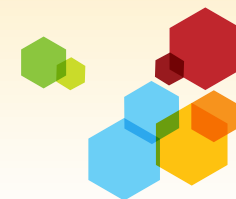




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## Functional Signatures of Alzheimer's Disease Progression and Severity Revealed by Magnetoencephalography

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## Background

- Despite recent progress with chemical and structural measurements of brain state, there remains a critical need for Alzheimer's Disease (AD) biomarkers that track disease progression and severity
- Useful severity markers are critically needed to support the development of effective treatments for AD
- Quantitative measures of human brain electrical activity measure functional states in health and disease
- Such features may be more likely to track functional responses to changes in severity and the effect of treatment
- Orasi has previously conducted a cross-sectional study of AD patients and healthy controls (Verdoorn et al, 2009) using brief, resting-state magnetoencephalography (MEG)
- We have extended these observations to include additional study subjects as well as longitudinal scans on 78 subjects from the original study cohort
- These results have helped identify a preliminary multivariate model of disease severity that could track progression or measure the effect of treatments over shorter periods of time.

## Objectives

1. Derive objective measures of brain activity based on brief, resting-state MEG scans that can serve as reliable endpoints for AD drug development.
2. Develop reproducible and informative measures of functional connectivity that complement and enhance commonly used physiological evaluations of drug action such as relative spectral power.
3. Measure and characterize patterns of synchronous brain activity that are specifically altered by AD and may change reliably in concert with independent measures of disease severity.

## Methods

### Study Protocol

- The study cohort included 205 subjects (99 AD, 6 MCI, 100 healthy controls) from an Orasi-sponsored multicenter, cross-sectional study of previously diagnosed AD patients, and 122 subjects (33 AD, 18 MCI, and 71 healthy controls) from an earlier study of similar design conducted by the Brain Science Center of the Minneapolis VA Medical Center and included in the Orasi database
- In addition, 78 subjects (32 AD, 46 healthy controls) from the Orasi study cohort were scanned and evaluated a second time approximately 9 months after their original scan
- All subjects were evaluated by review of medical records, neurological examination and the Mini Mental State Examination (MMSE). Cognitively impaired subjects from the Orasi study also were tested with the cognition subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) and Clinician's Dementia Rating (CDR) scale
- The experimental protocol was approved by the Western Institutional Review Board, and the Institutional Review Boards of Minneapolis VA Medical Center and the University of Colorado, Denver.

### Data Analysis

- MEG recordings were obtained with whole-head magnetoencephalography instruments (4D Neuroimaging WH3600 Gradiometer) at the Minneapolis VA Medical Center and the University of Colorado, Denver with a sampling rate of 1000 Hz.
- One minute long resting-state scans (eyes open, fixating on digitally projected white dot) were analyzed separately over all sensors and over 8 predefined groups of sensors for **relative power spectra**, and the **Synchronous Neural Interaction Index (SNI)**. A series of global and regional features were extracted to characterize changes in brain function associated with AD.
- Time series from each sensor of the 248 sensor array were filtered (0.1 – 400 Hz) and sent to Orasi over the internet using Orasi's secure web server.

### Spectral Analysis

Time series were transformed to frequency domain using standard fast fourier transform. Power spectra were derived for each sensor in the array and either averaged across all 248 sensors for global measures or across all sensors (n = 31) in each of 8 regional areas of interest. Relative power for each frequency band (delta: 1-3 Hz, theta: 4-8 Hz, alpha: 8-13 Hz, beta: 14-20 Hz, gamma: 22-50 Hz) were calculated from the area under the power spectral density curves.

### Synchronous Neural Interaction (SNI) Test

Functional connectivity was assessed by the SNI test. Raw time series were downsampled 10-fold and digitally filtered (0.1 – 50 Hz) prior to prewhitening to generate stationary time series. Prewhitening was done by fitting the data to a 5<sup>th</sup> order autoregressive model after 1<sup>st</sup> order differencing and taking the residuals. Zero-lag cross correlations (c0s) were calculated for each sensor pair within the 248 sensor array (30,628 correlation values). To assess the functional integrity of cortical communication networks, a modest set of global attributes were measured including the average value of all c0s, and the absolute value of correlations in local sensor pairs (distance < 0.137 m), medium distance pairs (distance between 0.137 and 0.222 m) and long distance pairs (distance > 0.222 m). Regional correlation values were measured by averaging the c0s of all pairs within each regional area of interest (Figure 1) as well as all pairs that connect each pair of regions, and generated 28 regional SNI values.

### Statistical Analysis

- Statistical analyses were performed first on global frequency domain and SNI values and followed-up with tests of regional values. Group values were compared with t-tests.
- A multivariate model of disease severity was generated using a linear, least-squares fit of MEG data attributes to MMSE scores using subjects evaluated in the initial phase of the Orasi-sponsored study. This model was applied to the result obtained in the longitudinal follow-up phase of the Orasi study.

## Results

### Relative spectral power

Alzheimer's disease was associated with widespread redistribution of spectral power in the resting-state scans. The relative contribution of low frequency signals in the delta and theta bands increased at the expense of high frequency signaling in the alpha, beta and gamma bands. Delta and alpha band changes were distributed uniformly whereas theta and beta alterations were focused on temporal, parietal and occipital areas. The MCI group did not exhibit significant differences in relative spectral power compared to healthy controls.

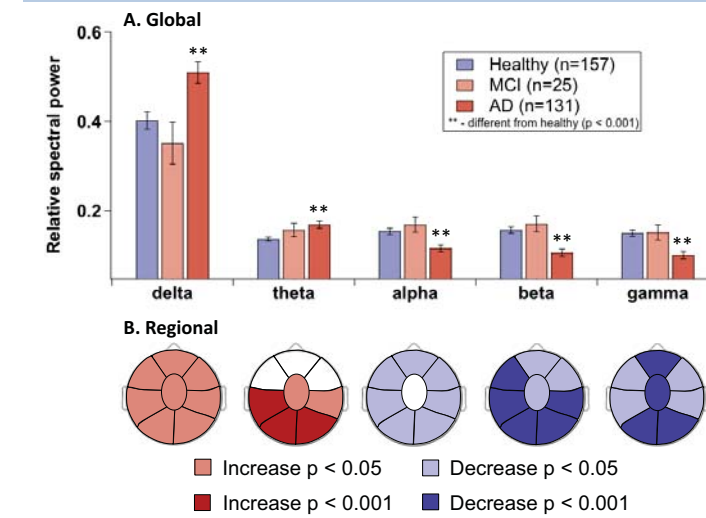
### Functional connectivity measured by the SNI Index

SNI analysis revealed global changes in the level and distribution of correlated signaling in the AD group. The average value of all network c0s increased significantly in AD. This was due to increased correlations among neighboring sensor pairs and decreased correlations among more distant sensor pairs, which are normally negative values in healthy subjects. Regional analysis revealed that changes were focused in parietal, temporal and occipital areas. SNI also detected changes in the MCI group that were similar to those seen in AD, but less extensive.

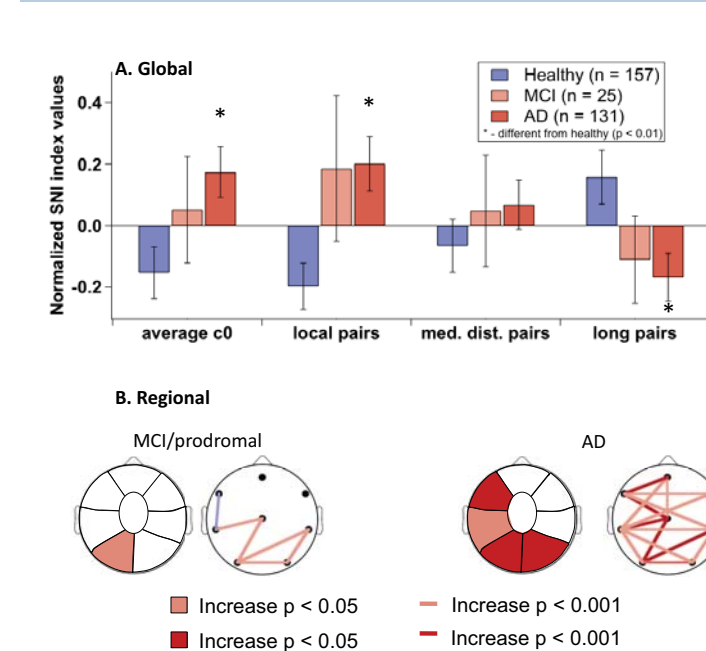
### Multivariate model of disease severity

We developed a preliminary model of disease severity using the MMSE score to represent severity and a set of correlation values among sensors over parietal and temporal brain regions. Theta and beta relative in parietal and temporal regions also were used in developing the model. This model was tested using scans collected in a previous AD study and contained in our database. We also used this model to examine the progression of 32 AD subjects and 46 healthy controls who were followed longitudinally for approximately 9 months. The model was relatively accurate in tracking disease progression as measured by the direction of change in the MMSE for the majority of the longitudinal cohort.

### AD patients have altered relative spectral power



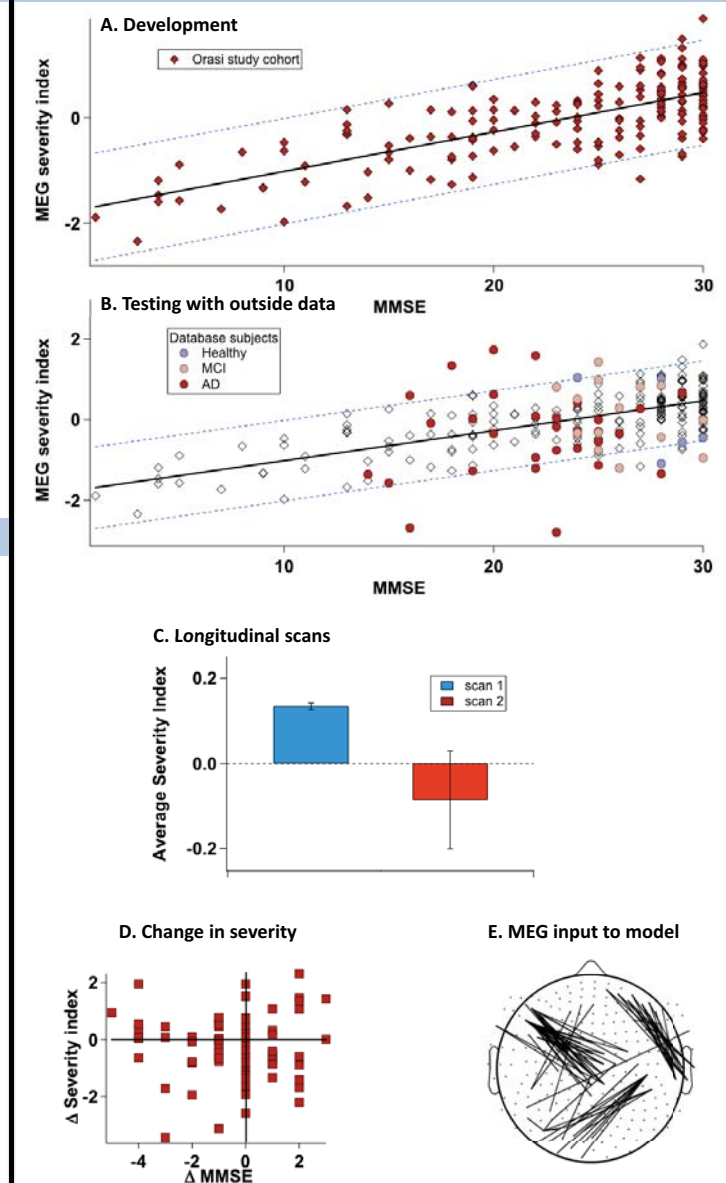
### Functional connectivity is disrupted by AD



## Conclusions

- Resting-state MEG scans readily detected changes in brain function associated with AD and MCI. Marked functional changes include:
  - Global slowing of brain activity measured by relative spectral power
  - Global increases in average zero-lag correlation values
  - Increased correlated activity among sensors that are close together
  - Decreased correlated activity among distant sensors
- MCI subjects **did not exhibit statistically significant changes in relative spectral power, but changes in correlated activity were detected.** These changes were generally lower in magnitude, but otherwise similar to those detected in AD patients
- A preliminary model of disease severity generated from these results generalized to 80% of subjects not used for building the model (outside data)
- For most subjects followed longitudinally for approximately 9 months the direction of change in MMSE (e.g. improvement or decline) was the same as the direction of change in the model's severity index suggesting that some facets of the model may track disease severity.

### Preliminary MEG-based model of severity



## Opportunities and Prospects

- Rapid, resting-state MEG scans represent a useful tool for evaluating brain function in AD patients
- The data indicate that MEG scans combined with Orasi's SNI technology is capable of detecting AD pathology early in the disease process
- Orasi is conducting additional clinical studies to further refine our understanding of functional pathology in AD using both cross-sectional and longitudinal study designs
- Additional longitudinal data from these ongoing studies will facilitate continuous improvement in the severity model and we anticipate building a useful tool for evaluating the effectiveness drug treatments
- Orasi's database of MEG scans and associated clinical information includes results from over 1600 scans and will support further advances.

## References Cited