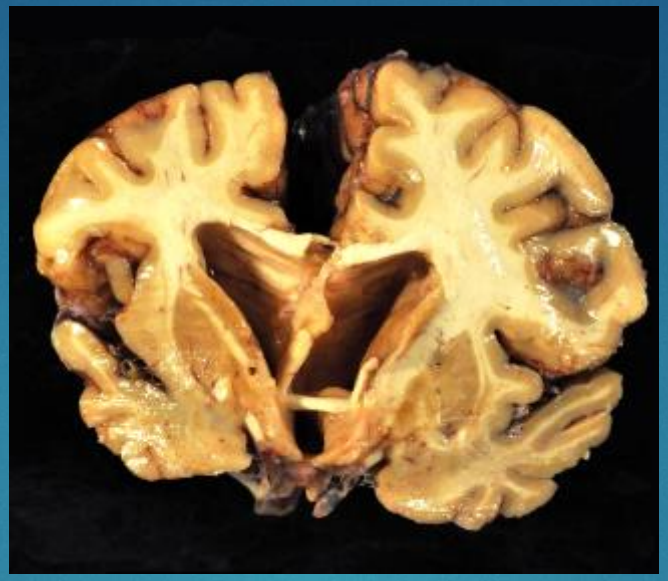

CTE: What's New?

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PEDIATRIC AND ADULT NEUROLOGY

UCNS BOARD CERTIFIED HEADACHE AND NEURO

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DENT
CONCUSSION CENTER
A Comprehensive Center of Excellence for Brain Injury

Potential Conflicts of Interest

Speaker for: Amgen, Avanir, Depomed, Eli Lilly, Oxtellar, Promius, and Teva Pharmaceuticals.

Grant and research support from Amgen, Avanir, Eli Lilly, Gammacore, Impax, Teva, and Dent Family Foundation.

Pathophysiology of TBI

- Primary Injury:

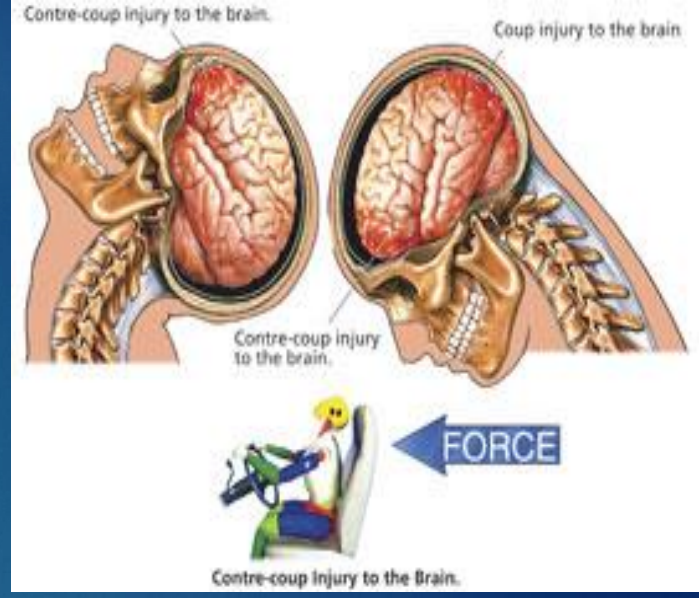
  Direct or indirect mechanical damage

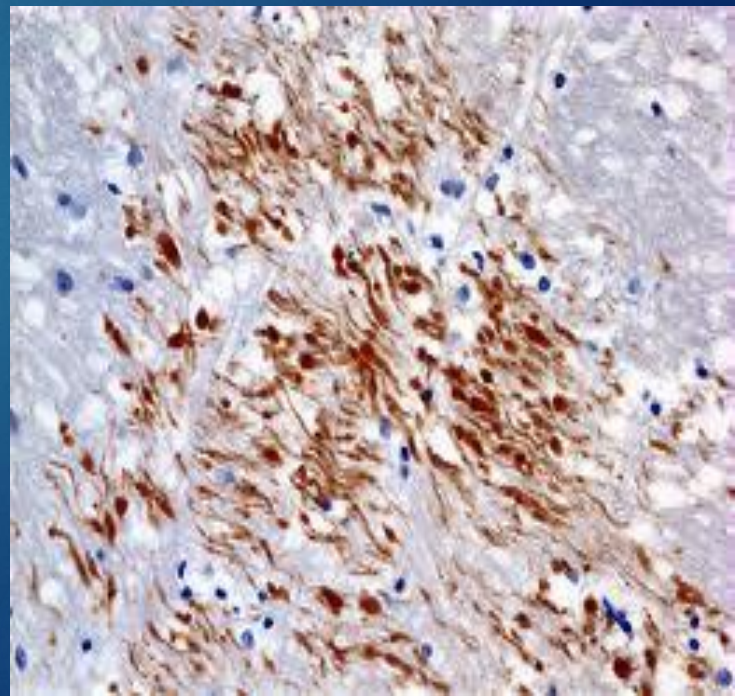
  Mechanical force, diffuse axonal injury (DAI), hematoma, skull fracture

- Secondary Injury:

  Neuronal disturbance

  Metabolic cascade, neuronal cell destruction, decreased cerebral blood flow (excitotoxic/hypoxic), release of ions





Chronic Traumatic Encephalopathy (CTE)

- CTE is thought to be caused by repetitive traumatic brain injuries.
- Aggregation and accumulation of hyperphosphorylated tau and TDP-43.
- This is diagnosed post mortem but newer blood studies are being developed. (not ready)
- There is a bias in the literature as most cases are self or family selected.

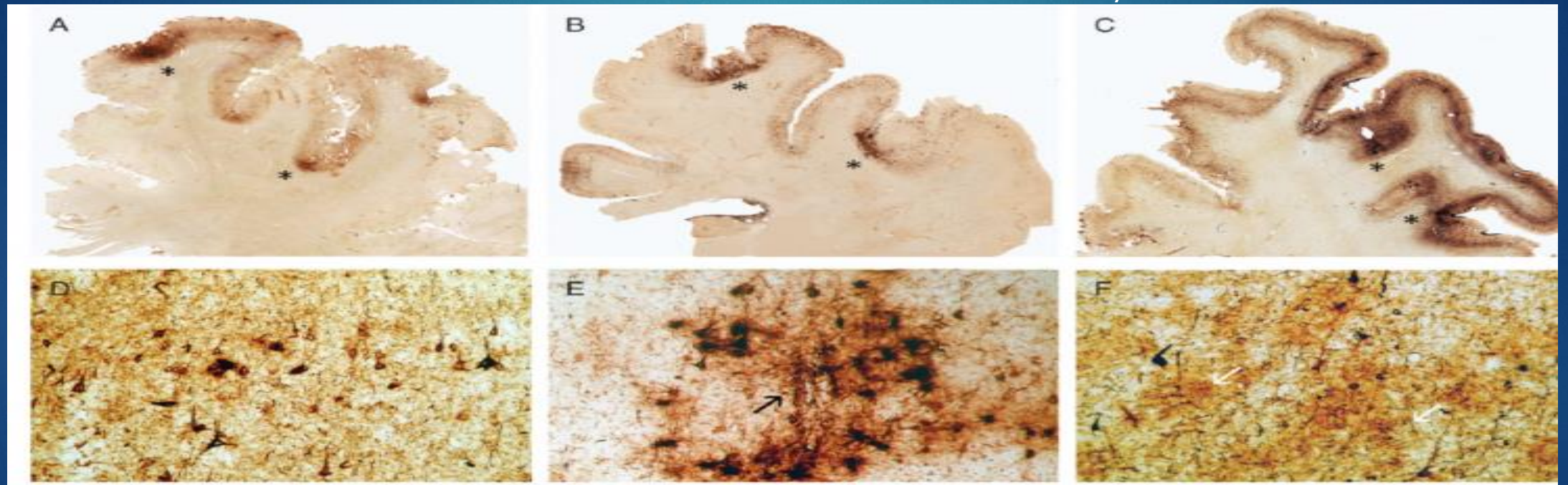
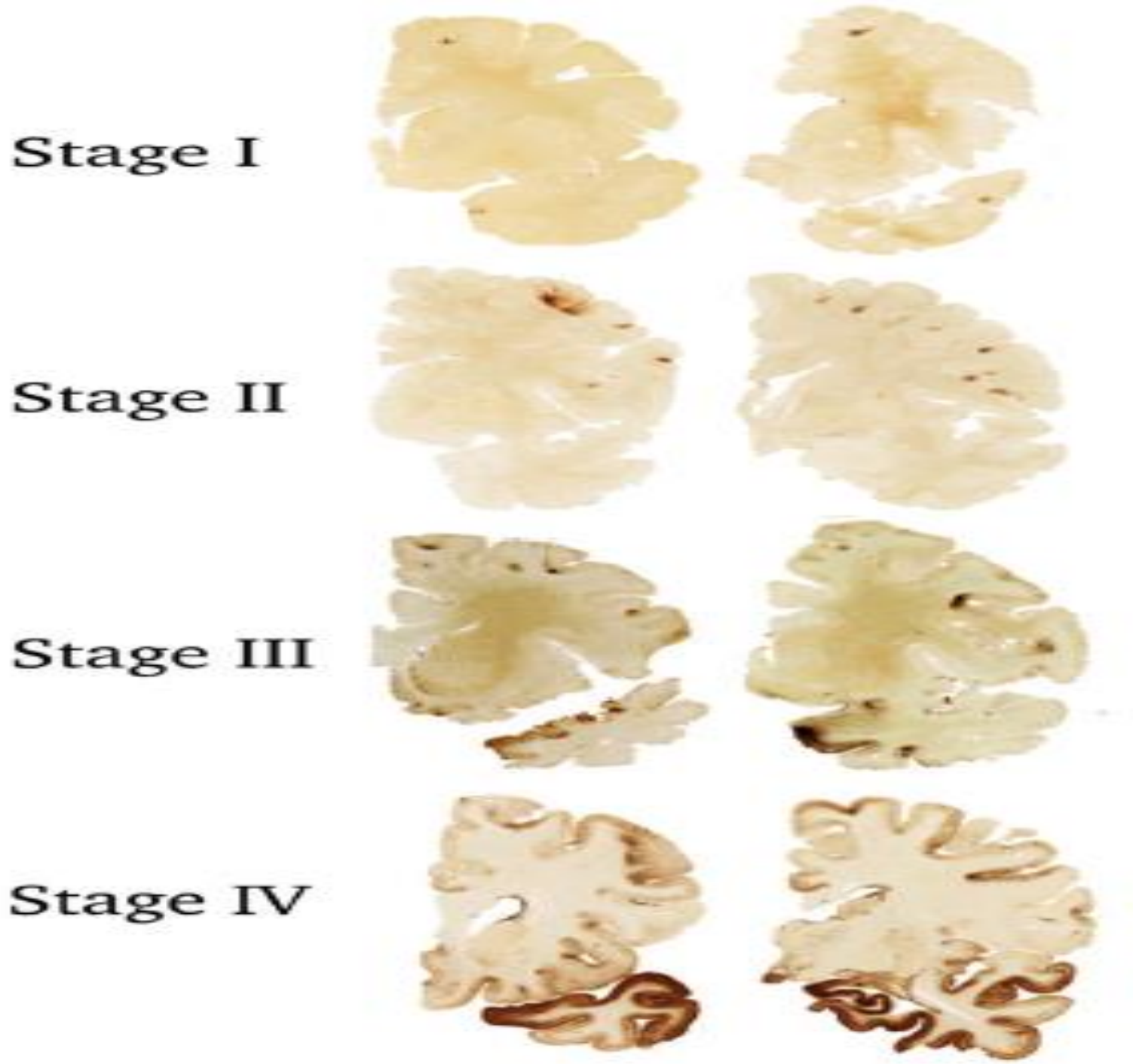


FIGURE 2. (A–C) Whole-mount 50-µm coronal sections of superior frontal cortex from Case A **(A)**, Case B **(B)**, and Case C **(C** immunostained for tau with monoclonal antibody CP-13 showing extensive immunoreactivity that is greatest at sulcal depth (asterisks) and is associated with contraction of the cortical ribbon. **(D–F)** Microscopically, there are dense tau-immunoreactiv neurofibrillary tangles (NFTs) and neuropil neurites throughout the cortex, Case A **(D)**, Case B **(E)**, and Case C **(F)**. There are foca nests of NFTs and astrocytic tangles around small blood vessels **(E**, arrow**)** and plaquelike clusters of tau-immunoreactiv astrocytic processes distributed throughout the cortical layers **(F**, arrows**)**.

From McKee (J Neuropathol Exp Neurol, V 68, July 2009, Fig. 2)

CTE Stages

Avg age at onset 30-50 yrs
Youngest case reported 18 yrs.



A. McKee

CTE

- 202 deceased former football players (47-76 yrs)
- CTE diagnosed in 177
- Non-CTE in 25 (9 WNL and 7 macrophages and axonal injury)

- Mild CTE (stage I and II) range 29-64 yrs. MC cause of death = suicide
- Severe CTE (stage II and IV) range 64-79 yrs. MC cause of death = neurodegeneration

- Phosphorylated tau highest –

  prefrontal cortex, amygdala, locus coeruleus (impulsive, anxiety, explosive)

  hippocampus, entorhinal cortex (episodic memory)

  prefrontal cortex (attention and executive function)

Mez, J, McKee, A, et al Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football. JAMA 2107;318(4):360-370.

< Articles

REVIEW ARTICLE
Front. Neurosci., 24 September 2015 | https://doi.org/10.3389/fnins.2015.00334

Neuroimaging assessment of early and late neurobiological sequelae of traumatic brain injury: implications for CTE

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[3]Duke Institute for Brain Sciences, Duke University Medical Center, Durham, NC, USA

- **Hyperphosphorylated Tau** = neurodegeneration of CTE (McKee et al., 2009; Wang et al., 2013).
- **P-Tau -** less affinity for binding with MTs = abnormal accumulation.
  - induces disassembly of MTs = abnormal accumulation of Tau, causes axonal transport inefficiencies and neurodegeneration (Khlistunova et al., 2006; Zilka et al., 2006; Wang et al., 2013).
- Tau : Progressive Supranuclear Palsy, Pick's disease, Corticobasal degeneration, Frontotemporal dementia, and Alzheimer's disease.

- CTE = topographic distribution of Tau, isoform profile, and phosphorylation state is different (Williams, 2006)
- Paucity of amyloid-Beta (Aβ) in CTE compared to AD (Braak and Braak, 1991).
- There may be inc in Lewy bodies compared to other **disease** states between 22-80%. (McKee et al., 2010, 2013).

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J Neurotrauma. 2015 Nov 15; 32(22): 1768–1776.

PMCID: PMC4651044

doi: 10.1089/neu.2014.3822

Age at First Exposure to Football Is Associated with Altered Corpus Callosum White Matter Microstructure in Former Professional Football Players

Julie M. Stamm,[1,2,3] Inga K. Koerte,[3,4] Marc Muehlmann,[3,4] Ofer Pasternak,[3,15] Alexandra P. Bourlas,[1,5] Christine M. Baugh,[1,6] Michelle Y. Giwerc,[3] Anni Zhu,[3] Michael J. Coleman,[3] Sylvain Bouix,[3] Nathan G. Fritts,[1] Brett M. Martin,[7] Christine Chaisson,[1,5,7,8] Michael D. McClean,[9] Alexander P. Lin,[3,10] Robert C. Cantu,[1,11,12,13] Yorghos Tripodis,[1,5,8] Robert A. Stern,[1,2,5,11,14,*] and Martha E. Shenton[3,15,16,*]

OPEN

Citation: Transl Psychiatry (2017) 7, e1236; doi:10.1038/tp.2017.197

www.nature.com/tp

ORIGINAL ARTICLE

Age of first exposure to American football and long-term neuropsychiatric and cognitive outcomes

ML Alosco[1,2], AB Kasimis[1], JM Stamm[1,3], AS Chua[4], CM Baugh[1,2,5], DH Daneshvar[1], CA Robbins[1,6], M Mariani[1], J Hayden[1], S Conneely[1], R Au[2,7,8,9], A Torres[10,11], MD McClean[12], AC McKee[1,2,13,14,15], RC Cantu[1,2,6,16,17], J Mez[1,2], CJ Nowinski[1,6], BM Martin[1,18], CE Chaisson[1,18], Y Tripodis[1,4,19] and RA Stern[1,2,9,16,19]

Previous research suggests that age of first exposure (AFE) to football before age 12 may have long-term clinical implications; however, this relationship has only been examined in small samples of former professional football players. We examined the association between AFE to football and behavior, mood and cognition in a large cohort of former amateur and professional football players. The sample included 214 former football players without other contact sport history. Participants completed the Brief Test of Adult Cognition by Telephone (BTACT), and self-reported measures of executive function and behavioral regulation (Behavior Rating Inventory of Executive Function-Adult Version Metacognition Index (MI), Behavioral Regulation Index (BRI)), depression (Center for Epidemiologic Studies Depression Scale (CES-D)) and apathy (Apathy Evaluation Scale (AES)). Outcomes were continuous and dichotomized as clinically impaired. AFE was dichotomized into <12 and $\geqslant 12$, and examined continuously. Multivariate mixed-effect regressions controlling for age, education and duration of play showed AFE to football before age 12 corresponded with $>2\times$ increased odds for clinically impaired scores on all measures but BTACT: (odds ratio (OR), 95% confidence interval (CI): BRI, 2.16,1.19–3.91; MI, 2.10,1.17–3.76; CES-D, 3.08,1.65–5.76; AES, 2.39,1.32–4.32). Younger AFE predicted increased odds for clinical impairment on the AES (OR, 95% CI: 0.86, 0.76–0.97) and CES-D (OR, 95% CI: 0.85, 0.74–0.97). There was no interaction between AFE and highest level of play. Younger AFE to football, before age 12 in particular, was associated with increased odds for impairment in self-reported neuropsychiatric and executive function in 214 former American football players. Longitudinal studies will inform youth football policy and safety decisions.

Age of first exposure to football and later-life cognitive impairment in former NFL players

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ABSTRACT

Objective: To determine the relationship between exposure to repeated head impacts through tackle football prior to age 12, during a key period of brain development, and later-life executive function, memory, and estimated verbal IQ.

Methods: Forty-two former National Football League (NFL) players ages 40–69 from the Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) study were matched by age and divided into 2 groups based on their age of first exposure (AFE) to tackle football: AFE <12 and AFE ≥12. Participants completed the Wisconsin Card Sort Test (WCST), Neuropsychological Assessment Battery List Learning test (NAB-LL), and Wide Range Achievement Test, 4th edition (WRAT-4) Reading subtest as part of a larger neuropsychological testing battery.

Results: Former NFL players in the AFE <12 group performed significantly worse than the AFE ≥12 group on all measures of the WCST, NAB-LL, and WRAT-4 Reading tests after controlling for total number of years of football played and age at the time of evaluation, indicating executive dysfunction, memory impairment, and lower estimated verbal IQ.

Conclusions: There is an association between participation in tackle football prior to age 12 and greater later-life cognitive impairment measured using objective neuropsychological tests. These findings suggest that incurring repeated head impacts during a critical neurodevelopmental period may increase the risk of later-life cognitive impairment. If replicated with larger samples and longitudinal designs, these findings may have implications for safety recommendations for youth sports. *Neurology*® 2015;84:1–7

Could PET be the way to predict CTE ?

- **2-(1-(6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl)-ethylidene)malononitrile (FDDNP)** (2002)first PET imaging probe capable of targeting P-Tau. FDDNP was approved for humans (Shoghi-Jadid et al., 2002; Agdeppa et al., 2003).
- **Study :** Aβ/Tau deposition in retired NFL players with cognitive and/or mood symptoms and significant exposure to head trauma.

  - - a small sample size

  -- FDDNP binding greater for former players in subcortical structures matching P-Tau deposition patterns observed in post-mortem examinations of CTE.

  -- FDDNP binding increase with extent of concussion history (Small et al., 2013).

Many other marker – being explored: **^{18}F-THK523**, **^{18}F-THK5105 and ^{18}F-THK5117**, **^{18}F-T807 and ^{18}F-T808**, **^{11}C-PBB3**

Zurich Statement-*Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012*

Neuroimaging of Concussion

TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

Concussion investigations

A range of additional investigations may be utilised to assist in the diagnosis and/or exclusion of injury. Conventional structural neuroimaging is typically normal in concussive injury. Given that caveat, the following suggestions are made: Brain CT (or where available an MR brain scan) contributes little to concussion evaluation but should be employed whenever suspicion of an intracerebral or structural lesion (eg, skull fracture) exists. Examples of such situations may include prolonged disturbance of the conscious state, focal neurological deficit or worsening symptoms.

Other imaging modalities such as fMRI demonstrate activation patterns that correlate with symptom severity and recovery in concussion.[10–14] Although not part of routine assessment at the present time, they nevertheless provide additional insight to pathophysiological mechanisms. Alternative imaging technologies (eg, positron emission tomography, diffusion tensor imaging, magnetic resonance spectroscopy, functional connectivity), while demonstrating some compelling findings, are still at early stages of development and cannot be recommended other than in a research setting.

Published studies, using both sophisticated force plate technology, as well as those using less sophisticated clinical balance tests (eg, Balance Error Scoring System (BESS)), have identified acute postural stability deficits lasting approximately 72 h following sports-related concussion. It appears that postural stability testing provides a useful tool for objectively assessing the motor domain of neurological functioning, and should be considered as a reliable and valid addition to the assessment of athletes suffering from concussion, particularly where the symptoms or signs indicate a balance component.[15–21]

Thank you

Any questions?