Fronto-subcortical hypoperfusion in presymptomatic FTD is associated with behavioral measures, but not cognitive deficits – the GENFI study

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Nothing to disclose
FRONTO-TEMPORAL DEMENTIA(S)-FTD

- A group of rare neurodegenerative disorders
- Age of Onset 45 to 65 years
- Primarily affecting frontal and temporal lobes
  - Behavioral variant (bvFTD)
  - Primary progressive aphasia (PPA)
    - Semantic variant of PPA
    - Non-fluent variant of PPA
  - Disturbances of motor function-ALS or parkinsonism

Frontotemporal Atrophy

Seelaar et al. 2011; Onyike and Diehl-Schmid 2013; Gorno-Tempini et al. 2011
Sporadic cases, 50-80%
Familial cases, 20-50%
Single gene mutations. Autosomal dominant

17q21
- MAPT
- PGRN
- Tau

9p21
- PGRN TDP-43

C9orf72
- TDP-43

Presymptomatic mutation carriers - a very important group to understand the long preclinical phase of FTD

In presymptomatic mutation carriers of these genes, identifying (Imaging) biomarkers of disease before the onset of clinical symptoms is crucial

- To predict disease onset
- To monitor disease progression, and
- To guide use of future disease modifying therapies
Volumetric Magnetic Resonance Imaging (MRI) – volume changes e.g. atrophy
\textit{Rohrer et al. 2015}

18F-Fluorodeoxyglucose Positron Emission tomography (FDG-PET) – hypometabolism
\textit{Jacova et al. 2013}

Resting-state functional MRI – information on functional networks
\textit{Premi et al. 2014}

Diffusion Tensor Imaging (DTI) – structural connectivity of white matter
\textit{Dopper et al. 2013}

Arterial Spin Labelling (ASL) – cerebral perfusion
\textit{Dopper et al. 2016}

- Increasing evidence suggests that perfusion changes precede structural brain changes in FTD
In pre-symptomatic family members of FTD cases [non-carriers: n=100; carriers: n=95 ($MAPT=17$, $GRN=48$, $C9orf72=30$)], we aimed to:

I. Explore differences in cerebral perfusion in mutation-carriers compared to non-carriers in same families utilizing Arterial Spin Labeling MRI data

II. Investigate if differences in perfusion (if any) identified in aim I are associated with cognitive or behavioral measures
- Multicentre consortium for tracking evolution of genetic FTD
- Common methodological platform across all sites
- 13 centres across Europe and Canada
- Includes FTD cases and unaffected family members
- Clinical, functional, neuropsychological, MRI, blood and CSF assessments
Presymptomatic family members of FTD cases, N=195 [100 non-carriers; 95 carriers (MAPT=17, GRN=48, C9orf72=30)]

- Cerebral perfusion data
- Cognitive measures
- Behavioural measures

Global cognition:
- MMSE
- Executive function:
  - Trail making test A & B
- Language:
  - Boston Naming & Verbal Fluency
- Memory:
  - Logical memory-Immediate and delayed recall
  - Working memory:
    - Forward and backward digit span

Cambridge Behavioural Inventory-CBI
- Memory and orientation
- Everyday skills
- Self-care
- Abnormal behaviour
- Mood
- Beliefs
- Eating habits and sleep
- Stereotype and motor behaviours
- Motivation
CEREBRAL (HYPO)PERFUSION-ASL

**Aim I:** To explore differences in cerebral perfusion between carriers and non-carriers in the same families.

- Cerebral perfusion measured by Arterial Spin Labeling MRI.
- In a voxel-based analysis (VBA), differences in cerebral blood flow between non-carriers and mutation carriers were explored (SPM-University College London).
- Linear mixed models used to test these differences to:
  - Account for random effects of family.
  - Fixed effects of sex, site, mutation carrier-status, and years to age of onset (YAO).
- YAO = age of participant - mean age of onset of FTD in their family.
- Analyses adjusted for the spatial coefficient of variation to account for vascular artifacts.
- Regions of hypoperfusion (ROIs - Regions Of Interest) in carriers vs non-carriers were identified on VBA, and then perfusion within these regions was corrected for partial volume effects.
To test associations of the identified ROIs of cerebral hypoperfusion with cognitive and behavioral measures, we used:

- Multiple linear regression models
  - Adjusted for age, sex, and education

First, we tested interactions between cerebral perfusion and mutation carrier-status in analyses of ROIs with both cognitive and behavioural measures.

Second, analyses were repeated stratified for carrier status (carriers and non-carriers) and subsequently stratified on mutation: MAPT=17, GRN=48, C9orf72=30
RESULTS
Six regions of interest (ROIs) of cerebral hypoperfusion in carriers compared to non-carriers were identified named according to their overlap with the Harvard-Oxford atlas 35.

- C1: Paracingulate gyri (B)
- C2: Orbitofrontal gyrus/insula (B)
- C3: Frontal pole (R)
- C4: Putamen (L)
- C5: Frontal pole (L)
- C6: Middle, Inf, and Sup frontal gyri (R)

B: bilateral; R: right; L: left
When testing perfusion in identified ROIs with cognitive tests:

- We did not find any associations between cerebral perfusion and cognitive test scores in any ROIs in mutation carriers or non-carriers.
<table>
<thead>
<tr>
<th></th>
<th>Non-carriers n=100</th>
<th>All carriers n=95</th>
<th>C9ORF72 n=30</th>
<th>PGRN n=48</th>
<th>MAPT n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paracingulate (B)</strong></td>
<td>-0.01 (-0.06, 0.04)</td>
<td>0.16 (0.08, 0.23)</td>
<td>0.03 (-0.08, 0.14)</td>
<td>0.03 (-0.08, 0.14)</td>
<td>0.33 (-0.19, 0.47)</td>
</tr>
<tr>
<td></td>
<td>0.59</td>
<td>&lt;0.001</td>
<td>0.56</td>
<td>0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Orbitofrontal/insula (B)</strong></td>
<td>-0.005 (-0.05, 0.04)</td>
<td>0.10 (-0.002, 0.18)</td>
<td>-0.04 (-0.16, 0.07)</td>
<td>-0.02 (-0.15, 0.10)</td>
<td>0.36 (0.07, 0.65)</td>
</tr>
<tr>
<td></td>
<td>0.83</td>
<td>0.056</td>
<td>0.42</td>
<td>0.70</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Frontal pole (R)</strong></td>
<td>0.02 (-0.01, 0.07)</td>
<td>0.14 (0.06, 0.22)</td>
<td>-0.01 (-0.11, 0.09)</td>
<td>0.07 (-0.04, 0.19)</td>
<td>0.35 (0.17, 0.54)</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>&lt;0.001</td>
<td>0.84</td>
<td>0.21</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Putamen (L)</strong></td>
<td>-0.01 (-0.09, 0.07)</td>
<td>0.20 (0.06, 0.34)</td>
<td>-0.006 (-0.19, 0.18)</td>
<td>0.04 (-0.15, 0.23)</td>
<td>0.76 (0.30, 1.21)</td>
</tr>
<tr>
<td></td>
<td>0.80</td>
<td>0.006</td>
<td>0.95</td>
<td>0.68</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Frontal pole (B)</strong></td>
<td>0.02 (-0.03, 0.06)</td>
<td>0.14 (0.06, 0.22)</td>
<td>-0.03 (-0.14, 0.08)</td>
<td>0.08 (-0.03, 0.19)</td>
<td>0.41 (0.23, 0.60)</td>
</tr>
<tr>
<td></td>
<td>0.46</td>
<td>&lt;0.001</td>
<td>0.61</td>
<td>0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Middle, inferior, and superior frontal gyri (R)</strong></td>
<td>0.02 (-0.03, 0.06)</td>
<td>0.13 (0.06, 0.21)</td>
<td>-0.01 (-0.10, 0.08)</td>
<td>0.03 (-0.08, 0.15)</td>
<td>0.36 (0.22, 0.49)</td>
</tr>
<tr>
<td></td>
<td>0.43</td>
<td>&lt;0.001</td>
<td>0.82</td>
<td>0.53</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All estimates are adjusted for age, sex, and education.
Cerebral hypoperfusion within frontal-subcortical regions in presymptomatic FTD is associated with early behavioral changes but not cognitive deficits.

This may be consistent with the natural history of FTD which most commonly shows behavioural dysregulation as an early feature.

The current approach uses an ROI analysis.

Future work will look at a direct voxel-based analyses associating perfusion with CBI and neuropsychological test scores.
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