Rapid Automatic Segmentation of the Human Cerebellum and its Lobules (RASCAL)—Implementation and Application of the Patch-based Label-fusion Technique With a Template Library to Segment the Human Cerebellum

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Abstract: Reliable and fast segmentation of the human cerebellum with its complex architecture of lobes and lobules has been a challenge for the past decades. Emerging knowledge of the functional integration of the cerebellum in various sensori-motor and cognitive-behavioral circuits demands new automatic segmentation techniques, with accuracies similar to manual segmentations, but applicable to large subject numbers in a reasonable time frame. This article presents the development and application of a novel pipeline for rapid automatic segmentation of the human cerebellum and its lobules (RASCAL) combining patch-based label-fusion and a template library of manually labeled cerebella of 16 healthy controls from the International Consortium for Brain Mapping (ICBM) database. Leave-one-out experiments revealed a good agreement between manual and automatic segmentations (Dice kappa = 0.82). Intraclass correlation coefficients (ICC) were calculated to test reliability of segmented volumes and were highest (ICC > 0.9) for global measures (total and hemispherical grey and white matter) followed by larger lobules of the posterior lobe (ICC > 0.8). Further we applied the pipeline to all 152 young healthy controls of the ICBM database to look for hemispheric and gender differences. The results demonstrated larger native space volumes in men than women (mean ($\pm$ SD) total cerebellar volume in women = 217 cm³ ($\pm$ 26), men = 259 cm³ ($\pm$ 29); $P < 0.001$). Significant gender-by-hemisphere interaction was only found in stereotaxic space volumes for white matter core (men > women) and anterior lobe volume (women > men). This new method shows great

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Key words: cerebellum; segmentation; MRI; lobules

INTRODUCTION

The human cerebellum is a fascinating brain structure not only in terms of its anatomy, but also in terms of its integrating role in multiple processes and its focus in neuro-psychiatric research. In comparison to the cerebrum, it is a small-sized structure which occupies only about 10% of the whole brain volume; however it shows a complex architecture of tightly folded cortical grey matter comprising far more neurons ($105,000 \times 10^6$) than the cerebrum [Andersen et al., 1992]. The grey matter covers a layer of white matter pathways in the so-called foliae, branching from the medullary core where the deep cerebellar nuclei (i.e., the dentate, emboliform, globose, and fastigii) are embedded [Voogd, 2003]. On a larger scale the fissures between the foliae help to organize the cerebellum into the different lobules of each cerebellar hemisphere, connected via the midline vermis. A further anatomico-functional distinction of the cerebellar hemispheres is often made in the anterior and posterior direction.

The cerebellum is known to play an important role in motor control and coordination. On the one hand it receives input from afferent sensory systems from the spinal cord, brainstem and cerebral cortical regions, and integrates these inputs to fine tune motor activity [Manto et al., 2013]. Efferent feedback projections on the other hand connect the cerebellar cortex via the deep cerebellar and thalamic nuclei with cortical regions such as the motor or prefrontal cortex [Stoodley and Schmahmann, 2010]. Disturbance of this loop through lesions, e.g. caused by ischemic stroke [Kase et al., 1993], multiple sclerosis [Compston and Coles, 2008; Davie et al., 1995] or neurodegenerative disorders [Klockgether, 2008], may lead to impairment of balance, gait and limb ataxia, dysarthria and oculomotor dysfunction. Furthermore the cerebellum has also been suggested to be part of non-motor circuits responsible for cognitive and affective processes, especially attention, emotion, and behavior [Leiner et al., 1993; Levi-sohn et al., 2000; Timmann et al., 2010]. Anatomical and functional imaging studies have shown a topographic organization of the human cerebellum with activation of the anterior lobe and dorsolateral dentate during sensorimotor tasks, whereas posterior lobe and ventrocaudal dentate activation was observed during language, spatial, executive, working memory tasks and affective stimulation [Kuper et al., 2012; Stoodley and Schmahmann, 2010]. Schmahmann and Sherman [1998] subsumed the non-motor symptoms of the cerebellum to the so called “cerebellar cognitive affective syndrome” (CCAS) and

could further localize it to the “limbic cerebellum” which includes the vermis and fastigial nucleus [Schmahmann, 1991; Schmahmann et al., 2007]. Schizophrenic patients for example show a reduction in size of the vermis [Loeber et al., 2001]. However studies in autism have presented controversial results regarding vermal volume [Courchesne et al., 1994, 1988; Piven et al., 1997], which is to some extent easily explained through numerous and partly inconsistent existing nomenclatures of lobules; this is especially true for past definitions of the vermis. A major step to improve the analysis of the cerebellum was taken with the publication of the MR atlas of Schmahmann et al. [1999] showing a T1-weighted scan of the cerebellum of a single male adult coregistered to the MNI305 template. Schmahmann et al. presented a consensus about the terminology on the basis of previously published data [Angevine et al., 1961; Bolk, 1906; Larsell and Jansen, 1972], helping to standardize the field. In addition to correct identification of cerebellar lobules, accurate volumetric measurements of the latter are essential to better investigate the role of the cerebellum in the healthy individual as well as in various diseases.

In the literature, different approaches have been described to segment the cerebellum, however only a few focused on the individual lobules [Schmahmann et al., 1999]. Manual segmentation of the cerebellum is a highly reliable [Loeber et al., 2001; Raz et al., 1998], but also, especially when considering the complex architecture, a far too time-consuming method, which may take up to 20 h to segment one subject. This is impractical if large numbers of subjects are involved. Different semi-automated segmentation methods have been introduced to reduce user input and at the same time preserve a high reliability, but most of these methods only refer to whole cerebellum segmentation or larger-scale parcellations of the cerebellar hemispheres [Pierson et al., 2002; Weier et al., 2012]. To overcome the problems of intense user input and inter- and intra-rater variability, automated, robust and accurate segmentation techniques become desirable. Concerning cortical or subcortical structures of the cerebrum, various different automated methods like region growing models [Chupin et al., 2007], appearance-based models [Hu and Collins, 2007], as well as atlas or template-warping techniques [Aljabar et al., 2009; Collins et al., 1995b; Fischl et al., 2002] have been developed. Regarding the automatic segmentation of the cerebellum in particular, Diedrichsen developed a high-resolution, spatially unbiased atlas template of the human cerebellum (known as SUIT; [Diedrichsen, 2006]) that is based on the anatomy of 20 young

healthy individuals and on the atlas of Schmahmann et al. [1999]. In comparison to a whole brain template atlas, this work improved the appearance of the cerebellum region, especially in terms of the individual fissure alignment. This atlas is used for atlas-warping based cerebellar segmentation [Balsters et al., 2010]. Further improvement in the general field of atlas-warping methods was achieved through the introduction of a template library rather than relying on a single template only, which already has been tested on smaller brain regions like the hippocampus [Barnes et al., 2008]. Whereas the structure of the hippocampus and its anatomical variations are relatively simple, Diedrichsen et al. [2009] discovered in their work on a probabilistic MR atlas of the cerebellar lobules, that the human cerebellum shows a high individual variability in healthy subjects (with more variability in the smaller, more caudally located lobules). This sometimes results in systematic mislabeling between lobules after the alignment to the MNI template space, thus underscoring an additional challenge in segmentation of the human cerebellum. Regarding segmentation of the hippocampus, Collins and Pruessner [2010] introduced an extension of the previous described automatic nonlinear image matching and anatomical labeling (ANIMAL) technique [Collins and Evans, 1997a; Collins et al., 1995b] with a template library incorporating a label fusion method to combine segmentations of the “*n*” most similar templates of the library yielding an optimal median Dice Kappa of 0.886. This approach was further adapted to a more local operating region with the so called patch-based label-fusion method, achieving comparable results in terms of Dice Kappa values [Coupe et al., 2011]. This work has inspired the methods presented here.

The aim of the current project was to develop a highly reliable automatic segmentation procedure to allow analyses of large patient cohorts and yet gain detailed information on the volumes of the individual cerebellar lobules. The manuscript describes the development and validation of a patch-based label-fusion strategy used with a library of cerebella from MRIs of sixteen healthy controls from the International Consortium for Brain Mapping database (ICBM; [Mazziotta et al., 1995]) data base, manually segmented using the protocol of Schmahmann et al. [1999]. The procedure was then applied to the MRIs of the 152 subjects that make up the ICBM data base [Mazziotta et al., 1995] to examine left–right and male–female differences.

METHODS

Subject Information, MRI Data, and Manual Labeling Procedure of the Template Library

The data, which were used for the template library of manually painted label volumes, were derived from a

randomly selected group of sixteen young, neurological healthy individuals (7 women, mean age 25.5 ± 5.1 years) acquired in the context of the ICBM database (Mazziotta et al., 1995). All subjects underwent the same acquisition protocol including T1-weighted (T1w), T2-weighted (T2w) and Proton density-weighted (PDw) sequences, but only T1w MRI data of these subjects were used in this study. Images were acquired at the Montreal Neurological Institute (MNI) on a Philips Gyroscan 1.5 T MRI scanner (Best, Netherlands) using a high-resolution T1-weighted, spoiled gradient echo sequence (sagittal acquisition, 140–160 contiguous 1-mm thick slices, TR = 18 ms, TE = 10 ms, flip angle 30°, rectangular field of view of 256×204 mm²). The Ethics Committee of the Montreal Neurological Institute gave approval and informed consent was obtained from all participants. The MRI raw data was pre-processed to correct for image nonuniformity [Sled et al., 1998] and then stereotactically registered into the MNI coordinate system [Collins et al., 1994]. For further details see next paragraph on the automatic segmentation procedure.

Manual segmentation of the cerebellum was performed by two trained raters (K.L. and K.W.) using two software packages and the Schmahmann et al. atlas [Schmahmann et al., 1999] as an anatomical guide. K.L. used the Display software, a program developed at the MNI that permits simultaneous viewing and painting in all three planes (axial, sagittal, and coronal) to ensure 3D continuity of segmentations. K.W. used ITKsnap [Yushkevich et al., 2006] to verify and correct the segmentations. On each individual data set we defined twelve lobules for each cerebellar hemisphere according to the atlas of Schmahmann et al. [1999]. To avoid substructures, which may be too small for a reliable automatic segmentation, we decided not to segment separate vermal lobules. The vermal lobules VIIA_f and VIIA_t were included in their corresponding hemispherical lobules Crus I and II. Cerebellar hemispheres were divided according to the midsagittal plane of the cerebellum, verified on the coronal and axial planes.

Manual segmentation was initiated with the identification of cerebellar fissures on both hemispheres beginning from the mid-sagittal plane (Fig. 1). Individual voxels within the center of the fissures were labeled with arbitrary color-coded, numerical labels in all three planes in order to segment the lobules and folia as previously described [Schmahmann et al., 1999]. Second, each cerebellar lobule was labeled using the three cardinal planes to ensure a consistent 3D segmentation. We also added labels for cerebellar white matter as well as for the medial cerebellar peduncles (MCP) and superior cerebellar peduncles (SCP) on both sides. Note that the MCP label included the inferior cerebellar peduncles. The borders defining the cerebellar peduncles were chosen arbitrarily and are presented in Figure 2. To differentiate the MCP from the medullary core, the coronal plane intersecting the anterior-most point of the vermis was chosen. The rostral border of the MCP was defined as the connection between the

Figure 1.

Manual segmentation was performed in different steps. The axial, sagittal and coronal planes (columns from left to right) ensure a consistent 3D segmentation (images in the upper row). First the fissures are traced and delineated according to the MRI-atlas of Schmahmann et al. [1999] (middle row). These further help to separate each lobule, which are also labeled with color and numerical codes in a second step (lower row).

Figure 2.

(A) From left to right: Demonstration of the separating coronal plane between cerebellar peduncles and white matter core. The coronal plane is chosen which shows the anterior-most point of the vermis, the dashed white line represents the axial plane cutting through the anterior-most point. Next, the axial and sagittal plane showing the posterior limitation of the peduncles (non-dashed line). (B) Display of anterior boundaries of the peduncles as the extension of the trigeminal (1) and vestibulocochlear (2) nerve (black dashed lines).

emerging trigeminal as well as vestibulocochlear nerve (both well-defined anatomical landmarks) to the fourth ventricle (Fig. 2B). The cerebellar nuclei were not included in the manual segmentation, as the T1, T2, and PD contrasts did not enable their visualization. Whenever the term “grey matter” is used in this manuscript, it refers only to cortical grey matter.

Automatic Segmentation Using the Template Library and Patch-based Label Fusion Technique

The automatic segmentation algorithm presented here is an improved version of the methods published previously in Coupe et al. [2011], and incorporates ideas from [Landman et al., 2012]. The main differences from Coupe include a different strategy for intensity normalization, majority voting to account for multiple labels, and the use of nonlinear registration. The method consists of the following four stages: (i) image preprocessing, (ii) nonlinear registration, (iii) customized template library preparation and (iv) structure segmentation. All steps are described below. Manual segmentations of cerebellar subregions

Figure 3.

Segmentation algorithm parameter optimization. A number of combinations yielded equivalent results with median kappa of ~ 0.84 . A patch size of $9 \times 9 \times 9$ voxels and a search area of $5 \times 5 \times 5$ voxels (highlighted on the graph) were chosen as best parameters.

were performed using images that passed the pre-processing stage.

1. Image preprocessing stage. All steps applied to the T1w MRI scan P
 - a. T1w MRI scans of the whole head were corrected for intensity non-uniformity using the N3 algorithm [Sled et al., 1998]. The intensity range of the whole image is linearly normalized to the range 0.0–100.0 by histogram matching towards the ICBM 2009c template [Fonov et al., 2011; Mazziotta et al., 1995] in order to account for gross inter-scanner and inter-subject variability.
 - b. Linear nine-parameter registration to the ICBM 2009c template (shift, rotations and scale in x,y,z) was performed using normalized mutual information as part of the ANIMAL software [Collins and Evans, 1997b; Collins et al., 1995a].

- c. Nonlinear registration using the ANIMAL software and ICBM 2009c template was applied to obtain a rough brain mask, which was further used to perform a second linear intensity normalization using histogram matching, this time only inside the brain ROI. The brain mask is not used in any subsequent analysis.
 - d. Next, a region of interest (ROI) around the subject's cerebellum was extracted as defined by the ICBM 2009c template.
 - e. Adaptive patch-based noise reduction was conducted [Manjon et al., 2010].
 - f. Finally, a third linear histogram-based intensity normalization was performed to reduce residual intensity differences within the cerebellar mask.
2. Nonlinear registration stage with an output of forward (F) and inverse (I) non-linear transformations.

- a. Nonlinear registration using the ANTs software [Avants et al., 2008] was performed in the cerebellum ROI toward the ICBM2009c template with the following parameters: number of iterations $100 \times 100 \times 50$, cross-correlation metric with four voxel local support radius, Gaussian regularization of gradient field with sigma of 1.0 and deformation field sigma of 1.0, Symmetric Normalization (SyN) transformation model with 0.25 time-discretization step.
3. Customized template library generation stage in order to create a subject-specific segmentation library consisting of pairs of intensity template images P_t and discrete segmentation images S_t'
 - a. For each entry of the template library (P_t, F_t, I_t, S_t) the nonlinear transformation, mapping it to match the subject, was calculated by concatenating F and I_t :
$$T_t = F \cdot I_t.$$
 - b. The template intensity image P_t was then warped using the inverse of T_t by 2nd order b-spline interpolation, producing P_t' .
 - c. Finally the template segmentation image S_t is warped by applying the inverse of T_t to each of the labels separately, using 2nd order b-spline interpolation followed by voxel-by-voxel majority voting across all the label volumes, in order to obtain discrete labels, while reducing aliasing artefacts, producing S_t' .
4. Segmentation stage to generate a discrete segmentation map S
 - a. The algorithm described in [Coupe et al., 2011] is implemented using P as the input image and subject specific template library consisting of pairs (P_t', S_t'). To account for multiple discrete labels used in the template library, fuzzy segmentation results for each of the labels are compared in a majority voting scheme, assigning label with highest weight to a given voxel.

Template Library Construction

All scans that were manually segmented were processed with the 1st and 2nd stages of the algorithm described above. In addition, a left-right flipped version of each anatomical sample was computed to double the number of samples in the database.

Segmentation Algorithm Parameter Optimization

To find the best parameters for the patch-based segmentation (search area and patch size) leave-one-out experiments were performed, excluding one subject

(and its left-right flipped version) from the training library. The segmentation algorithm described above was applied and the overlap with the manual segmentation results was measured using generalized kappa metric [Crum et al., 2006]. The results are shown in Figure 3. A patch size of $9 \times 9 \times 9$ voxels and search area of $5 \times 5 \times 5$ voxels was chosen as providing the best trade-off between segmentation accuracy (with best generalized dice kappa), while avoiding unnecessary processing.

Further, intraclass correlation coefficient (ICC) model 3 (mixed-effect model) was calculated for reliability measurements of volumes [Shrout and Fleiss, 1979].

Application to Healthy Control Data Base

The proposed automatic segmentation method was applied on 150 T1w data sets of the previously mentioned ICBM database that included 152 neurologically healthy subjects aged 18–44 years (mean 24.9 ± 4.9 years; 66 women; 129 right-handed; ethnic background: 130 caucasian, 15 asian and eight others). Two subjects (one woman and one man) were excluded due to motion artifacts in their T1w images. Mean volumes and standard deviation for cerebellar grey matter lobules, medullary core and peduncles of both hemispheres were calculated for the whole cohort. A mixed model ANOVA was used to analyse gender (between-subject) and hemispherical (inter-subject) differences with cerebellar volumes as dependent variables and age as a covariate. All statistics were analysed using SPSS 21 (IBM, New York). P values of <0.05 were considered significant.

RESULTS

Manual Segmentations

Manual segmentation of the 16 randomly selected healthy cerebella of the ICBM data base revealed a mean total grey matter volume (CGV) of $117 \text{ cm}^3 \pm 11$ (mean $\pm$ standard deviation, range $101\text{--}139 \text{ cm}^3$) and mean total white matter volume (CWV), including the peduncles, of $16 \text{ cm}^3 \pm 1.8$ ($12\text{--}19 \text{ cm}^3$) in native space. Mean values and standard deviations as well as the range for each individual lobule of either hemisphere are shown in Table I. Comparison of both hemispheres did not reveal any significant difference except for crus II, which was significantly larger on the left side (mean = 6.6 cm^3) on average compared to the right hemisphere (mean = 5.4 cm^3 ; $P = 0.05$). A high anatomical variation was found between individual subjects resulting in low overlap of lobules, predominantly for the anterior lobe (lobules I–V) but also lobule X, Crus II and VIIIa bilaterally. Figure 4 displays nicely the areas of lowest overlap.

TABLE I. Demonstration of both manual and automatic segmented volumes for both hemispheres of $n = 16$ healthy subjects from the ICBM data base

		Manual segmentation ($n = 16$)				Automatic segmentation ($n = 16$)				t	ICC	95% CI	
		Minimum	Maximum	Mean	Std. deviation	Minimum	Maximum	Mean	Std. deviation			Lower bound	Upper bound
TCV		112791	157621	133244	12243	113042	164236	134600	13564	2.29*	0.992	0.976	0.997
CGV		100743	138531	116948	10771	98686	144979	117834	12165	1.41	0.988	0.966	0.996
CWV		12048	19090	16296	1779	13055	19258	16766	1607	2.44*	0.946	0.844	0.981
Total hemi- spherical GM	Right	50586	69816	58730	5965	49301	72651	58918	6102	0.45	0.981	0.944	0.993
	Left	49951	68714	58218	5090	49386	72327	58915	6101	1.56	0.974	0.926	0.991
Total hemi- spherical WM	Right	6167	9690	8173	921	6735	9887	8554	847	3.06**	0.914	0.753	0.970
	Left	5880	9812	8123	926	6320	9371	8212	796	0.40	0.941	0.831	0.979
Anterior lobe	Right	5138	9428	7442	1501	5694	9073	7384	905	-0.21	0.762	0.319	0.917
	Left	5316	10034	7699	1207	5672	9588	7831	1024	0.47	0.656	0.016	0.880
Posterior lobe	Right	44211	60388	51289	5224	43222	63579	51534	5415	0.73	0.984	0.953	0.994
	Left	42192	60094	50519	5088	42939	63213	51085	5433	1.97	0.988	0.966	0.996
Lobule I,II	Right	50	140	92	27	49	103	77	16	-3.8**	0.859	0.597	0.951
	Left	46	194	83	39	48	103	78	16	-0.64	0.454	-0.562	0.809
Lobule III	Right	425	1248	776	235	535	1078	777	181	0.03	0.773	0.350	0.921
	Left	458	1053	757	179	647	1297	826	160	1.17	0.039	-1.750	0.664
Lobule IV	Right	1179	4596	2665	817	1887	3589	2689	445	0.12	0.414	-0.677	0.795
	Left	1298	4598	2710	1022	1870	3714	2856	578	0.69	0.645	-0.016	0.876
Lobule V	Right	2620	5260	3909	943	2903	5360	3841	641	-0.34	0.685	0.098	0.890
	Left	2289	6192	4149	1194	3038	4985	4071	510	-0.28	0.385	-0.761	0.785
Lobule VI	Right	6725	12046	9278	1374	7882	11124	9175	862	-0.40	0.746	0.273	0.911
	Left	6682	12083	8771	1435	7391	10969	8892	995	0.52	0.832	0.518	0.941
Crus I	Right	10288	18319	13934	1916	11576	17382	14018	1650	0.33	0.912	0.749	0.969
	Left	10122	18441	13163	2012	11271	16918	13763	1596	1.96	0.872	0.634	0.955
Crus II	Right	3209	9128	5438	1671	3729	6816	5529	1020	0.25	0.626	-0.071	0.869
	Left	4250	8846	6608	1570	4459	7025	5639	953	-2.80*	0.605	-0.132	0.862
Lobule VIIb	Right	5875	12568	9710	1977	7716	11698	9523	1394	-0.46	0.703	0.149	0.896
	Left	4998	12600	9173	2129	7197	12602	9476	1523	0.60	0.58	-0.203	0.853
Lobule VIIla	Right	3203	7269	5092	1009	4123	7204	5422	819	2.34*	0.897	0.704	0.964
	Left	3571	7811	5088	1035	4036	6992	5457	750	2.00	0.8	0.426	0.930
Lobule VIIlb	Right	2727	5443	3830	791	3074	5574	3737	646	-0.74	0.864	0.611	0.952
	Left	1789	4829	3598	775	2906	4774	3791	573	1.12	0.656	0.016	0.880
Lobule IX	Right	2585	5980	3833	986	3021	5867	3989	824	1.67	0.956	0.874	0.985
	Left	2616	5827	3977	1010	2894	5386	3913	772	-0.61	0.942	0.835	0.980
Lobule X	Right	97	274	174	63	101	194	141	26	-2.7*	0.674	0.066	0.886
	Left	80	206	142	42	99	205	153	29	0.89	0.224	-1.220	0.729
MCP	Right	1952	4462	3105	599	2324	3680	3121	410	0.16	0.813	0.464	0.935
	Left	2155	4298	3135	615	2359	3655	3131	385	-0.02	0.634	-0.048	0.872
SCP	Right	100	247	192	39	142	234	190	30	-0.19	0.484	-0.477	0.820
	Left	117	243	191	36	147	241	189	28	-0.24	0.237	-1.183	0.734
Cerebellar peduncles	Right	2188	4618	3296	597	2466	3885	3310	434	0.14	0.835	0.528	0.942
	Left	2347	4490	3326	613	2506	3896	3320	402	-0.04	0.661	0.031	0.882
WM core	Right	3979	6362	4876	698	4269	6049	5244	464	2.27	0.574	-0.220	0.851
	Left	3533	6115	4797	740	3815	5599	4893	430	0.60	0.626	-0.070	0.869

Minimum, maximum, mean and standard deviation are displayed in native space. Paired t tests were calculated in order to test whether automatic volumes were larger (positive t value) or smaller (negative t value) than manual segmented volumes: P level: * = 0.05, ** = 0.01. Intraclass correlation coefficient (ICC-model 3) as well as the 95% confidence interval (CI) are presented for comparison of methods.

Figure 4.

Display of major overlap of manual segmented lobules of the 16 healthy cerebella from the template library before nonlinear registration in sagittal ($x = -5, 11, 32$), axial ($z = -20, -34, -52$) and coronal ($y = -56, -78, -82$) planes. The different shades of gray correspond to the level of overlap and where white color shows 100% overlap.

Leave-One-Out Validation of Segmentation Method

Leave-one-out validation of the automatic labels against the gold standard manual labels yielded a generalized Dice kappa (k) of $=0.82$. Individual kappa values are displayed in Figure 5 showing better results ($k > 0.85$) for the larger lobules VI, Crus I and IX as well as for the white matter core and medial cerebellar peduncles. The lowest kappa ($k = 0.60$) was found for the small lobule I_II bilaterally.

Direct comparison of mean volumes (see Table I for native space volumes and Table Ib in the Supporting Information for volumes in stereotaxic space) revealed an almost perfect agreement of the global measures like the total volumes TCV, CGV, and CWV with ICC values of 0.992, 0.988, and 0.946, respectively, as well as for hemispherical GM and WM total volumes (avg ICC of 0.98 and 0.93, respectively). Furthermore, strong to excellent agreement was found for the posterior and part of the anterior lobe volumes as well as the major lobules VI, Crus I, lobule VIII a + b and IX with (left+right) average ICC values of 0.789, 0.892, 0.845, 0.760, and 0.949, respectively. Depending on the anatomical variability and size of the remaining structures agreement varied between moderate to poor. Both manual and automatic segmentation roughly calculated the same lobule volumes. Only for TCV, CWV, right total WM and right lobule VIIa did the automatic method slightly overestimate volumes. For right lobule I/II, left Crus II, and right lobule X the automatic segmentation slightly underestimated volumes.

Application to the ICBM Cohort

Automatic segmentation of 150 healthy subjects of the ICBM database was also performed. Minimum and maximum volume, mean values and standard deviation for the cerebellar lobules of the right and left hemisphere in standard stereotaxic space as well as native space are displayed in Table II. These volumes were analyzed with paired t tests and an ANOVA.

With paired t tests, we found hemispheric asymmetries of stereotaxic volumes in Crus I (right > left; $t = 2.117$, $P = 0.035$), Crus II (right < left; $t = -2.307$; $P = 0.022$), lobule X (right < left; $t = -3.141$, $P = 0.002$), the white matter core (right > left; $t = 5.172$, $P < 0.001$) and total WM (right > left; $t = 3.436$, $P = 0.001$).

Except for both sides of lobule IX, and the right anterior lobe, group t tests showed women had overall larger stereotaxically normalized cerebellar volumes than men. However this was not the case for native space volumes that showed a significantly smaller TCV (mean $\pm$ standard deviation: women = 217 ± 26 , men = 259 ± 29 ; $P < 0.001$), CGV (women = 119 ± 12 , men = 135 ± 12 ; $P < 0.001$) as well as CWV (women = 17 ± 2 , men = 18 ± 2 ; $P < 0.001$) in women than men.

The mixed model ANOVA for the stereotaxic cerebellar volumes showed a significant hemisphere by gender interaction for the total WM volume (incl. peduncles) ($F(1,147) = 7.3$, $P = 0.008$, $\eta_p^2 = 0.047$), pointing out a significantly larger hemispherical difference in men (right > left) than in women. Furthermore there was a significant group effect of gender ($F(1,147) = 16.01$, $P < 0.001$) as well as age

Figure 5.

Box- and whisker plots of Dice kappa of individual lobules. The boxplots display the median (bold line), the minimum (lower T-line) and maximum (upper T-line) as well as the first quartile (lower part of the box) and third quartile (upper part of the box) of kappa.

($F(1,147) = 6.6$, $P = 0.01$) on the total cerebellar WM volume. Another significant hemisphere by gender interaction was observed for anterior lobe volume ($F(1,147) = 4.5$, $P = 0.036$, $\eta_p^2 = 0.03$) demonstrating a significant greater hemispherical difference in women (left > right) than men. However in this case no significant group effect was found for the anterior lobe volume. In the case of the total GM, the posterior lobe, and its individual lobules, no significant hemisphere by gender interaction was found. Analysis of main effects showed a significant effect of gender showing larger volumes in females for total GM ($F(1,147) = 7.8$, $P = 0.006$), posterior lobe volume ($F(1,147) = 8.8$, $P = 0.004$), lobule VI ($F(1,147) = 13.2$, $P < 0.001$), Crus I ($F(1,147) = 3.9$, $P = 0.049$), and lobule VII B ($F(1,147) = 6.6$, $P = 0.01$), however there was no significant group effect for Crus II, lobule VIII A + B, IX and X ($F < 1$, $P > 0.3$).

The performance of the mixed model ANOVA on the native space volumes revealed no significant hemisphere

by gender interaction for any of the analyzed volumes. However the main effect of gender was significant over all volumes ($P \leq 0.001$), demonstrating larger volumes in men than women.

DISCUSSION

The present study describes the further development of a previously established automatic segmentation procedure for the hippocampus and its application to the human cerebellum using a template library of 16 manual segmented cerebella combined with a patch-based label-fusion technique in a large healthy control data base. In a leave-one-out validation procedure, the method yielded robust and accurate results for segmentation of the cerebellum, total WM, total GM and posterior lobe as demonstrated by high ICC and Kappa values. Automatic

TABLE II. Demonstration of mean cerebellar volumes (and standard deviation (SD)) in standard stereotaxic as well as native space for both hemispheres of $n = 150$ healthy subjects from the ICBM data base

Group statistics ($n = 150$)		Standard stereotaxic space				Native space			
Cerebellar sub- structure	Hemisphere	Mean	SD	t	Sig. (2-tailed)	Mean	SD	t	Sig. (2-tailed)
Total grey matter	Right	82860	6256	0.626	0.532	61104	6571	0.442	0.659
	Left	82415	6053			60772	6427		
Anterior lobe grey matter	Right	10711	1207	-1.513	0.131	7910	1159	-1.111	0.268
	Left	10927	1262			8056	1115		
Posterior lobe grey matter	Right	72149	5721	1.020	0.308	53194	5754	0.722	0.471
	Left	71488	5499			52716	5713		
Lobule I,II	Right	116	26	0.300	0.764	86	20	0.361	0.718
	Left	115	29			85	22		
Lobule III	Right	1167	244	0.513	0.608	859	190	0.372	0.710
	Left	1153	247			851	204		
Lobule IV	Right	3892	592	-1.722	0.086	2878	533	-1.415	0.158
	Left	4017	668			2968	566		
Lobule V	Right	5536	794	-1.085	0.279	4087	689	-0.830	0.407
	Left	5642	891			4153	675		
Lobule VI	Right	12596	1669	0.590	0.556	9269	1273	0.545	0.586
	Left	12481	1715			9187	1336		
Crus I	Right	20179	2298	2.117	0.035	14878	2024	1.728	0.085
	Left	19605	2395			14463	2136		
Crus II	Right	7672	1262	-2.307	0.022	5656	1028	-2.103	0.036
	Left	8017	1327			5913	1089		
Lobule VIIb	Right	13202	1739	0.215	0.830	9731	1449	0.235	0.814
	Left	13158	1776			9692	1428		
Lobule VIIa	Right	7622	963	0.590	0.556	5626	872	0.477	0.634
	Left	7559	886			5579	818		
Lobule VIIb	Right	5297	646	1.466	0.144	3909	580	1.179	0.239
	Left	5190	613			3831	562		
Lobule IX	Right	5385	804	1.261	0.208	3979	717	1.023	0.307
	Left	5265	839			3893	744		
Lobule X	Right	197	46	-3.141	0.002	145	35	-3.035	0.003
	Left	213	41			157	34		
Total cerebellar white matter	Right	12137	987	3.436	0.001	8962	1094	2.458	0.015
	Left	11742	1008			8661	1020		
Total cerebellar peduncles	Right	4745	469	0.013	0.990	3508	501	0.067	0.947
	Left	4744	490			3500	488		
White matter core	Right	7392	658	5.172	0.000	5454	663	4.019	0.000
	Left	6997	665			5148	620		

T tests show hemispherical asymmetries, with positive values for bigger volumes on the right side. Significant P level of < 0.05 .

segmentation of the smaller anterior lobe lobules resulted in lower ICC and Kappa values, probably due to the smaller size of these structures, combined with their higher inter-subject anatomical variability.

Manual segmentation of each lobule of the human cerebellum is a time consuming procedure, which may easily take from 20 to 35 h per subject. The manual segmented cerebella demonstrated that there is a large variability in how the fissures occur, separating each lobule. The highest variability was found for lobules I-III, VIIa and b, X as well as in the structure of crus II. Schmähmann et al. pointed out in their atlas an asymmetry of the ansoparamedian fissure, showing that Crus II laterally on the left

side is not adjacent to lobule VIIb [Schmähmann et al., 1999]. Whereas Dietrichsen et al. [2009] reported in their work of a probabilistic atlas that only 3/50 hemispheres show this variant, we could find it in 25/32 hemispheres. These variabilities make automatic segmentation challenging.

To develop a technique that requires no user input (when segmenting a new subject) while obtaining highly accurate segmentations, we have chosen to use a template library of manual segmented cerebella together with a patch-based label-fusion technique. This technique was shown to be highly accurate in segmenting the hippocampus, which is a comparably small structure, embedded

between CSF spaces and surrounding grey matter tissue, a situation similar to the cerebellar lobules [Collins and Pruessner, 2010; Coupe et al., 2010]. While other template-based registration schemes use non-linear registration to multiple templates before fusing labels [e.g., Collins and Pruessner, 2010; Wang and Yushkevich, 2013], this strategy did not improve segmentation accuracy with our data for the cerebellum. However it considerably extended the processing time, which is why we did not follow this approach.

When evaluated against the gold standard of manual labels of the cerebellar lobules, the technique presented here yielded a median Dice Kappa of 0.82. To the best of our knowledge, this is the most accurate result achieved for automatic segmentation of the cerebellar lobules. Previous commonly mis-segmented areas like the venous sinus are no longer present. The technique works well, especially in segmenting the global volumes as well as in major lobules, e.g., like VI or VII. Still, the smaller substructures and lobules showing high anatomical variability remain challenging and leave room for improvement. One possibility for improvement would be most likely to increase the number of manual segmented templates in the library, a manually demanding task that will be completed in the future.

The literature predominantly reports on semi-automated segmentation approaches, reporting results either only on partial manual labelling or results from an ensemble of merged lobules. In either case, the inter- and intra-observer agreement is expected to be artificially high: semi-automatic methods are biased towards the automatic boundaries as it takes effort to change them, and with a smaller surface to volume ratio, larger regions have proportionally less surface voxels to make errors on. Makris et al. introduced a semi-automated method (using Cardviews and Freesurfer) with a detailed parcellation of the cerebellum [Makris et al., 2003, 2005]. Very similar to our approach, they follow the anatomical fissures (according to the MRI atlas of Schmahmann et al. [1999]), separating each individual lobule. This is however performed on the basis of an inflated cortical map or flattened surface generated by Freesurfer. They identify the outer trace of the fissure on the surface, and then trace the full fissure in 3D directly in the MRI. In contrast to our approach a final automated parcellation in the anterior-posterior direction is used, dividing the cerebellar hemispheres into medial and lateral zones as well as dividing the vermis from the hemispheres. In total, 64 regions (32 per hemisphere) are obtained. In their work from 2005 (Makris et al., 2005) two experts applied the mentioned method to 10 healthy cerebella. The inter- and intrarater reliability was tested using intraclass correlation coefficient of absolute agreement and showed an average ICC of 0.81 (range -0.23 to 0.99). In particular, the smaller regions lacked good reliability. Therefore, the authors chose to cluster the original

parcellation units according to anatomical lobes and could show an improved ICC of 0.99 in anterior and posterior lobes and ICC of 0.74 in the flocculonodular lobes. The pattern of better performance in the larger scale lobules/lobes is similar to ours. In contrast to Makris method, Tiemeier et al. explicitly disclaim a detailed segmentation technique [Tiemeier et al., 2010]. They follow another semi-automated method, starting with a rough parcellation approach for the cerebellum introduced by Pierson et al. [2002], as they believe that changes cannot reliably be detected in volumes of <10 mL. They report similar good reliability (ICC > 0.8) measures for their method. Okugawa et al. report of excellent (ICC > 0.95) reliability measures of their manual approach to trace the outer contours of the vermis and hemispheres [Okugawa et al., 2002]. As they identify only large compartments, their technique is less specific and far less time-consuming. Since our method used to segment the template library is completely manual, and very time consuming (25–30 h per cerebellum), we decided not to redo the segmentations of multiple datasets to estimate intra- and interrater reliability measures for the templates.

The segmented cerebellar grey and white matter volumes in native space are generally in agreement with previous reported values ranging between 130 and 155 cm³ for total cerebellar volume and 114–131 cm³ for total cerebellar grey matter volume in native space [Diedrichsen et al., 2009; Dimitrova et al., 2008; Luft et al., 1998; Weier et al., 2012]. The differences are mainly explained by different segmentation techniques as well as whether white matter and/or peduncles were included.

When looking at the group as a whole, we found significant hemispheric asymmetry of the total white matter (right > left), but not for total grey matter, in line with Giedd et al. where they found no volumetric differences of the cerebellar hemispherical grey matter in the developing brain of a fairly large sample of children and adolescents [Giedd et al., 1996]. On a smaller scale we found asymmetries only in the following substructures: Crus I and the white matter core were larger on the right whereas Crus II and lobule X seem to be bigger on the left. Interpretation of these asymmetries should be made with caution, as they are relatively small in magnitude and Crus II as well as lobule X have been shown to be difficult to be segmented reliably (as demonstrated by a relatively low ICC). One may argue that part of the asymmetries (Crus I and white matter core) might be explained by lateralization of speech and motor function, which in our cohort would be the right hemisphere, because of the predominantly seen right-handed subjects. Dietrichsen et al. [2009] describe in their small cohort of 20 subjects a left-right asymmetry for the cerebellar hemispheres (left > right), for anterior lobules III and IV (right > left) as well as lobule VI (left > right). This was not the case in our cohort. These differences may be explained by the analysis of a different, larger sample here.

In terms of gender differences, the results show significantly larger native space volumes in men than women, which is in line with the literature [Diedrichsen et al., 2009; Dimitrova et al., 2006; Giedd et al., 2012]. Further significant gender-by-hemisphere interactions were found for white matter and the anterior lobe, pointing out a larger white matter core on the right for men compared to women and vice versa a larger anterior lobe GM volume in women when compared to men. However, these findings were only significant for the stereotaxic volumes but not for native space volumes. This may be due to the large inter-subject variability. Cosgrove et al. [2007] nicely summarized findings on sexual dimorphism of brain structures in humans, an increasing focus of neuroimaging studies over the past 20 years. Tiermeier et al. [2010] have shown in their study on cerebellum development during childhood and adolescence that the growth of the cerebellum peaks during puberty in girls earlier than in boys (girls 11.8 years and boys 15.8 years). For adults, due to the various methods and different cohort sizes, there has been inconsistency of gender differences in brain structures in general and of these, only a small number have focused on the cerebellum. As for the cerebrum and its substructures, most of these studies showed larger native space volumes in men than in women and almost equal volumes when normalizing for intracranial cavity volume, height or weight [Diedrichsen et al., 2009; Dimitrova et al., 2006; Giedd et al., 1996; Good et al., 2001]. It is however worthwhile mentioning that in our cohort, the cerebellum in women is larger in relation to the overall brain and intracranial cavity volume when compared with men, a result supported by the data from Dimitrova et al. [2006].

Overall these gender differences in brain structures are still not well understood. Peri- and postnatal processes may play a role as the full size of the adult cerebellum is reached in puberty [Tiermeier et al., 2010]. Furthermore the proof of gender-specific differences in gene expression, such as the specific sex chromosome-linked gene XIST, which is highly represented in the female cerebellum [Vawter et al., 2004], are one of various attempts to explain these differences.

Because age has also a known effect on morphologic changes of the brain, especially the cerebellum [Raz et al., 2005], we corrected for age in our ANOVA models. Except for white matter, we did not find any significant effect of age on the brain volumes. This may be explained by the limited age range in the young ICBM cohort, in which the effect growth has stopped and atrophy associated with old age has not yet started [Raz et al., 2005].

In summary, the implementation of the patch-based label-fusion technique in combination with a template library shows great potential for the automatic segmentation of the cerebellum and its substructures, yielding more detailed results in a very efficient way compared to other atlases available. This will enable its application in MRI

studies with large numbers of subjects and will help to better understand the human anatomy of the cerebellum and its disorders.

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