

## VBM study of Diurnal Variations of Brain Diffusion in Healthy Adults

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### Introduction:

Brain physiology varies diurnally [1, 2] that may be reflected by diffusion changes [3-6] in brain tissue. Diffusion tensor imaging (DTI) has been extensively used in exploring brain physiology and pathology under healthy and diseased conditions. The aim of this investigation is to explore the diurnal alterations in brain diffusion of normal adult brain using voxel-based morphometry (VBM).

### Materials and Methods:

15 healthy subjects were recruited (6 males, 9 females, 23-31 years, mean age  $24.8 \pm 2.1$  years). DTI was performed using directional sensitized diffusion-weighted single-shot echo-planar sequence with  $b$  values of 0, 1000, 1200, 1400, 1600, 1800, 2000  $\text{s/mm}^2$  in 20 gradient directions (TR/TE = 4300/104 ms, FOV = 250\*250  $\text{mm}^2$ , in plane resolution 3.0  $\text{mm} \times 3.0 \text{ mm} \times 3.0 \text{ mm}$ ). In addition, 3D MPRAGE was applied to obtain continuous high resolution T1-weighted images (TR/TE/TI = 1900/2.53/900 ms; flip angle = 9°; field of view = 250 mm; in-plane resolution 1.0  $\text{mm} \times 1.0 \text{ mm} \times 1.0 \text{ mm}$ ). Both DTI and MPRAGE were performed in the morning (8:30 a.m.  $\pm 0.5$  h) and repeated in the evening (7:30 p.m.  $\pm 0.5$  h) over a 24-hour period for each participant. Image processing was performed using DTI Studio (<http://cmrm.med.jhmi.edu/>). FA, RA, VR, mean ADC,  $\lambda_{\parallel}$  (longitudinal diffusivity) and  $\lambda_{\perp}$  (transverse diffusivity) were computed pixel by pixel with correction of distortion induced by eddy currents and head motions by an affine transformation algorithm. Voxel-based analysis was performed using SPM8 (Statistical Parametric Mapping; <http://www.fil.ion.ucl.ac.uk/spm>) software implemented in Matlab2010b (The Mathworks Inc., Sherborn, MA).  $b_0$  images were aligned to the Montreal Neurologic Institute (MNI) space by using the echo-planar imaging template in SPM8 to estimate the normalization parameter which was then used to map FA, ADC,  $\lambda_{\parallel}$  and  $\lambda_{\perp}$  images, and the voxel size was resampled to 3  $\text{mm} \times 3 \text{ mm} \times 3 \text{ mm}$ . Finally, the normalized maps were smoothed using an isotropic Gaussian filter (filter size = 8 mm). Voxel based differences in FA, ADC,  $\lambda_{\parallel}$  and  $\lambda_{\perp}$  between the repeated scans were examined using paired student  $t$ -test with REST software (<http://www.restfmri.net/>). Clusters with  $P < 0.05$  (AlphaSim corrected) and size  $> 10$  voxels were considered as statistically significant. The corresponding  $t$  score was color coded (warm color: morning > evening; cold color: evening > morning).

### Results:

Significant diurnal alterations of FA, ADC,  $\lambda_{\parallel}$  and  $\lambda_{\perp}$  were observed in grey and subgyral white matter of bilateral frontal, occipital and temporal lobes (representative images shown in Figure 1) with a greater change rate in left hemisphere. The complete detail of sub-gyral regions, cluster volume and MNI coordinates were summarized in tables (not shown). Significant altered ADC,  $\lambda_{\parallel}$  and  $\lambda_{\perp}$  were predominantly observed in the bilateral occipital lobe (lingual and calcarine regions) (Table 1) (Figure 1B, 1C and 1D), while FA alterations was observed mainly in frontal lobes (Figure 1A) (TABLE 1).

Table 1. Maximal percentage of increase in FA, ADC,  $\lambda_{\parallel}$  and  $\lambda_{\perp}$  of the morning compared to evening.

Brain Regions of voxel with peak $t$ value	Peak $t$ value	% (Am-Pm)/Am			
		FA	ADC	$\lambda_{\parallel}$	$\lambda_{\perp}$
Right Frontal lobe	3.04	13.0	-	-	-
Left Frontal Lobe	4.00	28.0	-	-	-
Right Occipital	4.55	-	19.5	16.7	22.2
Left Occipital	4.38	-	30.6	33.4	30.6

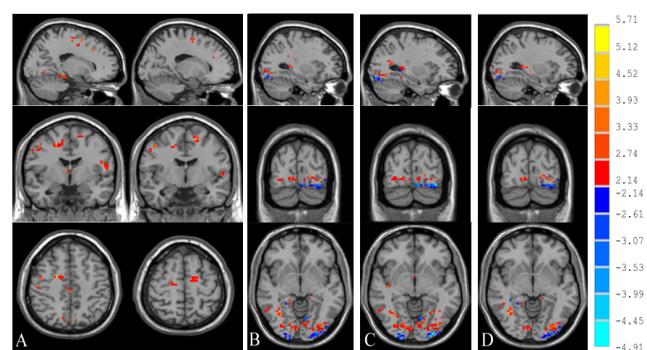


Figure 1.  $t$  map of FA (A), ADC (B),  $\lambda_{\parallel}$  (C) and  $\lambda_{\perp}$  (D). Significant regional alterations in anisotropy and diffusivity were observed in bilateral medial frontal gyri, occipital and temporal lobes ( $P < 0.05$ , cluster size  $> 10$  voxels).

**Conclusion:** Diurnal changes of brain anisotropy and diffusivity suggested the underlying alterations of the extracellular volume and tortuosity that may attribute to the variation in ion and neurotransmitter concentrations which is coupled with the diurnal physiological variations of the brain.

### References

[1] Smale L, et al. Biological Rhythm Research 2008; 39: 305-318. [2] Sykov E, et al. Physiology Rev 2008; 88: 1277-1340. [3] Le Bihan et al. PNAS 2006;103: 8263-8268. [4] Kim et al. Biophys J 2007; 92:3122-3129. [5] Miller et al. PNAS 2007; 104:20967-20972. [6] Hansen B, et al. Neuroimage 2011; 57: 1458-1465.