Voxel-based morphometry reveals localised cerebral atrophy in a mouse lemur model of aging

S. J. Sawiak[1,2], and M. Dhenain[3]
[1]Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, England, United Kingdom, [2]Behavioural and Clinical Neurosciences Institute, University of Cambridge, Cambridge, United Kingdom, [3]MIRCen, I2BM Institute of Biomedical Imaging, Fontenay aux Roses, France

Introduction

The mouse lemur (*Microcebus murinus*) is a new world primate well-suited for studying human aging due to the relative sophistication of their brain compared to rodents, their short maximum life span (12 years) and small size (12 cm). Voxel-based morphometry (VBM) is a fully-automated technique which can detect morphological differences based on changes in apparent grey or white matter (GM/WM) concentrations[1,2]. The technique is used widely in the human brain but has seen little application in animal models due to limited availability of relevant software packages. Here we show that the SPMMouse plugin[3] for SPM5 shows ageing effects consistent with previous studies in the mouse lemur and human brain, revealing differences more subtle than were detected with laborious manual techniques. This has the dual effect of supporting the use of this model to study ageing and showing that VBM is an important technique for assessment of morphology in the animal brain.

Methods

Thirty mouse lemurs (2-11 years, mean 5.6 years ± 2.8 SD) were scanned at 4.7 Tesla *in vivo* according to previously described 3D T2-weighted protocols (isotropic resolution=234μm)[4]. After correction for intensity non-uniformity, images were loaded into SPM5 and coregistered to a randomly chosen brain according to a rigid transformation. All such transformed brains were averaged together to form a target for affine registration. After affine registration the brains were transformed again and the result segmented into GM, WM and CSF tissue classes. DARTEL[5] was used to create templates for a VBM analysis looking at GM, WM and CSF changes with age using overall brain volume as a covariate. GM proportions were fitted to a general linear model and tested for negative correlation with age, with $p < 0.05$ (FDR-corrected for multiple comparisons) accepted as being statistically significant.

Results

Fig 1a shows smoothed prior tissue probability maps of GM, WM and CSF generated for the mouse lemur and fig 2 shows sections from the 3D SPM image showing GM changes with age. GM reductions are seen in frontal cortex, basal ganglia and temporal cortex. Of particular note are the cingulated (cing) and entorhinal cortical (Ent) differences seen, both of which are typical findings in studies of human aging. The VBM method also shows changes in contrast related to increased iron deposition in the thalamic nuclei (fig 1b, marked thal).

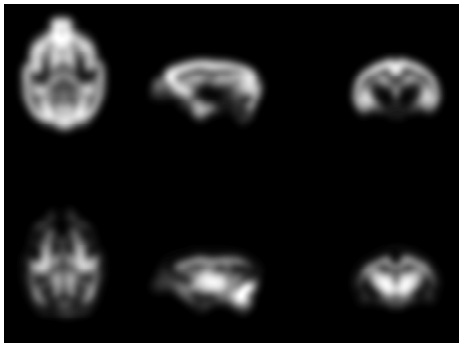
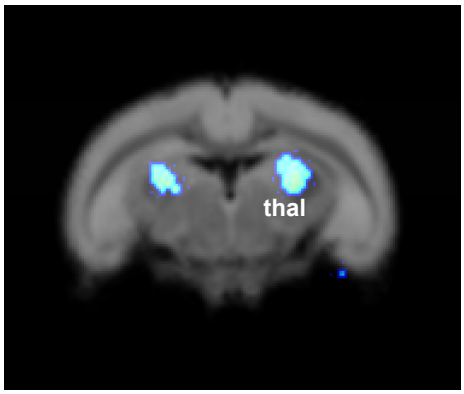


Fig 1a Smoothed GM (top) and WM probability maps for the mouse lemur brain, shown in axial, sagittal and coronal sections.

Fig 1b Signal changes related to iron deposition with aging[6] are detected as "GM signal" changes in VBM.



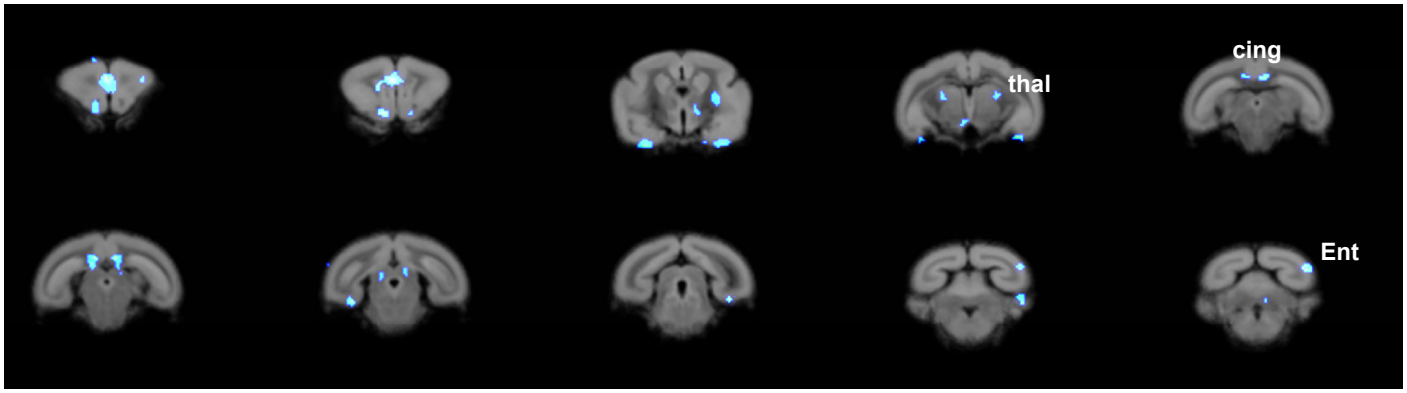


Fig 2. Statistical parametric map showing age-related reductions in GM signal in the mouse lemur ($p < 0.05$, corrected)

Conclusions

The mouse lemur has been shown to demonstrate age-associated cerebral atrophy typically seen in senescence and Alzheimer's disease, adding further support to its utility as a model of brain aging. Voxel-based morphometry has found areas of the brain showing increased atrophy with age with minimal manual processing, showing that it is an important technique in the non-human brain. Furthermore, this automated approach validates previous studies in this model which gave similar findings[7,8]

1. Ashburner, J. *Magn Reson Imaging* **27**, 1163-1174 (2009). 2. Sawiak, S.J. et al. *Neurobiol Dis* **33**, 20-27 (2009). 3. Sawiak, S.J., *ISMRM 17th Scientific Meeting* 1086 (Honolulu, Hawaii, 2009). 4. Dhenain, M., et al *Magn Reson Med* **50**, 984-992 (2003). 5. Ashburner, J. *Neuroimage* **38**, 95-113 (2007). 6. Dhenain, M. et al (1998) Neurobiol Aging 19(1): 65-69. 7. Kraska, A., O. Dorieux, et al. Neurobiol Aging (in press). 8. Picq, J.-L., F. Aujard, et al. (2010) Neurobiol Aging (in press)