GWVI is a distinct brain disorder: Evidence from MEG

Apostolos P. Georgopoulos, M.D., Ph.D.

Regents Professor of Neuroscience
University of Minnesota

Director of Brain Sciences Center
Minneapolis VA Medical Center

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

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J. Neural Eng. 7 (2010) 016011 (7pp) doi:10.1088/1741-2560/7/1/016011

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]

[1] Brain Sciences Center, US Department of Veterans Affairs Medical Center (11B), Minneapolis, MN 55417, USA
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[8] Centre for Cognitive Neuroimaging, University of Glasgow, 58 Hillhead Street, Glasgow G12 8QB, UK

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Post-traumatic stress disorder: a right temporal lobe syndrome?

B Engdahl[1,2,3], A C Leuthold[3,4], H-R M Tan[3,4,9], S M Lewis[3,5], A M Winskowski[1,3], T N Dikel[6] and A P Georgopoulos[3,4,5,7,8,10]

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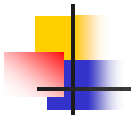
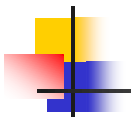
October 28, 2010



Outline of the Lecture

- Foundations: Neural communication
- Signal: Magnetoencephalography (MEG)
- Applications: Diagnosis of brain diseases
- GWVI: The latest application!

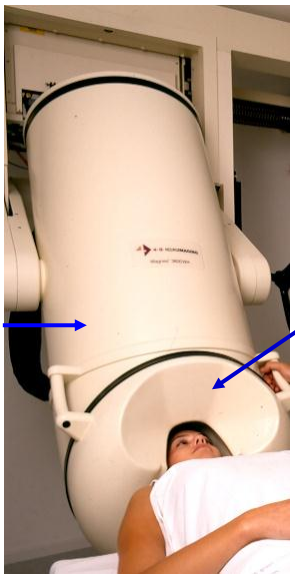


Neural Communication - 1

- 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

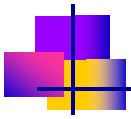
- Neural communication is accomplished by ongoing, dynamic interactions among multiple neuronal ensembles.
- These interactions can be positive or negative and can occur at different time lags.
- They can be estimated using the cross correlation function (CCF).



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

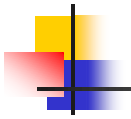
MEG

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



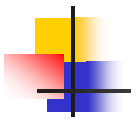
The MEG Signal

- 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).



The Synchronous Neural Interactions (SNI) test

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

- Duration: 60 s (no task: subjects fixate a spot or keep their eyes closed)
- 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

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

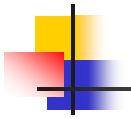
- If not, the CCF can be misleading by reflecting influences of the series themselves, unrelated to the true relations between the series

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

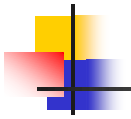
The Challenge

- 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



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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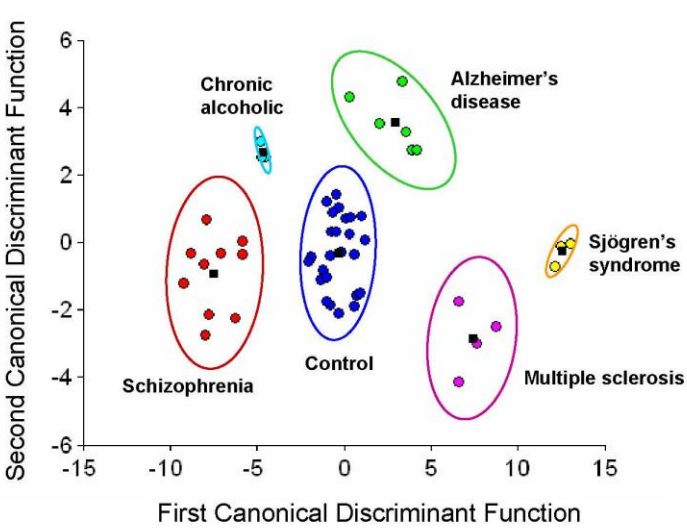
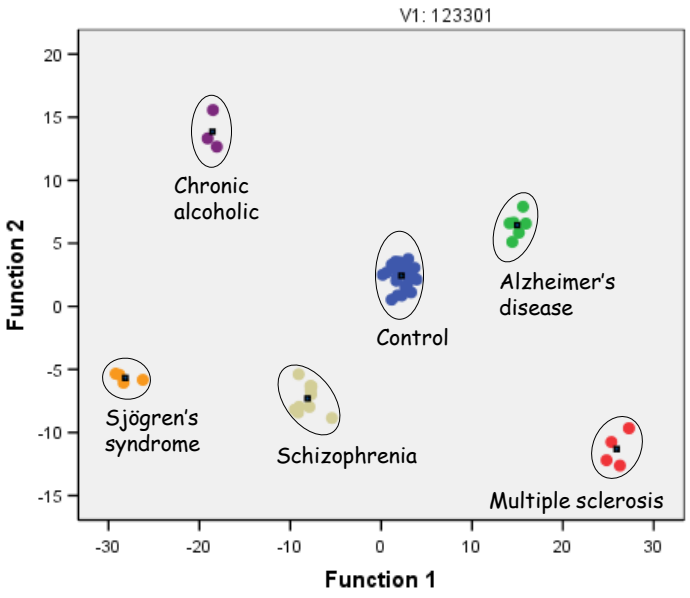
Discriminant Classification Analysis

- 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

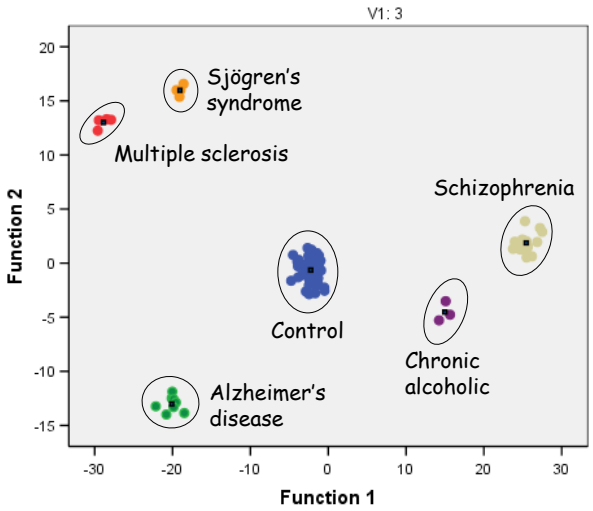


52 subjects, 20 predictors

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



52 subjects, 40 predictors (another set)



79 subjects (Total N published = 146)

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?

A new basic science principle

Fine-level synchronicity is a fundamental aspect of cortical function that is differentially disrupted by different disease processes, yielding a disease-specific signature.

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 …*"

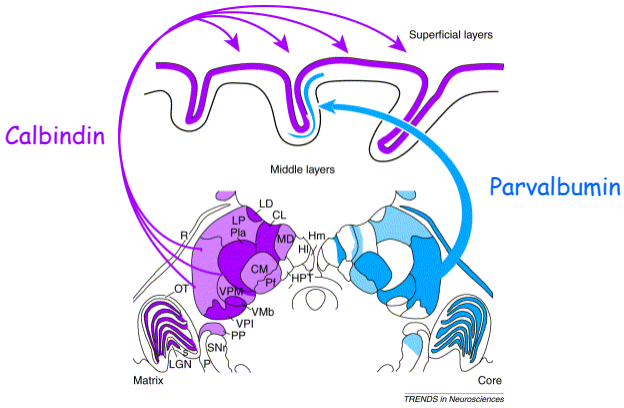
Stefanis, C. & Jasper, H. (1964)

Thalamocortical Synchrony

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

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

Thalamocortical projections



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

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

Current studies: Targeted Subject Groups

Age 8-100+ y

Brain diseases

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

Brain and PTSD

- Four steps in investigating brain and PTSD
  - 1. Prove it is a brain disease.
  - 2. Identify the specific brain abnormality.
  - 3. Quantify the brain abnormality and relate it to disease severity.
  - 4. Find out how the PTSD brain signature combines with other brain diseases in comorbidities

Brain & PTSD: Proof

- Find a brain measure that classifies PTSD and control subjects with high accuracy
  - Yes, the synchronous neural interactions
  - Georgopoulos et al. 2010
  - Current accuracy (80 PTSD, 284 controls):
    - ✓ 96% sensitivity
    - ✓ 98% specificity

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January, 2010

Brain & PTSD: Abnormality

- Discover the brain patterns that differentiate PTSD subjects from controls: PTSD brain signature
  - Yes, abnormal synchronicity
  - Engdahl et al. 2010
    - ✓ Right hemisphere
    - ✓ Node in temporal lobe

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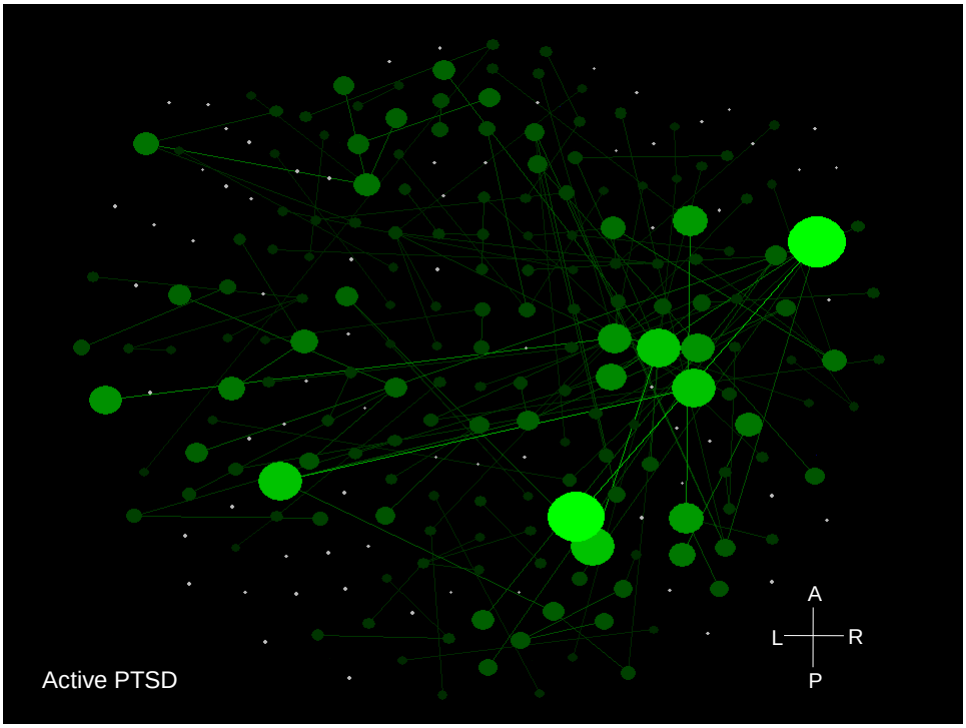
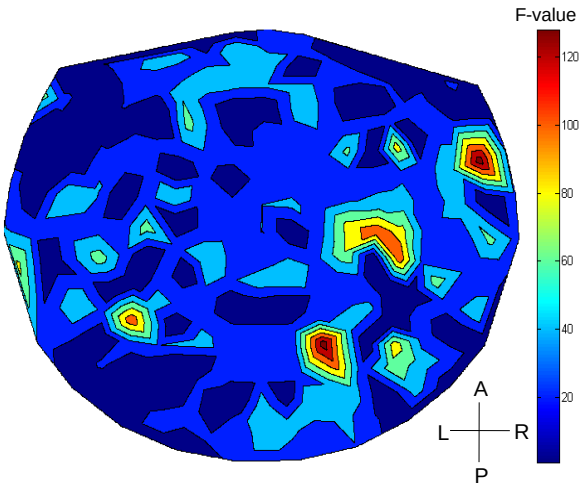
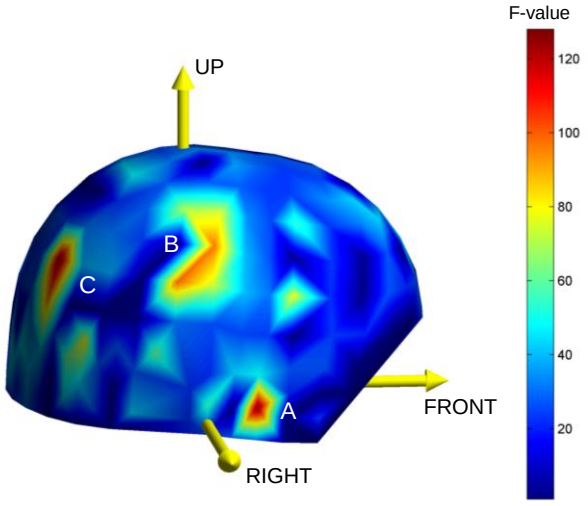




Active PTSD



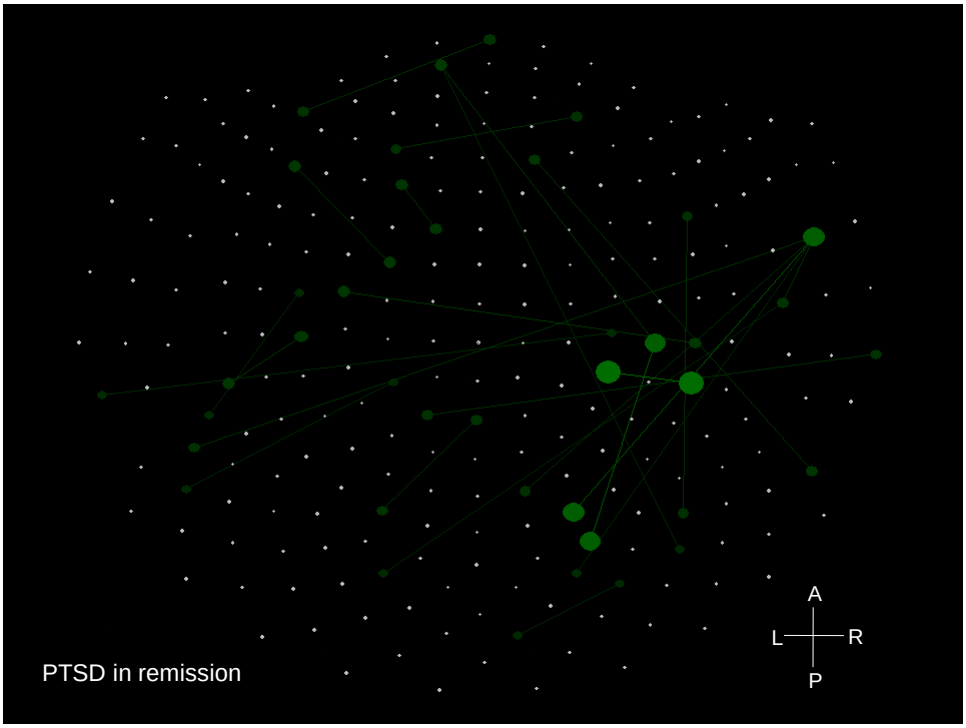
Active PTSD

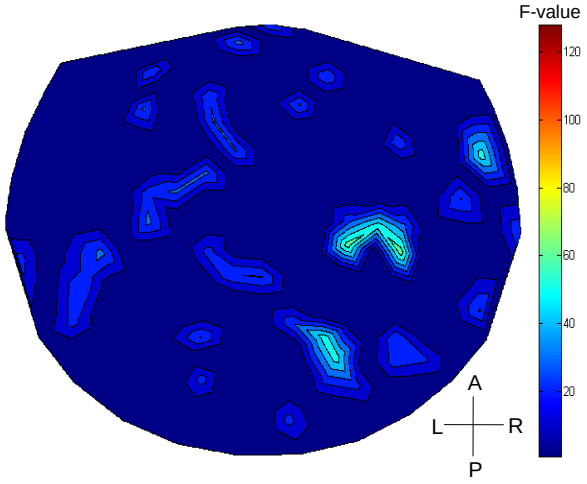
PTSD: A Temporal Lobe Syndrome

- These findings are consistent with observations by Penfield (1958), Gloor (1990), Banceaud et al (1994), Fried (1997), and others, that electrical stimulation of the temporal cortex in awake human subjects, mostly in the right hemisphere, can elicit the re-enactment and re-living of past experiences.
- Based on these facts, we attribute our findings to the re-experiencing component of PTSD and hypothesize that it reflects an involuntarily persistent activation of interacting neural networks involved in experiential consolidation

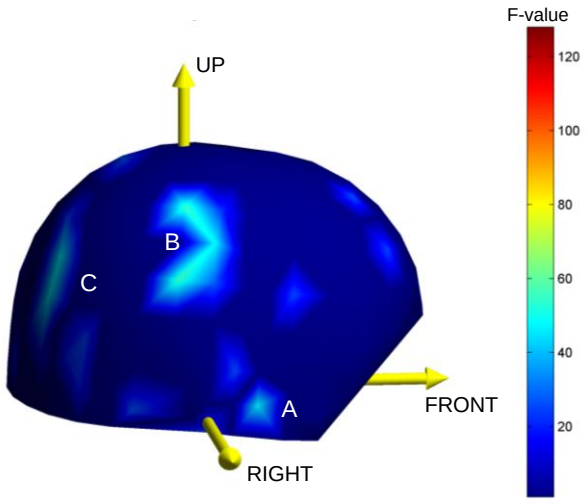
Brain & PTSD: Quantification

- Show that your measure varies with PTSD severity
  - Yes, SNIs much attenuated in PTSD in remission
  - Engdahl et al. 2010





PTSD in remission



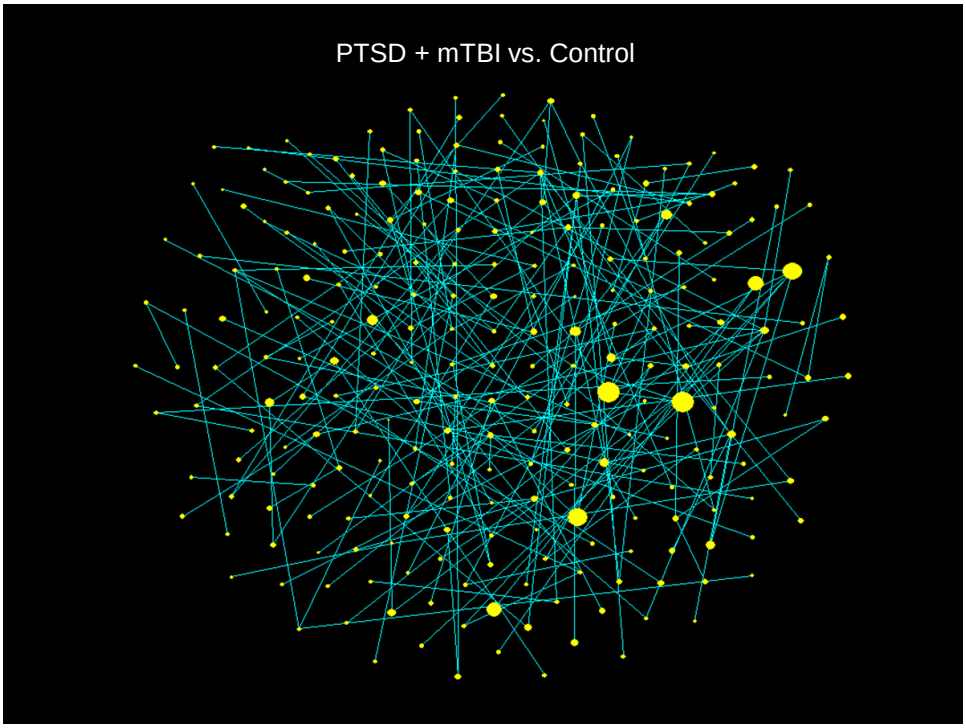
PTSD in remission

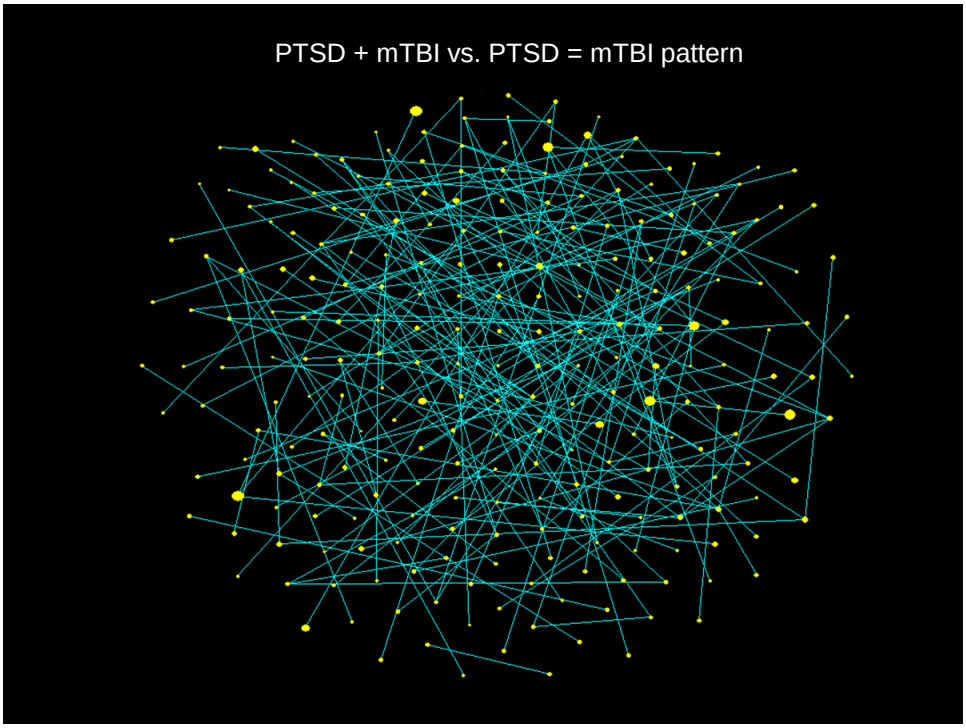
Brain & PTSD: Comorbidities

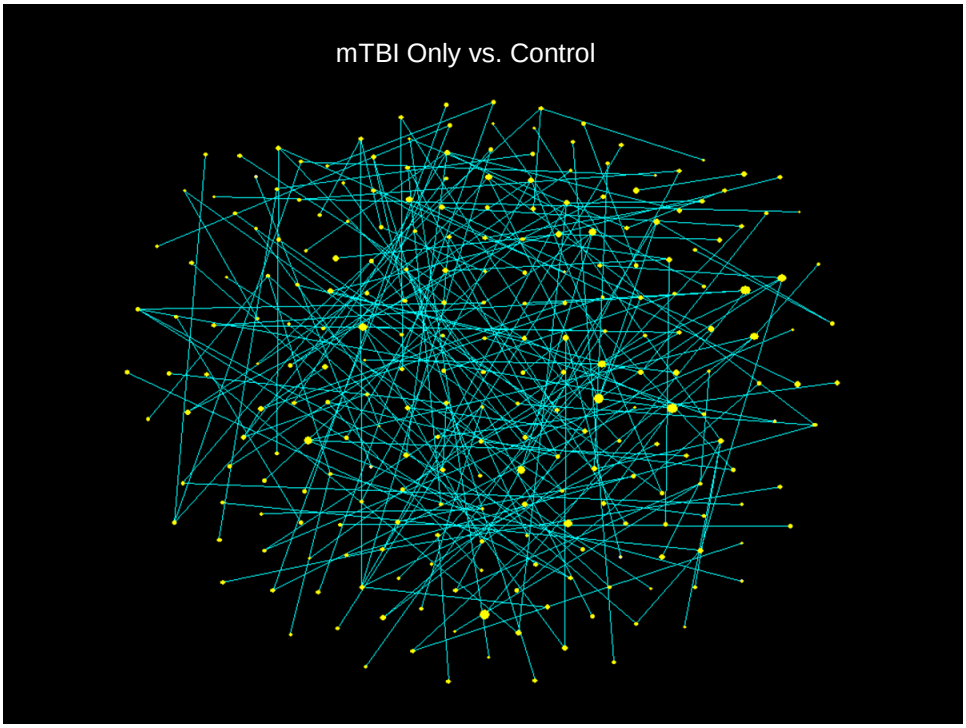
- How does PTSD brain signature combines with other brain diseases?
  - Yes, PTSD keeps its own signature!
  - mTBI (paper in preparation)

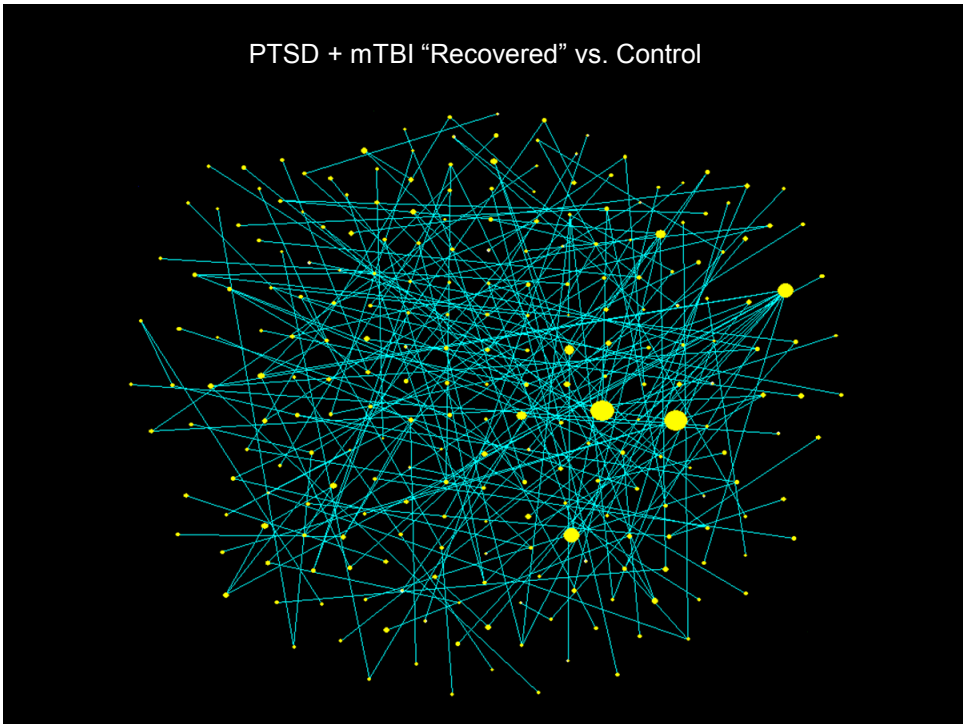
PTSD & mTBI

- Preliminary studies of subjects with
  - PTSD + mTBI
  - mTBI
  - PTSD + "recovered" mTBI

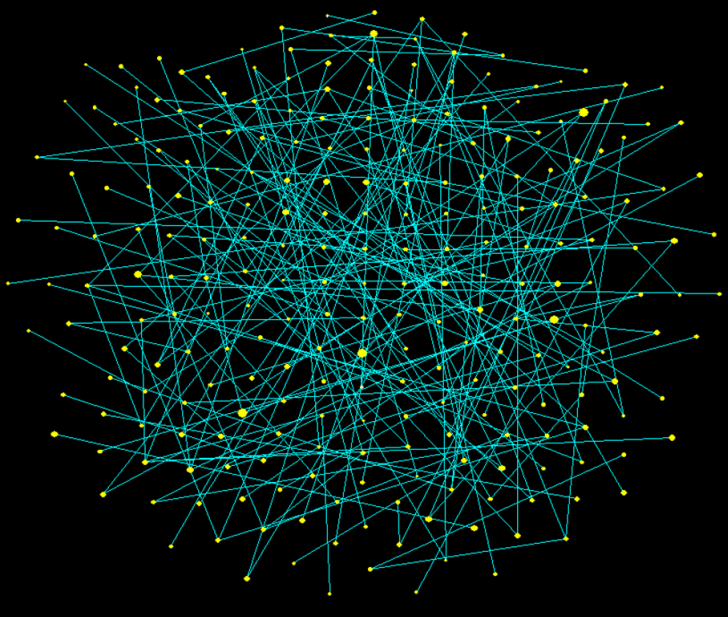

PTSD + mTBI vs. Control


PTSD + mTBI vs. PTSD = mTBI pattern

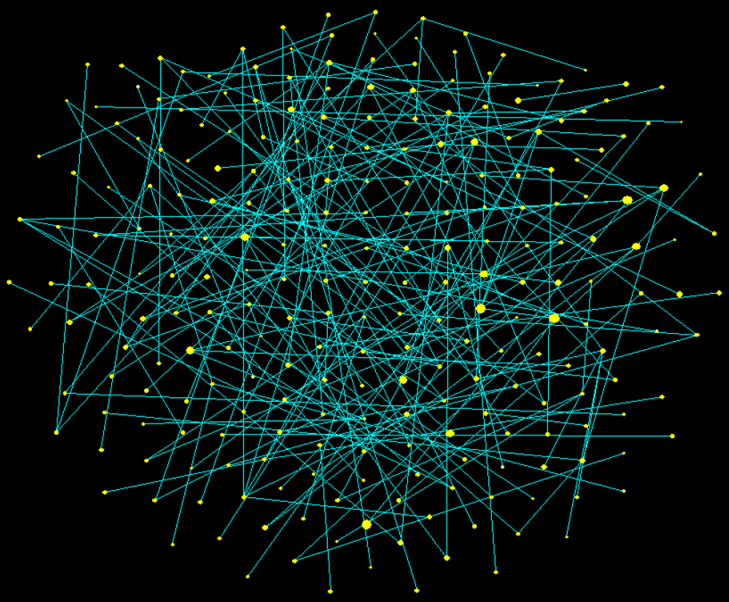

mTBI Only vs. Control


PTSD + mTBI “Recovered” vs. Control

PTSD + mTBI “Recovered” vs. PTSD
(mTBI abnormalities, still …)



mTBI Only vs. Control



PTSD: Conclusions

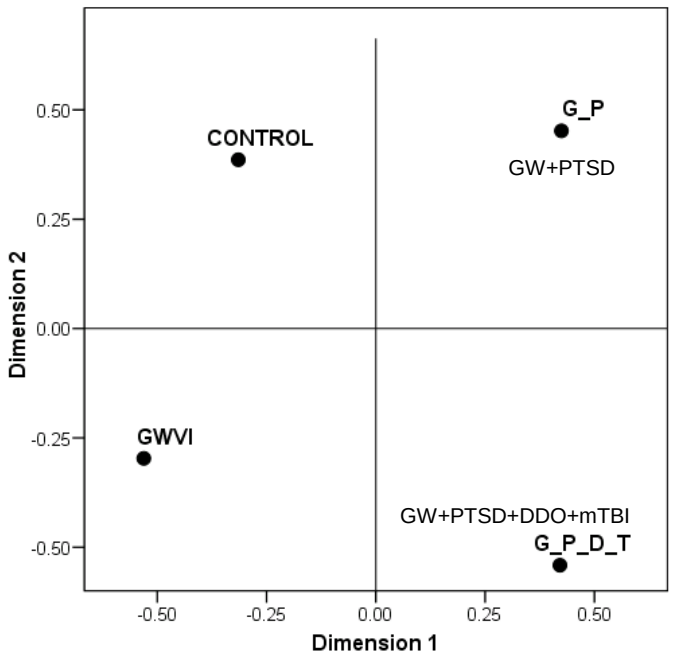
- PTSD is a brain disease
- It involves abnormal dynamic communication of brain areas mostly in the right hemisphere
- This miscommunication is graded with PTSD severity
- The SNI can aid in differential diagnosis, severity scaling and monitoring the effects of treatment
- The PTSD miscommunication pattern is additive to other abnormal brain patterns (e.g. due to mTBI)

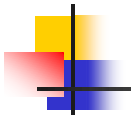
GWVI – 1

- Goal: To apply the SNI test and evaluate potential abnormalities in neural communication in GWVI, as compared to control GWV
- Pilot study funded by the VA (started 10/1/11)
  - 13 GWV control
  - 28 GWVI (20 meeting both Fukuda CDC and Kansas GW criteria; 8 meeting only Fukuda criteria)
  - 11 GWVI with comorbidities (mental health, mTBI)
  - Investigators: L. James, PhD; B. Engdahl, PhD; A. Leuthold, PhD; S. Lewis, MD, PhD; A.P. Georgopoulos, MD, PhD

GWVI - 2

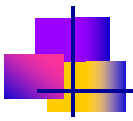
- SNI test: 30,628 partial correlations (PC) per subject
- Comparison of PC distributions between groups using the Kolmogorov-Smirnov test
- Distributions different from each other (P<0.001)
- Mapping of conditions: Multi-Dimensional Scaling (MDS)





GWVI - Conclusions

- GWVI is a distinctly separate entity
- The current study needs to be extended to larger numbers
- Detailed examination of subgroups with comorbidities
- Identification of a "core" brain abnormality?
- The MEG/SNI approach can lead to firm outcomes



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The End

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