Cerebellum Lobe Tracing Guidelines

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Manual Tracing Guidelines

The continuous classified, T1 weighted and discrete classified images were used during tracing. The continuous image was the primary image used, but the discrete image provided a reliable, consistent guide for definition of the GM-CSF border (surface of the cerebellum where it borders the CSF) and GM-WM border of the corpus medullare in areas where lack of detail prevented clear definition. For poorly defined borders where partial voluming causes misclassification (cerebellum-tentorium-cerebrum interface and WM-CSF interfaces such as the peduncles) the T1 weighted image was referenced for verification.

For the purposes of our study, we have divided the cerebellar cortex into three sections, bordered by the primary fissure and the horizontal fissure. Our parcellated structures are listed below, with the corresponding lobules using the nomenclature of Larsell and Jansen.

Anterior Lobe	I, II, III, IV & V
Superior Posterior Lobe	VI & Crus I of VIIA
Inferior Posterior Lobe	Crus II of VIIA, VIIB, VIII, IX & X
Corpus Medullare	Central white matter and output nuclei

In this study no distinction was made between the vermis and hemispheres.

The output nuclei and central white matter were designated as the corpus medullare, which was traced as a structure separate from the lobes. The output nuclei are not reliably visible on MR images at this resolution, and no attempt was made to delineate the nuclei. White matter branching off the corpus medullare into the folia was defined to be included in the lobes. The cerebellar peduncles were excluded at the point where they extended past the cerebellar grey matter.

The BRAINS2 software package was used for this tracing project. (Available to be shared with research groups. Download requests may be made at http://moniz.psychiatry.uiowa.edu.) All measured regions of interest (ROI's) were traced in the sagittal plane. Besides providing separate windows for coronal, axial, sagittal and three-dimensional ROI views, BRAINS2 allows the operator to adjust the characteristics of ROI intersections with other planes. For instance, the intersection of an ROI traced in the axial plane can be viewed as an X in the sagittal slices throughout its extent. Guide traces are placed in one plane to assist in consistent identification of fissures and borders while tracing in another plane.

The boundary between right and left cerebellum was defined prior to tracing. Viewing the most posterior point of the 4th ventricle in the coronal plane, the midline was determined from the vertex of the 4th ventricle and the midline of the corpus medullare. Slices were defined as either right or left. As a convention, the midline slice was considered to be part of the right cerebellar structures. If there were two slices that might equally be considered the midline, the right slice was chosen.

Guide Traces

Guide traces were used to assist in identification of the two major fissures that subdivide the cortex and to establish the limits of the corpus medullare. Representative guide traces used in this method are shown in Figure 2.

Primary Fissure Guide Trace. The primary fissure was identified on the midline sagittal slice (see Figure 3A). The anterior lobe lies anterior to the primary fissure, and lobules IV and V are a single tree-like structure with a single trunk. The primary fissure is the uninterrupted fissure extending from the cerebellar surface to the white matter center, just posterior to lobule V. With the crosshairs approximately 1/3 of the way in from the edge of the cerebellum and centered in the primary fissure, viewing was switched to the axial plane (Figure 2A). The crosshairs were left in the same location to accurately identify the primary fissure. It was identified in the axial view as the dark region at the crosshairs that extends laterally as a continuous space between the folia. The axial guide trace was placed in the primary fissure along its entire extent on that slice. Additional guide traces were placed on all consecutive axial slices inferior to the slice containing the first trace until the corpus medullare came into view and the primary fissure no longer extended uninterupted across the entire cerebellum.

The guide traces were then reviewed in the sagittal viewer by scrolling through sagittal slices to ensure the X's from the intersecting ROI's consistently marked the same fissure. In the hemispheres the primary fissure appears nearly identical to neighboring fissures when viewed in the sagittal plane. To ensure proper identification, the primary fissure guide traces were evaluated starting at the midline and scrolling laterally in each direction. Sublobules Vf and VIf straddle the base of the primary fissure on the midline (see Figure 3A). As the review continued laterally, sublobules Vd-f and VId-f were carefully followed until they either became too small to view or joined with other sublobules to become continuous with a major folium in the hemisphere.

Cerebellar Peduncle Guide Trace. The cerebellar peduncles were excluded from the corpus medullare regions of interest at the point at which they emerged beyond the grey matter of the cerebellar cortex, as viewed in the axial plan. Traces were placed in the axial plane to assist in "cutting off" the peduncles where they emerged from the cerebellum (Figure 2B). The trace started at the anterior-most grey matter on the lateral border of the peduncle. The trace then extended to the anterior border of the grey matter on the midline, then to the grey matter-peduncle border on the other side. The trace followed the anterior edge of the brainstem to close back to the origin. These guide

traces were completed on every other slice where a clear connection from the cerebellum to the brainstem existed.

Horizontal Fissure and Corpus Medullare Guide Traces. The horizontal fissure was identified in the coronal view while scrolling anteriorly in the cerebellum. The horizontal fissure is bordered by crus I of VIIA superiorly and crus II of VIIA inferiorly, and forms a broad inverted "V". A guide trace was placed on the first slice where the horizontal fissure was clearly identified. At the midline the trace was made continuous from one side to the next across the dura. On more anterior slices the cerebellum became visible near the midline, where the horizontal fissure was often difficult to follow. Crus I of VIIA is a hemispheric designation, and the corresponding vermian structure is VIIAf, also known as the folium. In some subjects VIIAf is absent, and in most subjects it is not visible on MR images at this resolution. For most scans the horizontal fissure and the superior posterior fissure appear to meet and become continuous near the medial portions of the cerebellum. Therefore, the horizontal fissure guide trace followed the superior posterior fissure in the vermis.

The guide trace was complete on every third slice until the corpus medullare came into view. The corpus medullare is a white matter structure which, as the view scrolls anteriorly, is seen to interrupt the horizontal fissure on both sides approximately 15 mm lateral to the midline. At this point the guide traces for the corpus medullare were begun. An ROI was traced around each portion of the corpus medullare on every third slice, continuing anteriorly until the peduncles emerge from the cerebellum. The guide traces followed the grey matter/ white matter border through the majority of the border, but care was taken to "cut off" the white matter centers of the folia at the point where they emerge from the corpus medullare (see Figure 2D).

Measured Traces

Measured traces are shown in Figure 3, with the guide traces intersecting the sagittal plane shown as X's. As a convention for all measured regions, cerebrospinal fluid (CSF) that could be viewed on a single slice as continuous with regions external to the cerebellum was excluded from the traces. Internal CSF, not extending outside of the cerebellum, was included in the measured traces. Internal CSF that bordered on two or more structures was divided equally between the adjacent structures, unless the trace would greatly divert from its normal course. Since the grey matter-CSF borders were often indistinct and occasionally blurred, the definition of this border was based on the discrete classified image, with reference to the other images for review of validity.

Corpus Medullare. The corpus medullare includes the entire central white matter structure and the output nuclei. However, the white matter that branches off into the folia was defined to be a part of the neighboring regions. The guide traces were used to assist in identification of the points where the white matter extends into the folia, especially into the tonsils, and where the peduncles are to be excluded. The intersections of the corpus medullare guide traces and the cerebellar peduncle guide traces were set to display. Beginning on the midline sagittal slice, the right corpus medullare was traced on every slice where it appeared. The left corpus was traced starting on the first slice to the

left of the midline. The corpus medullare was defined to not extend laterally past the point at which the horizontal fissure extends uninterrupted from the anterior to posterior border of the cerebellum.

Anterior Lobes. The anterior lobe is composed of lobules I-V (Figure 3). Lobules I and II appear as a single structure, and lie against the superior medullary vellum. Lobule III has a variable number of sublobules, but takes on a general appearance similar to that shown in Figure 3A. Lobules IV and V have a relatively constant, distinctive shape in the midline, with sublobules V d, e and f located on the interior of the primary fissure. These sublobules and those of lobule VI were carefully identified prior to tracing to ensure accurate parcellation.

The intersections of the primary fissure guide traces were displayed while tracing the anterior lobe. Starting at the midline for the right side, the trace began at the most posterior point of the 4th ventricle, proceeding anteriorly and superiorly following the GM-CSF border. Both the continuous and discrete classified images were referenced for this border. At the most superior point, near the peak of lobule IV, the trace followed posteriorly the border between grey matter and the tentorium. The continuous classified and T1 weighted image were used when tracing this region. At the primary fissure, as identified with the guide traces, the trace proceeded into the cerebellum to the base of the primary fissure. The trace followed the darkest portion of the primary fissure, or when that was not clear due to partial voluming or a very tight fissure, it equally divided the area between the white matter folia centers. CSF in the primary fissure that was not continuous with the exterior CSF was divided equally by the trace and shared with the adjacent structure. The trace then closed to the point of origin at the 4th ventricle. Where the corpus medullare is present, the trace followed its border until meeting up with the 4th ventricle. On more lateral slices, the guide traces were useful in identification of the primary fissure to avoid errors (Figure 3B).

Superior Posterior Lobes. The superior posterior lobe was defined to include lobules VI and VIIAf (folium) in the vermis regions and lobule VI and crus I of VIIA in the hemispheres (Figure 3). The intersections of the horizontal fissure guide traces were displayed while tracing the posterior superior lobes. Starting at the base of the primary fissure, the trace followed the posterior border of the anterior lobe to the surface of the cerebellum. At the surface of the cerebellum, the trace turned posteriorly to reach the horizontal fissure, as indicated by the intersections of the guide traces. The T1-weighted image was referred to regularly to ensure the border with the tentorium and cerebral cortex was correctly followed throughout this region. The trace followed the guide traces into the horizontal fissure. At the base of the horizontal fissure the trace continues along the superior border of the corpus medullare back to the origin. Near the midline the horizontal fissure doesn't extend all the way to the corpus medullare; it reaches the base of the fissure in the highly branched vermian lobules VI, VIIAf and VIIAt. When the base of the horizontal fissure is reached, the trace followed the white matter center of the folia to the corpus medullare, then back to the origin. Near the midline care was taken to avoid inclusion of dura and blood vessels in the trace, as these are prominent intrusions into the midline areas.

*Inferior Posterior Lobes***.** The inferior posterior lobe consists of lobules VIIAt (tuber) through X in the vermian regions, and crus II of VIIA through lobule X in the hemispheres (Figure 3). The inferior posterior lobe was traced starting at the anterior inferior border of the corpus medullare, continuing along the inferior border of the superior posterior lobe to the posterior end of the horizontal fissure. The trace followed the edge of the cerebellar grey matter inferiorly and anteriorly to the 4th ventricle, then closing to the origin. On medial slices care was taken to avoid inclusion of blood vessels and dura that extend into the cleft between the hemispheres. On the lateral slices care was taken to include the flocculus within this trace. The flocculus was often best visualized on the T1 weighted image.

Review of Traces. Displays used for review of ROI's are shown in Figure 4. With the intersections of all sagittal ROI's displayed, the traces were viewed in the coronal plane for accuracy and consistency from slice to slice (Figure 4A). Dynamic review was accomplished by using the viewer's slider to quickly page through the image while paying close attention to the traces. ROI's were also reviewed in the 3D viewer (Figure 4B). Outliers and inconsistent traces were located and revised.

Semiautomated Method

To produce an automated method for parcellation, the artificial neural network (ANN) implemented by our lab was employed. To remove some of the variability in cerebellar size and position with respect to each scan's Talairach bounds and ACPC points, a coordinate space for the cerebellum was defined for each scan, with bounds defined as the most superior, inferior, left, right, and posterior points at which the cerebellum was visualized. The most anterior point of the pons was used as the anterior bound, and the most posterior point of the fourth ventricle at the midline, as defined in the manual method, was used as an internal reference point.

To further reduce variability in the images and structures "seen" by the ANN, each structure and image was warped using a three-dimensional point-based thin-plate spline method. The 9 points defined by the coordinate space (8 points of the box and the midline fourth ventricle notch) and an additional 22 anatomic features were chosen, making a total of 31 landmarks picked on each scan (Figure 5).

Paging anteriorly in the coronal view, three points were chosen in the horizontal fissure on the first slice where the corpus medullare interrupted the horizontal fissure, one where each corpus first appeared and one in the midline (l_horiz, r_horiz and mid_horiz in Figure 5A). In the midline sagittal view (Figure 5B) landmarks were chosen at the most anterior and most superior points of the anterior lobe (mid_ant and mid_sup). The landmark for the most posterior extent of the fourth ventricle on the midline is also shown (mid_4v). Paging inferiorly in the axial view (Figure 5C), three points were chosen in the primary fissure on the first slice where the corpus medullare came into view, one at each of the extremes of the primary fissure and one on the midline (l_prim, r_prim and mid_prim). At the most lateral extent of the corpus on each side (Figure 5D shows the right side), 4 points each were chosen in the sagittal view. One was at the

middle of the last visible section of corpus (r_corp), one at the anterior and one at the posterior ends of the horizontal fissure (r_ant and r_post), and one on the superior point of the cerebellum, midway from the most anterior to the most posterior point on that slice (r_sup). Finally, points were chosen on both left and right sides for the most lateral visible parts of the primary fissure (r_prim_ext in Figure 5E for the right side), horizontal fissure and superior posterior lobes (l_horiz_ext and l_ext in Figure 5F). The landmark points for the extremes of the primary fissure, horizontal fissue and superior posterior lobes were chosen using the sagittal view. These were then reviewed in the axial and coronal views to ensure accuracy.

To use the ANN to generate the structures for a scan, the cerebellum coordinates and landmarks were chosen and the ACPC-aligned image was warped to the landmark averages. Then, the neural net was run on this warped image. After the ANN generated the structures, they were warped back to the original ACPC aligned image using the inverse warp transform. They were then reviewed and edited to conform to the original manual tracing guidelines before being measured. An example of these manually edited traces is shown in Figure 6.

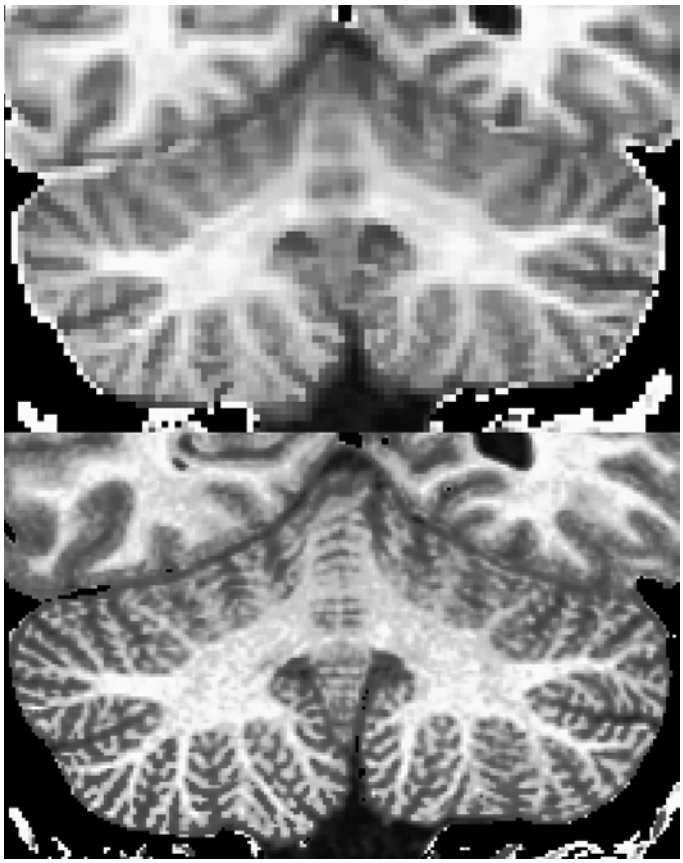

Figure 1. Coronal views of standard resolution (top) and high resolution (bottom) continuous-classified segmented images. High resolution images were used as reference for clarification of anatomical detail while developing manual tracing guidelines. All tracing and measurements were completed on standard resolution images.

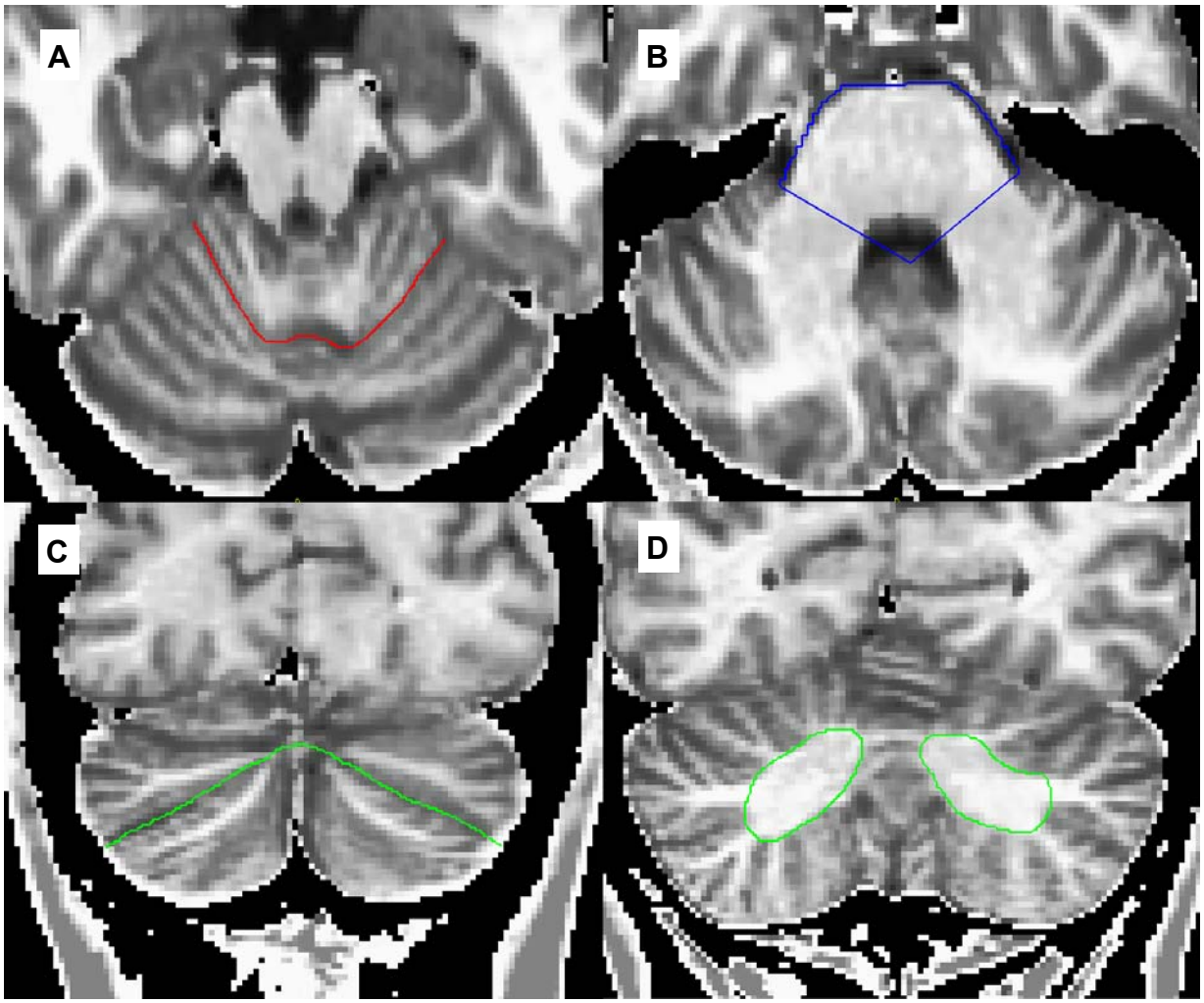

Figure 2. Representative guide traces. **A,** Primary fissure guide trace in the axial plane. The primary fissure was first identified in the midline sagittal view, then viewing switched to the axial view. In this axial view the primary fissure is continuous without interruption throughout its extent in the cerebellum. **B,** Cerebellar peduncle cutoff guide trace in the axial plane. The peduncles are excluded beyond the point at which they extend past the grey matter in the axial view. The guide trace connects the points where the grey matter ends on the lateral borders of the peduncles to the most anterior point of cerebellar grey matter at the midline. **C,** Horizontal fissure guide trace in the coronal plane. The guide trace extends through the dura near the midline in this coronal view. **D,** Corpus medullare guide traces in the coronal plane. The guide traces enclose the central white matter but exclude the white matter that branches off into the lobules.

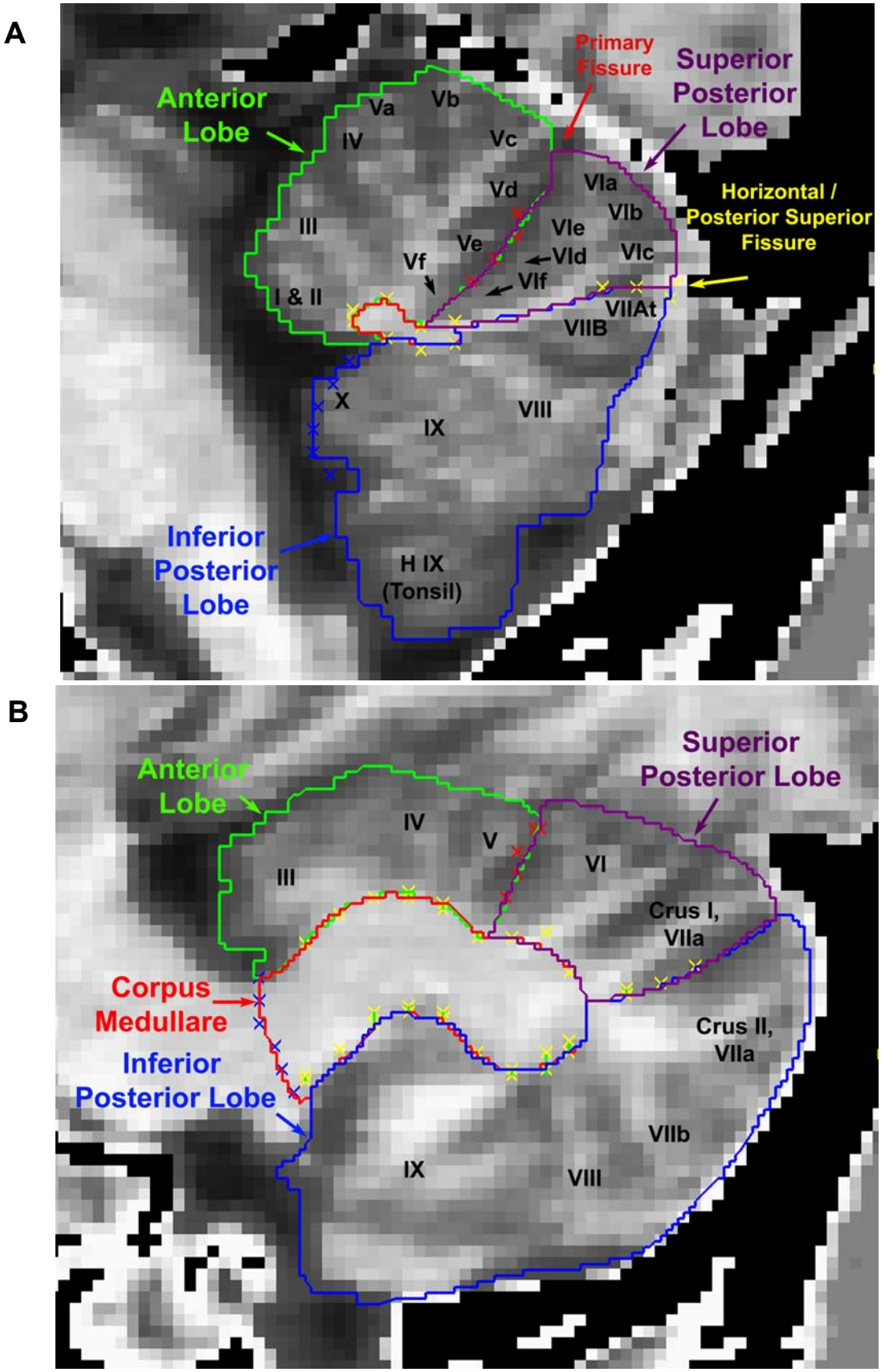

Figure 3. Regions of interest traces in the sagittal plane at the midline (**A**), and approximately 10 mm lateral to the midline (**B**). Intersections of guide traces are shown as red X's for the primary fissure, blue X's for the peduncle cutoff, and yellow X's for the horizontal fissure and corpus medullare. The guide traces assist in the identification of the fissures separating the cerebellar lobes and in the definition of the limits of the corpus medullare. Measured ROI's are the anterior, superior posterior and inferior posterior lobes, and the corpus medullare.

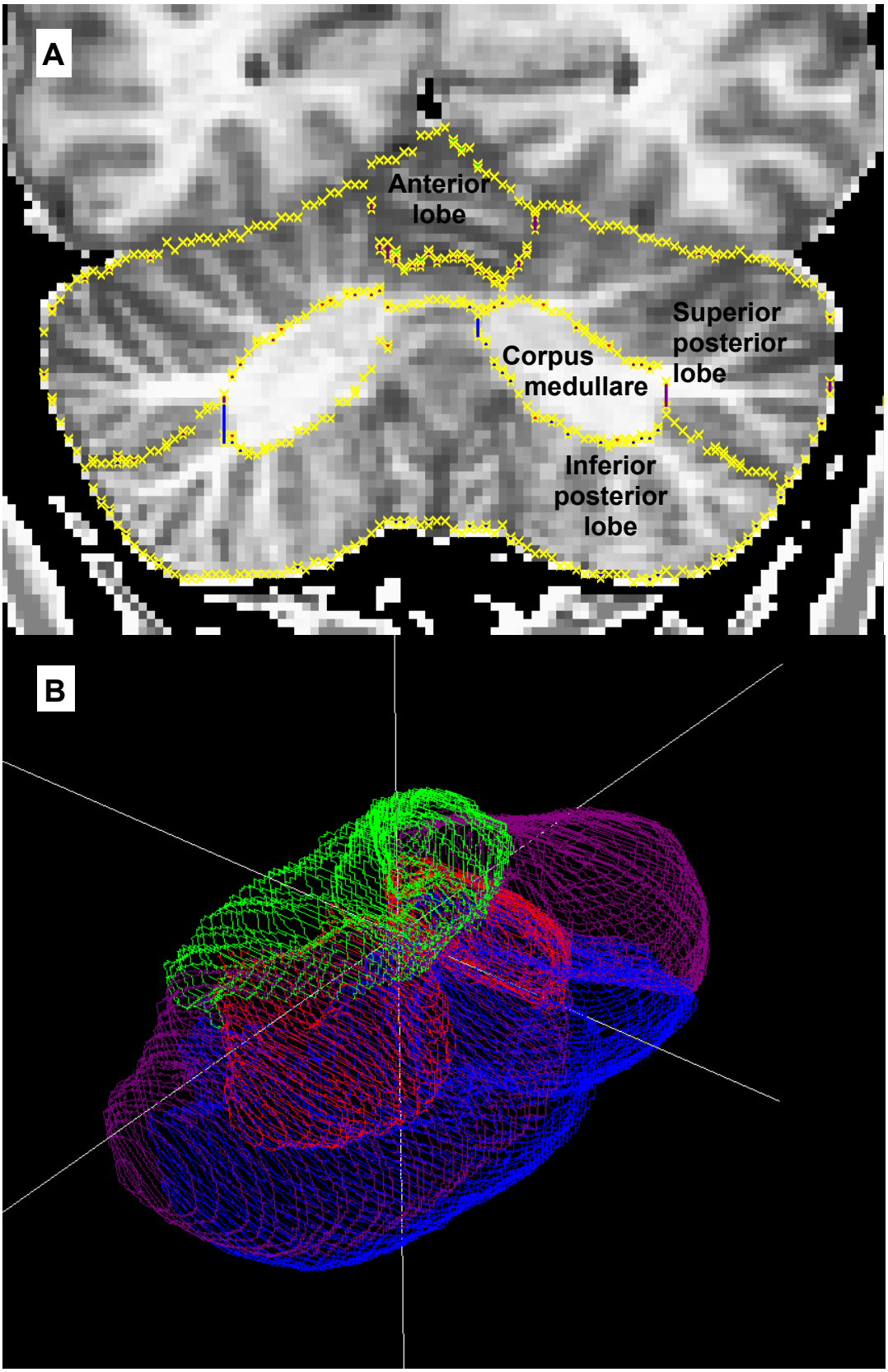

Figure 4. Review of sagittal traces by viewing intersections in the coronal plane (**A**) and by viewing traces in the three dimensional surface viewer (**B**). These views facilitate comparison of traces from all sagittal slices to locate outliers, which can be edited to ensure consistency.

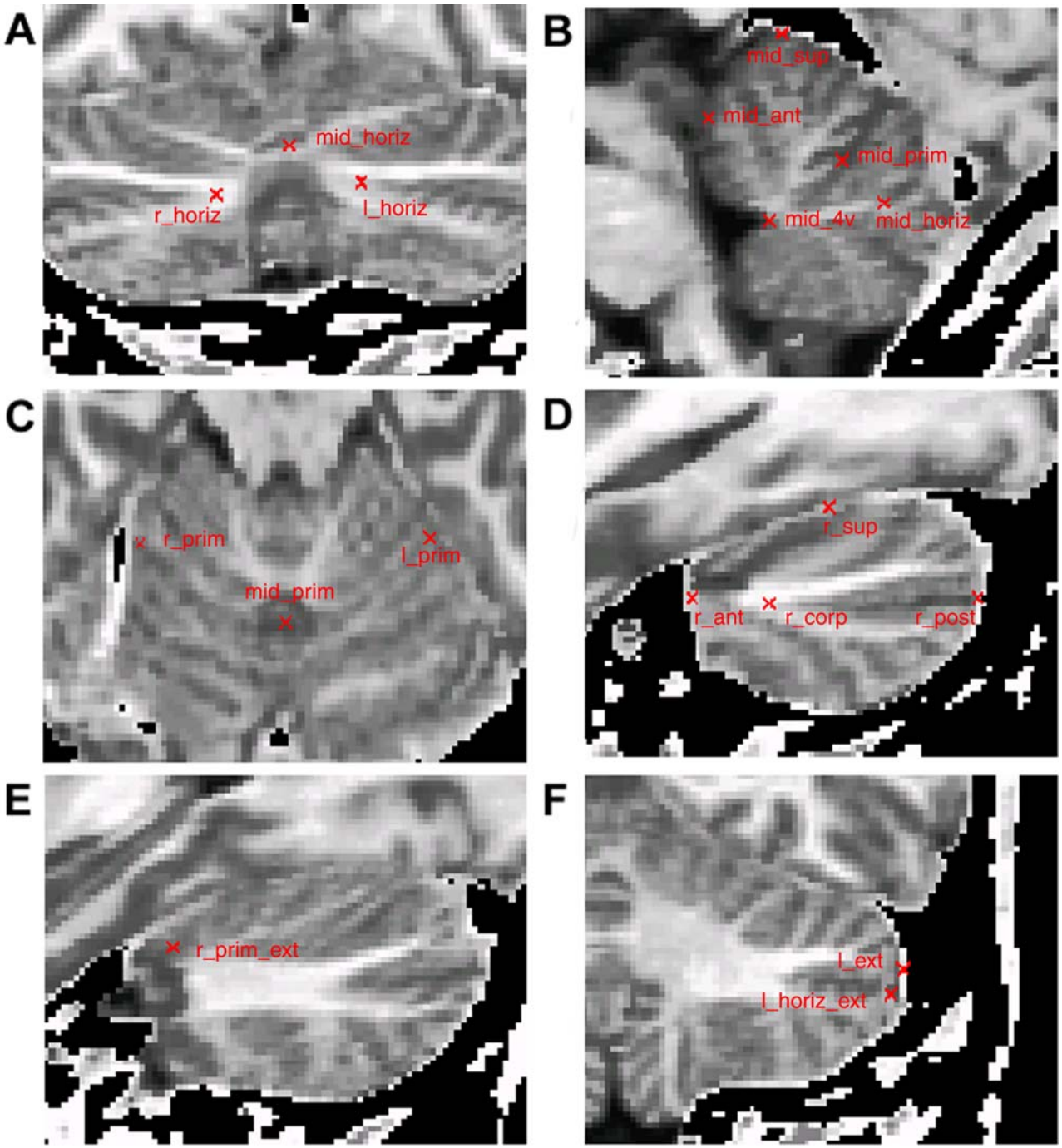

Figure 5. Landmarks used for warping images for neural net training and cutout. **A,** Horizontal fissure landmarks at the left and right posterior extremes of the corpus (r_horiz and l_horiz), and at the midline (mid_horiz). **B,** Landmarks picked on the midline sagittal slice are the anterior and superior extremes (mid_ant and mid_sup) and the posterior extreme of the fourth ventricle (mid_4v). **C,** Primary fissure landmarks at the midline (mid_prim) and left and right extremes on this axial slice (l_prim and r_prim). **D,** Landmarks picked on the sagittal slice that includes the lateral extreme of corpus. Shown for the right side are the landmarks for the last vestige of the corpus (r_corp), the anterior and posterior extremes of the horizontal fissure (r_ant and r_post) and the most superior point of the cerebellum (r_sup) halfway between most anterior and posterior points. **E,** Landmarks at the lateral extremes of primary fissure, shown here in the sagittal view on the right side (r_prim_ext). **F,** Landmarks at the lateral extremes of the superior posterior lobe (l_ext) and the horizontal fissure (l_horiz_ext), shown in the coronal view on only the left side.

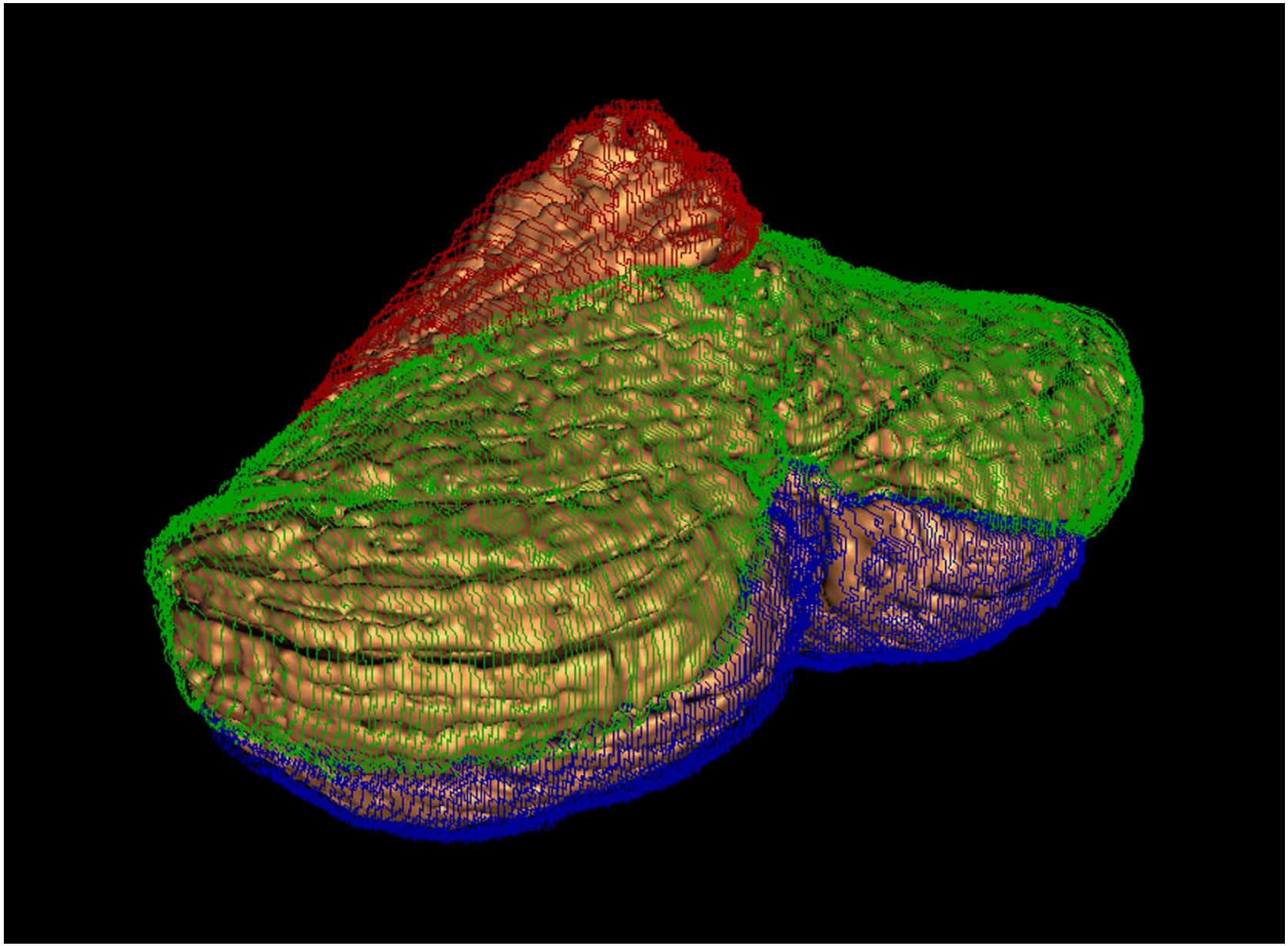

Figure 6. Surface of the cerebellum displayed with traces generated by semiautomated method and manually edited. Editing time was approximately 30 minutes. Anterior lobe: red, superior posterior lobe: green, inferior posterior lobe: blue.