Frontotemporal dementia update: Review and New Data

Monica K. Crane, MD
Associate Director
Director of Research
Cole Neuroscience Center
Assistant Professor, UTMCK

Frontotemporal dementia (FTD) Overview
- Background and clinical definition
- Prevalence
- FTD clinical subtypes
- Neuropathology and genetics of Frontotemporal lobe dementia (FTLD)
- Treatment updates

“Dementia That's Neither Alzheimer's Nor Easy”

FDG-PET images of metabolic activity: healthy controls, AD, and FTD. Scale red (high FDG uptake)-yellow-green-blue (low FDG uptake).

Photo Credit: Dr. Janet Miller, Dr. Susanna Lee, MGH/ Harvard, Radiology Rounds April 2006
FTD = a clinical neurodegenerative disease affecting frontal & temporal lobes

http://www.uphs.upenn.edu/ftd

FTD International Research Criteria

1. Early behavioral disinhibition
2. Early apathy or loss of motivation
3. Loss of emotional recognition, sympathy, empathy
4. Perseverative, compulsive, ritualistic behavior
5. Hyperorality/ dietary change
6. FTD neuropsych profile
7. Frontal and/or anterior temporal atrophy on MRI or other radiologic findings
8. Presence of a known mutation

Brain 2011: 134; 2456–2477
Mendez and Perryman, 2002; Mendez et al., 2007; Rascovsky et al., 2007a; Piguet et al., 2009; the International Behavorial Variant FTD Criteria Consortium (FTDC) issued guidelines for the diagnosis of bvFTD.

FTD Prevalence

FTD: Alzheimer’s disease (AD) ratio is 1:1 in those aged 45-65.

FTD is more common that AD below age 60.

FTD spectrum comprises near 15% or more of the total dementia cases.
>50% of FTD subtypes misdiagnosed as primary psychiatric disease

Figure. % of patients initially misdiagnosed prior to ND diagnosis

Frontotemporal dementia subtypes

- Behavioral variant (bvFTD)
- Semantic dementia (SD)
- Progressive nonfluent aphasia (PNFA)
- Progressive Supranuclear Palsy (PSP)
- Corticobasal degeneration (CBD)
- FTD with motor neuron disease (FTD-MND)

Boxer AL, Miller BL. Clinical features of frontotemporal dementia. Alzheimer Dis Assoc Disord. 2005;19:S1:S3-6

Behavioral Variant
FTD
Behavioral variant FTD (bvFTD)

- 60% of FTDs are bvFTD
  - “Pick’s disease” is term only reserved for a small subset of autopsy confirmed FTLDs with Pick bodies.

Clinical Features of bv-FTD

- Gradual onset
- Impaired judgment and planning
- Apathy
- Impaired insight
- Loss of empathy and emotion recognition
- Disinhibition
- Abnormal eating behavior
- Stereotypical or ritualistic behavior
- Personal neglect

Is it AD or FTD?

- Patients with clinical bvFTD most likely to have FTLD pathology if:
  - Early executive dysfunction (first problem)
  - Early personality changes
  - Apathy
  - Disinhibition
- Patients with clinical bvFTD most likely to have AD pathology if:
  - Early age of onset
  - Neuropsychiatric features without personality changes
  - Greater memory difficulties rather than executive dysfunction

<table>
<thead>
<tr>
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<th>FTD</th>
<th>AD</th>
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<tr>
<td>Behavior &amp; Social problems</td>
<td>Early disinhibition</td>
<td>Mild, increase with disease severity</td>
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<tr>
<td>Motor signs</td>
<td>Common</td>
<td>Unusual</td>
</tr>
<tr>
<td>Mood</td>
<td>Apathy, irritability</td>
<td>Depression</td>
</tr>
<tr>
<td>Psychotic features</td>
<td>Somatic, religious, bizarre delusions</td>
<td>Delusions increase with disease severity</td>
</tr>
<tr>
<td>Appetite/hunger/diet</td>
<td>Overeating, weight ↑↑; carbohydrate craving</td>
<td>Weight loss, anorexia; misses meals</td>
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**IFTD: Loss of Fear and Disgust in bvFTD**

- What is the anatomy underlying abnormal emotional recognition in FTD?

- Previous fMRI studies isolate 2 areas:
  - Fear = amygdala
  - Disgust = insula

Presented at iFTD 2012: Discrete Neural Correlates for the Recognition of Basic Emotions in FTD, Fiona Kumfor, Australia

**Neuroimaging (fMRI) results by emotion**

(response to Eckman 60 and Caricatures)

Presented at iFTD 2012: Discrete Neural Correlates for the Recognition of Basic Emotions in FTD, Fiona Kumfor, Australia
Neuroimaging (fMRI) results by emotion

**Fear:**
Right amygdala and ACC

**Disgust:**
Left insula and temporal pole

**Anger:**
Left superior temporal sulcus

**Sadness:**
Subcallosal cingulate

Conclusion of emotions and FTD

- Deficits in emotion recognition:
  - bvFTD
  - Semantic dementia
  - Progressive nonfluent aphasia

- Negative emotions more severely affected than positive emotions in bvFTD.
- Deficits due to atrophy across multiple discrete brain regions in the frontal and temporal lobes.

VIDEO example of bvFTD
Agnosia of facial expression
ANCIENT GREEK ἀΦΑΣΙΑ (ἀΦΑΤΟΣ, ἀ- + ΦΗΜΙ) "SPEECHLESSNESS"
AN IMPAIRMENT OF LANGUAGE ABILITY

Semantic dementia and the aphasias

Semantic dementia (SD)

LEFT predominance
- Language features: fluent speech but loss of word choice

RIGHT predominance
- Profound deficits in understanding emotional expression
- Difficulty recognizing faces
- Loss of empathy

Clinical genetic and pathological heterogeneity of frontotemporal dementia J Neurol Neurosurg Psychiatry Seelaar et al. doi:10.1136/jnnp.2010.212225
Semantic dementia and music

• How does SD affect recognition of famous tunes and musical emotions?
• Aspects of music cognition relies on the anterior temporal lobe (ATL) bilaterally.
• Findings contribute to our understanding of the neurobiology of semantic memory.
  Left: naming, verbal fluency, musical emotions
  Right: famous people/ famous tunes, emotions


Higher order aspects of music processing, (recognition of famous tunes) affected in SD

Hsieh Brain 2011; Weinstein Arch Neurol 2011

Semantic dementia and music

• Emotional sounds produce greater physiological responses as measured by pupillometry in healthy controls
• Semantic dementia patients:
  – Impaired subjective emotional ratings of normally emotional sounds
  – Loss of normal increased physiological responses to emotive sounds


Conclusion: Semantic dementia and emotions

• Recognizing famous tunes and emotions in music is impaired in SD and associated with bilateral anterior temporal lobe (ATL) atrophy
• Music recruits areas in the brain known to be important verbal semantics
• Processing aspects of music is part of verbal knowledge

Progressive Nonfluent Aphasia (PNFA)

• 20% of FTD cases

• Hesitant, effortful speech; stutter or return of childhood stutter

• Anomia, agrammatism, sound errors ("gat" for "cat")

• Eventually develop severe movement disorder that overlaps with PSP and CBD

Marcel Ravel, (1875-1937) French composer.

Ravel was in the early stages of PNFA/FTD when composing the orchestral work Boléro (1928).

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Progressive nonfluent aphasia (PNFA)

Coronal T1 weighted MRI:
Case 1: mild PNFA, atrophy of temporal lobe & frontal operculum.
Case 2: moderate PNFA, global atrophy with L-sided and perisylvian predominance.

J Neurol Neurosurg Psychiatry Seelaar et al; doi:10.1136/jnnp.2010.212225
Primary Progressive Aphasia (PPA) subtypes

<table>
<thead>
<tr>
<th>Nonfluent agrammatic PPA (PNFA)</th>
<th>Semantic variant PPA (SV-PPA)</th>
<th>Logopenic PPA (LP-PPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 must be present:</td>
<td>Both must be present:</td>
<td>Both must be present:</td>
</tr>
<tr>
<td>1. Agrammatism</td>
<td>1. Impaired confrontation</td>
<td>1. Impaired single word</td>
</tr>
<tr>
<td>2. Apraxia of speech</td>
<td>naming</td>
<td>retrieval</td>
</tr>
<tr>
<td>2. Impaired single-word</td>
<td></td>
<td>2. Impaired repetition</td>
</tr>
<tr>
<td>comprehension</td>
<td></td>
<td>of sentences and phrases</td>
</tr>
</tbody>
</table>

At least 2 of 3 features:
1. Impaired syntax
2. Spared comprehension of single words
3. Spared object knowledge

At least 3 of 4 features:
1. Impaired object knowledge
2. Dyslexia or dysgraphia
3. Spared repetition
4. Spared motor speech

4. Absence of agrammatism

Gorno-Tempini 2011; Physiological phenotyping of auditory emotion processing in common syndromes of FTLD, Phillip Fletcher, UK

Four types PPA speech therapy

Errorless Learning
- Passive
  - This is a round yellow juicy citrus fruit
  - It tastes sour.
  - LEMON
- Active **BEST** in SD
  - Is this a fruit?
  - Is it round?
  - Is it juicy?
  - Is it red?
  - Is it an APPLE?
  - Please repeat.

Errorful learning
- Active
  - What is this?
  - Where does it live?
  - What is its name. Record errors.
  - TIGER. Please repeat.
- Passive
  - This is not a giraffe, not a lion, not a hippopotamus.
  - It does not live in the water or the dessert.
  - What is it? Record errors.
  - HORSE. Please repeat.

Best Novel Therapy for PPA
- Example of patient focused therapy for a piano teacher
- Front of card
  - Piano.
  - The instrument I play.
  - It has white and black keys and a pedal.
  - I teach (name) how to play piano.
- Back of card

Results: improved performance on treated words with improved naming and comprehension.

(Jakel et al 2006)
Summary: Principles of language treatment
• Greater success with personally relevant items (possible maintenance of gains with practice?)
• Semantically or phonologically based treatment successful.
• Patient is involved in item selection.
• More effective in patients with partially spared semantics (SvPPA).
• Incorporate retrained vocabulary into daily life.
• Errorless active approach more effective than traditional errorful approach for SvPPA.

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP)
KEY FEATURES
• Postural instability
• Falls
  • Vertical supranuclear opthalmoparesis
    • Upward gaze paresis with abnormal saccadic eye movements
• Axial rigidity
• Cognitive decline

Dudley Moore
(1935-2002)
Corticobasal degeneration

Corticobasal Degeneration (CBD) criteria

<table>
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<tr>
<th>Core</th>
<th>Supportive Features</th>
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<tbody>
<tr>
<td>• Cortical dysfunction</td>
<td>• Cognitive decline with preserved memory</td>
</tr>
<tr>
<td>– Ideomotor apraxia</td>
<td>• MRI: Asymmetric atrophy of parietal &amp; frontal cortex</td>
</tr>
<tr>
<td>– “Alien limb”</td>
<td>• FDG-PET: ↓ glucose uptake in parietal, frontal cortex</td>
</tr>
<tr>
<td>– Sensory hemineglect</td>
<td>basal ganglia &amp; thalamus.</td>
</tr>
<tr>
<td>– Asymmetric myoclonus</td>
<td></td>
</tr>
<tr>
<td>– Non-fluent aphasia</td>
<td></td>
</tr>
<tr>
<td>• Extrapyramidal dysfunction</td>
<td></td>
</tr>
<tr>
<td>– Asymmetric rigidity lacking and focal dystonia</td>
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</table>

Neuropathology
Frontotemporal Lobar Degeneration (FTLD) = FTD with histopathology

- Associated with biochemical abnormalities of at least 3 proteins (tau, TDP-43, FUS)
  - The term Pick’s disease can only be used for FTLD with Pick bodies.
- Each protein is associated with different pathologies & different genetic abnormalities.
- Wide range of clinical syndromes with heterogeneous pathologies.
  - Hypothesis: clinical and imaging markers that may predict pathology

Tau immunopositive inclusions in FTLD

Pick inclusion bodies in FTLD Pick's disease. (A) Round, circumscribed, amphophilic Pick bodies seen on H and E-stained sections, but are more easily visualized in (B) highlighted with silver stains (arrow).


TDP-43 and FUS proteinopathies

TDP-43/FUS pathology:
- numerous neuronal cytoplasmic inclusions (NCIs), with marked reduction of nuclear TDP-43 but also of nuclear FUS staining (see arrowheads) in the dentate granule (DG) cells of the hippocampus

Can we link clinic FTD to pathology to genetics?
Rohrer Biochimica et Biophysica Acta 1822 (2012) 325–332

Genetics

Human chromosomes and autosomal dominant mutations
FTD inheritance

Genetic (40%)
10-15% have a single gene mutation (autosomal dominant inheritance)

Sporadic (60%)
First in the family to have FTD (family not at risk)

FTD is heterogenous:
Genes → pathology → clinical syndrome

5 single gene mutations

- **MAPT gene**
  - c17 makes tau

- **GRN gene (PGRN)**
  - c17 makes progranulin

- **VCP gene**
  - c9 codes for valosin-containing protein

- **CHMP2B gene**
  - c3 makes multivesicular body protein 2B (chromatin modifying protein 2B).

- **TARDBP gene**
  - c1 produces transactive response DNA-binding protein, 43-kDa molecular weight (TDP-43)

- **C9ORF72, unknown function**
MAPT gene mutation

- Tau maintains the structure of neurons but mutation causes tau to clump abnormally.
- MAPT mutation patients have MORE hippocampal atrophy than AD patients.
  - Presymptomatic carriers followed for over 17 years.
  - Decline in episodic and working memory.
  - Clinical syndrome of bvFTD and FTDP-17.

GRN mutations

- 5-10% of all FTLD, 13-25% of familial FTLD
- Reduced progranulin production (haploinsufficiency) and increased neuronal inclusions made of TDP-43 and ubiquitin.
- GRN mutations are associated with bvFTD, PNFA and movement disorders but generally NOT MND/ALS

C9ORF72

- GGGGCC repeats in the open reading frame
- Mutation leads to TDP-43 positive pathology.
- 20-67% of familial ALS, 7% of sporadic ALS.
- 25% of familial FTD, 5% of sporadic FTD.

(Majounie et al 2012)
C9ORF72 origins

• Unknown physiologic function.
• People with mutant variant share a haplotype containing dozens of single-nucleotide polymorphisms in the region surrounding the C9 gene, many scientists suspect a single founder.
  – C9ORF72 began expanding 6,300 years ago, but said it could have been any time between 1600 and 16,500 years ago (Smith et al 2012, Ishiura et al 2012, Tsai et al 2012)
  – Shared haplotype itself is somehow predisposed to repeat expansions.

C9ORF72

• Symptomatic: Age 50, 9%; Age 85, 74% of carriers
• Clinical: ALS with bulbar symptoms, bvFTD, or FTD with parkinsonism.
• Genetic anticipation
  – Occurs in 1/4 of kindreds carrying the C9ORF72 variant.
  – Children with symptom onset 7 years earlier than parent, possibly from repeats growing in successive generations.

Investigational drugs and vitamin therapies
Memantines

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Design</th>
<th>Outcome cognition</th>
<th>Outcome behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boxer et al 2009</td>
<td>21 bvFTD, 13 SD, 9 PNFA ex. 43</td>
<td>Open 26 wks 20mg</td>
<td>N/A</td>
<td>Transient improvement in NPI for bvFTD</td>
</tr>
<tr>
<td>Dietl-Schmid et al 2008</td>
<td>16 bvFTD</td>
<td>Open 6 months 20mg</td>
<td>ADAS-cog increased</td>
<td>No change in NPI, FBI</td>
</tr>
<tr>
<td>Vercelletto et al 2011</td>
<td>49 bvFTD (23 treatment, 26 placebo)</td>
<td>Phase II 52 wk random DB placebo</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>NCT0054947</td>
<td>Phase IV 26wk random, multicenter DB placebo controlled</td>
<td>In progress</td>
<td>In progress</td>
<td></td>
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</tbody>
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Antidepressants

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<th>Outcome cognition</th>
<th>Outcome behavior</th>
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<tr>
<td>Deakin et al 2004</td>
<td>10 bvFTD</td>
<td>6 wks paroxetine 40mg</td>
<td>Worse paired learning, reversal learning, pattern recognition</td>
<td>No difference NPI or FBI</td>
</tr>
<tr>
<td>Moretti et al 2003</td>
<td>16 bvFTD</td>
<td>14 months of paroxetine 20mg versus piracetam 1200mg</td>
<td>Paroxetine improved</td>
<td></td>
</tr>
<tr>
<td>Lebert et al 2004</td>
<td>26 bvFTD</td>
<td>Trazadone Random placebo control 12wk</td>
<td>No effect</td>
<td>Improved NPI</td>
</tr>
<tr>
<td>Swartz et al 1997</td>
<td>11 bvFTD</td>
<td>3 months open label: fluoxetine paroxetine, sertraline</td>
<td>Improved disinhibition, depression, compulsions, less carb cravings</td>
<td></td>
</tr>
</tbody>
</table>

Antipsychotics

- Antipsychotics have a statistically significant benefit for behaviors in FTD. (Curtis and Resch 2000, Fellgiebel 2007)
- Open label study with olanzapine in 17 bvFTD patients over 24 months, showed improved behavioral symptoms. (Moretti et al 2003)
Clinical studies in progress

- DB placebo controlled randomised parallel group, 12 month safety and efficacy trial of TRx0237 (tau aggregation inhibitor) in bvFTD (NCT01626378).
- Phase I dose finding study of intranasal oxytocin in bvFTD (NCT01386333). Oxytocin mediates social behavior.
- Effects of tolcapone on FTD (NCT00604951). Tolcapone increases dopamine.

### Potential treatments (Vossel and Miller 2008)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Target</th>
<th>Drugs</th>
<th>Disease stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPT</td>
<td>Inhibit tau kinases</td>
<td>Lithium, valproic acid</td>
<td>preclinical</td>
</tr>
<tr>
<td></td>
<td>Inhibit/Reverse tau aggregation</td>
<td>Anthraquinones, phenylthiazolylhydrazides, Tau Rx</td>
<td>preclinical</td>
</tr>
<tr>
<td></td>
<td>Reduce tau expression</td>
<td>Several compounds</td>
<td>preclinical</td>
</tr>
<tr>
<td></td>
<td>Block tau cleavage</td>
<td>Calpain inhibitor A-705253</td>
<td>preclinical</td>
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<td>Immunosuppression</td>
<td>FK-506</td>
<td>preclinical</td>
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<td>Alter chaperone system to enhance tau degradation</td>
<td>Hsp60</td>
<td>preclinical</td>
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<tr>
<td></td>
<td>Interfere with splicing to normalize 3R &amp; 4R ratio</td>
<td>Splicing regulators</td>
<td>preclinical</td>
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<tr>
<td></td>
<td>Stabilize microtubules</td>
<td>Paclitaxel</td>
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FTD Non-rx management

- Education
- Med-alert bracelet
- Occupational and financial advice
- Genetic counseling if relevant
- Specific driving advice
- Environmental modification
  - Visual, hearing, mobility aids, continence aids
- Behavioral intervention (communication aids, routines, reassurance)
- Caregiver support

The central problem in all neurodegenerative disease...

How do protein alterations (an autopsy finding) or a manifest is an actual patient in your clinic?
Can we predict pathology from the clinical presentation (clinical)...

Questions?