A New Test for Brain Function Based on Magnetoencephalography

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

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

Chronic Alcoholic Beginning Sobriety: Day 1
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

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)
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

52 subjects, 40 predictors (another set)
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)
The synchronous neural interactions test as a functional neuromarker for post-traumatic stress disorder (PTSD): a robust classification method based on the bootstrap

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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

Thalamocortical Synchrony

“Cortex is driven by weak but synchronously active thalamocortical synapses”


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)
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The End
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