Morphological study of mouse brain models with Down syndrome using MEMRI

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Purpose/Introduction

In the transgenic research era, the understanding of the functional consequences of the genes deletions or mutations in order to investigate the origin of human transgenic disease requires the development of non invasive study methods on murine models. Our aim is to develop new Down syndrome models and a 3D reconstruction software using MEMRI at 9.4T. To improve contrast and spatial resolution at high magnetic field, the Mn2+ contrast agent shows powerful paramagnetic properties leading to a significant increase of MRI signal [1]. Mn2+ is a unique marker for neuroarchitecture, neuronal connections and functions therefore particularly interesting for neuropathological studies *in vivo*. In order to investigate the morphological and structural consequences on the central nervous system development in new mice models of human chromosome 21 aneuploïdies, we used MEMRI and we also developed a powerful tool in order to perform an automatic segmentation and 3D reconstruction of three brain structures.

Subjects and Methods

Ts1Yah and Ts2Yah mice correspond to trisomic models of various human chromosome 21 homologous areas located respectively on the murine chromosome 17 and 16, 2n mice are their reference. Ts65Dn and Tg(Pcp4) mice were also studied. These new models were bred at the IEM, Institute of Transgénose (CNRS, Orléans). Mice were submitted to IP injection of 50mM $MnCl_2$ solution 48h before MRI acquisition. MRI experiments were carried out on a spectrometer 9.4T/21 USR Biospec (Bruker, Wissembourg, France) using a stereotaxic setup, a homogeneous 35mm ID birdcage RF coil. The mice were anaesthetized with isoflurane (1.5-2.5%) in an O_2/N_2O 1:1 mixture. Breath and temperature physiological parameters were monitored throughout the experiment. 3D FLASH experiments were recorded using, TR= 150ms, TE=2ms, $\alpha = 60°$, FOV = 3x1.3x1.3cm, matrix 256x110x110, duration 2h. The image processing was carried out with final resolution of $(88\mu m)^3$. They were segmented manually with OSIRIX and automatically using a specially developed segmentation and reconstruction software (Matlab™ R2007 and VTK 5.0.1 environments). The segmentation method is an active contour model based on Mumford–Shah segmentation techniques and the level set method. This method has been shown to detect objects whose boundaries are not necessarily defined by gradient or with very smooth boundaries. Based on this 2D method, we proposed a 2D technique to automatically segment one desired cerebral object from the 3D MRI image. The volumes were compared using Student Test and one factor variance analysis (Excel).

Results

The images on adult mice *in vivo* with high spatial resolution (~80 microns out of the three directions) display new contrasts at 9.4T compared to mice without contrast agent. In particular, we were able to distinguish subregions of the brain: cerebellum, thalamus, hippocampus, (fig1). Starting from an initial ellipse positioned roughly on the desired structure, an automatic algorithm segments a set of 2D axial images, then refined using classical morphological operations to define a unique contour of the targeted structure (fig. 2, fig 3 for brain segmentation).

The whole automatic process is carried out in an average of 20 minutes, compared to 4 hours when manually segmented using an independant image processing software (OSIRIX). The results obtained manually on the same type mice (for example, on 2n mice, mean brain volume = $448\pm20mm^3$) confirm the results provided by the automatic segmentation method (on 2n mice, mean brain volume = $447\pm13mm^3$, Student test p=0.91, one factor variance analysis p=0.89). On 15 brain volume estimations (2n, Ts1Yah and Ts2Yah) obtained after automatic and manual segmentation, numerical results show that the automatic segmentation gives volumes which are very comparable to those obtained by manual segmentations (for example between mice, mean brain volume reference= $447\pm13mm^3$, Ts1Yah = $432\pm35mm^3$, Ts2Yah=453 ± 28 no significant difference, Student test 2n/Ts2Yah : p=0.41, 2n/Ts1Yah : p = 0.75).

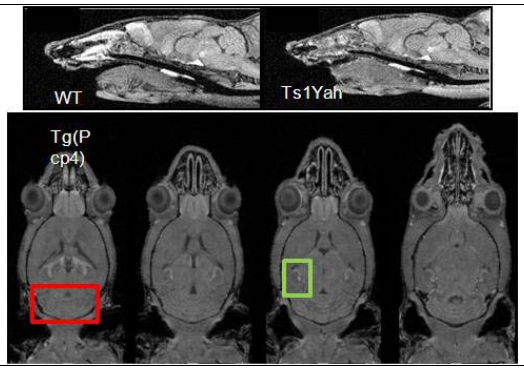

Figure 1 : MEMRI images of trisomic mice brain at 9.4T

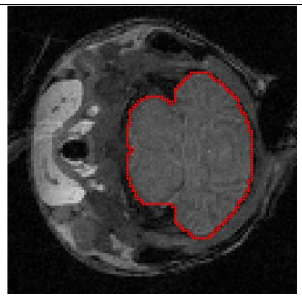

Figure 2: Segmentation after morphological operations

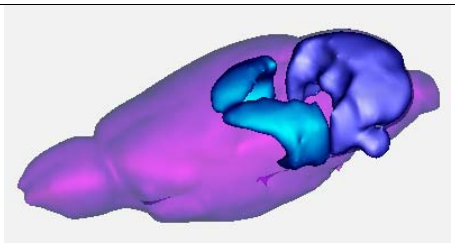

Fig 2: 3D segmentation of brain, cerebellum and hippocampus.

Discussion/Conclusion

MEMRI makes it possible to obtain at high magnetic field morphological images with strong contrast and to target neuroarchitecture. Using the dedicated software, a semi-automatic quantitative study of the whole brain and subregions, averaging and alignment of images (fig 2) has been performed and compared to a manual segmentation method. Subregions volumes were comparable, but processing time is drastically reduced by a factor of 13, whereas segmentation quality and accuracy are improved. The analysis of the whole brain volume reveals no significant morphological differences on the studied trisomic mice. The next step regarding the automatic segmentation method is to develop a fully 3D algorithm.

References

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