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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 \(2-((1-\{(2-\{F-18\text{fluoroethyl(methyl)amino}\}-2-naphthyl)\text{ethyldene}\})\text{malononitrile}) \) (FDDNP) has shown sensitivity for in vivo detection of tau in addition to \(\beta\)-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.

**15. SUBJECT TERMS**

Traumatic Brain Injury  
Positron Emission Tomography  

**16. SECURITY CLASSIFICATION OF:**

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<tr>
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</table>

**19a. NAME OF RESPONSIBLE PERSON**  
USAMRMC

**19b. TELEPHONE NUMBER (include area code)**

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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-[(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:**

Upon receiving approval from the Human Research Protection Office, enrollment of participants began in March, 2015. We have completed 45 PET FDDNP studies, with 6 additional subjects scheduled within the next 4 weeks. Recruitment progress is reflected in the following grid:

<table>
<thead>
<tr>
<th>Type of Fighter</th>
<th>Scheduled</th>
<th>Completed</th>
<th>Req’d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3</td>
<td>8</td>
<td>8/20</td>
</tr>
<tr>
<td>Active, Unimpaired</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Active, Impaired</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Retired, Unimpaired</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Retired, Impaired</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td><strong>TOTAL:</strong></td>
<td>6</td>
<td>45</td>
<td>51 / 68</td>
</tr>
</tbody>
</table>

Each subject is to be followed yearly for 3 years as part of the Professional Fighters Brain Health Study. Of the 26 participants due for follow up in 2016, 23 participants completed follow-up (88% retention).
those who are overdue for year one follow up, 2 have been unable to return due to work (we will continue attempting to schedule their follow up) and 1 is lost to follow up due to moving permanently to Australia).

Once 50% of the cohort was enrolled, we undertook several analytical approaches to the acquired data that has resulted in three abstract presentations. Traditionally, PET FDDNP images were analyzed using manually drawn region of interests (ROI). Because this is not likely to be a clinically practical method of interpreting the images, the FDDNP data were processed using the automated MIAKAT (Imanova) kinetic analysis software. Parametric images of distribution volume ratio (DVR) were generated with the cerebellum as the reference region. Regional DVR measurements were obtained using the built-in brain template with gray mask applied. The results indicate a relationship between increased exposure to head trauma (measured by number of fights) and increased FDDNP uptake in the amygdala and other temporal lobe structures.

In addition, there was an association between increased uptake in the parahippocampal cortex and worse performance on several cognitive measures:

<table>
<thead>
<tr>
<th>Table 3: Uptake and cognitive tests</th>
<th>Verbal Memory</th>
<th>Processing Speed</th>
<th>Psychomotor Speed</th>
<th>Reaction Time</th>
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</thead>
<tbody>
<tr>
<td>amygdala</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>hippocampus</td>
<td>ns</td>
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<tr>
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<td>-.313</td>
<td>.374</td>
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<tr>
<td>brainstem</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>temporal</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

We have also conducted analyses of the FDDNP images using manual ROI techniques. While many
areas of uptake were strongly associated with age, there does appear to be a relationship between FDDNP uptake and both exposure (total number of fights) and reaction time in the lateral temporal lobe.

This project has provided a training opportunity for our post-doctorate student, Bern Lee, who has worked on assessing the relationship between FDDNP imaging results and neuropsychological measures.

Preliminary results noted above have been accepted for presentation at three national conferences: Lancet Neurology Conference on Preclinical Neurodegenerative Disease (London, 10/16), Human Amyloid Imaging (Miami, 1/17), International Neuropsychological Society (New Orleans, 2/17).

Over the next reporting period, emphasis will be placed on completing enrollment (hopefully by 7/17) and continuing follow up of the subjects. We will also be exploring different methods of image analysis taking into account the problems that we have identified so far (see #5), as well as examining further potential relationships between imaging modalities (PET FDDNP and MRI).

4. Impact:

At the current stage, the impact from this project is limited. The preliminary data we have presented has extended what we know about PET FDDNP imaging beyond the small series that was done with retired football players.

5 Changes/Problems:

The major problem we have encountered is with rate of recruitment, particularly for control subjects. Several factors that slowed enrollment were: 1) the unavailability of the FDDNP tracer over the month of December, 2) Replacement of our MRI scanner during October and November (because we coregister the PET scan with the MRI image, we had to postpone enrollment during that time). Both issues have now been resolved.

We have broadened our recruitment efforts by tagging on to other studies at our center that will be recruiting control subjects, as well as continuing to reach out to other organizations in the community. Given that age seems to have an important relationship to FDDNP uptake, we have placed particular attention to enroll control subjects that are adequately matched for age with our subjects.

In order to complete the 3 year follow up of subjects, we will need to extend the completion date accordingly.

Another challenge that has arisen as we have completed preliminary analyses of the imaging is determining the optimal way to interpret the scans. Because the distribution of tau in Chronic Traumatic Encephalopathy tends to be more widespread and heterogeneous, examining small ROIs may fail to detect specific patterns of FDDNP uptake. Thus, we plan to explore assessment of uptake in clusters of
regions that may result in a more reliable means to detect abnormal tau deposition.

6. Products:

The following conference presentations have been presented at national conferences:


Sarah J. Banks, Vladimir Kepe, Frank P. DiFilippo, Bern Lee Jorge Barrio, and Charles Bernick Regional FDDNP Uptake and Exposure to Professional Fighting (Human Amyloid Imaging, Miami, 1/17)


No other 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 – no change

Jorge Barrio - no change

Vladimir Keppe -

Project role - Image analyst

Contribution to project - Processing of PET FDDNP Images

Funding Support – Cleveland Clinic

Frank DiFillipo –

Project role – image analyst

Contribution to project – Processing of PET FDDNP Images

Funding Support – Cleveland Clinic
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

Timeline and Cost

<table>
<thead>
<tr>
<th>Activities</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
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<tbody>
<tr>
<td>Baseline PET FDDNP</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Annual MRI, cognitive, behavioral assessments</td>
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<td>Analysis</td>
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<td>$46</td>
<td>$46</td>
<td>$48</td>
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Goals/Milestones

CY13 Goal – Develop SOP and train coordinator
IRB approval obtained
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

CY17 Goal – Complete enrollment and continue annual follow up visits, analyses

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. Projected enrollment completion 7/16.