<table>
<tr><th>Study</th><th>Study Population</th><th>Treatment/ intervention</th><th>Results</th><th>Validity /Conclusion</th></tr>
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<td>Clark et al, 2011, 2012.

Study type
Prospective cohort with a control group.

Aim:
To determine the accuracy of F-18 florbetapir -PET in detecting the presence of ß-amyloid in the brain.

Endpoints:
Accuracy of florbetapir in detecting amyloid and its correlation with postmortem histopathology.

N of patients:
152 autopsy cohort near end of life. n=35 had postmortem brain autopsies.

N=74 control cohort (young individuals 18-50 years).

Blinding:
Yes, PET images were interpreted blindly to clinical, demographic, and neuropathological information.</td>
<td>Inclusion criteria:
Physician’s assessment that the individual was likely to die within 6 month of study enrollment, absence of any known destructive lesion in the brain (e.g. stroke or tumor), and the willingness to have florbetapir-PET imaging followed by a brain autopsy at death.
Patients characteristics:
<u>Autopsy cohort</u>
Patients were enrolled from long-term care, hospice and community health care facilities. Their mean age was 79.3 years (range 47-103), 51.4% men, 48.6% had AD as their diagnosis (time from onset to enrollment 9 years), 8.6% had mild cognitive impairment, 17% had another dementing disorder, and 25.7% were cognitively normal. Mean Mini-Mental State Examination score was 21.2, mean interval between brain scan and death was 89.4 days, and death to autopsy 11.2 days.
<u>Young cognitively normal control cohort</u>
The mean age was 26.7 years (range 18-50), 64.9% males, and the mean Mini-Mental State Examination score was 29.7.</td>
<td>Each participant underwent a 10-minute Florbetapir-PET imaging at one of 23 study sites.
The images we assessed visually by 3 nuclear medicine physicians using a semiquantitative score ranging from 0 (no amyloid to 4 (high level of cortical amyloid).
The initial 6 postmortem evaluations were rated by 4 readers and the median rating of the 4 readers served as the primary outcome. Five scans were invalid due to poor quality.
For the younger cohort, the PET images were mixed in random with 40 images from the autopsy cohort and had median visual read between 2 and 4 (inclusive).The majority reads were used as the primary outcome variable.

Gold standard:
Postmortem biopsy. Automated immune-histochemistry to quantify ß-amyloid burden and silver stain to identify and quantify neuritic amyloid plaques.</td>
<td>-35 participants underwent autopsy; the first 6 were used in an interim analysis and the next 29 were used in the primary analysis. Of these 29 individual 31% were not considered to be cognitively impaired by the enrolling physician, 7% were mildly impaired but without dementia, 45% had a clinical diagnosis of AD, and 17% had a clinical diagnosis of non-AD dementia.
-Second part of the study followed the patients for up to 1 year after initial study or up to 2 years after the initial florbetapir PET scan.
-24 additional autopsies were performed with a total of 59 (Clark 2012)

Correlations for the primary analysis cohort (Clark 2011)
<table>
<tr><th>Cortex Region</th><th>Florbetapir -PET measure</th><th>Pathology reference standard</th><th>Bonferroni p* (95% CI)</th></tr>
<tr><td>Whole brain</td><td>Visual</td><td>ß-amyloid area</td><td>0.78 (0.58-0.89)</td></tr>
<tr><td>Whole brain</td><td>SUVr</td><td>ß-amyloid area</td><td>0.75 (0.53-0.88)</td></tr>
<tr><td>Whole brain</td><td>Visual</td><td>NPS</td><td>0.71 (047-0.86)</td></tr>
<tr><td>Whole brain</td><td>SUVr</td><td>NPS</td><td>0.74 (0.51-0.87)</td></tr>
<tr><td>Whole brain</td><td>SUVr vs. visual</td><td>NA</td><td>0.82 (0.64-0.91)</td></tr>
<tr><td>Whole brain</td><td>N/A</td><td>ß-amyloid area vs. NPS</td><td>0.88 (0.76-0.94)</td></tr>
<tr><td>Precuneus</td><td>Visual</td><td>ß-amyloid area</td><td>0.75 (0.54-0.88)</td></tr>
<tr><td>Parietal</td><td>Visual</td><td>ß-amyloid area</td><td>0.77 (0.56-0.89)</td></tr>
<tr><td>Frontal</td><td>Visual</td><td>ß-amyloid area</td><td>0.69 (0.44-0.85)</td></tr>
<tr><td>Temporal</td><td>Visual</td><td>ß-amyloid area</td><td>0.68 (0.42-0.84)</td></tr>
<tr><td>Posterior Cingulate</td><td>Visual</td><td>ß-amyloid area</td><td>0.70 (0.44-0.65)</td></tr>
<tr><td>Anterior cingulate</td><td>Visual</td><td>ß-amyloid area</td><td>0.74 (0.51-0.87)</td></tr>
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*Adjusts for multiple comparisons. Significant correlation between the whole brain and 6 cortical regions florbetapir-PET visual image scores and postmortem amyloid pathology NPS-=neuritic plaque score, SUVr= semiautomated quantitative analysis of ratio of cortical to cerebellar PET signal.
-The 74 young healthy participants had florbetapir-PET image that was rated as amyloid negative. Pairwise agreement between visual ratings ranged from 91-99%.

Accuracy of florbetapir (Clark 2012)
<table>
<tr><th></th><th>Sensitivity</th><th>Specificity</th><th>Accuracy</th></tr>
<tr><td colspan="4">Individuals <12 months from scan to autopsy n=46</td></tr>
<tr><td>Majority reading</td><td>27/28
96% (80-100%)</td><td>18/18
100% (78-100%)</td><td>45/46
98% (87-100%)</td></tr>
<tr><td>Median reader</td><td>96% (range75-100)</td><td>94% (range89-100)</td><td>96% (range80-98)</td></tr>
<tr><td>Mean of readers</td><td>91% ± 10.0</td><td>96% ± 4.6</td><td>93% ± 7.3</td></tr>
<tr><td colspan="4">All autopsy participants n=59</td></tr>
<tr><td>Majority reading</td><td>36/39
92% (78-98%)</td><td>20/20
100% (80-100%)</td><td>56/59
(85-99%)</td></tr>
<tr><td>Median reader</td><td>92% (range 69-95)</td><td>95% (range 90-100)</td><td>93% (range 76-95)</td></tr>
<tr><td>Mean of readers</td><td>87% ± 10.4</td><td>95% ± 3.5</td><td>90% ± 7.9</td></tr>
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Sensitivity and specificity were calculated on binary visual rating moderate to frequent plaques vs. no or sparse (Clark 2012)
Adverse events: no serious adverse events, only 2 incidences of headache.</td>
<td>Advantages/ limitations:
The study had the advantage comparing florbetapir-PET results with the gold standard of histopathological findings at autopsy. However, it had several limitations listed in detail on page 3 of the current report.

The study was designed by Avid Radiopharma-ceuticals who also supported the collection, analysis, and interpretation of the data, as well as writing the report.</td>
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