Automated cerebellar segmentation: Validation and application to detect smaller volumes in children prenatally exposed to alcohol ☆

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ABSTRACT

Objective: To validate an automated cerebellar segmentation method based on active shape and appearance modeling and then segment the cerebellum on images acquired from adolescents with histories of prenatal alcohol exposure (PAE) and non-exposed controls (NC).
Methods: Automated segmentations of the total cerebellum, right and left cerebellar hemispheres, and three vermal lobes (anterior, lobules I–V; superior posterior, lobules VI–VII; inferior posterior, lobules VIII–X) were compared to expert manual labelings on 20 subjects, studied twice, that were not used for model training. The method was also used to segment the cerebellum on 11 PAE and 9 NC adolescents.
Results: The test–retest intraclass correlation coefficients (ICCs) of the automated method were greater than 0.94 for all cerebellar volume and mid-sagittal vermal area measures, comparable or better than the test–retest ICCs for manual measurement (all ICCs > 0.92). The ICCs computed on all four cerebellar measurements (manual and automated measures on the repeat scans) to compare comparability were above 0.97 for non-vermis parcels, and above 0.89 for vermis parcels. When applied to patients, the automated method detected smaller cerebellar volumes and mid-sagittal areas in the PAE group compared to controls (p < 0.05 for all regions except the superior posterior lobe, consistent with prior studies).
Discussion: These results demonstrate excellent reliability and validity of automated cerebellar volume and mid-sagittal area measurements, compared to manual measurements. These data also illustrate that this new technology for automatically delineating the cerebellum leads to conclusions regarding the effects of prenatal alcohol exposure on the cerebellum consistent with prior studies that used labor intensive manual delineation, even with a very small sample.

1. Introduction

The cerebellum is involved in postural control, gait, balance, and co-ordination of bilateral movements. Recent work has demonstrated that the neocerebellum, comprising of the lateral hemispheres, vermal lobules VI–VII, and the dentate nucleus, is involved in cognitive tasks, such as executive function (Berman et al., 1995; Raichle et al., 1994; Schlosser et al., 1998), verbal fluency (Appollonio et al., 1993), verb generation (Fiez et al., 1996), working memory (Fiez et al., 1996), and source memory (Tamagni et al., 2010). Moreover, the cerebellum is of special interest to the study of brain development since it has been

shown to have greater vulnerability to damage in the perinatal period (Tam et al., 2011). Despite the clear evidence that the cerebellum underlies cognitive and motor functions and is vulnerable during neurodevelopment, very few human neuroimaging studies have measured cerebellar volumes in part due to the paucity and limitations of automated cerebellar segmentation algorithms. Instead, imaging studies of the human cerebellum have relied on manual segmentation to delineate the cerebellar hemispheres and vermis.

Manual segmentation has problems when used in large scale imaging studies, as it is slow, and error-prone, and consistency between operators is difficult to obtain and maintain. A few automatic or semi-automatic cerebellar segmentation algorithms have been published (Cerasa et al., 2009; Hwang et al., 2011; Powell et al., 2008; van der Lijn et al., 2012; Weier et al., 2012; Zhao et al., 2010), but these methods (including Freesurfer) only provide a delineation of the total cerebellum or cerebellar hemispheres (and *not* the cerebellar vermis). Given that the cerebellar vermis has been repeatedly implicated in diseases such as alcoholism (Andersen, 2004; Baker et al., 1999; Cavanagh et al., 1997), fetal alcohol spectrum disorders (Archibald et al., 2001; Maier

et al., 1999; O'Hare et al., 2005; Ramadoss et al., 2007; Sowell et al., 1996), and autism (Brambilla et al., 2003; Scott et al., 2009; Webb et al., 2009), these existing cerebellar segmentation methods that do not delineate the vermis are highly limited for clinical research.

Many techniques exist to divide a medical image into regions with similar properties such as gray level, color, texture, brightness and contrast. Medical image segmentation based on texture features has been explored, but has never gained popularity (Haralick et al., 1973). Early techniques based on gray level features such as histogram thresholding, edge based segmentation, and region based segmentation generally do not perform well on images with complex anatomy such as the brain (Sharma and Aggarwal, 2010). Segmentation of the cerebellum is especially challenging, because the cerebellar foliations are <0.5 mm, leading to extensive partial voluming within the cerebellum at the standard 1 mm^3 resolution of T1-weighted images. Therefore, any segmentation method that seeks to delineate more than the outer cerebellar boundary must use prior knowledge. The state of the art and most popular methods for medical image segmentation are atlas based approaches (e.g., Freesurfer) and model based approaches (e.g., deformable models, active shape and appearance modeling), both of which use prior knowledge of the structure to be segmented. Atlas based segmentation relies on appropriate atlas formation and selection, and accurate registration of the image to be segmented to the atlas. At least two atlases of normal adult human brain anatomy include delineation of the cerebellar vermis and lobes (Diedrichsen et al., 2009; Rohlfing et al., 2010), and may be used to parcellate the cerebellum. In our experience, atlas-based methods do not provide reliable estimation of cerebellar volumes or mid-sagittal areas (test–retest reliabilities range from 0.15 to 0.70, work in progress) and are better suited for integration with functional imaging methods to identify anatomical regions where functional activation occurs, which is the use recommended by the developers of these atlases. Therefore, we have developed a Bayesian implementation of active appearance modeling for measurement of cerebellum volume. In this model the structure of the cerebellum and its subparcels is assumed to have a repetitive form of geometry that can be modeled probabilistically from hand-delineated examples. The probabilistic model of cerebellar geometry can be used to enforce a strong prior during segmentation, where candidate segmentations matching the model are more likely to be chosen as the correct parcellation.

Accurate automated cerebellar segmentation would be valuable in the study of clinical samples, such as fetal alcohol spectrum disorders (FASD). Although not all children with histories of prenatal exposure to alcohol meet the diagnostic criteria for fetal alcohol syndrome (FAS) (Kuehn et al., 2012), many with heavy exposure exhibit functional abnormalities. Children with FASD show difficulties with cognitive processes that may be related to alcohol-induced cerebellar dysfunction, including memory, verbal learning, and executive functions (Mattson et al., 2011, 2013; Vaurio et al., 2011). Alcohol's negative impact on cerebellar development is also likely to contribute to deficits in motor behaviors observed in children, adolescents and adults prenatally exposed to alcohol, such as longer reaction times, slower movement, problems generating isometric and isotonic forces, bimanual coordination, and postural balance (Connor et al., 2006; Debaere et al., 2004; Nguyen et al., 2013a, b; Roebuck et al., 1998a, b; Simmons et al., 2010, 2012). Moreover, neuropathology documented in animal and clinical research has repeatedly shown that the cerebellum is particularly sensitive to early exposure to alcohol (Bauer-Moffett and Altman, 1975; Goodlett et al., 1990a, b; Hamre and West, 1993; Phillips and Cragg, 1982; Thomas et al., 1998), specifically the cerebellar vermis (Clarren et al., 1978; Goodlett et al., 1990a; Jones et al., 1973; Peiffer et al., 1979; Wisniewski et al., 1983). MRI studies of children prenatally exposed to alcohol report reduced volume of the cerebellar hemispheres and vermis (Autti-Ramo et al., 2002; Mattson et al., 1992, 1994). Previous quantitative cerebellar imaging studies in FASD have used manual tracings to detect smaller cerebellar mid-sagittal vermis

area (O'Hare et al., 2005; Sowell et al., 1996) or total cerebellar volumes (Bookstein et al., 2006).

In this paper, we use T1-weighted images to automatically segment the cerebellum using a novel algorithm under continuing development by Neurobehavioral Research, Inc. (NRI) under an SBIR Phase I grant. We demonstrate that our automated cerebellar segmentation has high validity when compared to gold-standard manual delineation obtained from Neuromorphometrics, Inc., a small business originating from the Center for Morphometric Analysis at the Massachusetts General Hospital, whose manual delineations have been used to validate accepted image processing tools such as Freesurfer and FSL. In addition, we demonstrate the clinical validity of our algorithm by using it to segment the cerebellum on a sample of adolescents prenatally exposed to alcohol (PAE) and age-matched controls. Based on previous studies that manually delineated the cerebellum, we expected that PAE children would show smaller total cerebellar volumes and smaller mid-sagittal vermal areas of the anterior lobe (vermis lobules I–V) and posterior inferior lobe (vermis lobules VIII–X).

2. Methods

2.1. Cerebellar Analysis Toolkit (CATK) overview

CATK functions as a fully-automated T1 MRI cerebellum delineation and parcellation tool. An active profile–appearance modeling (AAM; Patenaude, 2007; Cootes, 2000; Cootes et al., 2001) framework is used and the toolkit is currently capable of parcellating the cerebellum into five structures: left and right hemispheres, and three vermal lobes (I–V, VI–VII, and VIII–X), although further development is planned to extend the algorithm to segmentation of the left and right cerebellar nuclei. The CATK is based on statistical shape and appearance models learned from a training set of examples hand-delineated by Neuromorphometrics, Inc. The advantage of this is that strong prior knowledge about the cerebellum inherent in the data (such as the overall shape of the cerebellar vermal lobes) is taken into account during segmentation, resulting in a segmentation method that enforces smoothness according to probable variations specific to the structures. Fig. 1 shows a broad overview of the components of the algorithm. The basic components are: data preparation (e.g., intensity normalization, pose correction, cerebellum localization), statistical model generation, and model fitting (for new samples).

2.1.1. CATK description

To create the statistical shape model, the training images are first linearly aligned using a 9 degrees of freedom model (rotation, translation, and scale) (Woods et al., 1998a,b) with the ICBM-152 template. Shapes are parameterized by a point distribution model (Cootes, 2000; Cootes et al., 2001) derived from stellar meshes. Once training images are aligned, projecting rays from a central point to a label boundary implicitly provides vertex correspondence. For subparcels (like the hemispheres and vermal lobes), multiple projection centers are used to maximize correspondence with the ground truth labels while allowing the covariance between related surfaces to be modeled. For example, the three lobes of the vermis are modeled by a single statistical model containing three surfaces. While the spherical assumption limits the topology of the mesh, modeling errors are minimal for the designated structures, and a number of computational benefits are provided. For instance, the connectivity of the points is implicit which allows fast conversion to triangular mesh surfaces, and models can be easily resampled at multiple resolutions which enables both coarse and refined fitting. The ability to control the shape dimension in this way is a significant advantage for statistical modeling as it impacts directly on the number of examples required to obtain good shape parameterization. The point distribution model projects each high-dimensional shape vector (i.e. the raw vertices) into a low-dimensional eigenspace, having at maximum as many principal modes as examples in the training set.