Reliable Measures of Regional Brain Activity – Towards Neuroelectric Diagnostics

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Those shown in light green are experienced clinicians.

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The goal of our effort is to better understand, diagnose, and treat traumatic brain injury (TBI).

What we know:

Several million patients present to ER’s in the US each year who sustained an impact to their head. Most are children and teenagers.

Less than 20% show any evidence of anatomic injury to the skull or brain. Those who do typically show a skull fracture or intracranial blood on a CT scan. This same group demonstrates GFAP in their blood, a brain-bound protein which normally does not cross the blood-brain barrier.

Many experience headache, nausea, photo-phobia, dizziness, and other non-specific symptoms. About 20% will go on to experience chronic symptoms including sleep problems.

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What we don't know … everything else, for example:

Why do people lose consciousness when hit in the head?

What is the neurophysiological mechanism which produces symptoms when the CT demonstrates blood or a skull fracture … or when it doesn't?

What is the physical relationship between impact and injury and symptoms?

Does everyone with symptoms have an anatomic/physical injury?
If not, what is the mechanism which produces the symptoms including loss of consciousness?

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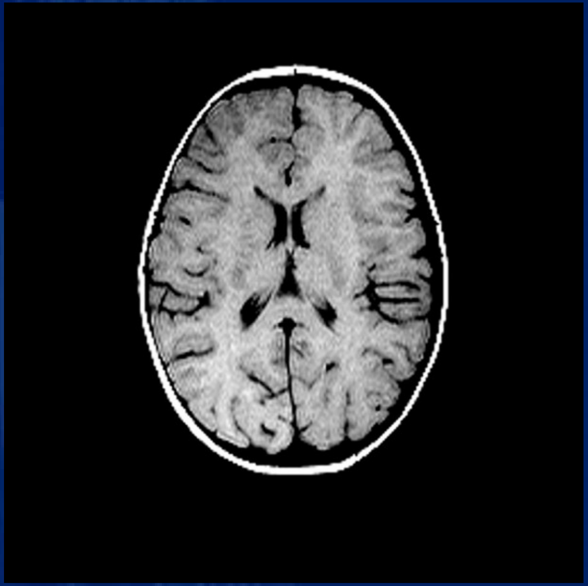
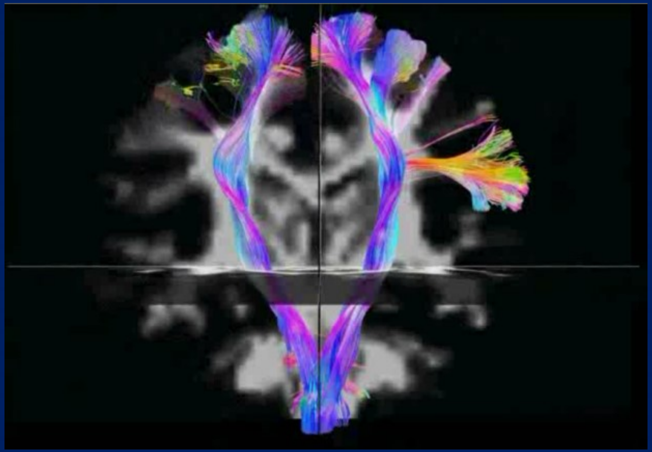
The goal of our effort is to better understand, diagnose, and treat traumatic brain injury (TBI). We utilize anatomic imaging



T1-weighted MRI Structural imaging



Diffusion tensor MRI Tractography

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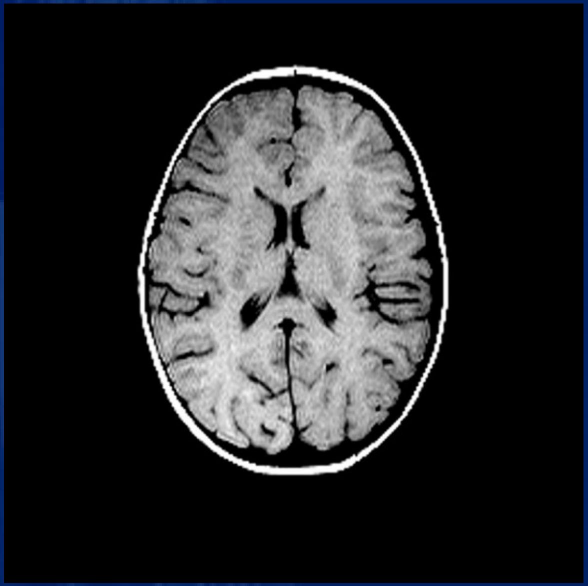
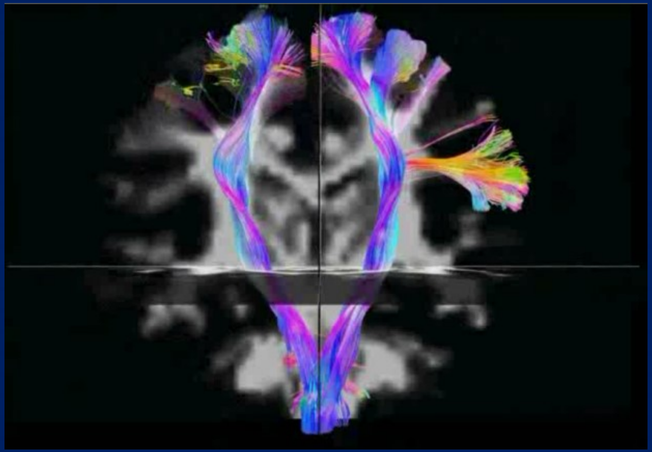
The goal of our effort is to better understand, diagnose, and treat traumatic brain injury (TBI). We utilize anatomic imaging and magnetoencephalography, MEG.



T1-weighted MRI Structural imaging



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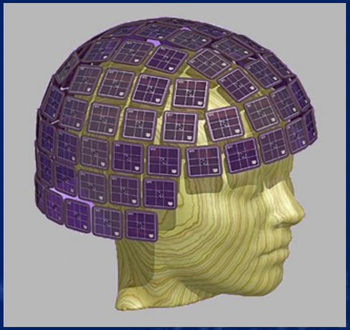

MEG Functional imaging

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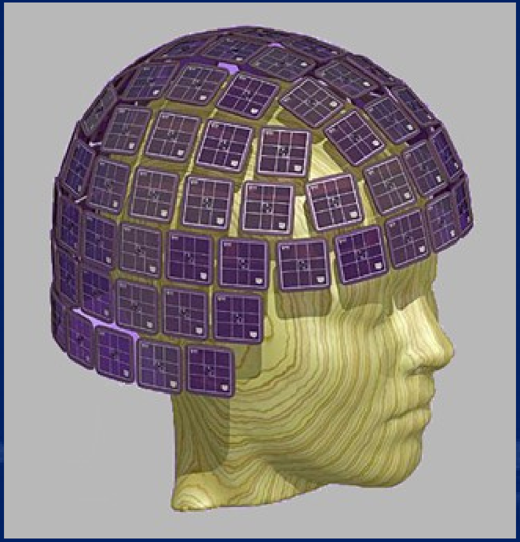
The MEG scanner is a liquid helium dewar which contains 102 super-conducting chips. Each chip includes 1 magnetometer, 2 figure-8 gradiometers at right angles to each other, and a SQUID for each for signal transduction to room temperature electronics.



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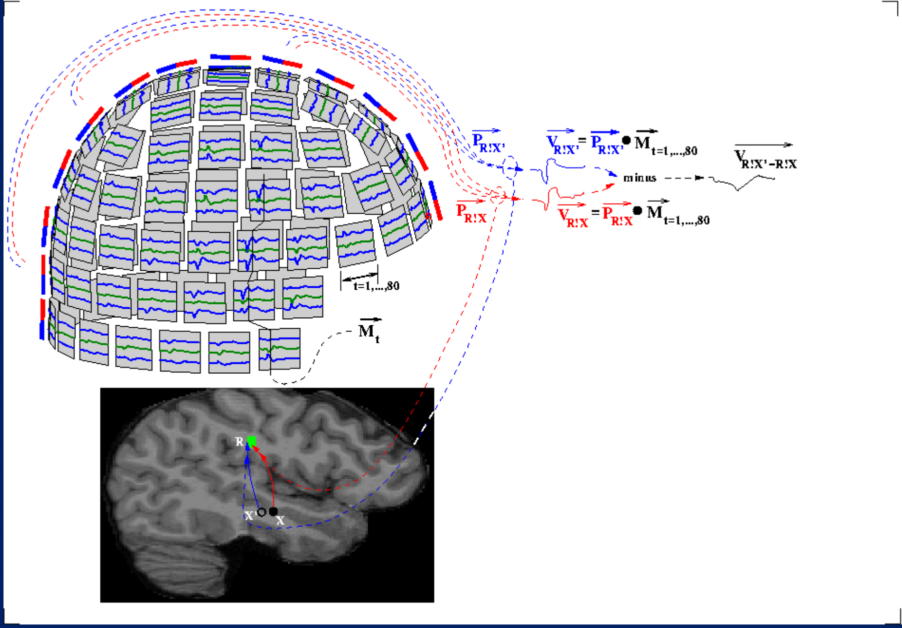
Nov 2011: Discovery of the referee consensus solver.
Dec 2011: Startup XSEDE allocation on Blacklight

The solver embodies a new and powerful deconvolution method.

It uses families of spatial interference filters, highly tuned signal space separation projection operators. The filters isolate and identify one neuroelectric current at a time using a gradient search.



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This ability to isolate one signal in the presence of innumerable others translates directly into the signal processing independence required for efficient high throughput computing.

Typically ≈ 400 simultaneously active currents are identified at each 40 msec step through a recording, i.e. ≈ 10,000 validated currents are identified and localized per second of data.

When applied to human magnetoencephalographic recordings (MEG), the method localizes neuroelectric currents with millimeter resolution, each validated with high confidence, $p < 10^{-12}$.

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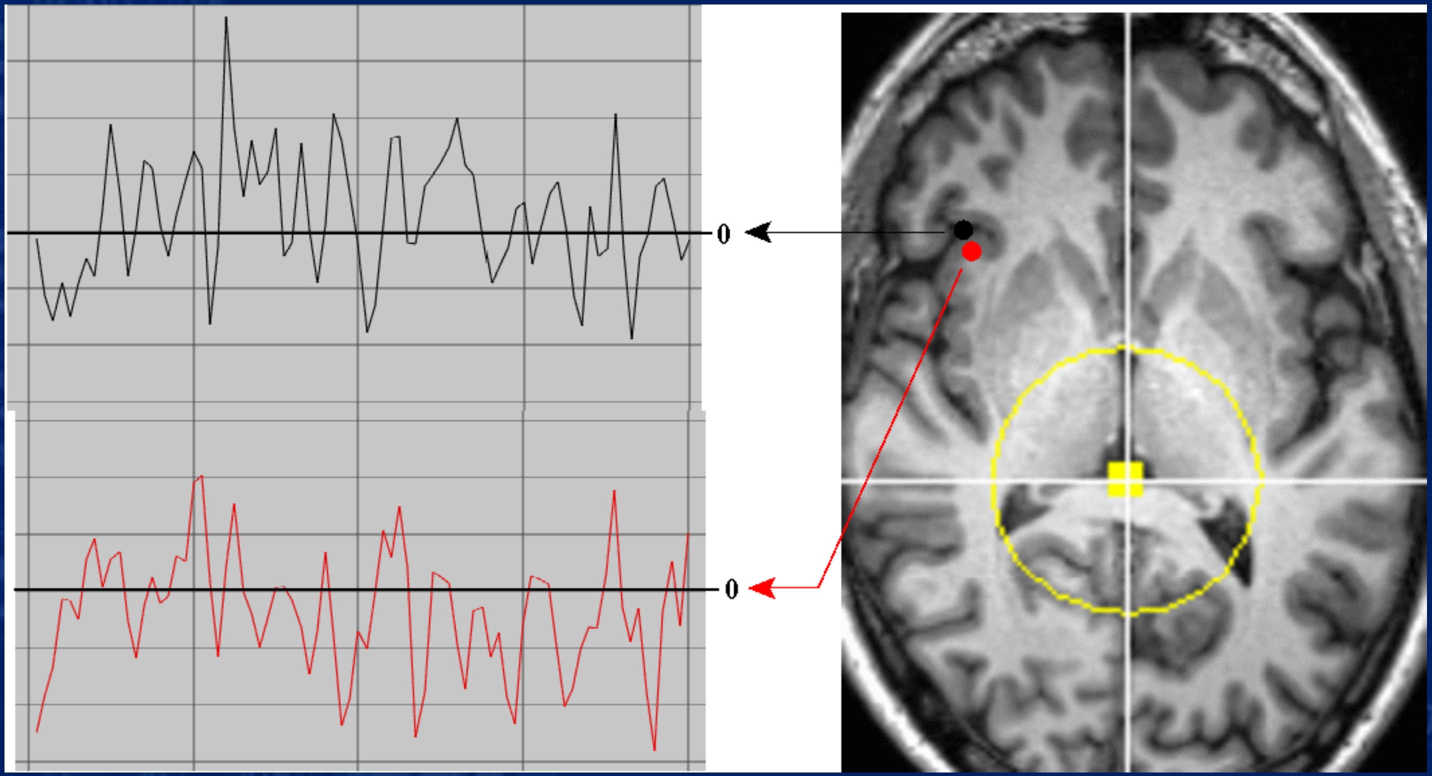
Feb 2012: Finding … The solver’s spatial and temporal resolution is comparable to direct indwelling recordings.

Two typical simultaneously active neuroelectric currents are shown. Each waveform has duration of 80 msec sampled at 1000 Hz. These currents are 5 mm apart with zero-lag cross-correlation of 0.157 .



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Jul 2012: Startup XSEDE allocation on the OSG
Aug 2012: Production runs begin on the OSG

The solver requires about 35 core hours per second of data.

Each OSG job searches a single 8x8x8 mm^3 brain volume for 20-60 seconds of data. Each job runs in a single thread:

- 12-150 minutes
- Memory: 700 Mbytes
- Input data: 50-200 Mbytes
- Output data: ≈50 Kbytes

A 30-minute session for a single research subject: ≈ 150,000 jobs

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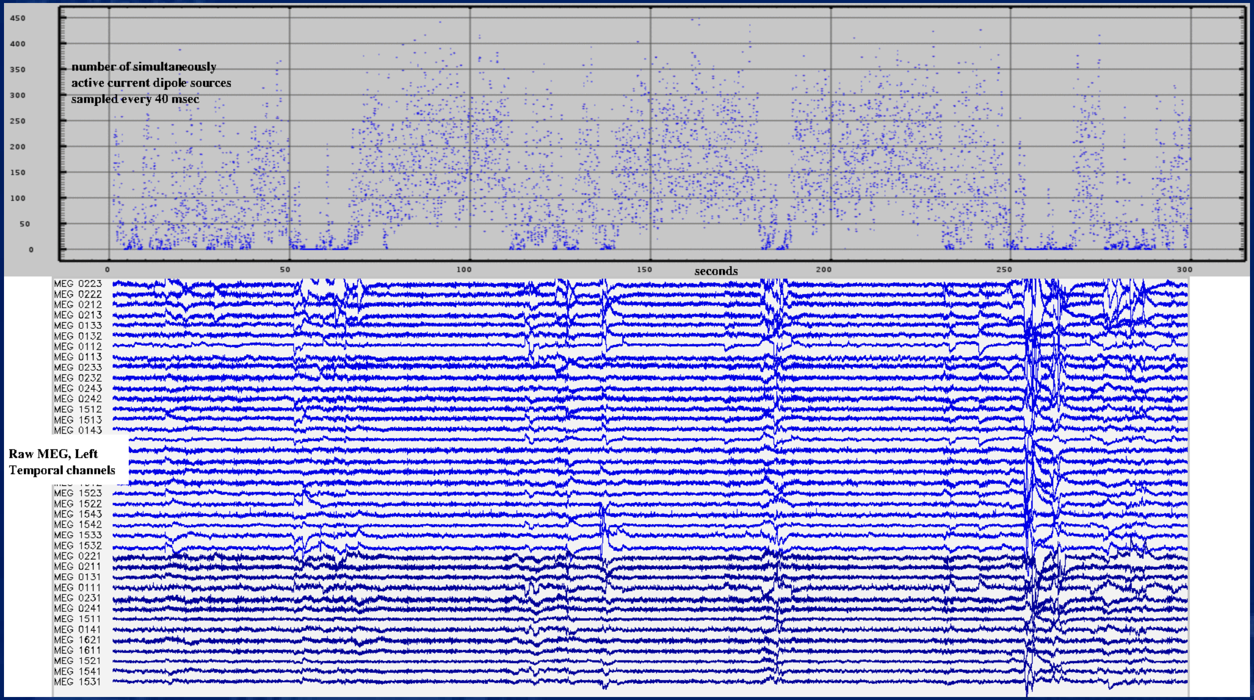
Jan 2013 – Finding … The solver is defeated by data artifacts.
Mar 2013 – Method and initial findings presented to AHM.
Jul 2013 – Method published [Proceedings of the 2013 XSEDE Conference, ACM Concurrency]

Lower panel: 300 second MEG recording. Upper panel: # neuroelectric sources identified during each 40 msec period



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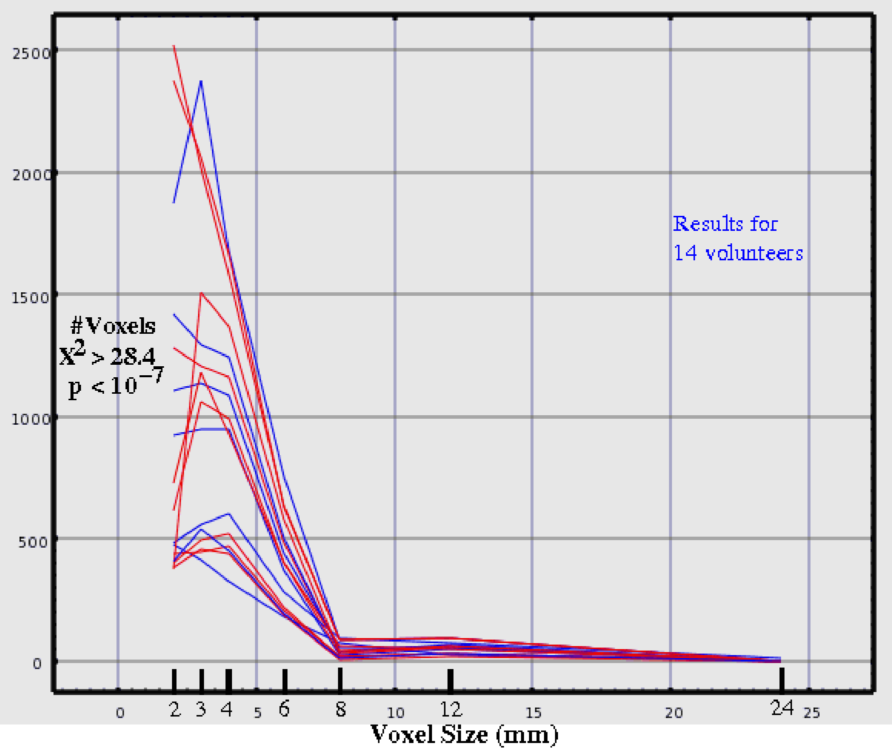
Jan 2014: Finding … The spatial scale of the brain's functional neuroelectric unit is smaller than 8 mm^3.

Local neuroelectric activity differs under different conditions for small voxels but not for large voxels.

The number of neuroelectric currents was counted within each voxel under two different task conditions. The number of voxels for which the count was different ($\chi^2 > 28.4$, $p < 10^{-7}$) is shown as a function of voxel size.



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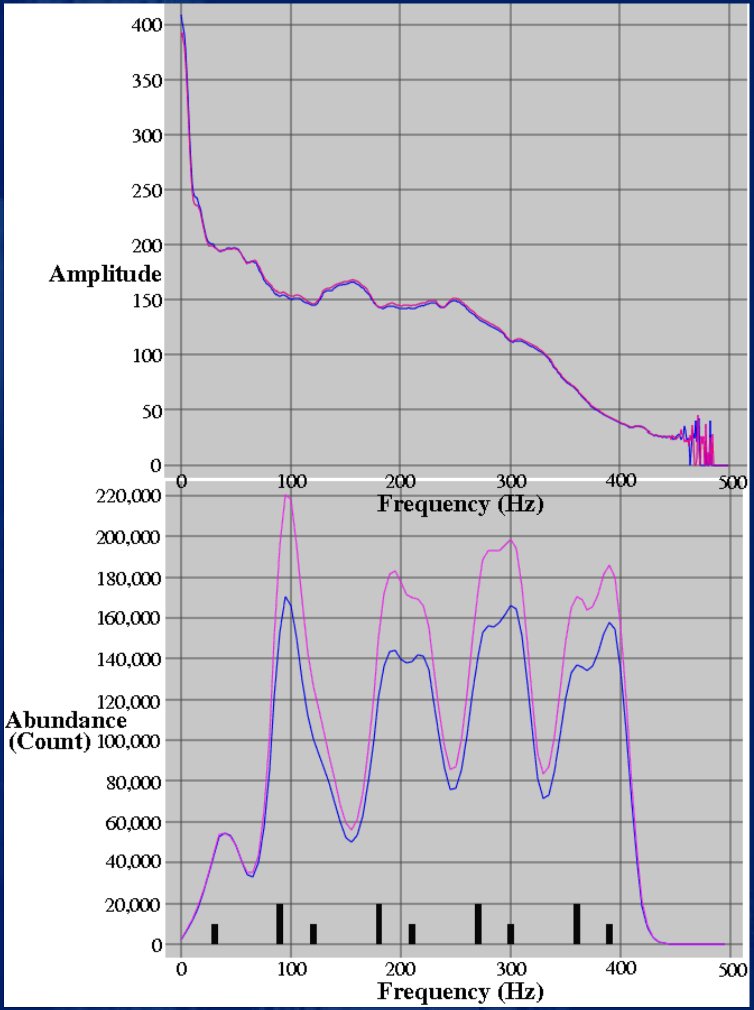
March 2014: Finding Clinical Neurophysiology 125, Suppl 1(2014): S1-S339



Resonant neuroelectric activity differs under different conditions. The upper panel shows Fourier amplitude spectra under two conditions. The lower panel shows the abundance of resonant activity.

These results are from one typical subject. Kalman time series modeling was used to identify up to 5 resonant oscillations from each single trial 80 msec waveform. This yields …

- a well-defined frequency estimate,
- the amplitude at that frequency,
- a measure of synchronicity.

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Jan 2014: Findings published. Int’l J Adv’d Computer Sci, 4(1),15-15
Mar 2014: Findings published. Proc’s 30th Int’l Congress of Clinical Neurophysiology

Nov 2014 – Sep 2017: TEAM-TBI DOD-funded concussion study.

- Combat veterans, history of concussion with chronic symptoms.
- Normal anatomic imaging
- Symptoms assessed by clinical exam, neuropsychiatric testing, symptom inventory, with researcher/clinician team adjudication and consensus on diagnosis and treatment recommendations.
- 64 individuals studied at baseline.
- 39 individuals studied at 6-month follow-up.

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Jul 2015: XSEDE booster allocation … Comet (SDSC)
Aug 2016: XSEDE booster allocation … Bridges (PSC)
Oct 2018: XSEDE booster allocation … Wrangler (TACC)
Jan 2019: XSEDE booster allocation … Stampede2 (TACC)

HPC booster resources are used to run glideins which add the HPC cores to the OSG condor pool. The software effort to add a booster resource is minimal. A primary objective is to avoid competing with other HPC users' jobs, i.e. to use backfill and other unused cycles.

- Each glidein is queued with minimal priority, i.e. –nice=10000 .
- No more than 1 non-running glidein is maintained in the queue.
- Glidein run time is limited to 2 hours

Each OSG job requires download of 20-100 Mbytes of data. ≈3000 jobs use the same data. Local shared storage on the HPC machines is used to minimize the number of downloads. Many jobs using the same data use a 2-tier token system to fetch and share a single copy.

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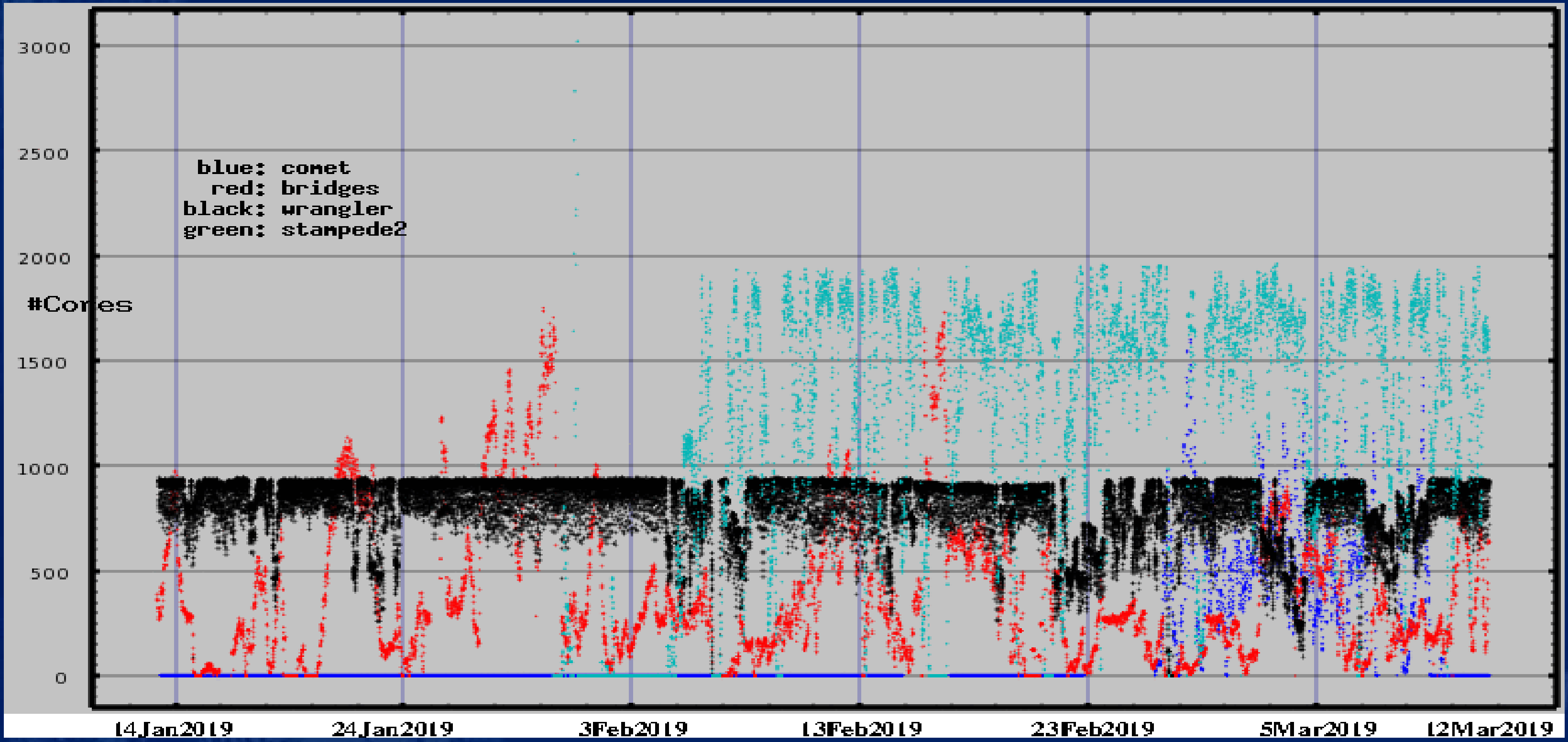
Jul 2015: XSEDE booster allocation … Comet (SDSC) ---- blue
Aug 2016: XSEDE booster allocation … Bridges (PSC) ---- red
Oct 2018: XSEDE booster allocation … Wrangler (TACC) ---- black
Jan 2019: XSEDE booster allocation … Stampede2 (TACC) ---- green

The panel shows the number of cores awarded on the 4 HPC machines from January 14 to March 12. More than 70% of our OSG jobs are run on dedicated HPC glideins.



Display Current OSG Usage

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The University of Cambridge (UK) normative lifespan data set.

Nov 2016 – Jan 2018: Baseline CamCAN recordings acquired and processed, *n* = 621, ages 18-87. Aug 2017: TEAM-TBI recordings end.
Apr 2018: CamCAN tractography MRI's acquired and processed.
May 2018: Normative atlas paper posted to arXiv and submitted for peer review (https://arxiv.org/abs/1805.01552)
Oct 2018 – Nov 2018: Follow-up CamCAN resting data acquired and processed, *n* = 255, *mean* time between studies = 16 months.
Jan 2018 – Oct 2019: Follow-up CamCAN task data acquired and processing … , *n* = 255.

This large lifespan normative dataset enables a search for diagnostics, i.e. measures with both (a) good repeat reliability and (b) sensitivity to pathology.

(a) Measures at baseline and at follow-up must be nearly the same.
(b) Measures must distinguish between those with and without symptoms, CamCAN vs TEAM-TBI.

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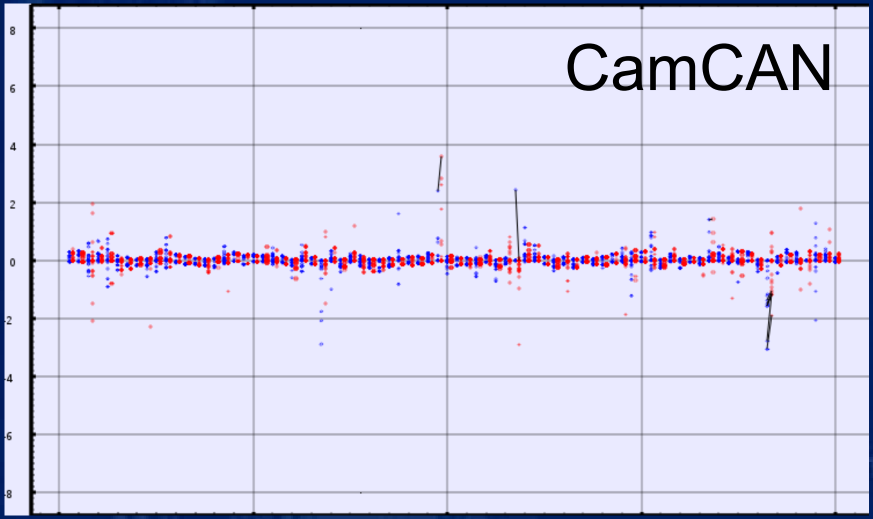
Our measures of activity in the white matter tracts fit the criteria for diagnostics. 5 of 39 TEAM-TBI participants (right panel) show stable measures which are significantly below the CamCAN norms (left panel). Everyone in the TEAM-TBI cohort has a normal anatomic MRI scan. Hence these findings represent diagnostics for likely white matter injuries which were previously undetectable.



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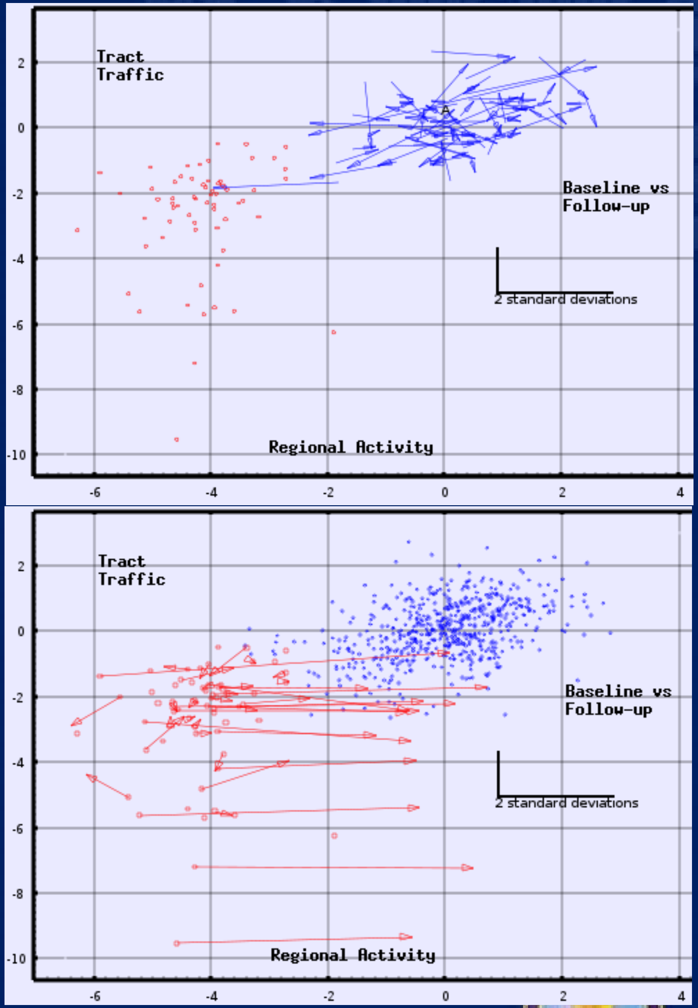
Two measures which are linear composites of neuroelectric activity (1) in the white matter tracts (y-axis) and (2) in cortical regions (x-axis) fit the criteria for diagnostics.

Both measures enable classification to the correct cohort with better than 90% accuracy. Both measures repeat well for the CamCAN group (blue) from baseline (arrow base) to follow-up (arrow head).

12 of the 39 TEAM-TBI participants (red) moved significantly towards the norm at 6-month follow-up. The group of 6 shows significant improvement in their symptoms, p = 0.02.



Summary

We are using a fundamentally new method of deconvolution which enables characterization of brain function with far greater detail than previously available.

We utilize XSEDE-supplied HPC resources with nearly nil startup and maintenance effort to boost the condor pool to which we have access through the OSG. We do not compete for the HPC resources. Rather we run in a manner which opportunistically utilizes cycles which would otherwise go unused. Our solver runs efficiently at scale regardless of system throughput up to 35,000 simultaneously executing jobs.

Summary

We have processed several large high value human datasets. Processing the normative dataset has enabled generation of atlases of normative neuroelectric brain function. That effort required 16 months. Running on the OSG at large without the booster allocations on bridges, comet, wrangler, it would have taken 5 years. All of these computing resources have been and will continue to be essential to this work.

The atlases represent seminal contributions to the field as they provide, for the first time, normative measures of brain function. They also provide target functional patterns which may be used to guide and monitor treatments for symptoms of mental or emotional distress by drug and other therapies.