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MRI-based surface-assisted parcellation of human cerebellar cortex: An anatomically specified method with estimate of reliability

Nikos Makris,[a,b,c,*] John E. Schlerf,[a,b,c] Steven M. Hodge,[a,b,d,e] Christian Haselgrove,[a,b,c] Matthew D. Albaugh,[a,b,c] Larry J. Seidman,[f] Scott L. Rauch,[c,d,f] Gordon Harris,[e] Joseph Biederman,[f] Verne S. Caviness Jr.,[a,b,c] David N. Kennedy,[a,b,c,d] and Jeremy D. Schmahmann[b]

[a]Center for Morphometric Analysis, MGH-East, 149 13th Street, Charlestown, MA 02129, USA
[b]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
[c]A. Martinos Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
[d]NMR Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
[e]Radiology Computer Aided Diagnostics Laboratory, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
[f]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

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We revisit here a surface assisted parcellation (SAP) system of the human cerebellar cortex originally described in Makris, N., Hodge, S.M., Haselgrove, C., Kennedy, D.N., Dale, A., Fischl, B., Rosen, B.R., Harris, G., Caviness, V.S., Jr., Schmahmann, J.D., 2003. Human cerebellum: surface-assisted cortical parcellation and volumetry with magnetic resonance imaging. J Cogn Neurosci 15, 584–599. This system preserves the topographic and morphologic uniqueness of the individual cerebellum and allows for volumetric analysis and representation of multimodal structural and functional data on the cerebellar cortex. This methodology integrates features of automated routines of the program *FreeSurfer* as well as semi-automated and manual procedures of the program *Cardviews* to create 64 cerebellar parcellation units based on fissure information and anatomical landmarks of the cerebellar surface. Using this technique, we undertook the parcellation of ten cerebella by two independent raters. The reliability of the resulting parcellation units (64 total) was high, with an average Intraclass Correlation Coefficient (ICC) of 0.724 in the vermis and 0.853 in the hemispheres. Clusters of parcellation units were then created, based on lobar and connectivity data and functional hypotheses. These 36 clusters, when treated as anatomical units, had an average ICC of 0.933. Whereas the individual units provide a high level of detail and anatomical specificity, the clusters add flexibility to the analysis by providing higher reliability.

Keywords: Human cerebellum; MRI; Morphometry; Volumetrics; Functional MRI; Reliability

Introduction

The cerebellar contribution to the organization of higher order brain functions in addition to sensation and movement has been emphasized by several recent studies (Albus, 1971; Desmond and Fiez, 1998; Gilman, 1981; Haines et al., 1997; Leiner et al., 1986; Marr, 1969; Parsons et al., 1997; Schmahmann, 1991, 1997; Schmahmann and Pandya, 1997a; Schmahmann and Sherman, 1998). The connections of the cerebellum with the cerebrum, brainstem, and spinal cord are the structural platform for cerebellar organization and integration within the central nervous system (Haines et al., 1997; Middleton and Strick, 1994). The morphologic homogeneity of corticonuclear microcomplexes in the cerebellar cortex (Ito, 1984) led to the hypothesis that the function of the cerebellar microcircuitry is also homogeneous throughout the structure (i.e., the universal cerebellar transform (Schmahmann, 2000a)). Superimposed on this notion is the knowledge that the cerebellum is topologically linked to different cerebral primary sensorimotor and association areas through the pons via the feedforward pathway, and by way of the thalamus via the feedback pathway (Allen et al., 1997; Middleton and Strick, 1994; Schmahmann, 1991; Schmahmann and Pandya, 1997b; Schmahmann and Sherman, 1998; Thach and Jones, 1979). This connectional heterogeneity leads to the notion that the cerebellum is functionally heterogeneous, with different topological regions subserving sensory, motor, cognitive, and affective processing. Given these new conceptual advances in the understanding of the cerebellum, there is need for a method sensitive and specific enough to test hypotheses in humans in vivo using MRI in clinical populations and in structural and functional imaging studies.

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* Corresponding author. CMA, MGH-East, 149 13th Street, Charlestown, MA 02129, USA. Fax: +1 617 726 5677.
E-mail address: nikos@cma.mgh.harvard.edu (N. Makris).

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In a previous publication (Makris et al., 2003), we adopted an MRI-based technique for cerebellar parcellation and volumetric analysis which relies on the identification and tracing of visible topographic characteristics of the individual brain. This mapping strategy based upon morphological features of the individual cerebellum provides a method to approach the problem posed by inter-individual topographic variability. The advantage of this system lies in the fact that it is not affected by inter-hemispheric and inter-individual variation in the morphology of a structure defined by the framing landmarks used in other approaches that rely on a referential dataset such as a set of templates or a co-registered atlas (Rademacher et al., 1992). In its original formulation (Makris et al., 2003), it was principally an "anatomic idea" for the subdivision of the cerebellar cortex in terms of specific topographic landmarks that are observable in MR images of the brain while remaining consistent with current views of the connectional (Chambers and Sprague, 1955; Haines, 1981; Middleton and Strick, 1994; Schmahmann and Pandya, 1989, 1997a), and functional (Chambers and Sprague, 1955; Ito, 1984; Schmahmann, 2000b) organization of the human and nonhuman primate cerebellum. Following this rationale, the designation of cerebellar subdivisions, or parcellation units (PUs), makes this system flexible and capable for in vivo morphometric analysis, that is, volumetry and topography, and also adaptable for anatomic localization in functional neuroimaging studies. Thus developmental or acquired cerebellar pathological conditions may be characterized in terms of their effects on the volume and/or function of specific subterritories of the cerebellum. As a general method, it also allows the integration of multispectral imaging modalities, facilitating a broad spectrum of behavioral, cognitive, and clinical neuroscience studies (Jenkins et al., 1999).

In Makris et al. (2003), parcellation of the cerebellar cortex was guided by the principal fissures of the individual cerebellum and two sagittal borders determined by points along the horizontal fissure specified by conventions. This methodology was previously applied in one cerebellum by one operator in order to demonstrate its feasibility as a basic principle. In the present study, we make this anatomic idea operational by applying this method in 10 subjects by two different operators. The objectives of this study are threefold. First, we present revisions to optimize the previous cerebellar parcellation system. Second, we introduce a set of computer-assisted algorithms that allow the execution of the parcellation procedure in a manageable period of time. Finally, we test inter-rater and intra-rater reliability in the implementation of this methodology.

Methods

Magnetic resonance images

The analyses were performed in magnetic resonance datasets from the brains of ten subjects. The images were acquired on a Siemens Sonata 1.5 Tesla Signa system. The acquisition included a conventional sagittal scout, coronal T2-weighted sequences and volumetric T1-weighted images. The parameters for the volumetric scan, which was used for the cerebellar segmentation and parcellation, were as follows: coronal 3D-SPGR T1-weighted spoiled gradient echo pulse sequence, TR = 2730 ms, TE = 3.39 ms, flip angle = 7°, FOV = 24 cm, 124 contiguous 1.5 mm slices, matrix = 256 × 256, averages = 2.

Image preprocessing: standard orientation and segmentation

The coordinate system defined for each brain in this MRI dataset defined the Y axis (anterior–posterior) as the bicommissural line (anterior commissure–posterior commissure). The superior–inferior Z axis was orthogonal to the Y axis, passing through the interhemispheric fissure. The medial–lateral X axis was perpendicular to both the Y and Z axes (Filipek et al., 1988, 1994; Talairach and Tournoux, 1988; Talairach et al., 1967). Within this coordinate system, the coronal plane was specified by the X–Z axes, the sagittal plane by the Y–Z axes and the transaxial planes by the X–Y axes. This positional normalization procedure allowed the reconstruction specified by the X–Z axes of a new set of coronal images at the slice thickness of the original acquisition (1.5 mm). The images were not rescaled.

Parcellation

Parcellation of the cerebellum divides the cerebellar cortex into 32 Parcellation Units (PUs) per hemicerebellum (64 for the entire cerebellum). This subdivision is based on a grid of a constant set of eleven mediolateral "limiting" fissures (fissures forming boundaries between units (Rademacher et al., 1992)), which intersect with the longitudinal paravermian sulcus and two longitudinal sagittal borders (Makris et al., 2003). The fissures divide the cortex into lobules, while the longitudinal divisions separate the vermis from the hemisphere, and subdivide the hemisphere into medial and lateral zones.

To parcellate the cerebellum, two different environments are used interactively, namely *Cardviews* (Caviness et al., 1996), which allows manipulations in the volume domain, and *FreeSurfer* (Dale et al., 1999) for operations in the surface domain. The general approach is to segment the cerebellar cortex using *Cardviews*, use *FreeSurfer* to create a flattened surface upon which the fissures are labeled, and finally complete the parcellation in *Cardviews* (Makris et al., 2003). The MRI Atlas of the Human Cerebellum (Schmahmann et al., 2000) was referenced to identify landmarks and fissures in the three cardinal planes, without referring to the specific coordinate space.

Specifically, the method is executed in the following eleven steps, which are further detailed below: (1) segmentation of the cerebellum in *Cardviews*; (2) identification and tracing of the posterolateral and precentral fissures and parcellation of the nodulus, flocculus, and lingula; (3) conversion of the volumetric *Cardviews* information to a surface for *FreeSurfer*; (4) correction of topological defects, smoothing, and inflation of the surface; (5) creation of a cut in the inflated surface, and its flattening; (6) drawing and labeling of the fissures on the flattened surface; (7) translation of the labeled fissures into the volume and the *Cardviews* environment; (8) completion of the fissures using *Cardviews*; (9) manual parcellation of the cerebellar cortex into 20 initial parcellation units per hemicerebellum (40 PUs for entire cerebellum); (10) return to *FreeSurfer* and map the PUs onto the surface to check for errors; (11) finalization of the parcellation in two automated steps, dividing the cerebellar parcellation units into medial and lateral units and dividing the vermis from the hemisphere in the anterior lobules.

(1) Segmentation of the cerebellar cortex

The first step is to segment the cerebellum and cerebellar white matter using intensity contours, in the program *Cardviews* (Fig. 1A). Across the hemispheric midline (vermis), the contour method often leaves an erroneous gap in the white matter outline