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. Recently, automated brain mapping methods, such as tensor-based morphometry (TBM) of structural MRI, have outperformed cognitive measures in their precision and power to track disease progression, greatly reducing sample size estimates for drug trials. In the largest TBM study to date, we studied how sample size estimates for tracking structural brain changes depend on the time interval between the scans (6-24 months).

**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. Recently, automated brain mapping methods, such as tensor-based morphometry (TBM) of structural MRI, have outperformed cognitive measures in their precision and power to track disease progression, greatly reducing sample size estimates for drug trials. In the largest TBM study to date, we studied how sample size estimates for tracking structural brain changes depend on the time interval between the scans (6-24 months).

**METHODS**

**Subjects:** \(N = 1,309\) longitudinal brain MRI scans and clinical data (ADAS-cog, CDR-SB, MMSE).

**Mean atrophic rate:** 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. A numeric summary—the mean atrophic rate—was computed for each person, to summarize change within an anatomically (Temp-ROI) or statistically-defined ROI (Stat-ROI).

**Power analysis:** 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, 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**

Figure 1: Mean level of progressive atrophy in AD and MCI groups after intervals of 6, 12, and 24 months, respectively. The profile of atrophy, and group differences, are easier to distinguish at later time points. The MCI mean atrophic rate is lower than that seen in AD, at every time-point.

Figure 2: Average level of cumulative temporal lobe atrophy (as a % of the baseline tissue volume) and sample size estimates (n80 and n90) at 6, 12, 18, and 24 months

**CONCLUSION**

TBM shows superior sample size estimates over traditional clinical measures; fewer patients are needed for evaluating new drugs.

A 24-month trial provides more power, except when patient attrition exceeds 15-16/16/year, in which case a 12-month trial is optimal.