A New Test for Brain Function Based on Magnetoencephalography

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Synchronous neural interactions assessed by magnetoencephalography: a functional biomarker for brain disorders*

Apostolos P Georgopoulos[1,2,3,4,5,6,7,16], Elissaios Karageorgiou[1,2], Arthur C Leuthold[1,2,7], Scott M Lewis[1,3,7], Joshua K Lynch[1,2], Aurelio A Alonso[1,8], Zaheer Aslam[4,9], Adam F Carpenter[3], Angeliki Georgopoulos[10,11], Laura S Hemmy[4,12], Ioannis G Koutlas[1,13], Frederick J P Langheim[1,6,7], J Riley McCarten[3,12], Susan E McPherson[3,9], José V Pardo[4,9], Patricia J Pardo[1,4,7,14], Gareth J Parry[3], Susan J Rottunda[12], Barbara M Segal[10], Scott R Sponheim[1,9,14], John J Stanwyck[15], Massoud Stephane[4,9] and Joseph J Westermeyer[4,9]

Outline of the Lecture

- Current approaches for evaluating brain status
- The need for assessing dynamic brain function
- The Synchronous Neural Interactions (SNI) test
- The future

The Need - 1

- Like any other organ of the body, the function of the brain needs to be assessed to evaluate its status in health and disease. However, unlike any other organ of the body, no good tests of brain function are available.
- Typically, we rely on behavioral examination, be it standard neurological examination, psychiatric interview, or neuropsychological testing. These exams are typically lengthy and can take up hours or days.

Current Approaches for Evaluating Brain Status - 1

- Behavioral
  - History (routine)
  - Neurological examination (if indicated)
  - Structured psychiatric interview (if indicated)
  - Battery of neuropsychological tests (if indicated)
- Structural
  - Magnetic Resonance Imaging (MRI, if indicated)
  - Diffusion Tensor Imaging (DTI, research)

Current Approaches for Evaluating Brain Status - 2

- Chemical
  - Magnetic Resonance Spectroscopy (MRS, research)
  - Positron Emission Tomography (PET, research)
  - Other (if indicated: cerebrospinal fluid, blood, etc.)
- Electrophysiological
  - Electroencephalogram (EEG, if indicated)

Current Approaches for Evaluating Brain Status - 3

- "Functional"
  - fMRI (research)
  - O^{15} PET (research)

The need for Assessing Dynamic Brain Function

- Obvious
- Current tests
  - None, really
  - The previous tests/examinations address structure, chemistry or, only indirectly and non-specifically, brain function

Neural Communication - 1

- The essence of brain function is communication among neural ensembles.
- Therefore, alteration in brain function should be reflected in disturbed communication.
- Conversely, disturbed communication can be informative about disordered brain function.

Neural Communication - 2

- Neural communication is accomplished by ongoing, dynamic interactions among multiple neuronal ensembles.
- These interactions can be positive or negative and can occur at different time lags.
- They can be estimated using the cross correlation function (CCF).

Magnetoencephalography (MEG)

- Measures magnetic signals in the brain
  - Direct (true) brain activity
  - High fidelity
  - High accuracy
  - High temporal resolution (ms)
- The ideal tool for measuring neural interactions

The Dewar
Liquid helium

- 248 axial gradiometers (low noise)
- 1 kHz sampling rate

The MEG instrument at the Minneapolis Brain Sciences Center (Magnes 3600WH, 4-D Neuroimaging, San Diego, CA)

The MEG Signal

- MEG reflects integrated synaptic activity of neuronal populations → direct neural measure.
- It is not distorted and not delayed passing through tissues → faithful and instantaneous information about brain events.
- Provides outstanding temporal resolution (in milliseconds).

MEG Instruments and Signals

- Current MEG instruments consist of a dense array of sensors (SQUIDs) that cover the whole head
- Sensors are magnetometers or gradiometers (axial or planar)
- The MEG instrument at the Brain Sciences Center has 248 axial gradiometers
- Raw MEG data are time series of sampled MEG signal
- Data are typically collected at a sampling rate of 1,017 Hz for a single trial of 60-s duration, yielding 60,000 data values

The Synchronous Neural Interactions (SNI) test - 1

This test
assesses dynamic brain function
by evaluating neural interactions
at high temporal resolution
using MEG

The Test is:

- Simple (eye fixation only)
- Noninvasive (no sensors touching the head)
- Safe (just recording MEG activity)
- Short (~1 min in duration)
- Dynamic (temporal resolution of 1 ms)
- Robust (almost identical results from subject to subject)
- Sensitive to changes in brain function (excellent discriminating power for disease groups).

Data Acquisition

- Subjects fixate a spot for 60 s
- Data acquired @1017 Hz (hardware filters: 0.1-400 Hz)
- This yields 248 time series of ~60,000 values each

Data Analysis - 1

Data are analyzed as:

- Single trials
- Unsmoothed
- Unaveraged
- Free of cardiac artifact

Data Analysis - 2

Analyses are performed to estimate quantitatively the synchronous (i.e. zero-lag) interactions between signals from pairs of sensors to assess dynamic brain function.

- Step 1: Calculate all pairwise zero-lag cross-correlations
- Step 2: Calculate the partial zero-lag cross-correlations within the 248-sensor network

Data Analysis - 3

- To calculate any true (i.e. non-spurious) cross-correlation, the time series should be stationary (or quasi stationary) and non-autocorrelated
- If not, the CCF can be misleading by reflecting influences of the series themselves, unrelated to the true relations between the series

Data Analysis - 4

- Therefore, MEG time series are "prewhitened" by fitting an ARIMA (AutoRegressive Integrative Moving Average) Box-Jenkins model and taking the residuals
- This procedure yields practically stationary and non-autocorrelated series from which CCF is estimated

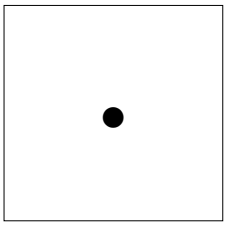
The Problem

- Given 30628 values, find subsets of size k that could perfectly separate groups of subjects with various brain diseases

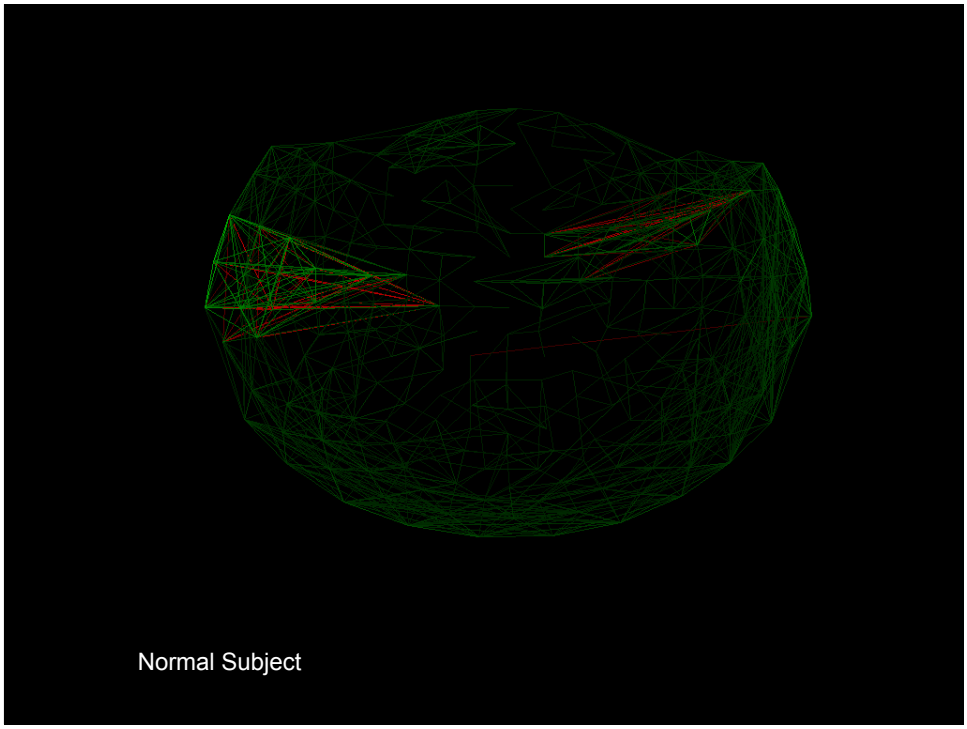
The Solution

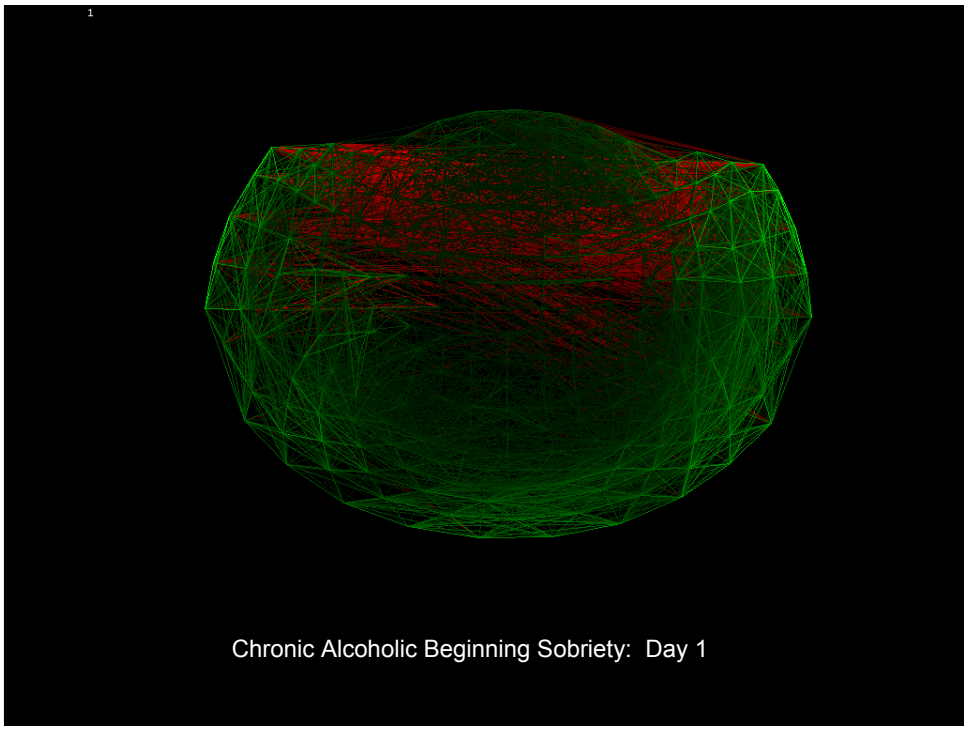
- First pass (2007)
  - Genetic algorithms to search the immense space
  - Linear discriminant analysis to estimate percent correct classification
- Currently (2010)
  - Simple reduction of space parameters
  - Bootstrap-based classification

Test (60 s)



Just fixating the spot


Normal Subject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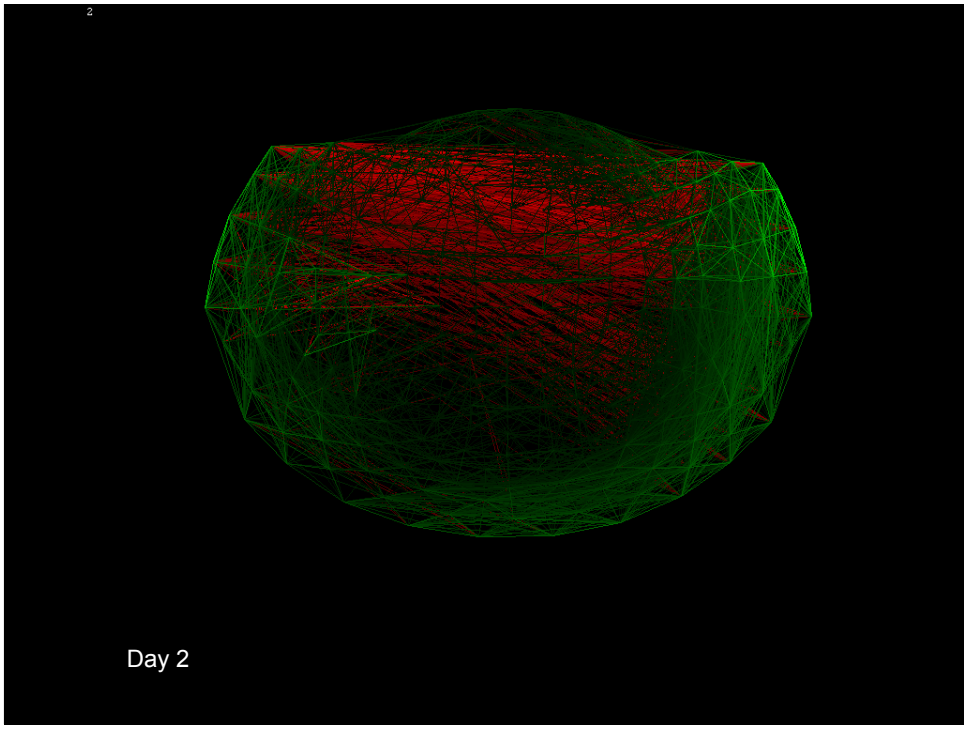
Chronic Alcoholic Beginning Sobriety: Day 1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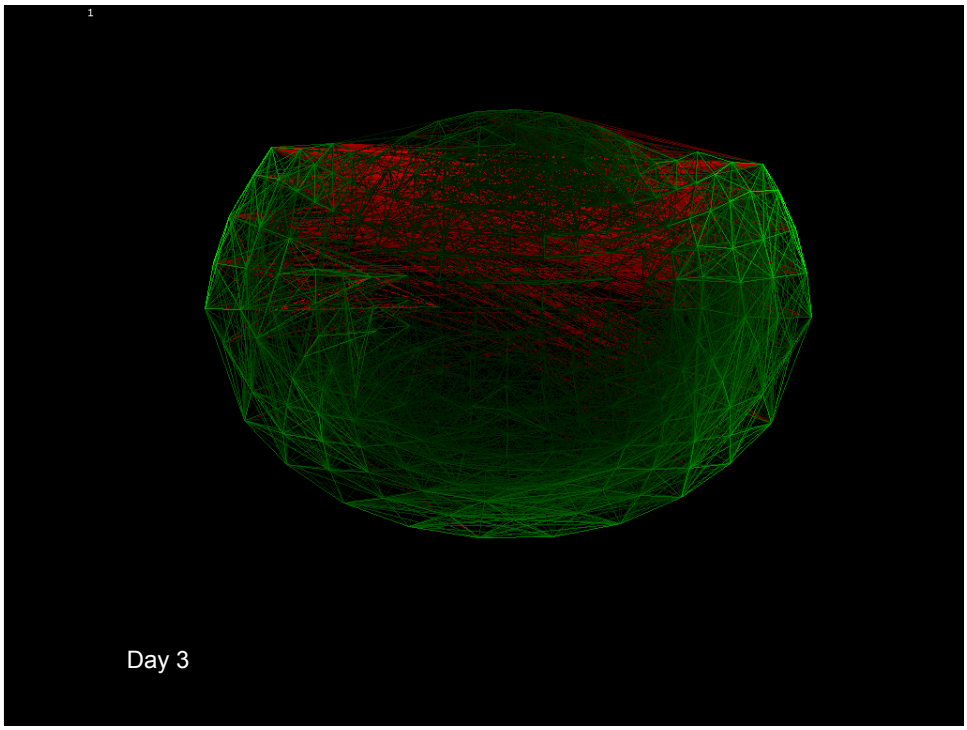
Day 2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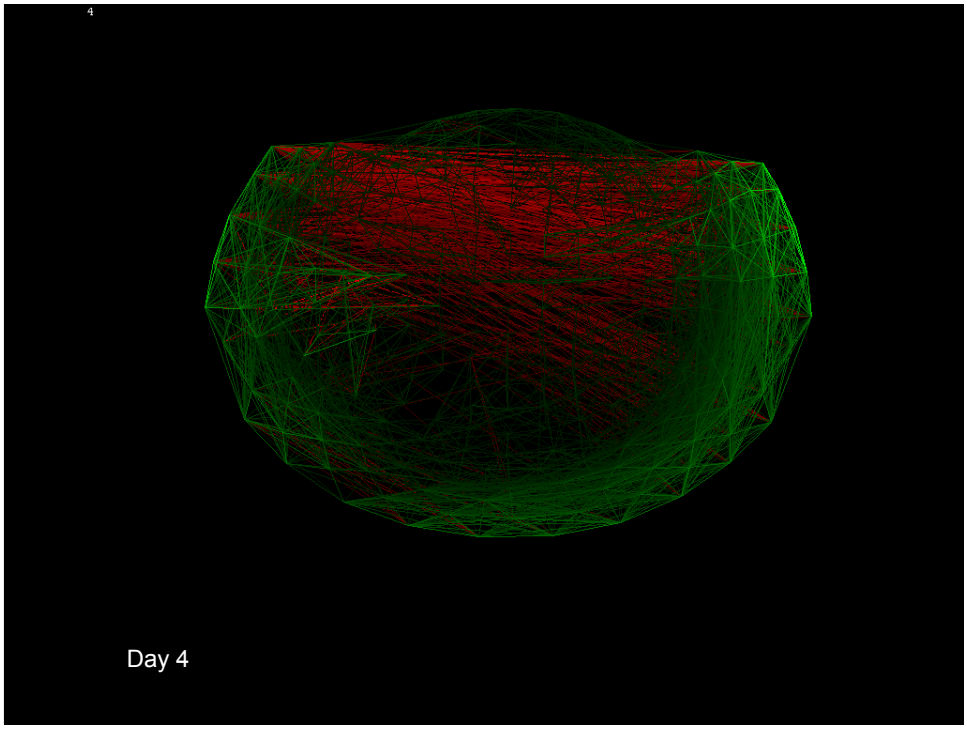
Day 3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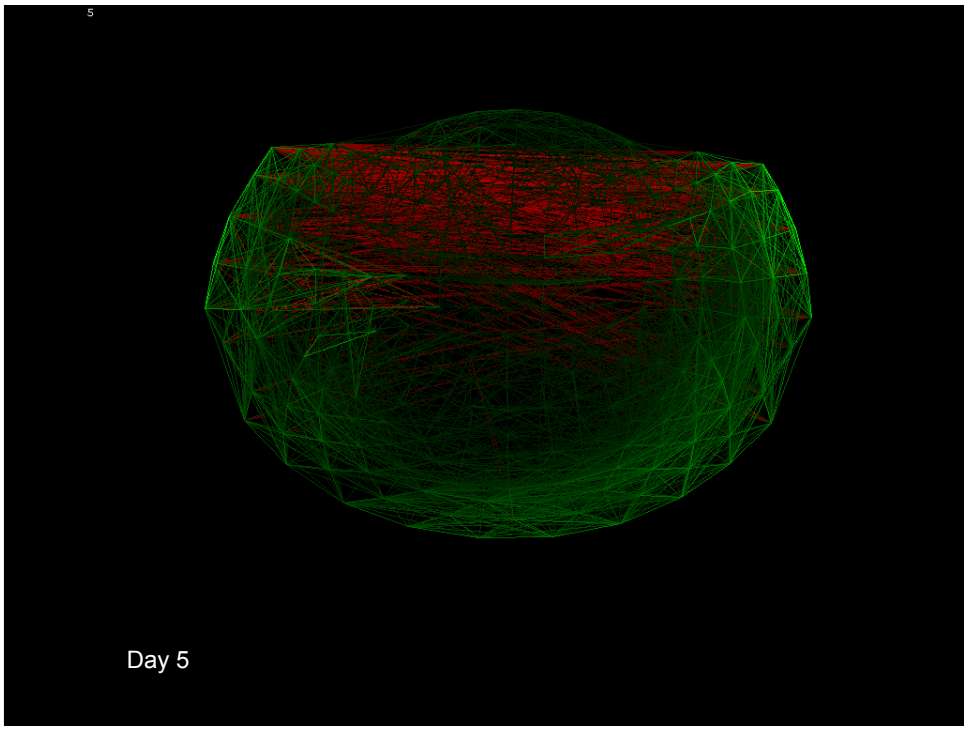
Day 4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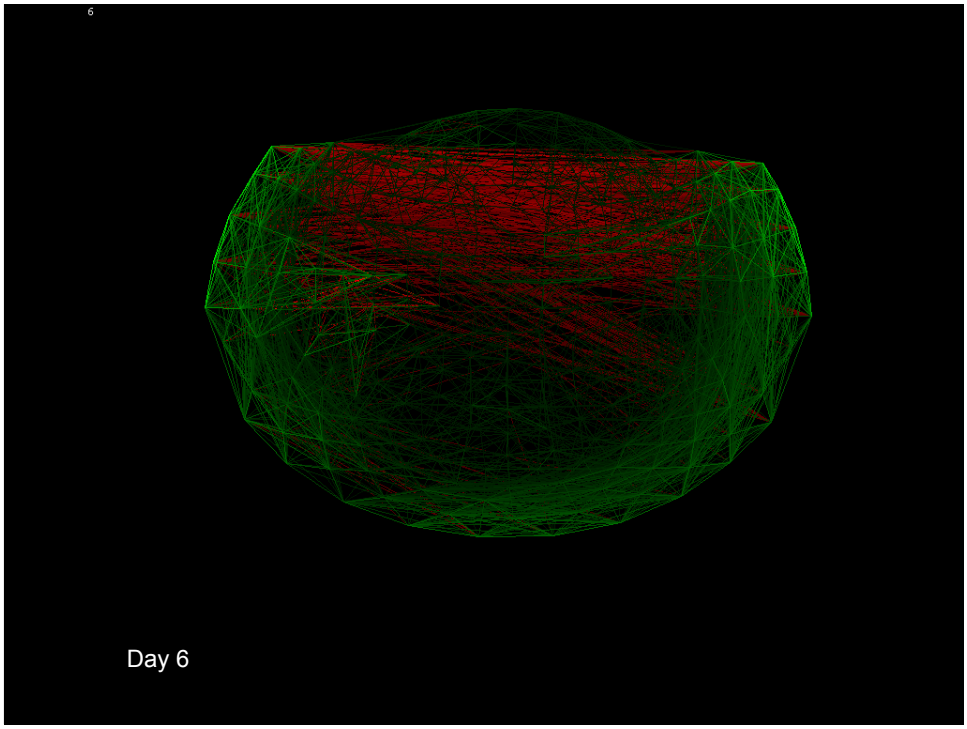
Day 5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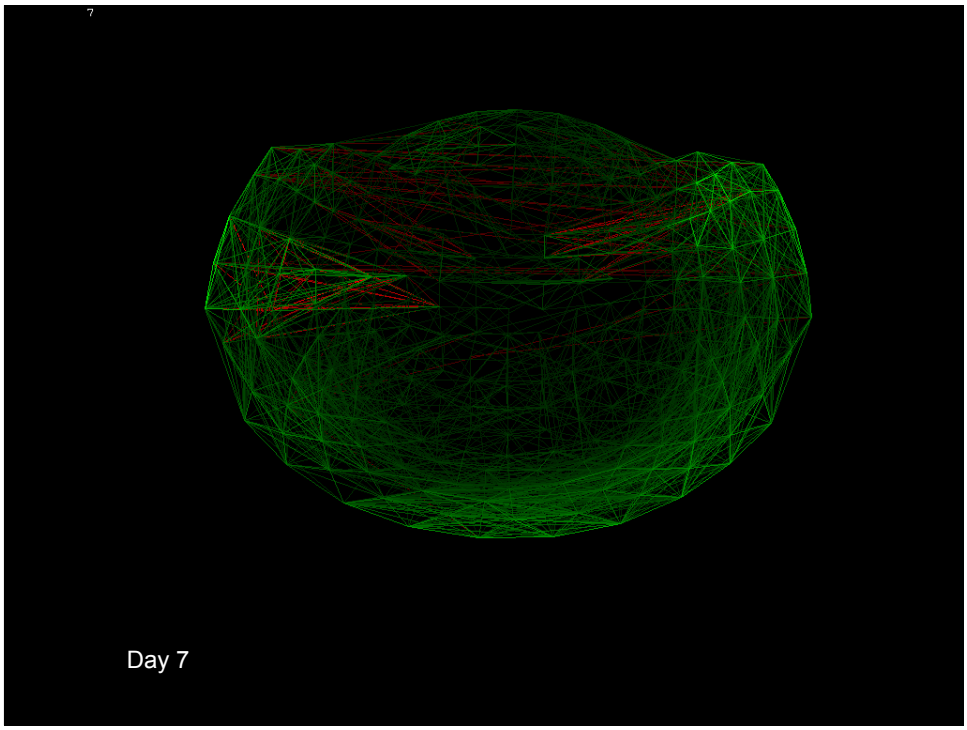
Day 6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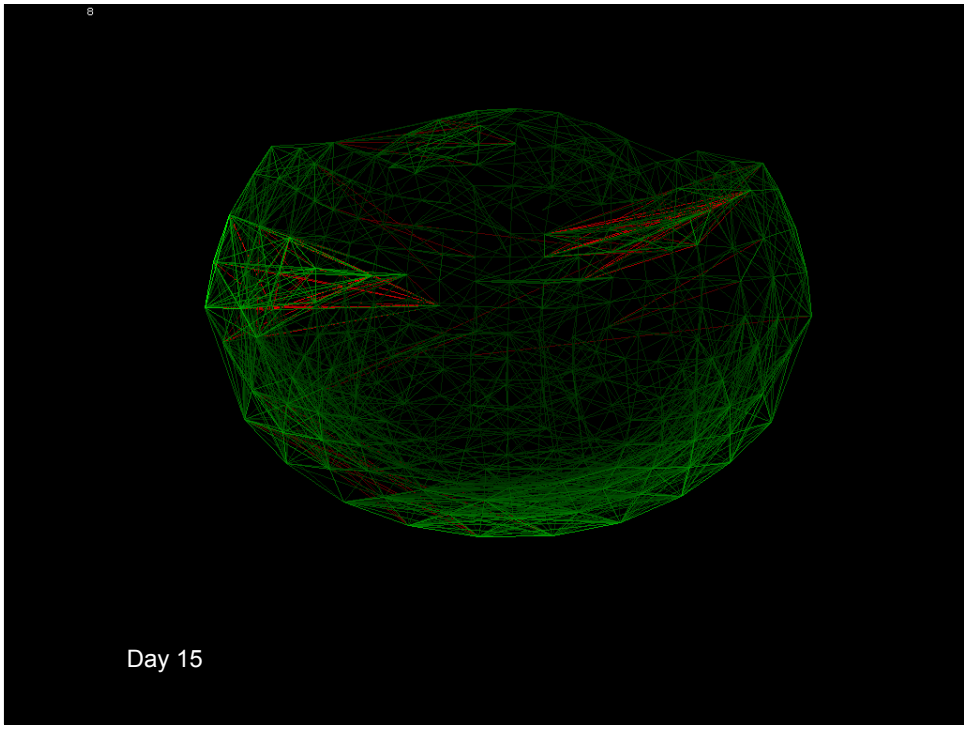
Day 7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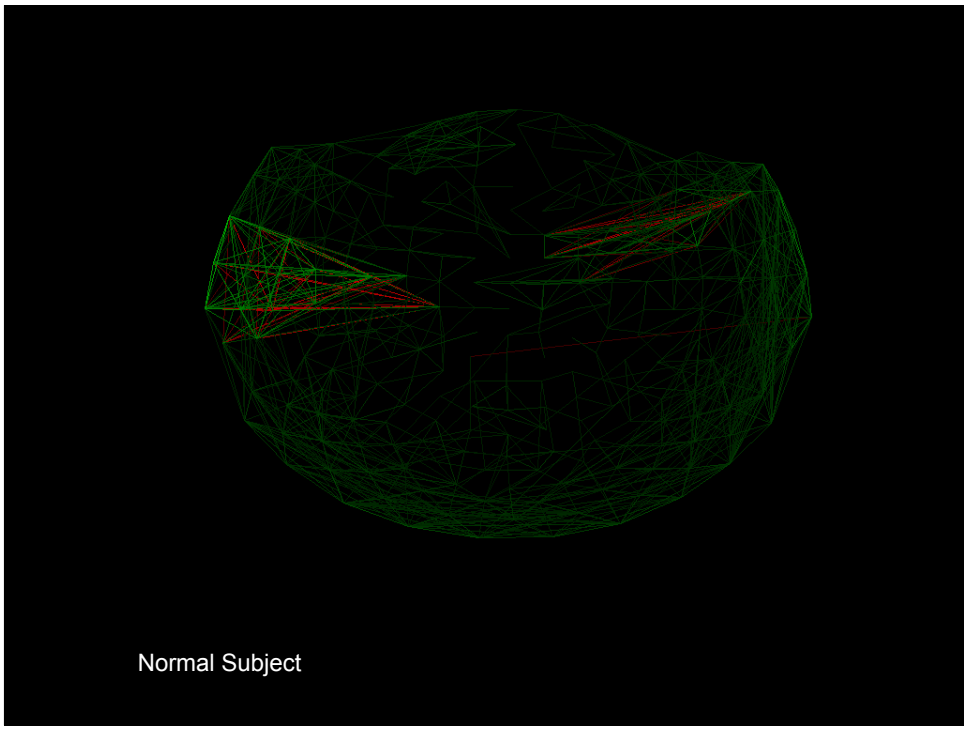
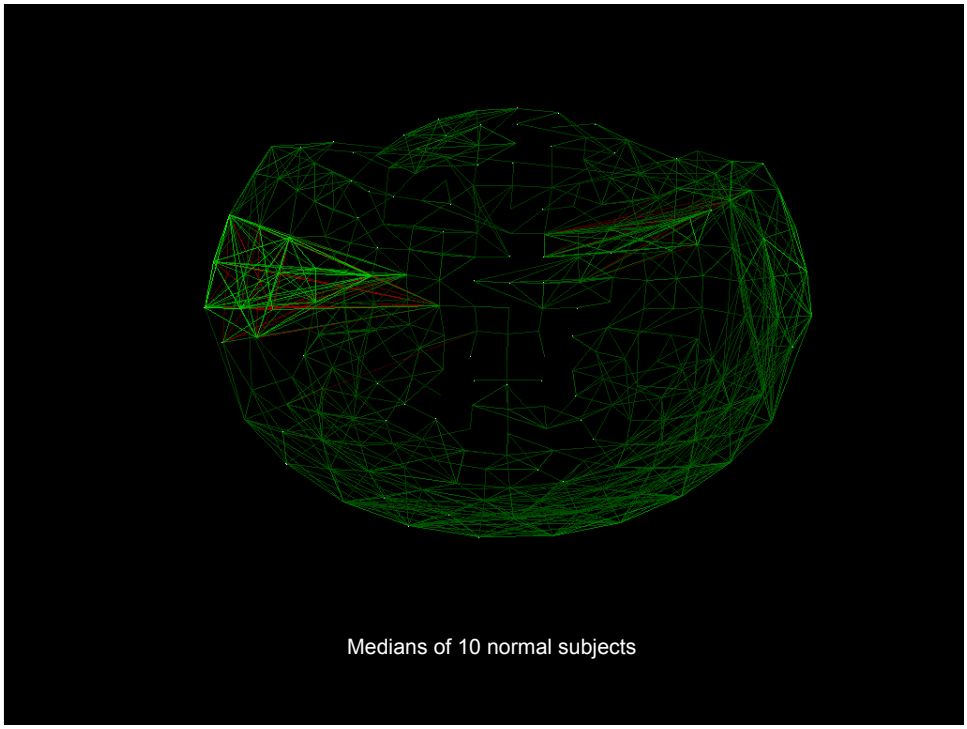
Day 15


Normal Subject

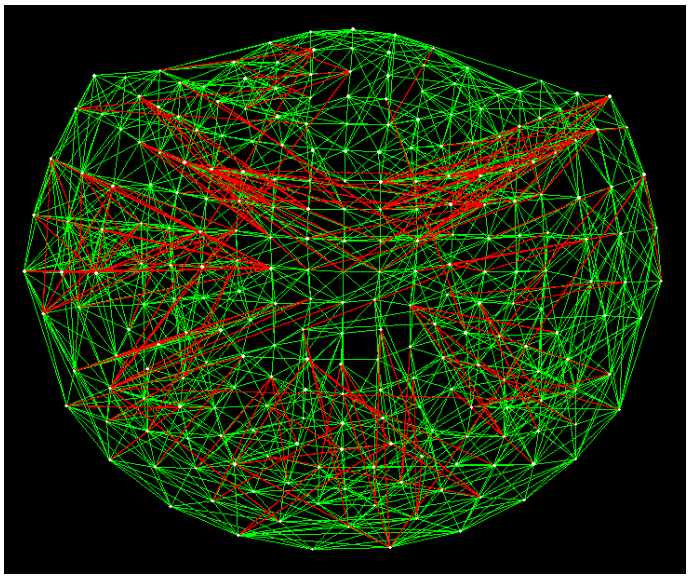


Assessment of Dynamic Brain Function: Synchronous Neural Networks

- All possible zero-lag partial cross-correlations between 248 sensors (= 30,628)
- Positive or negative
- 1-ms temporal resolution = true synchronicity
- Simple fixation

Langheim, F.J.P., Leuthold, A.C. and Georgopoulos, A.P. (2006) Synchronous dynamic brain networks revealed by magnetoencephalography (MEG) Proceedings of the National Academy of Sciences USA 103: 455-459.

Zero-lag (1-ms synchronous) Partial Correlations
Of Prewhitened (stationary) MEG Time Series



Langheim et al., PNAS, 2006

Initial Application to Six Groups

- Healthy control
- Alzheimer's Disease
- Schizophrenia
- Chronic alcoholism
- Multiple sclerosis
- Sjögren's syndrome (with brain involvement)

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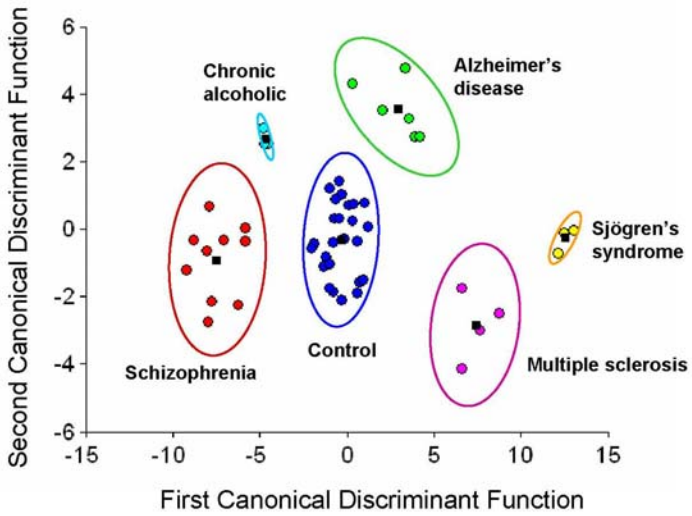
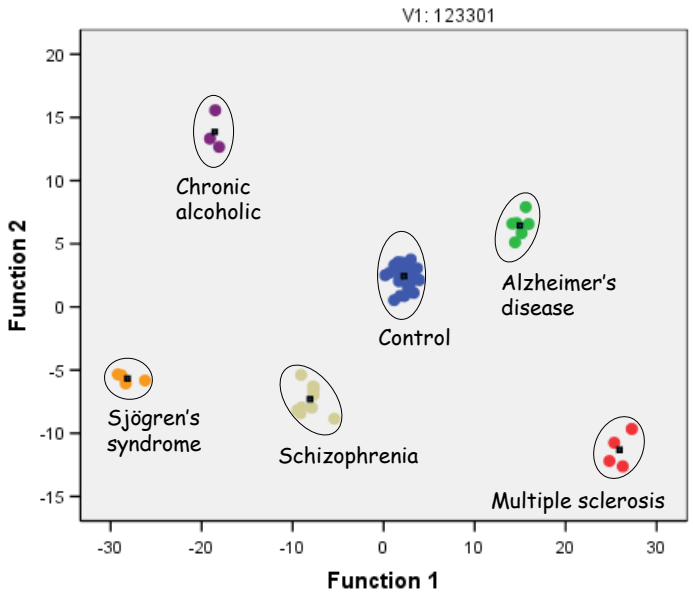
Discriminant Classification Analysis

- Linear discriminant analysis
- Robust, cross-validated leave-one-out method
- 100% correct classification of 52 subjects to one of 6 groups:
  - Healthy control
  - Alzheimer's Disease
  - Schizophrenia
  - Chronic alcoholism
  - Multiple sclerosis
  - Sjögren's syndrome
- Such sets are found using as few as 10 predictors and in numbers far in excess of those expected by chance

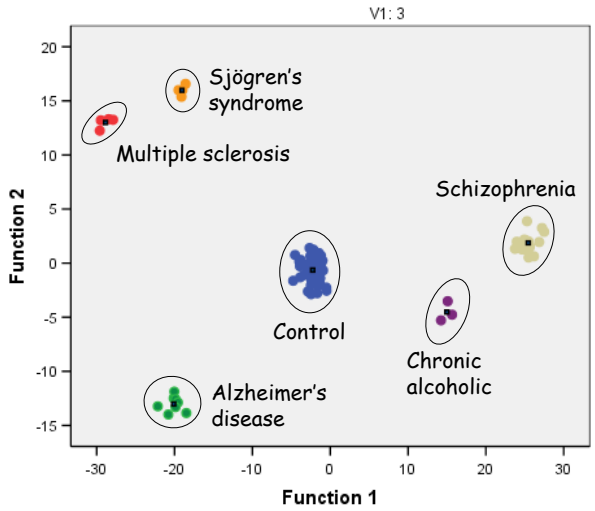


52 subjects, 20 predictors

Georgopoulos et al. (2007) J Neural Engineering 4: 347-355



52 subjects, 40 predictors (another set)



79 subjects

Current studies: Targeted Subject Groups

Age 8-100 y

Brain diseases

Alzheimer's disease
Autism
Autoimmune disorders
Bipolar disorder
Chronic pain
Chronic alcoholism
Depression
Down syndrome
Fetal alcohol syndrome
Fronto-temporal dementia
Gambling
Hyperthyroidism
Mild cognitive impairment
Multiple sclerosis
Parkinson's disease
Post-traumatic stress disorder
Schizophrenia
Gulf War Illnesses (starting)

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The synchronous neural interactions test as a functional neuromarker for post-traumatic stress disorder (PTSD): a robust classification method based on the bootstrap

A P Georgopoulos[1,2,4,5,6,9], H-R M Tan[1,2,8], S M Lewis[1,3], A C Leuthold[1,2], A M Winskowski[1,6], J K Lynch[1,2] and B Engdahl[6,7]

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PTSD – Classification

- SNI test on 74 veterans with PTSD as the primary disorder vs. 250 healthy people
- Externally cross-validated, bootstrap-based classification
- Excellent results (published): 97% sensitivity, 88% specificity
- Update: 80 PTSD veterans, 284 controls:
  96% sensitivity, 95% specificity
- Best promise for a PTSD **neuromarker**

The Basic Science Behind the Test: Small-scale, High Temporal Resolution Synchronicity

- Our findings indicate a problem (in brain disease) with synchronous interactions among small neuronal populations
- A new basic science principle?

Sources of Synchronicity

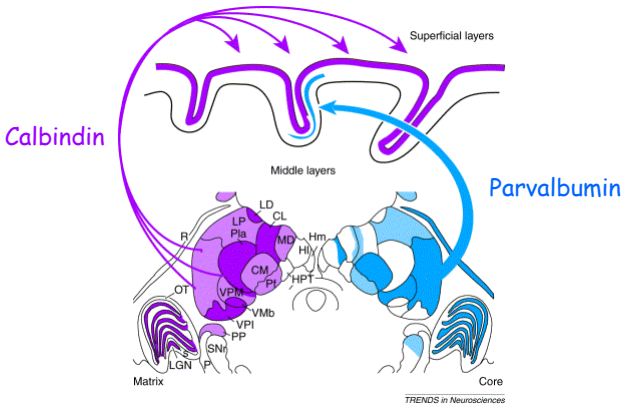
- Recurrent collaterals of pyramidal cells
- Thalamocortical afferents
  - Specific (parvalbumin)
  - Widespread, multifocal (calbindin)

Recurrent pyramidal cell collaterals

".. In the resting cortex, assemblies of idling neurons may be forced in synchronous grouped discharges by the diffuse interaction of interconnecting axon collaterals and cortical interneurons, synchronizing their spontaneous activity …"

Stefanis, C. & Jasper, H. (1964)

Thalamocortical projections



Jones EG (2001) The thalamic matrix and thalamocortical synchrony. TINS 24:595-601

Thalamocortical Synchrony

"Cortex is driven by weak but synchronously active thalamocortical synapses"

Bruno, R.M. & Sakmann, B. (2006)

A new basic science principle?

The present results suggest that fine-level synchronicity may be a fundamental aspect of cortical function that is differentially disrupted by different disease processes, yielding a disease-specific signature.

The Roadmap

- Study as many subjects and diseases as possible
- Stratify healthy controls (gender, age)
- Disease groups
- Excellent throughput (10-15 subjects/day)

Future

The SNI test has the prospect of becoming the first routine test for:

- Assessing dynamic brain function
- Aiding in differential diagnosis
- Monitoring disease progression
- Evaluating the effects of intervention
- The invention has been patented (University of Minnesota & US Government) and licenced to Orasi Medical, Inc. (Minneapolis, MN)

The support of the

University of Minnesota and the
Department of Veterans Affairs

is gratefully acknowledged

The End

Τέλος

In group comparisons using the nonparametric Kolmogorov-Smirnov test to assess the difference between SNI distributions, we found that the distributions of healthy veterans (N = 234), veterans with PTSD (N = 160), veterans with GWVI alone (N = 84), and veterans with GWVI+PTSD (N = 7) differed highly significantly from each other (P<0.001), except for the comparison of PTSD vs. GWVI+PTSD, which was not statistically different. Interestingly, there was a pattern in the relative SNI distances among those groups, as follows. We used Smirnov's Z statistic as a proximity (e.g. distance) measure in a nonmetric multidimensional scaling analysis (MDS).

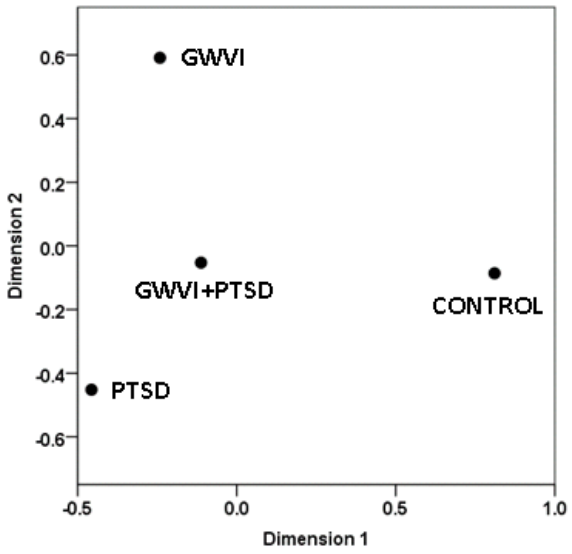
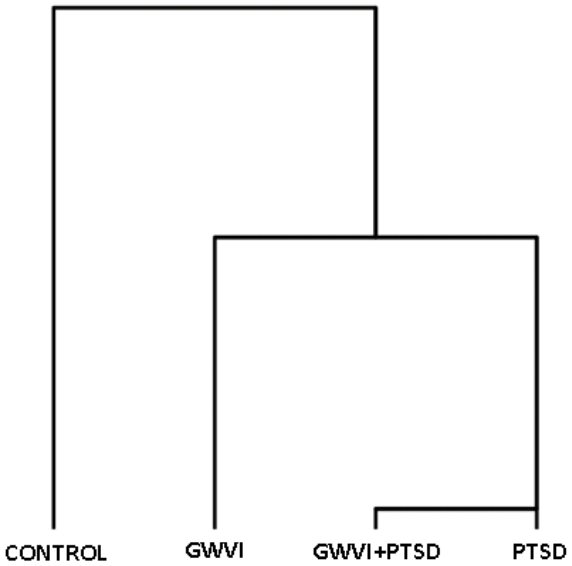


Fig. 1. MDS plot of four groups based on distances between their SNI distributions. Notice the distinct placement of the 4 groups, the unique location of the Control group far away from the other 3 groups, and the orderly progression of the disease groups along Dimension 2, where PTSD and GWVI occupy extreme locations with the GWVI+PTSD group in-between.

It can be seen in Fig. 1 that the control, GWVI, and PTSD-related groups occupied distinct locations in the MDS space; specifically, Controls were farthest away from all other groups in Dimension 1, which attests to the unique property of this group being healthy. In contrast, the other 3 groups lined up on the other side of Dimension 1 in a fashion that was orderly along Dimension 2, starting from the bottom (PTSD) to the middle (GWVI+PTSD) to the top (GWVI).



In a different analysis, we performed a hierarchical tree modeling on the same data to better identify possible clustering of subject groups. The results are shown in Fig. 2.. The following can be seen. (1) There are 2 branches in the tree (from the top, the tree's origin) separating healthy (control) from diseased veterans. (2) The Disease branch (to the right) further splits in 2 distinct branches, identifying two distinctly different disease entities, namely GWVI and PTSD. (3) Finally, the composite group (GWVI+PTSD) falls in-between. Notice the independence of Controls, the clustering together of the PTSD and GWVI+PTSD groups, and the intermediate location (within the disease cluster) of the GWVI group.

The MDS and tree modeling results, taken together, demonstrate unequivocally that GWVI is a distinct brain disease, separate from PTSD.