Striatal Volume Contributes to the Prediction of Onset of Huntington Disease in Incident Cases

Supplemental Information

Supplemental Methods & Materials

MRI Scan Acquisition

All scans were obtained on a 1.5T MRI scanner (428 from a GE scanner; 79 from a Siemens scanner, and 35 from a Philips scanner) using a standard multi-modal protocol that included an axial 3D volumetric spoiled gradient echo series (~1 x 1 x 1.5 mm voxels) and a dual echo proton density/T2 (~1 x 1 x 3 mm voxels) series. There were 12 cases where the baseline (Time 1) and follow-up (Time 2) scans were obtained on scanners made by different manufacturers; in all other cases, both scans were obtained on scanners from the same manufacturer. Identical scanners were used in 60.1% of cases.

The scan sequence included a sagittal localizer, an axial 3D volumetric Spoiled GRASS (Gradient Recalled Acquisition in Steady State) image (TR = 18, TE = 3, field of view (FOV) = 24, thickness = 1.5 mm, 0 gap, matrix = 256 x 192 with ¾ phase FOV, number of excitations (NEX) = 2, flip angle = 20, bandwidth = 15, 124 slices) and a coronal T2/PD (proton density) image (TR = 3000, TE = 28, FOV = 26, thickness = 3.0, 0 gap, matrix = 256 x 192, NEX = 1, flip angle = 90, 64 slices). Scans were sent to The University of Iowa for analysis either via mailed CD or secured electronic file transfer protocol.

Image Analysis

Scans were processed through AutoWorkup (1), an automated procedure implemented with BRAINS (2) and AFNI's 3dSkullStrip (3). The T1 image was reoriented by stepwise coregistration using BRAINSfit (4) to a set of template images, using the result of each coregistration as the initialization for the next step. First, the rough outline of the brain provided

by 3dSkullStrip was coregistered to an average brain mask probability that was created from 108 anterior commissure - posterior commissure aligned scans. Next, a coregistration was completed to allow scaling of the participant's brain mask to allow maximal overlap, but scaling was then stripped from the transform to preserve the participant's brain size. Finally, the template image was resized to approximately the size of the participant's brain, and coregistration was completed using the full detail of the entire brain in both the participant and the template. The anterior commissure (AC point) was set to be the center of the image, and the scan was resampled to 1 mm resolution in a 256 x 256 x 256 matrix. The T2 and PD images were then coregistered to the final T1 image and resampled to the same size and resolution.

An initial discriminant tissue classification was then accomplished using the T1 and T2 images (5). A brain mask was then created using an artificial neural network (ANN) (1,6), and cleaned with a brain mask generated by the maximum uniformity summation heuristic (1). The cleaned brain mask contains all intracranial gray matter, white matter, and cerebrospinal fluid (CSF) below the dura mater. Using the brain mask and tissue intensities on each of the three modalities, a multiplicative inhomogeneity correction was estimated using third order Legendre polynomials and applied to each of the modalities (7). The final images were intensity normalized to map all regions inside the brain to intensities from 0 to 255, then saved.

A second tissue classification was then completed using all three modalities, a new brain mask was generated and cleaned, and the Talairach bounds of the cortex were automatically determined. Measures of the tissue volumes were then completed using the standard Talairach method (8). Measures of gray matter, white matter, and CSF were completed for each of the cerebral lobes. Cortical gray matter for each lobe was measured excluding the basal ganglia, brainstem, and cerebellum. "Cortical" white matter included all white matter in the frontal, temporal, occipital, and parietal lobes, but excluded white matter in the subcortical region and in the cerebellum and brainstem. Additionally, the CSF not connected to the surface was measured for each region (internal CSF), which allows the surface CSF to be found by

subtraction. Ventricular CSF was also measured. These measures were used to calculate intracranial volume (ICV), defined as all gray and white matter plus all CSF (internal and surface CSF).

Probability maps of the subcortical structures, used as input to the ANN software, were warped to the individual scans. The ANNs were applied to each scan to identify subcortical structures, including caudate and putamen. The volume of each of these structures was then calculated. Volumes of caudate and putamen were summed to create a measure of total striatum.

After completion of AutoWorkup, all scans were individually inspected for correct realignment and coregistration, tissue classification, and accuracy of brain and subcortical structures. Greater than 90% of the scans analyzed passed all stages successfully. The most common reasons for failure were poor coregistration and inclusion of non-brain tissues in the brain mask, especially near the eyes and neck. No known variable that was the subject of this report, including gender and Huntington disease (HD) gene-expansion status, significantly predicted scan failures.

It is important to note that absolute volumes of caudate and putamen are somewhat smaller than those found in previous studies that involved manual tracing of striatum in prodromal HD (9,10). The automatic segmentation method used in this study generates images by coregistering T1 and T2 images, which creates a different definition of the border between gray and white matter and between gray matter and CSF. The ANN method identifies the probability that each voxel belongs within the template for each subcortical structure. The threshold that was selected for voxel inclusion was probably higher than the criteria used by human raters who relied on the expected shape of each structure as well as voxel intensity in deciding which voxels to include within structure boundaries.

Supplemental References

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