The scanning time lasted 20 minutes. Data were acquired in list mode and were reconstructed using 3D OSEM 6 interactions 8 subsets, and a 2mm Gaussian filter at Full Width and Half Maximum, resulting in images with 400x400 matrix with 1.01mm isotropic voxels.

Amyloid-PET - ^{18}F-FBP late images were acquired 50 min after the intravenous administration of 210±18.77 MBq (3 × 5-min image frames). ^{18}F-FMM late images were acquired 90 min after the intravenous administration of 166±16.73 MBq (4 × 5-min image frames). Images were then averaged into a single 15- or 20-minutes frame. All amyloid-PET late images were visually assessed by an independent, board-certified specialist in nuclear medicine (VG) applying the standard operating procedures approved by the European Medicines Agency (https://www.ema.europa.eu/documents/product-information/vizamyl-epar productinformation_en.pdf;https://www.ema.europa.eu/documents/product-information/amyvid-epar-

product-information_en.pdf). Subjects were classified based on the visual inspection of the late images into "Aβ+" or "Aβ-" (i.e., subjects that presented high levels and low levels of cortical amyloid binding, respectively).

Data were acquired in list mode and were reconstructed using 3D OSEM 4 interactions 8 subsets, and a 2mm Gaussian filter at Full Width and Half Maximum, resulting in images with 400x400 matrix with 1.01mm isotropic voxels.

3. MRI and PET normalization processing

MRI 3D T1 sequences were aligned to a reference plane passing through the anterior commissure, segmented into gray matter, white matter, and cerebrospinal fluid tissue compartments, and normalized to the Montreal Neurologic Institute (MNI) space using tissue probability maps. 18F-^{18}F-FDG and eFBP/eFMM images were aligned to the subject's respective T1 MRI image and normalized to the MNI space using the transformation matrix that was generated during the registration of the MRI images to the standard space. PET images were spatially smoothed with an isotropic 3D 8mm Gaussian kernel (Full Width and Half Maximum).

4. Dice similarity coefficient

We compared the resulting hypometabolism and hypoperfusion maps using the Dice as a measure of concordance. Dice coefficient for binary maps A and B is defined as:

$$Dice = \frac{2 * (A \cap B)}{A + B}$$

It takes the value of 1 if A and B assume the same logical value in every pixel (high concordance), and a value of 0 if they always disagree (null concordance). It is interpreted as follows: <0.2, poor; 0.2–0.4, fair; 0.4–0.6, moderate; 0.6–0.8, good; and >0.8, excellent agreement (*3*). In addition to the whole-brain voxel-by-voxel concordance, an ROI-based Dice coefficient was calculated to measure the ^{18}F-FDG and eFBP/eFMM agreement only in core areas of AD-related metabolic impairment (*4*,*5*).

5. Visual assessment of ^{18}F-FDG-PET and eFBP/eFMM uptake distribution images

Before applying SPM analyses, ^{18}F-FDG-PET and eFBP/eFMM uptake distribution images (standard images) were visually inspected by nuclear medicine experts (DP and VG). Images were classified into patterns suggestive of neurodegenerative conditions or the presence of neurodegeneration was excluded. All images were visually inspected at the individual level to define the visual agreement between metabolism and perfusion. The classifications of ^{18}F-FDG-PET uptake distribution images were consistent with early-phase ones for 76% of subjects at visual assessment. Supplemental table 1 shows the rate of ^{18}F-FDG-PET images and early-phase images as measured by visual assessment in the whole sample. 30 out of 124 subjects (24%) showed a mismatch between ^{18}F-FDG-PET and eFBP/eFMM images' classification. A chi-square test of independence was performed to examine the statistics between match/mismatch and the visual classification of uptake distribution images and SPM maps. The result was significant (χ2=5.23, p-value=0.022), indicating that the number of mismatches was higher using the visual classification of uptake distribution images compared to the SPM maps.

Comparing the visual assessment of ^{18}F-FDG-PET uptake distribution images and SPM hypometabolic maps (Supplemental table 2), we found significantly more normal scans with ^{18}F-FDG-PET uptake distribution images (N of normal scans=65) compared to the SPM maps (N of normal scans=32) (χ^2=18.43, p-value<0.05). Notably, with the visual assessment of ^{18}F-FDG-PET uptake distribution images, no DLB-like patterns were identified and only 3 limbic-predominant patterns were identified compared to 14 that emerged with SPM analyses (Supplemental table 2).

Comparing the visual assessment of eFBP/eFMM uptake distribution images and SPM hypoperfusion maps (Supplemental table 3), we found significantly more normal scans with the former (N of normal scans=68) compared to the SPM maps (N of normal scans=32) (χ^2=21.71, p-value<0.05). Notably, with the visual assessment of eFBP/eFMM uptake distribution images, no DLB-like or limbic-like patterns were identified. Fewer neurodegenerative patterns (AD-like and FTD-like) were identified with eFBP/eFMM uptake distribution images' classification compared to SPM one (Supplemental table 3).

Overall, these results highlight the added value of SPM maps to visual classification both for early perfusion and ^{18}F-FDG-PET images. Visual assessment of PET uptake distribution images raises the

issue of possible false negatives. It is more difficult to identify neurodegenerative patterns without SPM maps with both tracers (^{18}F-FDG and eFBP/eFMM). These results are in agreement with a previous study, showing that SPM-based tool for the analysis of ^{18}F-FDG-PET imaging has shown high diagnostic accuracy (sensitivity=96%; specificity=84%) in clinical settings compared to visual inspection of ^{18}F-FDG-uptake distribution (78% and 50%) (*6*). The importance of a voxel-based statistical comparison with healthy controls is here further supported for the interpretation of early-phase of amyloid-PET imaging.

6. Single-subject early FBP/FMM and ^{18}F-FDG patterns in different clinical stages

CU– 18 out of 30 subjects (60%) showed negative ^{18}F-FDG-PET scans for neurodegenerative patterns and 17 of them (94%) consistently showed also negative eFBP/eFMM scans. Almost all positive scans showed a good visual agreement between ^{18}F-FDG and eFBP/eFMM maps, showing AD-like (N=4), limbic-like (N=1), and unclassified (N=7) patterns. Among the 12 individuals with positive findings, Dice indicated poor-to-fair agreement between hypoperfusion and hypometabolism maps only in 3 subjects (0>Dice>0.4), whereas 9 out of 12 subjects (75%) showed a moderate-to-good concordance (0.4<Dice>0.8). Among the 3 subjects with low Dice, the hypometabolism maps showed more extensive abnormalities than corresponding hypoperfusion maps except for one case where the deficit was more extensive on the eFBP map than the ^{18}F-FDG one, associated with severe atrophy and vascular lesions visible on T1-weighted MRI.

MCI - 14 out of 73 subjects (19%) showed negative ^{18}F-FDG-PET maps for neurodegenerative patterns and 12 of them (85%) consistently presented negative eFBP/eFMM maps. As for the 59 positive ^{18}F-FDG-PET scans, suggesting different underlying neurodegenerative etiologies (Table 3), 50 of them presented a good visual agreement with eFBP/eFMM maps, whereas 9 were mismatched. For all mismatches between ^{18}F-FDG and eFBP/eFMM, the hypometabolism maps were more clearly defined and extended than hypoperfusion ones.

Dice scores indicated a moderate-to-good degree of overlap in most MCI cases (50 out of 73 subjects (68%) with 0.4<Dice<0.8; Dice average= 0.48 and 0.55 for Aβ+ MCI and Aβ- MCI, respectively)

(Figure 2). However, within the MCI group there was variability, with subjects presenting limited overlap between ^{18}F-FDG and eFBP/eFMM: one Aβ- MCI subject presented a Dice of 0.22 and an unclassified hypometabolism pattern and 9 Aβ+ MCI subjects presented a poor-to-fair agreement with a Dice score lower than 0.4 and hypometabolism patterns classified as AD-like, limbic-like, and unclassified.

Dementia – The hypometabolism patterns of 21 patients with dementia supported neurodegenerative conditions, mostly AD-like patterns (Table 3). In 18 out of 21 patients (85%) the eFBP/eFMM patterns matched the hypometabolism maps according to the visual agreement. Patients with ADD, in addition to having an extended pattern with both tracers, also showed good voxel-by-voxel concordance as measured by Dice scores between hypometabolism and hypoperfusion maps (Dice average=0.62) (Figure 2) with an agreement of 0.65 in AD-related regions. Notably, only 2 out of 13 ADD patients showed Dice scores indicating poor overlap (0.24-0.34) with hypometabolism patterns more extended than the hypoperfusion ones. As for the 3 Aβ- cases with dementia, the hypometabolism and hypoperfusion patterns were consistently suggestive of other neurodegenerative etiologies (FTD-like) or unclassified patterns (Figure 2) (Dice average= 0.46).

Table 1 The contingency table reporting the visual classification of FDG-PET and eFBP/eFMM uptake distribution images

FDG-PET uptake distribution images classification	**eFBP/eFMM uptake distribution images classification**						
	AD-like	***FTD-like***	***DLB-like***	***limbic- like***	***Unclassified***	***Normal***	**Total FDG-PET uptake distribution images**
AD-like	18	0	0	0	9	3	**30**
FTD-like	0	4	0	0	3	2	**9**
DLB-like	0	0	0	0	0	0	**0**
limbic-like	0	0	0	0	1	2	**3**
Unclassified	0	0	0	0	14	3	**17**
Normal	1	1	0	0	5	58	**65**
Total eFBP/eFMM-PET uptake distribution images	**19**	**5**	**0**	**0**	**32**	**68**	**124**

Abbreviations: AD= Alzheimer disease, FTD= frontotemporal disease, DLB= Lewy bodies disease

Table 2 The contingency table reporting the distribution of the SPM hypometabolic patterns and the FDG-PET uptake distribution images

SPM hypometabolic patterns classification	**FDG-PET uptake distribution images classification**						
	AD-like	*FTD-like*	*DLB-like*	*limbic-like*	*Unclassified*	*Normal*	**Total SPM hypometabolic patterns**
AD-like	24	1	0	1	4	9	**39**
FTD-like	1	4	0	0	3	2	**10**
DLB-like	1	1	0	0	0	1	**3**
limbic-like	0	1	0	1	1	11	**14**
Unclassified	3	2	0	0	7	14	**26**
Normal	1	0	0	1	2	28	**32**
Total FDG-PET uptake distribution images	**30**	**9**	**0**	**3**	**17**	**65**	**124**

Abbreviations: AD= Alzheimer disease, FTD= frontotemporal disease, DLB= Lewy bodies disease

Table 3 The contingency table reporting the distribution of the SPM hypoperfusion patterns and the early-phase uptake distribution images

SPM hypoperfusion patterns classification	**eFBP/eFMM uptake distribution images classification**						
	AD-like	***FTD-like***	***DLB-like***	***limbic-predominant***	***Unclassified patterns***	***Normal scans***	**Total SPM hypoperfusion patterns**
AD-like	16	0	0	0	9	7	**32**
FTD-like	0	3	0	0	5	3	**11**
DLB-like	1	0	0	0	0	1	**2**
limbic-predominant	1	0	0	0	4	14	**19**
Unclassified patterns	1	2	0	0	10	15	**28**
Normal scans	0	0	0	0	4	28	**32**
Total eFBP/eFMM uptake distribution images	**19**	**5**	**0**	**0**	**32**	**68**	**124**

Abbreviations: AD= Alzheimer disease, FTD= frontotemporal disease, DLB= Lewy bodies disease

Table 4 Discriminative ability of early FBP/FMM and FDG SUVR based on the AUC of the ROC curves to differentiate between A+/N+ AD patients versus healthy controls

	Whole sample			FBP group			FMM group		
ROIs	**FDG SUVR**	**Early AMY SUVR**	**DeLong Test**	**FDG SUVR**	**Early FBP SUVR**	**DeLong Test**	**FDG SUVR**	**Early FMM SUVR**	**DeLong Test**
Left Angular ROI	0.919 [0.860-0.977]	0.870 [0.786-0.955]	*p= 0.182*	0.937 [0.871-1]	0.960 [0.912-1]	*p= 0.431*	0.862 [0.723-1]	0.755 [0.556-0.953]	*p= 0.086*
Left Temporal ROI	0.831 [0.740-0.923]	0.789 [0.685-0.892]	*p= 0.198*	0.841 [0.727-0.956]	0.850 [0.742-0.958]	*p= 0.777*	0.836 [0.690-0.982]	0.698* [0.492-0.905]	*p= 0.060*
Posterior Cingulate	0.818 [0.724-0.912]	0.784 [0.680-0.888]	*p= 0.563*	0.784 [0.655-0.912]	0.773 [0.643-0.904]	*p= 0.863*	0.882 [0.757-1]	0.846 [0.691-1]	*p= 0.717*
Right Angular ROI	0.842 [0.755-0.929]	0.761 [0.651-0.872]	***p= 0.036***	0.870 [0.771-0.97]	0.784 [0.655-0.912]	***p= 0.044***	0.790 [0.620-0.961]	0.744 [0.543-0.946]	*p= 0.464*
Right Temporal ROI	0.712 [0.599-0.826]	0.618* [0.492-0.743]	***p= 0.012***	0.753 [0.616-0.890]	0.587* [0.427-0.747]	*p= 0.156*	0.612* [0.392-0.832]	0.658* [0.448-0.868]	*p= 0.367*

Results are presented as ROC AUC values [95% confidence intervals]
** marks the AUC values that do not reach the threshold of significance (p<0.05)*
The significant p-values resulted from DeLong test are reported in bold and italics; The null hypothesis of DeLong test is that the two AUCs are equal. When the threshold of significance is reached, we can reject the null hypothesis and conclude that there is a statistically significant difference between the two AUCs.
Abbreviations: FBP= florbetapir, FMM= flutemetamol, SUVR = Standardized uptake value ratios, ROIs = regions of interest, A= amyloid; N= neurodegeneration; AD= Alzheimer's disease

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