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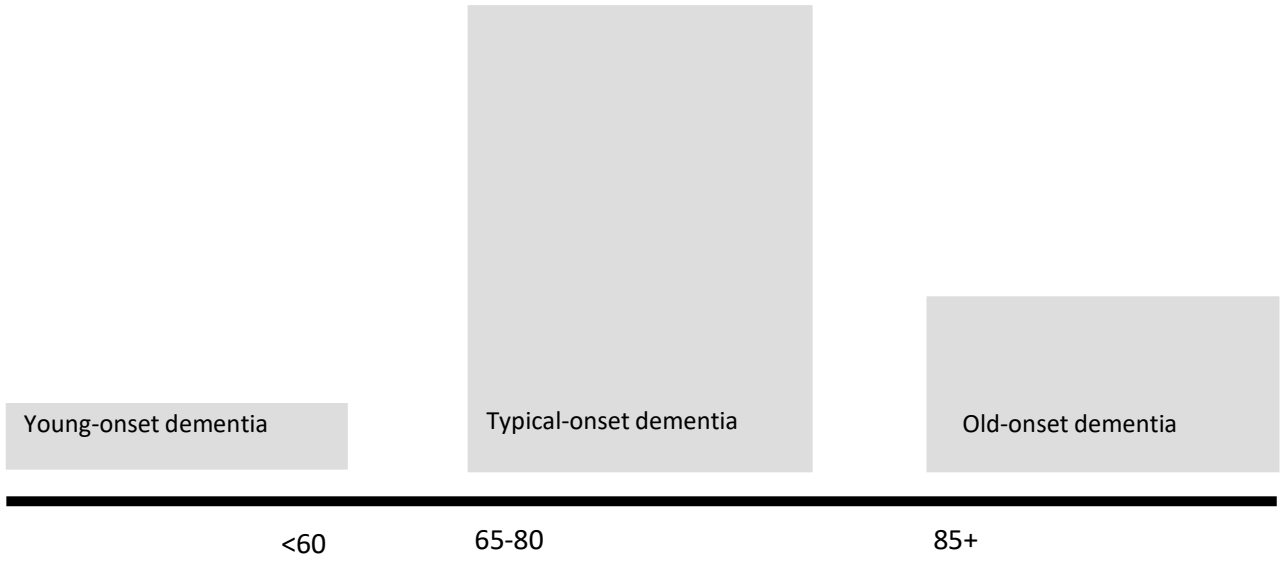
Understanding Young-Onset Dementias

Preface

- PI/CI of NIH and ADDF studies of dementia and SCA
- PI/CI of sponsored clinical trials
  - *Celecoxib and ibuprofen in AD (NIA/NIH) – Neurology 2007, 68:1800–1808*
  - *Memantine in FTD (Forest Inc.) – Lancet Neurology 2009, 12(2):149–156*
  - *LMTM in FTD (Tau Therapeutics) – TRx237-007 (NCT01626378)*
  - *Psychometric trajectories in FTD (Biogen) – just completed*
  - *AL001 in FTD (Alector) – in early implementation*
  - *TPN-101-C9-201 for C9ORF72 FTD and ALS (Transposon) – in development*
- Discussion of “off-label” prescribing is based on experience

Outline



- Characteristics:
  - Diverse presentations and phenotypes
  - Pathophysiology: neuropathology, genetics
  - Diagnosis and care
  - Contemporary research

Vignette 1

Onyike CU, images from the JH FTD-YOD Clinic archives

A technician of 55 had difficulty findings words, then dysfluency, repetitiousness, stereotypies and echolalia. In the 2nd year, his work efficiency deteriorated due to his poor comprehension and reasoning, so he was placed on disability leave.

He was childlike, impulsive and unfeeling. He insisted on the same TV shows. His manners coarsened – examples included intruding on strangers, eating out of a serving bowl, jumping queues, abruptness in conversations. He was restless–biking, swimming laps and running 6.5 miles each day. His wife arranged his "volunteering" at a local nursing home, where he made rounds with maintenance crews all day long.

On examination (year 3-4), he was pleasant, depression was not evident, and he did not have euphoria, psychosis or paranoia. Speech was mildly non-fluent. Verbal fluency was impaired. MMSE 29 (3MS 96). Brain MRI showed right temporal atrophy.

A year later he developed marked preference for sweets, and foraging and overeating. Two years later he was admitted to residential care. At the last visit 6 months ago, MMSE score was 27.

Defining frontotemporal dementia

Onyike et al., 2011; Onyike & Diehl-Schmid, 2013

"…hallmarks are progressive decline in [conduct]: coarsening of temperament, dispositions, judgment, and comportment; dysregulation of emotions, drives and self-control; and disintegration of language and communication…"

*"Thus results a **behavioral phenotype** beginning with combinations of indifference, impatience, carelessness, jocularity, insensitivity, distractibility, impulsiveness, stereotyped behaviors, compulsions and rigid routines; **or language phenotypes** featuring either effortful, dysfluent, agrammatical speech, plus impaired comprehension of sentences, **or** fluent, vacuous speech, with anomia and word (and object) agnosia".*

Vignette 2

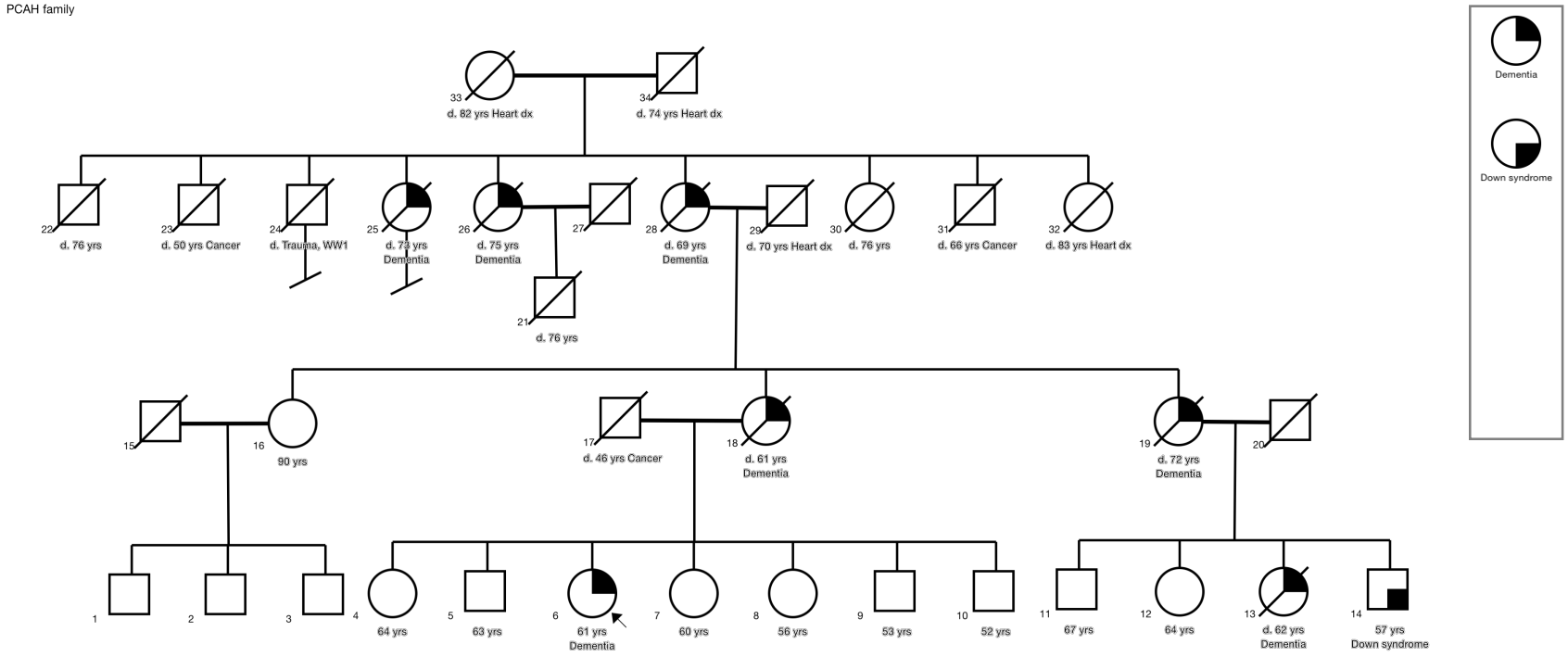
A 61 year-old former dental hygienist developed ***insidious*** *lqpses in memory and judgment, aloofness, poor self-control and rudeness. EXAMPLES: jocularity, incongruous laughing, racial talk, telling to a vagrant he had bad teeth, exuberant dancing in public, and childlike repetitiousness. There was compulsive grocery shopping. She had trouble learning new office technology. Sometimes she had word retrieval problems. Time and space orientation were preserved. She did not have difficulty with arithmetic.*

She was inefficient at work and she burned cooking at home. She maintained hygiene and grooming. Restless legs were observed during sleep, along with hypersomnia. She had a tendency to wander away. Fidgeting, finger rubbing and leg tapping had been observed.

She had mild gaze dyspraxia and right limb paratonia; the neurological examination was otherwise normal. A recent MMSE score was 28. Brain scanning showed reduced FDG-PET uptake in the frontal lobes.

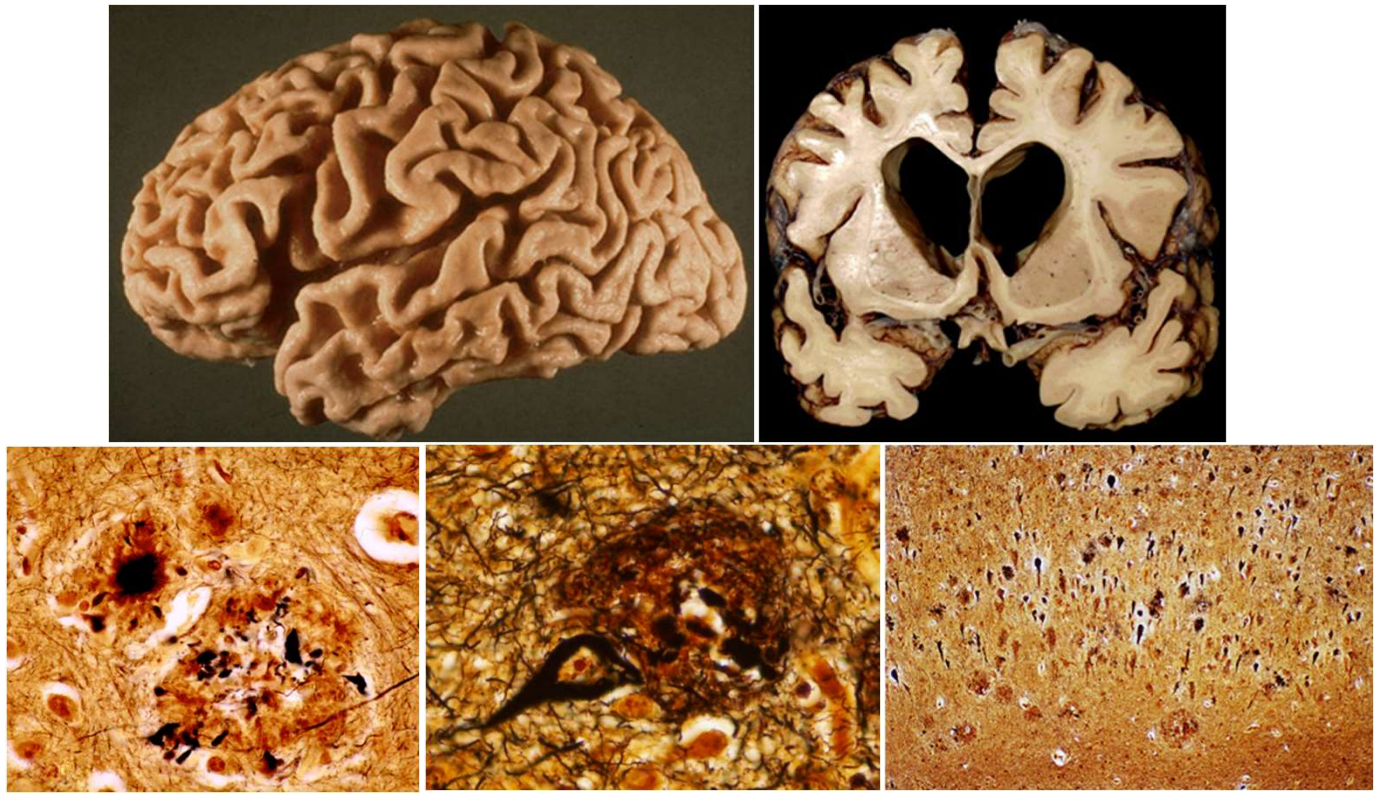
Vignette 2 pedigree

Onyike CU, data from the JH FTD-YOD Clinic

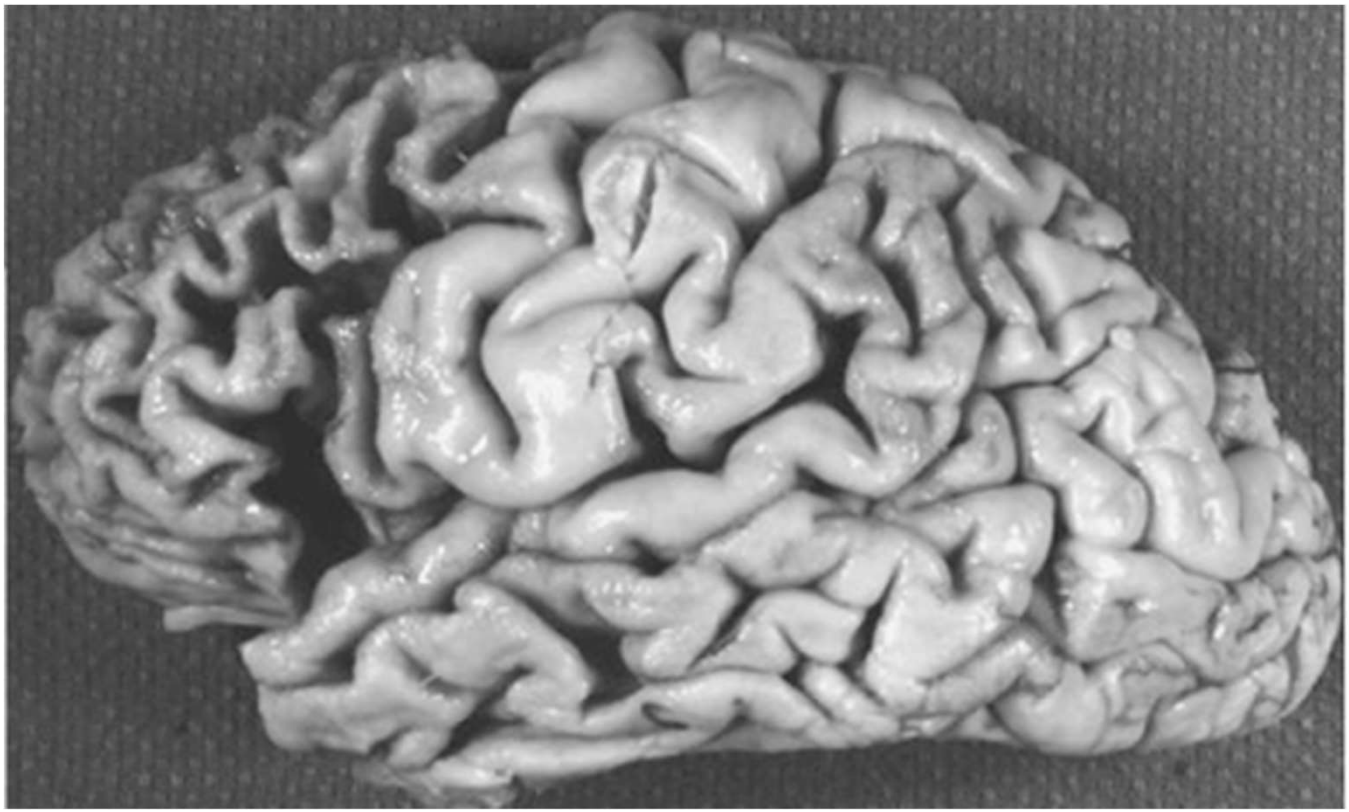


Pathological features of Alzheimer disease

http://neuropathology-web.org/chapter9/chapter9bAD.html



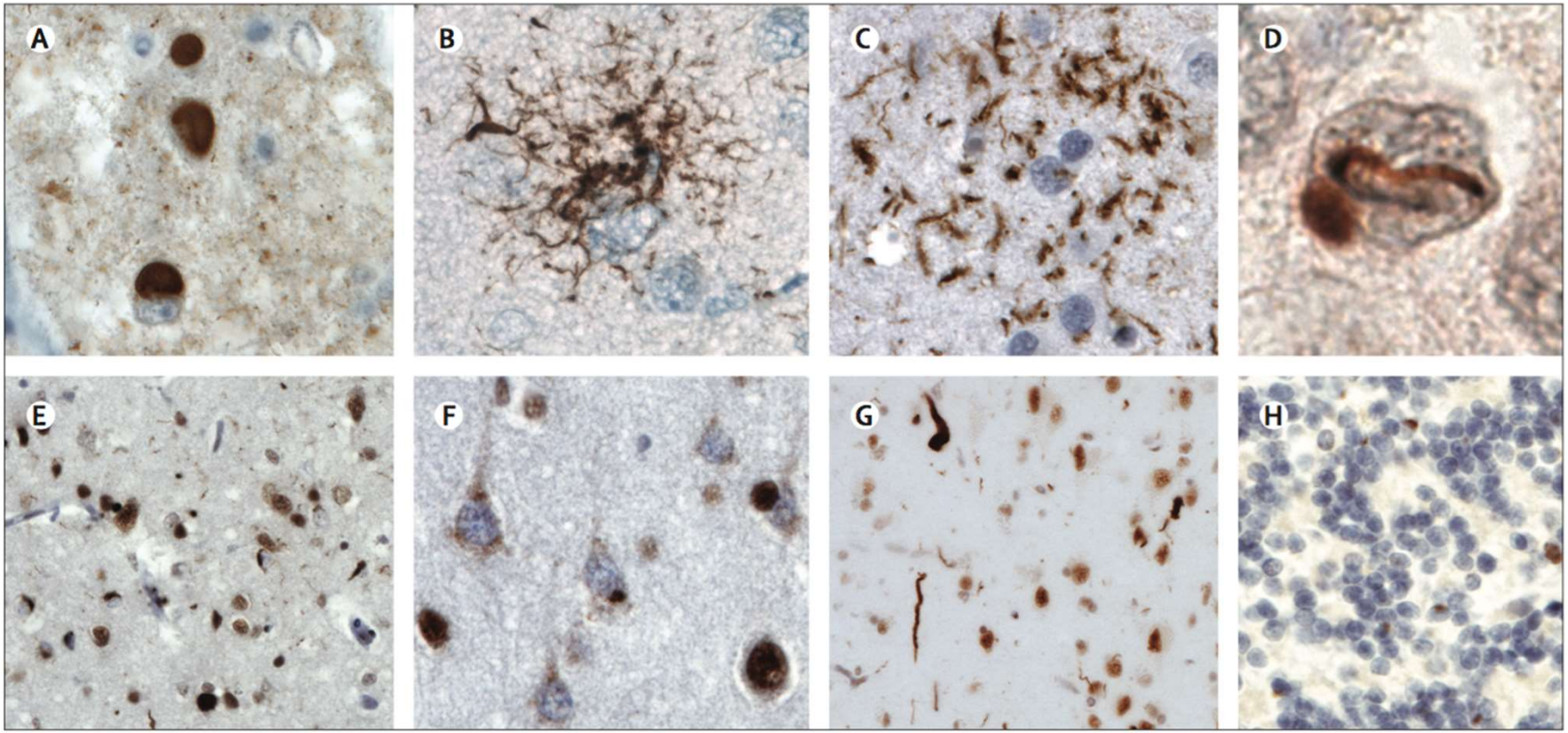
Top left, brain specimen shows diffuse cortical atrophy; top right, coronal section shows diffuse atrophy, enlarged ventricles, pallid white matter, and atrophy of both caudate nuclei; bottom left, amyloid plaques; bottom middle and right, amyloid plaques and neurofibrillary tangles



Lobar atrophy in FTD

Graff-Radford and Woodruff, 2007

Pathological appearance of the brain in Pick's Disease: "knife's edge" atrophy of the frontal lobe



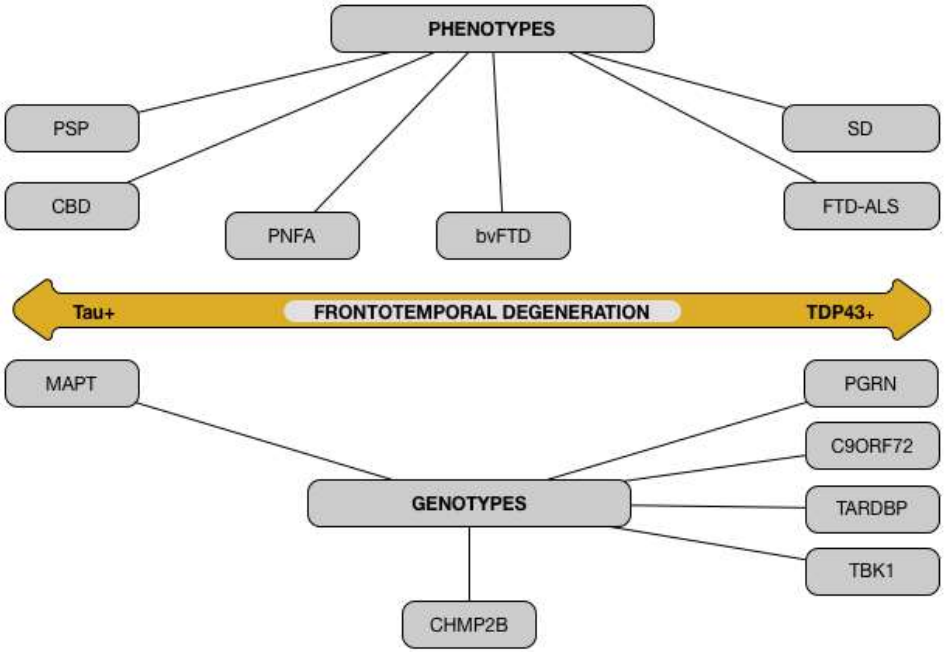
Histopathology in FTD *Bang et al., 2015*

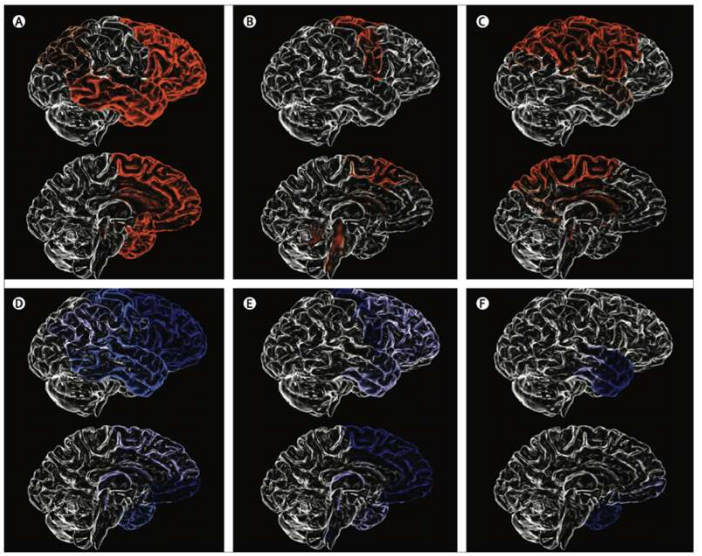
FTLD-tau (A) Pick bodies in Pick's disease; (B) a tufted astrocyte in progressive supranuclear palsy; (C) an astrocytic plaque in corticobasal degeneration; FTLD-TDP (E) small compact or crescentic neuronal cytoplasmic inclusions and short, then neuropil threads in FTLD-TDP type A; (F) diffuse or granular neuronal cytoplasmic inclusions (with a relative paucity of neuropil threads) in FTLD-TDP type B; and (G) long, tortuous dystrophic neurites in FTLD-TDP type C. TDP can be seen within the nucleus in neurons lacking inclusions but mislocalises to the cytoplasm and forms inclusions in FTLD-TDP. The remaining FTLD cases are characterised by FUS-immunoreactive inclusions that stain negatively for tau and TDP-43; a vermiform neuronal nuclear inclusion in a dentate gyrus granule cell is shown (D); this neuron contains an ovoid cytoplasmic inclusion. In patients with hexanucleotide expansions in *C9orf72*, small juxtanuclear ubiquitin-positive, TDP-negative inclusions (H) are pathognomonic for the disorder. These inclusions contain dipeptide repeat proteins translated from the GGGGCC repeat in one of six reading frames. Immunostains are 3-repeat tau (A), phospho-tau (B and C), FUS (D), TDP-43 (E–G) and ubiquitin (H). Sections are counterstained with haematoxylin. Scale bar applies to all panels and represents 50 µm in A, B, C, and H; 12 µm in D; and 100 µm in E and G. FTLD=frontotemporal lobar degeneration. TDP=TAR DNA-binding protein. FUS=fused-in-sarcoma.

FTD is associated with mutations at multiple genetic loci

Gene	Locus	%	Phenotypes	Pathologic type
MAPT	17q21	20-25	FTD ± parkinsonism; PNFA; CBD; PSP	Tau +
PGRN	17q21	20-30	FTD; SD	TDP43 +
C9ORF72	**9p21**	**25-40**	**FTD; FTD-ALS; ALS; amnesic; psychiatric**	**TDP43 +**
CHMP2B	3p11.2	<1	FTD	Ubiquitin + Tau –, TDP43 –
VCP	9p13	<1	MSP (i.e., ± IBM ± PBD ± FTD ± ALS)	TDP43 +
TBK1	12q14.1	<1	FTD; FTD-ALS; ALS	TDP43 +

Multilevel heterogeneity in FTD

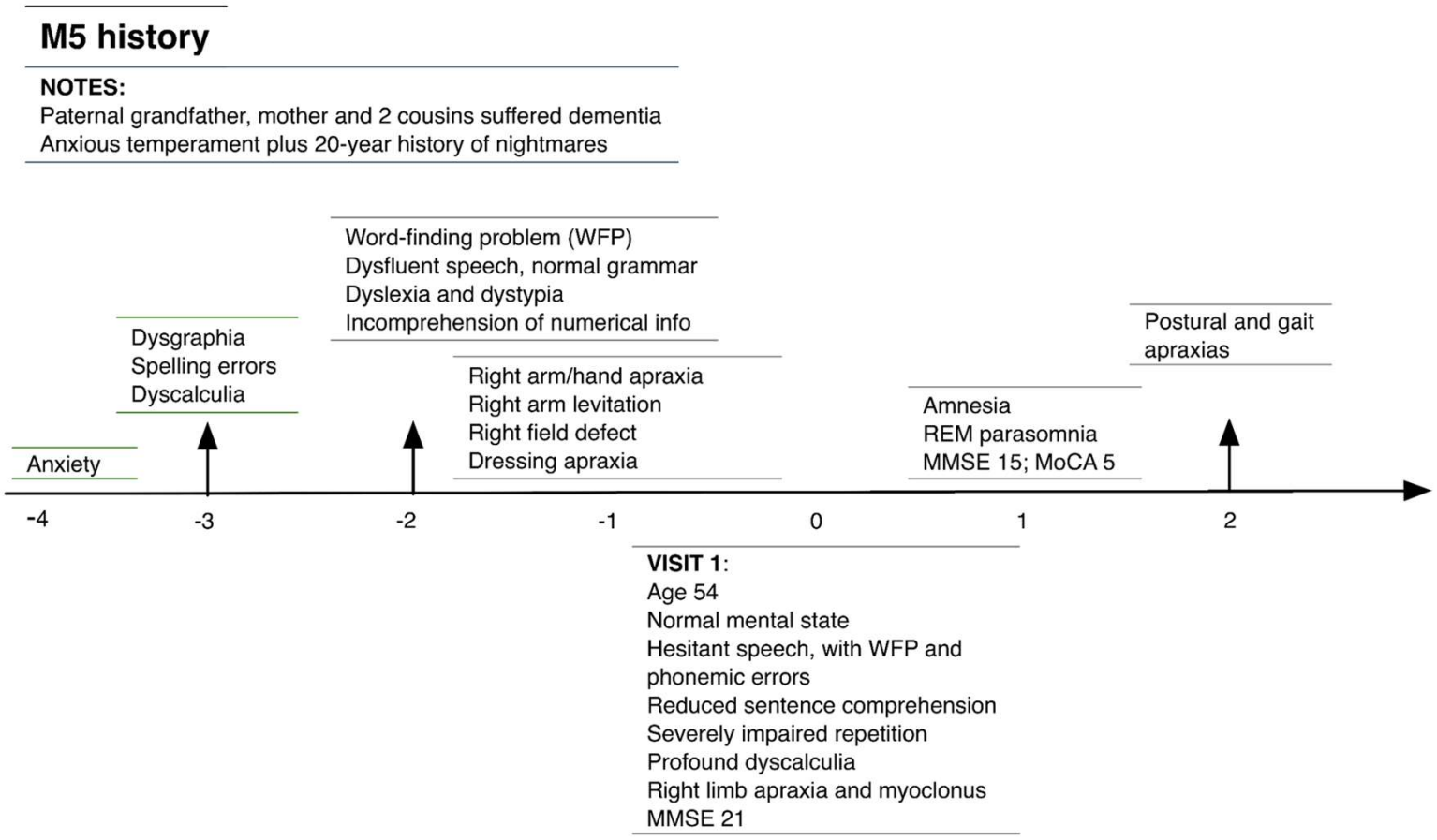




Patterns of atrophy in FTD *Bang et al., 2015*
(**A**) Pick's disease; (**B**) PSP; (**C**) CBD; (**D**) FTLD-TDP type A; (**E**) FTLD-TDP type B; (**F**) FTLD-TDP type C.

Vignette 3

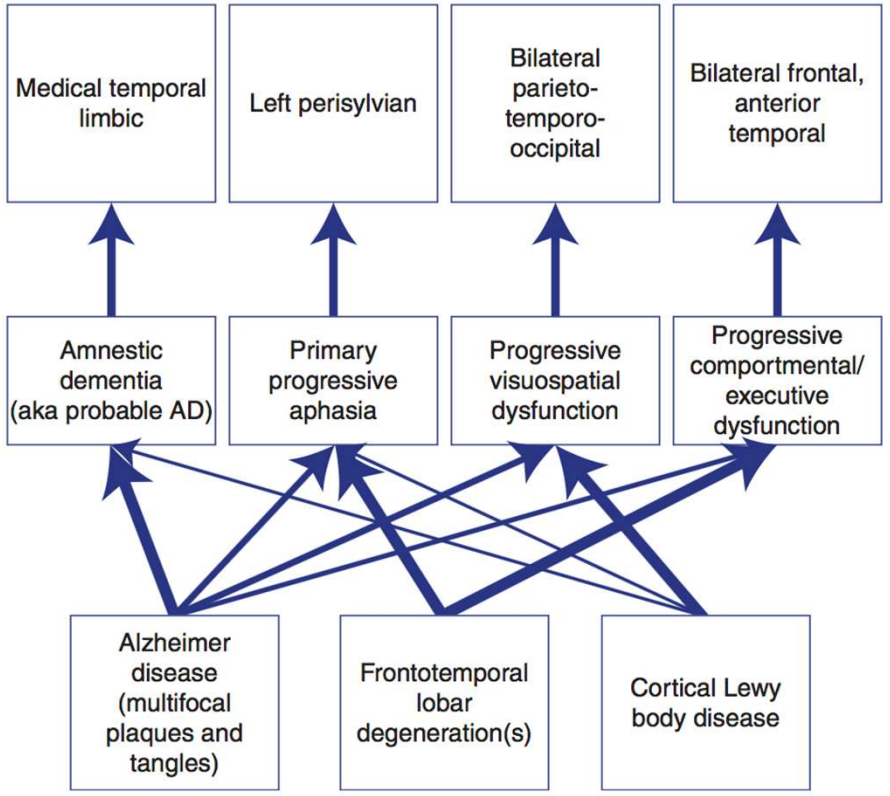
Onyike CU, images from the JH FTD-YOD Clinic archives



Phenotypes of YOAD

Lee and Rabinovici, 2011; Weintraub et al., 2012; Dickerson et al., 2017; Crane et al., 2017; Crutch 2017

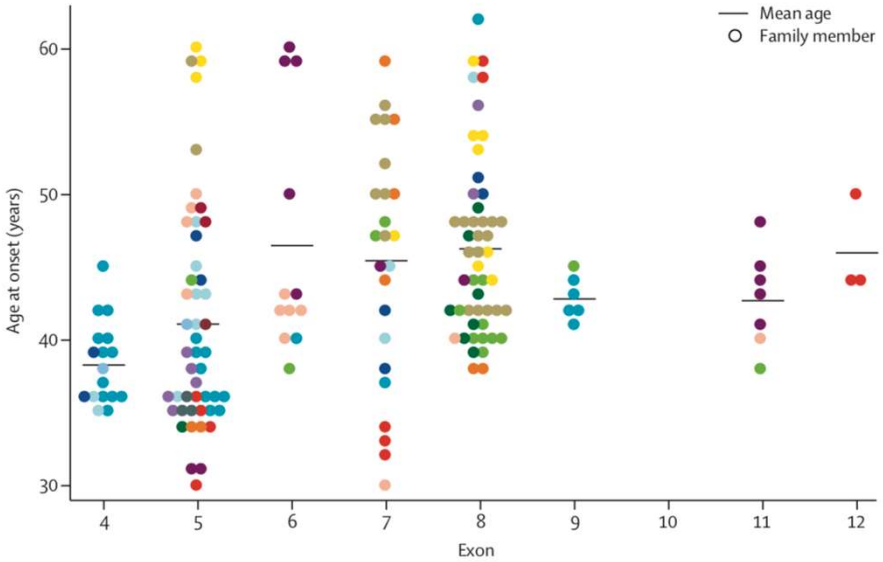
Syndrome	**Features**	***Onset***
Amnesic	**Amnesia** + disorientation, aphasia, apraxia, confusion, neuropsychiatric states (apathy, anxiety, depression, etc.)	*45+*
Aphasia	**Aphasia** (logopenic – mixed fluency and semantic deficits) + confusion, apraxias, affective states (anxiety, depression, irritability)	*65*
Visuo-appercetive (posterior cortical atrophy, PCA)	**Visual apperception** + inattention, aphasia, apraxia, anxiety, illusions, hallucinations, paranoias, myoclonus	*55*
Executive/behavioral	**Executive dysfunctions** (inattention, disorganization, confusion) + irritability, asocial behaviors, apathy	*45-60*
Apraxic (corticobasal syndrome, CBS)	**Apraxia** (ideomotor, limb kinetic, orofacial and speech) + aphasia, confusion, visuo-apperception, REM-parasomnias and myoclonus	*60*



Profiles of AD according to life stage at onset

Dickerson & Wolk, 2010; Cacace et al., 2016; Ryan et. Al, 2016

	YOAD	TOAD	OOAD	*Comments*
Phenotypes	Usually focal and frequently 'atypical'	Amnesia-predominant	Amnesic	*YOAD commonly non-amnesic*
Familial	↑↑; hereditary in 10-20%. Earlier onset in PSEN1	↓	--	*Age at symptom onset in fAD generally <60, but some older cases reported*



Onset is later for APP mutation carriers (mean ~50 years) than for those with PSEN1 mutations (44 years). Having an APOE ε4 allele is not associated with age at onset for PSEN1 or APP mutation carriers.

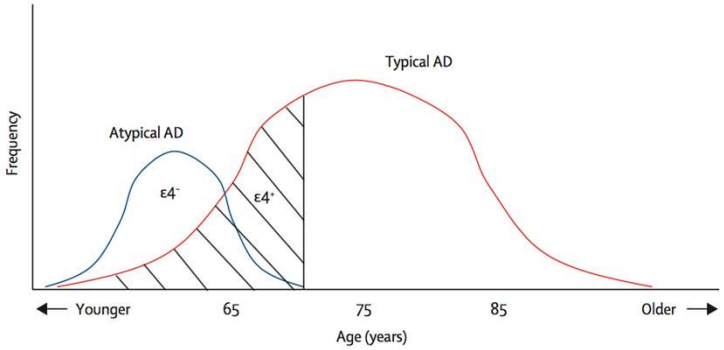
Profiles of AD according to life stage at onset

Wisniewski et al., 1998; Scheltens et al., 2002; van de Pol et al, 2006; van der Flier et al., 2006; Kester et al, 2009; Bouwman et al., 2009; Dickerson & Wolk, 2010; Weintraub et al., 2012; van Vliet et al., 2013; Van de Flier et al., 2014

	YOAD	**TOAD**	**OOAD**	***Comments***
Neuropsychiatry	Early REM-parasomnias, anxiety, depression, illusions, hallucinations	Apathy common in early stages	Apathy in early stages	*Preservation of insight may be a factor in YOAD*
Motor	Myoclonus + higher risk for seizures; apraxias and parkinsonism common	Late parkinsonism and gait dysfunction	Late parkinsonism and gait dysfunction	*Early neurological signs and seizures common in YOAD*
Psychometry	Focal profiles; worse in attention, executive, visuoperception than the LOAD	Amnesia-predominant, multi-domain	Markedly amnesic	*YOAD better on memory, worse in other domains*
Diagnosis and treatment	Lower recognition; delayed diagnosis. Insidious; frequent psychiatric and motor complications	--	High comorbidity and medical complexity; frailty	*Delay in diagnosis leads to stress. No differences in life expectancy. Survival 8-10 years for all*
Psychosocial	Child care issues; loss of job and linked benefits; high reliance on informal care; high stress	Earlier utilization of residential care	Earlier utilization of residential care	*Higher levels of carer stress in YOAD*

Physiological markers at different life stages

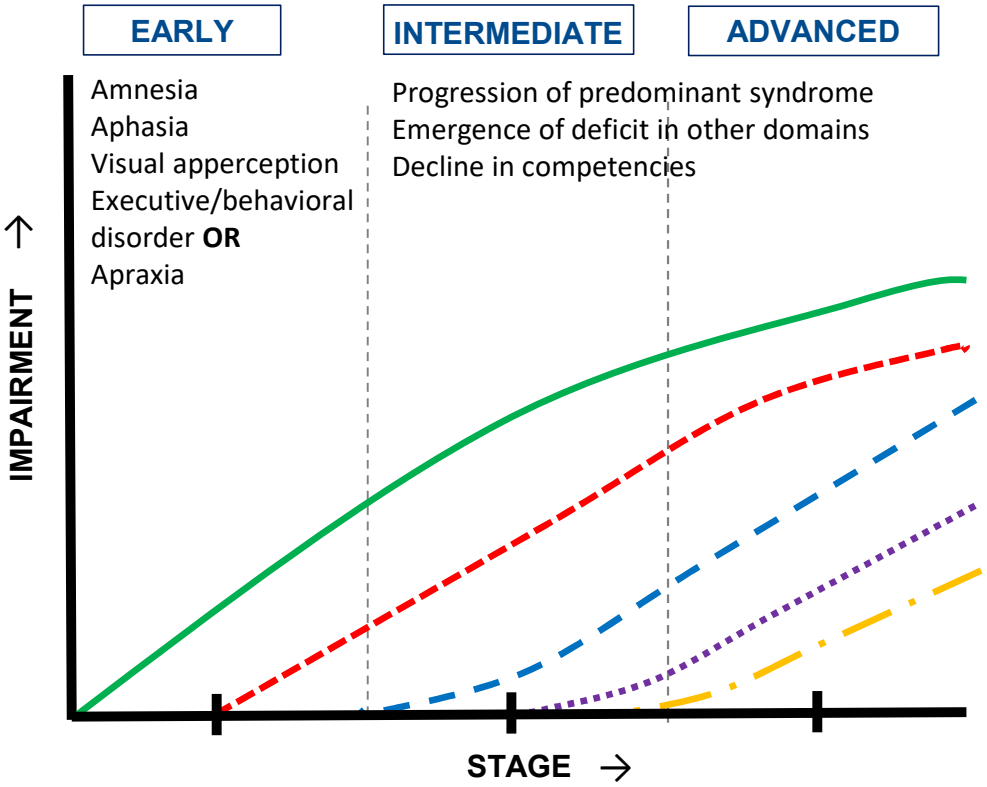
Dickson et al., 1994; Rasmusson et al., 1996; Barker et al., 2002; White et al., 2002; Zarow et al., 2008; Pao et al., 2011; Nelson et al., 2014; Ryan et al., 2016

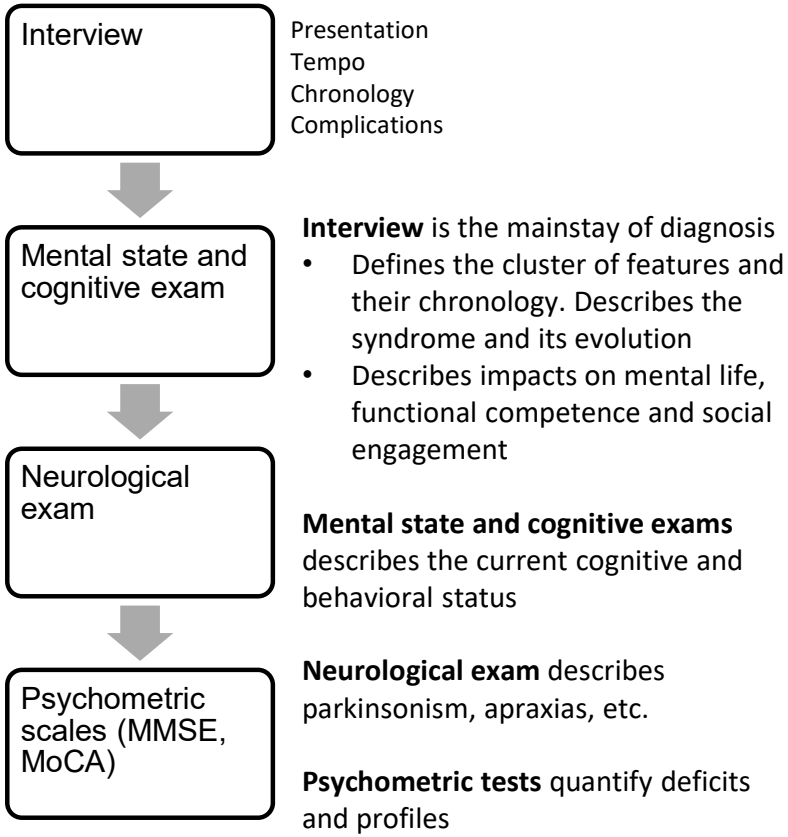


	YOAD	TOAD	OOAD	*Comments*
Brain MRI/FDG-PET	Focal or posterior predominant; may have let-right asymmetry	Hippocampal/global atrophy	Hippocampal/global atrophy; PVWH	*FDG-PET pattern mirrors expectation for MRI*
CSF Aβ/tau/p-tau	↓ ↓ Aβ, ↑tau, ↑ p-tau	↓↓ Aβ, ↑tau, ↑ p-tau	↓↓ Aβ, ↑tau, ↑ p-tau	*CSF useful, but results sometimes indeterminate*
ApoE4	--	↑	↑	*ApoE4 not related to risk in YOAD; no diagnostic value in general*
Histopathology	Focal early, posterior tendency; widespread in PSEN1 mutation carriers	Global	Global; high rate of co-pathology; amyloid negative in 12%	*Multi-etiology common in OOAD; HSD + TDP-43 pathology common*

Natural history informs diagnosis

Devineni and Onyike, 2015; Onyike 2017





Interview is the mainstay of diagnosis

- Defines the cluster of features and their chronology. Describes the syndrome and its evolution
- Describes impacts on mental life, functional competence and social engagement

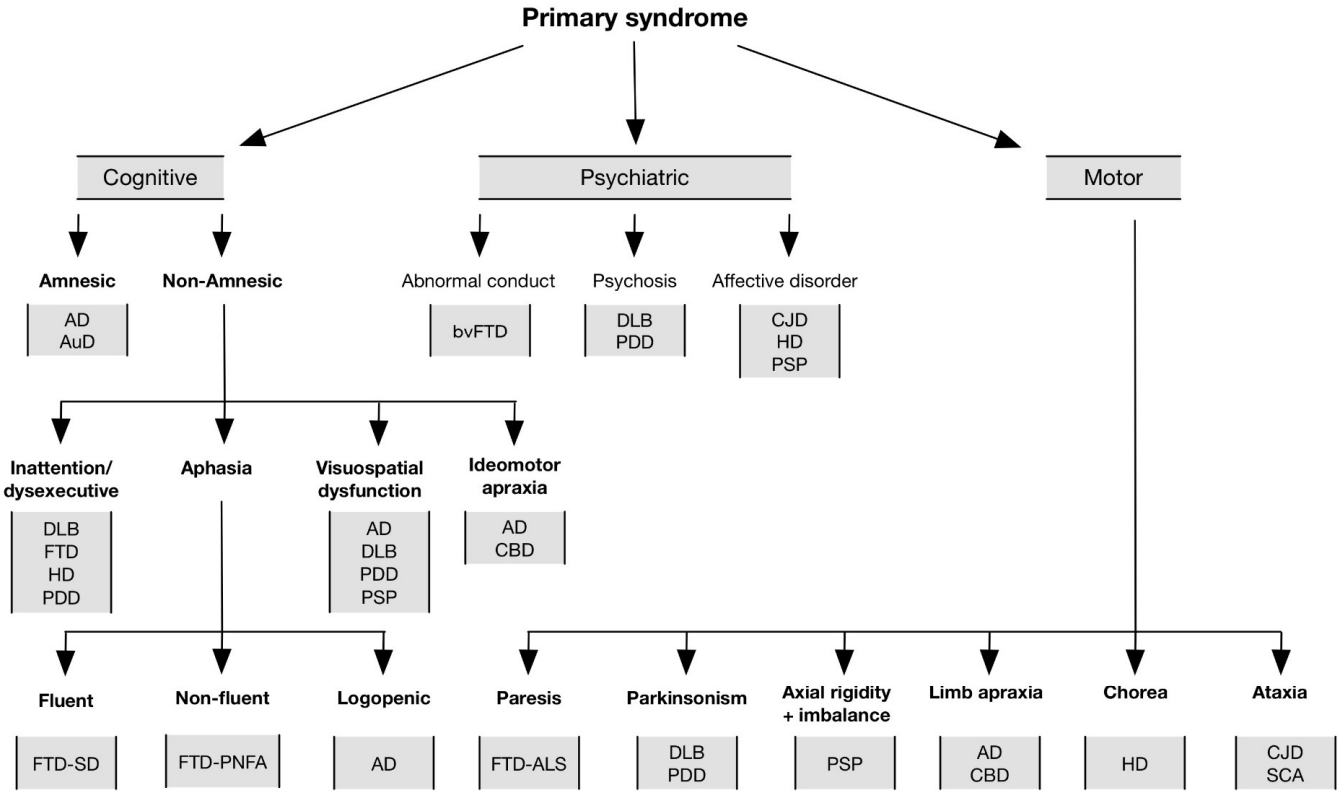
Mental state and cognitive exams describes the current cognitive and behavioral status

Neurological exam describes parkinsonism, apraxias, etc.

Psychometric tests quantify deficits and profiles

Clinical decision pathway

Devineni and Onyike, 2015; Onyike, in 2017

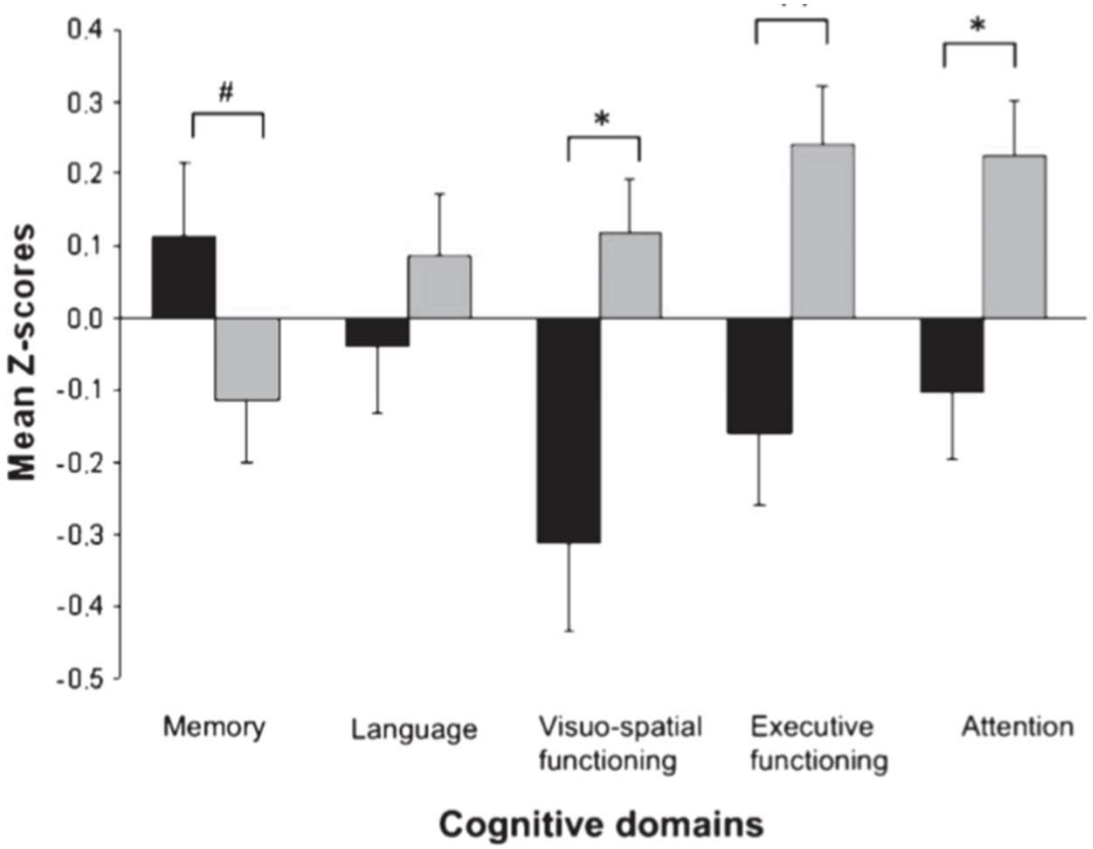


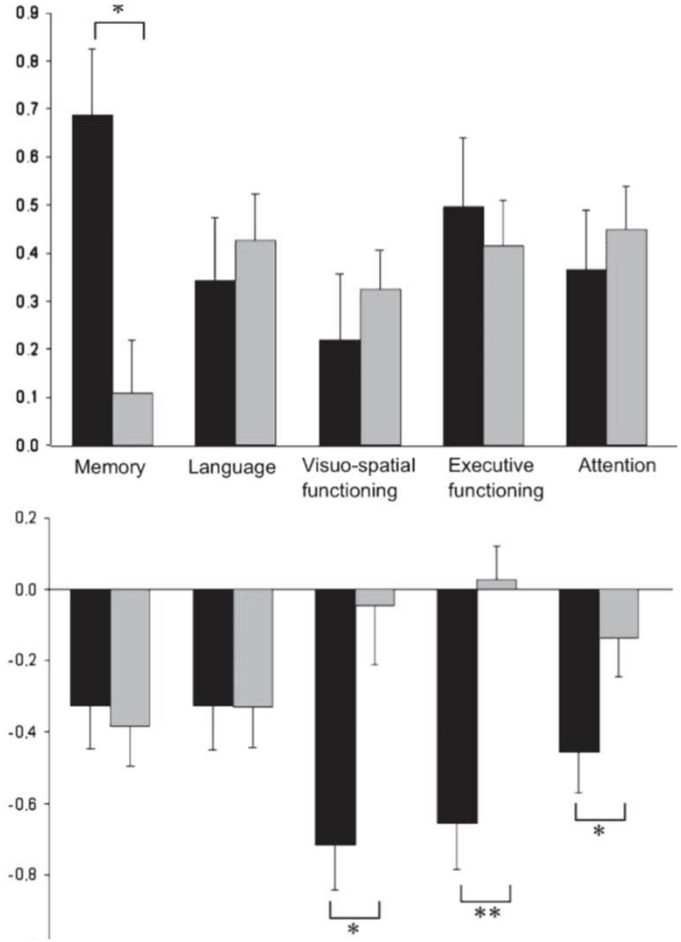
Flow diagram illustrating how cognitive, psychiatric and motor syndromes guide the differential diagnosis. The arrows indicate the diagnostic pathways, and grey boxes show the dementia types corresponding to the cognitive, psychiatric or motor category.
AD — Alzheimer disease; **AuD** — autoimmune dementia; **bvFTD** — behavior variant frontotemporal dementia; **DLB** — dementia of Lewy bodies; **PDD** — parkinson disease dementia; **CJD** — Creutzfeldt-Jakob disease; **HD** — Huntington disease; **PSP** – progressive supranuclear palsy; **FTD-SD** — frontemporal dementia, semantic dementia variant; **FTD-PNFA** — frontotemporal dementia, progressive non-fluent aphasia variant; **FTD-ALS** — frontotemporal dementia with amyotropic lateral sclerosis; **SCA** — spinocerebellar ataxia

Adapted from Devineni and Onyike, Psychiatr Clin North Am 2015; 38(2)233-248

Neuropsychological performance, YOAD v LOAD

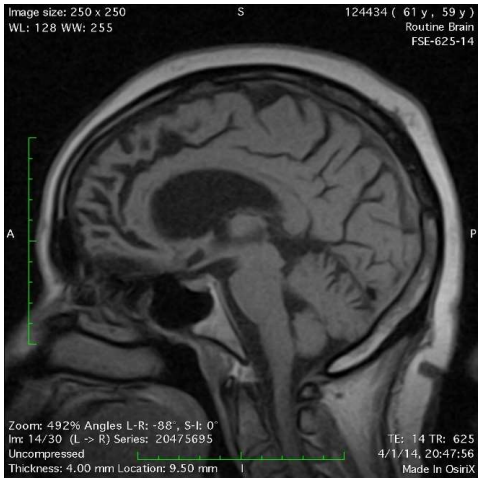
Smits et al., 2012

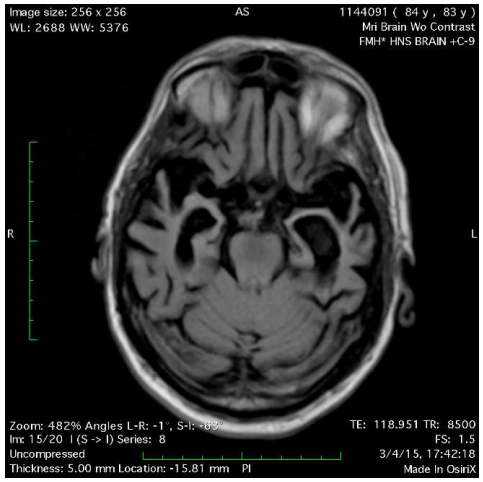


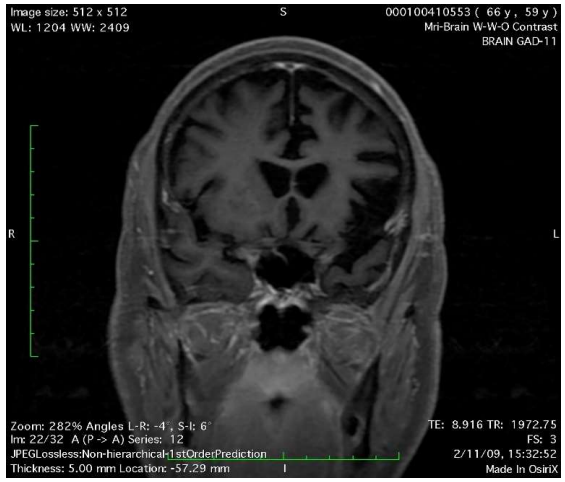


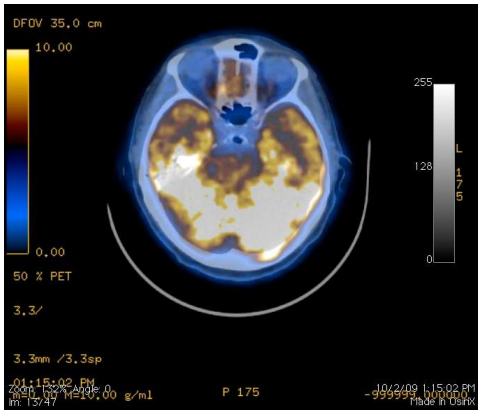
Brain imaging: MRI and FDG-PET

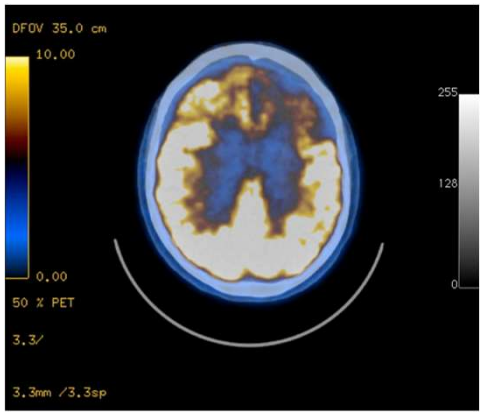
Onyike CU, images from the JH FTD-YOD Clinic archives

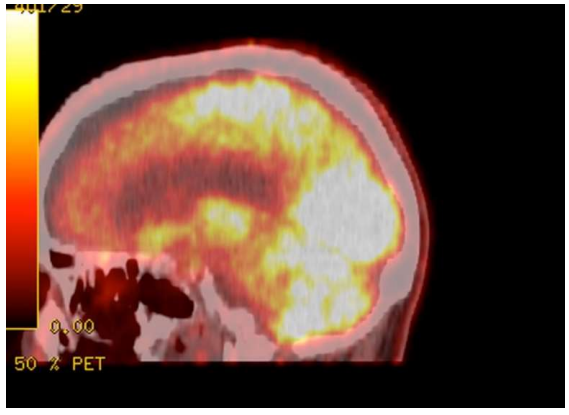












Visual ratings for diagnosis

Kipps, et al. 2007, Davies et al. 2009, Harper et al., 2015

Frontotemporal Rating Scale, FRS

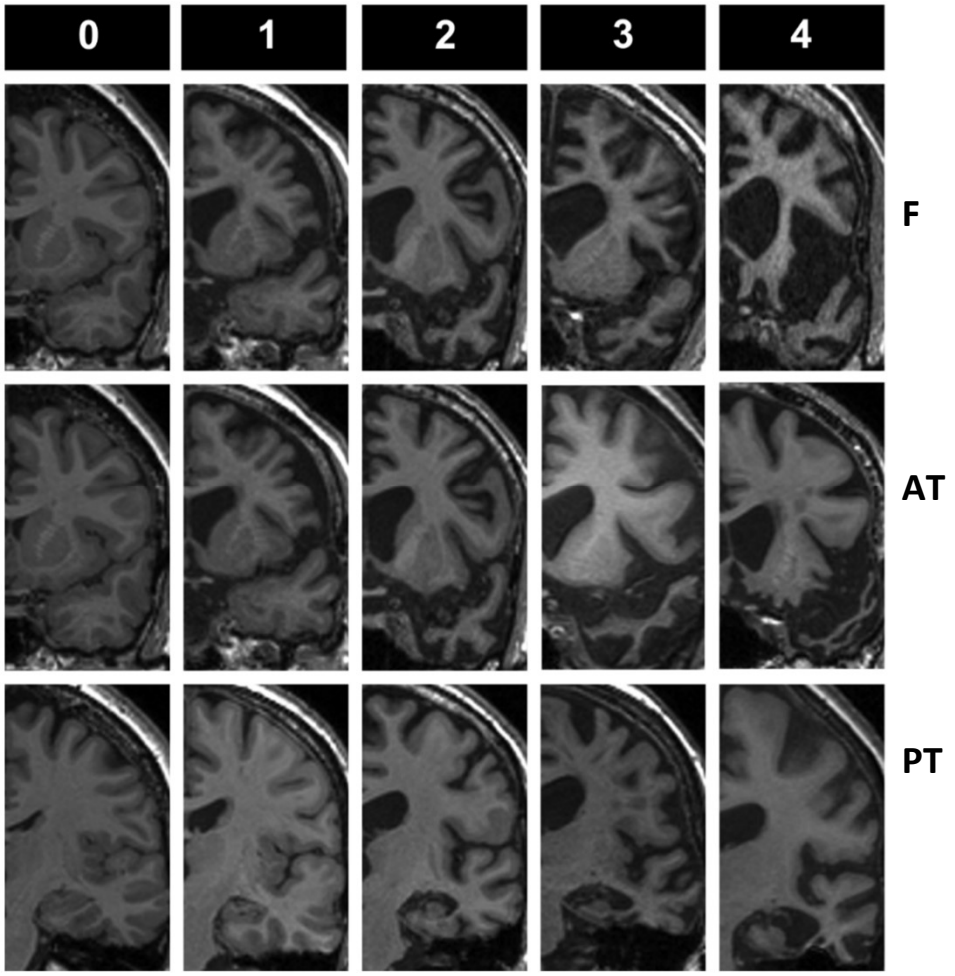
Characteristics:

- T1-weighted coronal
- 5 ranks defined
- Interrater reliability = 0.7
- Intrarater reliability ~ 0.8

Sensitivity:

- 100% for SD
- 73% for PNFA
- 53% for bvFTD

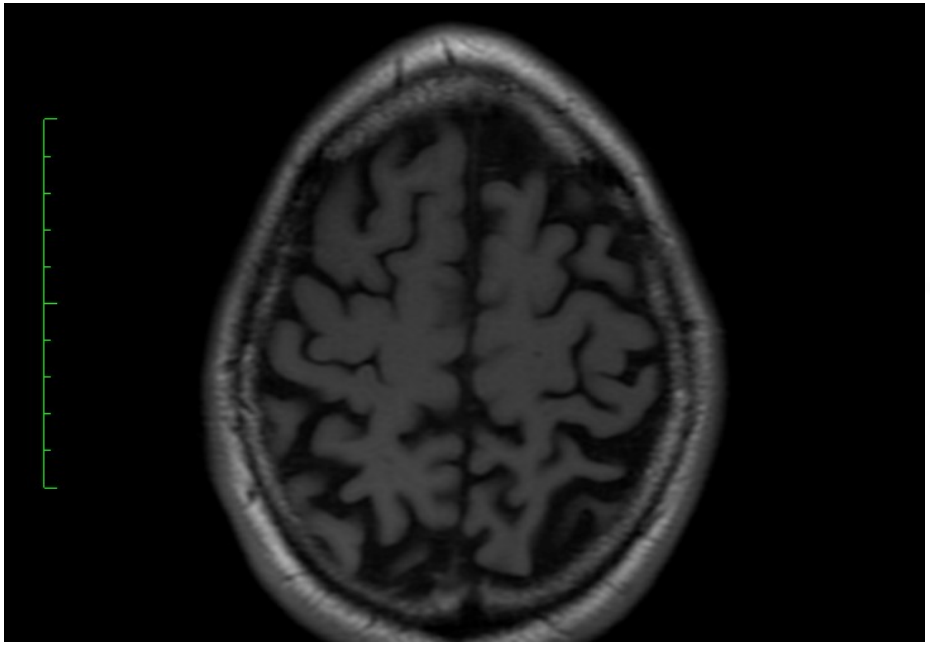
Insula vital for FTD diagnosis, anterior temporal lobe for SD

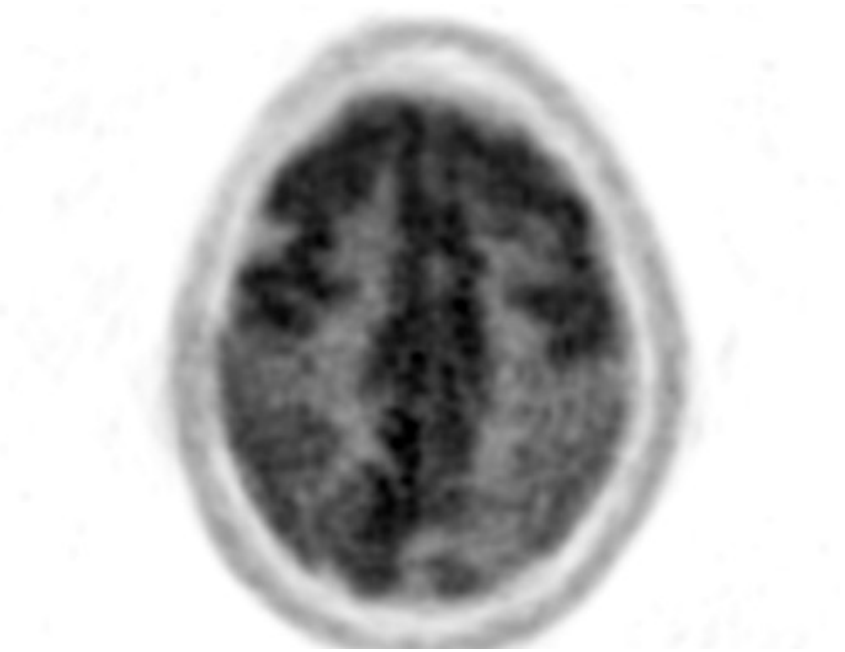


FRS, showing the 5 ranks. ROI are: F, frontal; AT, anterior temporal; PT, posterior temporal. The most widely used scoring system is binary, i.e., classifying 0-1 = normal and ≥ 2 = disease

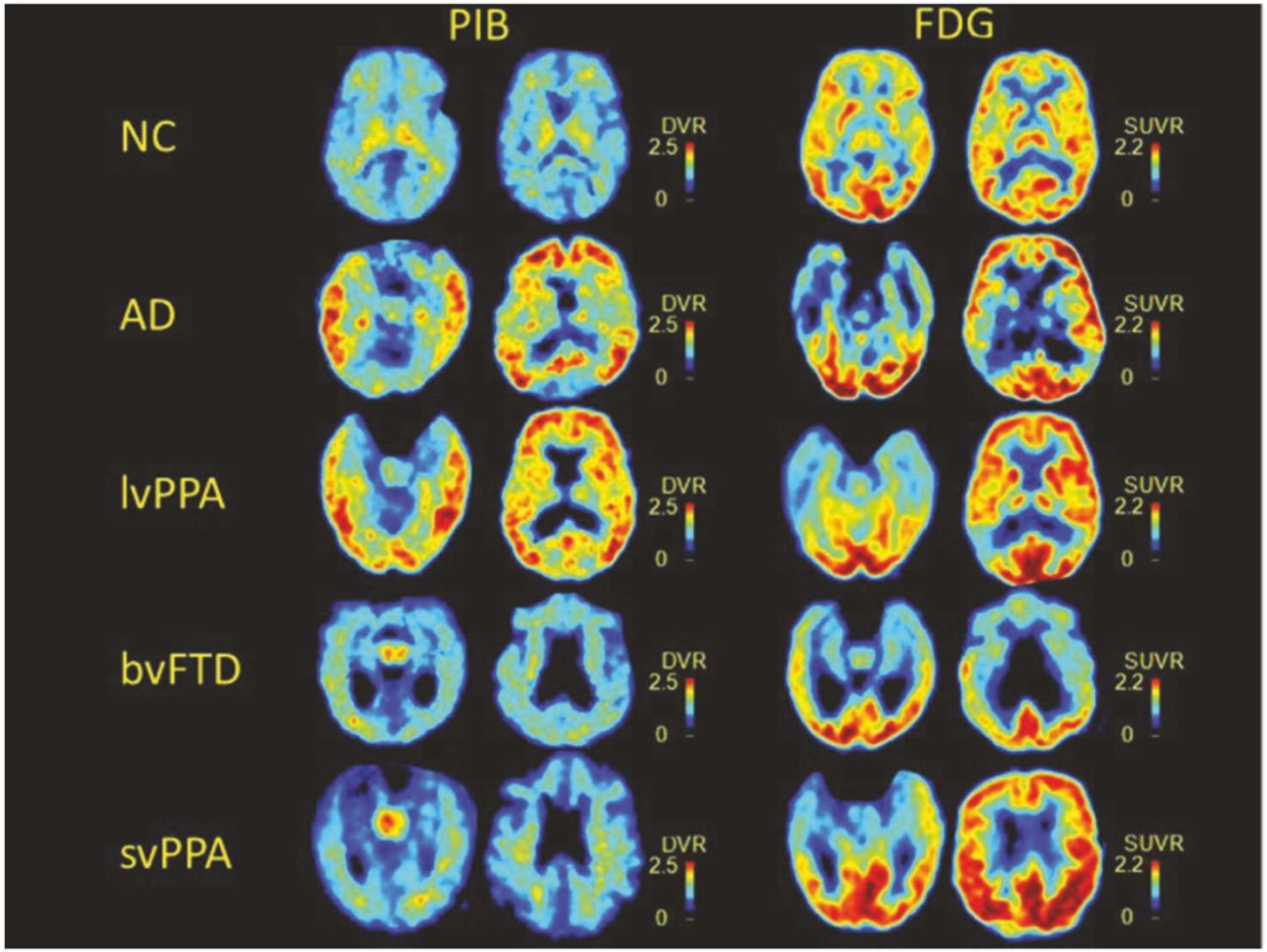
Brain MRI and FDG-PET in YOAD

Onyike CU, images from the JH FTD-YOD Clinic archives



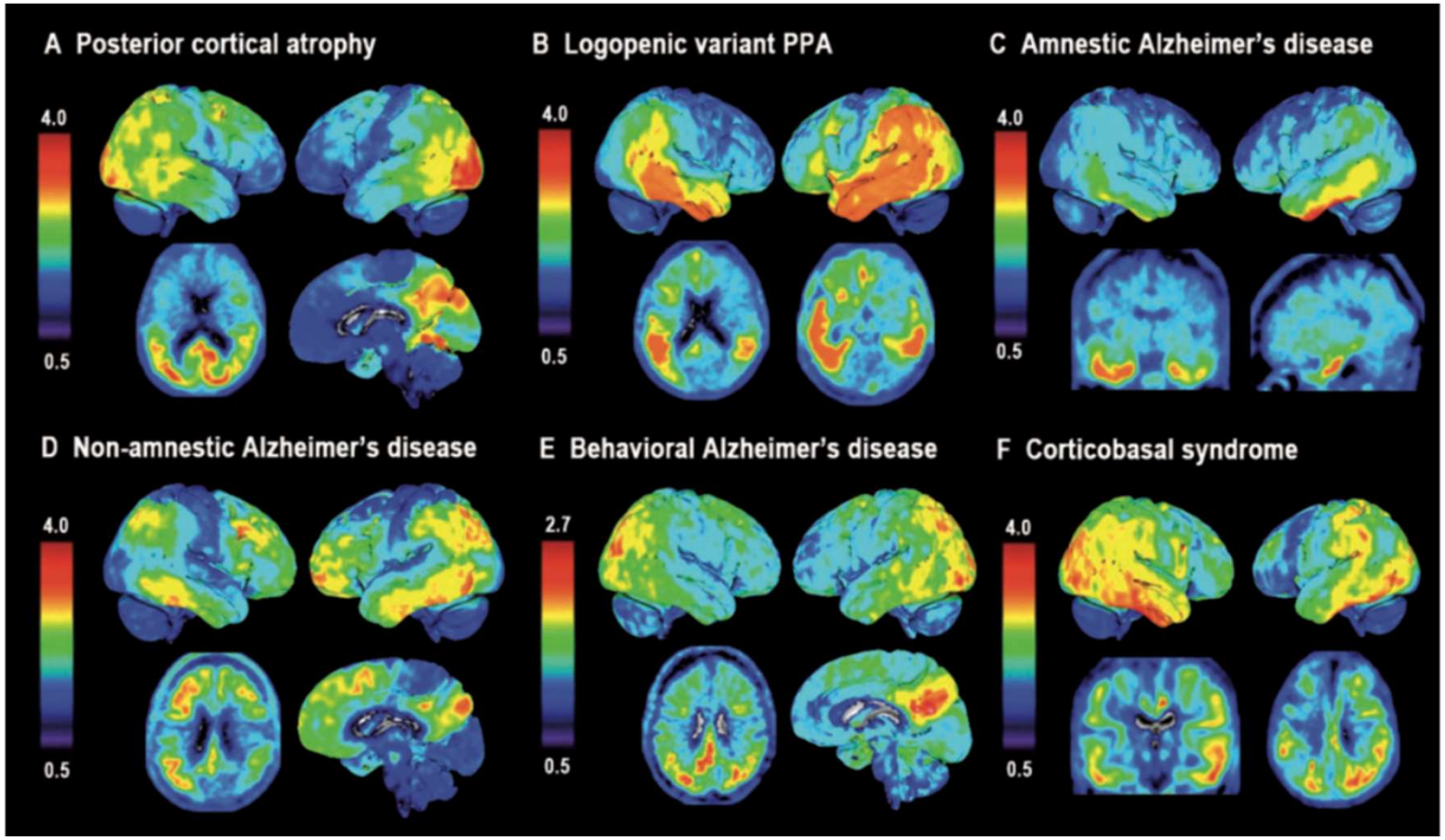


Brain MRI and FDG-PET images from a 54-year old man with AD .
T1 Flair image (left) showing cortical posterior (parietal) predominant cortical atrophy with mild left-right asymmetry; FDG-PET (right) shows marked reductions in tracer uptake in both parietal lobes



^{11}C-labeled Pittsburgh Compound B (PIB) binding and ^{18}F-deoxyglucose (FDG) uptake patterns in normal controls (NC), AD, logopenic variant of primary progressive aphasia (lvPPA), behavioral variant frontotemporal dementia (bvFTD), and semantic variant of primary progressive aphasia (svPPA).

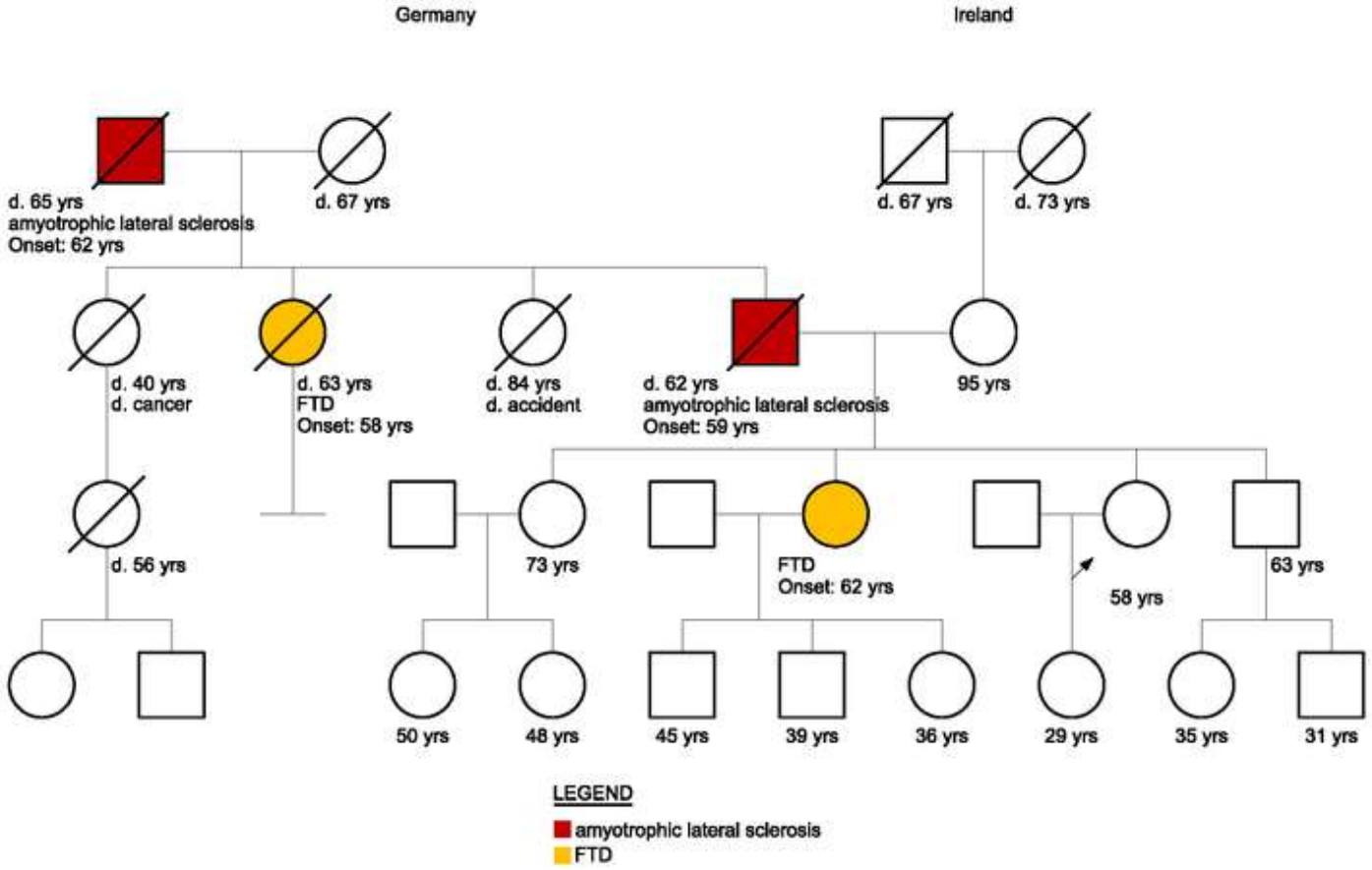
LaForce and Rabinovici, 2011



18F-AV1451 uptake in individuals with AD. (A) 59-year-old female (MMSE: 28) with PCA; (B) 77-year-old female (MMSE: 17) with logopenic PPA; (C) 71-year-old female (MMSE: 23) with amnestic AD; (D) 59-year-old female (MMSE: 27) with non-amnestic AD; (E) 59-year-old male (MMSE: 21) with a behavioral presentation of AD, and (F) a 60-year-old female (MMSE: 16) with a corticobasal syndrome affecting the left side.
Ossenkoppele et al, 2016

Genetic testing requires a 3-generation pedigree

ALLFTD – https://www.allftd.org/fftld

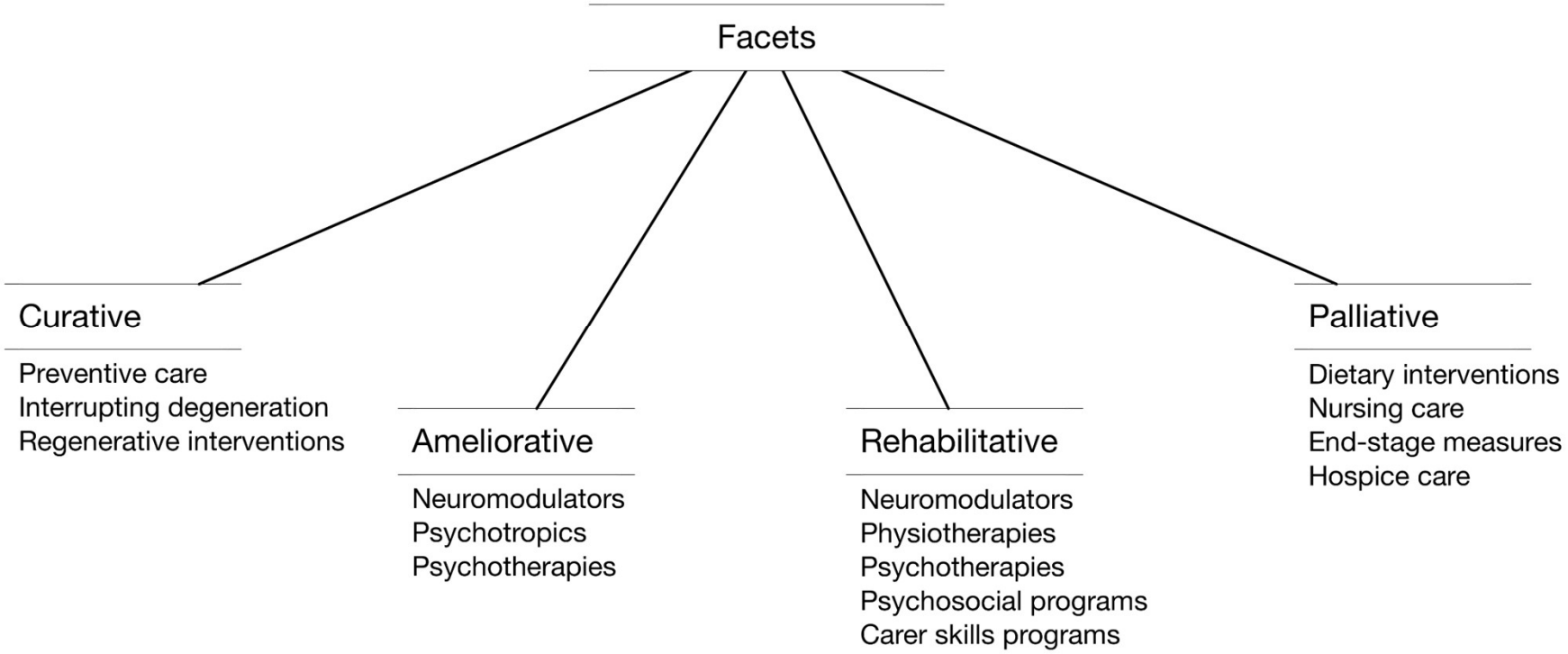


Elements of dementia care

Onyike & Huey 2013; Wylie et al., 2013

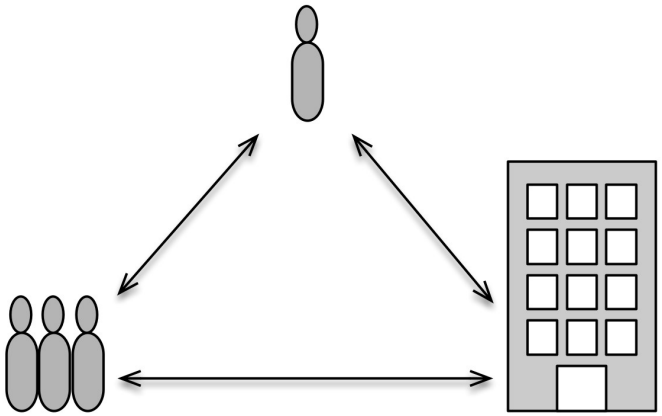
Problem	Role	Intervention
Disease/disorder	Diagnose	Provide evaluation, direct investigation, make referrals
Disability, crisis	Solve problems	Crisis interventions and psychosocial/rehabilitative care
Distress	Provide relief	Make prescriptions
Demoralization, stress	Guidance	Provide clarification, support and direction

Multifaceted, tiered, individualized care



Psychosocial interventions

Belle et al., 2006; Gitlin et al., 2010; Nichols et al., 2011; McKinnon et al., 2013; Wylie et al., 2013; Samus et al., 2014; Bier et al., 2015; Onyike, 2016



The care triad:

- Person
- Carer(s)
- Environment

- Psychotherapeutic methods
  - Social engagement, structured and unstructured activities, use of distractors
  - Behavior remodeling
  - Tailored Activities Program (TAP)
  - Describe, Investigate, Create, Evaluate (DICE)
  - Problem-Solving Therapy (PST) approaches
- Care support programs
  - Clinic-based case management
  - Advancing Caregiver Training (ACT)
  - Resources for Enhancing Alzheimer's Caregiver Health (REACH)
  - Care of Persons with Dementia in their Environment (COPE)
- Rehabilitative devices and programs
  - Alarms, trackers, and smartphone and tablet apps
  - Maximizing Independence in the Home (MIND@Home)
  - Care Pathway Model for Dementia (CARE-D)

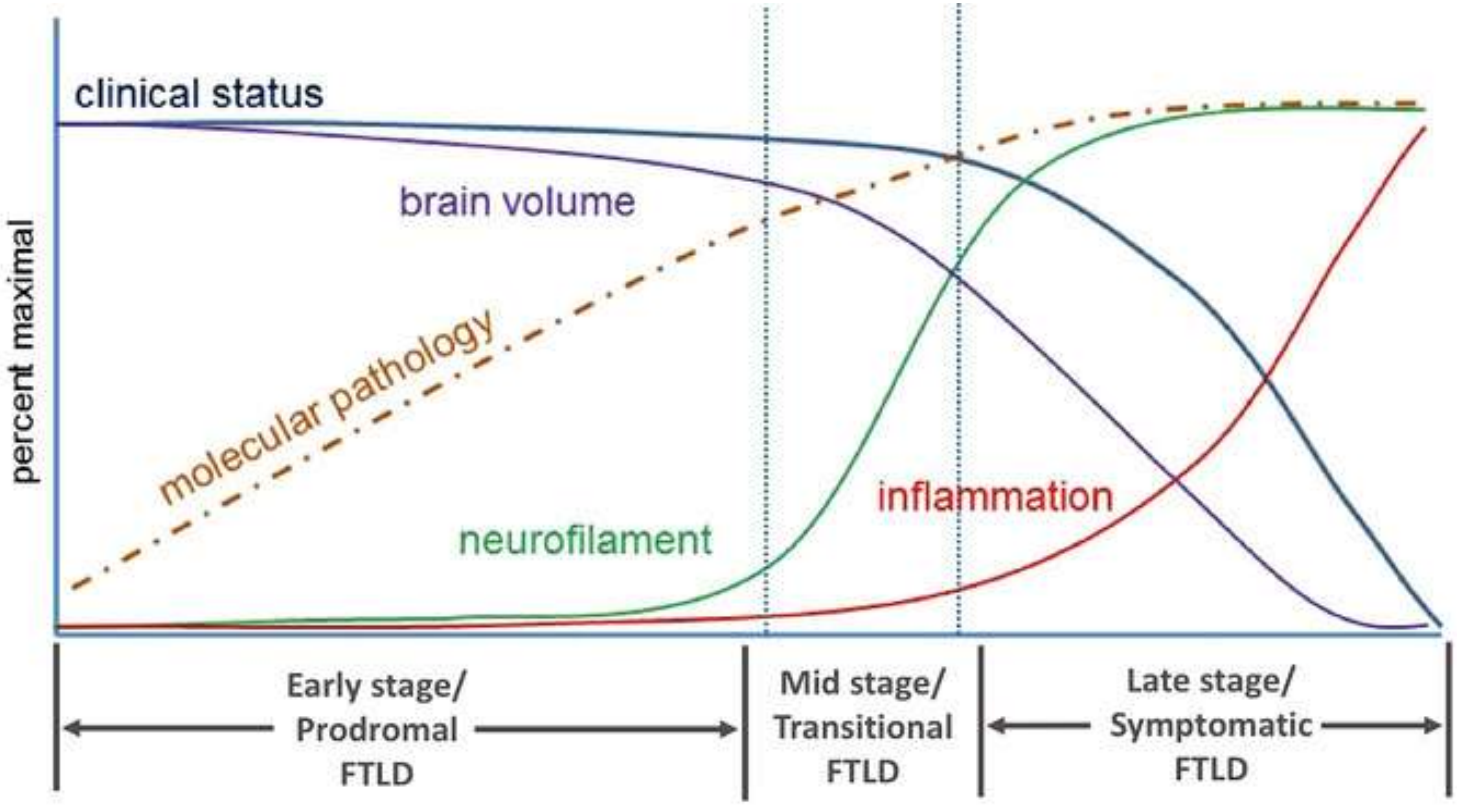
Pharmacologic interventions

Lebert et al., 1999; Moretti et al., 2002; Ikeda et al., 2004; Lebert et al., 2004; Huey et al., 2006; Cruz et al., 2008; Singam et al., 2013

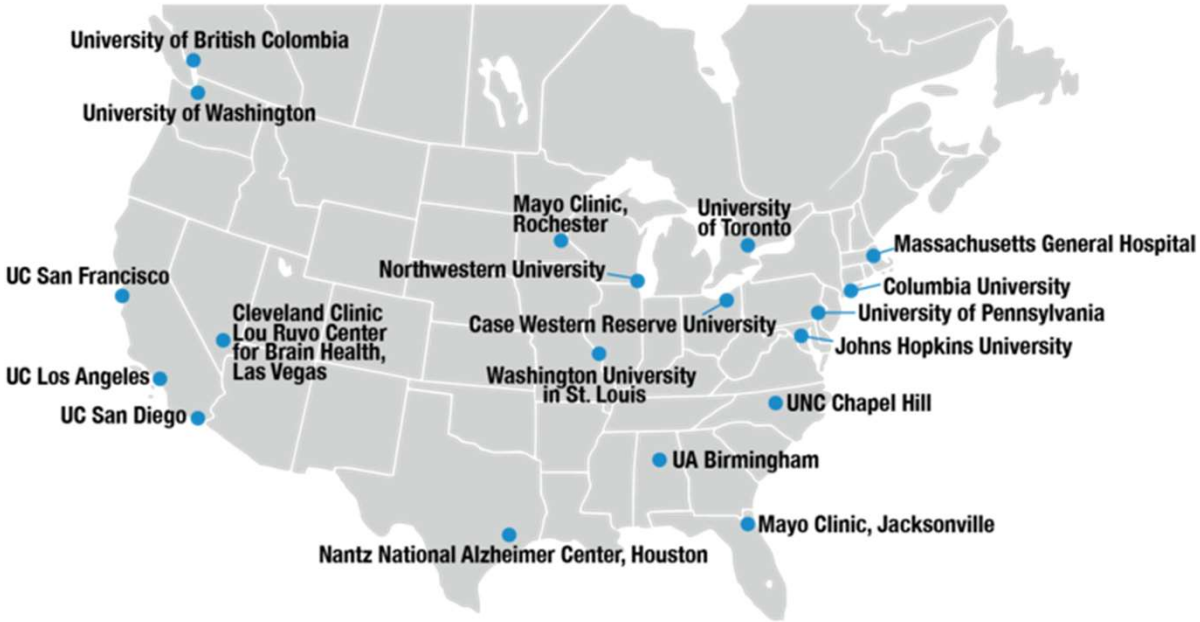
Class	**Target**
Neuromodulators	Cognitive functions
Amantadine	Inattention; perseveration
Bupropion	Inattention; depression
SSRI & SNRI	Depression; anxiety; irritability; impulsions; compulsions
Neuroleptics	Paranoia; hallucinations; irritability; agitation; aggression
Benzodiazepines	Anxiety; agitation; aggression; myoclonus; REM sleep behaviors
Stimulants	Inattention/distractibility; apathy
Mirtazapine	Dyssomnia/insomnia
Zolpidem	Insomnia
Topiramate	Hyperphagia; foraging

Working model for disease evolution

ALLFTD – https://www.allftd.org/fftld

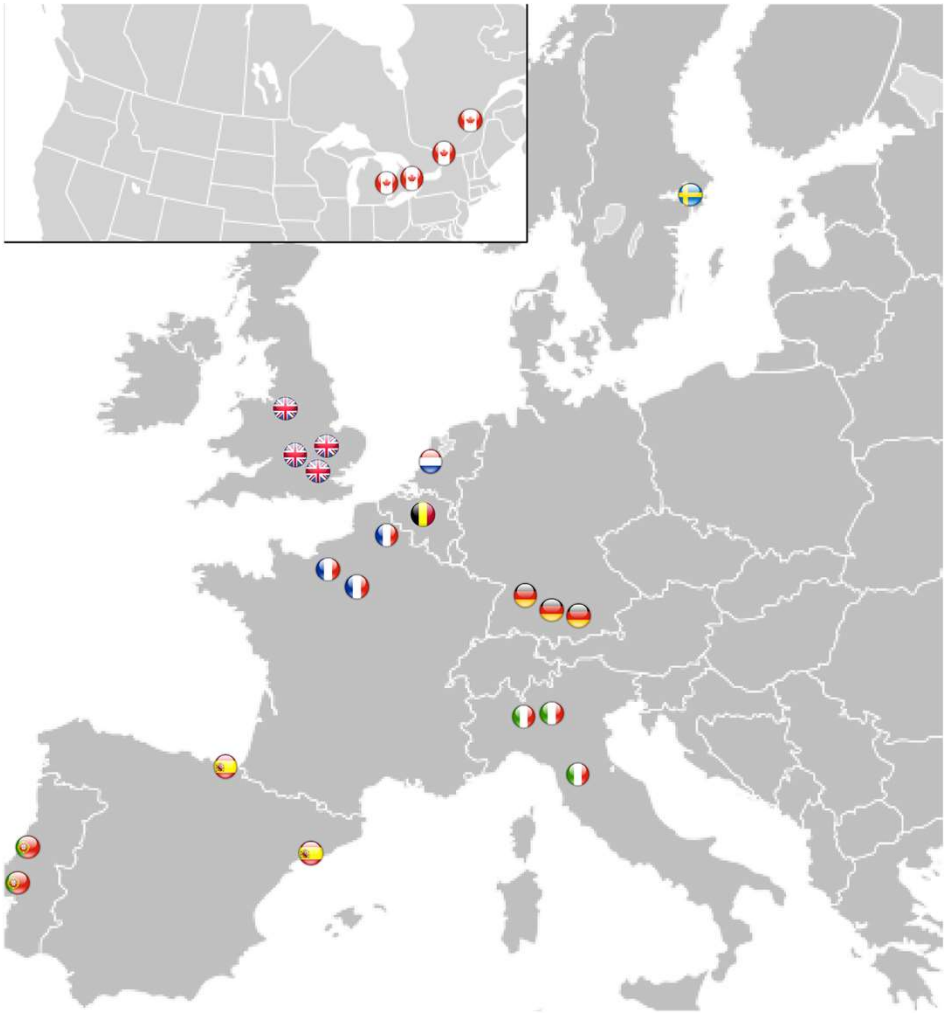


ALLFTD Consortium



LEADS Consortium

GENFI Consortium (Europe)

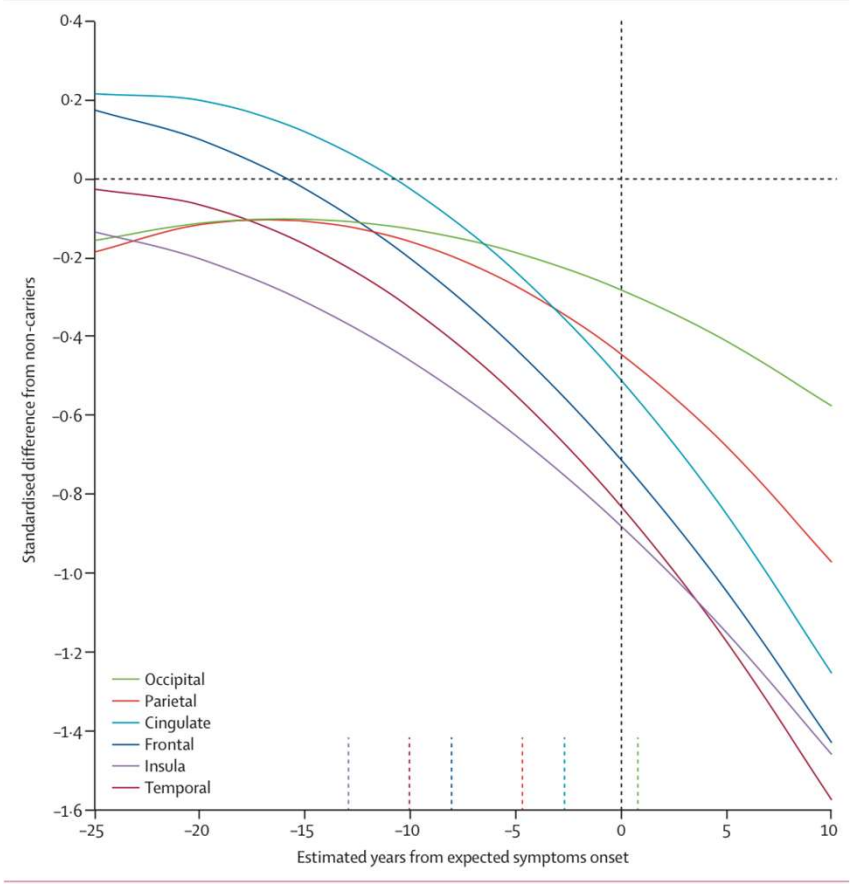


Preclinical states in hereditary FTD

Subclinical executive ± language dysfunction in carriers of MAPT, CHMP2B, and PGRN mutations. *Geschwind et al., 2001; Stokholm et al., 2012; Barandiaran et al., 2012*

Mild behavioral impairment has been described, but the construct lacks specificity. *Taragano et al., 2009; Ismail et al.,*

Relative decline in the cortex of MAPT, PGRN, C9ORF72 mutations carriers, see graph. *Rohrer et al., 2015*

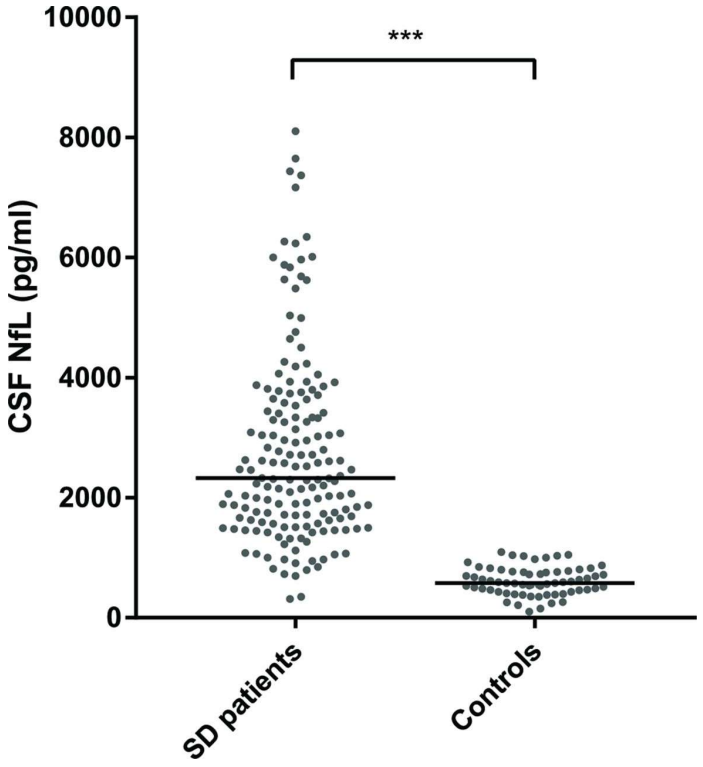


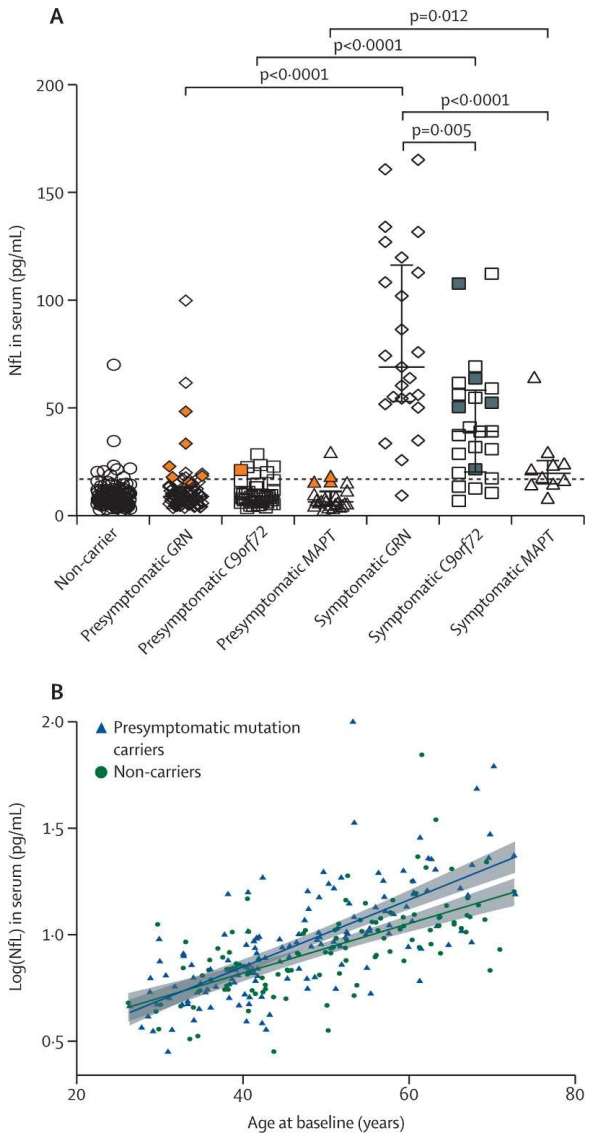
Standardised difference between all mutation carriers and non-carriers in cortical grey matter volumetric imaging measures versus estimated years from expected symptoms onset

Individual data points not plotted to prevent disclosure of genetic status. The time at which the upper 95% CI for each curve crosses zero on the y-axis (i.e., the point at which a significant difference exists between mutation carriers and non-carriers) is shown on the x-axis.

Neurofilament light chain assays

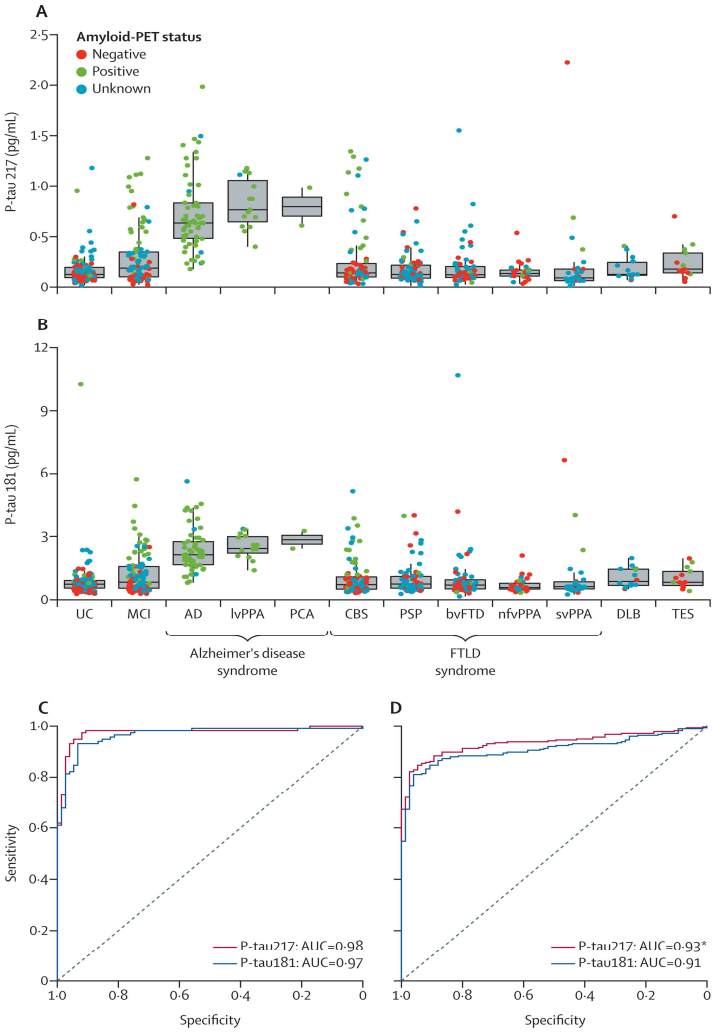
Jiskoot et al., 2016

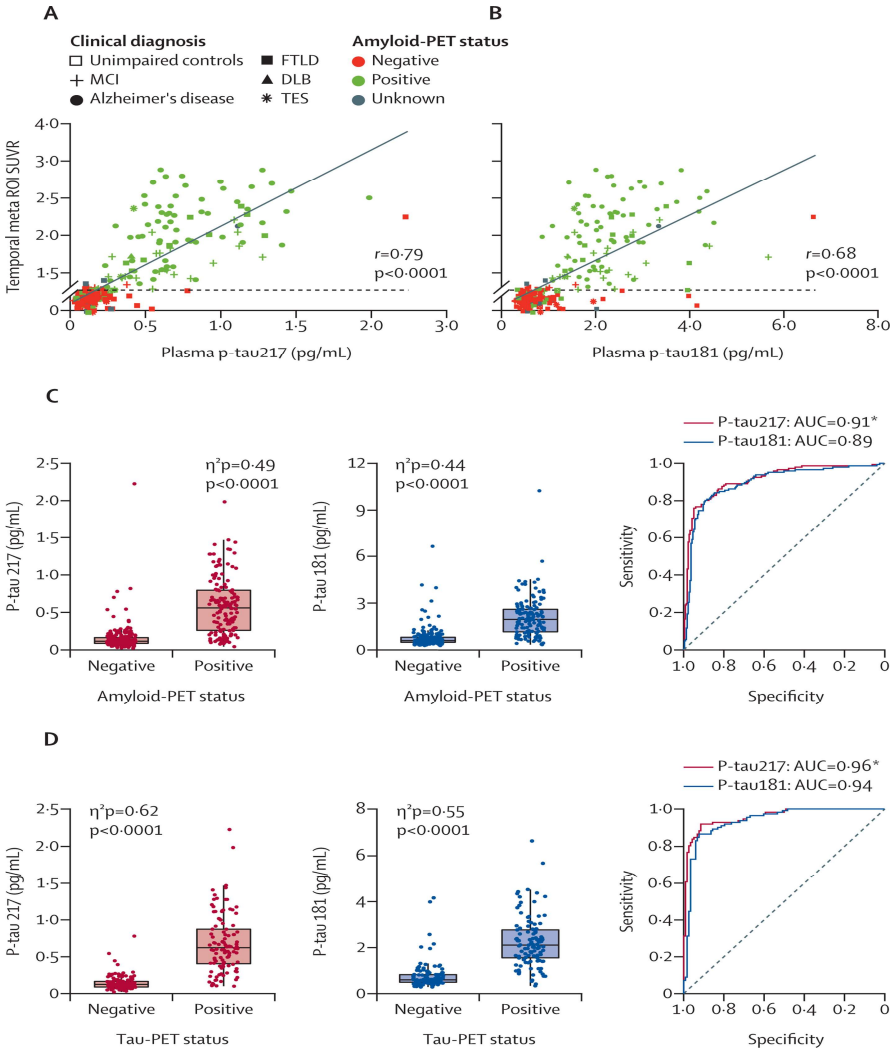




Plasma p-tau^{217} and p-tau^{181} assays

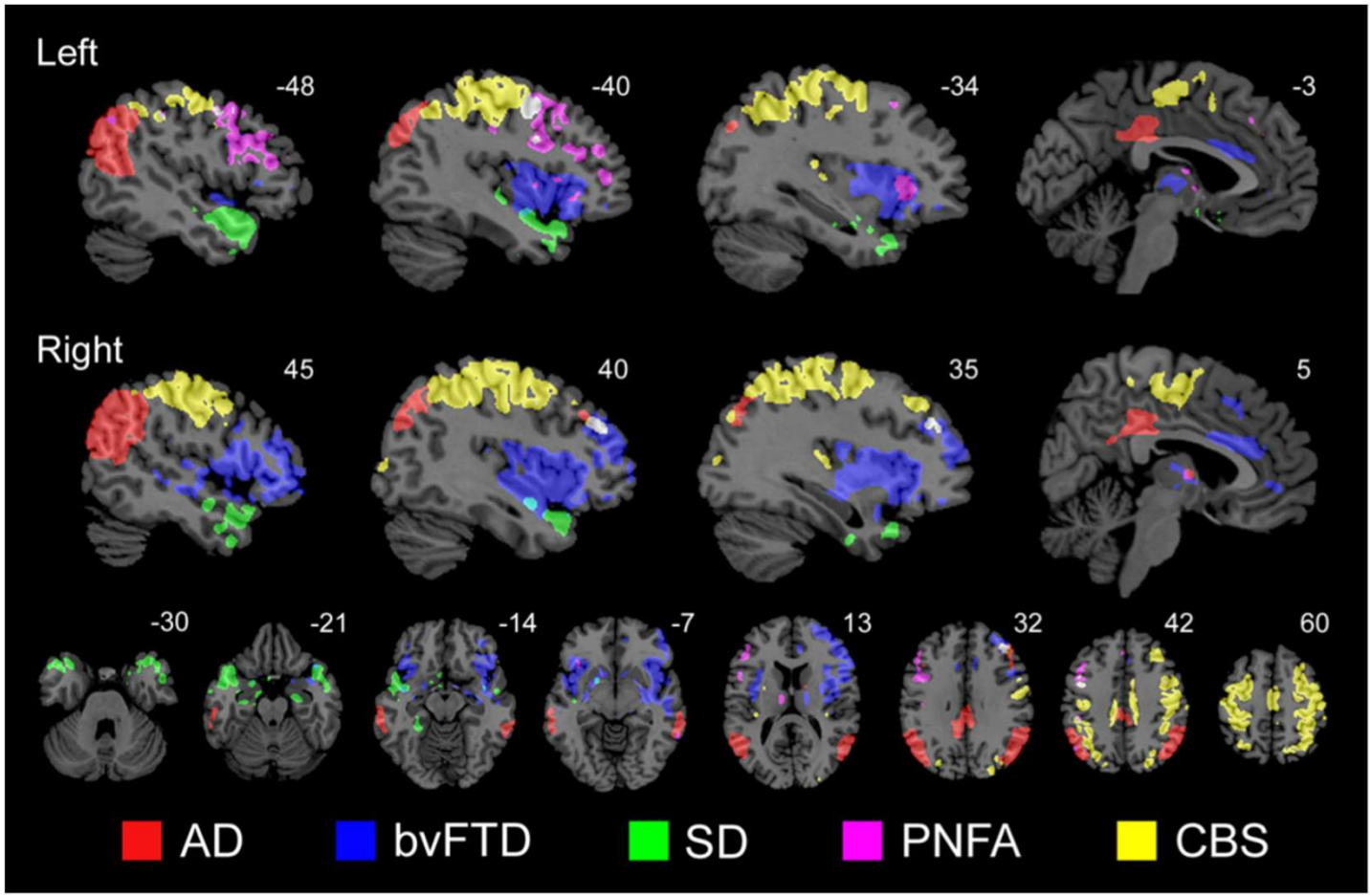
Thijssen et al., 2021





Mechanisms for expression of syndromes: selective atrophy in connectivity networks

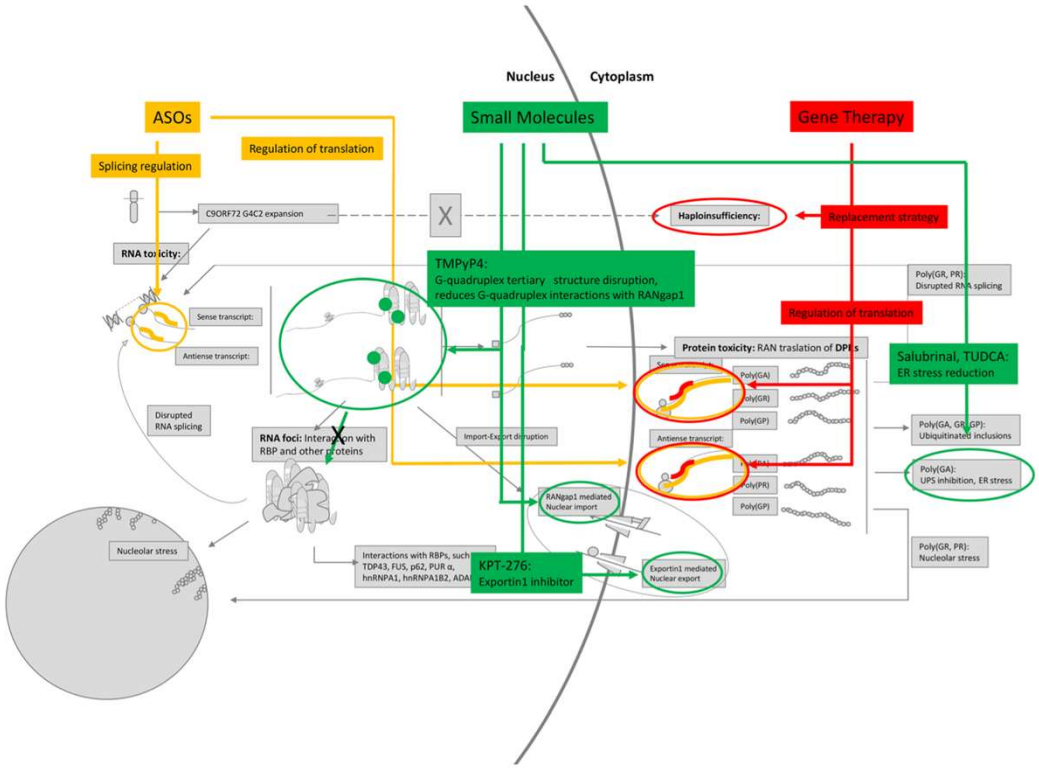
Seeley et al., 2009



Candidate mechanisms for neurodegeneration and drug development

Nalbandian et al., 2011; Cleary and Ranum, 2013; Ling et al., 2015; Mis et al., 2016

- Dysregulation of amyloid processing
- Dysregulation of cellular repair → apoptotis
- Tau polymerization → disruption of axonal transport
- Dysfunction of endosomal trafficking and autophagy
- Mitochondrial dysfunction – in MSP
- Activation of microglia and cytokines/interleukins
- Repeat associated non-ATG (RAN) translation – in C9 FTD/ALS, SCA8, DM1 and FXTAS – toxic dipeptide repeat proteins
- Compromise of TDP43 repression of non-conserved cryptic exons
- Prion-like propagation of neuropathology vs. regional differences in proteinopathy expression



Implications of an age-related model for care and research

"The life course is a complex phenomenon which intersects with [various] subjective, interactional and social factors"
Tolhurst, 2016

- Facilitates study of 'atypical' syndromes
- Promotes enriched diagnostic rules and protocols
- Value of novel diagnostic (e.g., molecular imaging) and psychometric approaches
- Proposes diverse care pathways and resources
- Explication of genetic and physiochemical markers and pathways

- Binary models leads to opposing constructs – defined by difference
- Risks artificial homogenization of wide experiential categories
- Highlights extremes at the expense of an "excluded middle", hence the value of a third age
- Risks promoting concepts of "on-time dependency"

Clinical care and research studies at Johns Hopkins

- **FTD and Young-Onset Dementias Clinic**
  - Myra Franklin, mfrank21@jhmi.edu, 410-955-5147

- **Observational studies and clinical trials for FTD, YOAD and spinocerebellar ataxias**
  - Ann Fishman, ann.fishman@jhu.edu, 410-502-5816
  - Haley Park, hpark88@jhmi.edu, 410-502-5816

- **Observational studies and clinical trials for DLB, PSP and other parkinsonian disorders**
  - Diane Lanham, dlanham1@jhmi.edu, 443-287-2965

- **Clinical and Research Genetic Counseling**
  - Weiyi Mu, wmu2@jhmi.edu, 443-287-2965

- **Neuromodulation in PPA**
  - Olivia Herrmann, oherrma1@jhu.edu, 410-736-2940

- **Brain donation for FTD and YOAD research**
  - Mary Anne Wylie, mwylie1@jhmi.edu, 410-502-5147

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- **JH ADRC:** Marilyn Albert, Carol Gogel
- **Cognitive Neurology:** Argye Hillis, Kyrana Tsapkini
- **Neuropsychology:** Vidya Kamath, Jason Brandt, Campbell Sullivan
- **Movement Disorders Neurology:** Alexander Pantelyat
- **Neuromuscular Neurology:** Jeff Rothstein, Nicholas Maragakis, Lora Clawson
- **Rehabilitation Psychology:** Kathleen Bechtold, Connie Jacocks, Marlis Gonzalez-Fernandez
- **Neuropathology:** Juan Troncoso, Olga Pletnikova, Karen Fisher
- **Neuroradiology:** Haris Sair
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- **Columbia University:** Edward Huey
- **UCSF:** Adam Boxer, Howard Rosen, Bruce Miller
- **Mayo Clinic Rochester:** Brad Boeve
- **Harvard University:** Brad Dickerson
- **Association for Frontotemporal Degeneration**
- **Frontotemporal Dementia Study Group**
- **Alzheimer's Association of Greater Maryland**
- **Jane Tanger Black Fund for Young-Onset Dementias; Nancy Hall Fund for Geriatric Psychiatry; Trovato Fund**