• Language is a uniquely human process
  – Single words are used to construct sentences
  – Sentences are used in conversations
• Inexpensive screening device with potentially high sensitivity and specificity for FTD spectrum pathology
• Disease-modifying treatment trials
Plan of talk

- Disorders of language in aphasic and non-aphasic variants of FTD
  - Semantic variant PPA
  - Non-fluent/agrammatic PPA
  - Behavioral variant FTD
- Impairments in FTD selectively compromise each level of language
- Markers for specific FTD pathology


FRONTOTEMPORAL DEGENERATION

• Two major phenotypes
  — Primary progressive aphasia
    • Semantic variant PPA (Semantic dementia)
    • Nonfluent/agrammatic PPA (Progressive non-fluent aphasia)
  — Behavioral variant frontotemporal degeneration
SEMANTIC VARIANT PPA

• Lexical semantic and object knowledge is compromised in
VISUAL FEATURE KNOWLEDGE IN SEMANTIC VARIANT PPA

- Degraded object concepts in svPPA
  - Difficulty with naming

Two-alternative forced-choice

Bonner et al, 2009
• Despite profound word comprehension and object knowledge deficits, svPPA patients are rapid and accurate at performing written number calculations.

\[
\begin{align*}
2+3 &= 5 \\
5+9 &= 14 \\
12+13 &= 25 \\
19+7 &= 26 \\
28+35 &= 63
\end{align*}
\]
Preserved music knowledge in svPPA

Weinstein et al, 2011
PATHOLOGY IN SEMANTIC VARIANT PPA

• Autopsy shows anterior temporal atrophy
• Neuronal dropout in superficial layers
• TDP-43 neuronal inclusions
  • Found in about 85% of cases
TDP-43 pathology in both FTLD and ALS

FTLD-ALS link confirmed by TARDBP mutation and C9orf72 expansion
SPECTRUM OF CLINICAL DISEASE IN TDP-43 PATHOLOGY

• ALS-classic
  – Pyramidal/neuromuscular disease

• ALS is a multi-system disorder
  – 10% with ALS-FTD
  – 34% with ALS-MCI
  – 15% with ALS-Plus

  • ALS with cerebellar, extrapyramidal, oculomotor, or autonomic features
  • Significantly poorer prognosis, marker for inherited disease

McCluskey et al, 2014
• Semantic variant PPA
  – Degraded representations of single word and object concepts
  – Preserved number and music concepts
  – Related to anterior and ventral temporal disease
  – Clinical marker for TDP-43 pathology
  – Pathology shared with ALS
NON-FLUENT/AGRAMMATIC PPA

• Speech fluency and grammatical comprehension are impaired in progressive
NON-FLUENT/AGRAMMATIC PPA

- Significantly slowed speech
- Significant grammatical deficit

- Grammatical deficit related to left inferior frontal and superior temporal atrophy

Grossman et al, 2014

Gunawardena et al, 2010

Ash et al, 2010

Grossman et al, 2014

Charles et al, 2014

Grossman et al, 2014

Grossman et al, 2014

Grossman et al, 2014

Grossman et al, 2014

Grossman et al, 2014

Grossman et al, 2014

Grossman et al, 2014
• naPPA deficit is selective
  • naPPA are good at naming and complex figure construction

Libon et al, 2010
NON-FLUENT/AGRAMMATIC PPA

• Gross pathology in non-fluent/agrammatic PPA
NON-FLUENT/AGRAMMATIC PPA

• Microscopic pathology in non-fluent/agrammatic PPA
  – H & E preparation
  – Tau-immunoreactive histopathology
    • Misfolded tau due to hyperphosphorylation
    • Disturbs microtubule structure
  – Tau found in about 75% of cases
SPECTRUM OF CLINICAL DISEASE IN TAU PATHOLOGY

• TaP

FTLD%  PSP/CBD%
• Anatomic distribution of tau pathology in PSP and CBD

Irwin et al, 2012
• Non-fluent/agrammatic PPA
  – Specific pattern of impaired language due to limited grammatical processing
  – Associated with left inferior frontal disease
  – Similar pathology in akinetic-rigid disorders such as CBD and PSP
  – Clinical screen for tau pathology
BEHAVIORAL VARIANT FRONTOTEMPORAL DEGENERATION

- Poor self-regulation, impulsive, disinhibited
- Rigid, obsessive, rituals
- Apathetic
- Lack of insight
- Poor empathy
• Frontal and anterior temporal gray matter
• Extensive white matter disease
• Impaired social judgment in bvFTD

<table>
<thead>
<tr>
<th>Components</th>
<th>empathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>bvFTD</td>
<td>0.87</td>
</tr>
<tr>
<td>Aphasia</td>
<td>0.72</td>
</tr>
<tr>
<td>Control</td>
<td>0.37</td>
</tr>
</tbody>
</table>
• Wordless picture story, 30 events, 7 episodes
• Single word expression
• Sentence expression
• Narrative organization
BEHAVIORAL VARIANT FRONTOTEMPORAL DEGENERATION

- Accurate description of children’s wordless picture
- Poor organization of narrative
  - No sense of the point

- Impaired global connectedness
- Impaired local connectedness
- Impaired theme maintenance

Reduced connectedness related to prefrontal atrophy

Ash et al, 2006
• Atrophy in behavioral variant frontotemporal degeneration
  – 50% TDP-43 pathology, 50% tau pathology
• Multimodal strategy for diagnosis
FAMILIAL FRONOTEMPORAL DEGENERATION

• FTLD autosomal dominant inheritance in 25.1%
  – Mutation identified in 20.1% of patients
  – Chromosome 17  MAPT
  – Chromosome 17  GRN
  – Chromosome 9  C9orf72
  – Chromosome 9  VCP
  – Chromosome 3  CHMP2B
  – Chromosome 1  TARDBP

• Specific pathology associated with each mutation
IMAGING BIOMARKERS FOR YOUNG ONSET FTD

- Eigenanatomy imaging distinguishes FTLD-tau from FTLD-TDP with known pathology

McMillan et al, 2013
BIOFLUID BIOMARKERS FOR FTLD

• CSF phosphorylated tau abnormal in tauopathy
• Elevated CSF ptau:ttau in tauopathy
  – Lower ptau:ttau in TDP-43 proteinopathy

• Related to motor and PFC in ALS

• Related to midbrain in PSP

Grossman et al, 2014
• Myelin oligodendrocyte basic protein
  – Stabilizes myelin
• rs1768208 (MOBP) is associated with reduced white matter fractional anisotropy in midbrain and superior longitudinal fasciculus

• Locus of white matter pathology in progressive pathology

McMillan et al, 2014
MOLECULAR BIOMARKERS IN HUMAN TAUOPATHY

- Minor “T” allele at rs1768208 of MOBP associated with reduced survival in clinical FTD and known tauopathy

- Validated by imaging-guided biopsy of SLF showing diseased myelin in risk allele carriers (right)

- Minor “T” allele at rs1768208 of MOBP associated with reduced FA in white matter of superior longitudinal fasciculus and brain stem
Language is a complex process that can serve as a sensitive and inexpensive screen for FTD

- Single words and object knowledge compromised in semantic variant PPA
  - Marker of TDP-43 pathology
    - Grammatical expression and comprehension impaired in non-fluent/agrammatic PPA
      - Marker of tau pathology
        - Narrative conversation difficulty in