



Surface-based characteristics of the cerebellar cortex visualized with ultra-high field MRI

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ARTICLE INFO

Keywords:

Cerebellum
Ultra-high field
T₁
T₂*
Surface
Tissue content

ABSTRACT

Although having a relatively homogeneous cytoarchitectonic organization, the cerebellar cortex is a heterogeneous region characterized by different amounts of myelin, iron and protein expression profiles. In this study, we used quantitative T₁ and T₂* mapping at ultra-high field (7T) MRI to investigate the tissue characteristics of the cerebellar gray matter surface and its layers. Detailed subject-specific surfaces were generated at three different cortical depths and averaged across subjects to create averaged T₁- and T₂*-maps on the cerebellar surface. T₁ surfaces showed an alternation of lower and higher T₁ values when going from the median to the lateral part of the cerebellar hemispheres. In addition, longer T₁ values were observed in the more superficial gray matter layers. T₂*-maps showed a similar longitudinal pattern, but no change related to the cortical depths. These patterns are possibly due to variations in the level of myelination, iron and zebrin protein expression.

Introduction

The cerebellar cortex is characterized by a relatively homogenous structure - in contrast to the **cytoarchitectonic** heterogeneity of the neocortex - which consists of three cellular layers named granular, Purkinje and molecular layer (Cajal, 1911). Nevertheless, a number of animal studies showed that the cerebellar cortex is parcelled into distinct “zones” (Apps and Hawkes, 2009; Cerminara et al., 2015; Voogd, 2011). Longitudinal zones were observed based on the spatial distribution of cerebellar connectivity (i.e. climbing and mossy fibers; Groenewegen and Voogd, 1977; Pijpers et al., 2005, 2006; Ruigrok, 2011; Sugihara, 2004; Fujita et al., 2010; Fujita and Sugihara, 2013) and parasagittal stripes were distinguished based on protein expression patterns, i.e. zebrin II, in

a subset of Purkinje cells (PCs; Brochu et al., 1990; Marzban and Hawkes, 2011). Parasagittal stripes and longitudinal zones represents functional units with distinct synchronous neuronal spiking activities which may, for instance, play a role in the parallel processing of sensory information (Apps and Hawkes, 2009; Tsutsumi et al., 2015; Witter and De Zeeuw, 2015). Moreover, non-longitudinal variations have been observed in the cerebellar cortex, due to variations in myelination at different cortical depths (Wyatt et al., 2005) as well as cell densities, sizes and distribution across lobes, phylogenetic areas or cortex concavities (Armstrong & Schild, 1970; Lange, 1982; Müller and Heinsen, 1983).

The above studies have been performed in animals using microscale techniques such as electrophysiology and immunochemistry. Whether microscale structural patterns can be seen at the submillimeter range in

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the human cerebellar cortex is still unknown.

In recent years, software and hardware developments in ultra-high field magnetic resonance imaging (UHF MRI) have provided images with adequate spatial resolution as well as sufficient contrast- and signal-to-noise ratios to perform quantitative investigations of the human cerebral cortex at a laminar level (Dinse et al., 2015; Duyn, 2012; van der Zwaag et al., 2015). Thanks to these developments, our group also achieved the visualization of the granular and molecular layers in the cerebellum in humans *in vivo* (Marques et al., 2010b). Studies on the cerebral cortex showed that, combining the advantages of UHF MRI with quantitative MR acquisitions, it is possible to observe macroscopic patterns of quantitative MR contrasts on the cortical surface and within its layers, which derive from the underlying tissue composition. Quantitative T_1 (qT_1) and T_2^* (qT_2^*) maps at 7T reflect the distribution in myelin and/or iron concentrations (Bonnier et al., 2014; Cohen-Adad, 2014; Helms, 2013; Hwang et al., 2010), as confirmed by histology studies (Fukunaga et al., 2010; Stüber et al., 2014). These contrasts have been used to map changes in healthy subjects (Cohen-Adad et al., 2012; Dinse et al., 2015; Sereno et al., 2013) and in multiple sclerosis (MS) patients (Bonnier et al., 2015, 2014; Mainiero et al., 2015). Quantitative T_1 - and T_2^* -maps of the cerebellar cortical surface may help to understand the physiopathology of a number neurological and psychiatric diseases affecting the cerebellar cortex (i.e. MS (Fartaria et al., 2016; Kutzelnigg et al., 2007), cerebellar ataxia (Schniepp et al., 2017), cortico-basal degeneration (Piao et al., 2002), progressive supranuclear palsy (Piao et al., 2002), post-traumatic stress disorder (Meabon et al., 2016)).

To date, however, microstructural studies of the cerebellar cortex in humans *in vivo* are lacking, mainly due to the small size of the cerebellar cortex and its convoluted structure. In this work, we performed a surface-based investigation of microstructural properties of cerebellar human cortex *in vivo* by leveraging the high-spatial resolution and the qT_1 and qT_2^* contrasts at ultra-high field MRI.

Methods

Participants

Nine healthy participants (2 females, age = 21–43, right-handed) were enrolled in this experiment. All participants provided written

informed consent and the studies were approved by the local ethics committee. All participants had no history of neurological, psychiatric or systemic diseases. These participants were the healthy controls of a larger study involving multiple sclerosis patients (Boillat et al., 2016).

Acquisition

Data were acquired on a head-only 7T scanner (Siemens, Germany) using a 32 channel head coil (Nova Medical USA). A whole-brain T_1 image was acquired using the MP2RAGE sequence (Marques et al., 2010a; repetition time $TR = 6000$ ms, echo time $TE = 2.84$ ms, first inversion time $TI_1 = 750$ ms, second inversion time $TI_2 = 2350$ ms, first flip angle = 4° , second flip angle = 5° , matrix size $300 \times 320 \times 160$, voxel size $0.75 \times 0.75 \times 0.9$ mm³). MP2RAGE is a sequence combining two images generated at different inversion times (INV_1 and INV_2 sampled at TI_1 and TI_2 , respectively) to create a synthetic T_1 -weighted image free of T_2^* and proton density contrast, reception bias field and transmit field inhomogeneity (first order). A map of the transmit B_1 field was acquired with a SA2RAGE sequence (Eggenchwiler et al., 2012; $TR = 2400$ ms, $TE = 0.72$ ms, matrix $116 \times 128 \times 64$, voxel size $2.3 \times 2.3 \times 4$ mm³, same transmit voltage as MP2RAGE). The T_2^* -maps were generated from a 3D multi gradient echo, MGE, dataset with nine echo times ($TR = 45$ ms, $TE_1 = 4.59$ ms, $TE_9 = 41.3$ ms, with an echo spacing, ΔTE , of 4.59 ms, matrix size $300 \times 320 \times 160$, voxel size $0.75 \times 0.75 \times 0.9$ mm³). Three dielectric pads were placed around the upper neck to improve the inversion efficiency over the cerebellum and whole brain B_1 homogeneity (Teeuwisse et al., 2012).

Data processing

For every dataset, a mono-exponential fit to the MGE data was used to obtain the S_0 (signal at $t = 0$) and T_2^* -maps (Van der Weerd et al., 2000). S_0 was registered with a rigid body transformation to the INV_2 image from the MP2RAGE using Elastix (Klein et al., 2010) and the obtained transformation was subsequently applied to the T_2^* -map. The parameters of this MP2RAGE protocol were carefully chosen to limit B_1 -sensitivity over the range of B_1 -values expected in the cerebellum (Fig. S1). In addition, the MP2RAGE T_1 -maps were corrected for residual B_1 -inhomogeneities using the SA2RAGE B_1 -map, following the procedure

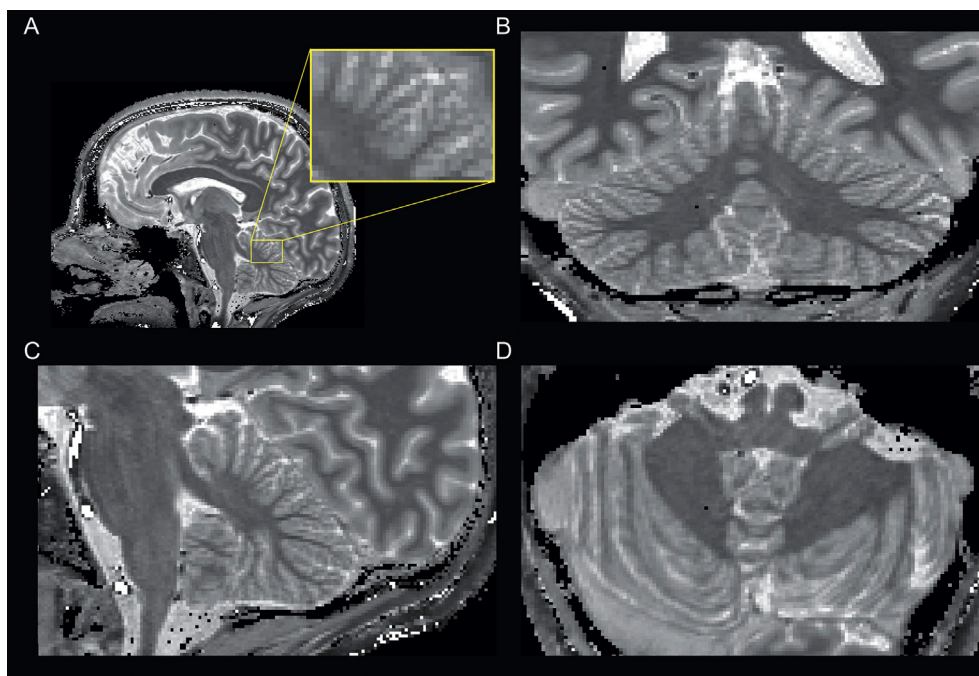


Fig. 1. Example of a raw T_1 -map (voxel size of $0.75 \times 0.75 \times 0.9$ mm³). A) A whole brain sagittal slice with a zoomed-in region on the folia (yellow square). B) Coronal, C) sagittal and D) axial slices through the cerebellum.

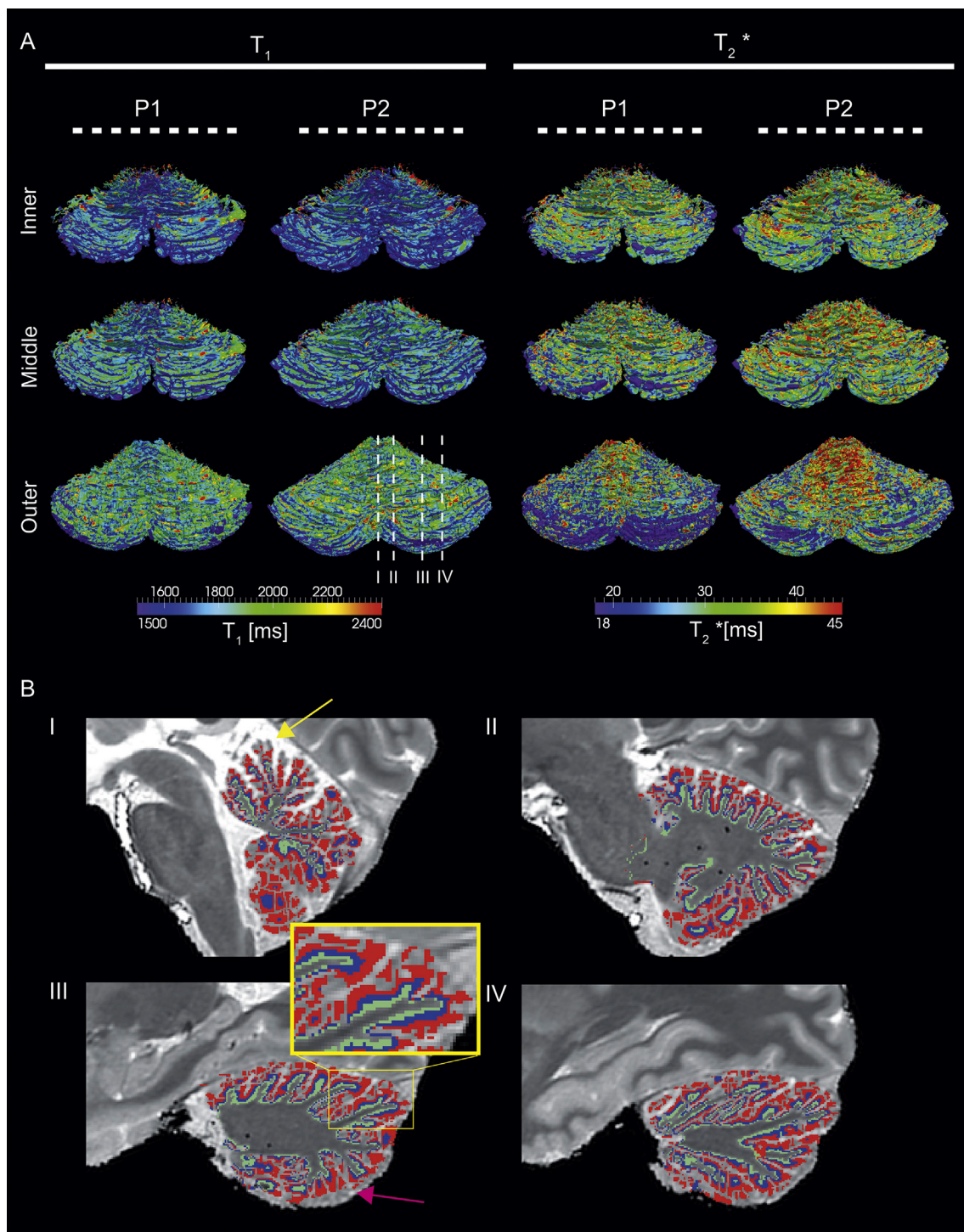


Fig. 2. A) Single-subject surfaces of two participants (P1 and P2) mapped with T_1 and T_2^* values. B) Sagittal cuts of P2 at four different positions from the medial to the more lateral part of the right hemisphere, indicated with a white dotted line on the outer T_1 surface. The segmentation results are shown overlaid on the T_1 -map for the inner (green), middle (blue) and outer (red) cortical depths. The yellow arrow indicates an underestimated part of the cerebellar cortex at the level of the vermis of the anterior lobe. The purple arrow indicates a similar region in the bottom part of the posterior lobe. No additional smoothing was applied to these surfaces.

described in Marques and Gruetter (2013). For the subsequent analysis steps the CBS tools toolbox (Bazin et al., 2013) was used. All images were skull-stripped using SPECTRE (Carass et al., 2011). The T_1 -weighted image was brought into the MNI space using a global linear registration algorithm based on FLIRT (Jenkinson and Smith, 2001) and the resulting transformation map was applied to the T_1 - and T_2^* -maps. The segmentation was performed with the T_1 image (thresholded at 4000 ms) as

input along with filters for dura matter, CSF and arteries (see Bazin et al., 2014), using the multi-geometric deformable model segmentation algorithm (MGDM; Bogovic et al., 2013). The MGDM algorithm segmented the brain in 30 different structures, including the cerebellum white (WM) and (GM) matter regions. The merging of WM and GM resulted in a cerebellar mask which was manually corrected to remove extra-cerebellar tissues (such as remaining small parts of the occipital

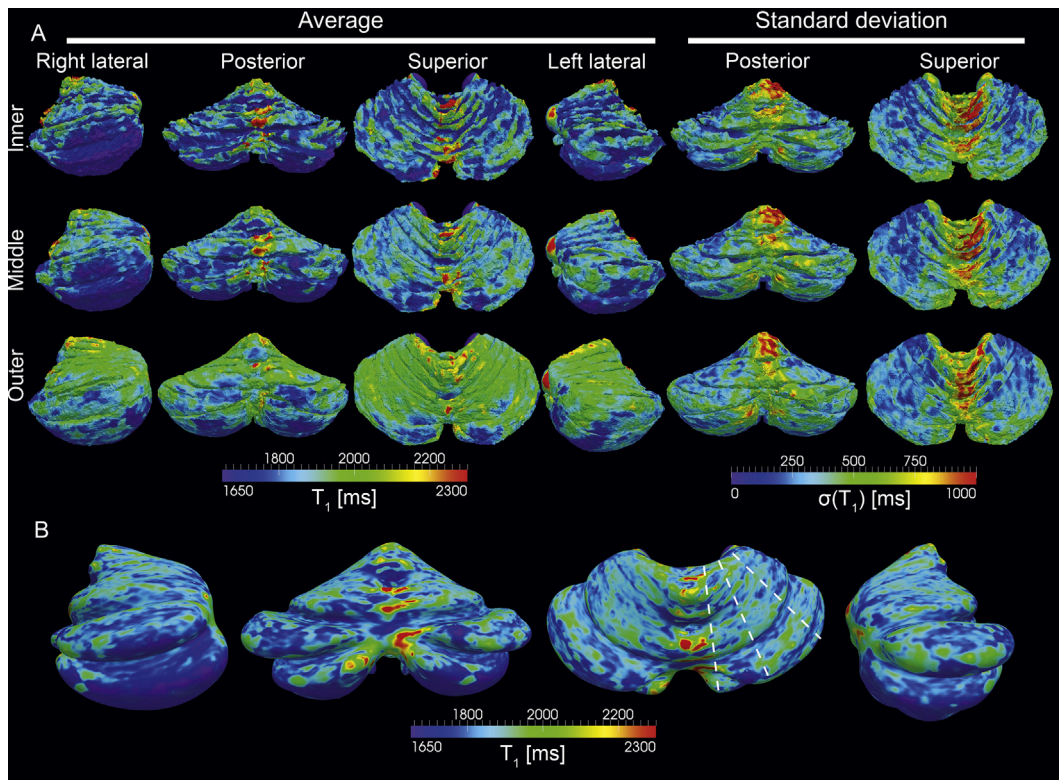


Fig. 3. T_1 mapping on the cerebellar surfaces. A) Mapping of the mean (left) and standard deviation (right) of T_1 values at the three cortical depths on their respective averaged folded surfaces brought into the CHROMA space. B) T_1 values mapped on the inflated surface of the CHROMA atlas T_1 -map at the middle cortical depth. The white dashed lines indicate the borders of zones with lower and higher T_1 values. A Gaussian function of 2 mm FWHM was applied for smoothing.

cortex or brainstem) with ITK-SNAP (Yushkevich et al., 2006). The masked T_1 -maps were then segmented using FANTASM (Pham, 2001) which provided a fine delineation of GM, WM and cerebrospinal fluid (CSF) borders. The WM-GM border and GM-CSF border level sets were extracted with an adaptation of the CRUISE algorithm (Han et al., 2004), a topology-preserving technique, ensuring spherical topology (Euler number of 2). Using the level sets, a continuous layering of the cerebellar cortex was built at three different cortical depths following a volume-preserving model of cortical folding where the volume fraction of a segment taken across the GM is constant across the whole cortical depth: the curvature is compensated by a change of the thickness of the cortical depth (Waehnert et al., 2014). On average, each layer represents one third of the total cortical thickness. While the complexity of the cerebellar folia cannot fully be captured at this spatial resolution each layer provides a different bias towards the deep, middle or superficial

layers of the cerebellar cortex (inner, middle and outer layer, respectively). A diffeomorphic image registration algorithm (ANTs; Avants et al., 2008) was used to realign the T_1 -maps to a high-resolution template (CHROMA atlas, a group-wise average of a T_1 -map acquired at 0.7 mm isotropic resolution) from the CBS Tools. The transformation map obtained from the previous procedure was applied to the inner, middle and outer surfaces to realign them. The aligned level set representations of the surfaces are then averaged across subjects for each separate surface, and the final group average surface is extracted as their zero-level set. Averaged T_1 and T_2^* values were then mapped onto the inner, middle and outer averaged surfaces as well as their standard deviation. Inflated surfaces generated from the CHROMA atlas T_1 -map were overlaid with the mean T_1 and T_2^* values from this group of subjects. For a better visualization, averaged surface values were smoothed along the cortex with a Gaussian function of 2 mm FWHM.

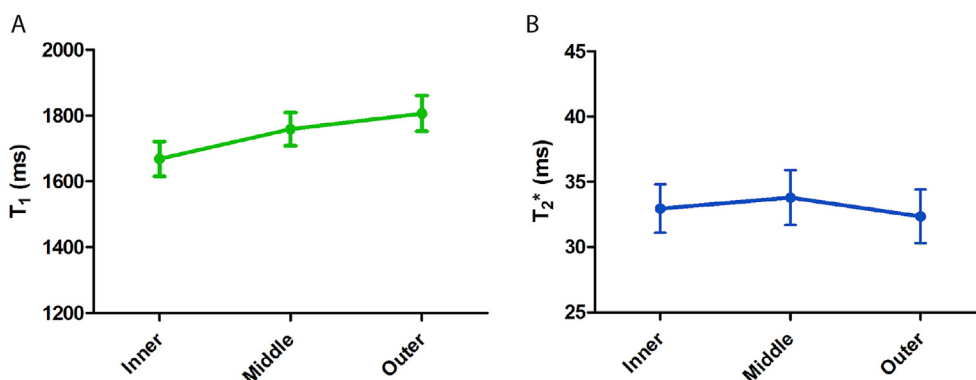


Fig. 4. Average T_1 (A) and T_2^* (B) values of the inner, middle and outer cortical depths. Values were averaged across spatial location and subjects. The error bars represent the standard deviation of the subject means.

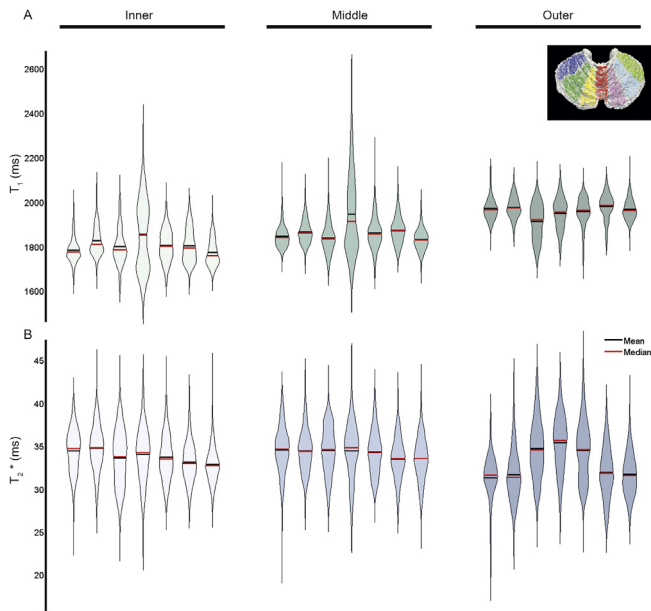


Fig. 5. Violin plots representing A) T_1 and B) T_2^* values extracted from seven different parasagittal regions of the anterior lobe (including lobule VI) of the averaged cerebellar surfaces for the three cortical depths. The seven regions are the ones indicated by different colours on the small cerebellar surface in the top right corner.

Results

Layer segmentation and single-subject surfaces

The main parts of the arbor vitae and folia of the cerebellum were distinguishable at the present resolution (Fig. 1), however the finer branching inside a single folium were difficult to distinguish due to partial volume effects (see Fig. S2 in the supplementary material for more

examples of single subject T_1). The cerebellar gray matter of all participants could be segmented into inner, middle and outer cortical depths. Although a clear delineation of the different lobules and the general shape of the arbor vitae was achieved, many individual folia were not completely resolved. Hence, these cortical depths refer predominantly, but not exclusively, to the expected tissue types in the cerebellar cortex (Fig. 2B). However, some parts such as the anterior vermis and the bottom region of the posterior lobe were underestimated (yellow and purple arrow in Fig. 2, respectively). The surfaces of each single participant showed a consistent preservation of the anatomy, in which the different lobules could be observed (Fig. 2A). Single-subject mapping of T_1 and T_2^* revealed consistent patterns as can be judged from the surfaces of P1 and P2 shown in Fig. 2.

T_1 mapping

Qualitative analysis of the T_1 -maps near the vermis showed highest values for each of the three cortical depths (Fig. 3A), while the lowest values were observed on the posterior lobe. On average, the T_1 values increased by 8.3% going from the inner to the outer cortical depths (Fig. 4A). The hemispheres showed low T_1 values that increased when going more laterally to decrease again in the very lateral regions. This pattern is mainly observed on the inner and middle surfaces and remains visible on the inflated surfaces (Fig. 3B with the dashed lines indicating the borders between stripes of higher and lower T_1 values). These observations are consistent with values extracted from the anterior lobe (Fig. 5A), where the plots depicting the inner, middle and outer surfaces show alternating mean T_1 values. The seven sagittal stripes of the violin plots were chosen based on a data-driven approach as the actual spatial frequency of these parasagittal stripes in humans is currently not known. Globally, T_1 values were lower in the posterior lobe. The inter-subject variability was higher in the vermis than in the cerebellar hemispheres. The latter was reduced in the cerebellar hemispheres, especially in the lateral regions. Confirming the high quality of the segmentation, no systematic pattern was observed between the apex of the lobules.

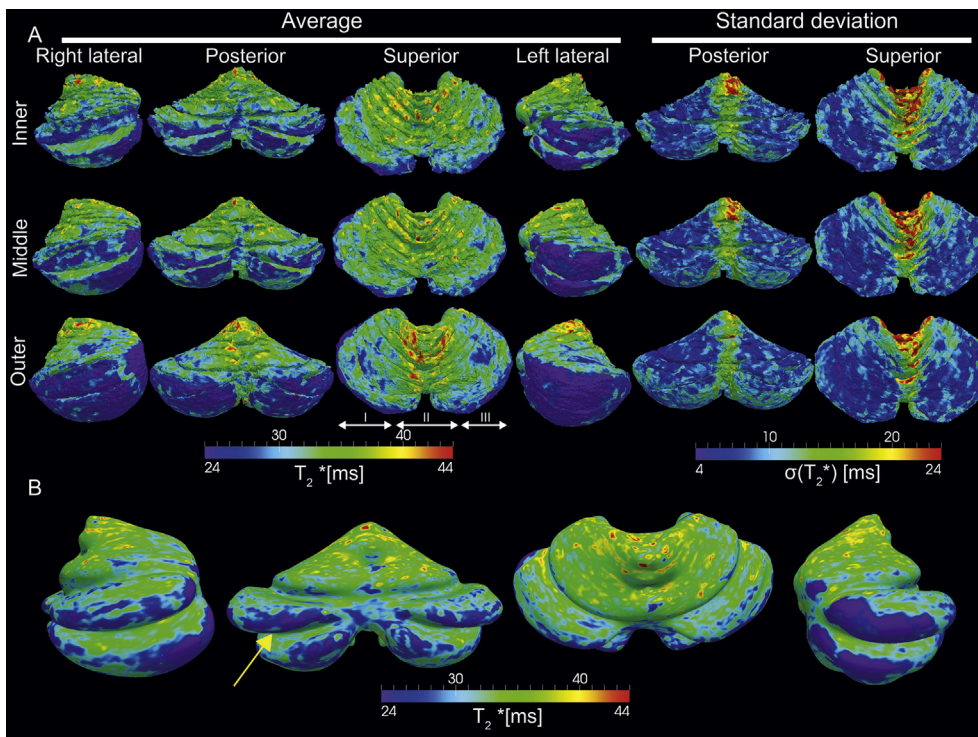


Fig. 6. Cerebellar surfaces mapped with T_2^* values. A) The averaged T_2^* values (left) with their standard deviation (right) mapped on averaged folded surfaces of the nine participants brought in the CHROMA space with the inner, middle and outer surfaces. The white arrows indicate the change of longitudinal patterns alternating between lower (I and III) and higher (II) T_2^* values. B) Averaged T_2^* values mapped on the middle inflated surface created from the CHROMA atlas T_1 -map. The yellow arrow indicated the “concavity-related” pattern on the folia’s apex. A Gaussian function of 2 mm FWHM was applied for smoothing. View from left to right of the averaged surfaces: right lateral, posterior, superior and left lateral.

T_2^* mapping

T_2^* values showed a different pattern than the T_1 values. Mean T_2^* values did not vary much between the different cortical depths (Fig. 4B). Lower T_2^* values were found on the apex of the folia of the posterior lobe, while the fissures showed higher values. Patches with high T_2^* values were found on the anterior lobe (Fig. 6). Similarly to the T_1 surfaces, the vermis had a high variability for T_2^* values, especially the anterior lobe. Again, the hemispheres showed much lower inter-subject variability. The posterior lobe showed low T_2^* values with a “concavity-related” pattern (Fig. 6B, yellow arrow) especially on the posterior region with lower values on the apex. These are likely driven by large-scale field gradients that affect the posterior lobe, but not the anterior lobe (see Fig. S2 in the supplementary material for examples of T_2^* -maps of the cerebellum with an evaluation of the goodness of fit of the nine GRE echos). On the anterior lobe, although different from the T_1 pattern, a medio-lateral pattern is also present (Fig. 6A, arrows I, II and III) with higher T_2^* values in the medial region to lower values in the lateral regions of the cerebellar hemispheres. This pattern is more pronounced on the outer surface, while being absent on the inner surface in the violin plots (Fig. 5B).

Discussion

In this study, we performed a cortical surface analysis of T_1 and T_2^* relaxation times in the human cerebellar cortex *in vivo*.

The spatial distribution of qT_1 evidenced a longitudinal pattern in the parasagittal direction alternating higher and lower T_1 values, which was observed at the three different depths from the cerebellar surface. Interestingly, a similar parasagittal pattern had been previously observed in the cerebellum of other species such as the rat (Brochu et al., 1990), cat (Sillitoe et al., 2003) and macaque (Sillitoe et al., 2000), which consisted of alternating stripes of higher and lower specific marker protein levels in Purkinje cells, such as zebrin (Apps and Hawkes, 2009). The stripes observed in these studies showed higher alternating frequencies of zebrin levels, but it is so far unknown what spatial frequency characterizes – if any – the human cerebellum. In alternative or in addition, the observed spatial pattern in qT_1 may be due to differences in myelin content (Lutti et al., 2014; Stüber et al., 2014) which might be linked to the zebrin expression. The observed decrease in mean T_1 values for the outer to the inner layers parallels a pattern, which has been previously reported in the cerebrum (Serenio et al., 2013; Waehnert et al., 2016) and that has been related to an increase in myelination level in the deeper layers of the cortex (Eickhoff et al., 2005; Walters et al., 2003). These studies also reported a modulation of mean T_1 values related to the concavity of the cerebral region (gyri or sulci), which we did not observe within the cerebellar surface as it is most probably dependent on the modelling of the cortical depth (Waehnert et al., 2014).

T_2^* surfaces also exhibited longitudinal variations in the parasagittal direction. As observed with qT_1 , spatial changes in the iron or myelin content (Cohen-Adad, 2014; Cohen-Adad et al., 2012) may be the cause of such changes. Interestingly, in contrast to the T_1 -maps, the T_2^* values did not change as a function of cortical depth, which could be due to the lower sensitivity to myelination of the T_2^* contrast compared to the T_1 contrast. Additional quantitative susceptibility mapping analysis (Deistung et al., 2011; Langkammer et al., 2012) might help to disentangle the respective contributions of myelin and iron to the contrasts observed here. The difference in T_2^* between the vermis and hemispheres is unlikely to be due to segmentation problems as those pointed out in Fig. 2, because the T_2^* varies little as a function of cortical depth.

Although high quality 7T data were acquired in this first study attempting a quantitative surface analysis of cerebellar cortex *in vivo* in humans, some limitations remain. These include the lack of spatial resolution to delineate the WM of the smallest embranchments of the arbor vitae, which may have led to some partial volume effects; to fully resolve the arbor vitae in fact, a spatial resolution of approximately 0.1 mm may

be necessary (Marques et al., 2010b), which is currently a challenge in human subjects *in vivo*. Therefore, a small systematic bias in the layer generation may be present in these data. Also, it would be preferable if surfaces were generated based on the phase contrast of a GRE image to make a separation driven by the different cellular layers, as observed in Marques et al. (2010b), rather than distance to the white matter. However, again, a spatial resolution of ~ 0.1 mm isotropic would be required for such a cortical surface analysis and this would imply prohibitive scan times *in vivo*. Consequently, the observed patterns of the present study revealed medio-lateral variations at the macroscopic level only, similar to the scale on which diffusion tractography is currently performed (Del-*l'Acqua* et al., 2013). While for most of the cerebellar cortical surface quantitative T_1 and T_2^* could be obtained with high confidence, the consistent low T_2^* and T_1 values in the most frontal part of the posterior lobe area are likely due to loss of SNR and corresponding poorer T_1 and T_2^* estimates. The cerebellum remains a challenging brain structure to image, the larger subject induced magnetic inhomogeneity resulted impaired T_2^* mapping in the most posterior end of the posterior lobe. The dependence of the cortical folding orientation with the B_0 field should also be considered as an additional source contributing to the concavity-related pattern (Cohen-Adad et al., 2012). Moreover, incorporating local magnetic field information in the T_2^* estimation might help reducing these large-scale field effects (Sedlacik et al., 2014). In addition, although the cortical geometry is more conserved across subjects in the cerebellum than in the cerebrum, we observed relatively high variability in the vermis, probably due to the underestimation of the cerebellar gray matter in this region during the layer generation or to an inappropriate registration algorithm for this region. Advanced cortical surface registration methods (Robinson et al., 2014; Tardif et al., 2015) may help further refine the T_1 and T_2^* patterns and reduce the high variability in the vermis. Despite these limitations, the parasagittal pattern in the cerebellar hemispheres and the differences between cortical depths are found in the T_1 - and not in the T_2^* -maps in the same subjects, strongly suggesting that these are indeed caused by myelin concentration differences rather than methodological limitations.

In summary, we observed macroscopic patterns of cerebellar cortical microstructure, which are possibly related to spatial variations in protein, myelin and iron content. Future studies combining 7T quantitative MRI with histological assessments should investigate and confirm the source of global macroscopic patterns we have observed in the human cerebellum cortex.

Conflicts of interest

K.O., M.J.F. and G.K. work for Siemens AG. The other authors have nothing to disclose.

Acknowledgment

We would like to gratefully thank Rolf Gruetter for his precious advice on the preliminary results. This work was supported by the Centre d'Imagerie BioMédicale of the UNIL, UNIGE, HUG, CHUV, and EPFL and the Leenaards and Jeantet Foundations and the Swiss National Science Foundation Grants 31003A_153070, 31003A_149983 and PZ00P3_154508.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.neuroimage.2018.01.016>.

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