S-1. Detailed visual assessment algorithm for [^{18}F]MK-6240

The visual assessment of [18F]MK-6240 is a three-step process. First, readers adjusted the image to standardize the orientation, windowing, and thresholding of the gray scale per explicit instructions for consistency when viewing images in all three planes (axial, coronal, and sagittal). Readers were not permitted to sample voxel values, draw regions of interest, or develop a quantitative measure. Next, technical adequacy for visual review was systematically queried to determine the overall quality of the scan for the following: positioning, motion, attenuation correction, field of view, image filtering, and count rate. Next the image volumes are reoriented in a standardized manner and the upper threshold on the window is set to 70-80% of maximum, depending upon the characteristics of the scan. An inverse linear grayscale is the recommended scale to use for interpretation based on previous data which suggests biases in applying many color scales including monochrome color scales.

Once the images are processed as described the next step is careful interrogation of neocortical regions for the presence or absence of focal uptake suggestive of tau deposition in eight pre-specified brain regions in each hemisphere of the cerebral cortex (16 regions total): hippocampus, mesial temporal, inferior temporal, lateral temporal, parietal, posterior cingulate, occipital, and frontal lobes. These regions are organized into clusters for temporal regions (Cluster 1), extra-temporal cortical regions are grouped under the designate (Cluster 2), and an additional Cluster 3 comprising subcortical regions suggestive of binding related to non-AD tauopathy.

For each of these 16 cortical regions the reader ascertains first, if there is abnormal increased radiotracer in the region relative to the cerebellum and as informed by a basic sense of abnormal levels of tissue uptake provided by the training. Uptake in the cerebellar gray is an internal reference for nonspecific distribution of the tracer; as a rule of thumb uptake greater than 1.5 times the cerebellar gray would be in keeping with increased [^{18}F]MK-6240 binding. Next, the reader determines for each region, what percentage of the region appears to show, if any, abnormal increased uptake in one of four categories: none (0%), 1-25%, 26-75%, or >75% involvement of the region.

Region by region assessment begins on the coronal views where the left and right temporal lobes are easily displayed. There are four regions of the temporal area read in sequence: hippocampus, mesial temporal lobe, inferior temporal lobe, lateral temporal lobe (Cluster 1). In assessing these regions readers identify focal uptake which may be asymmetric or limited to medial and inferior structures or medial structures alone. The sagittal image allows visualization of the anatomic distribution of abnormal uptake in the lateral temporal regions where there are distinct linear areas of increased uptake that track the lobar anatomy. The axial images are next viewed for initial assessment of the parietal, occipital, posterior cingulate and frontal regions (Cluster 2) for evidence of increased tracer uptake relative to the cerebellar gray. Regional positivity is defined by either focal or confluent uptake involving at least 1-25% of the region (Table 1). Readers are asked to judge the extent of abnormal increased uptake within the region rather than intensity of that uptake. The extension refers to the number of voxels with increased uptake, while the intensity is how high the uptake is in any given voxel or cluster of voxels with respect to cerebellar gray matter. Next, the reader reviews subcortical brain uptake (striatum/globus pallidus, thalamus, pons, midbrain, dentate nucleus; collectively “Cluster 3”). Finally, the reader assesses common areas of “off-target” uptake which might confound regional evaluation, including: meninges, substantia nigra, venous sinuses and other vascular uptake including scalp, bony structures at the skull base, eyeballs, and salivary glands. The last step is the application of the algorithm to the regional positivity findings to address the questions is this scan positive or negative for evidence of brain tau? If positive is it in an Alzheimer's pattern? If it is an Alzheimer's pattern is it typical or atypical?

S-2. Reader Confidence

Self-rated confidence was measured with a five-point Likert scale where 1 is no confidence and 5 is complete confidence. Of the total of 336 scans read, 295 scans (87.8%) were read with complete confidence while 41 scans (12.2%) were read with less than complete confidence; of those, 21 scans (6.2%) were read with moderate or less (score < 4) confidence. Of those scans scoring 4 or less, 17 (41.5%) were read as negative, 19 (46.3%) as positive, AD pattern, and 5 (12.1%) as positive, non-AD pattern. While differences between readers were small given the high number of completely confident reads, the number of reads rated <5 was less consistent, with readers reporting between 3 and 25 cases as less than completely confident. However, reader confidence had no bearing on the reader's concordance with other readers.

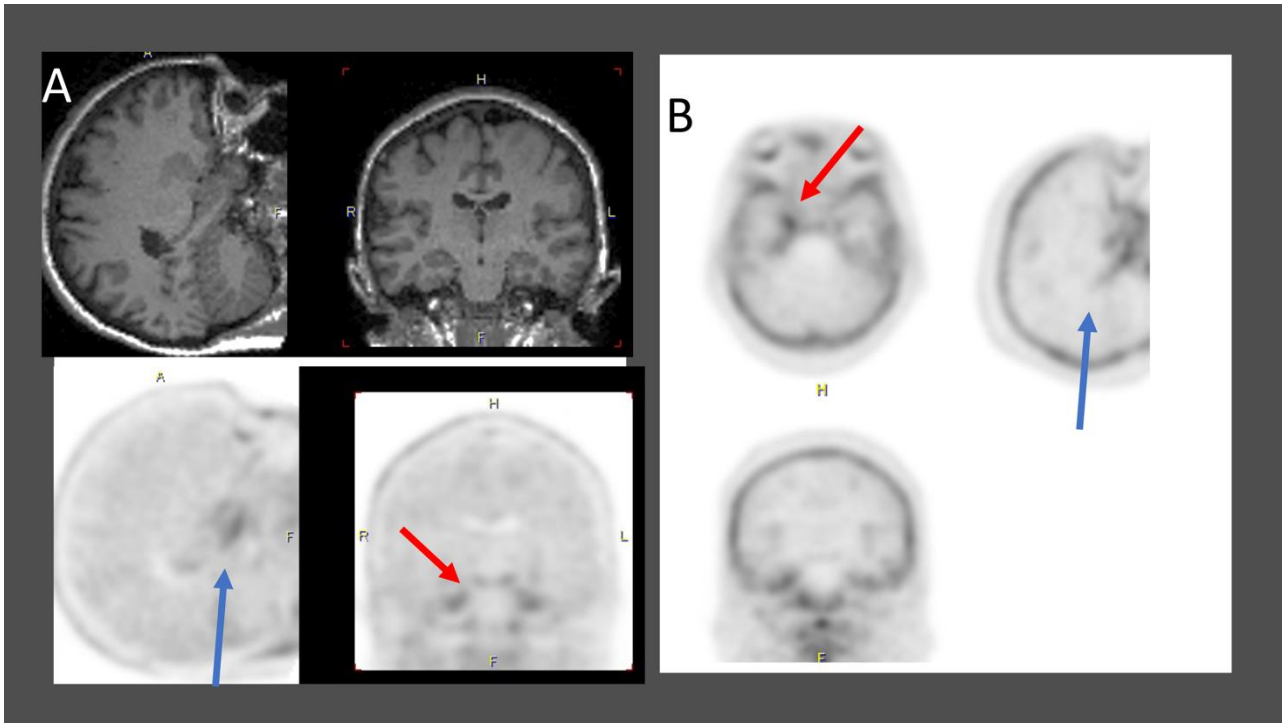
S-3. Details of image processing for SUVR determination

[^{18}F]MK6240 images were nonlinearly registered into MNI152 space using the subjects T1 MRI scan as part of a diffeomorphic nonlinear registration (DARTEL). First, the T1 structural MRI images were segmented into gray matter and white matter using SPM12. DARTEL then uses these tissue probability maps to create flow-fields which provide the parameters required to spatially normalize any images which are co-registered to the MRI image into MNI152 space. Each PET image was registered to the corresponding MRI using a rigid-body registration. Finally, the individuals' DARTEL flow-field was applied without modulation resulting in [^{18}F]MK6240 images in MNI152 space. The normalized maps were spatially smoothed with an 8mm full width at half maximum Gaussian kernel. SUVr images for [^{18}F]MK6240 were generated by dividing all intensities in the image by the mean uptake value of the reference region, for which we utilized the ventrolateral cerebellum VOI from the CIC atlas.

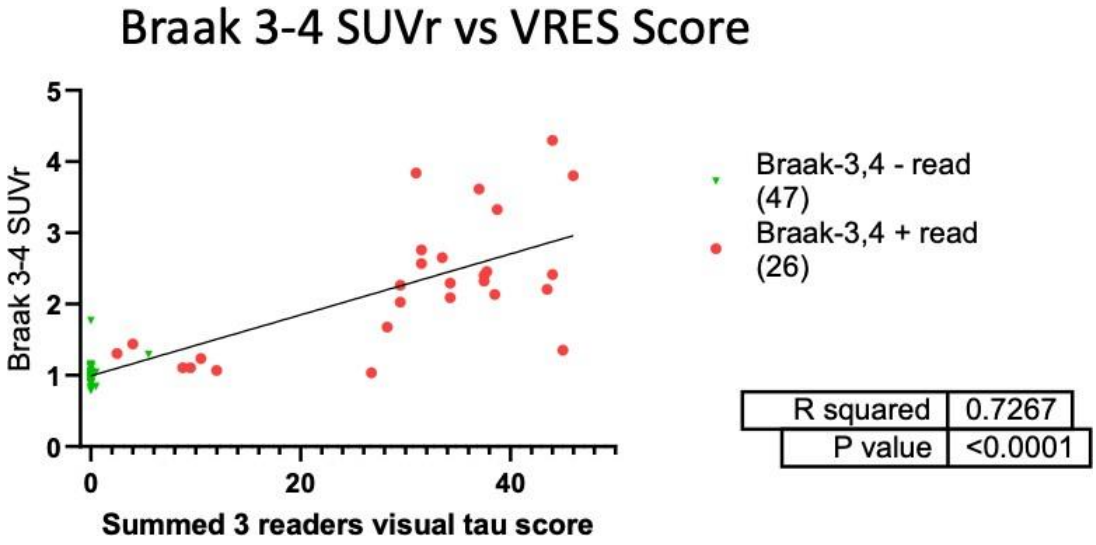
Supplemental Table 1

Standard uptake value ratios for different brain regions and volume of interest sampling strategies parsed by visual read status.

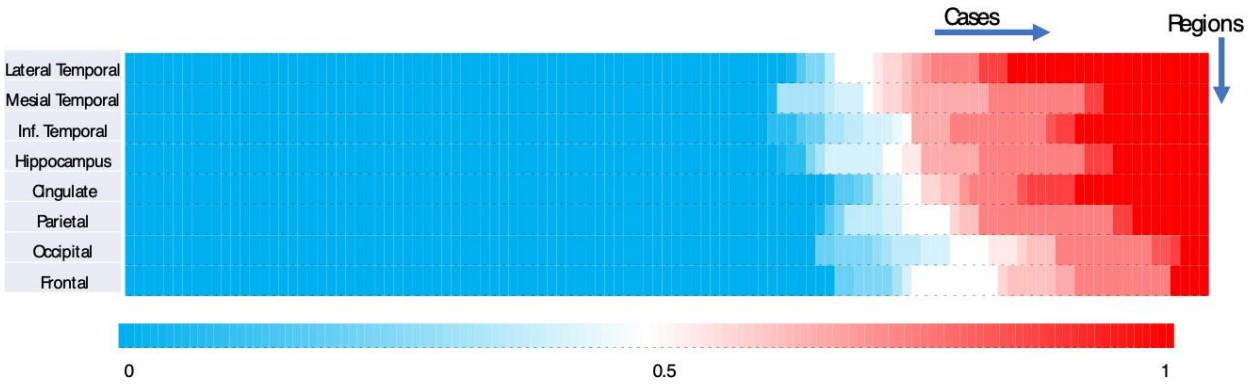
TABLE 1	Negative Read		Positive Read		Welch's t
SUVr	Mean	SD	Mean	SD	P
Braak_1	1.24	0.28	2.02	0.57	<0.0001
Braak_2	0.89	0.29	1.62	0.49	<0.0001
Braak_3	1.06	0.17	2.04	0.88	<0.0001
Braak_4	1.01	0.18	2.20	0.94	<0.0001
Braak_5	0.99	0.22	2.05	1.03	<0.0001
Braak_6	0.92	0.17	1.63	0.77	<0.0001
Braak_1-2	1.10	0.26	1.86	0.52	<0.0001
Braak_3-4	1.02	0.18	2.17	0.91	<0.0001
Braak_5-6	0.98	0.21	1.97	0.97	<0.0001
Jack VOI	1.10	0.21	2.20	0.80	<0.0001



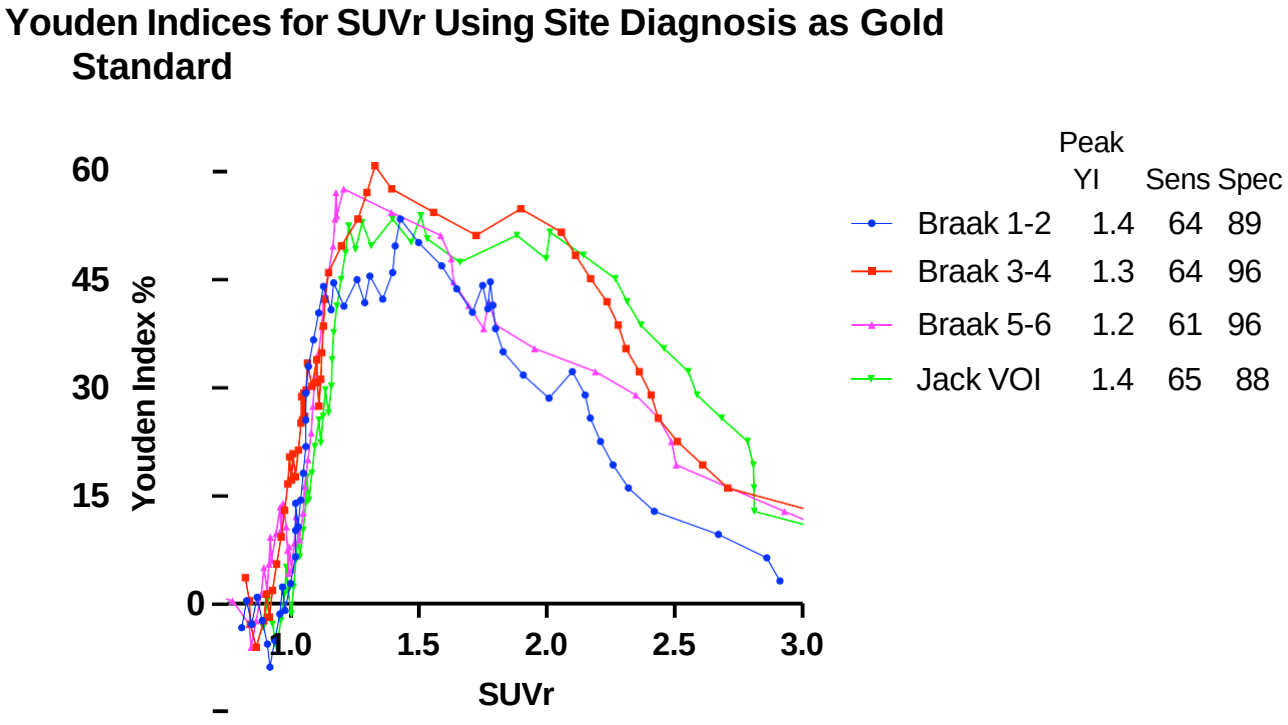
Supplemental Figure 1 Two difficult cases (A and B) with discordant reads. Case A lower gray scale 18-F MK-6240 shows small foci of uptake bilaterally in the mesial temporal lobes on the coronal view (red arrow) which has the appearance of meningeal uptake, but on sagittal view is linear and conforms to temporal lobe. This is confirmed on MRI. B is a patient with asymmetric uptake in the mesial aspect of the right temporal lobe (red arrow). The linear appearance on the sagittal images (blue arrow) is consistent with temporal binding.



Supplemental Figure 2. Braak 3-4 SUVrs plotted against the three reader summed visual reader extent score (VRES) and fit to a linear regression. Note the large majority of visually negative scans had visual tau scores = 0 and SUVrs clustering around 1.



Supplemental Figure 3. Composite mean cortical tau regional visual uptake score calculated for all 102 research participants by merging left and right hemisphere homotypic regions and averaging all three readers scores. Scores for each subject and region range from 0 (no uptake) to 1 (>75% of region involved).



Supplemental Figure 4 Sensitivity/specificity analysis for different SUVr sampling templates using site clinical diagnosis as the truth standard. Youden index is obtained by ROC curve and calculated as the sum of (sensitivity and specificity)-1, expressed as a percent for different SUVr strategies and cut-offs.