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TITLE: Early Recognition of Chronic Traumatic Encephalopathy Through FDDNP PET Imaging

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**14. ABSTRACT**

1. The PET biomarker, F-FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl(methyl)amino]-2-naphthyl} ethylidene) malononitrile) [FDDNP] has shown sensitivity for in vivo detection of tau in addition to □-sheet-containing brain amyloid neuroaggregates. Tau protein in a characteristic distribution is felt to be the cardinal pathologic feature of Chronic Traumatic Encephalopathy. This project will examine whether FDDNP PET imaging correlates with, and/or can predict, decline in cognitive function in those exposed to cumulative head trauma. All operational aspects of this study have been accomplished including local IRB approval, identification of potential subjects from the Profesional Fighters Brain Health Study to recruit, logistics of the study visit and PET FDDNP imaging, case report forms, and electronic data entry. Actual enrollment of subjects has been delayed awaiting approval from the Human Research Protection Office.

| 15. SUBJECT TERMS<br>Traumatic Brain Injury<br>Positron Emission Tomography | | | | | | |
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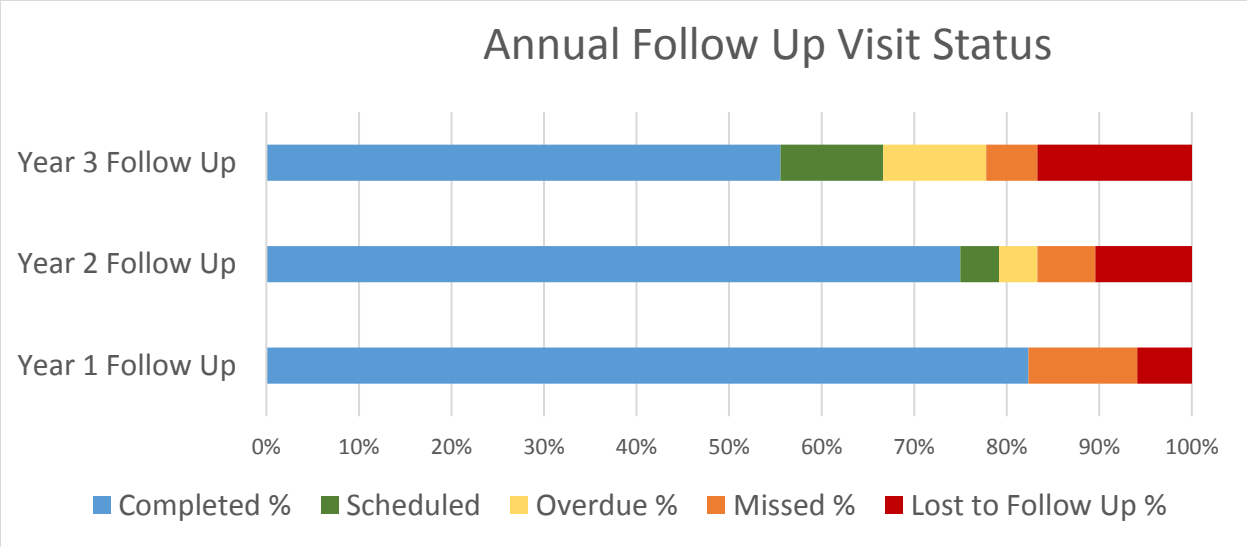
**1. Introduction:** Blast injuries and other head injuries sustained in battle have been associated with the development of chronic traumatic encephalopathy (CTE). Pathological series have indicated that a characteristic feature of CTE is accumulation of tau protein in the brain. Until very recently, there has been no reliable way of measuring tau deposition in the brain during life. One PET biomarker, F-FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl(methyl)amino]-2-naphthyl} ethylidene) malononitrile) [FDDNP] has shown sensitivity for in vivo detection of tau in addition to B-sheet-containing brain amyloid neuroaggregates. This project will examine whether FDDNP PET imaging correlates with, and/or can predict, decline in cognitive function in those exposed to cumulative head trauma.

**2. Keywords:** Traumatic Brain Injury, Chronic Traumatic Encephalopathy, PET imaging, Tau

**3. Accomplishments:**

*Major goals*: Upon receiving approval from the Human Research Protection Office, enrollment of participants began in March, 2015 and was completed in October, 2017, with 68 PET FDDNP studies performed. The goals in 2018 were to 1) track and retain study participants, 2) report baseline results examining the relationship between PET FDDNP regional binding and exposure to head trauma and cognitive performance.

*Major accomplishments*: Each subject is to be followed yearly for 3 years as part of the Professional Fighters Brain Health Study. Retention rate has been as predicted. Because of rolling enrollment over multiple years, follow up visits are staggered. The graph below indicates the number of subjects that have completed follow up visits through 12/22/2018, and the number who are overdue for their follow up. There are only 17% of the cohort who are considered lost to follow up. The projected time for completion of all 3 year follow up visits is 4$^{th}$ quarter, 2020.




Abstracts were presented at the Alzheimer's Disease International Conference ( Chicago, July 2018) and the MHSRS symposium (Kissimmee, August, 2018). We reported on 67 participants in the Professional Fighters Brain Health Study that underwent PET FDDNP imaging and computerized cognitive testing. Those who scored 1.5 standard deviations below age based norms on 2 out of 4 cognitive domains were categorized as cognitively impaired. The distribution volume ratio (DVR) parametric images were generated using cerebellum as reference region and analyzed with the use of regions of interest (ROIs) drawn bilaterally on the co-registered MRI scans for a number of cortical, limbic, and subcortical areas.

The study cohort was composed of 9 impaired active fighters ( mean age 34 years), 12 unimpaired active fighters ( mean 33), 15 impaired retired fighters ( mean 50.7), 10 unimpaired retired fighters ( mean 48.9) and 19 controls (mean 41.3). Regional DVR values were significantly higher in the impaired retired fighters compared to the active unimpaired fighters in the amygdala ( 1.35 v. 1.12, p=0.003), frontal lobe (1.17 v 1.01, p=0.016), thalamus ( 1.57 v. 1.31, p=0.017), putamen (1.55 v. 1.26, p=0.0046), caudate ( 1.55 v. 1.31, p= 0.03), pons ( 1.39 v. 1.98, p=0.019) and to lesser degree hypothalamus and lateral temporal lobe. However, after adjusting for age, these statistical relationships vanished with the exception of the frontal lobe which maintained a trend toward significance ( p= 0.07). Furthermore, there were no significant differences in DVR values between impaired and unimpaired active fighters or impaired and unimpaired retired fighters.

We concluded that PET FDDNP binding, using cerebellum as the reference region, is higher in certain regions that have been shown pathologically to have tau accumulation. However, when age is factored in, only the frontal region remains close to statistical significance.

*Training opportunities*: This project has provided a training opportunity for our post –doctorate student, Lauren Bennett, who has worked on further analyses of the cognitive data obtained on the cohort

*Dissemination of Results*: Nothing to report

*Future plans*: Over the next 12 months, the investigators focus on retention and completion of 3rd year visits. In addition, baseline findings will be submitted for publication. Other projects of interest will be

- FDDNP PET binding and multimodal MRI measures
- FDDNP PET binding and relationship to risk factors

4**. Impact:**

*Impact on development of principal disciplines*: At the current stage, the impact from this project is limited. However, the publication by Dr. Omalu and his group that reported the correlation between PET FDDNP binding and post-mortem findings in a retired NFL player has raised attention to this imaging method (Omalu B, et al. Postmortem Autopsy-Confirmation of Antemortem [F-18]FDDNP-PET Scans in a Football Player With Chronic Traumatic Encephalopathy. Neurosurgery. **2017** Nov 10. Epub ahead of print). In the case study, [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.

Our study is one of the largest series using PET FDDNP imaging in individuals exposed to repetitive head trauma and followed over time. This puts the study in position to determine if certain binding patterns correlate with clinical symptoms and brain structural imaging over time.

*Impact on other disciplines*: Nothing to report

*Impact on technology transfer*: Nothing to report

*Impact on society beyond science:* Nothing to report

5 **Changes/Problems:**

*Changes in approach*: No changes in approach to report

*Problems or delays:* the major problem/delay that has occurred in this study has been the slow rate of recruitment. In 2017, we completed recruitment and all baseline FDDNP scans. We have received a no cost extension for 2018 to allow for the ongoing follow up of the cohort, as some of the most impactful information will be gained by determining the clinical and radiological trajectory of the subjects and the correlation with baseline PET FDDNP imaging

We are also slowed by the relocation of one of the investigators on the study ( S.B.) to University of California, San Diego, which has slowed manuscript preparation and starting new analyses.

*Changes that impact expenditures*: None

*Changes in care of human subjects*: None. The study has received ongoing approval by the Cleveland Clinic IRB through 12/2/18.

6**. Products:**

No products resulted from this study over the last year.

7. **Participants and other Collaborating Organizations**

The individuals who have worked on this project include:

Charles Bernick – no change

Sarah Banks – Relocated to the University of California, San Diego

Jorge Barrio - no change

Pamela Dino

Project role: research coordinator

Person month worked: 4

Contributions to project: Subject scheduling, conduct of study visit

Funding support – Cleveland Clinic

*Change in active support*: Nothing to report

Other organizations:

ADMdx, Chicago, Ill

Contribution: Analyses and interpretation of PET FDDNP imaging using machine learning methods and multimodal approaches.

Financial support: In – kind contribution of their staff time and facilities to analyze PET FDDNP images

## 8. Quad Chart:

**Early Recognition of CTE through PET FDDNP Imaging**
PT120134

**PI: Charles Bernick  Org: Cleveland Clinic  Award Amount: $746,068**

### Study/Product Aim(s)

•**Study**: Exam the performance of PET FDDNP in a group of active and retired professional boxers and non trauma exposed controls.

•**Outcomes**: To determine if PET FDDNP imaging may be a potential biomarker of and diagnostic tool for CTE

### Approach

- Cohort derived from the Professional Fighters Brain Health Study
- Active and retired boxers , both cognitively normal and cognitively impaired
- Subjects undergo baseline PET FDDNP imaging and followed annually with cognitive, behavioral, and neurological testing

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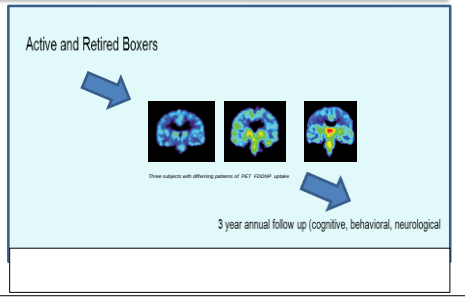


### Timeline and Cost

| Activities | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|
| Baseline PET FDDNP | | | | | | |
| Annual MRI, cognitive, behavioral assessments | | | | | | |
| Analysis | | | | | | |
| | | | | | | |
| **Estimated Budget ($K)** | **$304** | **$302** | **$140** | **$0** | **$0** | **$0** |

**Goals/Milestones**
**CY13 Goal** – Develop SOP and train coordinator
IRB Submission
Finalize logistics of transfer of FDDNP from production to site
**CY14 Goals** - IRB approval obtained
HRPO approval obtained
Identified eligible subjects
**CY15 Goal** – Enrollment of subjects, 1st subject enrolled 3/15
**CY16 Goal** – Continue enrollment and begin annual follow up visits, analyses
**CY 17 Goal** - Complete enrollment and continue annual follow up visits, analyses
**CY 20 Goal** - Complete 3 year follow up visits on all subjects

**Comments/Challenges/Issues/Concerns**
- Delay in completion of service agreement/IRB approval/HRPO approval delayed initial enrollment; PET FDDNP imaging began 3/15. MRI scanner replacement slowed 2016 enrollment.