Supplementary Methods:

ASL-MR sequence:

All patients were imaged on the same clinical 3 Tesla GE SIGNA Architect MRI scanner (GE Medical Systems, Milwaukee, WI, USA). The 3D pseudo-continuous ASL-MR product sequence had the following parameters: PLD 2025 ms, TR 4876, TE 53.6, 38 x 4 mm axial slices, FOV 24, matrix size 512; the scanning time was 4 minutes and 24 seconds. CBF maps were processed using the GE AW Server 3.2 ext 4.0, set to a range of 0-80 mL/100g/min using the rainbow color scheme. Images were visually interpreted in native space.

ASL-MR Z-score maps:

Twenty-eight patients (aged 45-88 years), who had been scanned on the same 3 Tesla GE MRI scanner, having initially presented with cognitive concerns, were used as a control cohort to construct Z-score maps. These control subjects had resulting normal MRI scans, as well as a clinical, cognitive, and laboratory workup that was not suggestive of a neurodegenerative disorder. Of note, a validated healthy comparison cohort and a standardized imaging processing pipeline for ASL-MR are not yet widely available from vendors and thus difficult to incorporate into routine clinical practice. In the literature, there is a wide range of image processing pipelines and parameters, which are largely lab-specific. Similarly, various “normal” control cohorts have been used in the literature, often including patients with headaches with variable confirmation by clinical/cognitive assessment, which limits widespread adoption of these Z-score maps.

In the Weill Cornell Brain Health Imaging Institute, we used the following image-processing pipeline. All subjects’ Freesurfer (FS) reconstructions were performed with FS version 7.10. The M0 image was coregistered to FS T1-weighted (T1w) space and the corresponding CBF map was converted to FS space using the transform matrix generated during M0 coregistration. Next, all subjects’ T1w in FS space were warped to the MNI152 template using the FSL fnirt command; the warping fields were saved and applied to the FS space CBF map. The mean and standard deviation (SD) of the CBF values in template space were computed for the 28 control subjects. Each patient’s CBF was Z-scored using the mean and SD of the control subjects. All processing was performed in FSL and MATLAB 2023a, and the final snapshots were taken from

FSLeyes by overlaying individual MNI space CBF on T1w. The 3D Z-score map was created by overlaying the CBF onto an MNI152 template for each subject using MRIcroGL. Images are shown in radiological convention.

Volumetric comparison:

FS segmentation was also used to obtain regional brain volumes in the 7 patients and the control cohort (n=28) as noted above. Frontal (including superior frontal, rostral middle frontal, caudal middle frontal gyri), parietal (posterior cingulate, precuneus, superior and inferior parietal lobules), temporal (superior, middle, inferior temporal gyri), and occipital (lateral occipital, lingual, cuneus) lobe regions were assessed, as well as hippocampal volumes. Brain regions were considered atrophic if volumes were 1.5 standard deviations below those of the control cohort.

FDG-PET Z-score maps:

FDG-PET images were post-processed using the widely clinically available syngo.via software (Siemens Healthineers, Erlangen, Germany). A control cohort of 33 individuals (aged 46-79), included in the software package, were used to generate Z-score maps of the SUV values using the MI Neurology workflow, overlaid onto MNI space.

Supplementary Data:

When comparing brain regional volumes of our 7 cases to our 28 controls:
Case 5 had regional volumes that were 1.5 standard deviations below the controls in the frontal (caudal middle frontal), parietal (inferior parietal, posterior cingulate, precuneus), temporal (superior temporal, middle temporal, inferior temporal), and occipital (cuneus, lateral occipital) lobes. Case 4 had atrophy that was 1.5 standard deviations below the controls in the caudal middle frontal region. None of the 7 cases had significant hippocampal atrophy.

Cortical gray matter CBF values of our 7 cases (units = mL/100g/min):

Case 1: 28

Case 2: 68

Case 3: 69

Case 4: 35

Case 5: 44

Case 6: 26

Case 7: 34

White matter hyperintensity burden for the 7 cases:

Case 1: Minimal (Fazekas grade 1)

Case 2: Mild (Fazekas grade 1)

Case 3: Mild (Fazekas grade 1)

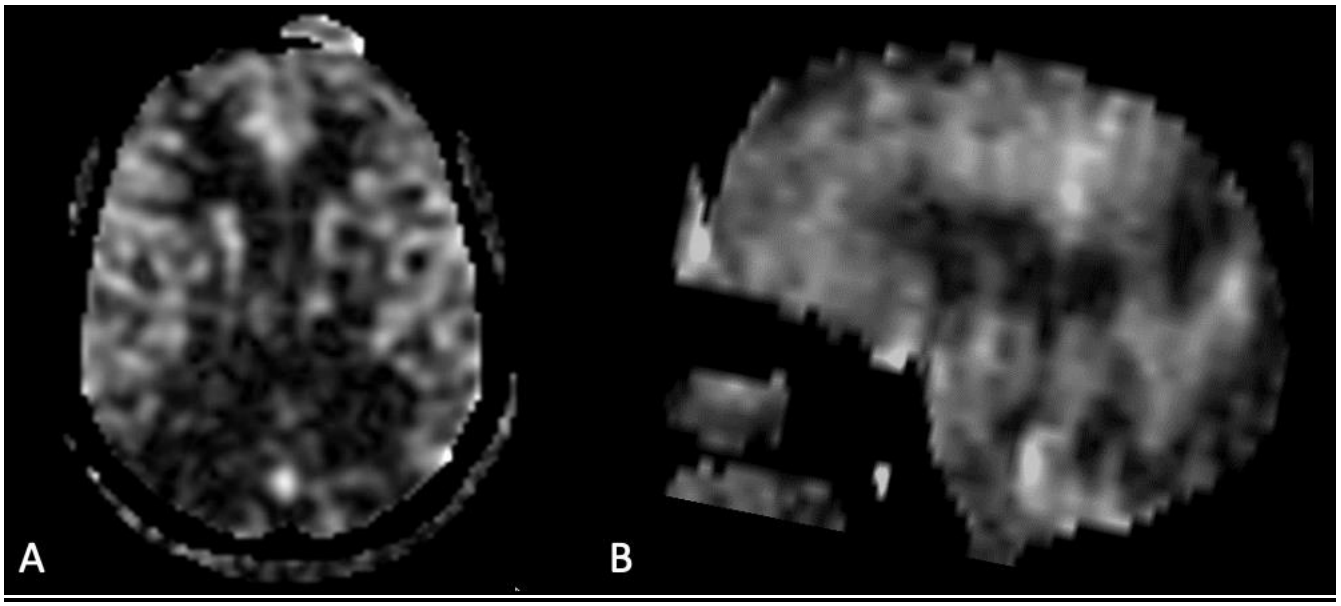
Case 4: Mild (Fazekas grade 1)

Case 5: Minimal (Fazekas grade 1)

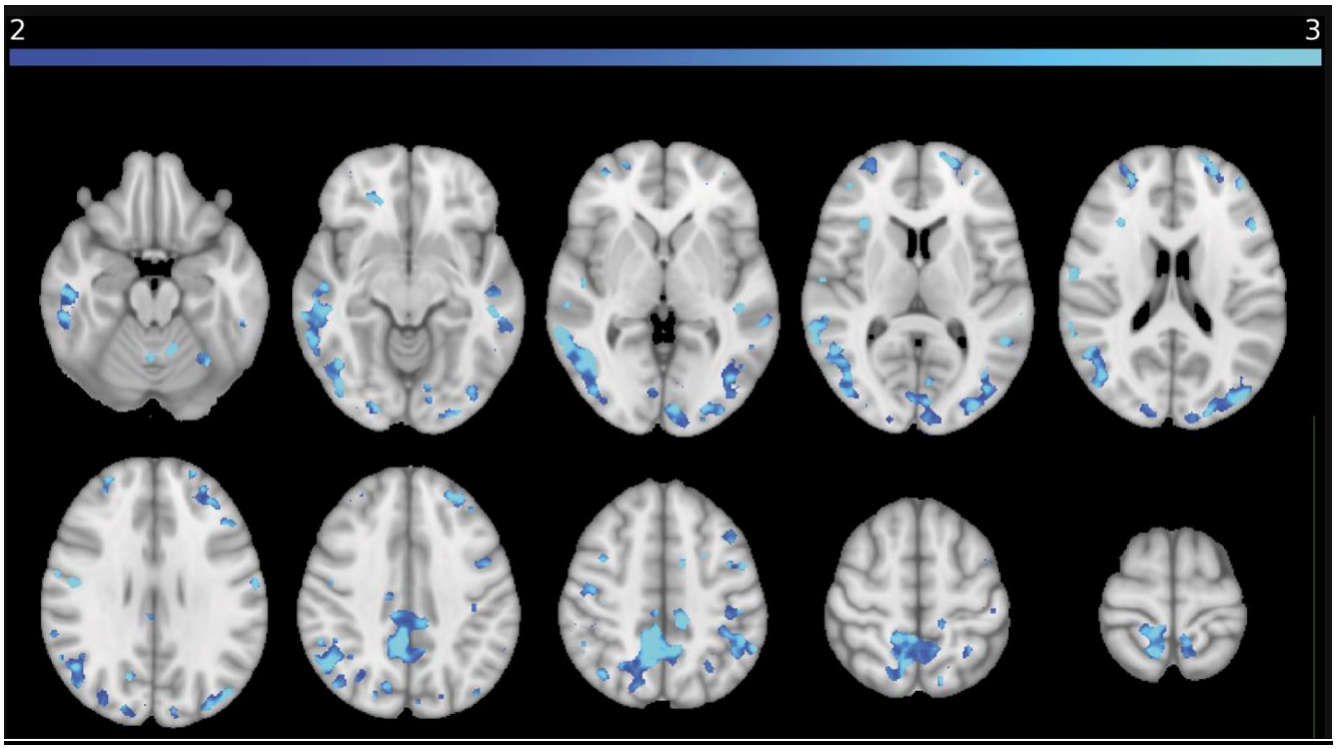
Case 6: Mild (Fazekas grade 1)

Case 7: Moderate (Fazekas grade 2)

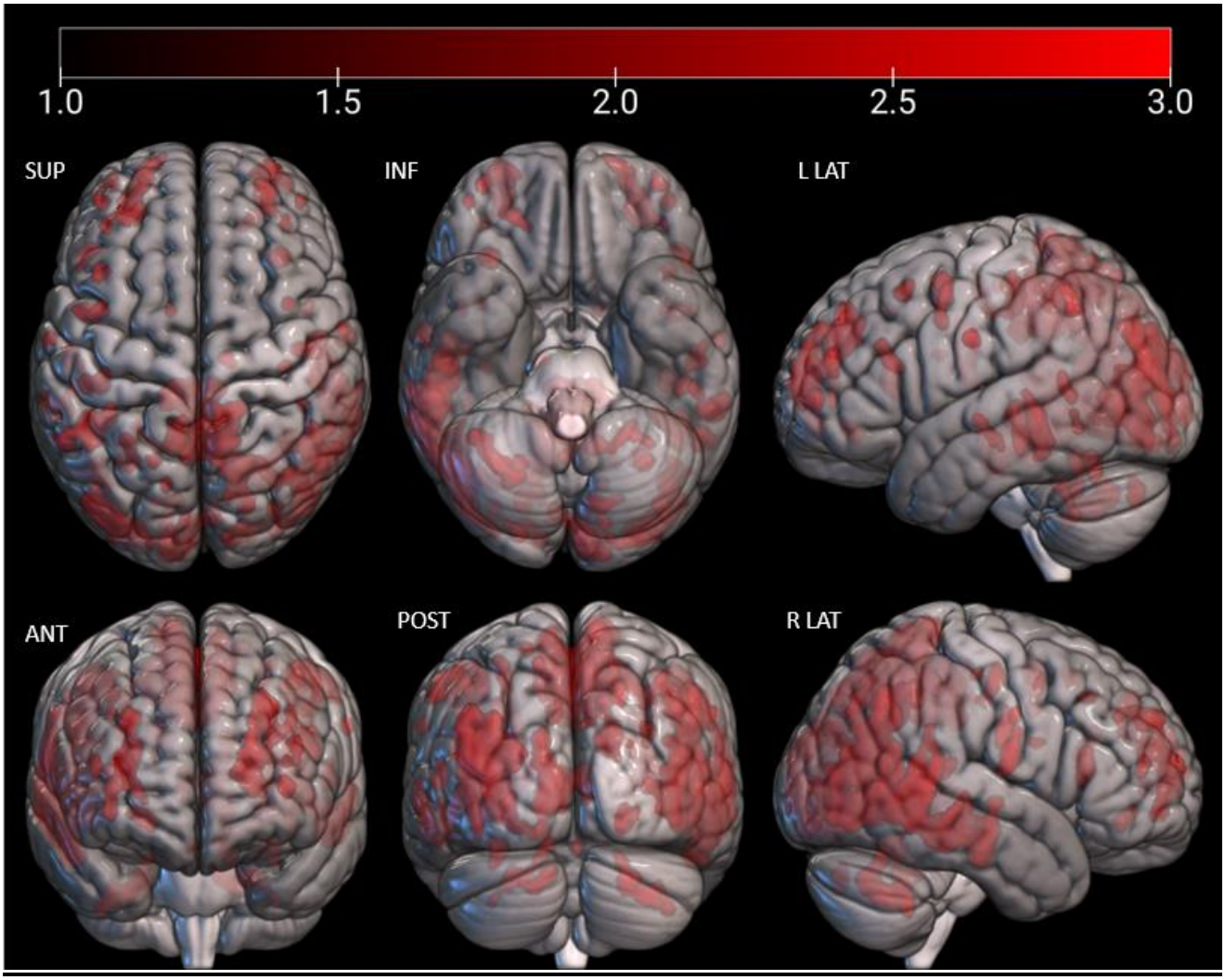
Supplementary Figures:



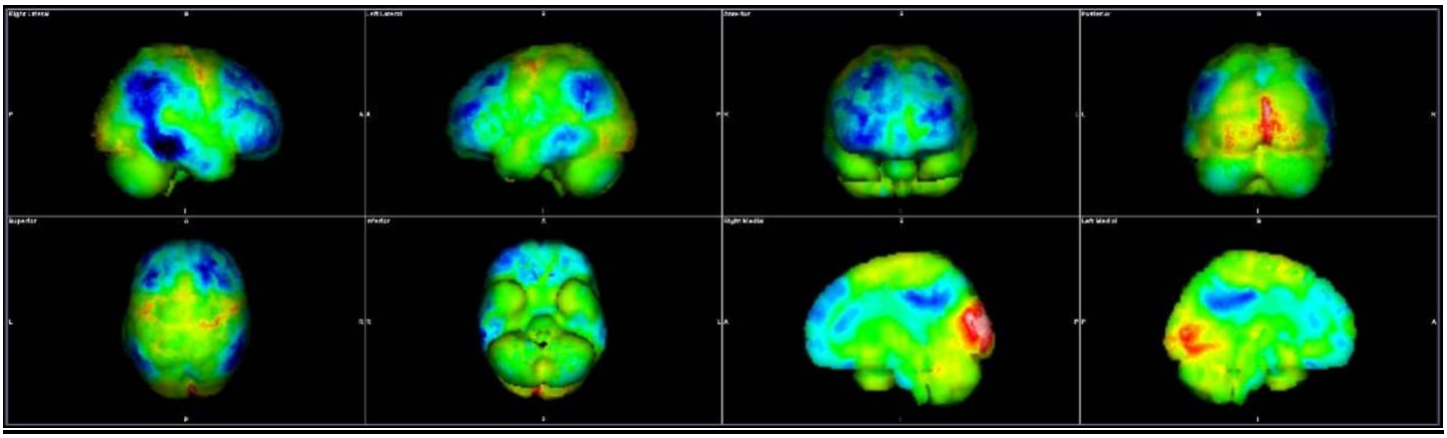
Supplementary Figure 1 (Case 1 Early-onset AD with presenilin mutation): Gray-scale axial (A) and sagittal (B) ASL-MR images showing decreased CBF in the bilateral parietal lobes, particularly on the right, and the precuneus – these are suggestive of AD.



Supplementary Figure 2 (Case 1): Axial Z-score maps, with blue corresponding to areas of decreased CBF, predominantly in the temporal and parietal lobes, as compared to our control cohort. Upper and lower Z-score thresholds of 2.0 and 3.0 are shown in the color bar.

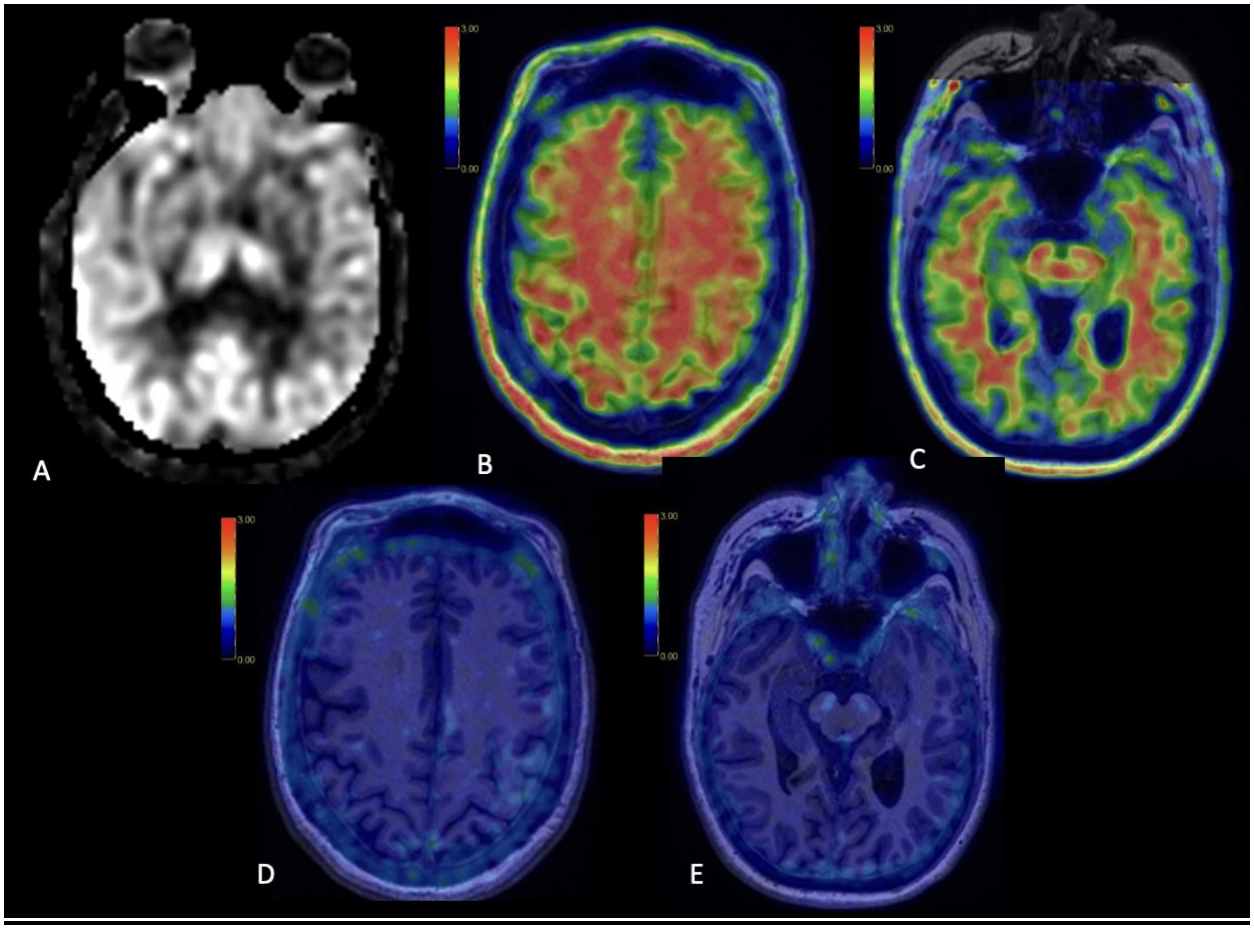


Supplementary Figure 3 (Case 1): Three-dimensional stereotactic surface projection images with red corresponding to decreased CBF, predominantly in the parietal and temporal lobes, as compared to our control cohort. Upper and lower Z-score thresholds of 1.0 and 3.0 are shown in the color bar.

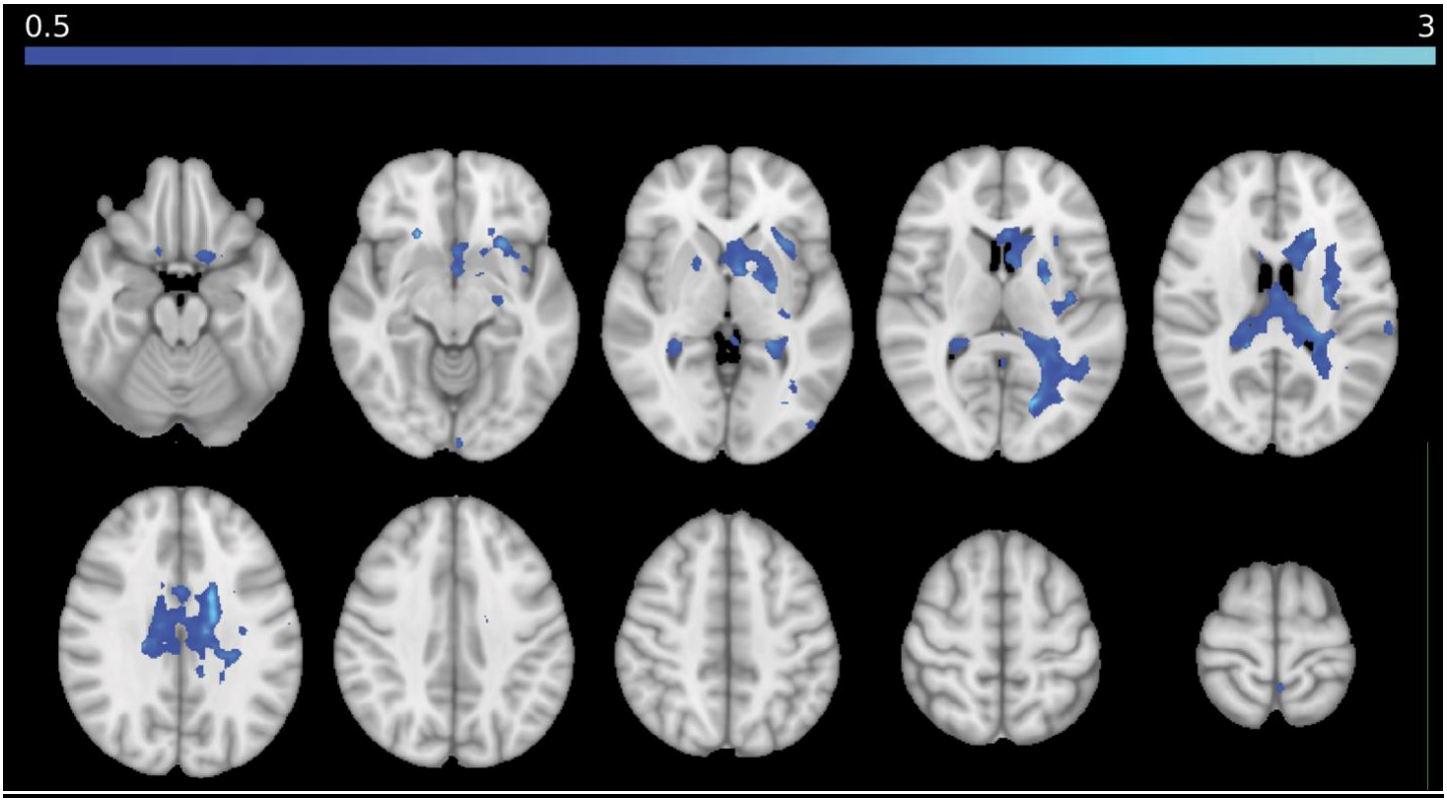


Supplementary Figure 4 (Case 1): Three-dimensional stereotactic surface projection images with blue representing the patient's decreased FDG avidity, as compared to a normative database, using the clinically available syngo.via software package.

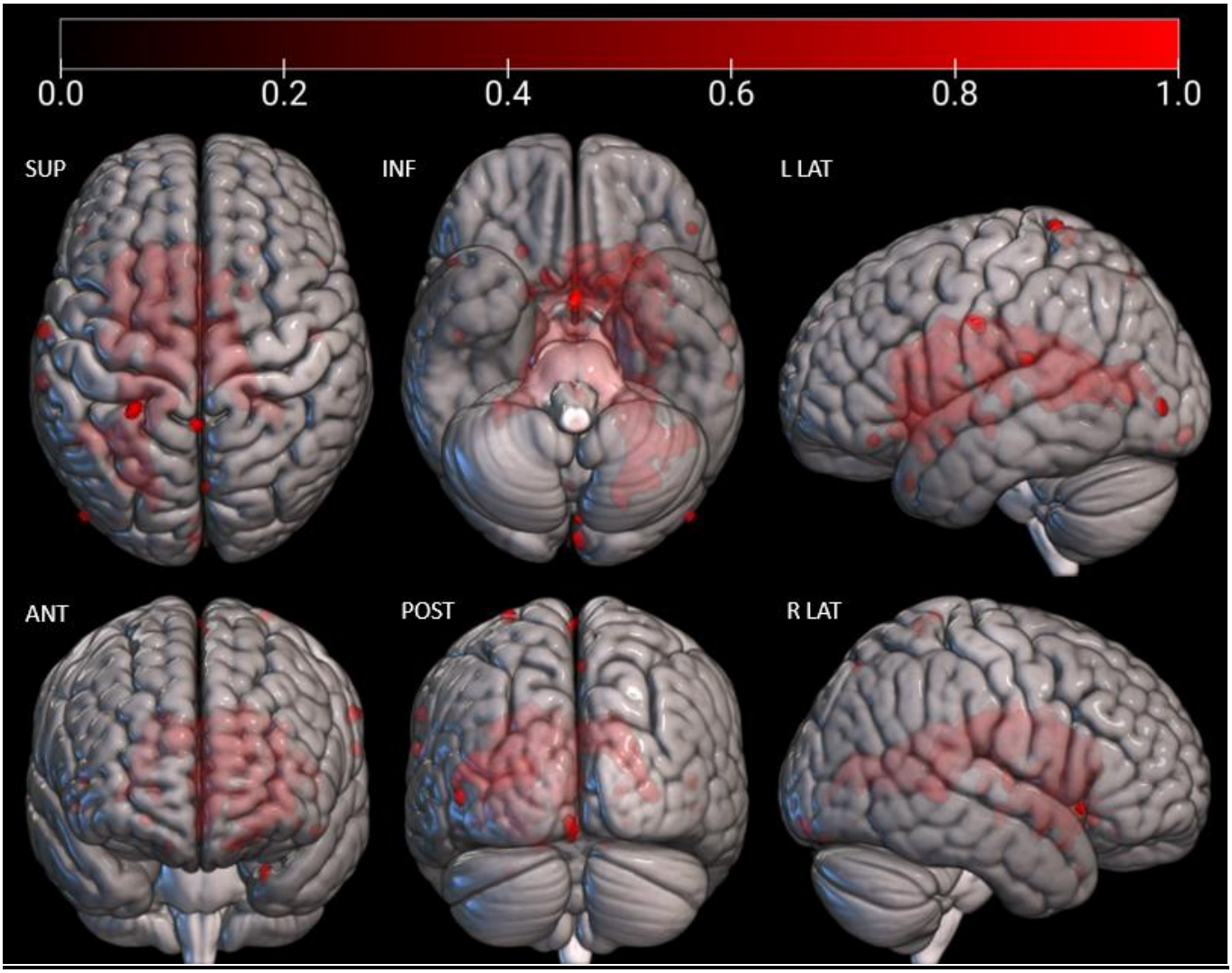
Supplementary Figure 5 (Case 1): Axial [18F]-florbetaben PET image demonstrating diffuse cortical amyloid deposition, consistent with AD.



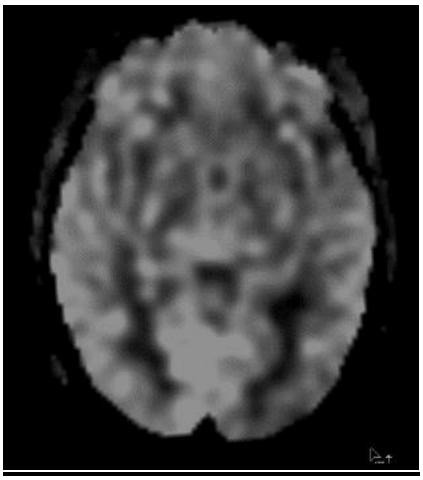
Supplementary Figure 6 (Case 2 Early-onset AD and post-COVID brain fog): Axial gray-scale ASL-MR image (A) demonstrating slightly decreased CBF at the left temporoparietal junction. Axial [18F]-florbetaben PET image (B and C) demonstrate cortical amyloid deposition in the parietal lobes and left temporal lobe. Axial [18F]-florbetaben PET images (D and E) show no evidence of cortical tau deposition in other parts of the brain.



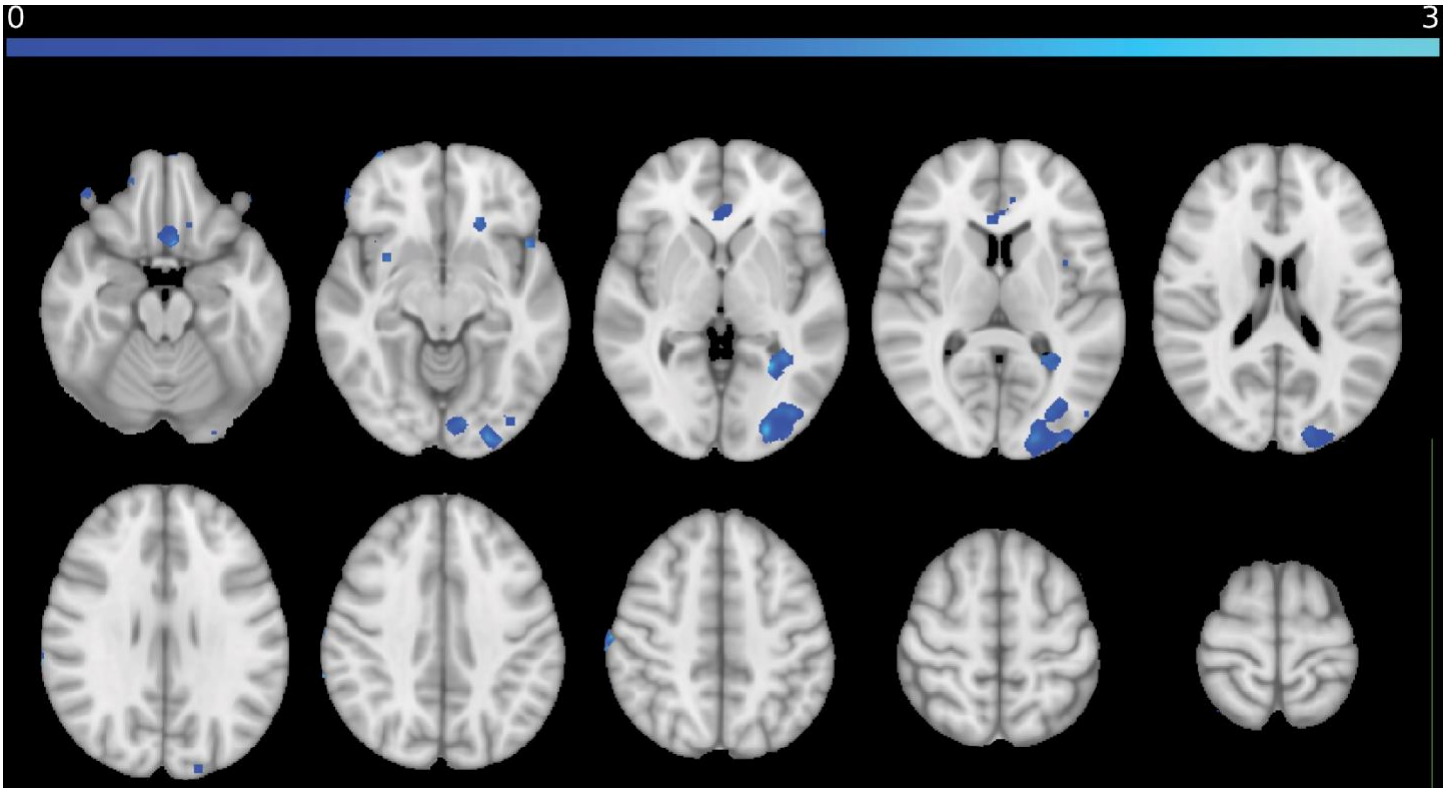
Supplementary Figure 7 (Case 2): Axial Z-score maps, with blue corresponding to areas of decreased CBF, asymmetrically involving the left temporoparietal region. Upper and lower Z-score thresholds of 0.5 and 3.0 are shown in the color bar.



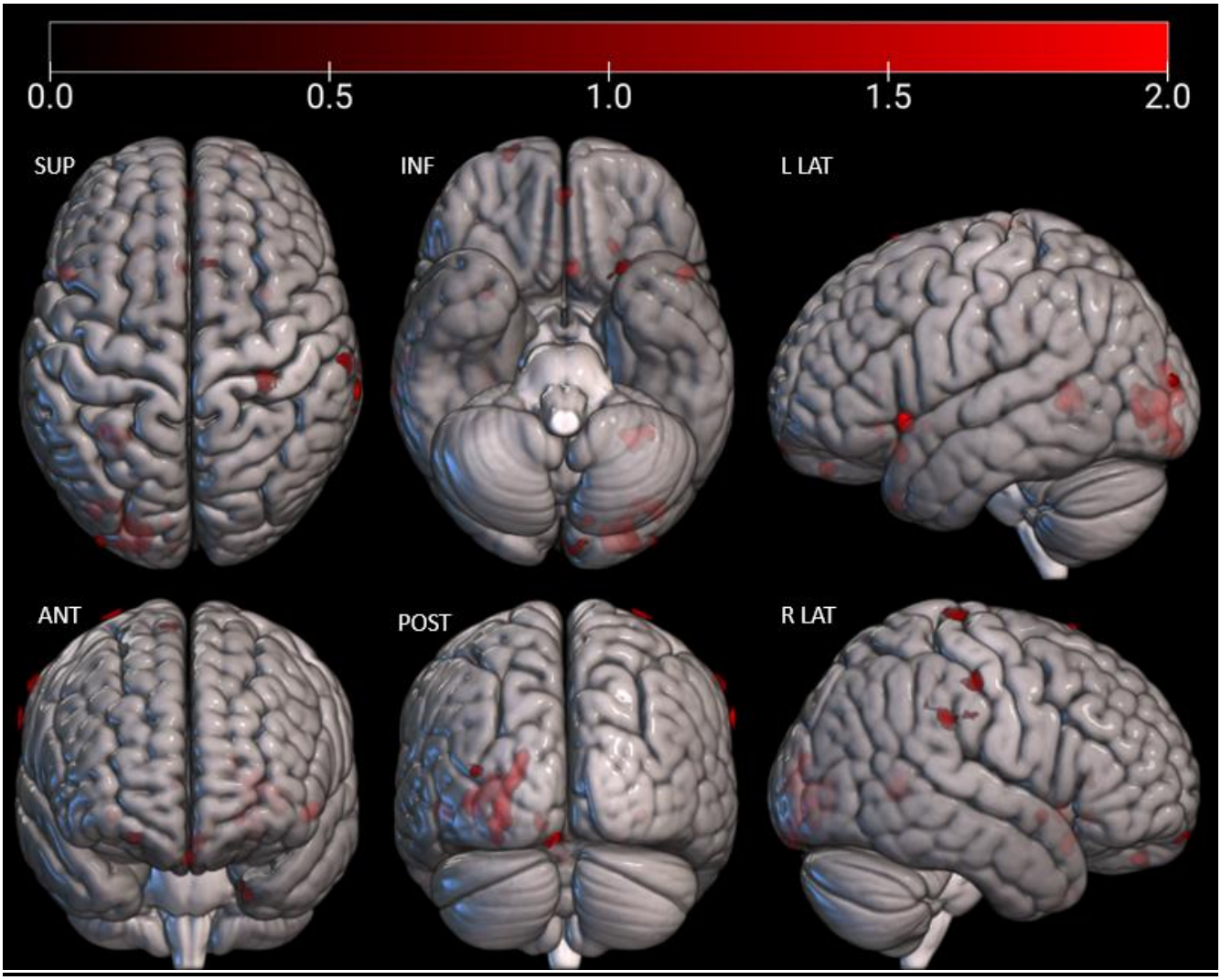
Supplementary Figure 8 (Case 2): Three-dimensional stereotactic surface projection images with red corresponding to subtle areas of decreased CBF, less clearly showing the focal area of decreased CBF in the left temporoparietal junction than on axial images. Z-score thresholds were lowered (0 and 1.0) to increase sensitivity.



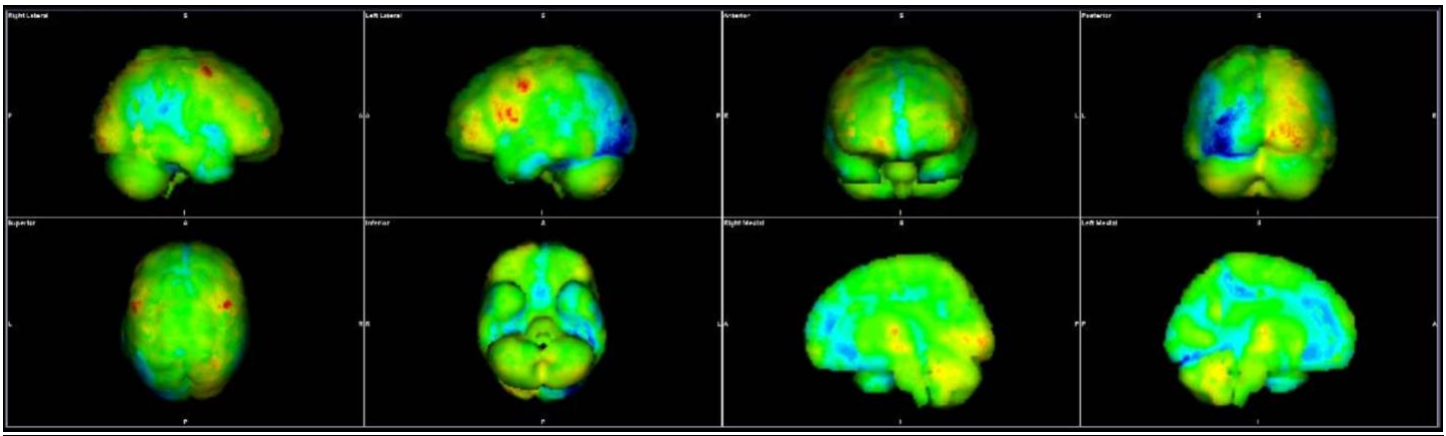
Supplementary Figure 9 (Case 3 Posterior cortical atrophy): Gray-scale axial ASL-MR image showing decreased CBF in the left occipital lobe.



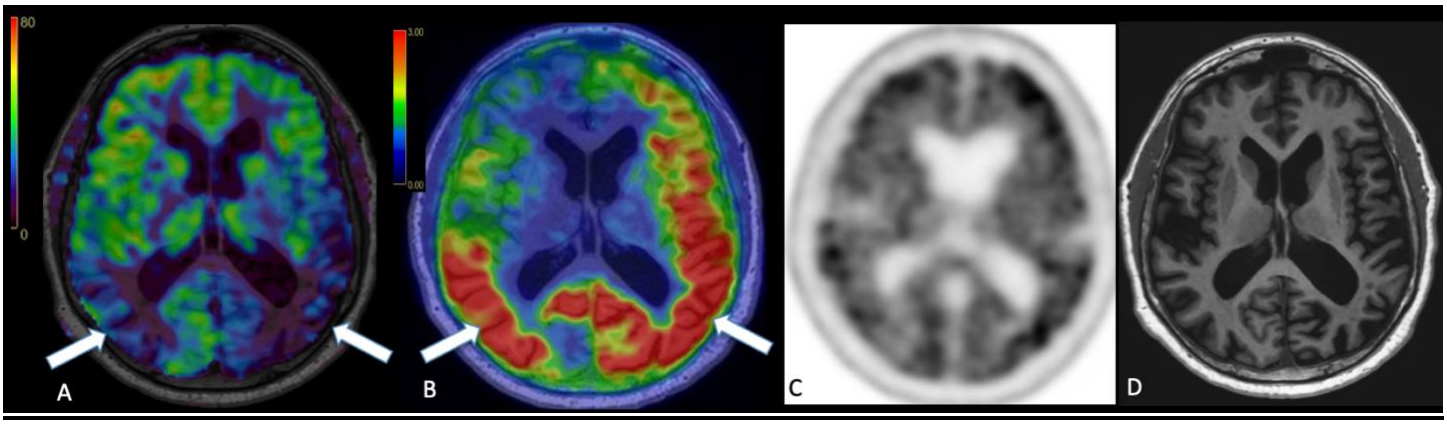
Supplementary Figure 10 (Case 3): Axial Z-score maps, with blue corresponding to areas of decreased CBF, predominantly in the left occipital lobe, as compared to our control cohort. Upper and lower Z-score thresholds of 2.0 and 3.0 were used.



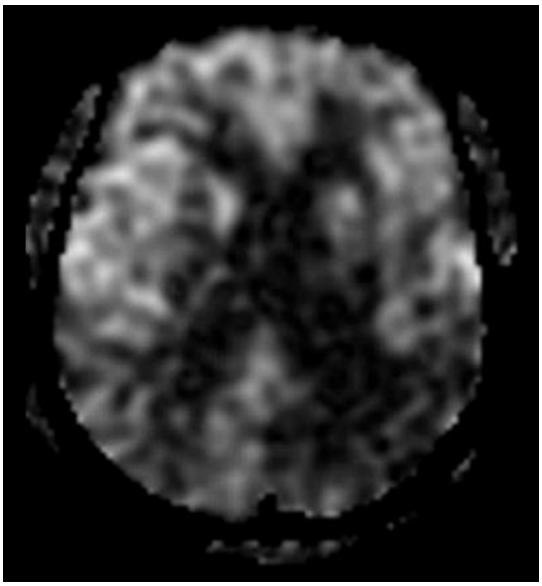
Supplementary Figure 11 (Case 3): Three-dimensional stereotactic surface projection images with red corresponding to decreased CBF, predominantly in the left occipital lobe, as compared to our control cohort. Upper and lower Z-score thresholds of 0 and 2.0 are shown in the color bar.



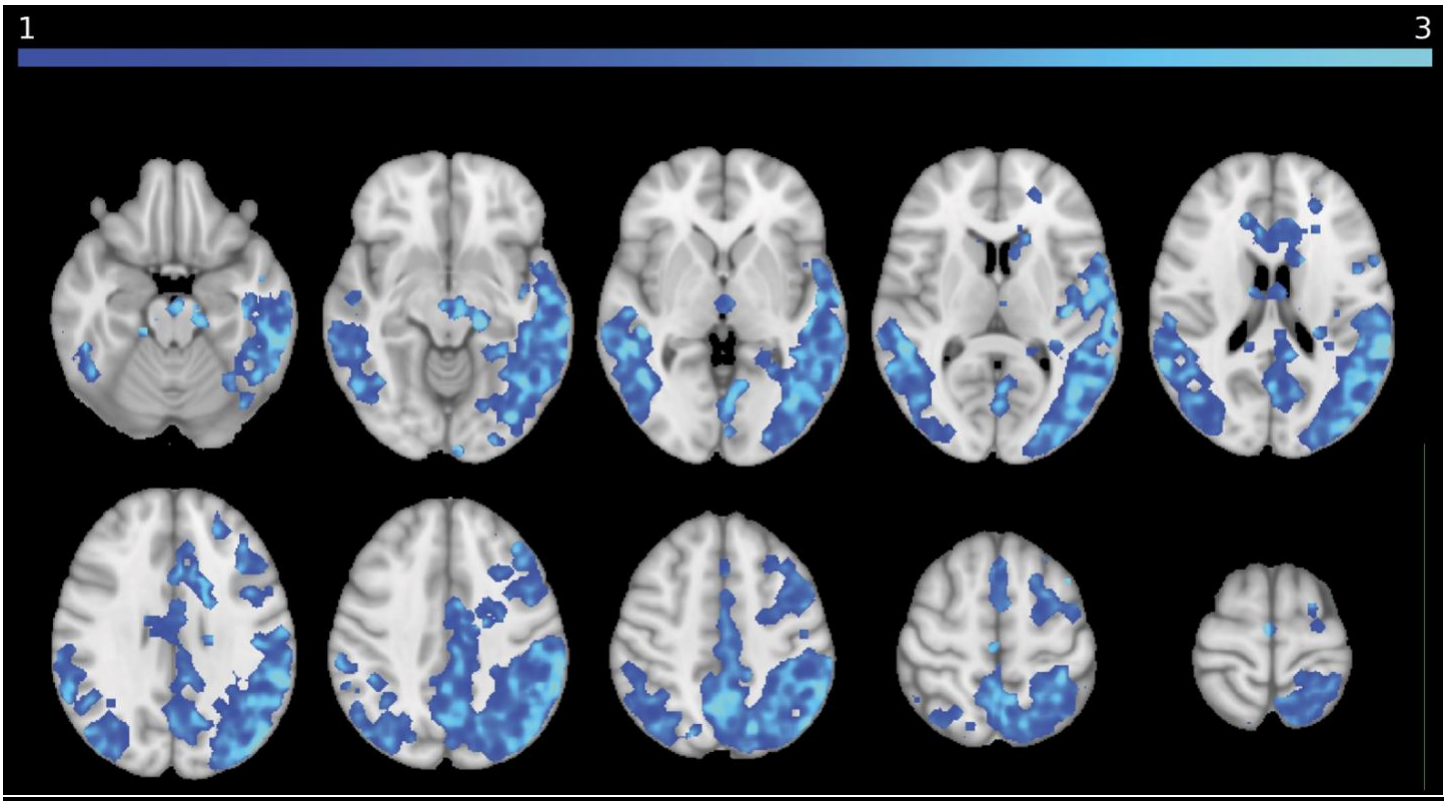
Supplementary Figure 12 (Case 3): Three-dimensional stereotactic surface projection images with blue representing the patient's decreased FDG avidity in the left occipital lobe, as compared to a normative database, using the clinically available syngo.via software package.



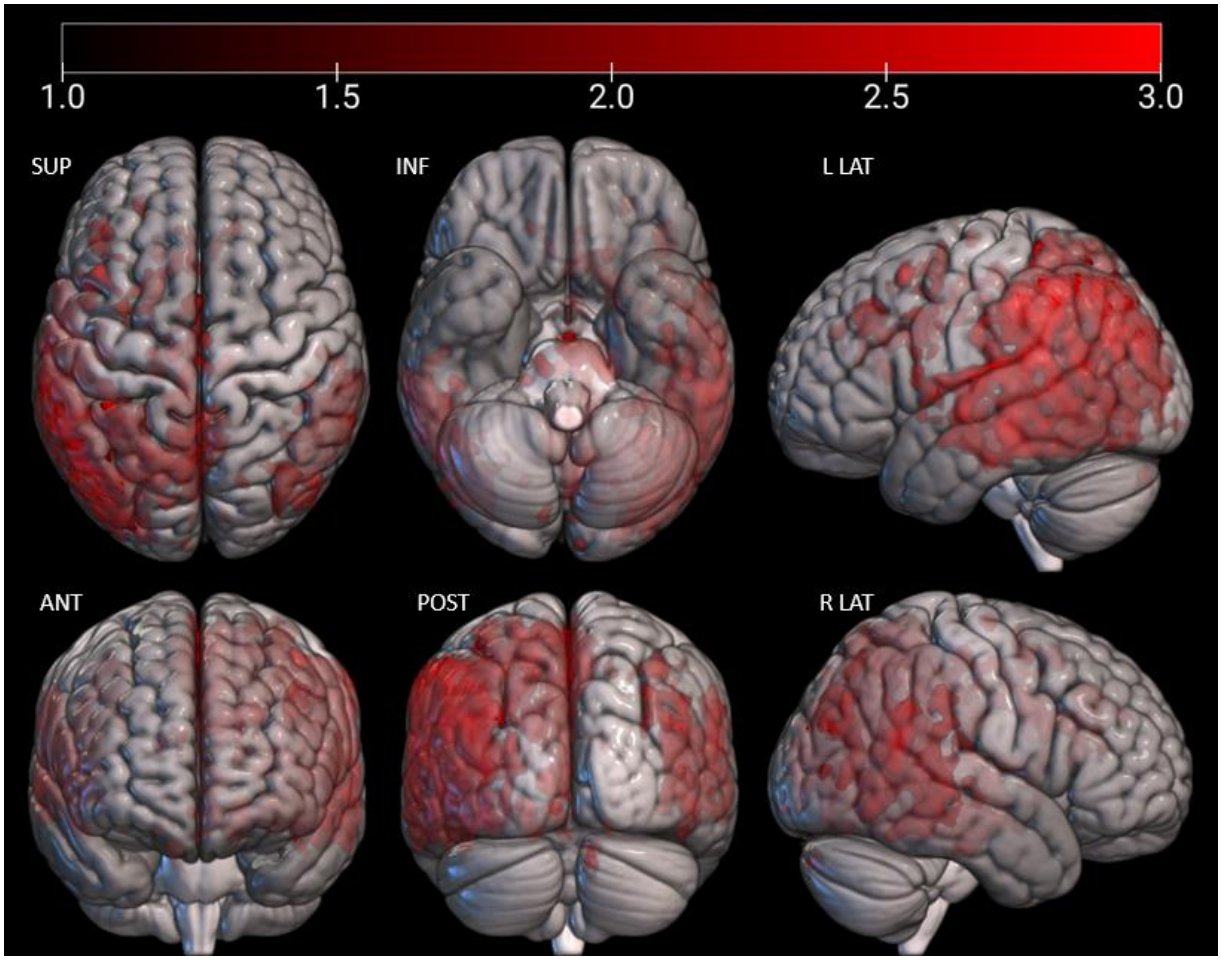
Supplementary Figure 13 (Case 4 Early-onset PCA): (A) Axial CBF image showing biparietal decreased CBF (white arrows), extending into the left occipital lobe. **(B)** Axial [18F]-MK6240 tau PET image showing cortical tau deposition corresponding to areas of decreased CBF. **(C)** Diffuse cortical amyloid deposition on the axial [11C]-Pittsburgh Compound B PET image. **(D)** Axial 3D T1 MPRAGE showing nonspecific moderate generalized atrophy.



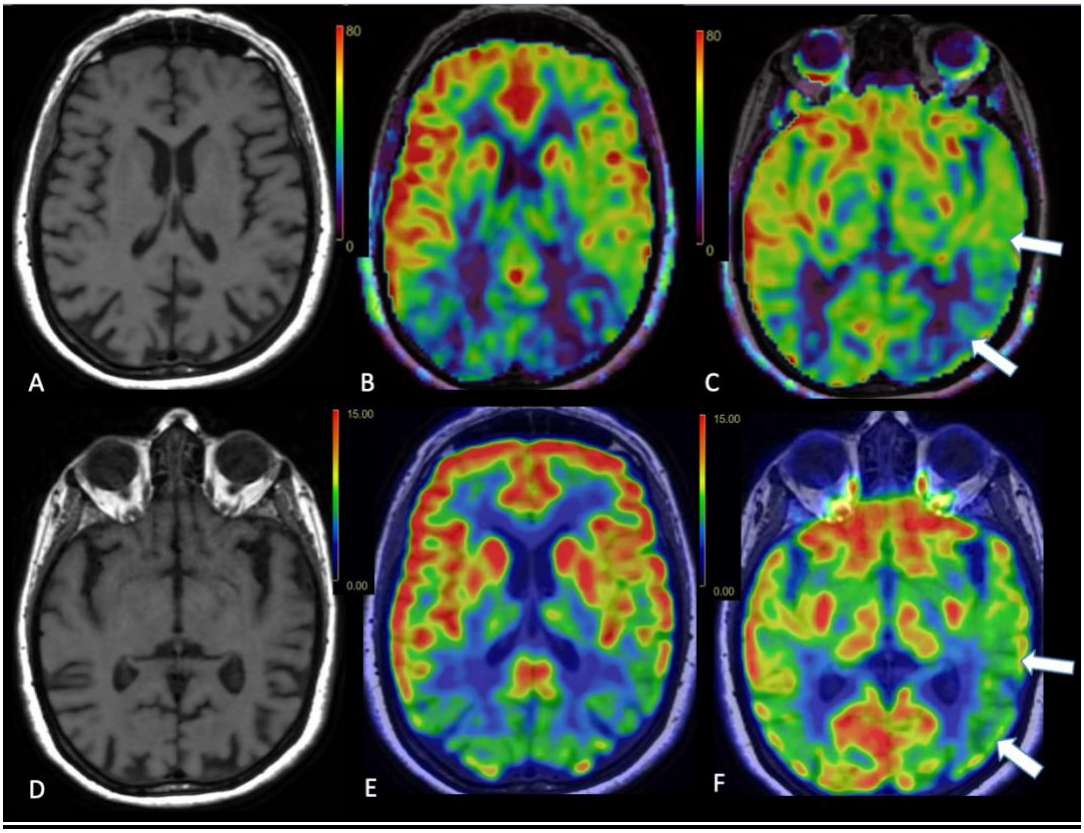
Supplementary Figure 14 (Case 4): Gray-scale axial ASL-MR image demonstrating decreased CBF in the bilateral parietal lobes, particularly on the left.



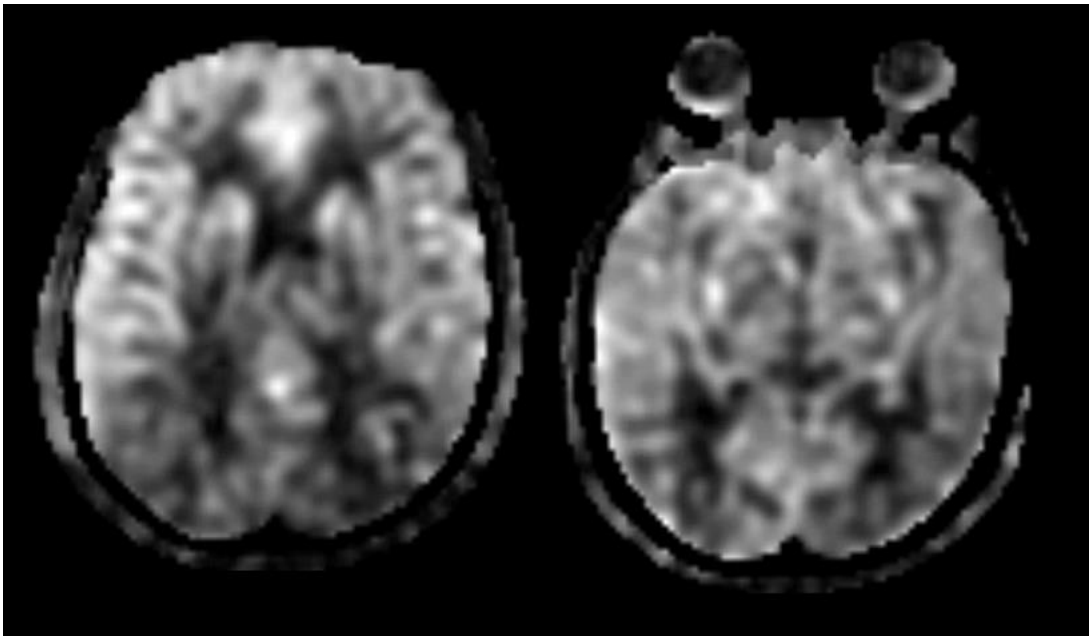
Supplementary Figure 15 (Case 4): Axial Z-score maps, with blue corresponding to areas of decreased CBF, predominantly in the temporal and parietal lobes, more pronounced on the left, as well as the left frontal lobe. Upper and lower Z-score thresholds of 1.0 and 3.0 are shown in the color bar.



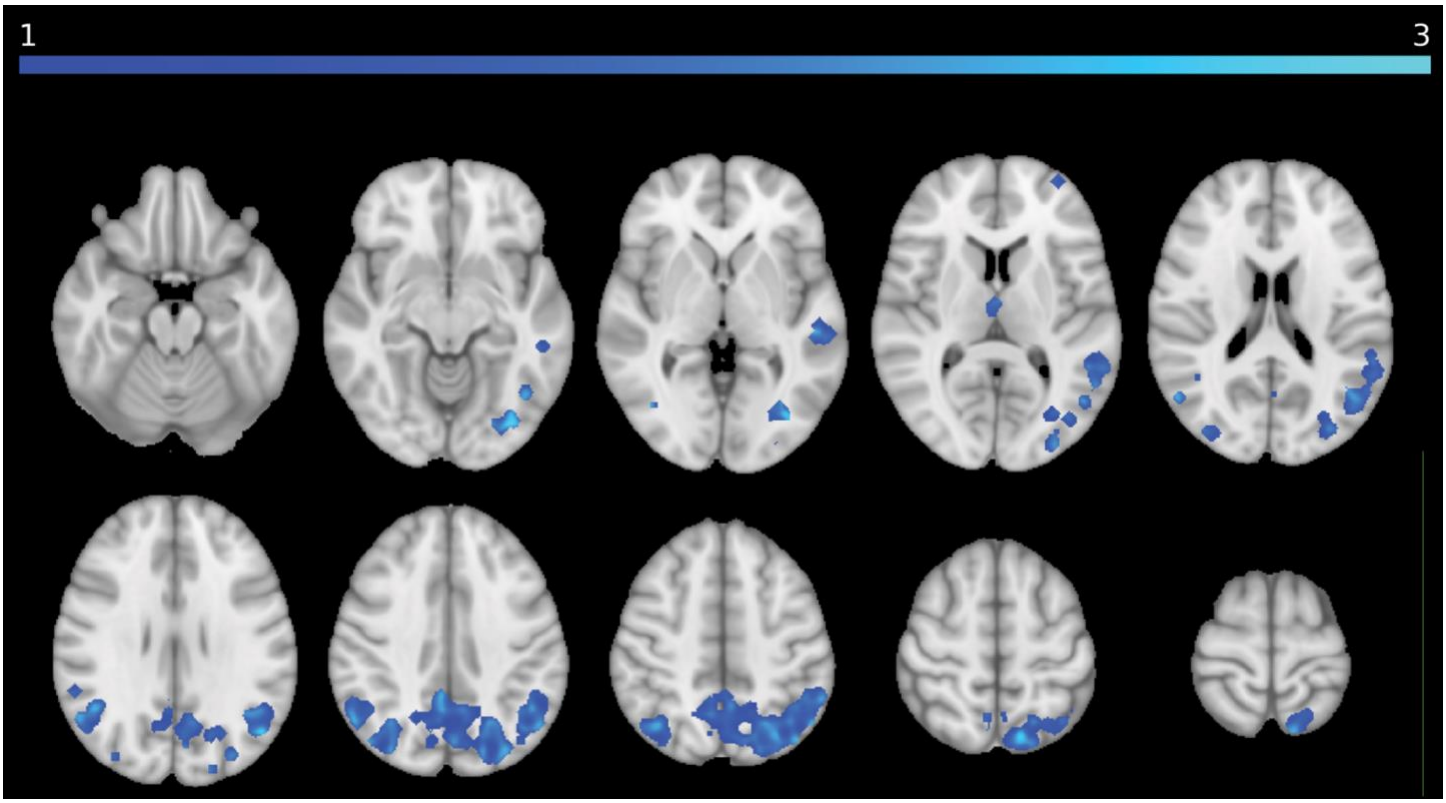
Supplementary Figure 16 (Case 4): Three-dimensional stereotactic surface projection images with red corresponding to decreased CBF, predominantly in the parietal and temporal lobes, as well as the left frontal lobe. Upper and lower Z-score thresholds of 1.0 and 3.0 are shown in the color bar.



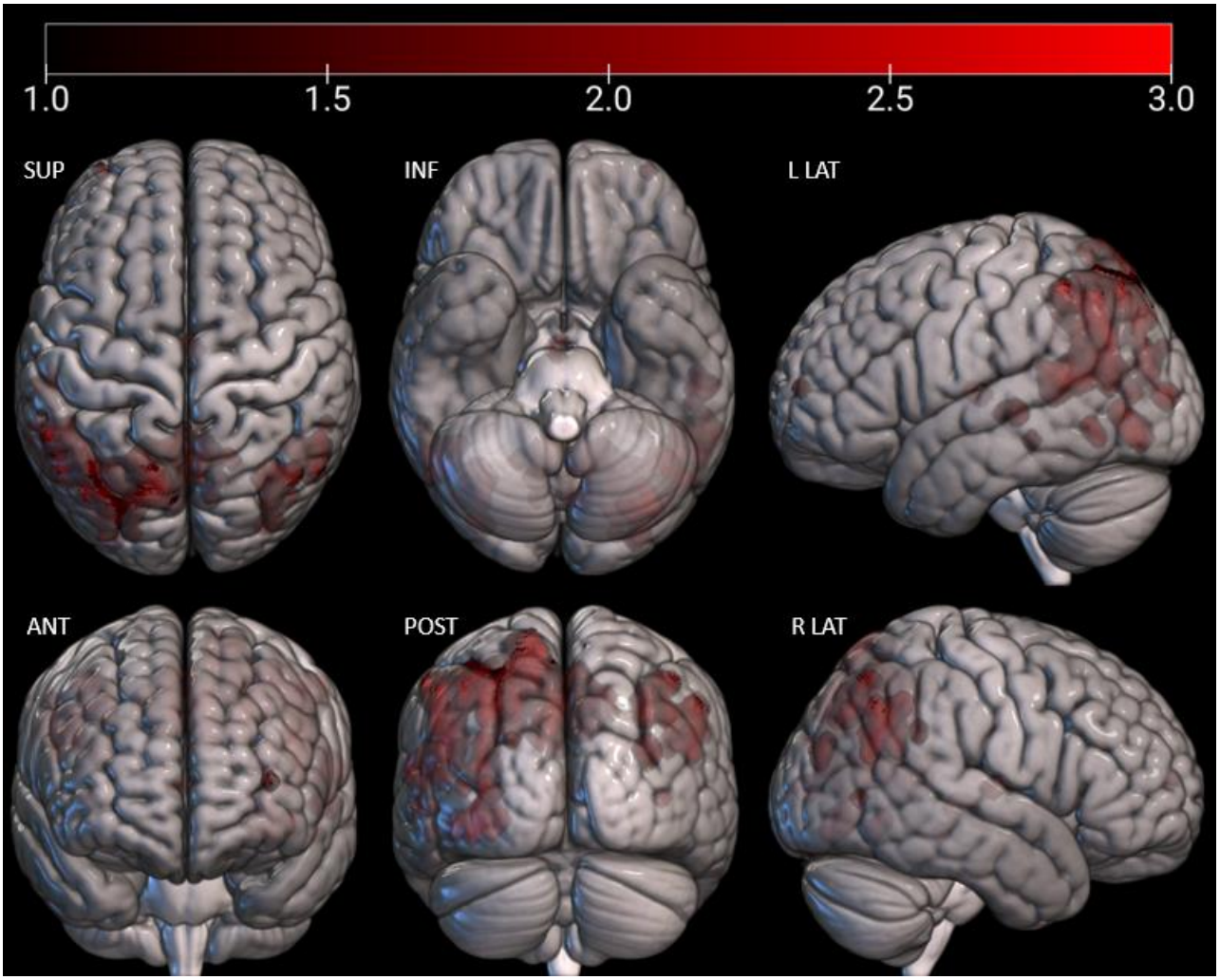
Supplementary Figure 17 (Case 5 Early-onset lvPPA AD): MR was notable for mild generalized volume loss with subtle asymmetric dilation of the left ventricular atrium **(A,D)**. ASL-MR showing decreased CBF in the bilateral parietal lobes **(B)**, also involving the left temporal lobe asymmetrically **(C) (white arrows)**, corresponding to decreased cortical FDG avidity on PET **(E,F)**.



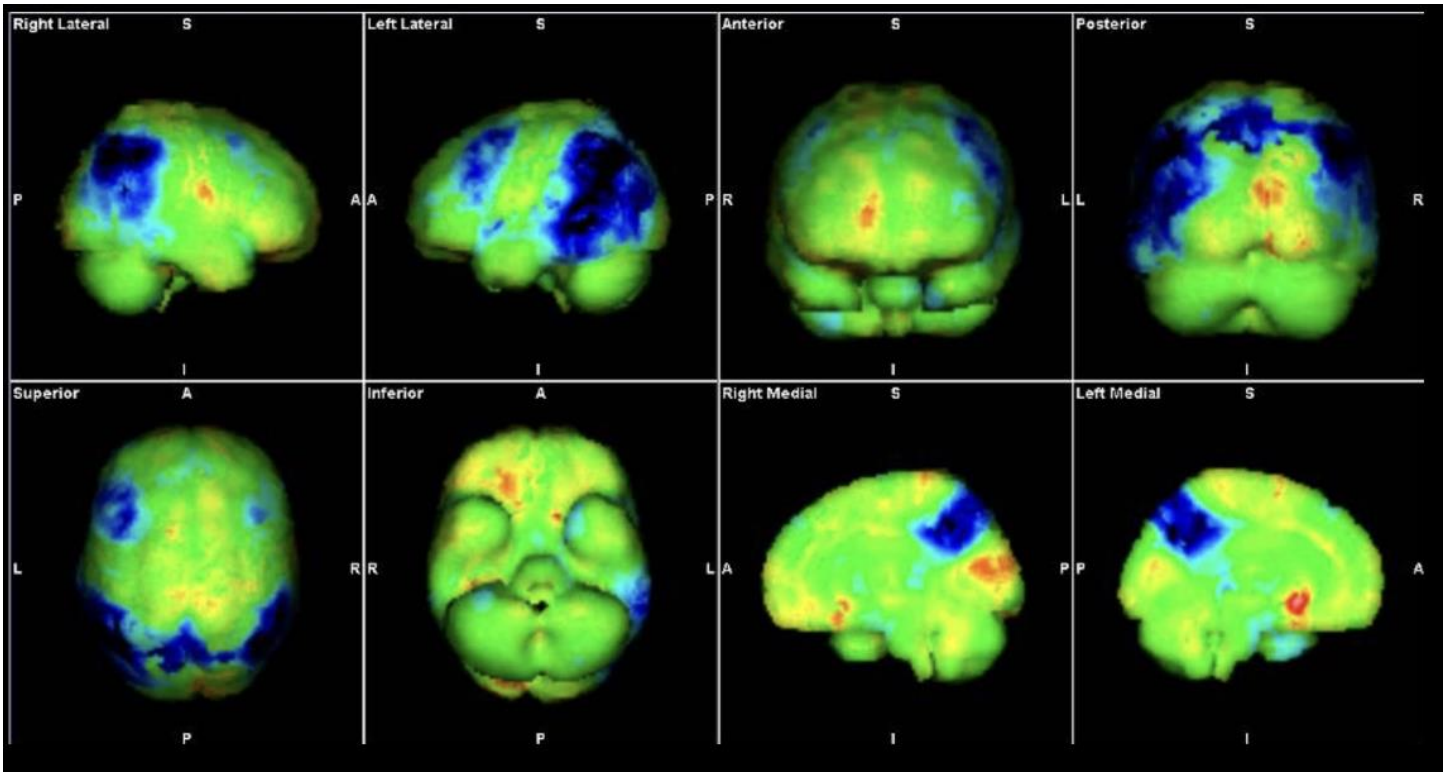
Supplementary Figure 18 (Case 5): Gray-scale axial ASL-MR images demonstrating decreased CBF in the bilateral parietal and left temporal lobes, suggestive of neurodegenerative disease.



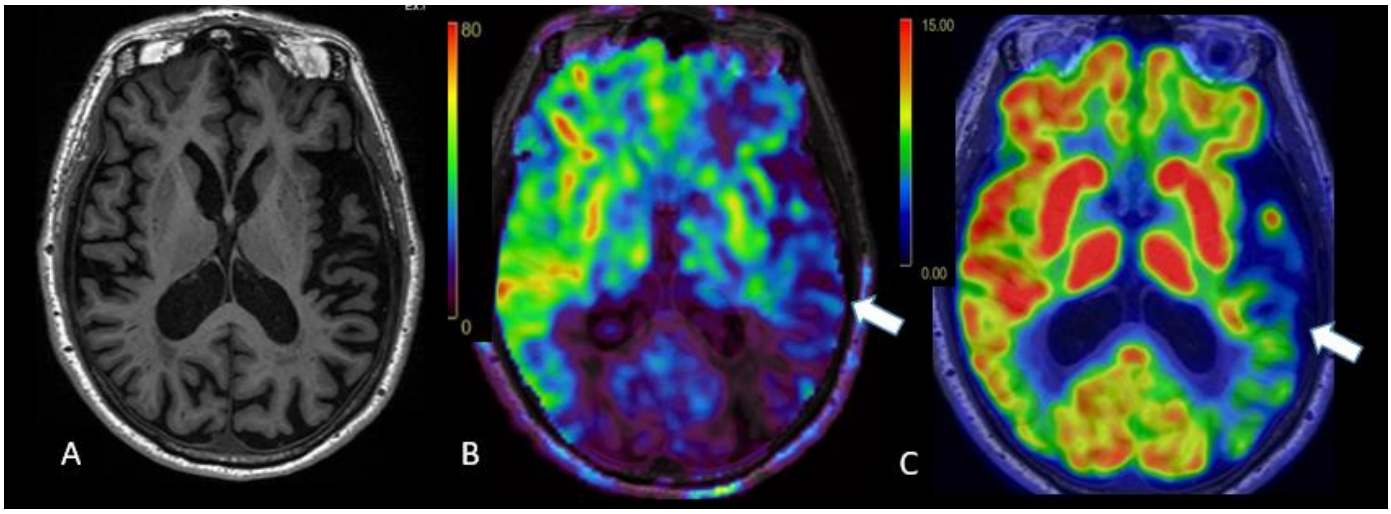
Supplementary Figure 19 (Case 5): Axial Z-score maps, with blue corresponding to areas of decreased CBF in the bilateral parietal and left temporal lobes, as compared to our control cohort. Upper and lower Z-score thresholds of 1.0 and 3.0 are shown in the color bar.



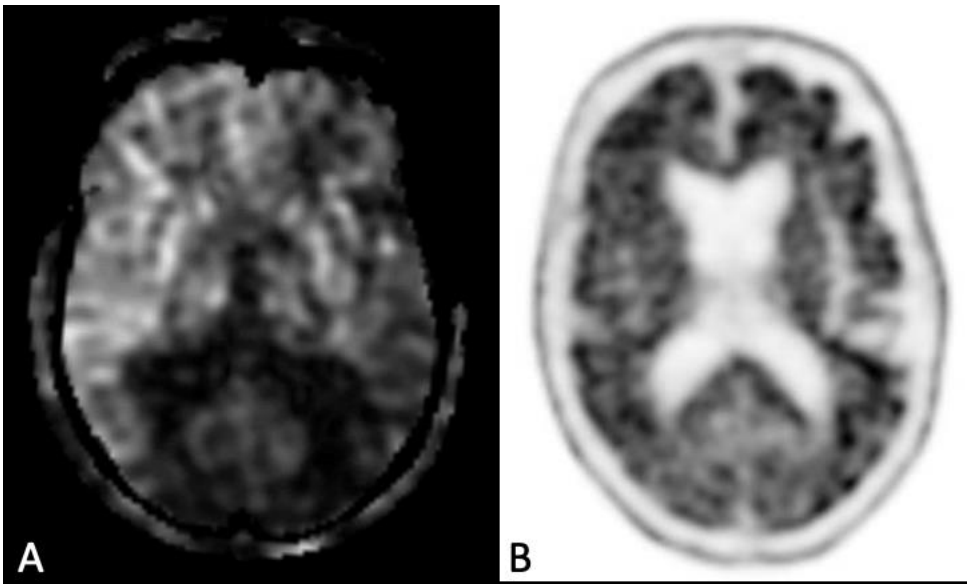
Supplementary Figure 20 (Case 5): Three-dimensional stereotactic surface projection images with red corresponding to decreased CBF in the bilateral parietal and left temporal lobes, as compared to our control cohort. Upper and lower Z-score thresholds of 1.0 and 3.0 are shown in the color bar.



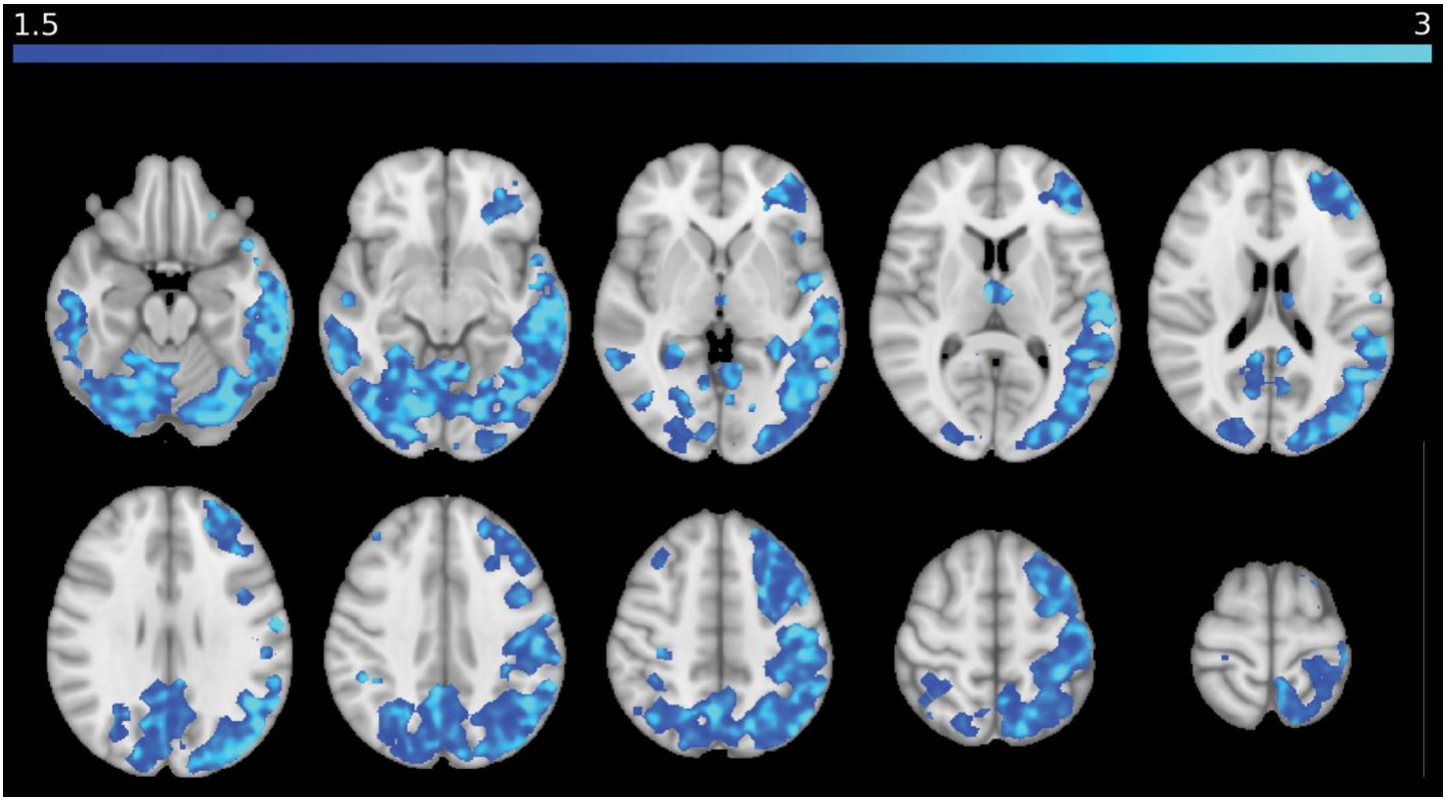
Supplementary Figure 21 (Case 5): Three-dimensional stereotactic surface projection images with blue representing the patient's decreased FDG avidity in the bilateral parietal and temporal lobes, as well as the precuneus bilaterally and left frontal lobe.



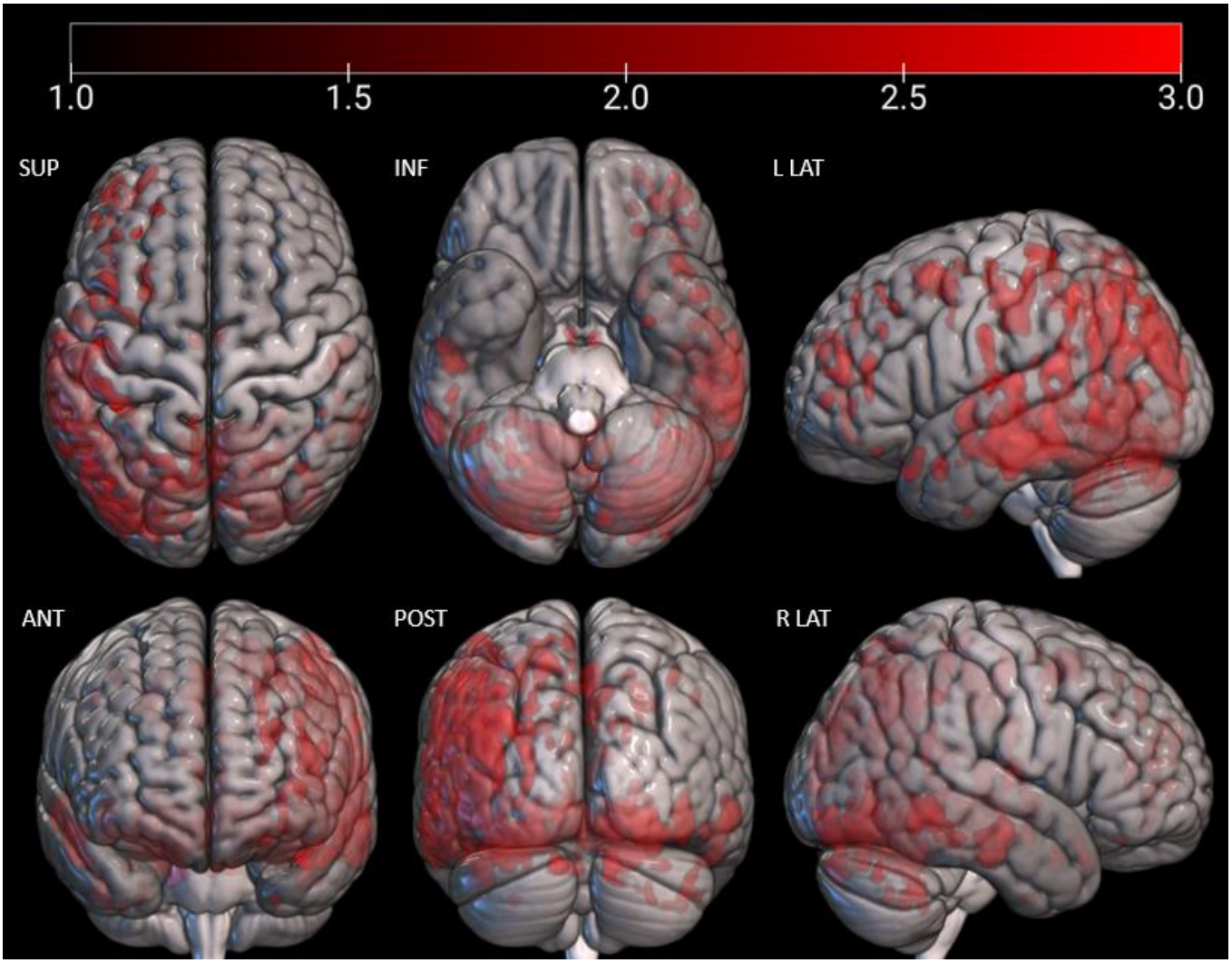
Supplementary Figure 22 (Case 6 lvPPA). (A) Axial 3D T1 MPRAGE image demonstrating moderate generalized volume loss. **(B)** Axial ASL-MR image showing decreased CBF in the bilateral parietal lobes, more pronounced on the left, as well as the left frontal and temporal lobes. **(C)** Axial FDG-PET image showing decreased FDG avidity in the left parietal (white arrow) and temporal lobes, as well as the right parietal and left frontal lobes to a lesser extent.



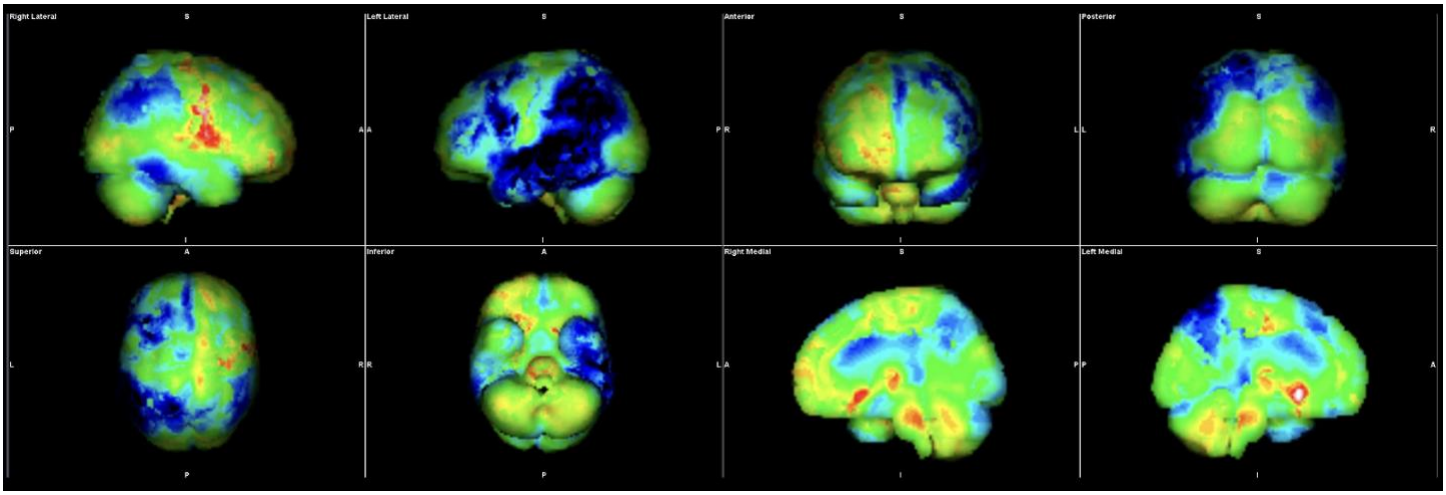
Supplementary Figure 23 (Case 6): (A) Gray-scale axial ASL-MR demonstrating decreased CBF in the bilateral parietal lobes (more pronounced on the left) and left frontal lobe, suggestive of neurodegenerative disease, particularly a primary progressive aphasia. **(B)** Axial [18F]-florbetaben PET image demonstrating diffuse cortical amyloid deposition, consistent with AD.



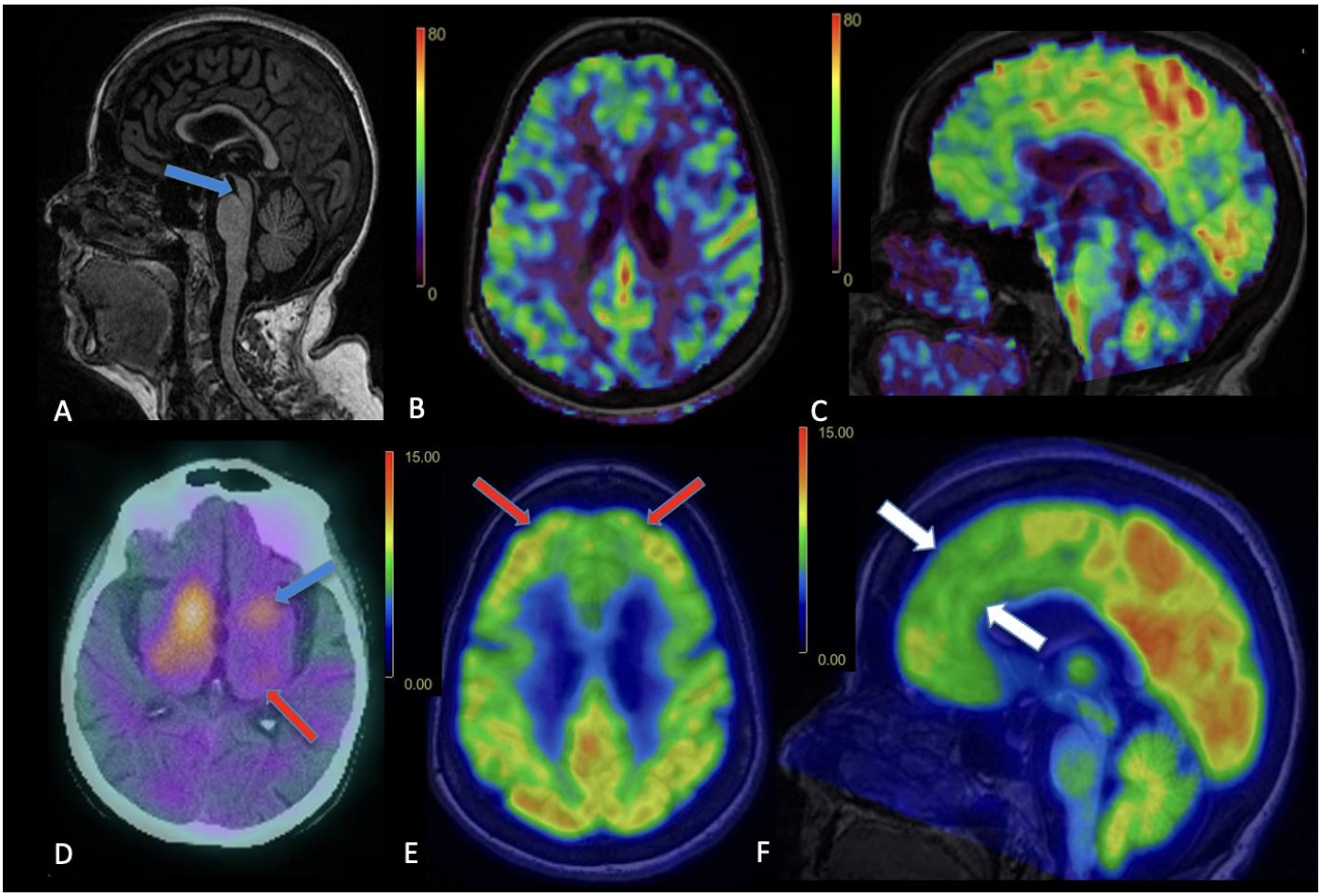
Supplementary Figure 24 (Case 6): Axial Z-score maps, with blue corresponding to areas of decreased CBF, predominantly in the temporal and parietal lobes, as well as the left frontal lobe. Upper and lower Z-score thresholds of 1.5 and 3.0 are shown in the color bar.



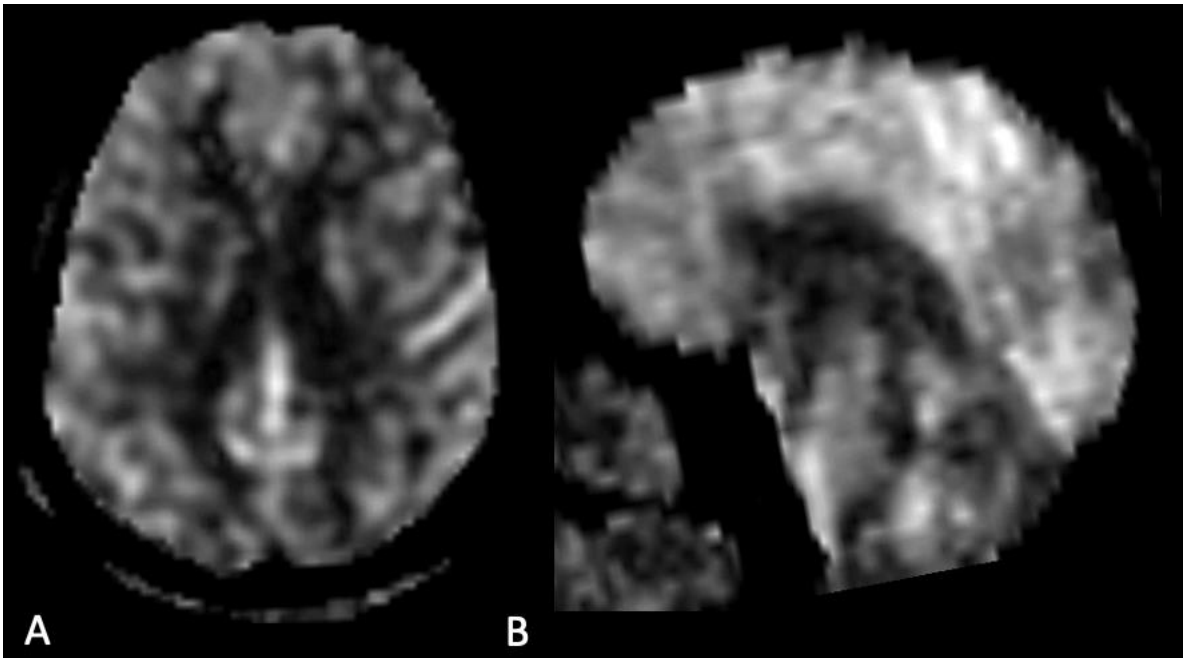
Supplementary Figure 25 (Case 6): Three-dimensional stereotactic surface projection images with red corresponding to decreased CBF, predominantly in the temporal and parietal lobes, as well as the left frontal lobe. Upper and lower Z-score thresholds of 1.0 and 3.0 are shown in the color bar.



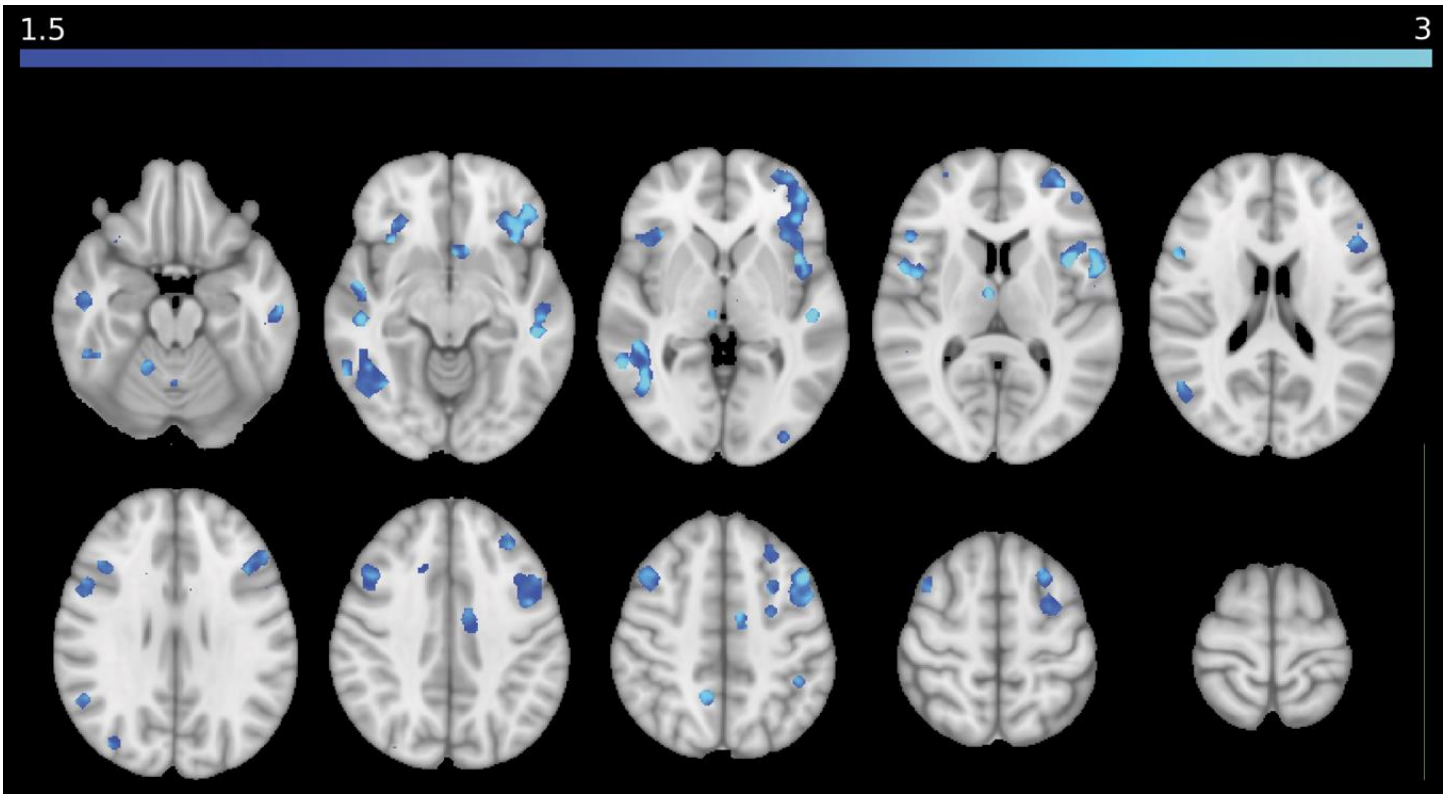
Supplementary Figure 26 (Case 6): Three-dimensional stereotactic surface projection images with blue representing the patient's decreased FDG avidity in the bilateral temporal and parietal lobes, as well as the left frontal lobe, using the clinically available syngo.via software package



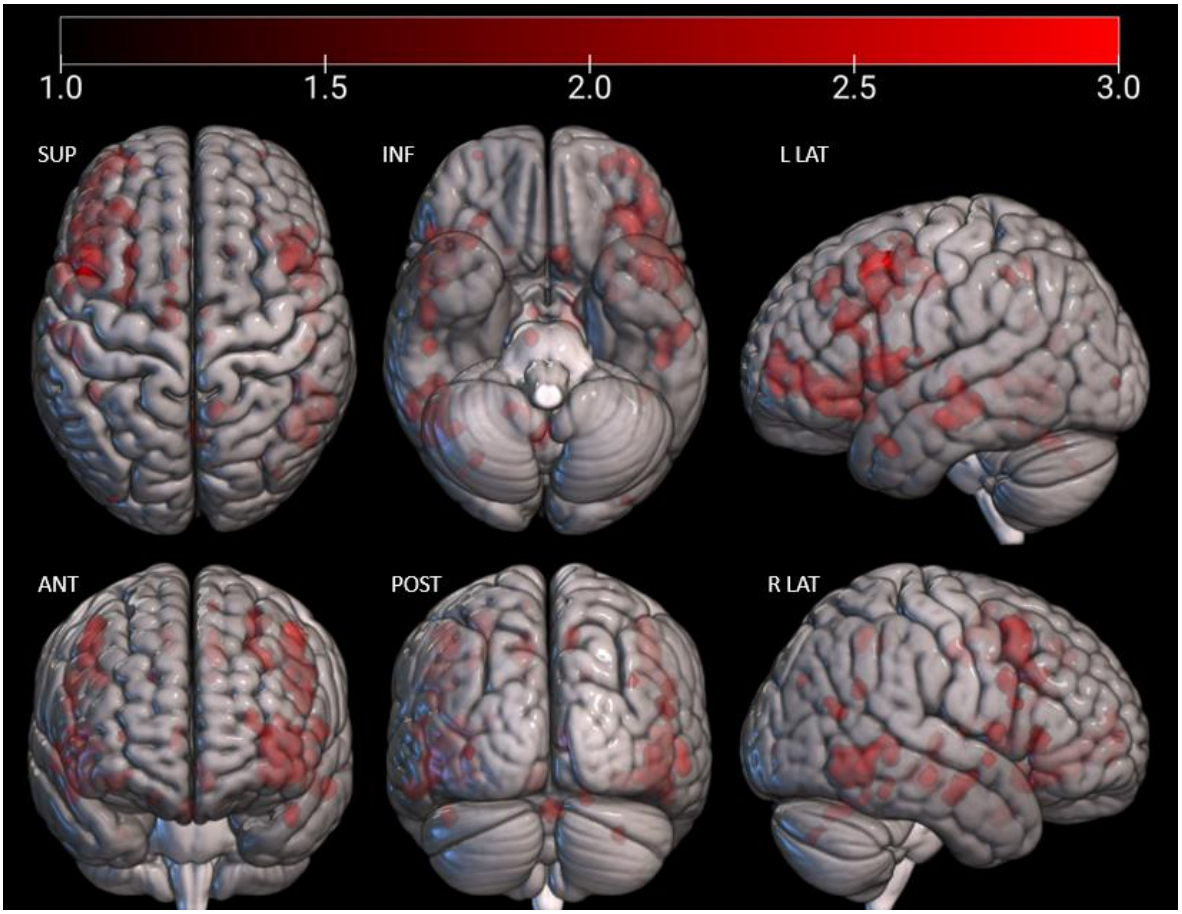
Supplementary Figure 27 (Case 7): Progressive Supranuclear Palsy. (A) Sagittal 3D T1 MPRAGE image showing midbrain atrophy (“hummingbird” sign) (blue arrow). Axial **(B)** and sagittal **(C)** CBF images showing decreased CBF in the bilateral frontal lobes, which was confirmed on axial **(E)** and sagittal **(F)** FDG-PET images. Axial image from a DaTscan **(D)** showing decreased radiotracer activity in the left caudate (blue arrow) and left (red arrow) greater than right putamina, supporting the diagnosis of progressive supranuclear palsy.



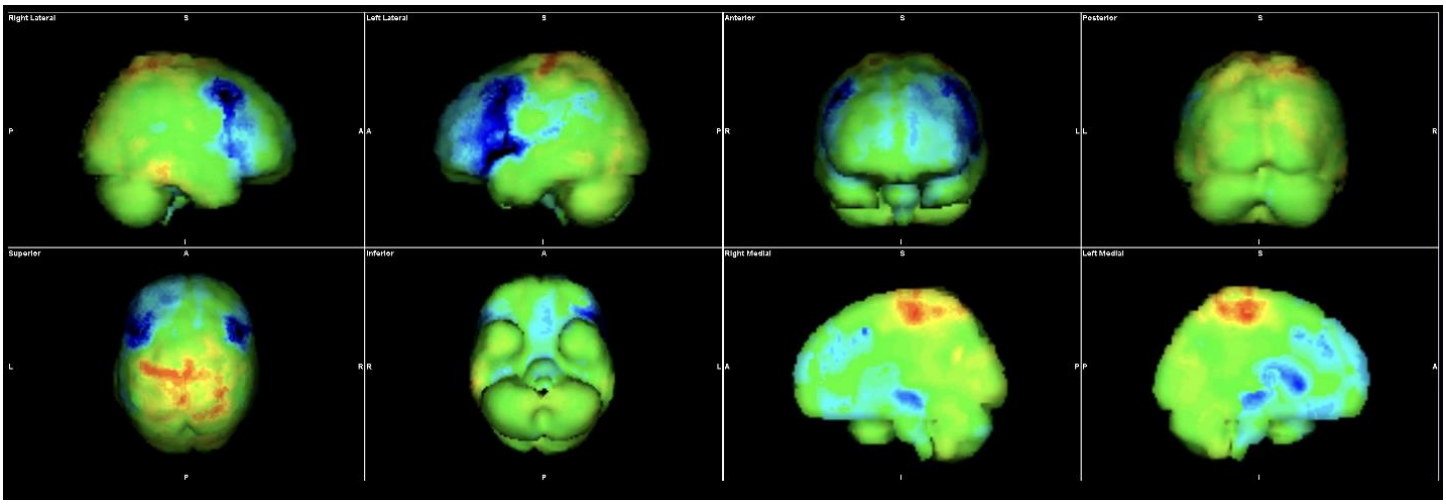
Supplementary Figure 28 (Case 7): Gray-scale axial and sagittal ASL-MR images demonstrating decreased CBF avidity predominantly in the bilateral frontal lobes (more pronounced on the left), suggestive of neurodegenerative disease.



Supplementary Figure 29 (Case 7): Axial Z-score maps, with blue corresponding to areas of decreased CBF, predominantly in the frontal lobes. Upper and lower Z-score thresholds of 1.5 and 3.0 are shown in the color bar.



Supplementary Figure 30 (Case 7): Three-dimensional stereotactic surface projection images with red corresponding to decreased CBF, predominantly in the frontal lobes. Upper and lower Z-score thresholds of 1.0 and 3.0 are shown in the color bar.



Supplementary Figure 31 (Case 7): Three-dimensional stereotactic surface projection images with blue representing the patient's decreased FDG avidity in the frontal lobes, using the clinically available syngo.via software package.