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Tensor Based Morphometry as Surrogate Marker for Alzheimer's Disease and Mild Cognitive Impairment: Optimizing Statistical Power

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Introduction: In a longitudinal MRI study, we applied tensor-based morphometry (TBM) to generate 3D maps tracking brain degeneration in Alzheimer's disease (AD) and mild cognitive impairment (MCI). To summarize annual change using a single variable, we computed the mean atrophic rate for each person, within a statistically defined region-of-interest (ROI). A power analysis was then used to seek the optimal experimental design that required the least sample size to detect a 25% reduction in mean annual change. The goal was to reduce time and cost for clinical trials.

Methods: As part of the Alzheimer's Disease Neuroimaging Initiative (ADNI), we analyzed the longitudinal MRI scans (1-year follow-up) of 104 AD patients (age: 76.7 ± 7.2 years) and 254 individuals with amnestic MCI (76.1 ± 7.2). Using a novel unbiased image registration technique with a symmetric Kullback-Leibler (sKL) regularizing function and mutual information (MI) as the fidelity term [1], we non-linearly registered each subject's follow-up scan to their baseline scan. The derived Jacobian maps that displayed regional tissue atrophy or ventricular expansion, over the one-year period, were further nonlinearly aligned to a standard space defined by a normal group mean template. A numeric summary – the mean atrophic rate – was computed for each person, to summarize annual change within the ROI. The ROIs were statistically defined based on voxels with significant atrophic rates ($p < 0.001$) in a non-overlapping training set of 22 AD patients - independent of the testing set used to compute the power numbers. We determined the optimal study design to detect atrophy with highest sensitivity, i.e., requiring the least sample size to detect a 25% reduction in mean annual change for a two-arm study (treatment versus placebo; alpha = 0.05, power = 80 or 90%). Power numbers were computed to gauge the effects of varying two registration parameters (lambda and sigma) controlling the sKL regularization and Jacobian field smoothness, respectively.

Results: Tables 1 and 2 show minimal sample sizes for the AD patients and the MCI subjects, excluding the training set used to define the ROI. The best power numbers were obtained using data from the left temporal lobe. Only 50 AD patients and 75 MCI subjects (sigma = 9 and lambda = 1 or 2; left temporal lobe) were needed to detect a 25% reduction in the mean annual change with 80% power. Lowering sigma (to 6) made the Jacobian fields less smooth and noisier, which adversely affected power for MCI but not for AD. Higher lambda values increased the weighting of the sKL regularization, driving the Jacobians towards constancy in homogeneous regions. The effect of lambda on power estimates followed a "U" shape, suggesting that the optimal amount of regularization can be empirically determined on independent training data.

Conclusions: The mean atrophic rate, computed within a statistically defined ROI, is a powerful surrogate marker for tracking disease progression in AD and MCI. Based on this single numeric summary for each person, statistical power can be optimized with respect to image analysis parameters, facilitating clinical trial design.

References:

Yanovsky, I. (2008), 'Asymmetric and symmetric unbiased image registration: statistical assessment of performance', *IEEE Computer Society Workshop on Mathematical Methods in Biomedical Image Analysis*, vol. 1, no. 1, pp. 1-8.

Table 1: Minimal sample sizes for detecting a 25% slowing of atrophic rates in AD. N80/N90 denote samples achieving 80% or 90% power; Left/Right: left or right temporal lobe; diagonal lines indicate combinations that were not tested, as each run requires fluid registration of 358 brains.

		Sigma = 9				**Sigma = 6**			
		Left		Right		Left		Right	
		N80	N90	N80	N90	N80	N90	N80	N90
Lambda	0.5	63	84	79	105				
	1	52	70	76	102	60	81	70	93
	2	**50**	67	81	108				
	5	52	69	113	151	49	65	78	104

Table 2: Minimal sample sizes for detecting a 25% slowing of atrophic rates in MCI.

		Sigma = 9				**Sigma = 6**			
		Left		Right		Left		Right	
		N80	N90	N80	N90	N80	N90	N80	N90
Lambda	0.5	84	113	110	147				
	1	**75**	100	109	146	93	124	122	164
	2	76	102	129	172				
	5	85	114	208	278	86	116	165	221