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Frontotemporal Degeneration and Primary Progressive Aphasia Caregiver and Professional Education Conference

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Objectives

- Define and clarify nomenclature
  - Frontotemporal disorders
    - Behavioral variant frontotemporal degeneration (bvFTD)
    - Primary progressive aphasia (PPA)
      - Agrammatic/Non-fluent
      - Logopenic
      - Semantic
    - FTD with motor abnormalities
      - Corticobasal degeneration
      - Progressive supranuclear palsy
      - FTD with motor neuron disease(FTD-MND)
        - » *Amyotrophic lateral sclerosis (FTD-ALS)*

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Objectives continued:

- Discuss diagnostic evaluation and ancillary testing
- Neuroimaging
- Discussion of role of genetics and genetic testing in certain cases
- Treatments
- Current research and future plans

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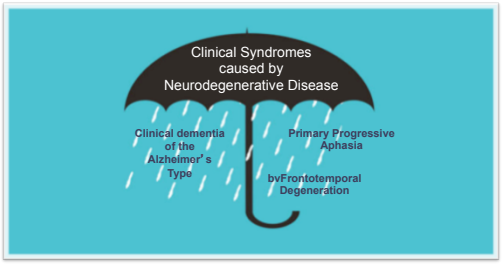

Dementia
- A general term for:
  1) The loss of memory or other thinking skills
  2) Significantly interferes with daily life (work, school, family)

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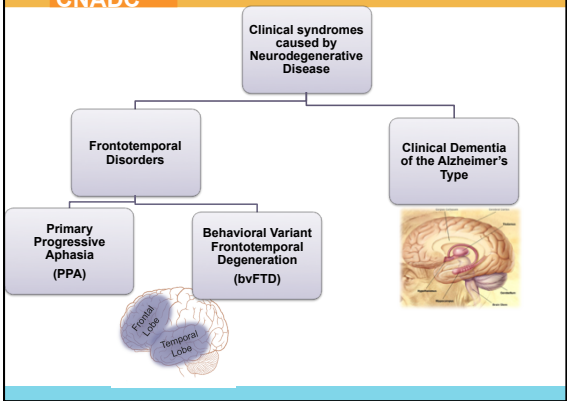

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bvFTD:

Diagnostic criteria

- Established clinical consensus criteria (Rascovsky et al., Brain 2011; 134:2456-77):
- Core features
  - Insidious onset and slow progression
  - Three of the following must be present
    - Behavioral disinhibition
    - Apathy or inertia
    - Loss of sympathy or empathy
    - Perseverative or ritualistic behavior
    - Hyperorality or dietary changes
    - Problems with executive function but spared memory and visuospatial functions

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PPA:

Diagnostic criteria

- Established clinical consensus criteria (Gorno-Tempini, 2011):
- Core features
  - Insidious onset and slow progression
  - Logopenic
  - Agrammatic/Non-fluent
  - Semantic

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How is the diagnosis made in bvFTD and PPA?

- Neurologic examination
  - Caregiver input is very important
  - Differential diagnosis of dementias in younger patients is often more broad
  - Additional testing maybe needed:
    - Lumbar punture (spinal fluid analysis for Tau and amyloid)
    - Electroencephalogram (EEG)
    - Other blood tests
    - Genetic testing in some cases

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What is neuropsychological testing?

- A battery of paper and pencil type tests designed to diagnose brain dysfunction by examining performance on tasks that model actual cognitive actions.
- Normed for the persons intelligence, age, education
- Can be 2-4 hours of testing
- Reliable
- Medicare covered

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bvFTD Diagnostic evaluations

- Neuropsychology:
  - Impaired frontal lobe tests in absence of severe amnesia, aphasia, or visuospatial deficits
  - Executive dysfunction often prominent
- Imaging:
  - Atrophy or decreased uptake in the frontal or anterior temporal lobes (bilateral or unilateral) by MRI, CT, PET, SPECT (The Lund and Manchester Groups, J Neurol Neurosurg Psychiatry 1994;57:416-418; Neary et. al, Neurology 1998;51:1546-1554)

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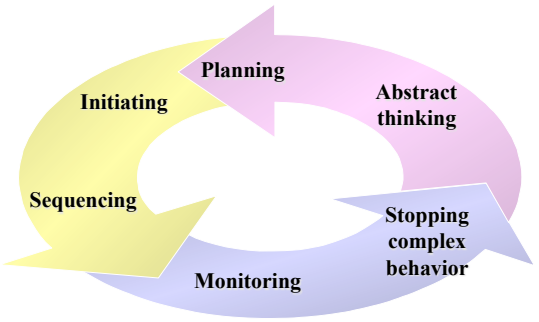
Elements of Executive Function



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PPA Diagnostic evaluations

- Neuropsychology:
  - Impairment is prominent in a single domain (language) with relative sparing of other domains early on (e.g., memory, personality, and perception)
- Imaging:
  - Focal atrophy in the left Temporal lobe

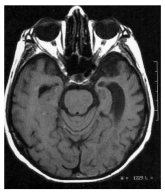

Figure 1 - MRI (axial T1) showing focal atrophy of the left temporal lobe.

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Neuroimaging

- Anatomic MRI
  - This is the most commonly used
- FDG-PET
  - Currently Medicare approved, other insurers require pre-certification for coverage
- Amyloid-PET
  - Used in Alzheimer's diagnosis
- FDDNP

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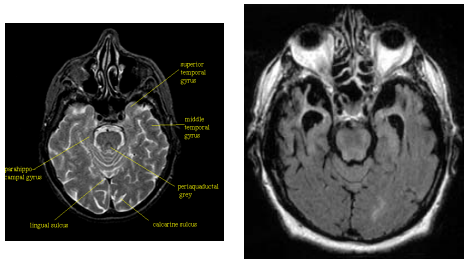
bvFTD Anatomic MRI



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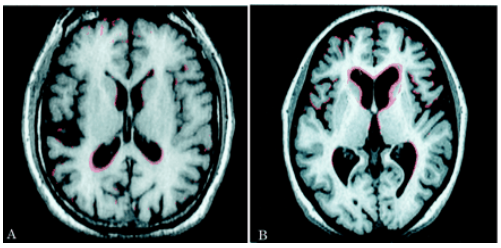
AD bvFTD



Chan, *Neurology* 2001

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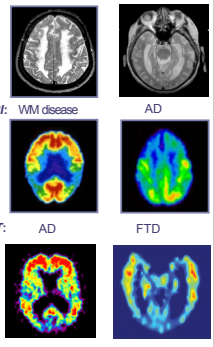
Neuroimaging and Dementia

American Academy of Neurology Practice Parameter Guidelines recommend structural imaging in initial evaluation of patients with dementia[1]

Positron emission tomography (PET) of fluorodeoxyglucose (FDG) may help differentiate Alzheimer's disease (AD) from frontotemporal dementia (FTD)[1,2]

Other PET imaging technologies are currently under development[3,4]



MRI=magnetic resonance imaging; WM=white matter; PIB=Pittsburgh Compound-B; FDDNP=2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile

Med. 2006;355:2652-2663. 4. Klunk WE, et al. *Ann Neurology* 2004;55:306-319.

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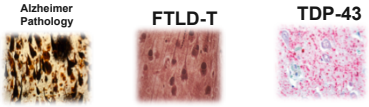
Neuropathology in PPA & bvFTD

- The term "frontotemporal lobar degeneration" (FTLD) is used to describe the specific pathological diseases that result in FTD syndromes. These too are united by their impact on frontal and temporal brain structures.
  - Subtyping is based on the specific proteins found within neuronal inclusions. Most FTLD subtypes are either:
    - FTLD-tau, which includes Pick's disease, CBD and PSP, all of which show tau-containing inclusions or
    - FTLD-TDP, which includes several subtypes in which TDP-43 containing inclusions are seen.
- In addition to FTLD pathology PPA can be caused by AD:



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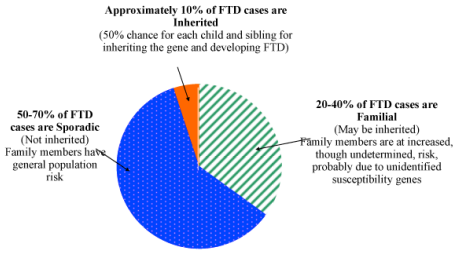
Genetics



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bvFTD/PPA Role of Genetics

- 1999 study showed of 42 FTD cases, 19 had at least 1 other family member affected
  - 1/3 had a positive family history in this study, however other studies lower
  - Showed an autosomal dominant inheritance
- Linked to chromosome 17 (tau gene) and chromosome 3
- Progranulin (PRGN) gene mutation linked with ubiquitin inclusions
  - Seen in both PPA and FTD
- Association with ALS (FTD-MND)
  - Chromosome 9

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FTD Genetics Recap

- Chromosome 17
- MAPT gene mutation ⇒ tau positive inclusions
  - Not shown specifically in PPA
- PRGN gene mutation ⇒ ubiquitin inclusions
  - Has been shown in both PPA and FTD families

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Frontotemporal Disorders

- Implications for bvFTD/PPA different from other dementias/AD:
  - Younger age at onset
  - Often person is mid-career and disability/ legal issues
  - Greater caregiver burden and increased dependency and health care costs due to the nature of the conditions

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bvFTD/PPA Treatments

- Cognitive enhancers
  - When Alzheimer's treatments may be used
  - The Memantine clinical trial and others
- Behavioral treatments
  - Antidepressants
  - Antipsychotics
  - Mood stabilizers
- Supportive therapies
  - Speech, Occupational, Physical, Cognitive

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Why investigate symptomatic treatments for FTD?

- No disease-modifying treatments for FTD
- Symptomatic treatments are in common use
- Improve quality of life for patients and families
- Even if we develop disease-modifying treatments, we will still need symptomatic treatments
- Symptomatic and disease-modifying treatments are not mutually exclusive and the distinction may not always be clear

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Comparison of prescribed treatments

	Bv-FTD	AD
Cholinesterase inhibitor	41%	55%
Memantine	30%	28%
Antidepressant	43%	30%
Anxiolytic	7%	11%
Antipsychotic	5%	10%

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"Borrowed" treatments for FTD

	Treatment	Borrowed from
Repetitive behaviors	SSRI	OCD
Apathy	None	
Empathy	None	
Socially inappropriate behaviors / agitation	Antidepressants / atypical antipsychotic	AD
Expressive aphasia	Speech therapy	Stroke
Hyperphagia	SSRI	Impulse-control psychiatric disorders
Executive dysfunction	None	
Neurodegeneration	Memantine	AD

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Medications for FTD

- Cholinesterase inhibitors
  - Results and effects contradictory, not currently recommended
- Memantine
  - Well tolerated in three open label trials and a randomized, double-blinded placebo controlled trial
  - May improve behavioral symptoms
  - Awaiting current clinical trial results

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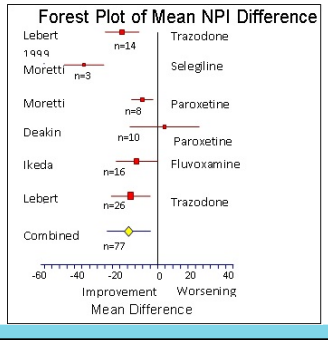
Antidepressants



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Which anti-depressant?

- Selective serotonin reuptake inhibitors
- Serotonergic dysfunction in FTD
- Open-label studies show improvement in neuropsychiatric behaviors
  - Citalopram
    - Improved irritability, depressed mood, disinhibition
  - Fluvoxamine
    - 12 wk study showed significant improvement in behavioral symptoms
  - Sertraline
    - Reduced verbal and motor sterotypic behaviors
  - Others: paroxetine, trazodone, Lexapro

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Atypical antipsychotics

- Generally, a second-line agent after antidepressants for behavioral symptoms
- In dementia, small effect size on behavioral symptoms (0.1 to 0.2)[1]
- Increased OR of death of 1.54 (95% CI, 1.06-2.23; NNH = 87) [1]
- Should be used very carefully due to potential severe adverse events
  - Cardiovascular, worsening motor, stroke

1. Maher et al., *JAMA*, 2011

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Atypical antipsychotics, cont

- Risperidone
  - Range: 0.5-2.5 mg
  - Can have more EPS than other atypicals at higher doses
- Quetiapine
  - Range: 50-200 mg
  - Sedating, possibly less efficacious
- Olanzapine
  - Range: 2-10 mg
  - Limited use in FTD because of appetite increase
- Aripiprazole
  - Range: 2-15 mg

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Pro-dopaminergic medications

- Few trials, but early evidence of improvement of behavioral symptoms[1,2]
- Dopamine-agonist bromocriptine in PPA
  - **A clinical trial of bromocriptine for treatment of primary progressive aphasia.** Reed DA, Johnson NA, Thompson C, Weintraub S, Mesulam MM. Ann Neurol. 2004 Nov;56(5):750.

1. Rahman et al., *Neuropsychopharmacology*, 2006
2. Huey et al., *J. Clin. Psychiatry*, 2008

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Tailored medication treatment for FTD syndromes

	Current	Future
Repetitive behaviors	SSRI	SSRI
Apathy	None	? Pro-dopaminergic meds
Empathy	None	Oxytocin
Socially inappropriate behaviors	SSRI / atypical antipsychotic	SSRI / atypical antipsychotic
Expressive aphasia	Speech therapy	Speech therapy
Hyperphagia	SSRI	SSRI
Executive dysfunction	None	? pro-dopaminergic meds
Neurodegeneration	None	? Memantine

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Future directions

- Tau treatments
  - Davenutide
  - GSK3, lithium, valproate
  - Methyl blue
  - Epothiline D
- Coenzyme Q 10
- Non-pharmacologic therapies
  - Direct brain treatments (e.g. TMS)
  - Behavioral interventions

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Conclusion

- Final remarks
- Question and answer session
- Thank you!

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Other Resources & Support

- Cognitive Neurology and Alzheimer's Disease Center
  - www.brain.northwestern.edu
  - A list of programs, educational support and Resources
- The Association for Frontotemporal Degeneration (AFTD)
  - www.ftd-picks.org
  - Serves as a hub for distributing news relevant to FTD and PPA
- National Aphasia Association
  - www.aphasia.org
  - Promotes education, research and support relevant to PPA
- FTD/PPA Caregiver & Professional Education Conference
- International PPA Registry:
  - http://www.ppaconnection.org/

PPACT International PPA Connection

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- Provides clinicians and researchers with a platform for exchanging knowledge about the latest developments in FTD
- The multidisciplinary program will address clinical diagnosis, management and care, epidemiology and neuropsychology, as well as other disciplines.
- The FTD conference will also feature a one day caregiver program for family members/FTD caregivers designed to provide education and offer support to those in close contact with this currently untreatable degenerative brain disease.

http://www2.kenes.com/ftd2012/Pages/Home.aspx