Temporal Tissue Assessment in non-Human Primate Cerebral Ischemia using Diffusion-weighted MRI Imaging and ISODATA Cluster Analysis

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Introduction

- Understanding the evolution of ischemic lesions on diffusion weighted MRI is important for better diagnosis and management of stroke patients [1,2,3].
- An ROI-based study of the temporal evolution of cerebral ischemic lesions in non-human primates showed more consistency to that of human stroke evolution than that of rodents [4,5].
- Manual outlines may be subjected to partial-volume averaging which may obscure heterogeneity in lesion development patterns .
- Cluster analysis may improve staging, identifying and quantifying progressive ischemic damage as a result of stroke.

Aim

- ✓ Establish the efficacy of voxel-by-voxel analysis for evaluating the time-course of changes in the acute, sub acute, and chronic stages after experimental stroke.
- ✓ Characterize differences in time-course of DWI indices between permanent and transient MCA occlusion.

Materials and Methods

Animal model

- 3-hour uni-lateral middle cerebral artery (MCA) obstruction in 3 adult male macaques (Macacca fasicularis). 2 animals received an injection of a small volume of cyanoacrylate thrombus to simulate a permanent occlusion.

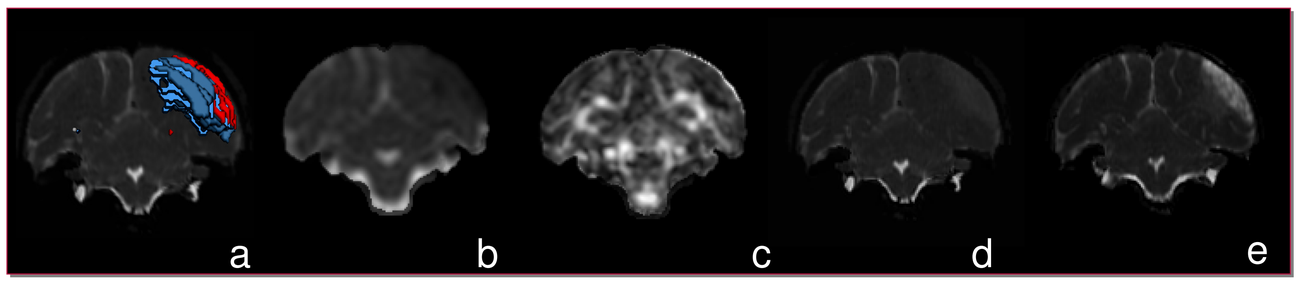
MRI

- MR imaging (GE Signa, Milwaukee, USA) at < 6 hours; 1, 3, 6, 10, 17, and 30 days after stroke onset.
  - DWI: (*single-shot EPI, TR/TE 6000/75, b=1000 s/mm²*)
    - ADC, FA.
  - T2-weighted: (*FSE, ETL 16, TR/TE 4200/95*)
    - T2 maps

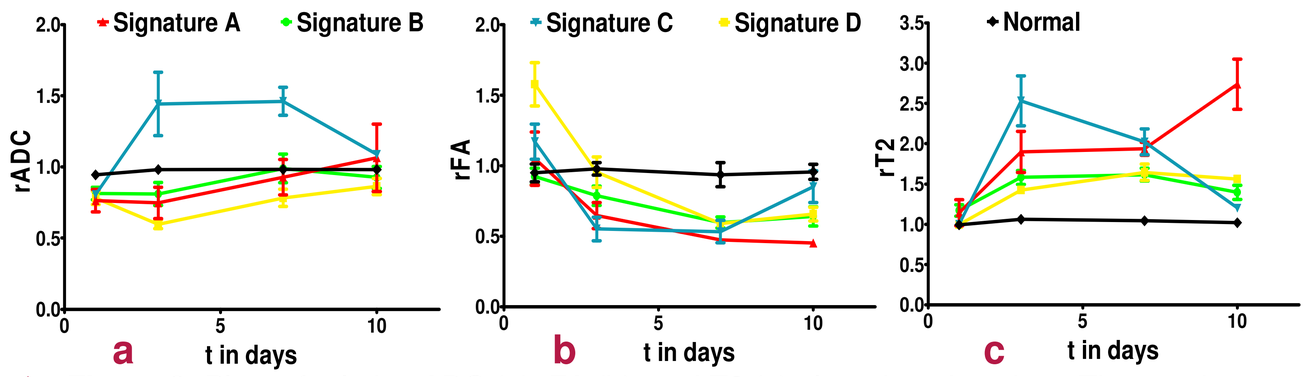
ISODATA analysis

- All volumes were co-registered to images acquired at the first timepoint (MNI autoreg [6]). Edema induced distortions were compensated for by using a B-spline based non-linear fitting algorithm with rigidity penalty to preserve lesion size (ISI Elastix [7]).
- ADC, FA, and T2 were normalized according to contra-lesional values and combined using an improved iterative self-organizing data analysis (ISODATA [8,9]) with spatial contiguity weighting [10].
- Resulting patterns where pruned using a coefficient of variance analysis. Variance above 0.005 was considered abnormal.
- Lesion evolution patterns from all 5 animals were pooled to correlate signatures in between animals and determine global ischemic lesion evolution.
- Inter-animal comparison (Pearson's Chi-squared test) of the signature distribution in the ischemic core (abnormal acute DWI and f/u T2) and rim (abnormal acute DWI and normal f/u T2) ROI's. Signature distribution between permanent and transient occlusion was also tested.

Results



▲ **Figure 1:** 3D rendering of tissue signatures (a) at 3 hour after uni-lateral MCA occlusion, created by combining ADC (b), FA (c), and T2 (d) up till 10 days after stroke. The signatures denoted in blue indicate initially abnormal diffusion and T2 which slowly returns to normal values. The red signature indicates areas of sustained damage which correspond well to the increased area of T2 on a 10 days follow-up T2 map (e).



▲ **Figure 2:** Plots of relative ADC (a), FA (b), and T2 (c) plotted against time. The graphs show four ischemic temporal patterns and one normal pattern as discerned from ISODATA analysis up till 10 days after stroke onset. The graphs clearly show a correlation between increasing ADC, and T2 with decreasing FA. Relative fast increase of ADC and T2, accompanied with fast decreasing FA, show pseudo-normalization at more chronic stages.

▼ **Table 1:** Distribution of clusters (%) in region of increased temporal variance

Signature	Transient	Permanent	Core	Rim
A	14	17	23	-
B	43	50	46	50
C	43	-	-	50
D	-	33	31	-

- 15-22 clusters were detected which could be reduced to 2-10 distinct signatures for each animal using variance pruning.
- 5 corresponding signatures were identified from the resulting signatures (Figure 1-2).
- Ischemic regions in particular were indicated as abnormal by cluster analysis.
- Ischemic evolution patterns varied across animals.
- Areas that showed rapid initial ADC and T2 increase with initial decreasing FA did not infarct and could primarily be assigned to transient MCA occlusions (table 1).
- Signature distribution differed significantly between transient and permanent MCA occluded brains (p=0.021), as well as between core and rim ROI's (p=0.024).

Discussion

- ✓ ISODATA analysis elucidated different stages of ischemic lesion evolution in brain areas after stroke.
- ✓ Within each brain ISODATA enabled to differentiate between areas of the ischemic core and rim signatures (table 1, figure 1a), which was not possible using ROI data analysis [5].
- ✓ Signatures correspond with previously reported serial pattern of DWI changes [3,5].
- ✓ Coefficient of variance successfully indicated lesion evolution patterns which correspond to ischemic tissue regions.
- ✓ Voxel-by-voxel analysis has great potential in objectively indicating different stages of ischemic lesion evolution without making any assumptions on possible 'viability' thresholds.

References

1. Kidwell CS, et al. Ann. Neurol. 2000; 47, 462-9;
2. Dijkhuizen RM, et al. Stroke. 1998; 29, 695-704;
3. Li F, et al. Ann. Neurol. 1999; 46, 333-42;
4. Tagaya M, et al. Stroke. 1997; 28, 1245-54;
5. Liu Y, et al. Stroke. 2007; 38, 138-45;
6. Collins DL, et al. J. Comput. Assist. Tomogr. 1994; 18, 192-205
7. Staring M. et al. Med. Phys. 2007; 34, 4098-4108
8. Jacobs MA, et al. Stroke. 2001; 32, 943-9;
9. Wu, O, et al. Stroke. 2007; 38:492-3.
10. Cai W, et al. Pat. Recogn. 2007; 40(4):825-38.

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