

An Update on Frontotemporal Dementia and Other Non-AD Dementias

Bruce L. Miller, MD
Memory and Aging Center,
Department of Neurology and Psychiatry,
University of California, San Francisco



Dementia with Abnormal Movement

- ◆ Idiopathic Parkinson's Disease (PD)
- ◆ Parkinson's Disease Dementia (PDD)
- ◆ Dementia with Lewy bodies (DLB)
- ◆ Parkinsonism in Alzheimer's Disease
- ◆ Pure AD without Parkinsonism
- ◆ Progressive supranuclear palsy
- ◆ Corticobasal degeneration
- ◆ Prion disorders

Dementia with Abnormal Movement

- ◆ Idiopathic Parkinson's Disease - α -syn
- ◆ Parkinson's Disease Dementia (PDD) - α -syn
- ◆ Dementia with Lewy bodies (DLB) - α -syn, A- β
- ◆ Parkinsonism in late Alzheimer's Disease - A- β
- ◆ Multi-system-atrophy (MSA) - α -syn
- ◆ Progressive supranuclear palsy - tau
- ◆ Corticobasal degeneration - tau
- ◆ Creutzfeldt-Jakob disease - prions

Mixed Pathology

- ◆ AD patients show Lewy body pathology
 - Tsuang 2006 (52.6% AD show Lewy body pathology)
 - Leverenz 2006 (96% PS1 Lewy body amygdala)
- ◆ PDD and DLB patients have AD pathology
 - Ballard 2006 - 2/3 DLB Braak 5-6
 - 14-22% PD Braak 5-6
 - PDD 3-fold lower plaque vs DLB, 20% less synuclein, but 30% greater loss ChAT

PATHOLOGY

Table 2 Relationship between pathology and duration of PD prior to dementia

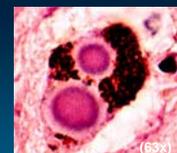
| | Plaques (CERAD) | Braak stage | Mean α -synuclein score | CHAT BA 36 |
|---|--------------------|--------------|--------------------------------|------------|
| DLB (n = 29) | Abundant, 18 (62%) | 5/6-3 (10%) | 13.2SD0.3 | 1.42SD0.67 |
| | Moderate, 6 (21%) | 3/4-10 (34%) | | |
| | Scarcely, 3 (7%) | 1/2-14 (48%) | | |
| | None, 2 (7%) | 0-2 (7%) | | |
| PD for 1-9.5 years prior to dementia (n = 14) | Abundant, 2 (14%) | 5/6-2 (14%) | 11.68D4.7 | 1.12SD0.51 |
| | Moderate, 8 (43%) | 3/4-5 (36%) | | |
| | Scarcely, 2 (14%) | 1/2-5 (36%) | | |
| | None, 4 (29%) | 0-2 (14%) | | |
| PD for >9.5 years prior to dementia (n = 14) | Abundant, 3 (21%) | 5/6-0 (0%) | 10.68D4.5 | 0.66SD0.99 |
| | Moderate, 1 (7%) | 3/4-5 (36%) | | |
| | Scarcely, 4 (29%) | 1/2-9 (64%) | | |
| | None, 6 (43%) | 0-0 (0%) | | |

PDD 3-fold less plaque VS DLB, 20% less α -synuclein pathology, but 30% greater loss ChAT

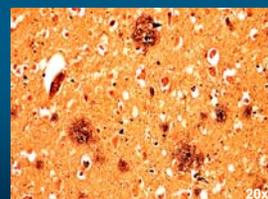
Ballard et al. (2006)

75 yo male with history of visual hallucinations that progressed to severe dementia.

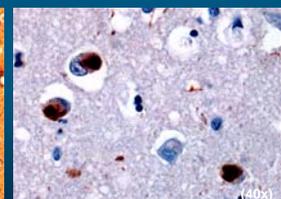
Dx: Mixed Alzheimer's disease and Lewy body pathology



Substantia nigra



Bielschowsky



Synuclein

Entorhinal Cortex

DIAGNOSTIC CRITERIA

1. **Dementia** (Cognitive & functional impairment)
2. **Core features:**
 - Fluctuations alertness/awareness
 - Recurrent visual hallucinations, well-formed detailed
 - Parkinsonian symptoms (e.g., axial rigidity, bradykinesia)
3. **Suggestive features** (1 sugg. + 1 core = probable; 1+ sugg. = possible):
 - REM-Behavior Disorder (RBD)
 - Neuroleptic sensitivity
 - Low DA transporter uptake SPECT/PET

McKeith et al. (2005)

Prevalence of Dementia in PD

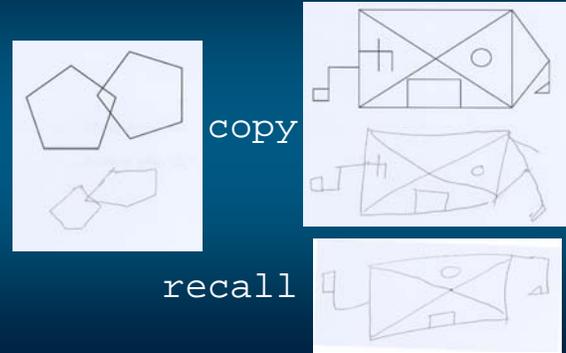
- ◆ Janvin 2005 J Geriatr Psych Neurol
 - 76 non-demented PD patients over 4 years
 - Twenty-five (42%) new dementia cases
 - Poor at Stroop predicted dementia
- ◆ Janvin 2006 Mov Dis
 - 72 PD patients (34 normal, 38 MCI)
 - 4 years 62% MCI and 20% PD demented

Cognitive Impairment in PD

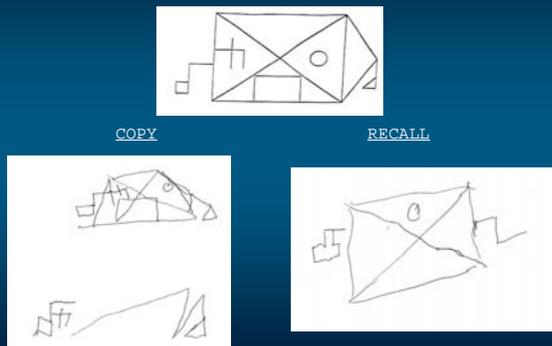
- ◆ 10% PD develop dementia over 3.5 years, 57% showed signs of cognitive impairment (largely executive control)
- ◆ *Predictors of cognitive decline:* baseline deficits in semantic fluency and pentagon copy and non-tremor dominant motor phenotype.
- ◆ Deficits related to posterior cortex (e.g., semantic fluency and pentagon copy) likely reflect cortical lewy body pathology.

Williams-Gray et al. (2007)

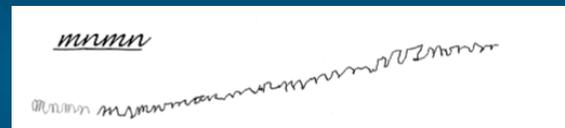
65 y.o. surgeon with MCI-DLB



MT - Neuropsych



MT - Neuropsych



ET - Neuropsych

2002



2003



Hallucinations & Illusion in DLB/PDD



Ellersbach et al. (2003)

FLUCTUATIONS in DLB

- ◆ 200 Normals, 70 DLB, 70 AD patients
- ◆ Distinguishing features suggestive of DLB:
 - daytime drowsiness and lethargy
 - daytime sleep lasting at least 2 hours
 - staring into space for long periods
 - episodes of disorganized speech
- ◆ 63% of DLB patients had 3/4 symptoms vs. 12% of AD patients = 83% pos. pred. value

Ferman et al. (2004)

DLB/PDD Lapses

- Lapses awareness (e.g., "detaches", "off with pixies", "stops talking mid-conversation") then returns
- No discernable trigger
- Confusion delusional/confabulatory quality (e.g., "one day says she's been to NY, next day lucid," "some days thinks there are extra people for dinner", "wife is not wife" or "home is not home")
- Degree of variation in awareness is extreme (e.g., some days can do checkbook vs. other days can not stay awake or hold conversation)

Bradshaw et al. (2004)

REM Sleep Behavior Disorder

- Parasomnia with complex motor activity in REM (e.g., kick, scream, act out dream)
- Predominantly men, mean age 50-65
- Frequently synucleinopathies (PD, PDD, MSA, DLB)
- Associated with LB pathology in brainstem
- May occur 10+ years prior to onset of a diagnosable clinical disorder (along with anosmia...earliest signs?)
- 65% RBD patients develop parkinsonian disorder

Boeve et al. (2004)

MOTOR DYSFUNCTION

- Tremor (postural, symmetric)
- Bradykinesia
- Rigidity (axial)
- Parkinsonian gait (stooped, shuffling)
- Decreased fine motor skills
- Masked facies

AUTONOMIC DYSFUNCTION

- ❑ Orthostatic hypotension
- ❑ Impotence
- ❑ Urinary incontinence
- ❑ Constipation

Why Cog/Behavioral Changes

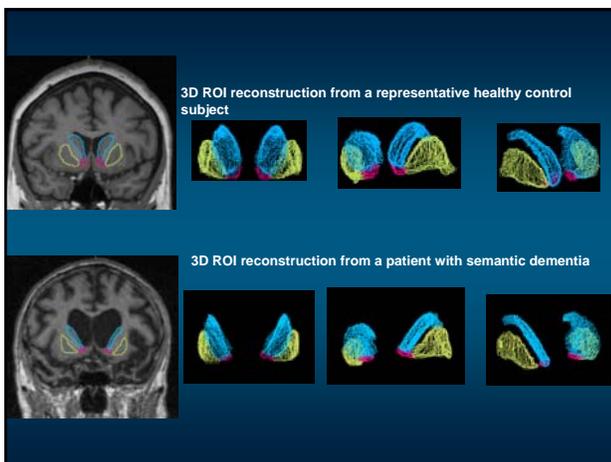
- ◆ Neurochemical
 - Cholinergic
 - Serotonergic
 - Dopaminergic
- ◆ Protein Aggregation
 - A- β 2
 - α -synuclein
 - Tau
- ◆ Circuit Degeneration
 - Ventral Stream
 - Frontal Subcortical Circuits
 - Locus coeruleus/brainstem

Prevalence

- ◆ Unknown (Lund, Manchester 16%)
- ◆ Common cause pre-senile dementia
 - Ratnavalli 1:1 with AD 45-64 years (Neurology 2002)
 - Knopman more common than AD below 60 years (Neurology 2004)
 - Broader spectrum even more common (PSP, CBD, ALS)
- ◆ Less common after 70?

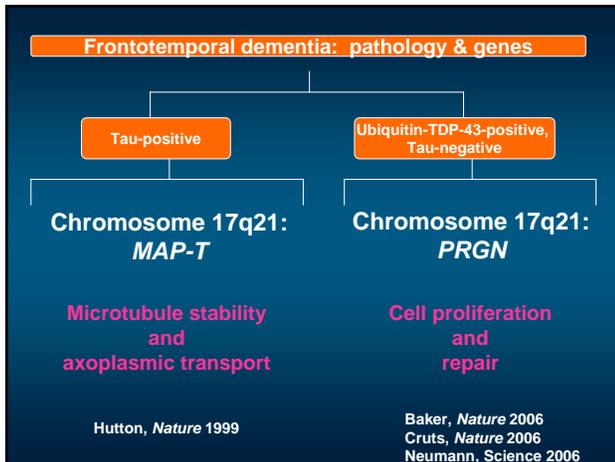
Clinical Heterogeneity

- ◆ Progressive frontotemporal dementia
- ◆ Genetic (40%) sporadic (60%)
- ◆ Frontal, temporal, left or right predominance of degeneration
- ◆ Motor overlap with PSP, CBD, ALS



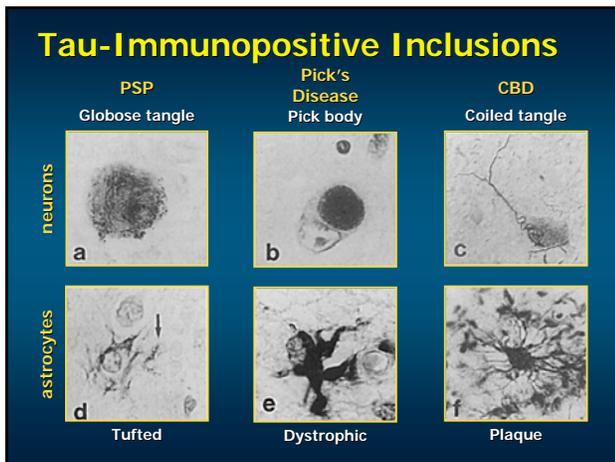
Is FTD Genetic?

- ◆ Chromosome 17
 - Tau – exon & intron mutations
 - Progranulin mutations
- ◆ Chromosome 9 FTD-ALS (almost always Ubiquitin-TDP-43)
 - Gene or genes remain to be discovered



FTD Pathological Syndrome

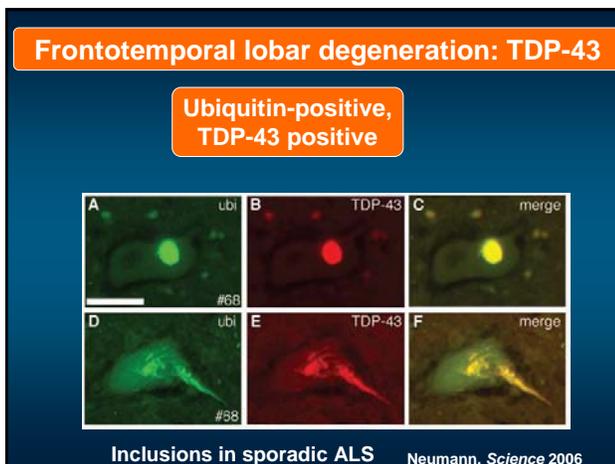
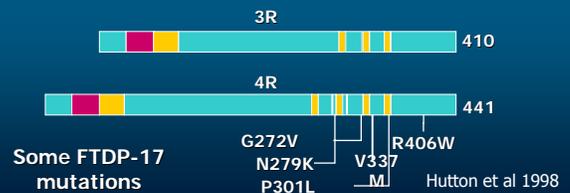
- ◆ Core features
 - Frontotemporal predominance
 - Gliosis, spongiosis, neuronal loss
- ◆ Variable histological features
 - Neuronal inclusions tau+ve
 - Neuronal inclusions with ubiquitin-TDP-43
 - Hippocampal sclerosis (Hatanpaa, Blass)



Tauopathies

Genetics of FTDs

| | Familial | Gene | Tau Path |
|----------------|----------|--------------|----------|
| Pick's Disease | Yes | Chr-17 (Tau) | 3R |
| FTDP-17 | Yes | Chr 17 (Tau) | 4R |

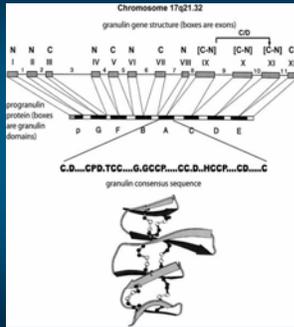


Progranulin: A New FTD Gene

- ◆ Hutton, Van Broeckhoven mutations in FTD families linked to 17q21 with no Tau mutations (Baker et al. 2006; Cruts et al. 2006, *Nature*)
- ◆ 5-10% all FTLD cases, 23% familial cases at Mayo Clinics (Gass 2006)
- ◆ 24% cases PA (PNFA, or SD) presentation, others FTD, CBD, Parkinsonian, AD
- ◆ Family members same mutation have different phenotypes (FTD vs. PNFA) (Snowden 2006)

Progranulin Gene Structure

- ◆ 593 amino acid (68.5 kilodaltons) cysteine-rich secreted molecule
- ◆ 7.5 tandem "granulin" repeats each forming a stacked β -hairpin structure similar to EGF

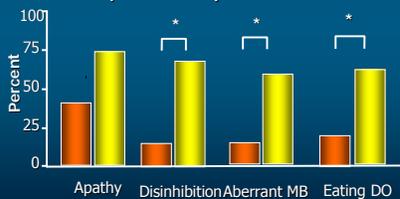


Progranulin Mutations - Haploinsufficiency

- ◆ 43 mutations, premature termination of codon or disrupt gene initiator codon
- ◆ mRNAs with premature termination codons degraded causing complete loss-of-function (disappearance progranulin)
- ◆ Dominant inheritance mediated through a "loss-of-function", "haploinsufficiency" rarely seen human genetics
- ◆ Progranulin growth, inflammation

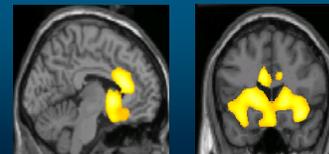
FTD: From Syndrome to Circuit to Cell & Molecules

- ◆ The syndrome
 - ◆ Disinhibition, addictive behavior, apathy, altered social regulation & personality



FTD: Syndrome to Region

- ◆ Syndrome: Disinhibition, addictive behavior, apathy, altered social regulation
- ◆ Region: Ventromedial, insula, anterior cingulate, ventral striatum



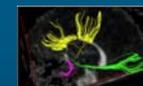
FTD: From Region to Circuit

- ◆ Syndrome: Disinhibition, addictive behavior, apathy, altered social regulation
- ◆ Regional degeneration: Ventromedial prefrontal cortex, insula, anterior cingulate, ventral striatum
- ◆ Circuit: Frontotemporal limbic/paralimbic

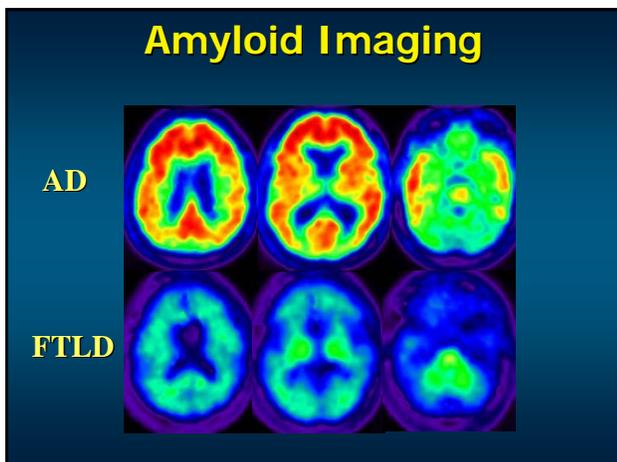
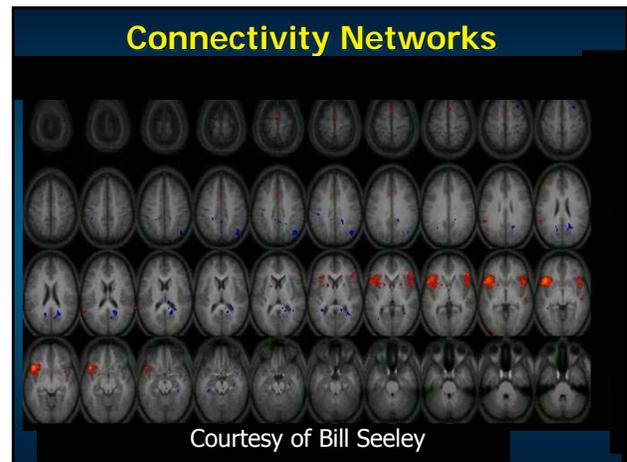
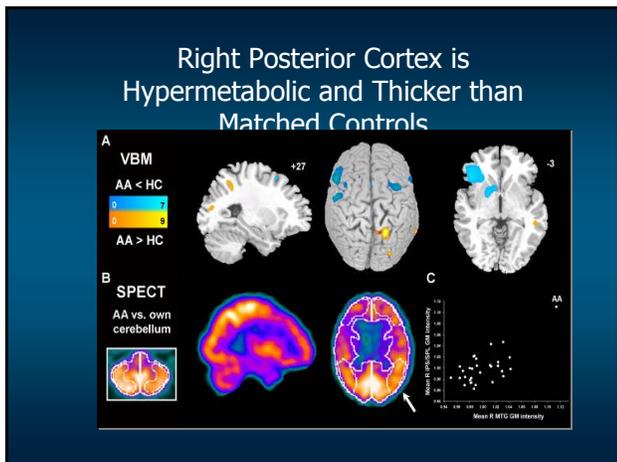
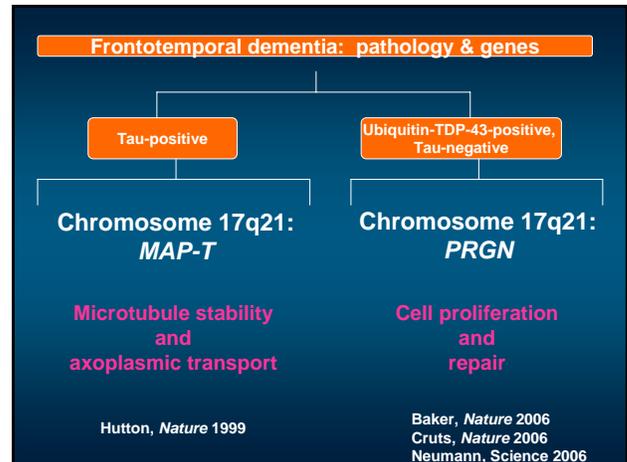
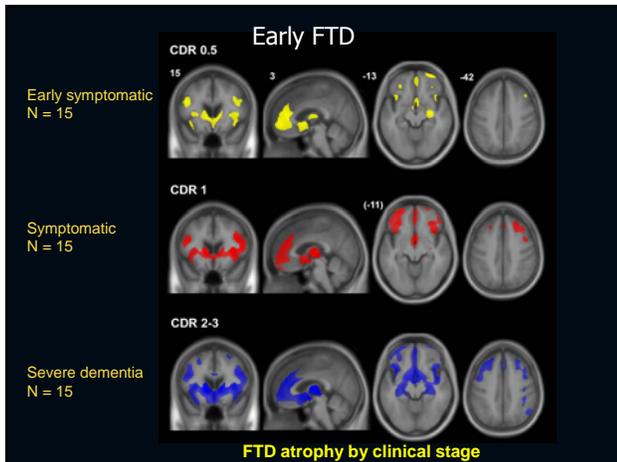


FTD: Syndrome to Circuit to Cell & Molecule

- ◆ Syndrome: Disinhibition, addictive behavior, apathy, altered social regulation
- ◆ Regional degeneration: Ventromedial prefrontal cortex, insula, anterior cingulate, ventral striatum
- ◆ Circuit: Frontotemporal limbic/paralimbic
- ◆ Cells, Molecules, Genes



Von Economo Neuron, tau, progranulin, TDP-43



- ### Pharmacological Intervention
- ◆ Correctly identify target symptoms
 - ◆ Review patient's medical history
 - ◆ Review drug's profile / drug:drug intx
 - ◆ Start with low doses
 - ◆ Increase slowly
 - ◆ Change one drug at a time
 - ◆ Educate caregivers
 - ◆ Monitor response and side-effects
 - ◆ Re-evaluate need for drug

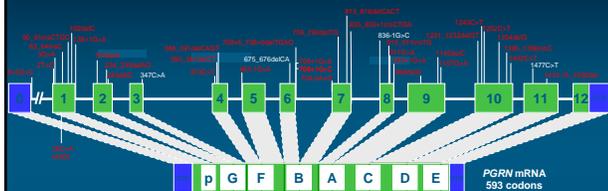
Treatment in FTD

- ◆ Carbohydrate craving, overeating, compulsions, irritability, depression due to low serotonin? Consider SSRI
- ◆ Consider NMDA-antagonist
- ◆ Avoid typical and atypical antipsychotics
- ◆ Avoid cholinesterase inhibitors
- ◆ Work on environment with family
- ◆ Family often disrupted prior to diagnosis

Conclusions

- ◆ FTD is a slow degenerative disorder
- ◆ Begins orbitofrontal, anterior cingulate, frontoinsula region (circuit), right > left
- ◆ VFNs selectively vulnerable
- ◆ Opportunity to understand dysfunction of these regions, cells in humans
- ◆ Treatment is feasible!

Progranulin (PGRN)



Screening for mutations done by direct sequencing all 12 coding exons, non-coding exon 0, core promoter region, and entire 3' untranslated region (UTR) of the gene.

Anatomy of Visual Hallucinations

- ◆ Anterior ventral – landscape, figures in hats
- ◆ Superior temporal - disembodied faces with exaggerated teeth
- ◆ Dorsal stream – palinopsia

Santhouse et al. Brain October 2000

