SESSION 4: CLINICAL DECISION SUPPORT, FROM DATA TO IMPACT

MULTIMODAL ELECTROPHYSIOLOGICAL BIOMARKERS

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Disclosure

- I am the Chief Scientific Officer of BrainScope and an inventor on intellectual property licensed by BrainScope from NYU School of Medicine
- This presentation reports results of independent prospective FDA Validation Studies, to which BSC was blinded. The Validation Studies were part of DoD funded research contracts (U.S. Army contract W81XWH-14-C-1405; U.S. Navy, contract #W911QY-14-C-0098)
- The views, opinions and/or findings contained in this presentation are those of the authors and should not be construed as a position, policy or decision of the funding sources

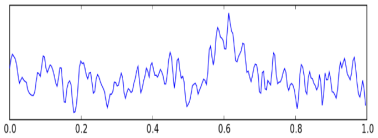
Overview

This presentation will include:

- Introduction to aspects of qEEG making it uniquely suited to reflect brain injuries seen in mTBI and concussion
- Independent validation results of FDA-cleared EEG-based multimodal concussion biomarker and its use in aiding diagnosis and evaluating change over time
- The potential importance of subtyping concussion
- Use of such biomarkers for quantitative tracking of recovery

qEEG Assessment Today: Beyond Conventional EEG

- **Quantitative EEG (qEEG)** processes the EEG waveforms to allow characterization of the signal into features that can be used to describe brain activity and changes with TBI not visible by visual inspection



Many factors contribute to the successful application of qEEG for the derivation of ML/AI biomarkers for the assessment of changes in brain activity that occur with TBI and concussion

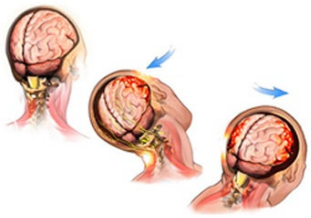
Technology
- EEG acquired on a handheld device and processed in real time

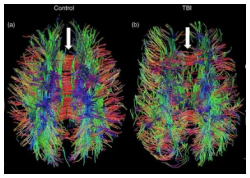
Signal Processing
- Advances in signal processing have enriched measures derived from the EEG

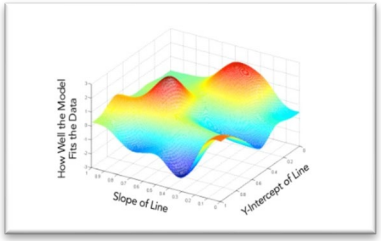
Machine Learning
- Sophisticated algorithms for prediction and classification (profile detection)

Features of Brain Electrical Activity (EEG) Change in TBI

- EEG is uniquely sensitive (millisecond time base) to brain changes associated with traumatic structural (intracranial bleeds) and functional brain injury (concussion), including importantly changes in:



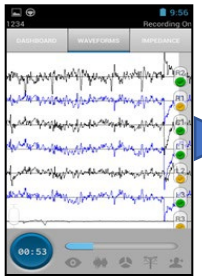




- **Connectivity:** reflecting disruption in neuronal transmission between brain regions (coherence, phase synchrony, phase lag, etc.)
- **Complexity:** reflecting disorganization of the neural networks (fractal dimension, entropy, scale-free)
- **Frequency distribution:** reflecting changes in neurochemistry, oxygen flow and glucose metabolism and presence of edema (shifts in power spectra)

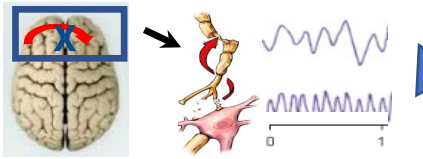
➢ Using AI/Machine Learning with qEEG features as inputs, **distinct profiles** of abnormalities are identified that optimally separate the groups of interest or predict outcome

How do we get from EEG to classification?



ARTIFACT

qEEG Features Extracted



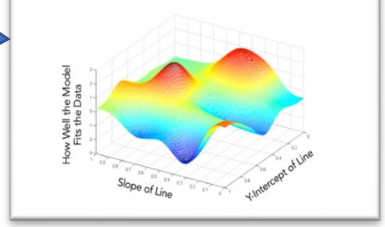
"CONNECTIVITY" "FREQUENCY"

Z SCORES

EEG Data Reduction 10000>2000>200

+Multimodal Features

Machine Learning - Classification



EQUATION

Data Acquisition and real-time artifact Detection and Removal

Quantitative Feature Extraction (10,000)

Transform for Gaussianity and Age regression → convert to Z-scores

Informed Feature Reduction:

[1] Initial Level e.g., replicability

[2] 2nd Level – e.g., Separability

Machine Learning Classifier Construction (GA, LASSO, SVM, RF)

Discriminant Function:

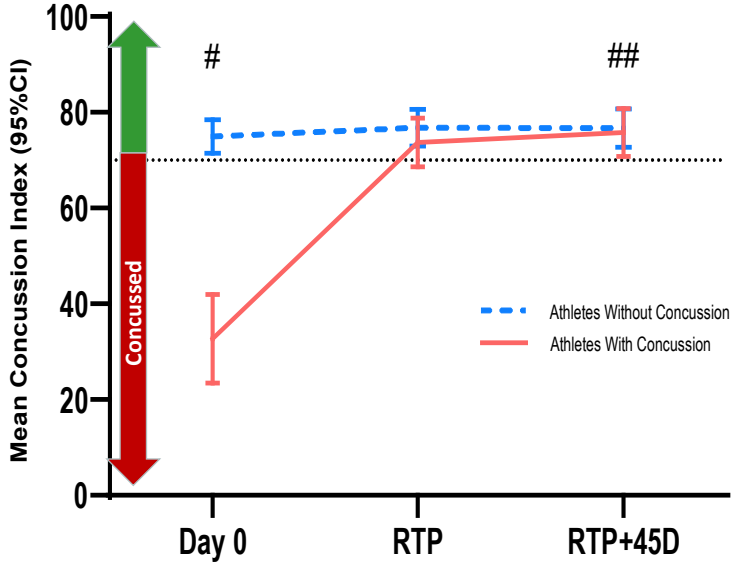
FINAL weighted combination of features for optimal separation

Using the same EEG data, three different algorithms were derived and FDA Cleared, one for the likelihood of structural brain injury (likely CT+) and two for the likelihood of functional brain impairment and concussion

The Focus of this presentation will be CONCUSSION

Validation of CI: Bazarian et al., *JAMA Network*, 2021

The Concussion Index (CI) is a multimodal ML/AI derived classifier function based on qEEG features ("connectivity") and includes multimodal inputs (vestibular and PRT)



- This data supported BrainScope's FDA clearance of the CI

- N= 580 (1577 evaluations) at 10 clinical sites
- **Controls:** Stable over time ($p<0.0001$), allowing changes to be reliably interpreted
- **Concussed:** CI at time of injury (Day0) is significantly lower than CI at RTP (# $p<0.0001$)
- **RTP:** Concussed returned to CI levels of Controls (80% within normal range); with no significant differences between groups at **RTP+45** days (##)
- **Time of injury** (not shown)**:** Concussed with **rapid RTP** (<14 Days) have a higher CI than those with **prolonged RTP** (≥ 14 Days), reflecting severity – **potential to predict rate of recovery**
- **At Day5** (not shown)**:** Those with rapid RTP have higher CI than those with prolonged RTP. **Suggesting that change in CI is tracking recovery**

Bazarian JJ, et al. *JAMA Network Open*. 2021;4(2):e2037349. doi:10.1001/jamanetworkopen.2020.37349
Jacquin A, et al. *J Concussion*. 2021;5:1-12. doi.org/10.1177/20597002211004333

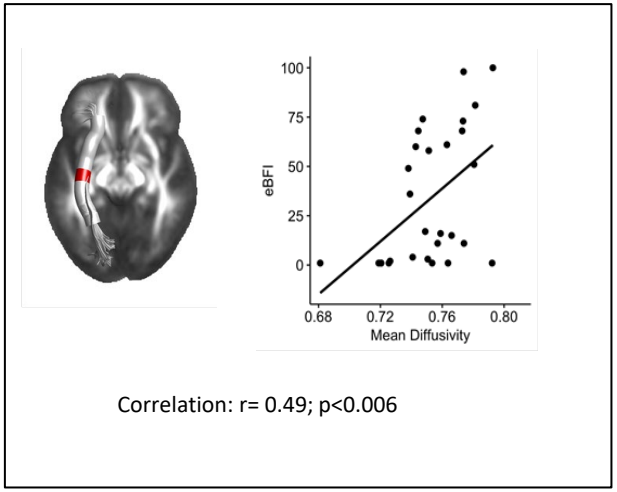
DTI White Matter Injuries Correlate with CI in Sports Related Concussion

Wilde et al., J Neurotrauma, 2018:

Results demonstrated:

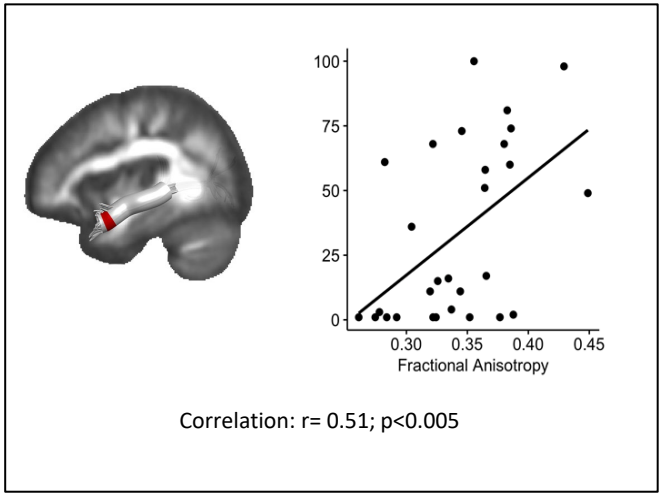
- Significant correlations between CI and DTI measures in the same concussed patients
- As DTI measures get more abnormal, CI is lower (more abnormal)
- **Suggest that changes in white matter integrity are reflected in CI**

Significance of the correlation between CI and Mean Diffusivity in the Left Inferior Fronto-Occipital Fasciculus (IFOF)



Correlation: r= 0.49; p<0.006

Significance of the correlation between CI and FA in the Left Inferior Longitudinal Fasciculus (ILF)

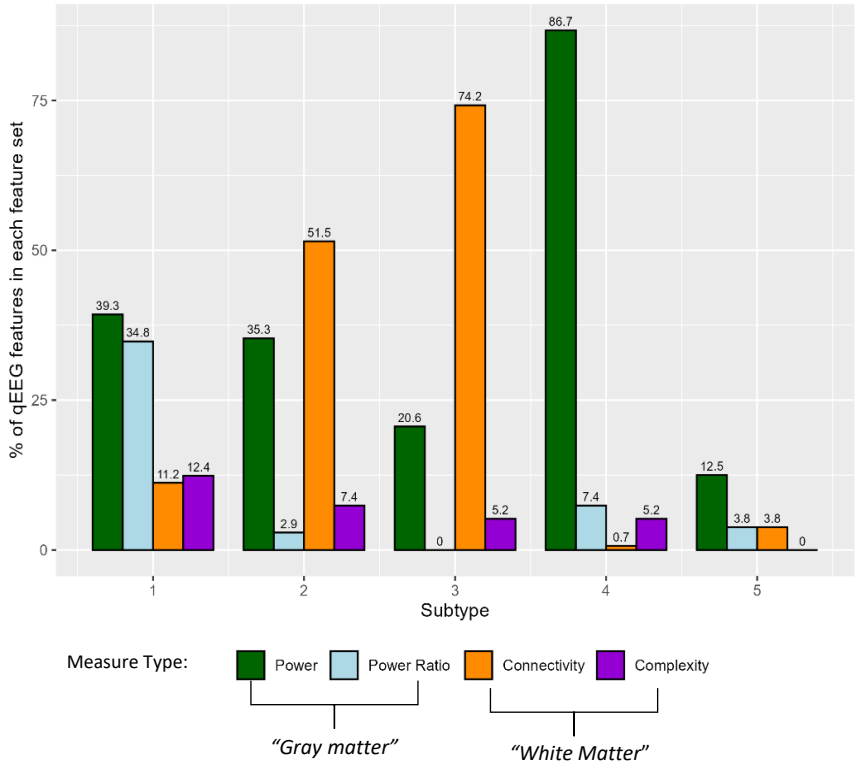


Correlation: r= 0.51; p<0.005

* eBFI name used in development of the CI

Heterogenity of Concussion: EEG-Based Phenotypes

- Using AI/ML approach the existence of **EEG-based phenotypes of concussion were demonstrated** for the first time



- Subtypes defined by different patterns of EEG feature abnormalities, reflecting different underlying pathophysiology (total n=771)
- Subtype membership was predictive of different outcome (days to RTA) and associated with different clinical features
- Potential to advance understanding of the underlying pathophysiology of concussion
- Can drive toward more **personalized** diagnosis, treatment recommendations and **improved outcomes**

Armañanzas et al., *JAMA Network*, 2024.

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Changes in EEG Complexity following Subconcussive Blast Exposure

Complexity of the EEG signal: reflects disorganization of the neural networks and has been shown to be related to cognitive and executive function (higher number=better). Each spoke represents complexity in different brain regions (all involving the DLPFC)

- Clear **decreases in complexity** were seen **6Hrs** ($p<0.000001$)and **24Hrs** ($p<0.006$) following blast exposure (lowest levels),
- Return to Pre-Blast baseline seen at **2wks**
- Trainee Controls show consistent responses (within a narrow range with no significances) for all sessions at the high level of complexity
- Mean age at Baseline of the Blast-Exposed group is 45.3 yrs

- First step in the development of an EEG-based biomarker for evaluation of subconcussive blast exposure
- Will be integration of other modalities collected as part of the INVICTA study

* Funded by DoD Award HU00012220025

CONCLUSIONS

- qEEG features can reflect changes in neuronal transmission, integrity of neural networks and neurochemistry (edema, etc)
- Patterns of qEEG features (biomarkers) have been identified using AI/ML models in populations of mTBI/concussed patients
- The Concussion Index (CI) was FDA cleared for indicating the likelihood of concussive brain injury. Further, stability over time in non-injured allows reliable interpretation of change over time
- Such EEG-based biomarkers can serve as decision support tools and aid in:
    - Initial diagnosis
    - Prediction of rate of recovery
    - Quantitative tracking of change over time
- The power of integrating different biomarkers remains to be explored
- Use of qEEG in identifying phenotypes (subtypes) may lead the to faster, more personalized treatment planning and potentially better outcomes

NOTE: Using the same approach several publications describe the use of FDA cleared EEG-based biomarkers for triage of GCS 13-15 closed head injured patients in the ED, with high sensitivity (99% to ≥1cc blood), with 100% NPV reported in clinical practice, with significant reductions in LOS (Hanley et al., 2018, Miller et al., 2022)

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