BIOMARKERS IN TBI AND ABI: PRESENT, FUTURE, AND GOING NOWHERE

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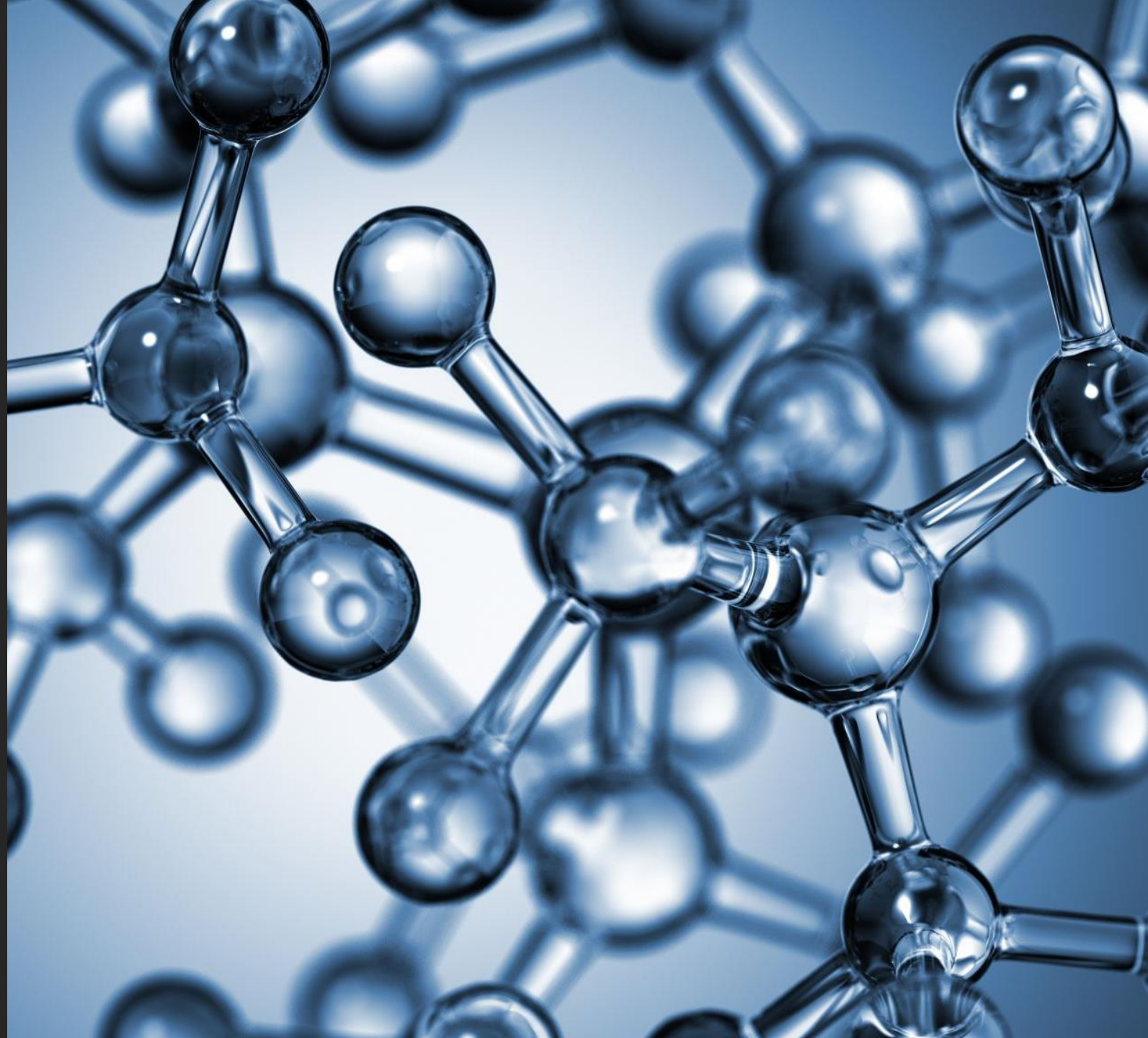


Disclosures:

- No ties to drug companies, labs, or medical equipment companies
- Studies being conducted by author at present are in area of Neuromoduation as an intervention in Autism, and Photobiomodulation as an intervention in TBI and ABI, not specifically in reliability of biomarkers for these conditions
- Author of presentation is primarily a clinician in practice (70%), not researcher (30%)

Lab assays:

1. **MEG3 and Interluekin:** Drops in MEG3 and rise in interleukin-1β (IL-1β), IL-6, and IL-8 correlate with poor prognosis in TBI. Thought to be specific to TBI, but research will tell… (Shao et al, May 2019, Eur Rev Med Pharmacol Sci). High likelihood for good use in future. Relatively easy to order.
2. **S100β:** calcium binding protein found in astrocytes, responsible for regulating intracellular levels of calcium; not brain specific, thus it shows up in injury not involving TBI. Must be considered along with trauma history. Also, must be taken an hour after concussion. Problem: Hard to obtain because of time limit. – probably going nowhere

(Linda Papa, MD, MSc., Sports Med Arthrosc. 2016 Sep; 24(3): 108–115)

3. **Glial Fibrillary Acid Protein (GFAP)**: Glial Fibrillary Acidic Protein (GFAP) is a promising, brain-specific glial-derived biomarker for MTBI in adults and children. GFAP is released in highly increased amounts into blood serum within an hour of an mTBI injury, and can remain elevated for several days after injury. More feasible, given extended detectability.

Papa L, Mittal MK, Ramirez J, et al.; . J Neurotrauma. 2016; 33:58–64; Papa L, Zonfrillo MR, Ramirez J, et al.; Acad Emerg Med. 2015; 22:1274–82

4. **Alpha-II Spectrin Breakdown Products**

Alpha-II-spectrin (280 kDa); a major structural component of the cortical membrane cytoskeleton, is particularly abundant in axons and presynaptic terminals. Apoptosis (pruning of dying neurons) and necrosis (death of neurons) is an early cleavage of several cellular proteins by activated caspases and calpains., caused by cleavage of common proteins (e.g. cytoskeletal αII-spectrin). Reliable after *severe* TBI, with significant relationship between severity of injury, SBDP's, and clinical outcome. Thought to be a warning of CTE process on its way. SBDP's can be meaningful even months after injury, BUT: only reliable in SEVERE TBI.

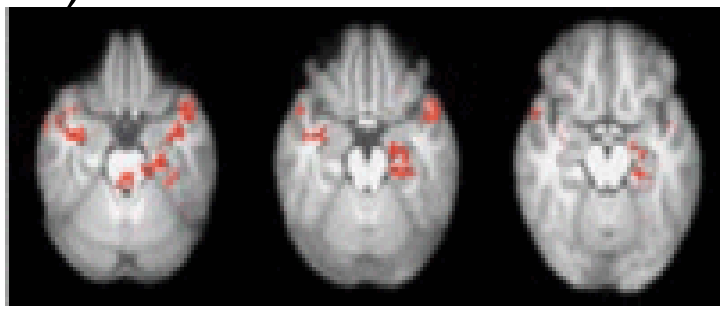
5. Tau Protein

Axons are the most vulnerable cortical structures to TBI damage. Tau protein is highly enriched in axons, and could thus be an interesting biomarker, since cumulative brain damage sustained in a severe single, or in repetitive concussions, can provoke the development of a tauopathy (marked accumulation of tau-immunoreactive astrocytes) and chronic traumatic encephalopathy (CTE). It is a reliable early marker: it can be observed in boxers even without amnestic or clinical symptoms of concussion or traumatic brain injury. Tau deposits are also found in the brains of Alzheimer's patients, but with different distribution. Systematic review shows Tau to be elevated even after break from sports of over 2 months. Problems: unreliable in mTBI, and hard to interpret, even in severe or repetitive TBI. (Papa L, Ramia MM, Edwards D, Johnson BD, Slobounov SM; Neurotrauma. 2015;32:661–73; Gatson JW, Barillas J, Hynan LS, Diaz-Arrastia R, Wolf SE, Minei JP; J Neurosurg. 2014;121:1232–8)

- Specific to severe TBI
- Easy to collect (spinal tap), but…
- Not practical in ER setting, because of the refinement needed in interpretation.

The same benefits, and concerns, apply to **Neurofilaments** (NFL-L).

7. Imagery: DTI (Diffuse Tensor Imaging), PET & fMRI, MRA, MRS Scans:
Promising neuroimaging techniques show potential to become sensitive and specific to TBI of various severity levels, including: functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET).



Problems: much research is still needed to establish parameters of imagery that can reliably be used diagnostically; these are expensive procedures, not usually available in ER or ICU as of now.

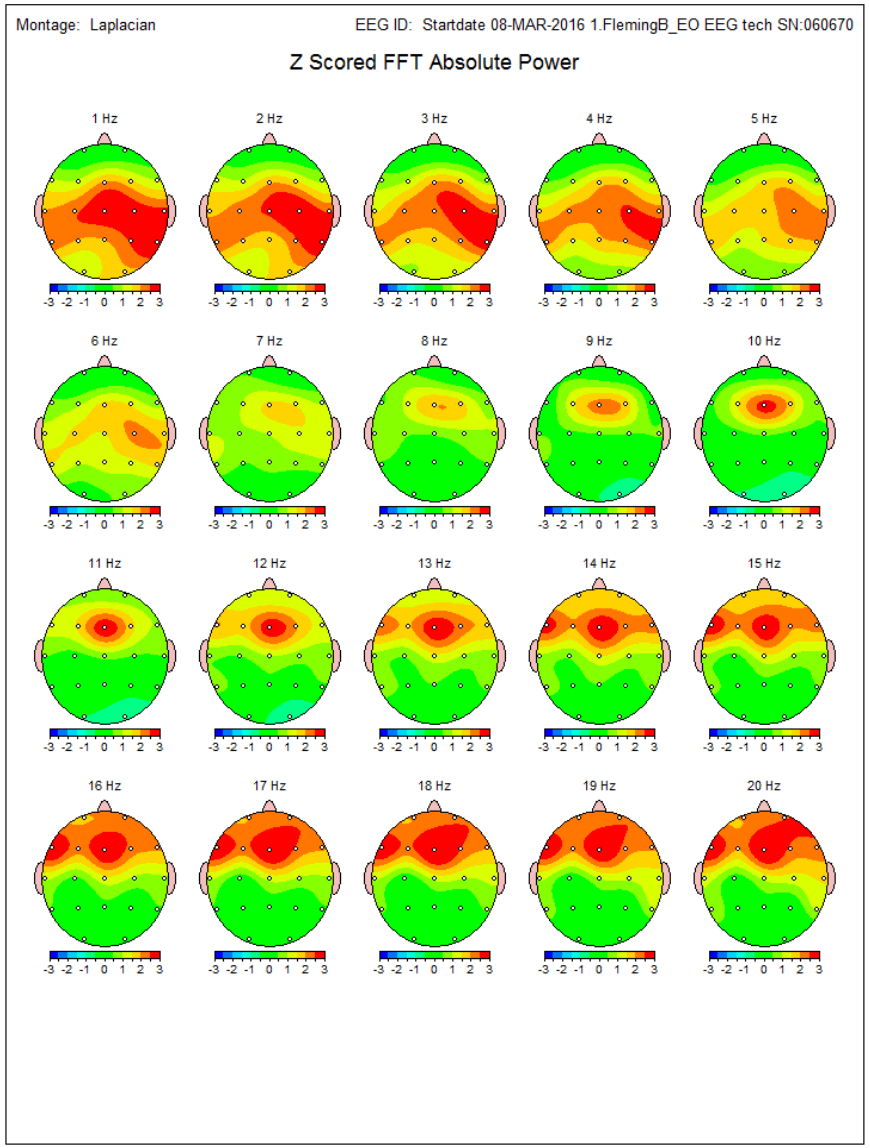
(Dashnaw ML, Petraglia AL, Bailes JE. An overview of the basic science of concussion and subconcussion: where we are and where we are going. Neurosurg Focus. 2012;33:E5, 1–9)

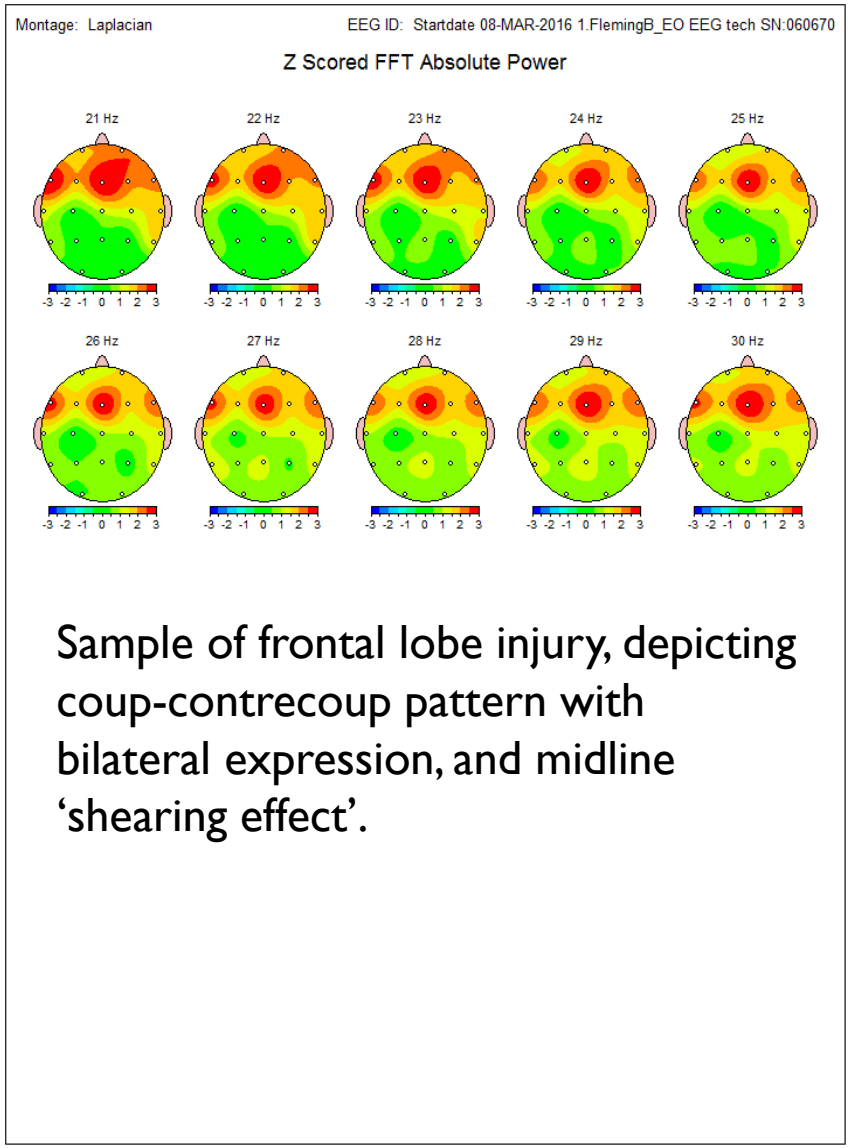
Barrio JR, Small GW, Wong KP, et al.; Proc Natl Acad Sci U S A. 2015;112:E2039–47

8. **qEEG: Quantitative EEG Analysis**: Digitization of the EEG recording, to be compared against peer-normalized brain activity. Where excess beta activity indicates inflammation and neuron excitotoxicity, deviances above the mean indicate signs of injury. This is true of TBI, or any form of ABI, in accord with writings of John Olney (Olney JW: Excitatory amino acids and neuropsychiatric disorders. Biol Psychiatry 1989; 26:505-525.

- Highly sensitive to changes in brain function
- Not specific unless combined with clinical picture (correlation of deviant sites with nature of accident)
- Inexpensive procedure; EEG is usually readily available in most hospitals

Problems: Clinics performing the digital analysis are not widespread; without baseline of patient in premorbid state, it is difficult to attribute deviances to TBI with certainty.





Sample of frontal lobe injury, depicting coup-contrecoup pattern with bilateral expression, and midline ‘shearing effect’.