

A new approach to mouse brain mapping

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Background:

Two dimensional paper based brain atlases provide detailed information of the cytoarchitecture of the brain's sub regions. The benefits of using digital, annotated MR-based atlases are immense. Unlike a paper-based atlas, images and its labels in 3D digital atlases allow manipulation, rotation and sectioning in any direction. In previous MR-based mouse brain atlases the brain's sub regions are amalgamated. The emergence of mutant mouse models makes it more important to define rules for digital 3D mouse brain segmentation in order to find minute volumetric and structural differences to normal models (Ma *et al.*, 2005), as those changes could be analogous to a variety of human disorders that are associated with structural changes.

Aims: The aim of the presented work is to focus on the complex cerebellar and hippocampal neuroanatomy and provide definitions for the delineations and boundaries of these anatomical structures in three dimensional MRI space.

Materials and Methods: The formalin fixed brain of a twelve-week old male inbred C57BL/6J mouse was imaged in a wide bore 700MHz wide bore Bruker microimaging system at 30 μ m isotropic resolution. A T₂*-weighted 3D-Flash sequence, (TR/TE = 50ms/12ms) was used. The coil was a 15mm custom-built SAW design (M2MImaging, Australia). To achieve a higher resolution 3D-image for segmentation the brain was scanned multiple times (three 8-average scans and seven 4-average scans). These scans were then non-linearly registered, upsampled with linear interpolation and the resulting images then averaged together (Walters *et al.*, 2003). Segmentation was performed using Display (MINC suite, Montreal Neurological Institute, Canada).

Results:

For the cerebellum 45 closed border labels were defined, which included grey and white matter regions, fissures and deep cerebellar nuclei. The hippocampus contained 35 different regions, which included the layers of the cornu ammonis and dentate gyrus. Guidelines were established using the knowledge base from previously mentioned publications, as well as the experience gained from our segmentation. These hierarchical rules mention the best practice first, followed by geometrical based approximation to the best practice.

- 1.) If natural boundaries were visible, they were chosen for segmentation (Figure 2), e.g. the fissures are the natural border of the lobules.
- 2.) If no borders were visible, neighbouring structures were chosen as reference points and the distances to those structures were calculated. This way, for the first time, rules for delineation of the cerebellar vermis in the mouse brain could be established.

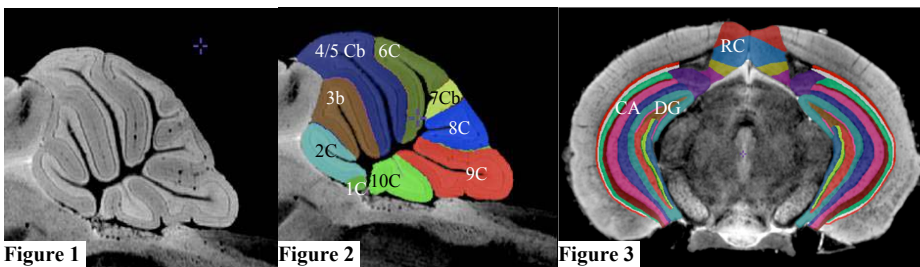


Figure 1

Figure 2

Figure 3

Fig. 1 shows the mid-sagittal section of the mouse brain, without labels.

Fig. 2 While all of the cerebellar regions were amalgamated in previous MR atlases, fig. 2 shows, that the 10 lobules of the cerebellum are easily separated with the help of the fissures.

Fig. 3 shows a slice from the hippocampus. Not only could the cornu ammonis (CA), dentate gyrus (DG) and part of the rhinocortex (RC) be differentiated, but also the various layers of these structures.

Discussion:

While the atlasing project is in the early stages, there are already more regions described than in other anatomical 3D MRI mouse brain atlases. In most anatomical detailed mouse brain atlases, the labels are placed in the appropriate region, but the exact border of e.g. the vermis of the cerebellum remains undefined. Therefore this atlas is more accurate than paper based atlases, as we defined closed border labels. The use of a single specimen to create a brain atlas has some limitations. Individual variation of the size and shape of particular structures cannot be completely accounted for. However, a comprehensive analysis of a single brain can provide the first step to the identification of brain structures in the mouse population (Schmahmann *et al.*, 1999). Furthermore, this atlas will provide the basis for the development of a probabilistic mouse brain atlas in the future.

Discussion:

1. Ma, Y., et al. A Three-Dimensional Digital Atlas Database of the Adult C57BL/6J Mouse Brain by Magnetic Resonance Microscopy. *Neuroscience*, 2005. 135(4), p.1203-1215.
2. Schmahmann, J., et al. Three-Dimensional MRI Atlas of the Human Cerebellum in Proportional Stereotaxic Space. *Neuroimage*, 1999. 10(1), p. 233-260.
3. Walters, N.B., et al. In vivo identification of human cortical areas using high-resolution MRI: An approach to cerebral structure-function correlation. *PNAS*, 2003. 100 (5), p.2981-2986