Advanced Neuroimaging in Concussion: A Translational Collaboration Opportunity

DAVID BARON, MSED, DO, DFACN
PROF. AND VP WESTERN UNIV OF HEALTH SCIENCES
CO-DIRECTOR, ENIGMA SPORTS CONCUSSION NEUROIMAGING GROUP, USC

EMILY DENNIS, PHD ENIGMA

INGA KOERTE, MD, PHD BWH HARVARD SCHOOL OF MEDICINE
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  • CDC Safety in Youth Sports, concussion group
  • Co-director, ENIGMA Sports Concussion Section
  • NCAA/ PAC 12 concussion research review panel
LEARNING OBJECTIVES:
AT THE CONCLUSION OF THIS PRESENTATION THE LEARNER WILL BE ABLE TO:

• Compare and contrast TBI and Concussion
• Discuss the role of biomarkers, specifically neuroimaging in concussion assessment and management
• List the challenges and opportunities for future research and collaboration in concussion neuroimaging
TBI VS CONCUSSION

• Kissing cousins, not identical twins
• Baron *Sunburn Analogy*
• Sensitization kindling model
  • Post et al
• Different role of neuroimaging
  • White matter vs grey matter impact
Introduction

- While all are vulnerable, certain groups have higher risk
  - Infants, children, adolescents
  - Athletes
  - Military service members

Source: CDC Website
ROLE OF BIOMARKERS

• Despite ongoing research in imaging and proteomics
  • GFAP, NFL, SB100, UCH-L1 (and others)
  • DTI, NIS
  • Balance
  • Eye-tracking

• No approved, FDA endorsed Biomarkers for Concussion
Diffusion MRI

- Multiple measures of white matter organization can be calculated from dMRI:
  - MD – mean diffusivity
  - RD – radial diffusivity
  - AD – axial diffusivity

- FA – fractional anisotropy, most commonly used measure of white matter organization
Tractography
Task fMRI

- Measures blood oxygen level dependent (BOLD) signal
  - Ratio of oxygenated to deoxygenated blood
  - Increases in brain activity are met with increased oxygenated blood

[Graph of BOLD response]

Brandt et al., 2013
MR Spectroscopy

- Spectra give levels of various neuro-metabolites
  - NAA (N-acetylaspartate) = marker of neuronal health
  - Choline = marker of gliosis, cellular turnover, inflammation
  - Creatine = indicator of cellular dysfunction
  - ml (myoinositol) = inflammation
  - Glx = involved in neuronal death
  - Lactate = anaerobic metabolism, can indicate diffuse axonal injury

- Most studies single voxel, but whole brain approaches possible
MR Spectroscopy in brain injury

- **Pediatric TBI**
  - Lower $N$-acetylaspartate (NAA) – poor neuronal health
  - Higher choline – inflammation or gliosis/cellular turnover
  - Presence of lactate or elevated myoinositol (ml) an indicator of poor outcome

- **Sports concussion**
  - Increased glutamate post-season -> cellular injury

- **Military brain injury**
  - Few studies in military
  - Initial decrease in NAA, recovers over time
  - Changes in glutamate or ml more long lasting
dMRI + MRS

- Magnetic Resonance Spectroscopy (MRS)
  - Spectrum of metabolites
    - NAA – $N$-acetylaspartate, marker of neuronal health
    - Choline – inflammatory marker, gliosis, cellular turnover
- Many papers use single-voxel approach
  - We use novel whole brain MRS sequence
- Combined dMRI and MRS
  - dMRI models WM organization, cannot separate causes of disruption
  - Improved ability to detect and interpret regions of WM disruption following TBI

Ashwal et al., 2006
Predicting cognitive outcome

- How does information from MRS improve our ability to predict cognitive outcome?
- Partial $F$ test comparing models:
  - Reduced: Time 2 Cognitive $\sim$ age + sex + T1 cog + IHTT + dMRL
  - Full: Time 2 Cognitive $\sim$ age + sex + T1 cog + IHTT + dMRL + MRS

This image is showing for which tracts the addition of MRS improved prediction of cognitive performance. Figure showing sig. $F$-stat.
NEED FOR LARGE INTERPROFESSIONAL COLLABORATIONS

• Puzzle with many pieces
  • Need for translational approach- *Molecules to Mainstreet*
    • *Basic neuroscience/neuroimaging/neurogenetics*
    • *Clinical perspective*
    • *Public health/public policy*
  • Osteopathic approach
EXAMPLE OF COLLABORATION

• ENIGMA
• NHSCA-ISSP
• NCAA-IOC-FIFA
ENIGMA

- Started in 2009 – increased power for GWAS with brain measures
  - Brain measures as intermediate phenotype between genetics and psychiatric and neurological disorders
- 28+ working groups dedicated to psychiatric, neurological, and developmental disorders
  - Working groups dedicated to methods as well
ENIGMA Brain Injury

- Working group PIs: Emily Dennis (USC), David Tate (UMSL), Elisabeth Wilde (Utah)
- 38 groups across 9 countries so far
- ENIGMA Military Brain Injury
  - David Tate (UMSL) & Elisabeth Wilde (Utah)
- ENIGMA Pediatric msTBI
  - Emily Dennis (USC), Karen Caeyenberghs (ACU), Elisabeth Wilde (Utah)
- ENIGMA Sports Concussion
  - David Baron (USC) & Inga Koerte (Harvard and LMU)
- ENIGMA Adult msTBI
  - Alexander Olsen (NTNU) & Frank Hillary (Penn State)
- ENIGMA ED Civilian mTBI
  - Pratik Mukherjee (UCSF) & Andrew Mayer (UNM)
- ENIGMA Intimate Partner Violence
  - Carrie Esopenko (Rutgers)
ENIGMA Sports

- 3 sites
  - Total: n=54 Repetitive Head Impacts (RHI); n=13 Controls
- Diffusion MRI
- Results in RHI compared to controls
  - Lower FA in fronto-occipital fasciculus and borderline lower FA in the tapetum.
  - Borderline higher MD in the posterior thalamic radiation and tapetum
  - Higher RD in the tapetum, borderline higher RD in the superior fronto-occipital fasciculus
  - Higher AD in RHI in the corona radiata.
Are you interested in how sports concussions affect the brain? Do you have MRI brain scans of individuals who have been injured? Consider joining the ENIGMA SPORTS CONCUSSION GROUP, a division of ENIGMA Brain Injury.

This group aims to identify imaging biomarkers of sports concussion. Such biomarkers have been elusive due to the heterogeneity of injury and the subtlety of concussion. Combining data across sites will give us greater power to probe these relationships. With data from thousands of subjects, we will be able to better understand the injury and recovery processes. ENIGMA Sports Concussion will include all ages and levels of play.

ENIGMA Brain Injury leadership

Using ENIGMA's successful model, you do not need to send us your data. We can send you simple protocols to run on your MRI data, and you can send us back just the anonymized statistics, facilitating an easy 'data sharing' without actually sharing raw data! We perform quality assurance on all scans received and run a meta-analysis on the statistics.

If you would like to contribute to ENIGMA Sports concussion or have questions, please contact David Baron at dave.baron@med.usc.edu, Inga Koerte at ikoerte@bwh.harvard.edu or Emily Dennis at emily.dennis@ini.usc.edu.

Visit enigma.usc.edu for further information.
Discussion

- MOU
- Harmonizing outcome scales
- Secondary proposals
- Grant possibilities
- Workflows for new modalities
Harmonizing outcome scales

- Common test data across cohorts
- Common domains; use or create standard scores to compare
  - Working memory
  - Memory
  - Processing speed
  - Executive function
- Set impairment threshold, use categorical grouping
- Other approaches?
CHALLENGES/ OPPORTUNITIES

• *Speak the same language*
  • Defend the clinical phenotype
• Stay focused on the *Science*, not the politics/economics
• View this as PH issue, as well as pt. issue
• Prospective, longitudinal trials
  • Consider confounding B-P-S factors Type 1 and 2 error
• Emerging science
REFERENCES: 2017 AND NEWER


Thank you for your time and attention!!

Enjoy OMED
REFERENCES-CONT.


