Power estimates for MRI-based Alzheimer's disease clinical trials with different scan intervals

Abstract No:

2588

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Introduction:

Alzheimer's disease (AD) affects over 24 million individuals worldwide, with no effective treatment. As the disease causes progressive tissue loss in the brain, new treatments can be evaluated using repeated MRI scanning. Voxel-based analysis of serial MRI scans has been proposed to track subtle brain changes over time. Tensor-based morphometry (TBM) gives 5- to 10-fold better sample size estimates than standard clinical scores when used for tracking disease progression over a one-year interval (Hua et al. 2009), and the changes are highly correlated with cognitive decline (Leow et al. 2009). Given the promise of TBM for tracking brain change in AD, it is of great practical value to know whether shorter or longer scanning intervals (6, 12, 18, or 24 months) provide better power to assess potential disease-modifying treatments. Shorter trials are more cost effective, but too short a trial risks missing a disease modifying effect as the brain changes may be too small.

Methods:

Longitudinal brain MRI scans (N=1,309) and associated clinical data were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) public database (http://www.loni.ucla.edu/ADNI). Serial scans were analyzed from 91 probable AD patients scanned at baseline (age: 75.4±7.5 years), 6, 12, and 24-month, and 189 individuals with amnestic MCI (a transitional state with 5-fold increased risk of imminent conversion to AD; age: 74.6±7.1) scanned at baseline, 6, 12, 18, and 24-month. Cognitive tests included the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog), sum-of-boxes Clinical Dementia Rating (CDR-SB), and Mini-Mental State Examination (MMSE). MRI images were adjusted for scanner calibration errors using 9-parameter linear registration. Individual Jacobian maps, illustrating local expansion or compression over time, were created by warping the follow-up scan to match the baseline scan, using a nonlinear sKL-MI registration method (Yanovsky et al. 2009). Tissue change maps were spatially normalized to a standard template for group statistical analyses. Group average maps were constructed by computing the mean of the Jacobian maps at each voxel across subjects.

A numeric summary – the mean atrophic rate – was computed for each person, to summarize change within an anatomically or statistically-defined ROI (Stat-ROI). The temporal lobes, delineated bilaterally on the MDT (Temp-ROI), served as the anatomical ROI. The Stat-ROIs were statistically defined based on voxels with significant atrophic rates ($p < 0.001$) inside the temporal lobes in a non-overlapping training set of 20 AD patients at 1-year follow-up. A modified power analysis was conducted to estimate how many patients would need to be recruited for clinical trials with the duration of 6, 12, 18, and 24 months respectively, to detect a 25% reduction in mean change for a two-arm study (treatment versus placebo; $\alpha=0.05$) with 80% and 90% power, denoted by n80 and n90 respectively.

Results:

Average Jacobian maps at a follow-up period of 6, 12, 18, and 24 months, showing the percentages of brain tissue loss (in blue colors) and ventricular enlargement (in red colors) relative to baseline, illustrated the pattern of disease progression in AD (Figure 1). Small but detectable ventricular expansion and temporal lobe atrophy were noted at 6 months, in AD and MCI; greater changes were detected at longer observation times.

Across the same set of patients with AD, longer intervals led to greater effect sizes for the measurement of temporal lobe atrophy, resulting in smaller sample size estimates (n80 and n90 in Figure 2a). MCI subjects showed the same trend as AD, with greater cumulative atrophy at longer follow-up intervals (Figure 2b). The MCI subjects were examined at an additional time point (18 months), but this time-point, when used on its own, offered little extra benefit relative to a 12-month follow-up, showing comparable n80 and n90 at 12 and 18 months. Sample size estimates based on numeric summaries derived from the Stat-ROI consistently outperformed the ones derived from the Temp-ROI (Figure 2) (all pair-wise comparisons, of the Stat-ROI versus the Temp-ROI, had corrected p-values less than 0.05). All TBM-derived neuroimaging markers demonstrated drastic sample size reductions relative to standard clinical measures (ADAS-Cog, MMSE, and CDR-SB) at all follow-up periods (Table 1).

Conclusions:

AD patients, re-scanned with MRI after 6, 12, and 24-month intervals, demonstrated successively greater cumulative brain atrophy, and progressively smaller sample sizes in a hypothetical clinical trial. In MCI, brain atrophy was detectable on MRI as early as 6 months, but progressively increased at 12, 18, and 24-month intervals. The 18-month follow up for MCI did

not exhibit a detectably improved sample size estimate compared to a 12-month trial. Even so, changes had greater effect sizes at longer intervals, illustrating the trade-off between recruitment requirements (and therefore costs) and the required observation time. More patients are needed for shorter trials, but patient enrollment may be reduced if a longer observation time is acceptable. Regardless of the scanning interval, TBM is a clearly a useful neuroimaging marker that may help reduce costs for clinical trials.

Figure 1: Mean level of progressive atrophy in AD and MCI groups after intervals of 6, 12, 18, and 24 months, respectively.

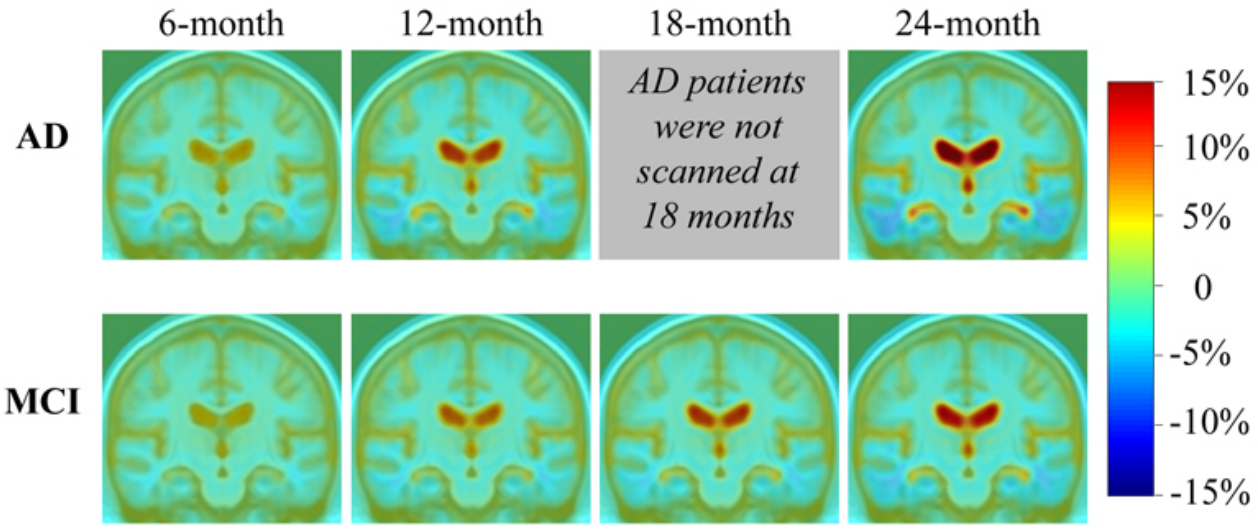

Figure 2: Average level of cumulative temporal lobe atrophy (as a % of baseline tissue volume) and sample size estimates required to detect a 25% slowing of degeneration with 80% (n80) and 90% (n90) power, with an observation time of 6, 12, and 24 months for AD (a) and 6, 12, 18, and 24 months for MCI (b).

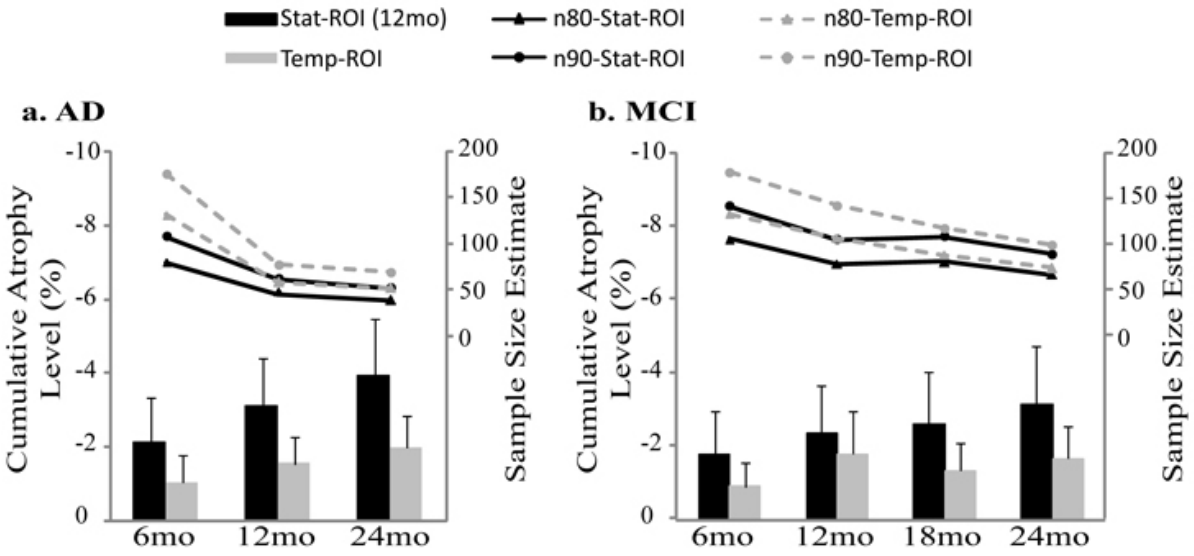

Table 1: Sample size estimates for TBM-derived measures of atrophy, compared with traditionally used clinical measures. Smaller numbers are better - fewer subjects are needed to demonstrate an effect size of fixed magnitude (a 25% slowing).

			Stat-ROI	Temp-ROI	ADAS-Cog	MMSE	CDR
AD	6mo	*n80*	80	131	1,371	2,224	1,709
		n90	107	176	1,834	2,975	2,285
	12mo	*n80*	46	58	483	809	577
		n90	62	77	647	1,082	771
	24mo	*n80*	39	52	215	365	215
		n90	52	69	287	488	288
MCI	6mo	*n80*	106	134	16,645	2,382	3,372
		n90	142	179	22,265	3,788	4,511
	12mo	*n80*	79	106	8,212	2,767	836
		n90	106	142	10,985	3,701	1,118
	18mo	*n80*	81	89	1,381	1,217	791
		n90	109	119	1,847	1,628	1059
	24mo	*n80*	67	75	1,013	879	626
		n90	90	100	1,355	1,176	838

References:

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Categories

- Alzheimer and Dementia (Disorders of the Nervous System)
- Anatomical MRI (Imaging Techniques and Contrast Mechanism)