What is Frontotemporal Dementia? (with an emphasis on PPA)

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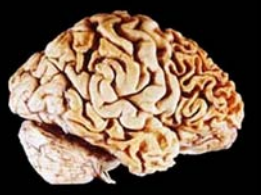
Overview

- Terminology and history of FTD
- Brief overview of FTD
- PPA subtypes
- Histopathological correlates
- Genetics
- Clinical Trials
- Current work here.



Demographics

- Highest ages 45 to 64, but can occur widely– 10% of FTD is under age 45, 30% older than 65.
- Likely under-recognized at the time

Functional Costs of FTD:

- Direct costs of medical care– hospital stays, consultant fees, medication etc.
- Indirect costs– lost productivity, job loss…
  - bvFTD tends to strike people earlier than AD.
  - Legal costs, marital counseling (or divorce), financial consequences of "poor judgements"

Diagnosis in the community

- About 28% of all neurodegeneration is first diagnosed with psychiatric disease.
- bvFTD is often first diagnosed as bipolar disease or schizophrenia (Khan 2012).
- PPA is often diagnosed as Alzheimer's disease (memory problems, but just memory for words).
- Alternatively:
  - People send in "bvFTD," but may be AD, phenocopy, "bvFTD by proxy" and others.
  - People send in "PPA," but may be broader dementia, vascular, or psychiatric disease among others.
  - PPA is sometimes confused with bvFTD and vice versa.
  - Also consider CTE, NPH, low ICP syndromes, and some metabolic diseases.

Tortured terminology

- Functional diagnosis – how much someone's life is impacted by a disorder, e.g. "dementia"
- Syndromic diagnosis – a collection of medical symptoms usually suggesting a common cause.
- Pathological diagnosis – a pattern of usually microscopic finding, considered the gold standard, e.g. "frontotemporal lobar degeneration."
- Genetic diagnosis – Underlying genetics leading (usually) to a distinct pathological diagnosis.

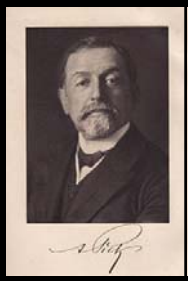
FTD terminology

- Behavioral variant frontotemporal dementia is the most common
- Two other forms of "Frontotemporal dementia" (at least)
- Nonfluent primary progressive aphasia (nfvPPA, PNFA, pnfPPA, PPA-G)
- Semantic variant primary progressive aphasia (svPPA, SD)
- Also, any form of FTD may coexist with other syndromes, like amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP) or corticobasal syndrome (CBS).
- FTD has sometimes been called FTLD (frontotemporal lobar degeneration), but we now just use this for a pathological diagnosis.

FTD Subtype	Supporting Clinical Features	Relevant Neuropsychological Tests	Anatomical Correlate	Common Histopathology	Underlying Genetics
bvFTD	Behavioral disinhibition, apathy, loss of empathy, compulsive behavior, hyperorality or dietary changes	Trails-B, letter fluency/design fluency, digit span, perseveration, Stroop, NIH EXAMINER	frontal and/or temporal lobes, often right-hemisphere predominant.	Tau, TDP-43, FUS, CHMP-2B	*MAPT, PGN, C9orf72, VCP, FUS, CHMP-2B, TAR-DNA*
svPPA	Poor confrontation naming, impaired single-word comprehension, poor object knowledge, surface dyslexia, spared repetition, spared motor speech and grammar.	Pyramids and Palm Trees, Boston Naming, Peabody Picture Vocabulary Test	Dominant anterior temporal lobe	TDP-43 type C	rarely genetic
pnfPPA	Agrammatism, effortful speech, impaired comprehension of syntactically complex sentences, spared single word comprehension and object knowledge	Grammatically compex sentences, Boston Naming, Northwestern Anagram Test	Dominant posterior fronto-insular region	Tau, TDP-43	*MAPT, PGN*

History

- Arnold Pick, 1892– first description
- Alois Alzheimer, 1911– describes pathological findings associated with this disorder
- Gans, 1922– suggests the term "Pick's disease" for all focal frontal neurodegeneration
- "Dark ages" of behavioral neurology, 1925-1970s…
- Constantinidis, 1974—3 path subtypes, which would now be called Pick's, TDP-C, and CBD.
- 1989– thought to not actually be so rare.
- 1994– Neary criteria for FTD
- 2011– Most recent international criteria for bvFTD and PPA consensus criteria
- Future dilemmas?



2011 bvFTD criteria

Possible (3/6 of the following)
- Early disinhibition
- Early apathy
- Early loss of sympathy/empathy
- Early perseverative, stereotyped, or compulsive ritualistic behavior
- Hyperorality or dietary changes
- Neuropsych: Executive/generation deficits with relative sparing of memory and visuospatial

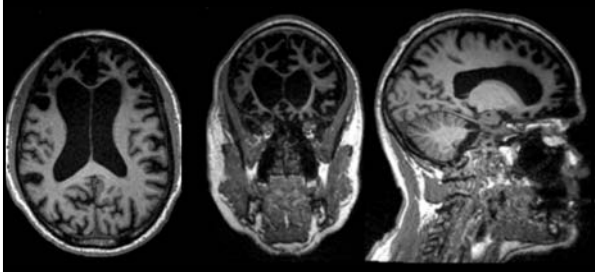
Probable
- Meets criteria for possible bvFTD
- Exhibits significant functional decline
- Magnetic Resonance Imaging or Positron Emission Tomography consistent with bvFTD
- Exclusion
- Deficits better accounted for by other non-degenerative disorders
- Behavioral disturbances better accounted for by psychiatric diagnosis.
- Biomarkers strongly indicative of AD or other neurodegenerative process.

Definite
- Histopathological FTLD evidence on biopsy or autopsy
- Meets criteria for possible or probable bvFTD
- Known pathogenic mutation (MAPT, PGN, CHMP2B, VCP, C9orf72, among others).

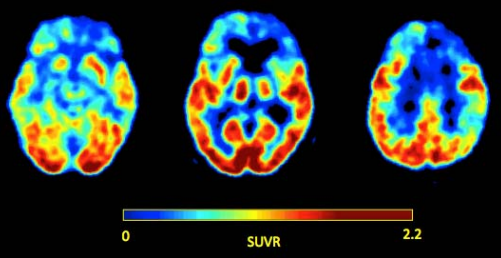
The right temporal variant

- Diminished "social semantics," i.e. loss of socially relevant knowledge.
- Executive function may initially be relatively spared.
- Diminished facial recognition.
- Tend towards more rigid or impulsive behavior.
- Changes in appetite and eating habits.
- Evolves into the left temporal variant, i.e. semantic variant of primary progressive aphasia.

Neuroimaging: MRI



Neuroimaging: PET



Three variants of PPA

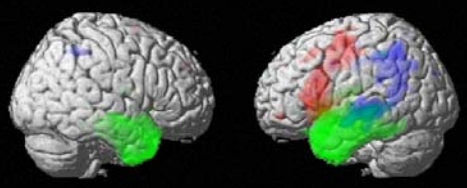
Nonfluent variant
- Impaired syntax and/or motor speech (AOS, dysarthria)
- FTD

Logopenic variant
- Impaired phonological processing (phonological loop)
- AD

Semantic variant
- Impaired semantic processing
- FTD

Gorno-Tempini et al., 2011

Three main PPA variants



Gorno-Tempini et al., Ann Neurol 2004

Nonfluent PPA: Clinical Features

Gorno-Tempini et al., 2011

Core Features:

One of the following must be present:

- Agrammatic production
- Effortful, halting speech with speech sound errors, including distortions, deletions, insertions, substitutions, transpositions (consistent with apraxia of speech)

Associated Features:

Two of the following must be present:

- Impaired syntactic comprehension
- Spared single-word comprehension
- Spared object knowledge

Stole this from Maya's slides.

Nonfluent Variant: Motor Speech and Syntax

Logopenic PPA: Clinical Features

Gorno-Tempini et al., 2011

Core Features:

Both of the following must be present:

- Impaired word retrieval in spontaneous speech and confrontation naming
- Impaired repetition of sentences and phrases

Associated Features:

Three of the following must be present:

- Phonological errors in speech
- Spared single-word comprehension and object knowledge
- Spared motor speech
- Absence of agrammatism

Stole this from Maya's slides.

Logopenic Variant: Word-finding and repetition deficits due to impaired phonology

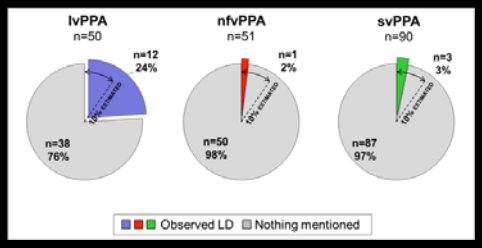
Progression of lvPPA (phonological deficit)

2009

2013

2015

Increased frequency in lvPPA only



Miller Z et al., in press

Semantic PPA: Clinical Features

Gorno-Tempini et al., 2011

Core Features:

Both of the following must be present:

- Impaired confrontation naming
- Impaired single word comprehension

Associated Features:

Three of the following must be present:

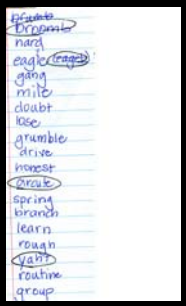
- Poor object knowledge
- Surface dyslexia/dysgraphia
- Spared repetition
- Spared grammar and motor speech

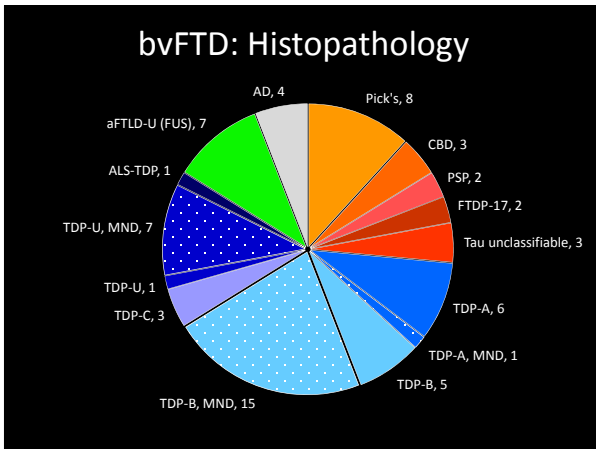
Stole this from Maya's slides.

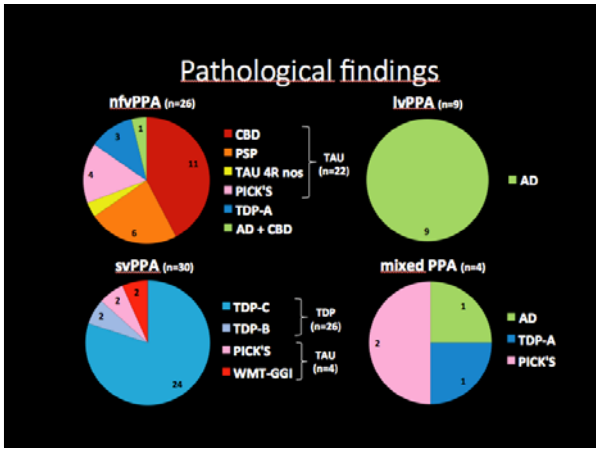
Semantic Variant: Word-finding and object knowledge

Picture Naming

SV: Surface dysgraphia

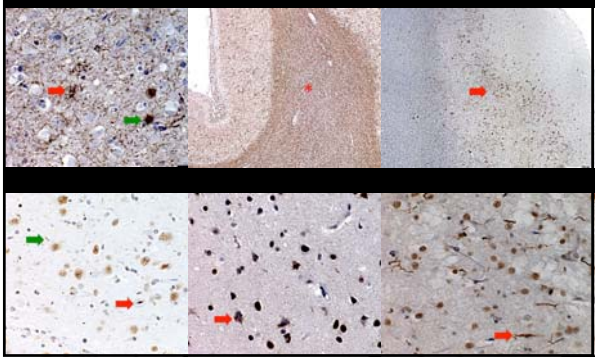






Pathological Diagnosis	Common Symptoms	Typical Neuroimaging	Common Genetics	Histopathology
Tau: Pick's	"classic" bvFTD, nfvPPA	"knife edge" bifrontal atrophy	MAPT	Pick bodies
Tau: PSP	PSP-syndrome, nfvPPA, depression	midbrain atrophy	MAPT	tufted astrocytes, globose tangles, glial threads
Tau: CBD	CBS among many others	dorsal atrophy near motor strip	MAPT	astrocytic plaques, ballooned achromatic neurons
TDP-43 A	CBS, nfvPPA	dorsal, asymmetric atrophy, frontal, inferior, parietal lobes as well as basal ganglia.	progranulin	many neurocytoplasmic inclusions and short dystrophic neurons in layer 2 of the cortex.
TDP-43 B	FTD-ALS, "psychiatric" symptoms such as delusions and hallucinations	symmetric volume loss in dorsolateral, medial, orbitofrontal, and anterior temporal cortex, cerebellum, thalamus	C9orf72	moderate numbers of neurocytoplasmic inclusions and few dystrophic neurons throughout the cortical layers
TDP-43 C	strong association with svPPA	Anterior temporal lobe atrophy	rarely genetic	few neurocytoplasmic inclusions and numerous long dystrophic neurons

Common Histopathologies



Genetics

- 40% of people with FTD have a family history of dementia, neuropsych, or movement disorder
- 10% of people with FTD have a single gene inherited in an autosomal dominant fashion (Chow 1999)
- *MAPT*
- *PGN* and *C9orf72*
- others

MAPT

- Predominantly on chromosome 17
- Original family described by Wilhelmsen in 1994
- Per Van Swieten, about 25% of all familial FTD is a tau mutation
- Rarely observed outside of a family history of FTD, dementia or parkinsonism (Selaar 2001)
- Usually causes 4R tauopathies rather than Pick's disease.

PGN

- Protein first discovered by Bateman in 1990. Baker and Cruts gave first descriptions simultaneously in 2006.
- Probably involved with inflammation and lysosomal processing.
- Mutations lead to less progranulin protein.
- Usually leads to TDP-A pathology.

C9orf72

- First family described in 2000 (Brown and Hosler)
- Mutation and mechanisms described by Renton and DeJesus-Hernandez in 2011.
- Get multiple repeats, causing aggregates of mRNA

Others

- Disease causing: VCP, CHMP2B, ESCRT2, EXT2, UBQLN2, SQSTM1, FUS, TARDBP…
- Disease modifying: TREM2, COMT, ATXN2…

Video-Implemented Script Training for Aphasia

"Tell me about your childhood."

Pre-Treatment **One week later…**

(Henry et al., *Brain*, under review)

Questions?

- There's a lot of speakers still to come…
- Please send us your FTD referrals!