Assessment of Water Diffusion Compartmentation in the Non-Human Primate Brain

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Introduction: Arterial spin labeling (ASL) perfusion MRI techniques have gained wide acceptance because ASL measures the cerebral blood flow (CBF) by magnetically labeling blood water molecules without the use of a paramagnetic contrast agent (CA) [1, 2]. ASL techniques combined with diffusion-weighted (DW) - MRI have also been employed to measure permeability-surface product (*PS*) of the capillary wall in brains [3, 4]. Estimates of the capillary permeability evaluate the status of blood brain barrier (BBB) in cerebrovascular diseases [5, 6], whereas apparent diffusion coefficient (ADC) evaluates the mobility of water molecules in normal and pathological tissues [7, 8]. Recently, DW- ASL perfusion technique detailed elsewhere [4] was applied to measure the capillary wall permeability in the human brain. Herein, we employed DW-ASL perfusion method in the non-human primate's brain. In the present study, ASL signals evolving from the vascular and tissue compartments acquired *via* DWI-ASL perfusion method were fitted to biexpoential diffusion decay for the fast and slow diffusion components to identify possible differences in diffusion compartmentation in white and gray matter in the non-primates brain using DWI-ASL perfusion data.

Material and Methods: Three healthy female rhesus monkeys (n=3, 7-11 years old) were utilized. All procedures followed the protocols approved by the Institutional Animal Care and Use Committee (IACUC) of Emory University. The DWI-ASL perfusion images were acquired using a Siemens 3.0 T Trio whole body scanner MR system (Siemens Medical, PA, USA) with an 8-channel high resolution knee coil (Invivo, Inc.) [9]. All the physiological parameters such as O_2 saturation, blood pressure, heart rate, respiration rate, body temperature etc. were monitored continuously in each scan session and were recorded and maintained in normal ranges of anesthesia (0.7-1.0 % Isoflurane). The DWI-ASL perfusion data were collected at b = 0, 10, 25, 50, 105, and 190 s/mm^2. The other MRI parameters were: TR/TE = 4100/43 ms, FOV = 96 mm × 96 mm, data matrix = 256 × 256, 16 slice with slice thickness = 1.5 mm. Regions of interest (ROIs) were selected in the white matter and gray matter on the first b = 0 s/mm^2 image in the series with weak diffusion weighting (Fig.1A). For all the three subjects, a total of 24 ROIs were placed in the white matter and gray matter with a mean area of 72 pixels. For each ROI, the average DWI-ASL perfusion signals were fitted to Eqn[4]: $S(b) = S_0 (a_f \exp(-bD_f) + a_s \exp(-bD_s)$[1] [4] where S(b) is the signal in the presence of diffusion sensitization, S_0 is the signal in the absence of diffusion sensitization, D_f and D_s represent the apparent fast and slow water diffusion coefficients (ADCs) and a_f and a_s (*i.e.*, $a_f + a_s = 1$) are the fractional weights associated with D_f (vascular) and D_s (tissue) components of the signal attenuation curve, respectively[4]. Data analyses were performed using Matlab (MathWorks, MA) and Image J (NIH.gov/ij/) software's. Data are expressed as mean (± standard deviation). Differences were examined by paired t-tests, and significance was inferred at $p \leq 0.05$

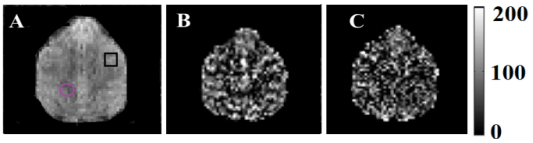

Fig.1.A. DW-ASL EPI image with ROIs in white matter (circle) and gray matter (square) at b = 0 s/mm^2. **B**. Cerebral blood flow map at b = 0 s/mm^2. **C**. Cerebral blood flow map at b=190 s/mm^2. Scale bar in ml/100g/min.

Results and Discussions: A typical DWI-ASL image of a normal non-human primate brain with b= 0 s/mm^2 is shown in Fig. 1A. Fig.1B and C represent the DWI-ASL cerebral blood map generated at b= 0 and b = 190 s/mm^2. Fig.2 represents the signal decay curve as a function of b value for the white and gray matter ROIs (Fig.1A). The biexpoential fitting yielded the following fitting parameter for the white matter a_f =0.055, a_s = 0.945, D_f = 0.112 × 10^{-3}mm^2/s, and D_s = 0.54 × 10^{-3} mm^2/s and gray matter: a_f =0.065, a_s = 0.935, D_f = 0.193 × 10^{-3} mm^2/s, and D_s = 0.55 ×10^{-3} mm^2/s. Table 1 summarizes the values of ADCs: Df, Ds, and fractional weights: a_f and a_s averaged over all the gray and white matter ROIs. Comparison of the fitted parameters a_f and a_S and D_f did show the differences but were not significant (p=0.12) for white and gray matter, whereas the slow diffusion component D_s showed a significant difference (p <0.05) for white and gray matter. The average, a_f and a_S differed by about 40% and <2% in white and gray matter, whereas D_f and D_S differed by about 80% and 14% in white and gray matter, respectively. The correlation coefficients (R^2) for the biexpoential fits were about 0.99, p < 0.0001.

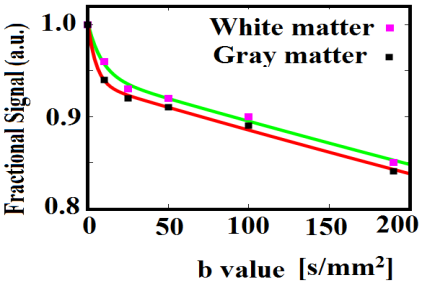

Fig.2. Typical biexpoential signal curves as function of b valve for a ROI in white (top) and gray matter (bottom).

Table1
ADC values are (Mean ± S.D.)×10^{-3} mm^2/s.

Parameter/ROI	WM	GM
a_f	0.039±0.007	0.052±0.023
a_s	0.960±0.008	0.957±0.013
D_f	1.073±0.835	1.064±0.911
D_s	0.561±0.006	0.606±0.005

Discussion and Conclusion: The DWI-ASL perfusion data of the monkey brain were compatible with a biexpoential model in all white and gray matter ROIs studied (*i.e.*, R^2 = 0.99, p < 0.0001). In this study, it was found that white matter D_s was smaller than gray matter D_s, while white matter D_f was larger than gray matter D_f. The white matter a_f was smaller than the gray matter a_f, whereas the white matter a_s was slightly larger than the gray matter a_s. The estimated fast diffusion coefficients D_f showed relatively large intersubject variability, whereas the D_s was quite stable. Biexpoential fitting of the signal decay data with diffusion sensitization gradient values can reveal a_f, a_s, D_f, and D_s as well as the rate constant of water exchange across the capillary wall (*i.e.*, PS/v_c), where v_c is the volume of the capillary, P is the permeability of the capillary wall, and A is the surface area of the capillary. In conclusion, DWI-ASL methodology for the water diffusion compartmentation is clearly an attractive method to further our understanding of tissue water diffusion dynamics and for assessing BBB integrity in the progression of pathologies such as strokes in animal studies.

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