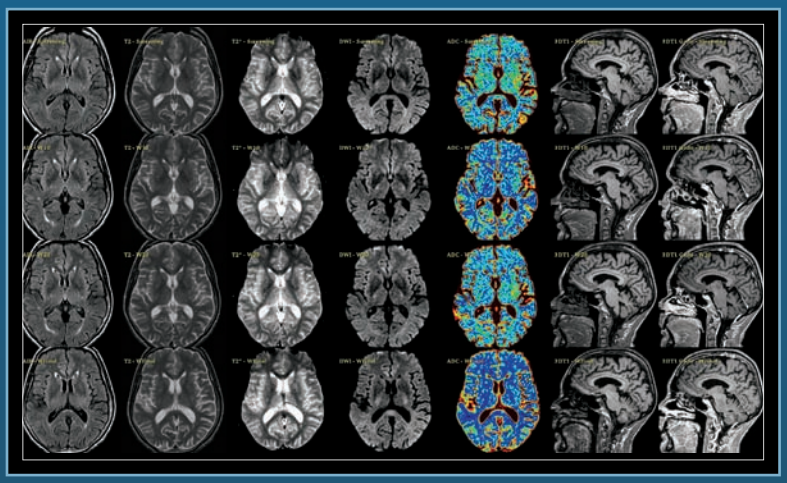
Image Analysis Capabilities

in Alzheimer's Disease (AD) Studies

Magnetic Resonance Imaging (MRI) has been increasingly used in the context of Alzheimer's Disease (AD) clinical trials. MRI-based eligibility, safety & efficacy endpoints now play a key role in the overall design of AD trials. Furthermore, the introduction of quantitative efficacy parameters such as longitudinal brain & hippocampal atrophy has added tremendous value in terms of enabling supportive data, clearing the path to faster registrations. This document provides a short overview of BioClinica's vision & capabilities for enabling such endpoints in AD trials.



Typical MRI datasets in multicenter AD trials
Rows: *4 consecutive MRI scans of one AD patient acquired over 1 year*
Columns: *FLAIR, T2, T2*, DWI (trace), DWI (ADC), T1 & Post-Gadolinium T1*

ACHIEVING ACCURACY & REPRODUCIBILITY THROUGH AUTOMATED PROCESSES

The most important requirements for introducing quantitative MRI endpoints in the design of AD trials are the accuracy & reproducibility of the analysis techniques. The processes and operational constraints should be scalable for a successful deployment in the context of large multicenter clinical trials. The biggest scientific and operational challenge is in making use of advanced quantitative image processing techniques in a highly regulated environment (FDA's 21 CFR Part 11 & software validation guidelines). The complex nature of the quantitative endpoints usually requires the use of automated image processing capabilities, enabling high-throughput analysis. The proposed approaches must be robust enough for variations in image quality (especially in multicenter contexts, where different MRI scanner manufacturers & models are used).

QUANTITATIVE ANALYSIS

The following image processing modules can be used in AD trials:

- 3D image registration
- MRI signal intensity inhomogeneity correction
- Correction of geometrical distortion
- Atlas-based segmentation
- Quantification of brain, hippocampal & ventricular atrophy
- Quantification of intracranial cavity volume
- Quantification of FLAIR/T2 hyperintense lesions
- Diffusion-Weighted Imaging (DWI)
- Diffusion-Tensor Imaging (DTI) data analysis

SITE STANDARDIZATION, QUALITY ASSURANCE, & IMAGE QC

Maximizing the quality of MRI data, minimizing intra/inter-site variability, providing vendor & model-specific MRI acquisition parameter and the ongoing quality control of MRI data performed within short turnaround times are among the most crucial tasks to increase the accuracy & reproducibility of image processing techniques. American College of Radiology (ACR) phantom is used for initial site qualification and for monitoring the image quality over time. Repeat scans may be requested whenever image quality is poor. Data collection can be expedited using web based electronic image transfer (WebSend).

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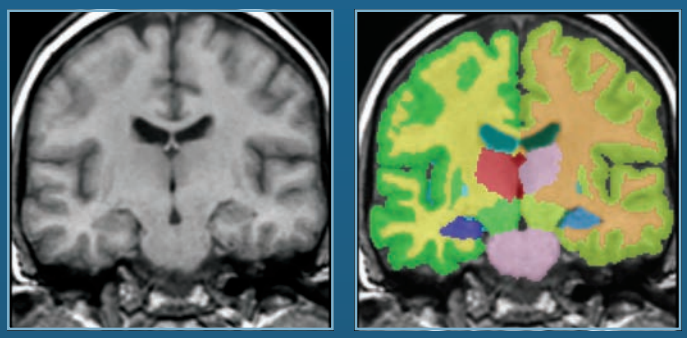
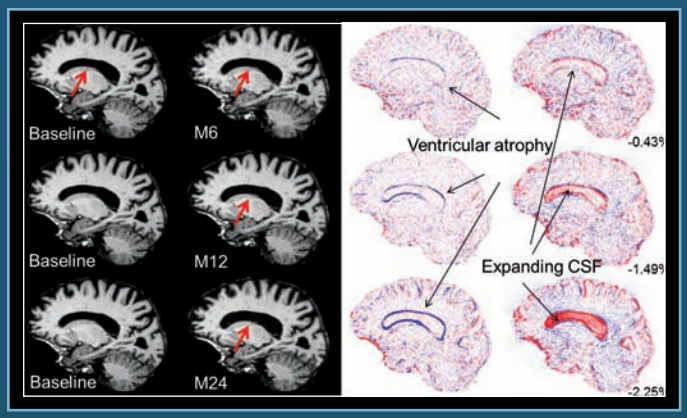
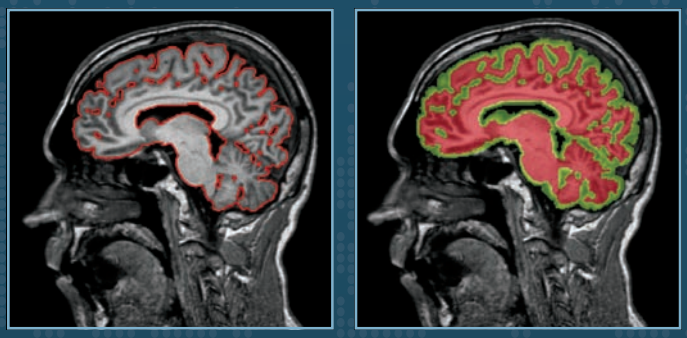


Fully automated atlas-based segmentation



Quantification of brain atrophy using Tensor – Based Morphometry (TBM) / Jacobian Integration (JI)
Rows: *Baseline, M6, M12 & M24 MRI scans of an AD patient*
3rd Column: *Difference maps,* ***4th Column:*** *Jacobian maps and associated whole brain atrophy values*



Quantification of brain atrophy using Boundary Shift Integration (BSI) after detection of brain parenchyma (left) and internal/external boundaries (right)

ATLAS-BASED SEGMENTATION

An atlas-based segmentation (Atlas Propagation and Classification-based Nearest Neighbor Transform) is used for the detection of brain, ventricles, hippocampus and other brain subcortical structures. The quality of brain structures delineation at baseline is of major importance for subsequent image analysis steps.

BRAIN, HIPPOCAMPAL & VENTRICULAR ATROPHY QUANTIFICATION

Several registration-based techniques can be used for the quantification of brain atrophy. The most commonly used techniques in ongoing Phase II/III AD trials are **Tensor-Based Morphometry – Jacobian Integration (TBM – JI)** and **Boundary Shift Integration (BSI). Test-retest reproducibility** results, using two three-dimensional T1 acquisitions per subject performed over the same day are close to 0.1% of total brain volume. This variability or "measurement error" inherent to the quantification process is well below the expected mean annual change of total brain volume in healthy elderly controls. Registration-based techniques have proved to be much more robust than segmentation-based techniques for detecting & quantifying subtle changes of brain structures over time.

INDEPENDENT IMAGE REVIEW BY EXPERT NEURORADIOLOGISTS

Board-certified Neuroradiologists independently assess both native and processed MRI data for the evaluation of eligibility, safety and efficacy endpoints. The conduct of remote read sessions can significantly increase the efficiency of central reading activities while minimizing the inherent costs. The image evaluation results are made available at the sponsor's site in a real-time manner to facilitate the tracking of operations and allowing fast decision making when it comes to patient monitoring, in case of safety findings.

For any technical questions or software demonstration, please contact us at +1.267.757.3000 or info@bioclinica.com

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