Supplementary Material

Visually Identified Tau ^{18}F-MK6240 PET Patterns in Symptomatic Alzheimer's Disease

Extended visual classification approach

Tau ^{18}F-MK6240 PET scans were viewed using MedView (version 12) display in white-black scale. It was left to the operator to set the intensity to the level of their choice. A color-scale was not used.

To visually rate tau in the mesial temporal lobe (MTL), raters evaluated the scan by sequentially:

1. Setting the axial plane to the middle of the orbital sockets (at the level of the entorhinal cortex and parahippocampal gyrus), then moving superiorly, reviewing each slice for the presence or absence of tracer retention within the mesial temporal lobe.

2. Setting the sagittal plane to the mid-sagittal slice, then moving laterally, reviewing each slice for tracer retention in MTL regions including entorhinal cortex, amygdala, hippocampus and parahippocampal gyrus.

3. Setting the coronal plane to the middle of the orbital sockets, then moving posteriorly, reviewing each slice for tracer retention in MTL regions, particularly at the level of the clivus.

To visually rate tau in the cortex, raters evaluated the scan by sequentially:

1. Selecting the axial sequences and reviewing each slice superiorly to inferiorly for the presence or absence of tracer binding in the following regions: parietal cortex, occipital cortex, posterior cingulate/ precuneus, frontal cortex, inferior and temporal cortex.

2. Verifying the presence or absence of tau in cortical regions on sagittal and coronal sequences.

In the training phase, for select cases, participants' spatially normalized ^{18}F-MK6240 PET scans were overlaid on their T1-weighted MRI sequence to differentiate between MTL retention and off-target binding around the clivus. However, aside from the training phase, MRI sequences were not required.

Supplementary Figure 1. Cerebellar cortex reference region
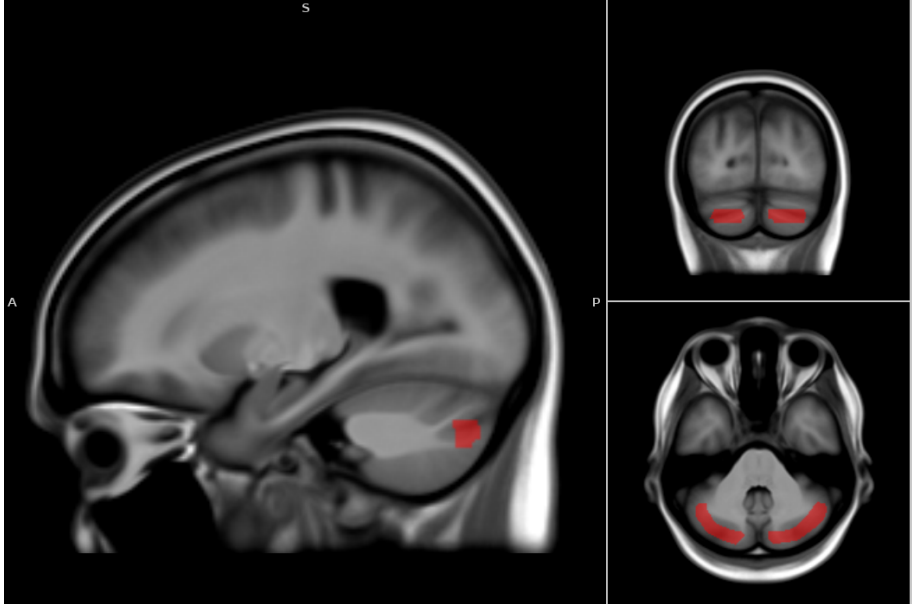
Supplementary Tables 1-4. Percentage agreement between the two readers for the four visual classification categories

Table 1. Tau negative

Reader #2	Reader #1	Yes	No
	Yes	18	3
	No	3	127
Percentage agreement = 96%			

Table 2. LP

Reader #2	Reader #1	Yes	No
	Yes	12	3
	No	0	136
Percentage agreement = 98%			

Table 3. MTL-sparing

Reader #2	Reader #1	Yes	No
	Yes	19	5
	No	3	124
Percentage agreement = 95%			

Table 4. Typical

Reader #2	Reader #1	Yes	No
	Yes	90	1
	No	6	54
Percentage agreement = 95%			

Supplementary Figure 2. "Hook sign"
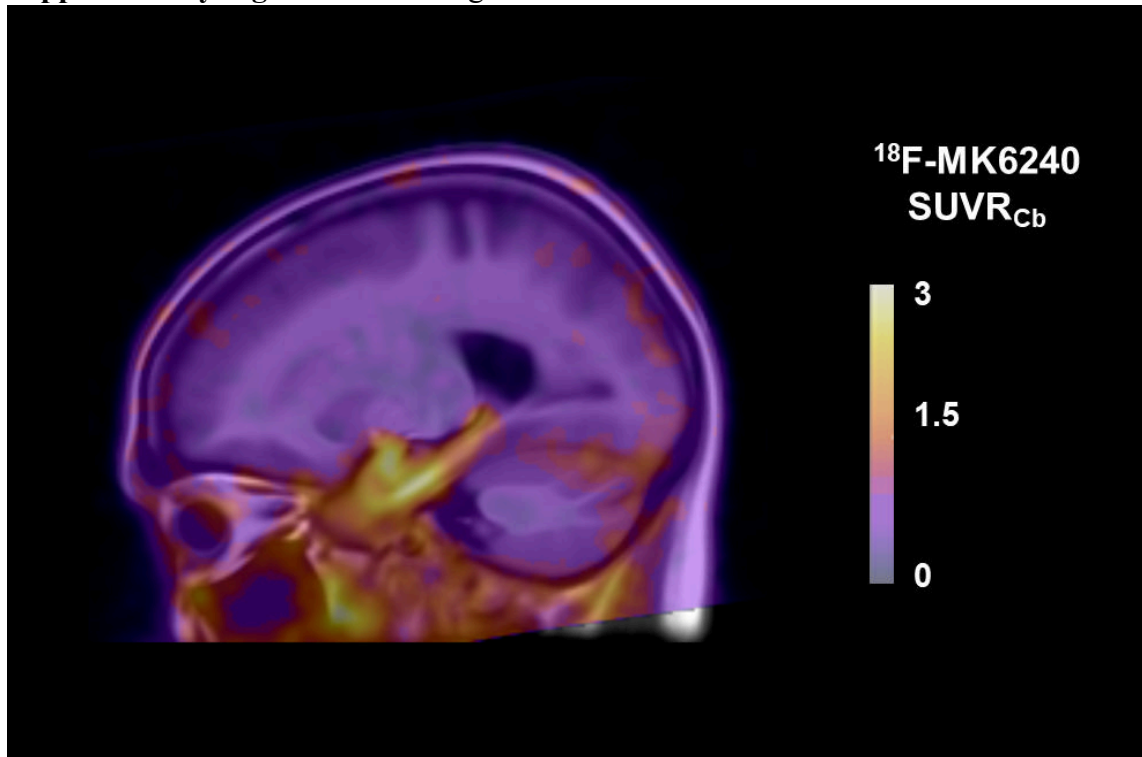

Representative tau ^{18}F-MK6240 PET scan (sagittal sequence) of a participant from the visually classified limbic predominant (LP) group in a 'fire' colorscale, showing an example of the "Hook sign," overlaid on a T1 MRI template. The hook appearance is generated from tracer binding in the parahippocampal gyrus (the shank and curve), the amygdala and the anterior hippocampus.

Supplementary Figure 3. Voxel-wise analysis showing LP > MTL-sparing
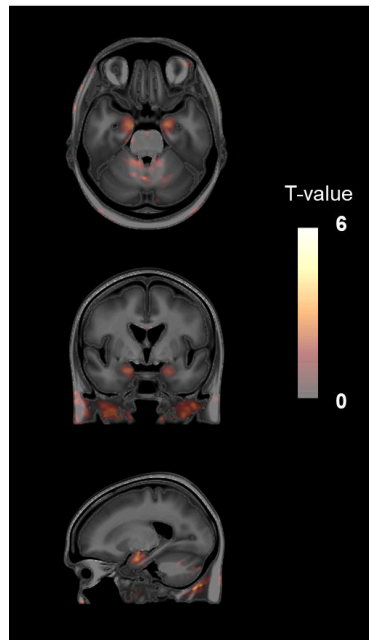
Voxel-wise contrasts (T-map images) showing regions of higher ^{18}F-MK6240 tracer retention in the limbic predominant (LP) group than the mesial temporal lobe sparing (MTL-sparing) group, overlaid on a T1 MRI template.

Supplementary Figure 4. Voxel-wise contrasts: Typical > MTL-sparing
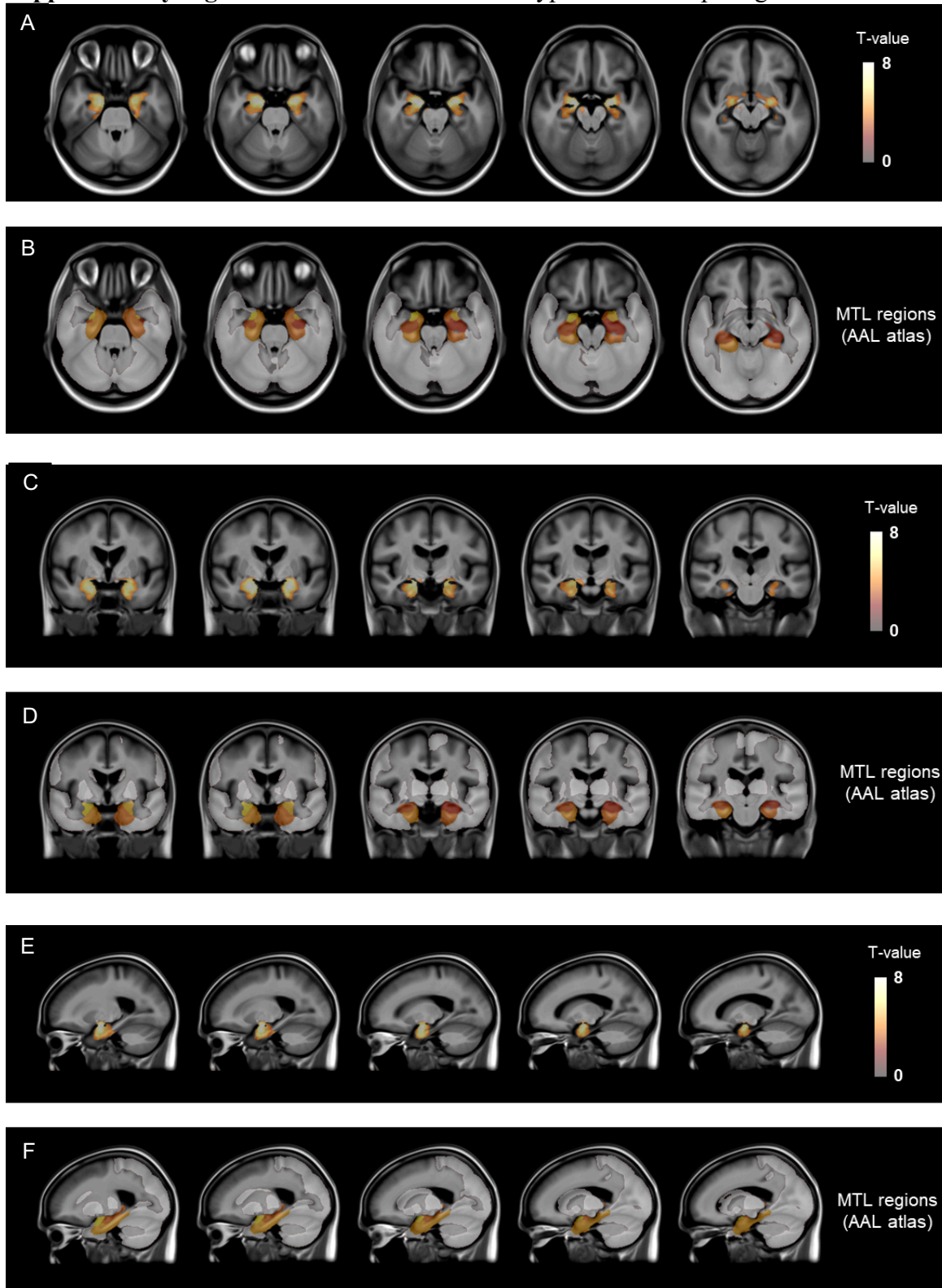
Voxel-wise contrasts (T-map images) A) trans-axial sequences; C) coronal sequences; and E) sagittal sequences showing regions of higher ^{18}F-MK6240 tracer retention in the Typical group

compared to the MTL-sparing group, overlaid on a T1 MRI template. For anatomical reference, B) trans-axial sequences; D) coronal sequences; and F) sagittal sequences for the AAL atlas overlaid on a T1 MRI template showing mesial temporal lobe structures, amygdala (yellow), hippocampus (red), and parahippocampus (orange).

Supplementary Figure 5. Tau ^{18}F-MK6240 SUVR in MTL and cortical ROI
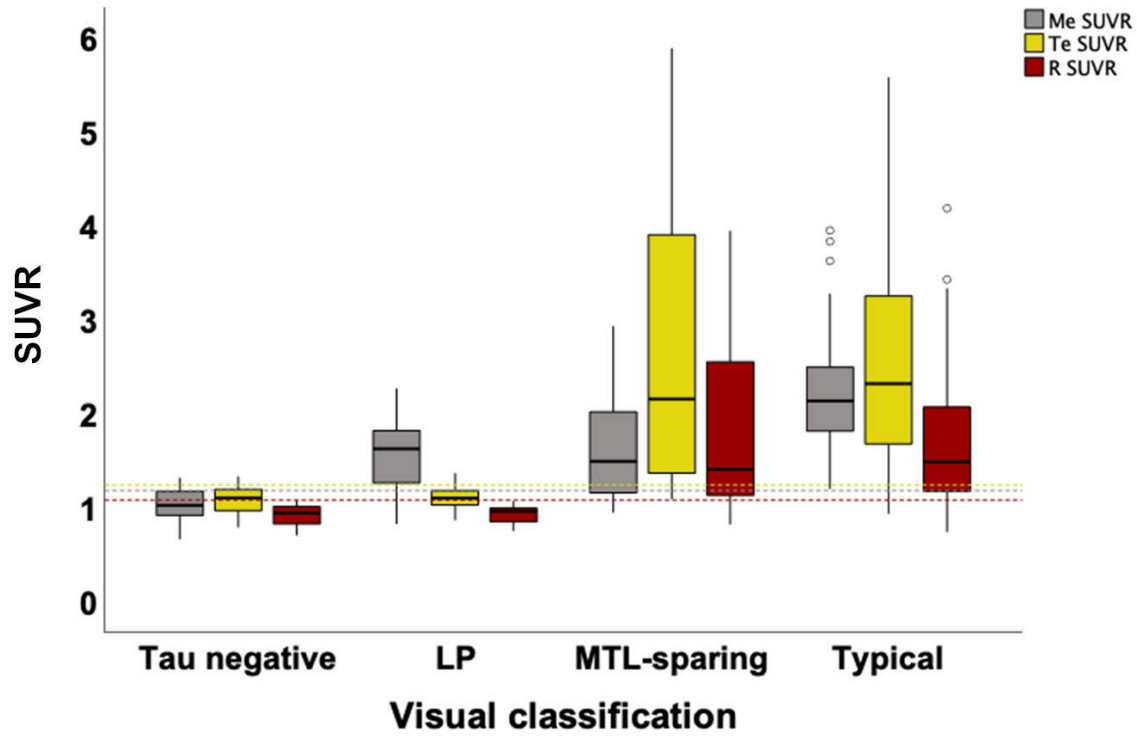
Boxplots showing tau ^{18}F-MK6240 SUVR in composite ROI: Me (mesial temporal); Te (temporoparietal); and R (rest of neocortex). The horizontal dashed lines represent the 95% percentile of the Aβ negative cognitively unimpaired participants from the AIBL cohort (Me = gray; Te = yellow; R = red). While the visually classified MTL-sparing and Typical groups had similar cortical SUVR (Te and R), the MTL-sparing group had lower SUVR in the mesial temporal lobe (Me). SUVR, standardized uptake value ratio; LP, limbic predominant; MTL-sparing, mesial temporal lobe sparing.