2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile (FDDNP) is the first positron emission tomography (PET) molecular imaging probe to visualize Alzheimer's disease (AD) pathology in living humans. The most unique features of FDDNP are that (1) it is the only currently available radiotracer to image neurofibrillary tangles, beside amyloid aggregates, in living humans; and (2) it is also the only radiotracer to visualize AD pathology in the hippocampal region of living humans. Shin et al., discuss FDDNP's unique ability to image tau pathology in living humans. Emphasizing tau pathology imaging capability using FDDNP in AD, as well as other tauopathies, is timely and beneficial considering that (1) post mortem histopathological studies using human specimens have consistently demonstrated that neurofibrillary tangles, compared with amyloid plaques, are better correlated with the disease severity and neuronal death; and (2) recently reported clinical trial failures of disease-modifying drugs in development, based on the amyloid-cascade hypothesis, suggest that some of the basic assumptions of AD causality warrant reassessment and redirection [1)].

Chen et al., has shown that in vivo tau brain binding patterns from FDDNP-PET scans in retired professional football players with suspected chronic traumatic encephalopathy differ from those of tau and amyloid aggregate binding observed in Alzheimer's disease (AD) patients and cognitively-intact controls.

OBJECTIVE: To compare these findings with those from military personnel with histories of mild traumatic brain injury(mTBI).

METHODS: FDDNP-PET brain scans were compared among 7 military personnel and 15 retired players with mTBI histories and cognitive and/or mood symptoms, 24 AD patients, and 28 cognitively-intact controls. Nonparametric ANCOVAs with Tukey-Kramer adjusted post-hoc comparisons were used to test for significant differences in regional FDDNP binding among subject groups.

RESULTS: FDDNP brain binding was higher in military personnel compared to controls in the amygdala, midbrain, medial thalamus, pons, frontal and anterior and posterior cingulate regions ($p < 0.01$-0.0001). Binding patterns in the military personnel were similar to those of the players except for the amygdala and striatum (binding higher in players; $p = 0.02$-0.003). Compared with the AD group, the military personnel showed higher binding in the midbrain ($p = 0.0008$) and pons ($p = 0.002$) and lower binding in the medial temporal, lateral temporal, and parietal regions (all $p = 0.02$).

CONCLUSION: This first study of in vivo tau and amyloid brain signals in military personnel with histories of mTBI shows binding patterns similar to those of retired football players and distinct from the binding patterns in AD and normal aging, suggesting the potential value of FDDNP-PET for early detection and treatment monitoring in varied at-risk populations [2)].

Omalu et al. present a modality that may be instrumental to the definitive diagnosis of CTE in living patients based on brain autopsy confirmation of [F-18]FDDNP PET findings in an American football player with CTE. [F-18]FDDNP-PET imaging was performed 52 mo before the subject's death. Relative distribution volume parametric images and binding values were determined for cortical and subcortical regions of interest. Upon death, the brain was examined to identify the topographic distribution of neurodegenerative changes. Correlation between neuropathology and [F-18]FDDNP-PET binding patterns was performed using Spearman rank-order correlation. Mood, behavioral, motor, and cognitive changes were consistent with chronic traumatic myeloencephalopathy with a 22-yr lifetime risk exposure to American football. There were tau, amyloid, and TDP-43 neuropathological

substrates in the brain with a differential topographically selective distribution. [F-18]FDDNP-PET binding levels correlated with brain tau deposition (rs = 0.59, P = .02), with highest relative distribution volumes in the parasagittal and paraventricular regions of the brain and the brain stem. No correlation with amyloid or TDP-43 deposition was observed. [F-18]FDDNP-PET signals may be consistent with neuropathological patterns of tau deposition in CTE, involving areas that receive the maximal shearing, angular-rotational acceleration-deceleration forces in American football players, consistent with distinctive and differential topographic vulnerability and selectivity of CTE beyond brain cortices, also involving midbrain and limbic areas. Future studies are warranted to determine whether differential and selective [F-18]FDDNP-PET may be useful in establishing a diagnosis of CTE in at-risk patients [3].

1)
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