# FBI Items: FTLD versus high-FBI AD

<table>
<thead>
<tr>
<th>FBI Item</th>
<th>FTLD  n=26</th>
<th>AD high FBI n=18</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspontaneity</td>
<td>1.7 (1.1)</td>
<td>2.3 (0.6)</td>
<td>.021</td>
</tr>
<tr>
<td>Perseveration</td>
<td>1.7 (1.2)</td>
<td>2.3 (0.8)</td>
<td>.033</td>
</tr>
<tr>
<td>Hyperorality</td>
<td>1.2 (1.2)</td>
<td>0.2 (0.6)</td>
<td>.001</td>
</tr>
</tbody>
</table>

All other items differed insignificantly between the 2 groups
- includes logopenia, inflexibility, personal neglect, inattention, excessive jocularity, hypersexuality.

The rest of the AD group scored very differently on most FBI items.
Cognitive, functional and neuropsychiatric scores

(SD in brackets)

<table>
<thead>
<tr>
<th></th>
<th>FTD</th>
<th>AD high FBI</th>
<th>AD low FBI</th>
<th>p value (FTD vs AD high FBI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>21.6 (8.7)</td>
<td>18.6 (5.9)</td>
<td>21.8 (5.9)</td>
<td>.114</td>
</tr>
<tr>
<td>3MS</td>
<td>68.9 (23.2)</td>
<td>56.9 (21.3)</td>
<td>70.8 (19.1)</td>
<td>.112</td>
</tr>
<tr>
<td>DAD</td>
<td>64.0 (22.8) (a,b)</td>
<td>57.8 (25.8) (a)</td>
<td>72.4 (20.7) (b)</td>
<td>.036 †</td>
</tr>
<tr>
<td>FRS *</td>
<td>23.0 (5.5) (a,b)</td>
<td>24.7 (5.9) (a)</td>
<td>20.6 (5.6) (b)</td>
<td>.044</td>
</tr>
<tr>
<td>NPI</td>
<td>29.0 (24.2) (a)</td>
<td>29.8 (20.9) (a)</td>
<td>8.3 (10.2)</td>
<td>.000 †</td>
</tr>
<tr>
<td>CIRS</td>
<td>3.1 (2.9)</td>
<td>3.5 (2.1)</td>
<td>4.1 (2.5)</td>
<td>.304</td>
</tr>
</tbody>
</table>

\(a,b= \) homogynous subsets by Student- Newman-Kleus analysis

†: p values remain significant after controlling for duration of symptoms
Conclusions: ACCORD database

- FvAD can be defined as “high FBI AD”
- This group resembles FTLD in clinical and other characteristics
  - and differs from the remainder of the AD group
- This is not accounted for by severity, where this is defined as longer symptom duration
Hypothesis: those with a clinically-defined syndrome of FvAD will, in aggregate, have statistically significantly different frontal lobe metabolism, as measured by FDG-PET, than those with non-frontal AD.

- FDG- PET demonstrates regional hypometabolism
  - greater AD pathology load associated with greater hypometabolism
  - If FvAD associated with greater frontal pathology load, would expect greater hypometabolism in these regions
Methods

• Sequential patients seen by the presenter in his rooms
• FDG PET used almost universally by the presenter if AD or FTLD suspected
• All who had FDG PET within 2 years of study start and had a final diagnosis of AD had FBI administered
• FBI scores arrayed and top quartile defined as FvAD
  – the lower 3 quartiles defined (non frontal) AD.
FBI results

- 53 AD cases included
- Using a cut point of 25/26 (as in the ACCORD study):
  - 40 AD cases below 25
  - 13 AD cases above 25 (none scored 25 itself)
<table>
<thead>
<tr>
<th>Feature, at time of PET (mean)</th>
<th>FvAD (high FBI)</th>
<th>(other) AD (lower FBI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr (SD)</td>
<td>81.6* (4.1)</td>
<td>79.9* (7.6)</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>38.5*</td>
<td>60.6*</td>
</tr>
<tr>
<td>Duration of symptoms (years)</td>
<td>1.75*</td>
<td>2.81*</td>
</tr>
<tr>
<td>MMSE</td>
<td>23.9*</td>
<td>23.8*</td>
</tr>
</tbody>
</table>

*P= not significant
FDG PET analyses

• FDG-PET scans scaled using the cerebellar cortex as reference region and normalized into standard stereotactic space

• A standard Regions Of Interest (ROI) template (AAL) used to assess glucose metabolism in frontal and anterior temporal cortical regions

• ROIs aggregated to lateral frontal, superior lateral frontal, orbitofrontal and medial frontal

• Z scores used to evaluate difference between subject’s metabolism and that of a pooled group of non demented age-matched controls for the ROI
## FDG PET RESULTS - mean Z scores (SD)

<table>
<thead>
<tr>
<th>Region</th>
<th>FvAD N= 13</th>
<th>(non frontal) AD N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral Frontal</td>
<td>2.61 (0.72)</td>
<td>2.19 (1.19)</td>
</tr>
<tr>
<td>Orbitofrontal</td>
<td>2.64 (0.99)*</td>
<td>2.11 (1.12)*</td>
</tr>
<tr>
<td>Superior Lateral Frontal</td>
<td>2.65 (0.86)</td>
<td>2.50 (1.17)</td>
</tr>
<tr>
<td>Medial Frontal</td>
<td>2.38 (0.63)**</td>
<td>1.82 (0.88)**</td>
</tr>
</tbody>
</table>

*p=0.03  **p=0.003
SPM- AD versus FvAD
The FvAD and AD (rest) groups were not different on MMSE and symptom duration at time of presentation, suggesting that they were not at different stages of disease duration – Consistent with the ACCORD database study

No significant differences in age and gender between groups
  – but substantially greater proportion of males in high FBI group
    • more prone to behavioural disturbances
DISCUSSION-2

• There is a significant difference in orbitofrontal and medial frontal metabolism in the 2 groups
  – suggestive of greater AD pathological load in these regions in the FvAD group
  – this may explain the more frontal presentation in the FvAD group
  – these regions are most associated with “frontal” features including mood and behaviour¹
    • less so than the other 2 frontal regions examined
    • but even these regions showed a trend to greater hypometabolism in the FvAD group

• These results strongly support a pathological explanation for FvAD
  – ie greater plaques and/or tangles in orbitofrontal and medial frontal regions
  – and not accounted for by differences in disease duration, disease severity or other clinical features
Using FAB to distinguish AD from FvAD and FTLD¹

- PRIME—a well-defined prospectively studied cohort of cognitively impaired subjects
  - included those with AD and with FTLD
- Frontal variant of AD (FvAD) defined as those AD subjects with the lowest quartile of scores on the Frontal Assessment Battery (FAB)
  - indicating greater executive dysfunction
- Compared them with the rest of the AD cases and those with FTLD

Using FAB to distinguish AD from FvAD
PRIME study

<table>
<thead>
<tr>
<th></th>
<th>FvAD N=114</th>
<th>AD N=408</th>
<th>FTLD N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age 78.1</td>
<td>Age 78.4</td>
<td>Age 71.1</td>
</tr>
<tr>
<td>MMSE</td>
<td>MMSE 16</td>
<td>MMSE 22</td>
<td>MMSE 24</td>
</tr>
</tbody>
</table>
Using FAB to distinguish AD from FvAD

- The FvAD group differed significantly from the other two groups on all but the behavioural scale, the Neuropsychiatric Inventory (NPI).
- The FTLD and AD groups were similar on all but the NPI and the caregiver burden scale.
- The FTLD group declined more rapidly on the FAB than the other two groups, which remained stable on this scale.
- In an analysis of subjects matched at baseline for functional impairment, the FvAD group was significantly different from the AD group in almost all assessment scales.
Using FAB to distinguish AD from FvAD

-conclusions

- defined a group of AD subjects with greater executive dysfunction that were distinguished from both the AD and FTLD subjects in almost all domains except behavioural disturbance and probably were just more severely affected subjects

- Controlling for functional severity allowed the definition of a subgroup of AD subjects that more closely resembled FTLD subjects than the remainder of the AD subjects

- Subjects with dementia and presenting with greater executive impairment but without prominent behavioural symptoms are likely to have AD rather than FTLD, especially if they are quite functionally impaired.

- With time FTLD subjects develop increasing executive dysfunction and increasingly resemble the FvAD subjects.
Conceptualisation

Dementia

1. FvAD-behavioural, mixed pathology
2. FvAD-dysexecutive, ? mixed pathology
3. Logopenic Aphasia, mixed or AD pathology
4. FvAD-AD pathology
5. AD, posterior/visuospatial-mixed pathology
6. DLB, visuospatial (Lewy Bodies)
Conclusions

• AD can have several presentations
  – Amnestic most common
• Likely reflects the early distribution of pathology
• Can make differential diagnosis difficult
  – FvAD vs FTLD
  – Logopenic aphasia vs language- varieties of FTLD
  – PCA vs DLB
• Neuroimaging helpful
• With time, most people with AD develop all these variant features.
  – likely reflects pathology spreading
• Mixed pathology frequent in end- stage dementia.