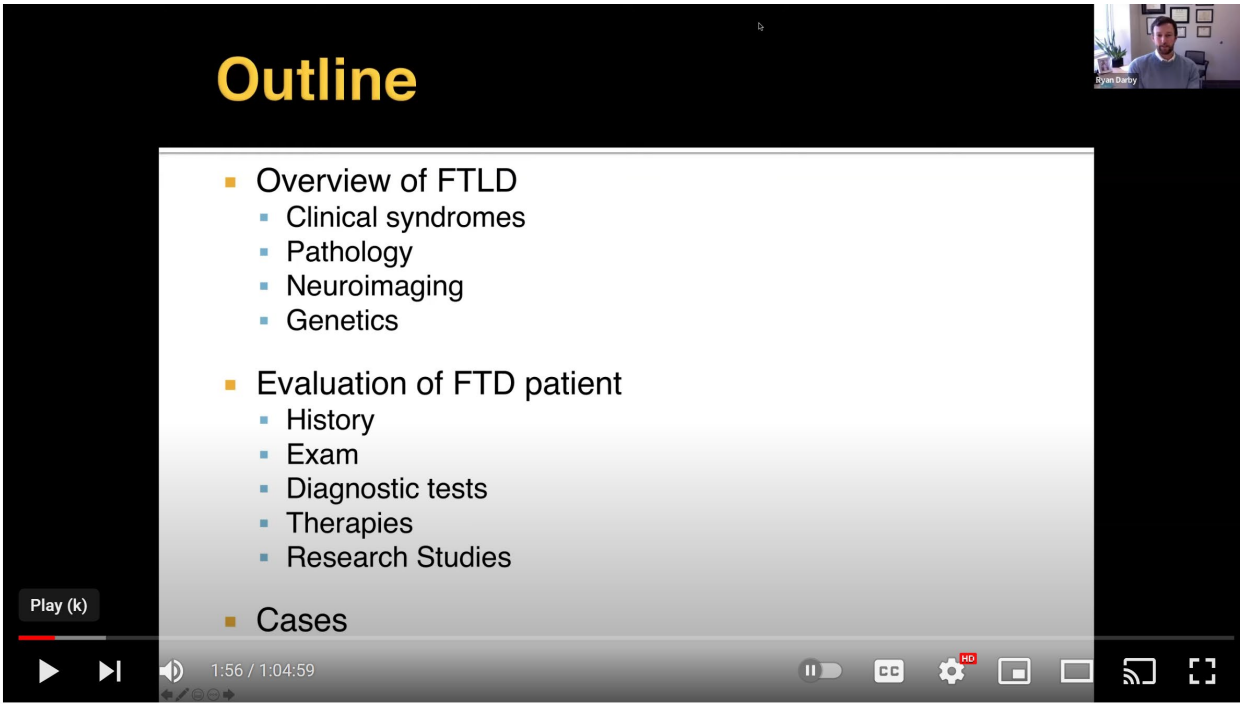
Frontotemporal Dementia (FTD)

Ryan Darby, MD

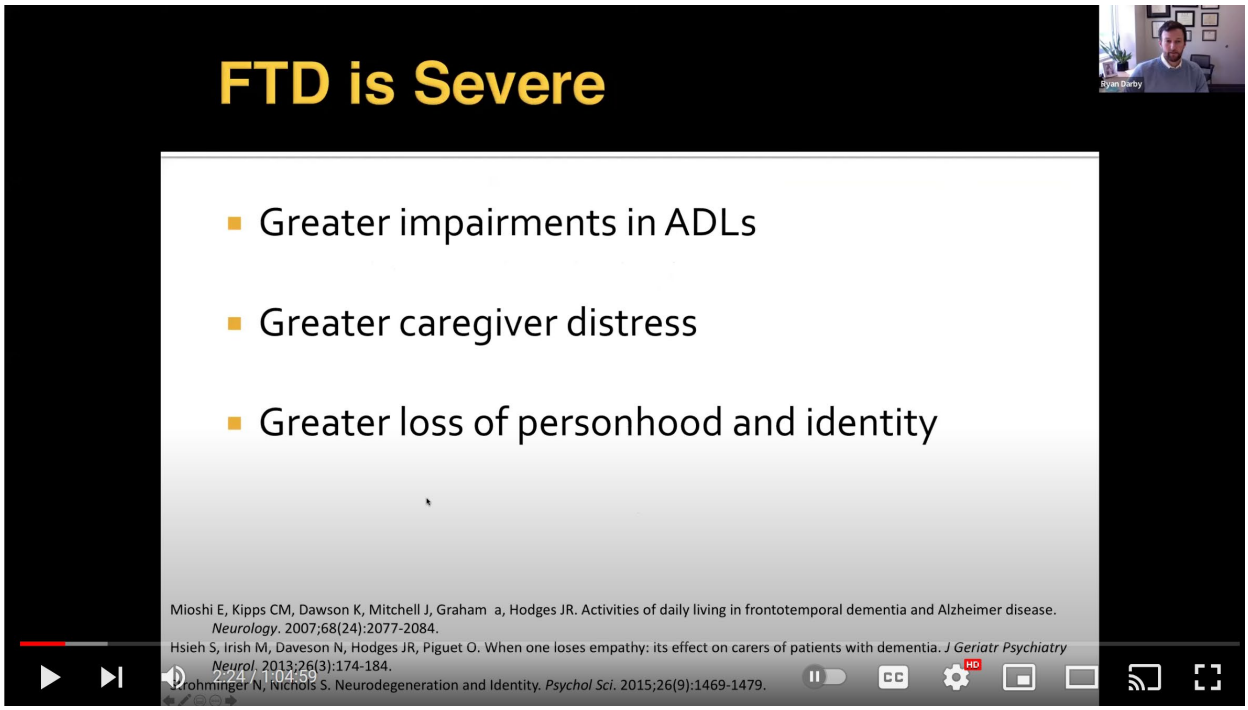
Assistant Professor of Neurology
Director, FTD clinic
Vanderbilt University Medical Center


Outline
Overview of FTLD
Clinical syndromes
Pathology
Neuroimaging
Genetics
Evaluation of FTD patient
History
Exam
Diagnostic tests
Therapies
Research Studies
Cases
Play (k)
1:56 / 1:04:59
Ryan Darby

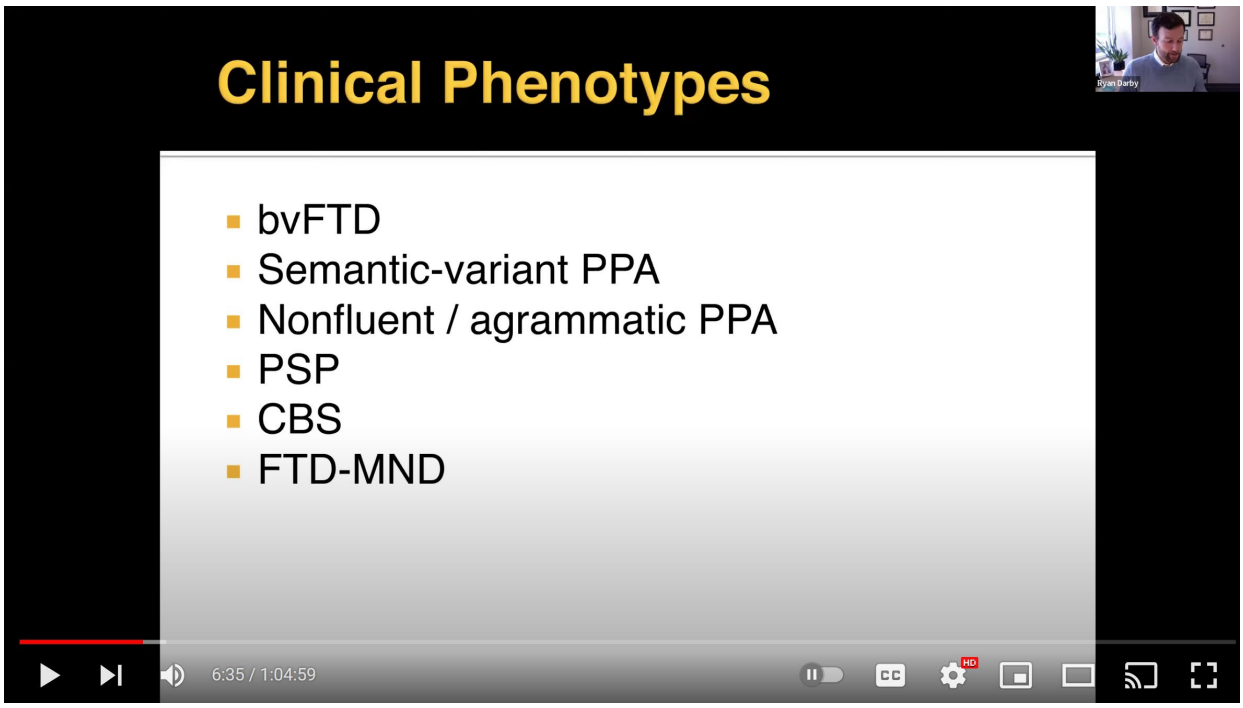
FTD is Not Rare

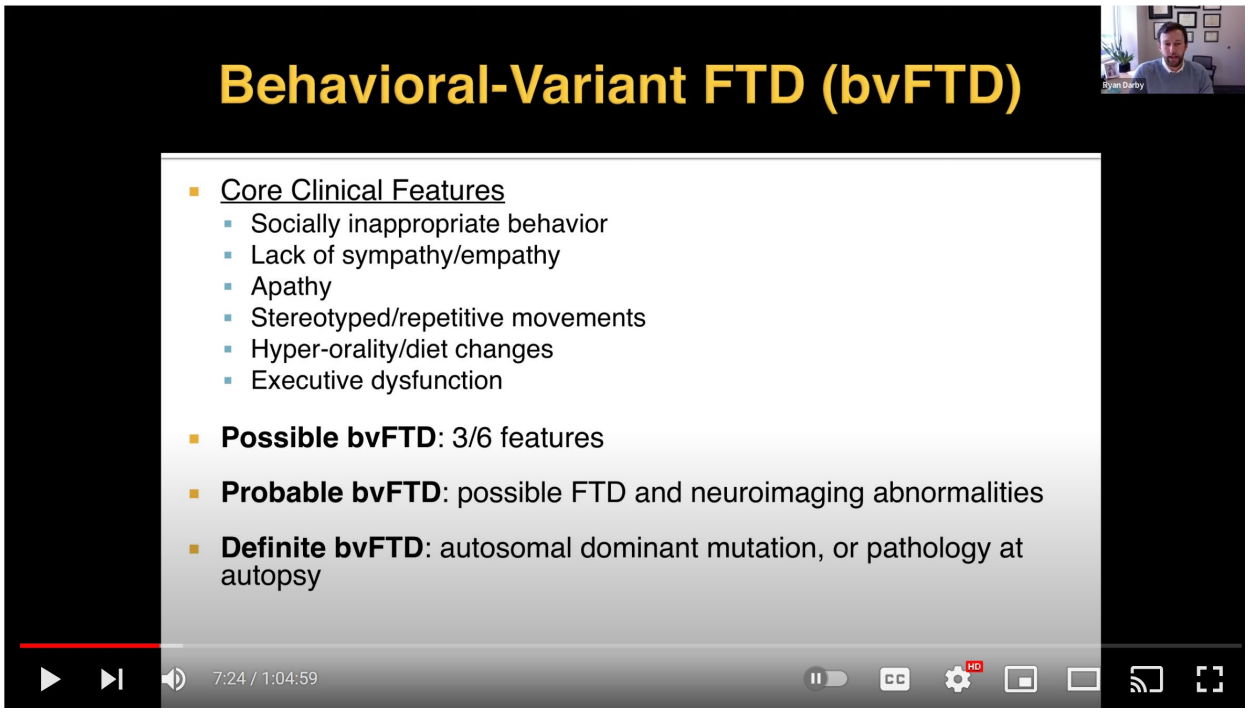
- Third most common cause of dementia across all ages (behind AD, LBD)
- Most common cause of dementia in patients under Age 60
- 50,000-60,000 cases in the US

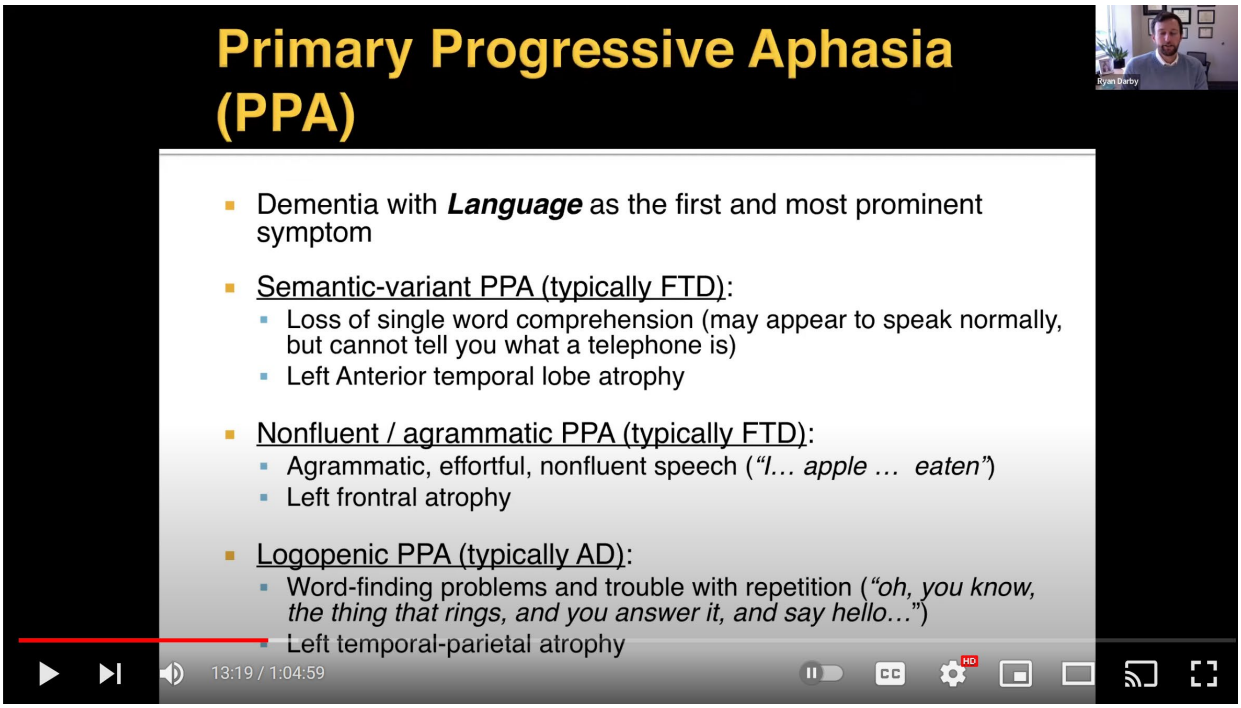
Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. *Neurology*. 2002;58(11):1615-1621.
Knopman DS, Petersen RC, Edland SD, Cha RH, Rocca WA. The incidence of frontotemporal lobar degeneration in Rochester, Minnesota,1990 through 1994. *Neurology*. 2004;62(3):506-508.

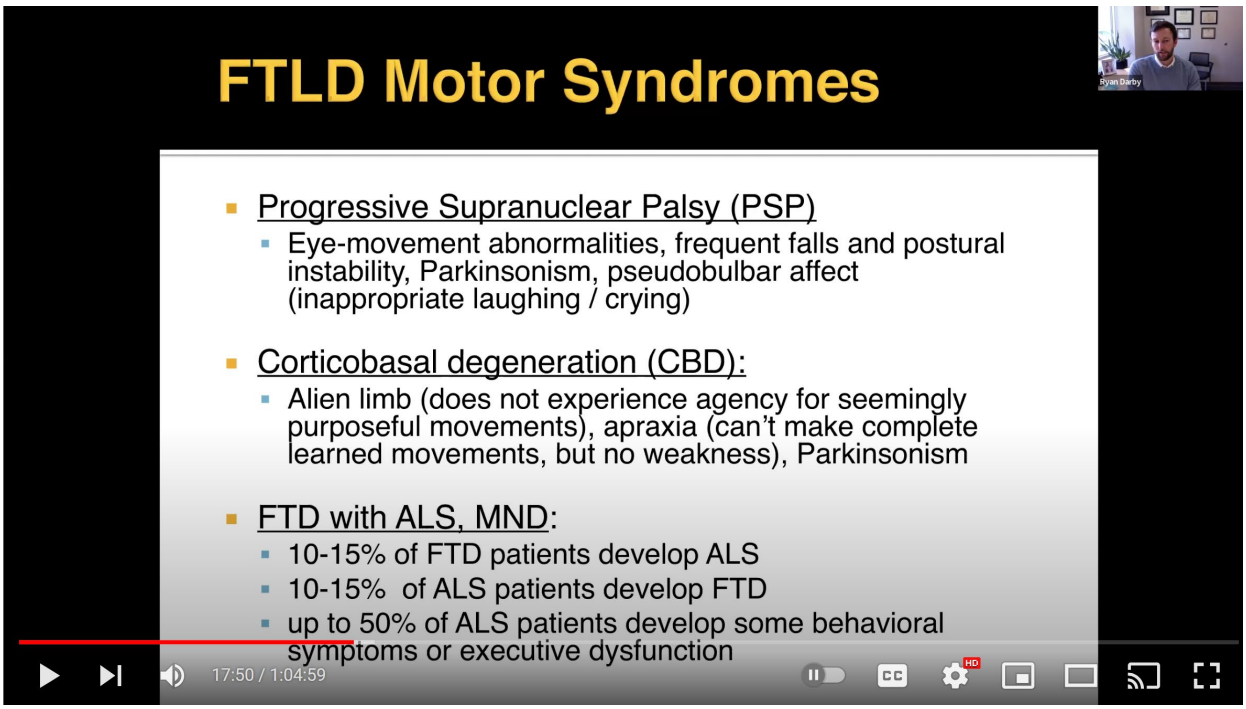

FTD is Severe
Ryan Darby
Greater impairments in ADLs
Greater caregiver distress
Greater loss of personhood and identity
Mioshi E, Kipps CM, Dawson K, Mitchell J, Graham a, Hodges JR. Activities of daily living in frontotemporal dementia and Alzheimer disease. Neurology. 2007;68(24):2077-2084.
Hsieh S, Irish M, Daveson N, Hodges JR, Piguet O. When one loses empathy: its effect on carers of patients with dementia. J Geriatr Psychiatry Neurol. 2013;26(3):174-184.
Strohminger N, Nichols S. Neurodegeneration and Identity. Psychol Sci. 2015;26(9):1469-1479.
2:24 / 1:04:59
HD

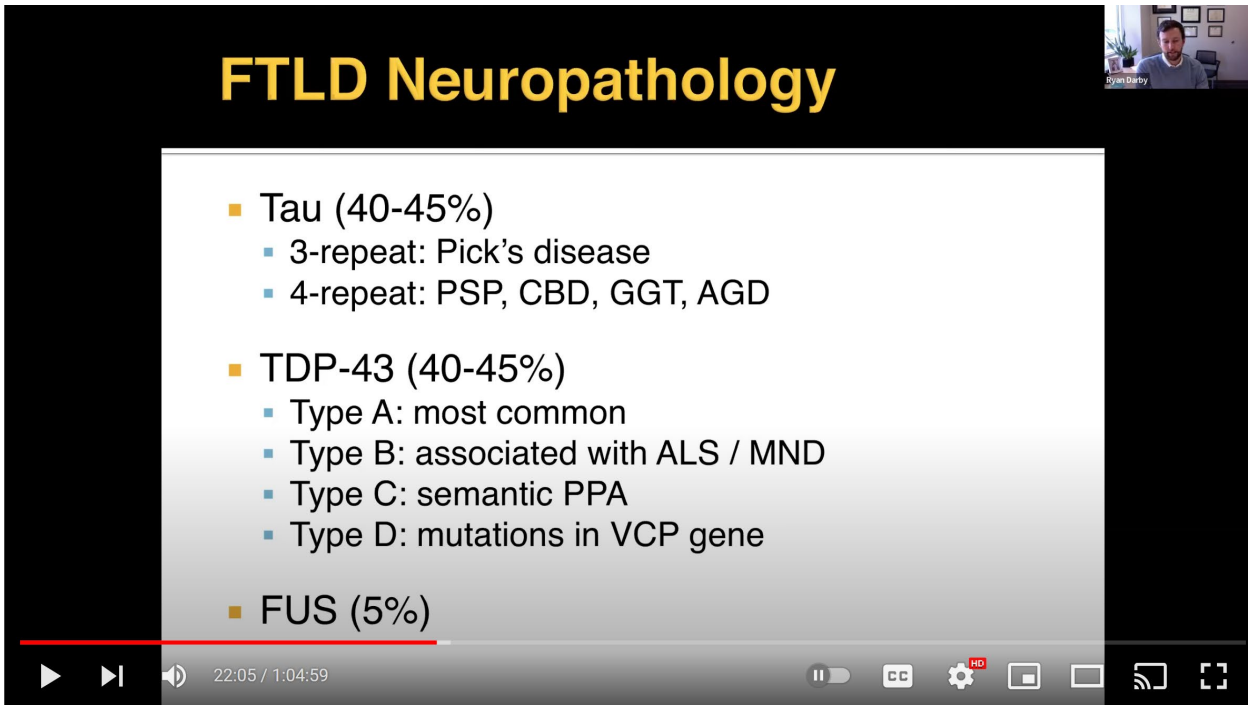

FTD is Often Misdiagnosed
Ryan Darby
Behavioral Symptoms misdiagnosed as psychiatric diseases
Motor Symptoms misdiagnosed as Parkinson's Disease
Cognitive Symptoms misdiagnosed as Alzheimer's disease
5:28 / 1:04:59

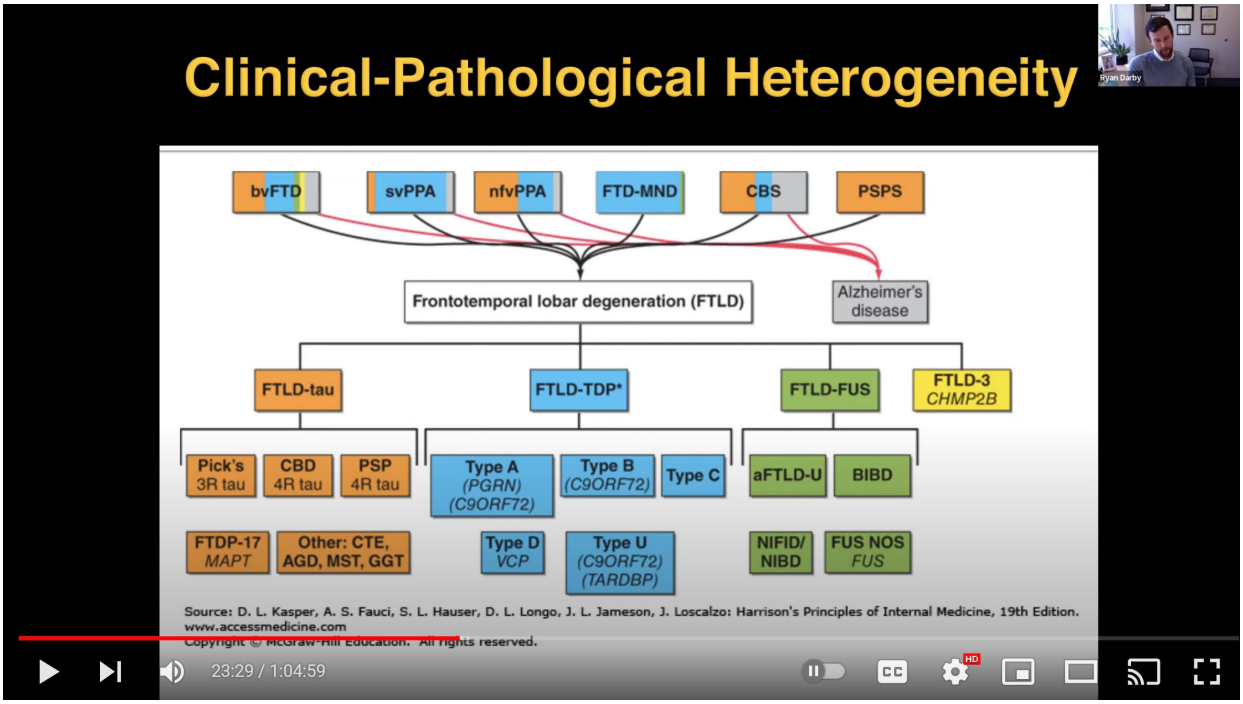

Clinical Phenotypes
Bryan Darby
bvFTD
Semantic-variant PPA
Nonfluent / agrammatic PPA
PSP
CBS
FTD-MND
6:35 / 1:04:59


Behavioral-Variant FTD (bvFTD)
Ryan Darby
Core Clinical Features
Socially inappropriate behavior
Lack of sympathy/empathy
Apathy
Stereotyped/repetitive movements
Hyper-orality/diet changes
Executive dysfunction
Possible bvFTD: 3/6 features
Probable bvFTD: possible FTD and neuroimaging abnormalities
Definite bvFTD: autosomal dominant mutation, or pathology at autopsy
7:24 / 1:04:59


Primary Progressive Aphasia (PPA)
Ryan Darby
Dementia with ***Language*** as the first and most prominent symptom
Semantic-variant PPA (typically FTD):
Loss of single word comprehension (may appear to speak normally, but cannot tell you what a telephone is)
Left Anterior temporal lobe atrophy
Nonfluent / agrammatic PPA (typically FTD):
Agrammatic, effortful, nonfluent speech (*"I… apple … eaten"*)
Left frontral atrophy
Logopenic PPA (typically AD):
Word-finding problems and trouble with repetition (*"oh, you know, the thing that rings, and you answer it, and say hello…"*)
Left temporal-parietal atrophy
13:19 / 1:04:59


FTLD Motor Syndromes
Ryan Darby
Progressive Supranuclear Palsy (PSP)
Eye-movement abnormalities, frequent falls and postural instability, Parkinsonism, pseudobulbar affect (inappropriate laughing / crying)
Corticobasal degeneration (CBD):
Alien limb (does not experience agency for seemingly purposeful movements), apraxia (can't make complete learned movements, but no weakness), Parkinsonism
FTD with ALS, MND:
10-15% of FTD patients develop ALS
10-15% of ALS patients develop FTD
up to 50% of ALS patients develop some behavioral symptoms or executive dysfunction
17:50 / 1:04:59


FTLD Neuropathology
Ryan Darby
Tau (40-45%)
3-repeat: Pick's disease
4-repeat: PSP, CBD, GGT, AGD
TDP-43 (40-45%)
Type A: most common
Type B: associated with ALS / MND
Type C: semantic PPA
Type D: mutations in VCP gene
FUS (5%)
22:05 / 1:04:59


Clinical-Pathological Heterogeneity
Ryan Darby
bvFTD
svPPA
nfvPPA
FTD-MND
CBS
PSPS
Frontotemporal lobar degeneration (FTLD)
Alzheimer's disease
FTLD-tau
FTLD-TDP*
FTLD-FUS
FTLD-3 CHMP2B
Pick's 3R tau
CBD 4R tau
PSP 4R tau
Type A (PGRN) (C9ORF72)
Type B (C9ORF72)
Type C
aFTLD-U
BIBD
FTDP-17 MAPT
Other: CTE, AGD, MST, GGT
Type D VCP
Type U (C9ORF72) (TARDBP)
NIFID/ NIBD
FUS NOS FUS
Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com
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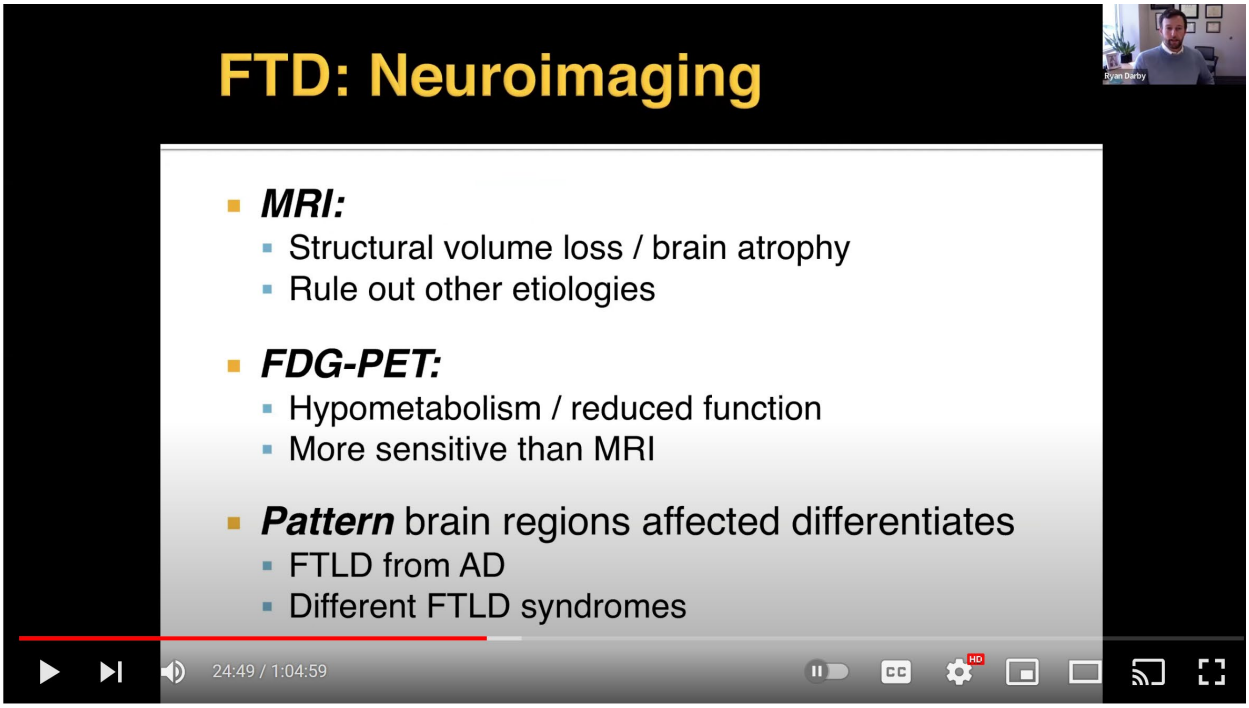
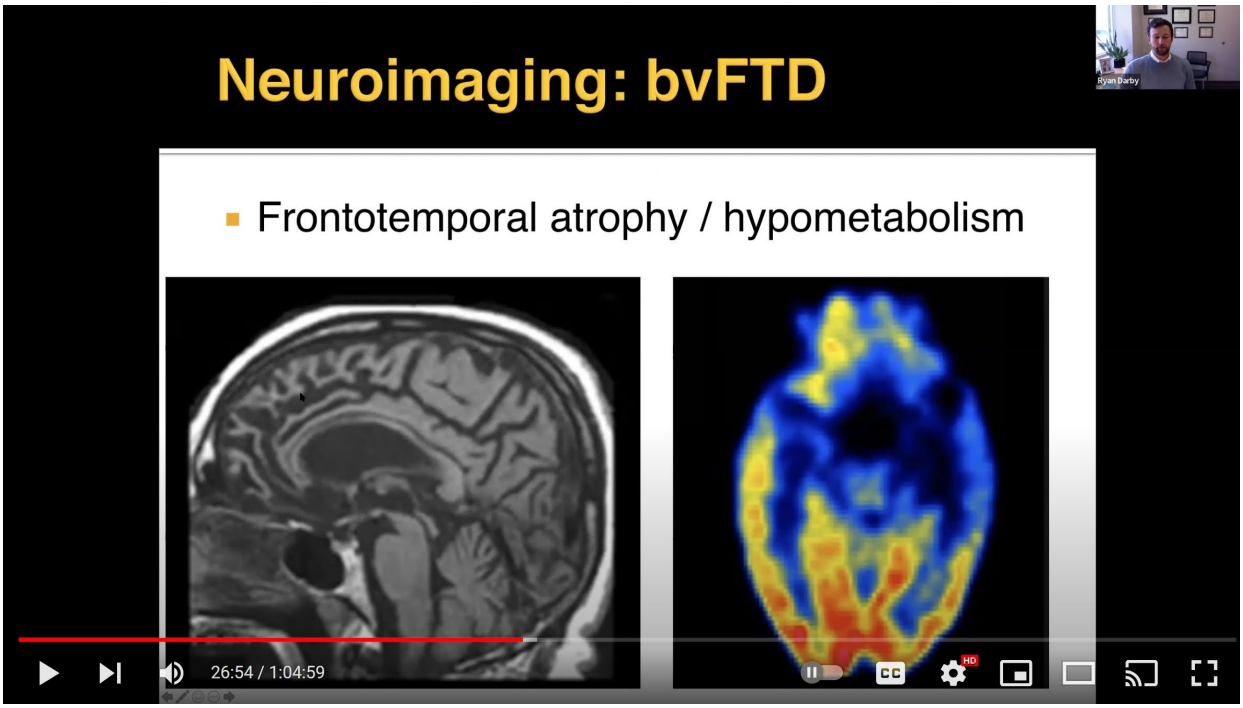
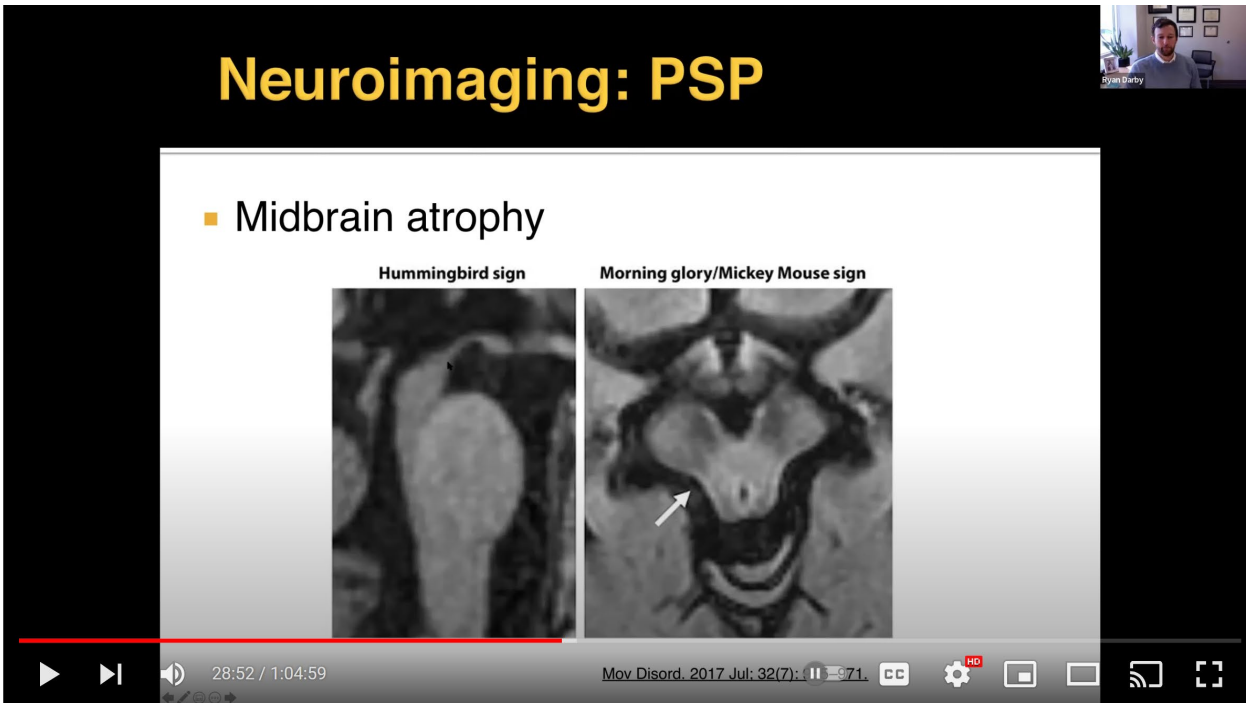
23:29 / 1:04:59


FTD: Neuroimaging
Ryan Darby
MRI:
Structural volume loss / brain atrophy
Rule out other etiologies
FDG-PET:
Hypometabolism / reduced function
More sensitive than MRI
Pattern brain regions affected differentiates
FTLD from AD
Different FTLD syndromes
24:49 / 1:04:59


Neuroimaging: bvFTD
Ryan Darby
Frontotemporal atrophy / hypometabolism
26:54 / 1:04:59


Neuroimaging: PSP
Midbrain atrophy
Hummingbird sign
Morning glory/Mickey Mouse sign
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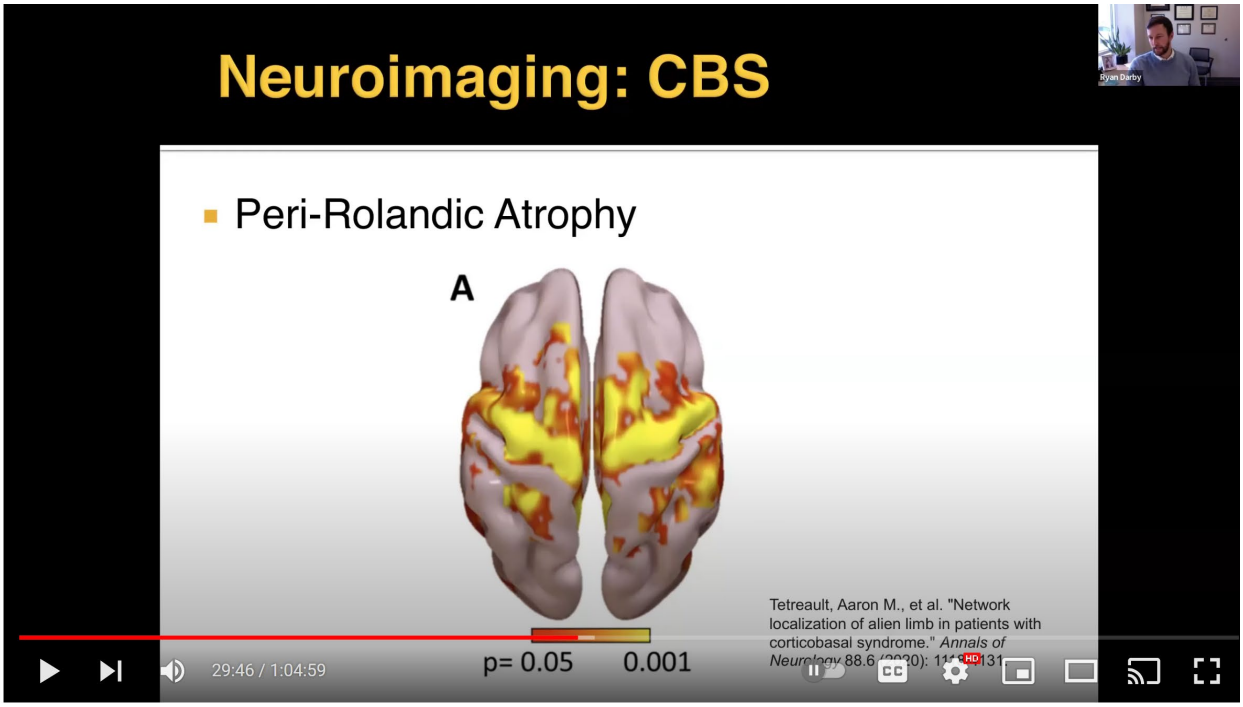
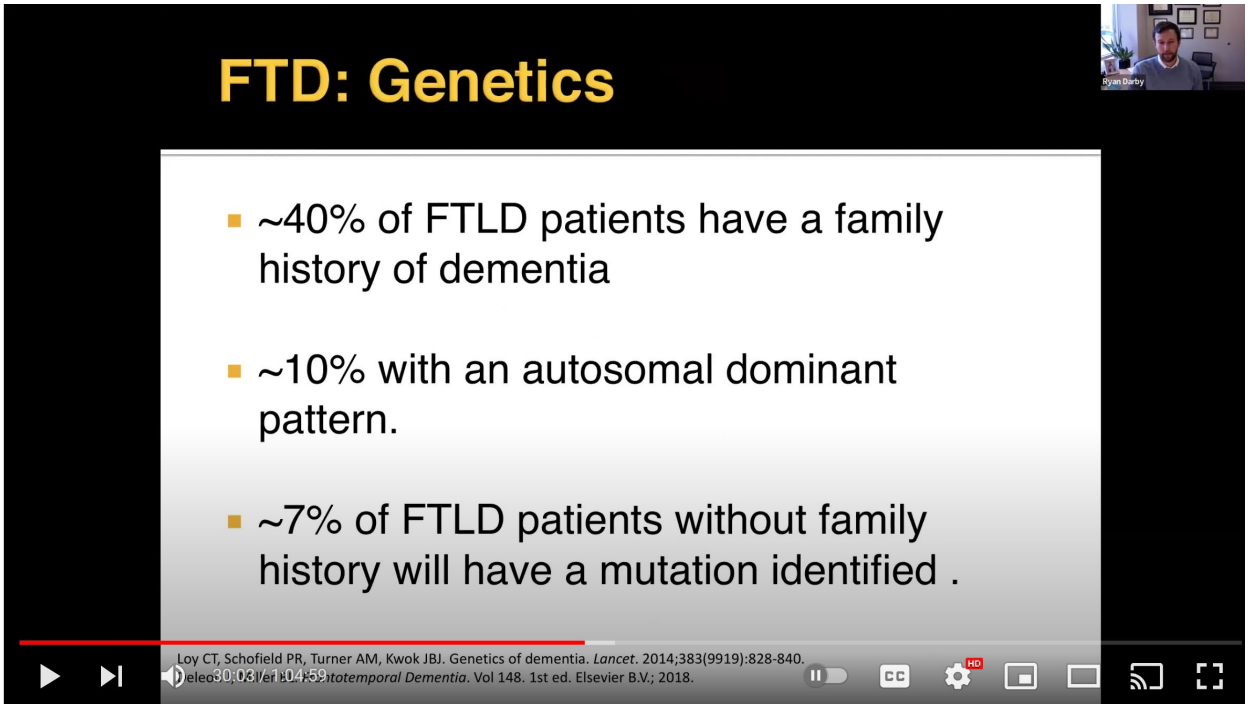

Neuroimaging: CBS
Ryan Darby
Peri-Rolandic Atrophy
A
p= 0.05
0.001
Tetreault, Aaron M., et al. "Network localization of alien limb in patients with corticobasal syndrome." Annals of
29:46 / 1:04:59


FTD: Genetics
Ryan Darby
~40% of FTLD patients have a family history of dementia
~10% with an autosomal dominant pattern.
~7% of FTLD patients without family history will have a mutation identified .
Loy CT, Schofield PR, Turner AM, Kwok JBJ. Genetics of dementia. Lancet. 2014;383(9919):828-840.
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Frontotemporal Dementia. Vol 148. 1st ed. Elsevier B.V.; 2018.
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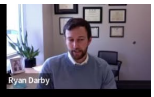
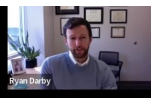
Common Genetic Mutations



	Prevalence among familial FTD cases	Geographic prevalence of mutation carriers	Atrophy patterns	Common clinical presentations	FTLD proteinopathy
C9orf72 (9p21.2)	13–50%	Scandinavia, west Europe, USA, Australia, rare in Asia	Symmetrical, orbitofrontal, medial and dorsolateral frontal, followed by temporal lobes, parietal and occipital lobes, cerebellum, posterior thalamus	BV-FTD FTD-MND ALS Parkinsonism Late-onset psychosis	TDP type B (less commonly type A) dipeptide repeat proteins in neocortex, thalamus, cerebellum, and hippocampus
MAPT (17q21.1)	5–20%	Northwest Europe, USA	Symmetric frontal, anterior cingulate cortex, insular, anterior, and medial temporal lobe	BV-FTD Parkinsonism	Tau (often unclassifiable, occasionally resembling Pick's disease), corticobasal degeneration or progressive supranuclear palsy
GRN (17q21.32)	5–20%	England, central and southern Europe, USA	Asymmetrical, anterior temporal, temporo-parietal, frontal (left > PPA; right > BV-FTD), anterior cingulate cortex, insular	BV-FTD NFV-PPA Parkinsonism CBS	TDP type A

Lancet 2015; 386: 1672–82

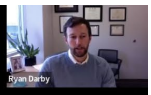
Genetic FTD: Clinical Features



	C9orf72	MAPT	GRN
Neuropsychiatric and behavioural features			
Behavioural abnormalities	Apathy, disinhibition, loss of empathy	Disinhibition, abnormal eating behaviour	Apathy, disinhibition, abnormal eating behaviour
Hallucinations and delusions	Hallucinations and delusions fairly common	Uncommon	Hallucinations seen in some patients
Cognitive features			
Executive dysfunction	Common	Common	Common
Language impairment	Small number of patients reported with a progressive aphasia, mostly non-fluent	Patients can develop semantic impairment but usually following behavioural symptoms, and non-fluent aphasia very rare	Some patients have a progressive aphasia—prominent anomia, non-fluent speech
Memory impairment	Can occur early in the disease (often leading to a clinical diagnosis of Alzheimer's disease)	Often later in the illness, but can occur early	Usually late in the illness, but can be prominent in some cases
Parietal lobe dysfunction	Seen in some patients particularly as the disease progresses	Can occur late in the disease	Seen fairly commonly, particularly as the disease progresses

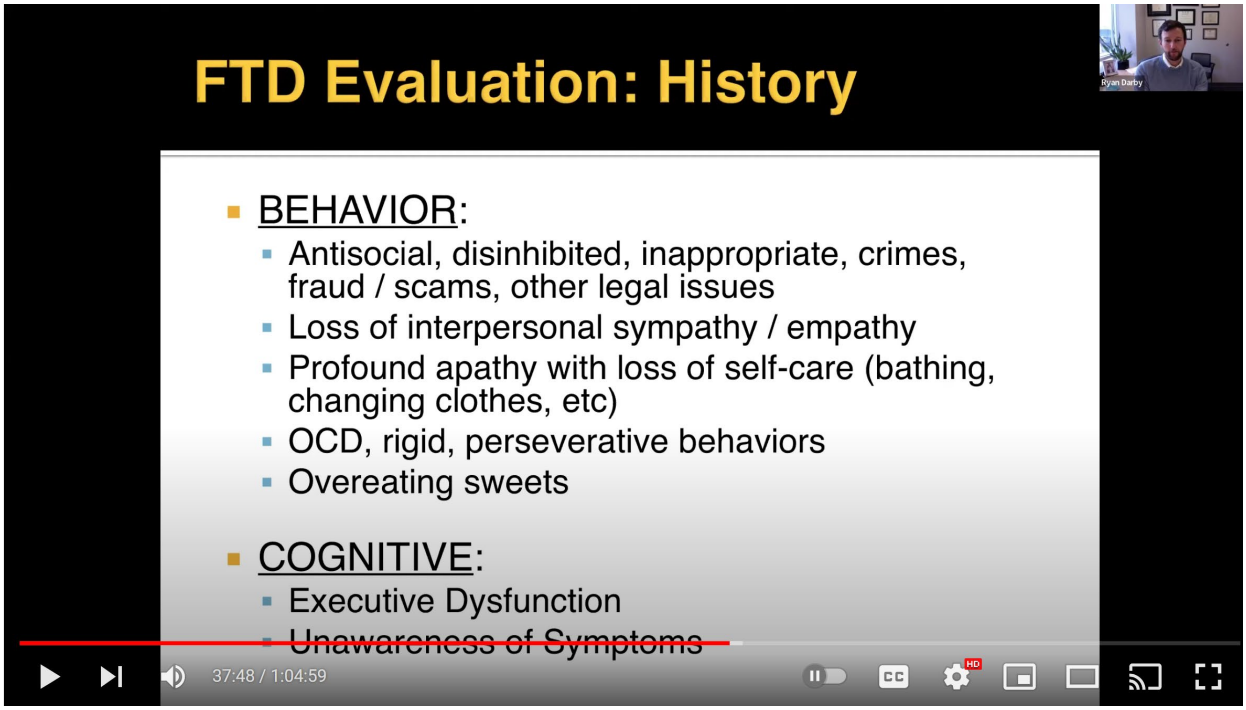
Lancet Neurol 2015; 14: 291–301

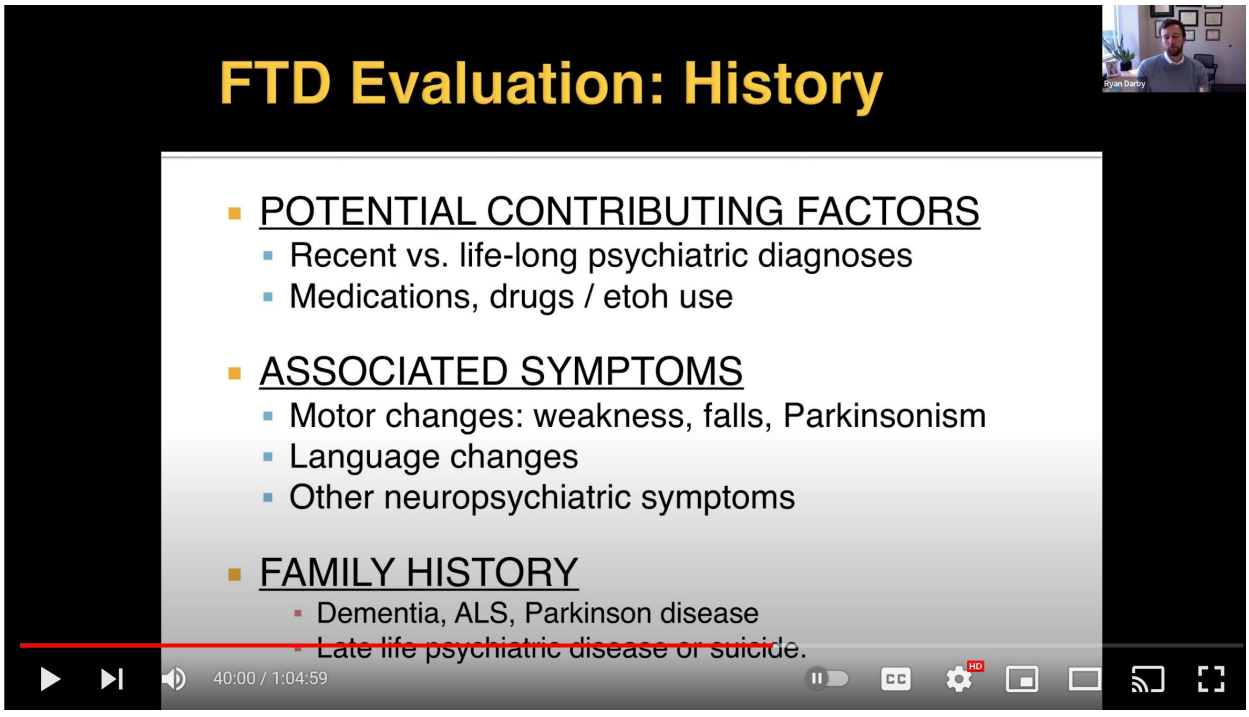
Rare Genetic Mutations

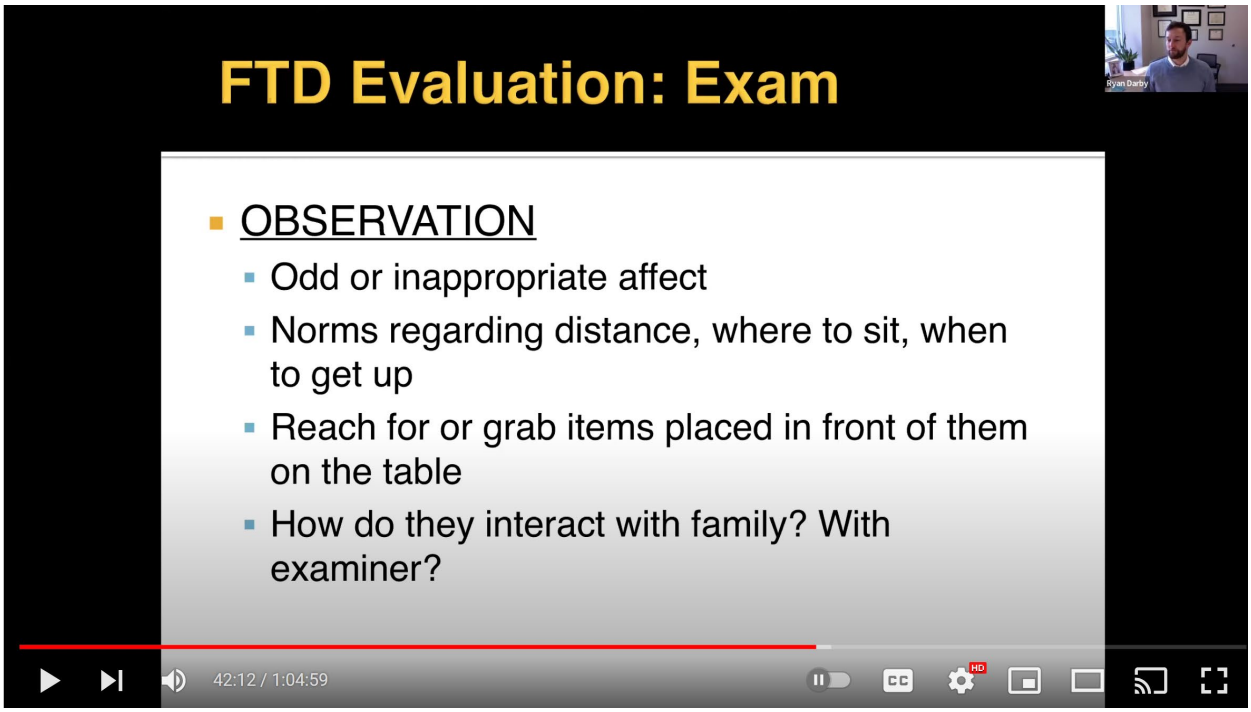


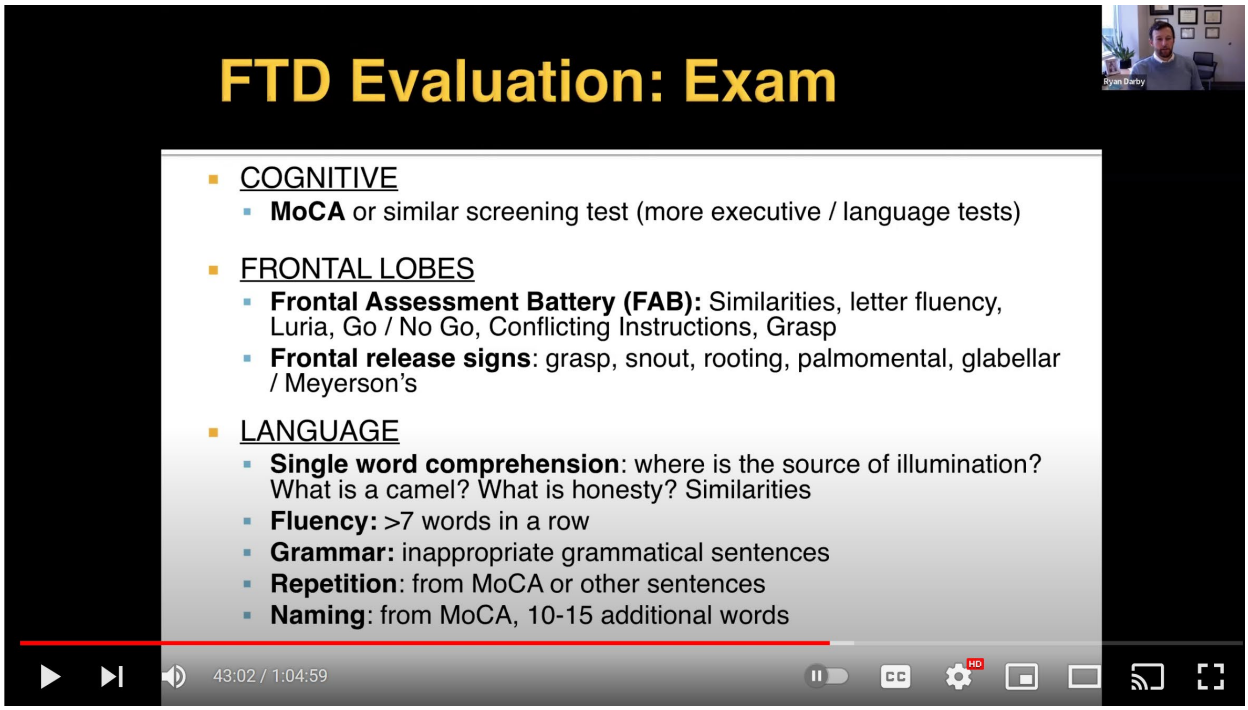
	Prevalence among familial FTD cases	Geographic prevalence of mutation carriers	Atrophy patterns	Common clinical presentations	FTLD proteinopathy
TARDBP (1p36.22)	Rare	Italy, France, North America, Japan, China, Australia	Symmetrical frontal (type A, DLPFC; type B, VMPFC), OFC, temporal atrophy	ALS FTD-MND	TDP type A or B
FUS (16p11.2)	Rare	Worldwide	Frontal and temporal atrophy with striking striatal atrophy	ALS FTD-MND	FUS
VCP (9p13.3)	Rare	West Europe, USA, Brazil, Korea, Australia	Frontal, temporal, and parietal lobes, especially prefrontal cortex and superior temporal gyrus; hippocampus, caudate nucleus, amygdala	BV-FTD FTD-MND Inclusion body myopathy Paget's disease of the bone	TDP type D
CHMP2B (3p11.2)	Rare	Denmark	Generalised cortical atrophy, mostly severe in frontal and temporal cortices	BV-FTD FTD-MND	Ubiquitin proteasome system proteins

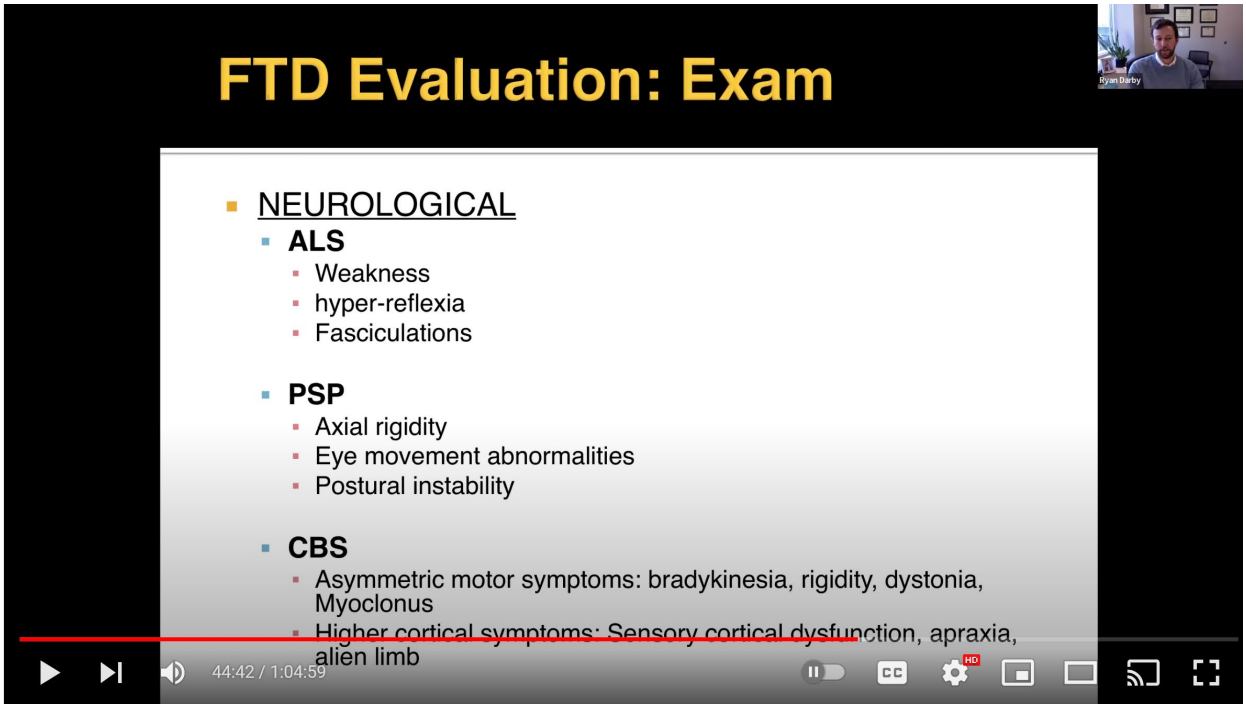
Lancet 2015; 386: 1672–82

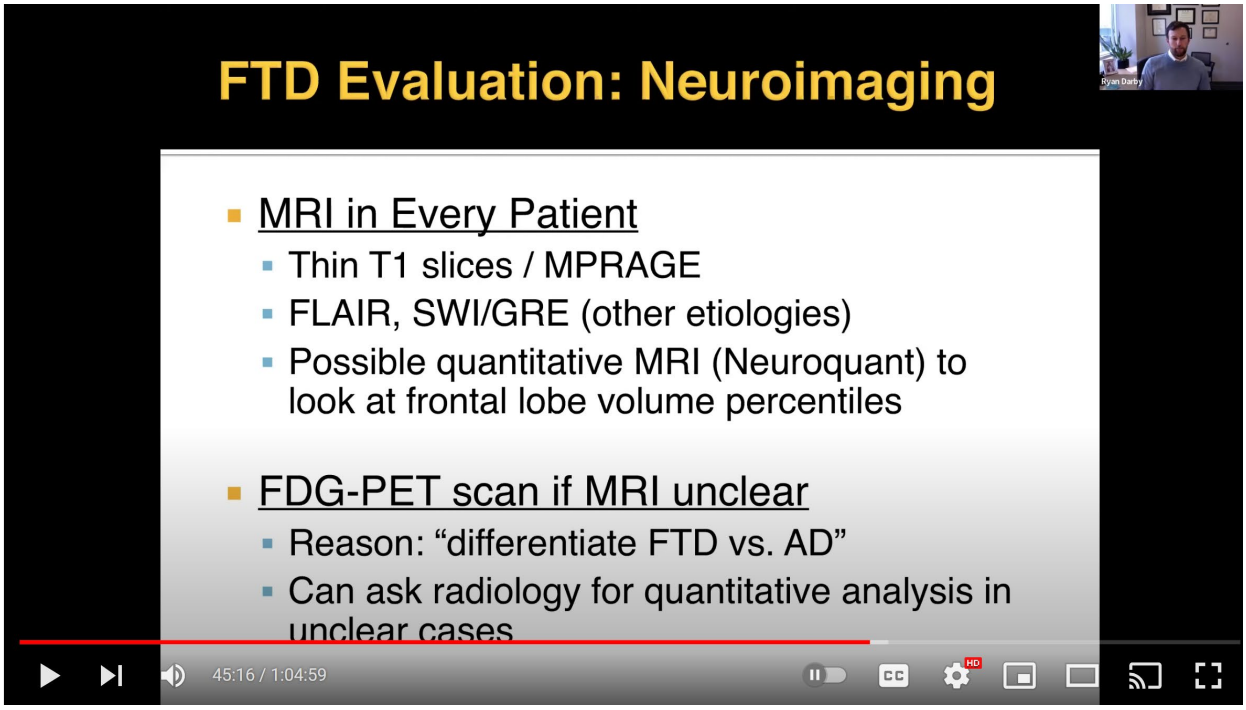

FTD Evaluation: History
Ryan Darby
BEHAVIOR:
Antisocial, disinhibited, inappropriate, crimes, fraud / scams, other legal issues
Loss of interpersonal sympathy / empathy
Profound apathy with loss of self-care (bathing, changing clothes, etc)
OCD, rigid, perseverative behaviors
Overeating sweets
COGNITIVE:
Executive Dysfunction
Unawareness of Symptoms
37:48 / 1:04:59

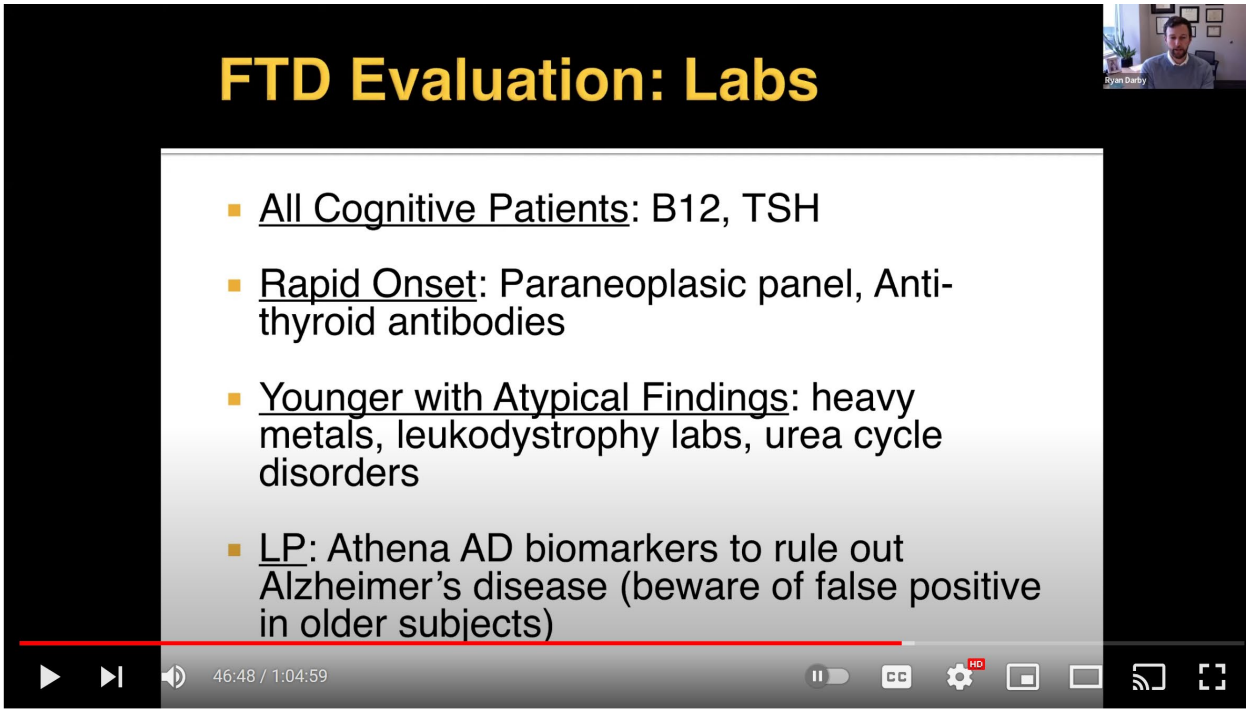

FTD Evaluation: History
Ryan Darby
POTENTIAL CONTRIBUTING FACTORS
Recent vs. life-long psychiatric diagnoses
Medications, drugs / etoh use
ASSOCIATED SYMPTOMS
Motor changes: weakness, falls, Parkinsonism
Language changes
Other neuropsychiatric symptoms
FAMILY HISTORY
Dementia, ALS, Parkinson disease
Late life psychiatric disease or suicide.
40:00 / 1:04:59

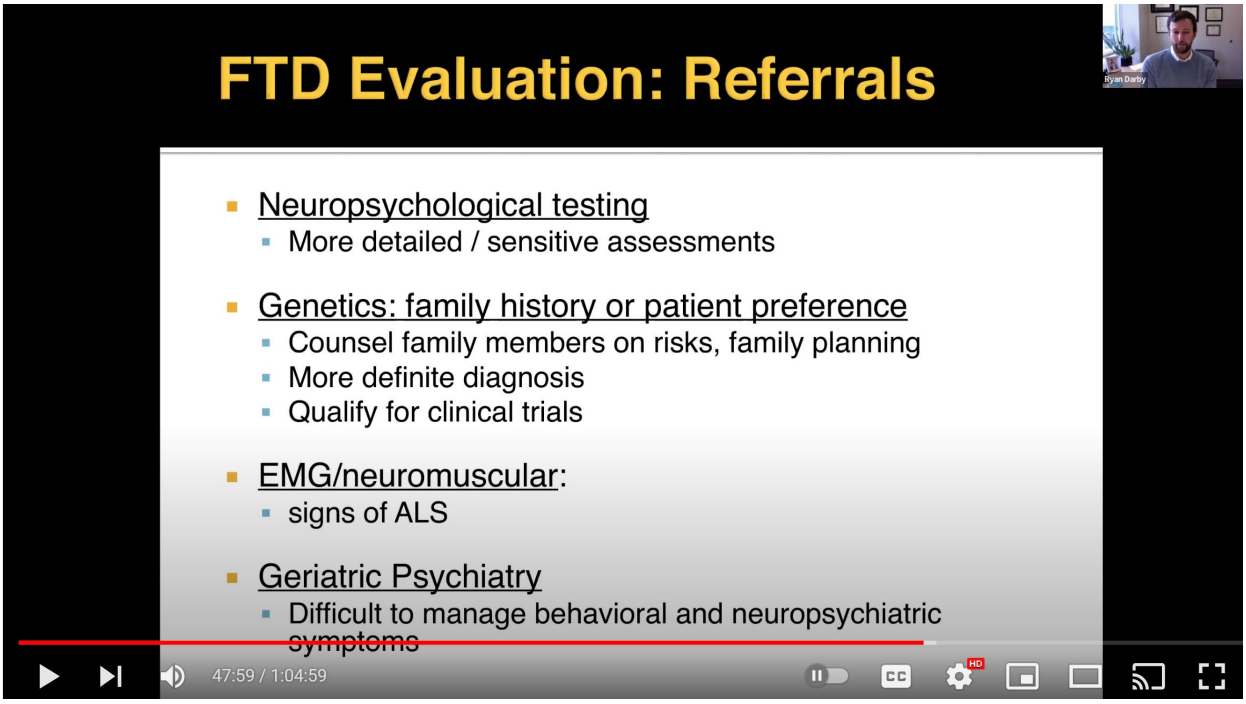

FTD Evaluation: Exam
Ryan Darby
OBSERVATION
Odd or inappropriate affect
Norms regarding distance, where to sit, when to get up
Reach for or grab items placed in front of them on the table
How do they interact with family? With examiner?
42:12 / 1:04:59

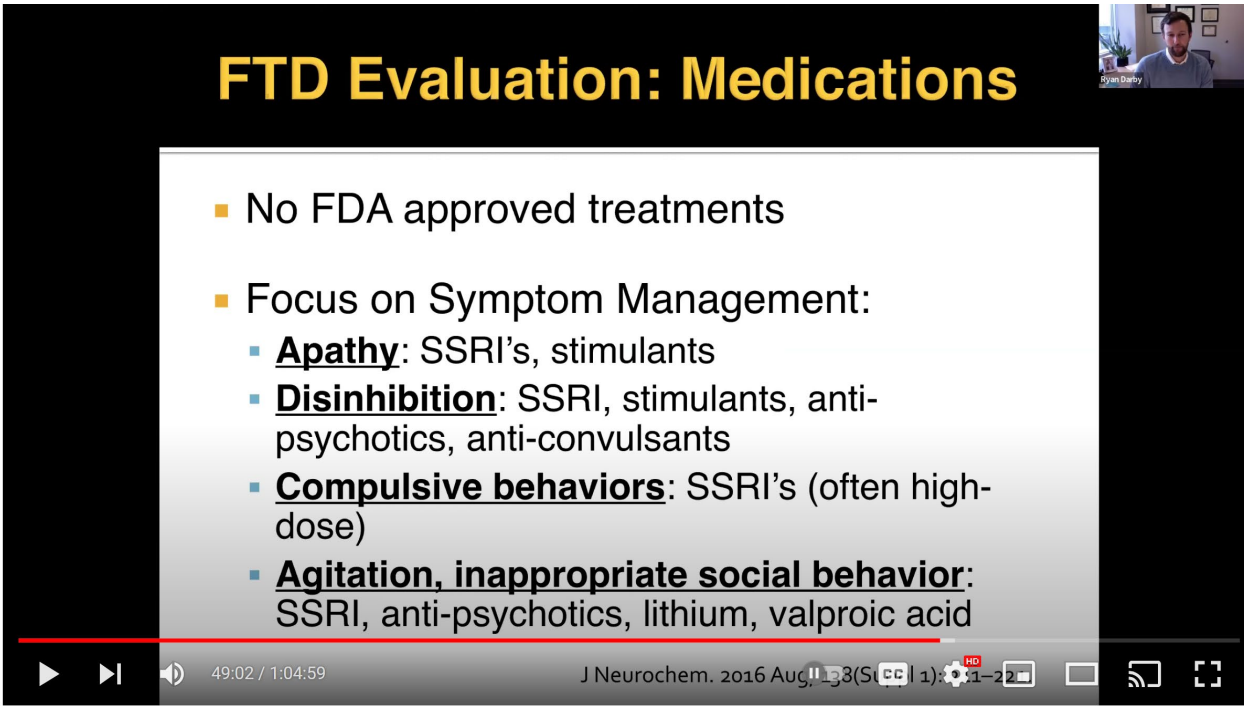

FTD Evaluation: Exam
Ryan Darby
COGNITIVE
MoCA or similar screening test (more executive / language tests)
FRONTAL LOBES
Frontal Assessment Battery (FAB): Similarities, letter fluency, Luria, Go / No Go, Conflicting Instructions, Grasp
Frontal release signs: grasp, snout, rooting, palmomental, glabellar / Meyerson's
LANGUAGE
Single word comprehension: where is the source of illumination? What is a camel? What is honesty? Similarities
Fluency: >7 words in a row
Grammar: inappropriate grammatical sentences
Repetition: from MoCA or other sentences
Naming: from MoCA, 10-15 additional words
43:02 / 1:04:59

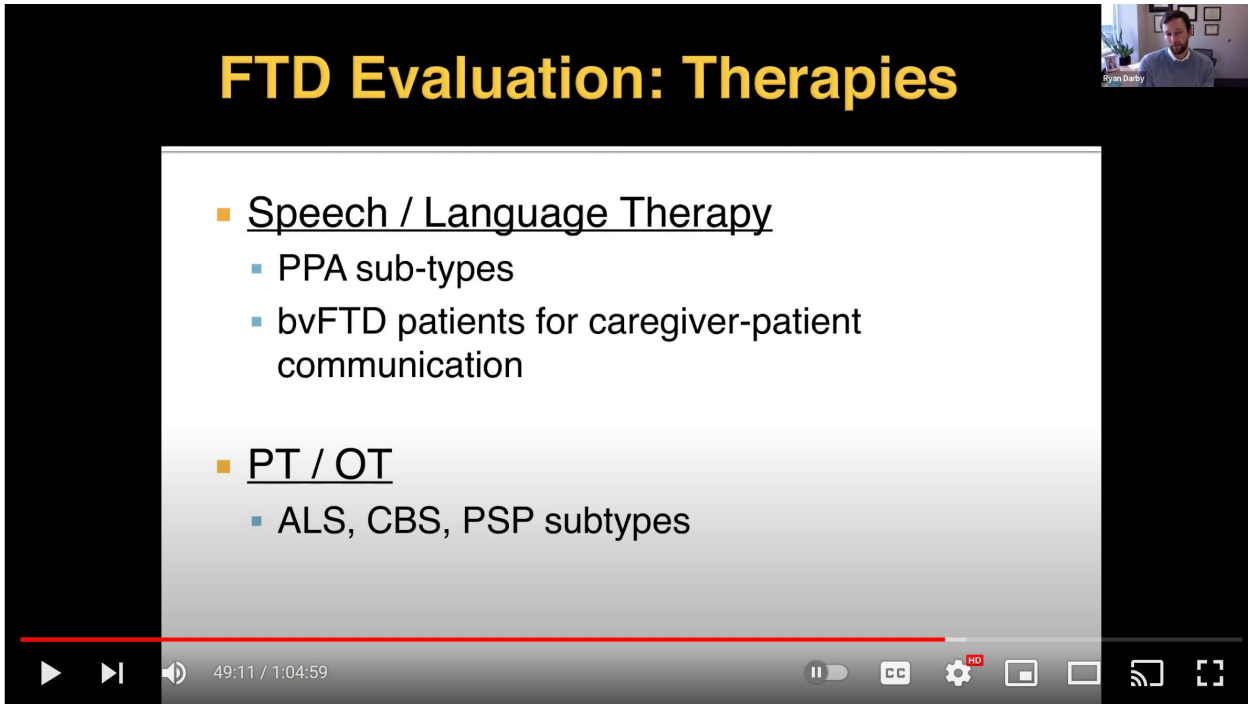

FTD Evaluation: Exam
Ryan Darby
NEUROLOGICAL
ALS
Weakness
hyper-reflexia
Fasciculations
PSP
Axial rigidity
Eye movement abnormalities
Postural instability
CBS
Asymmetric motor symptoms: bradykinesia, rigidity, dystonia, Myoclonus
Higher cortical symptoms: Sensory cortical dysfunction, apraxia, alien limb
44:42 / 1:04:59

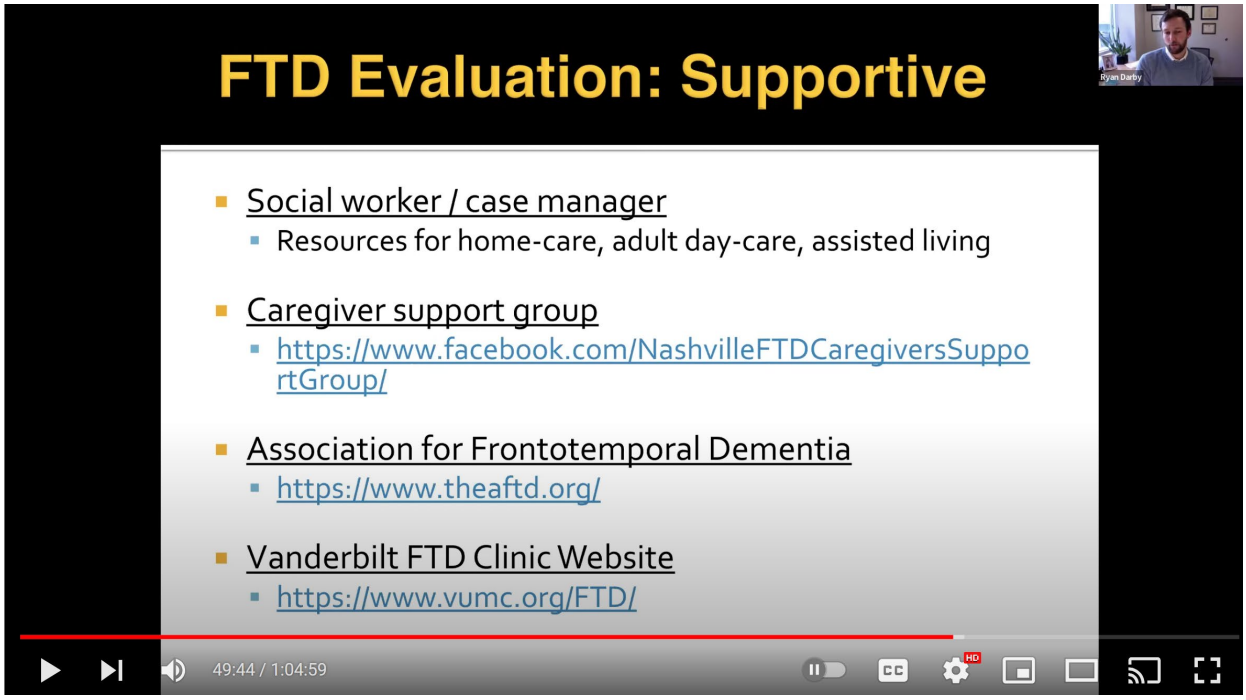

FTD Evaluation: Neuroimaging
Ryan Darby
MRI in Every Patient
Thin T1 slices / MPRAGE
FLAIR, SWI/GRE (other etiologies)
Possible quantitative MRI (Neuroquant) to look at frontal lobe volume percentiles
FDG-PET scan if MRI unclear
Reason: “differentiate FTD vs. AD”
Can ask radiology for quantitative analysis in unclear cases
45:16 / 1:04:59


FTD Evaluation: Labs
Ryan Darby
All Cognitive Patients: B12, TSH
Rapid Onset: Paraneoplasic panel, Anti-thyroid antibodies
Younger with Atypical Findings: heavy metals, leukodystrophy labs, urea cycle disorders
LP: Athena AD biomarkers to rule out Alzheimer's disease (beware of false positive in older subjects)
46:48 / 1:04:59


FTD Evaluation: Referrals
Ryan Darby
Neuropsychological testing
More detailed / sensitive assessments
Genetics: family history or patient preference
Counsel family members on risks, family planning
More definite diagnosis
Qualify for clinical trials
EMG/neuromuscular:
signs of ALS
Geriatric Psychiatry
Difficult to manage behavioral and neuropsychiatric symptoms
47:59 / 1:04:59


FTD Evaluation: Medications
Ryan Darby
No FDA approved treatments
Focus on Symptom Management:
Apathy: SSRI's, stimulants
Disinhibition: SSRI, stimulants, anti-psychotics, anti-convulsants
Compulsive behaviors: SSRI's (often high-dose)
Agitation, inappropriate social behavior: SSRI, anti-psychotics, lithium, valproic acid
49:02 / 1:04:59
J Neurochem. 2016 Aug;


FTD Evaluation: Therapies
Ryan Darby
Speech / Language Therapy
PPA sub-types
bvFTD patients for caregiver-patient communication
PT / OT
ALS, CBS, PSP subtypes
49:11 / 1:04:59


FTD Evaluation: Supportive
Ryan Darby
Social worker / case manager
Resources for home-care, adult day-care, assisted living
Caregiver support group
https://www.facebook.com/NashvilleFTDCaregiversSupportGroup/
Association for Frontotemporal Dementia
https://www.theaftd.org/
Vanderbilt FTD Clinic Website
https://www.vumc.org/FTD/
49:44 / 1:04:59
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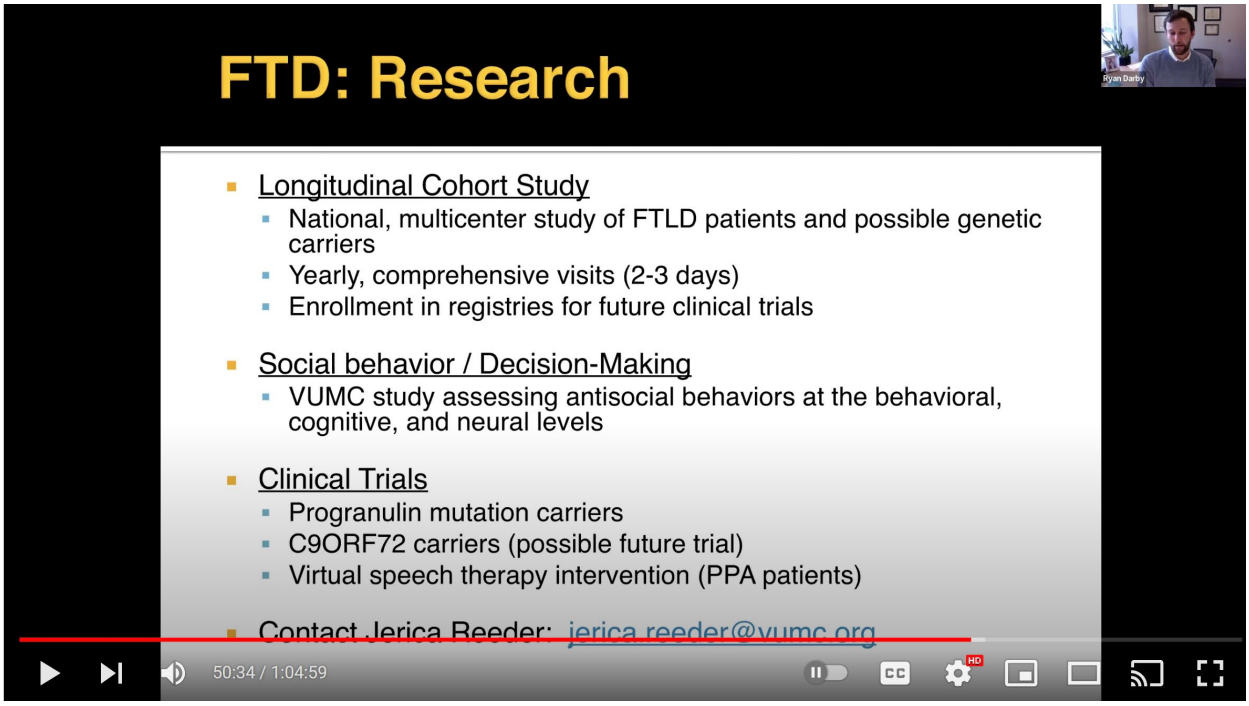
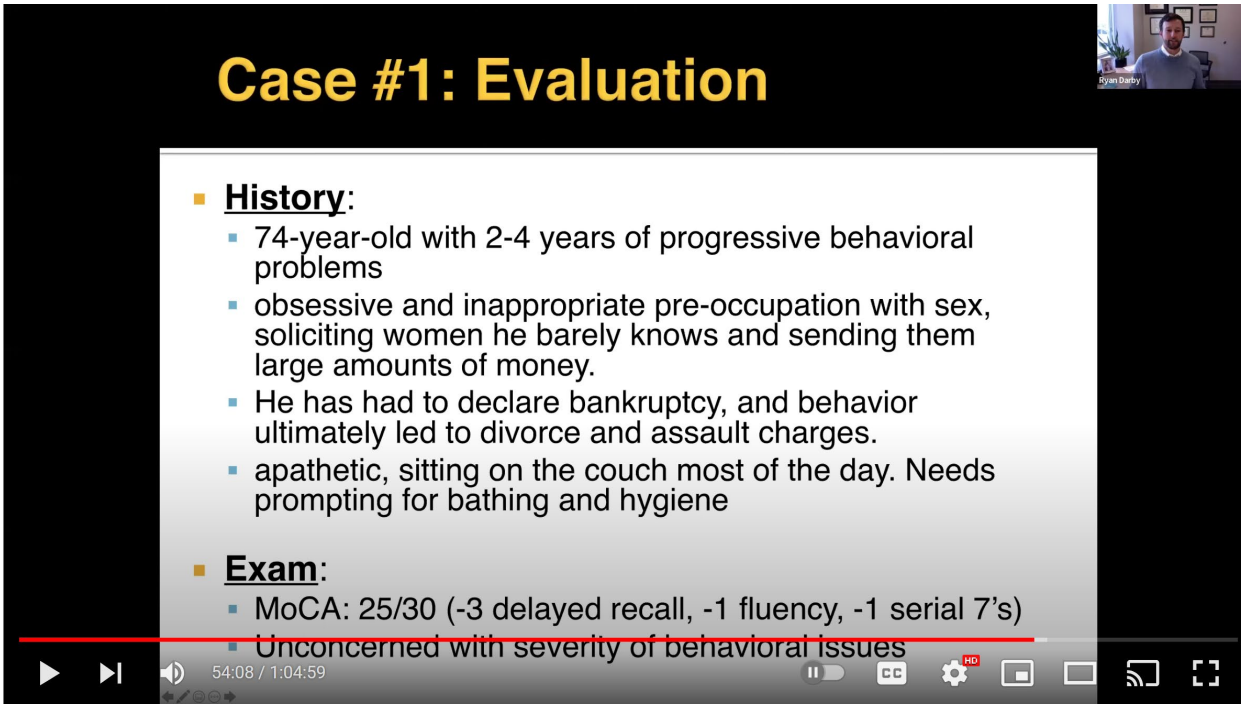
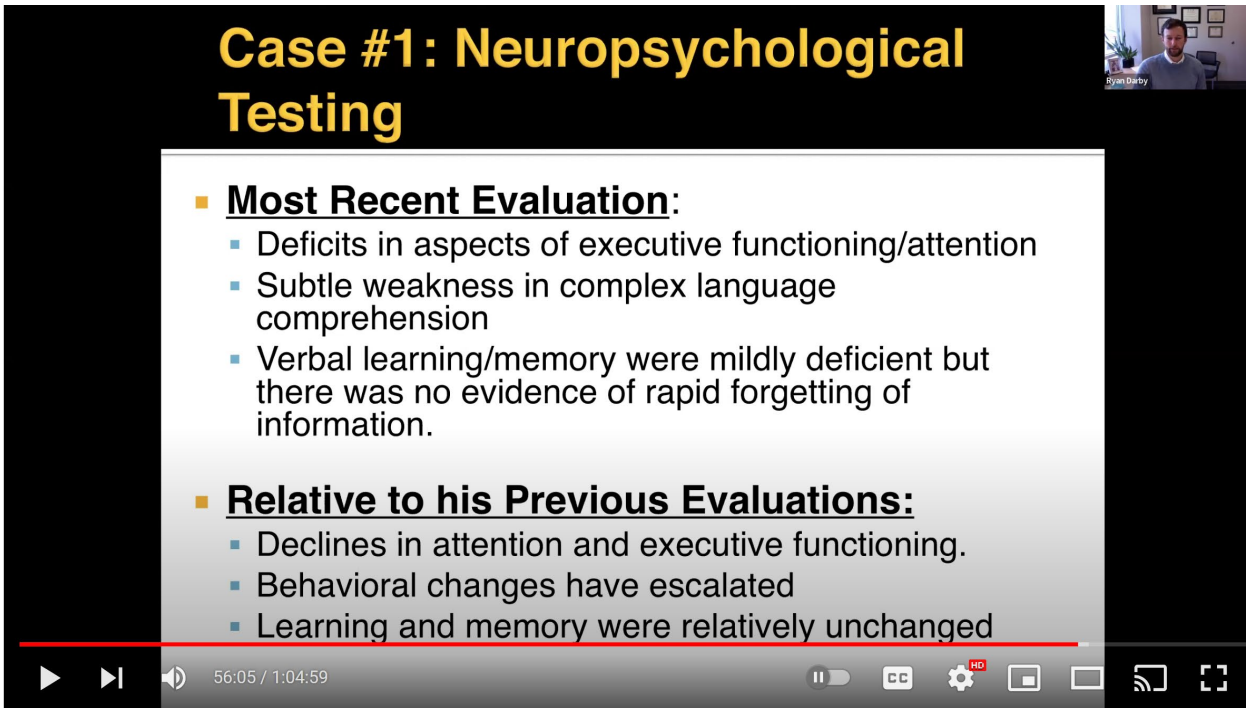
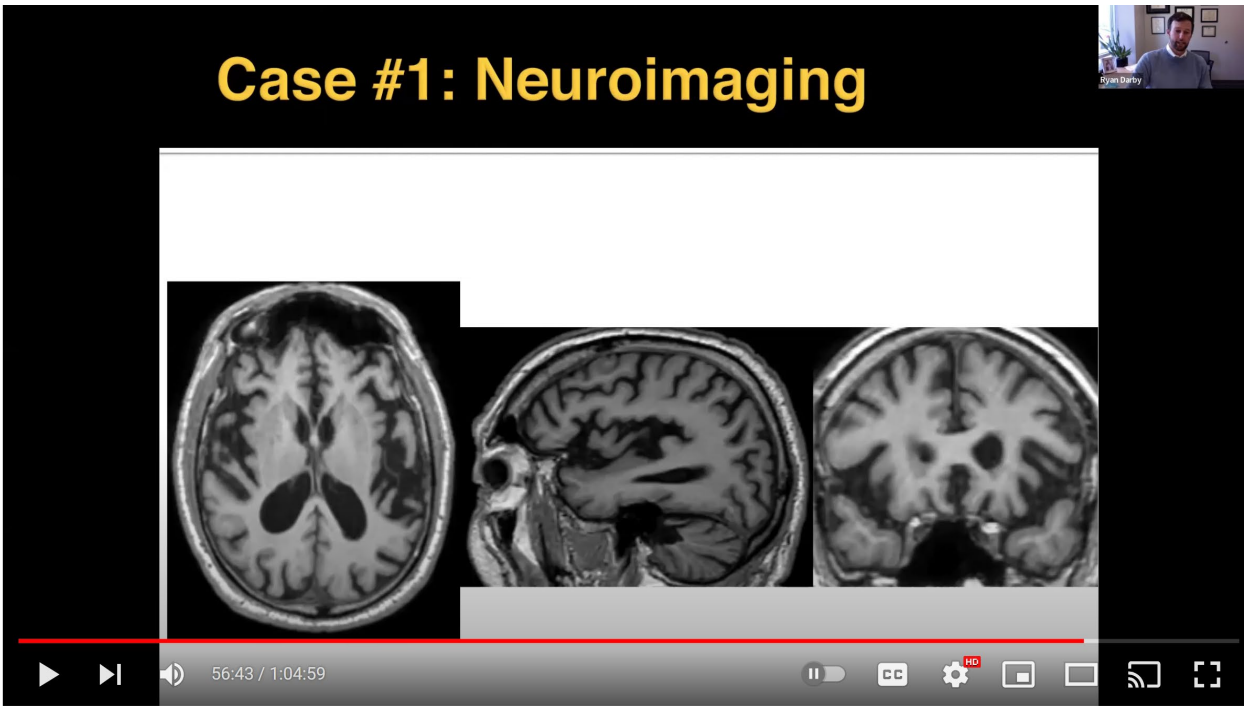
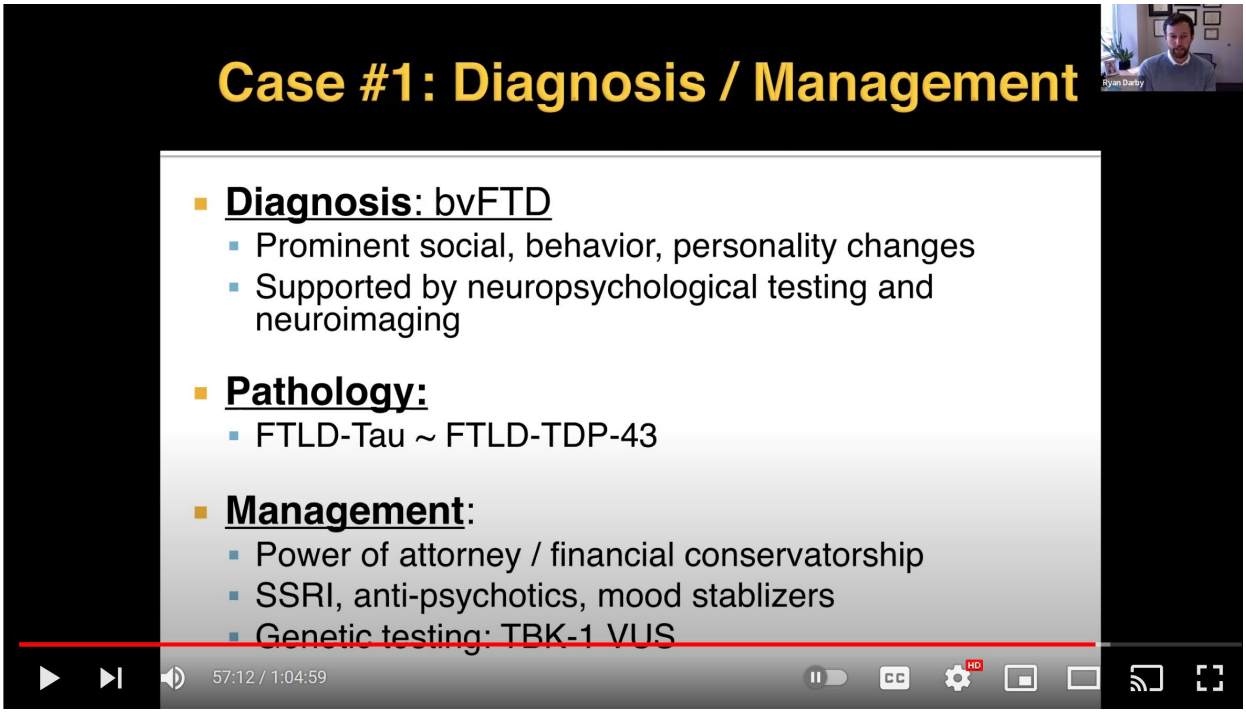
HD

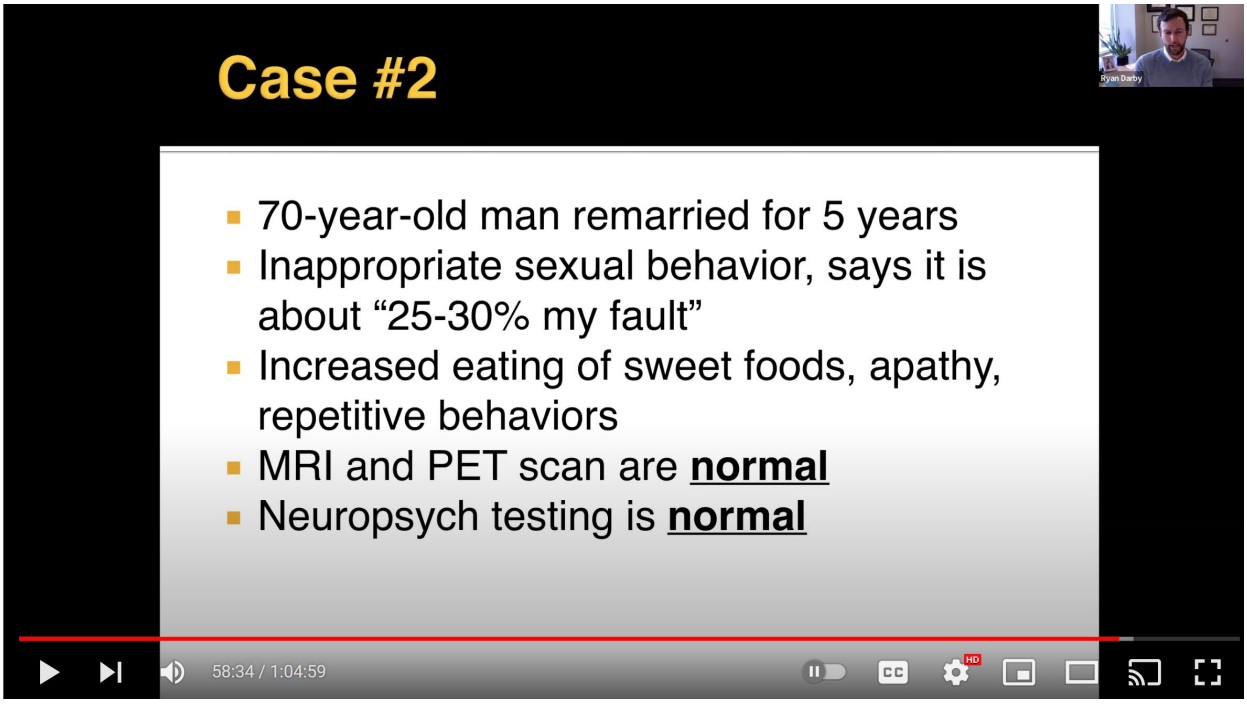

FTD: Research
Ryan Darby
Longitudinal Cohort Study
National, multicenter study of FTLD patients and possible genetic carriers
Yearly, comprehensive visits (2-3 days)
Enrollment in registries for future clinical trials
Social behavior / Decision-Making
VUMC study assessing antisocial behaviors at the behavioral, cognitive, and neural levels
Clinical Trials
Progranulin mutation carriers
C9ORF72 carriers (possible future trial)
Virtual speech therapy intervention (PPA patients)
Contact Jerica Reeder: jerica.reeder@vumc.org
50:34 / 1:04:59

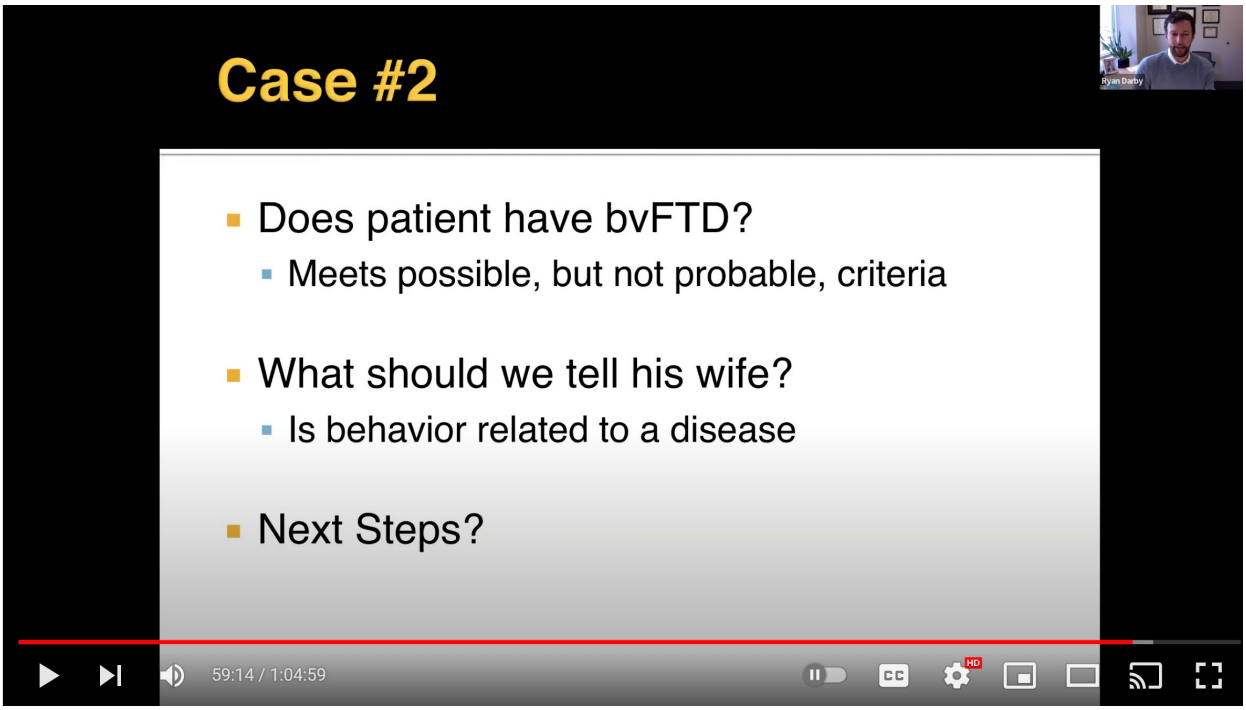

Case #1: Evaluation
Ryan Darby
History:
74-year-old with 2-4 years of progressive behavioral problems
obsessive and inappropriate pre-occupation with sex, soliciting women he barely knows and sending them large amounts of money.
He has had to declare bankruptcy, and behavior ultimately led to divorce and assault charges.
apathetic, sitting on the couch most of the day. Needs prompting for bathing and hygiene
Exam:
MoCA: 25/30 (-3 delayed recall, -1 fluency, -1 serial 7's)
Unconcerned with severity of behavioral issues
54:08 / 1:04:59

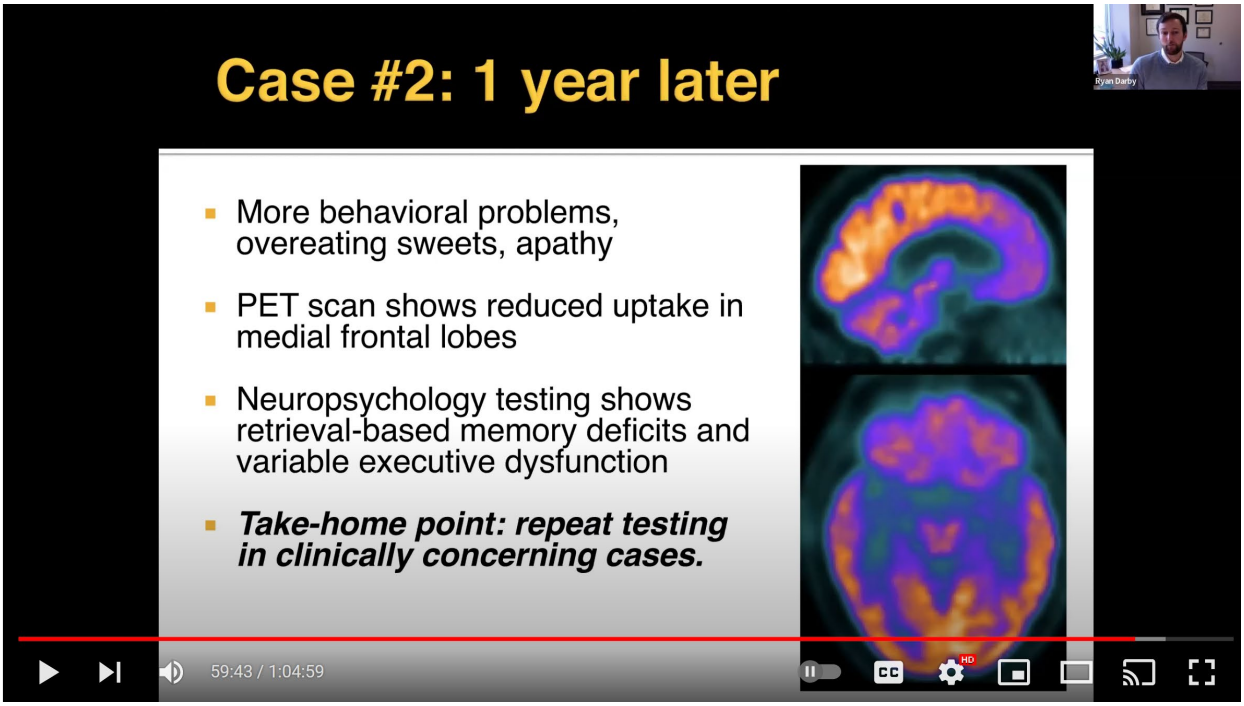

Case #1: Neuropsychological Testing
Ryan Darby
Most Recent Evaluation:
Deficits in aspects of executive functioning/attention
Subtle weakness in complex language comprehension
Verbal learning/memory were mildly deficient but there was no evidence of rapid forgetting of information.
Relative to his Previous Evaluations:
Declines in attention and executive functioning.
Behavioral changes have escalated
Learning and memory were relatively unchanged
56:05 / 1:04:59

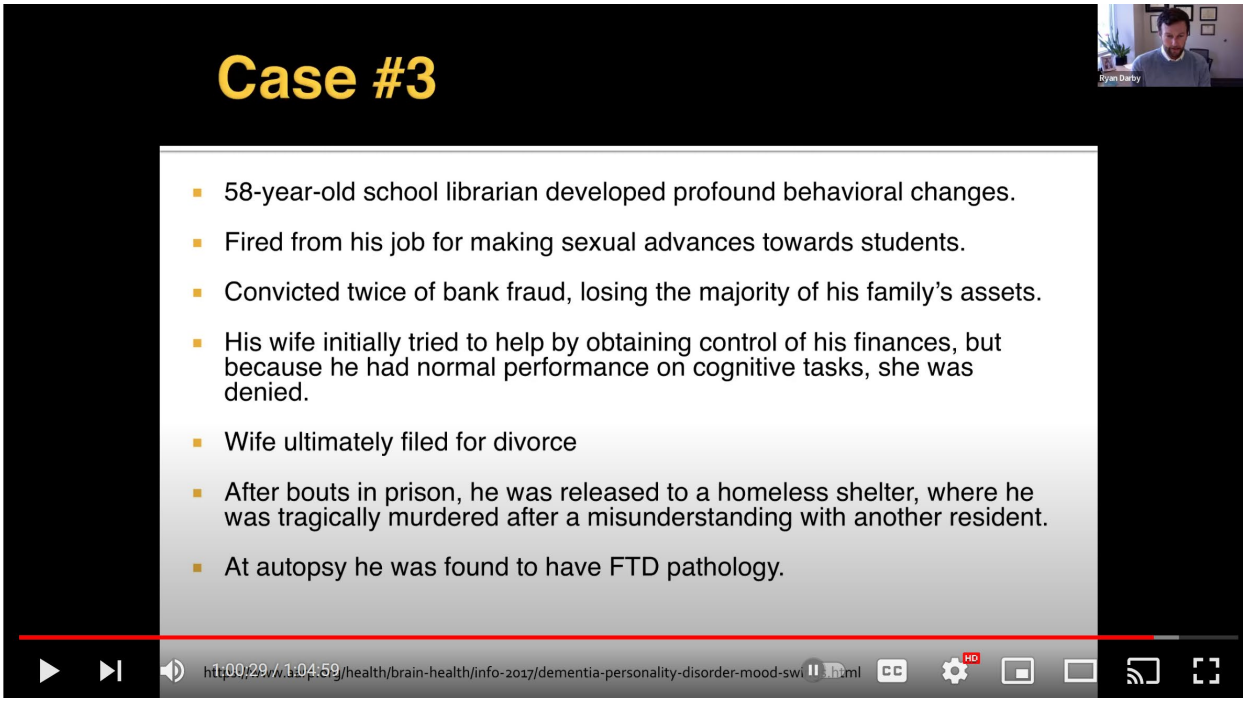

Case #1: Neuroimaging
Ryan Darby
56:43 / 1:04:59

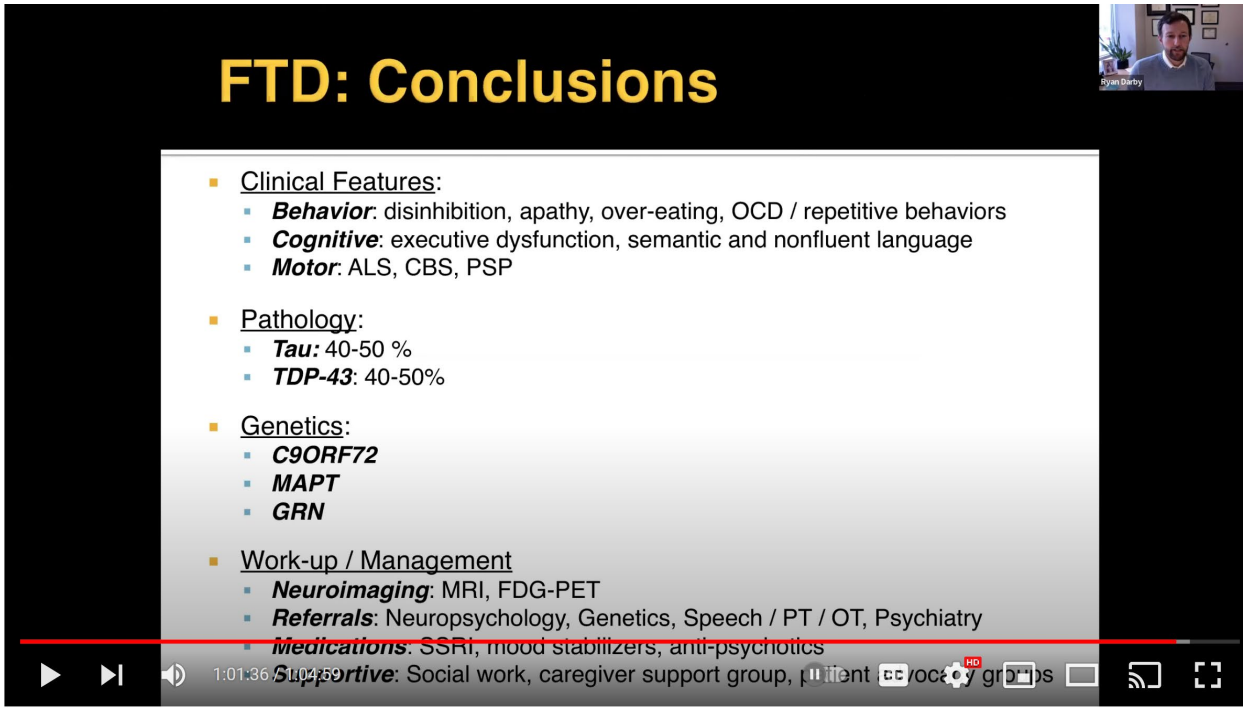

Case #1: Diagnosis / Management
Ryan Darby
Diagnosis: bvFTD
Prominent social, behavior, personality changes
Supported by neuropsychological testing and neuroimaging
Pathology:
FTLD-Tau ~ FTLD-TDP-43
Management:
Power of attorney / financial conservatorship
SSRI, anti-psychotics, mood stablizers
Genetic testing: TBK-1 VUS
57:12 / 1:04:59


Case #2
Ryan Darby
70-year-old man remarried for 5 years
Inappropriate sexual behavior, says it is about “25-30% my fault”
Increased eating of sweet foods, apathy, repetitive behaviors
MRI and PET scan are normal
Neuropsych testing is normal
58:34 / 1:04:59


Case #2
Ryan Darby
Does patient have bvFTD?
Meets possible, but not probable, criteria
What should we tell his wife?
Is behavior related to a disease
Next Steps?
59:14 / 1:04:59


Case #2: 1 year later
Ryan Darby
More behavioral problems, overeating sweets, apathy
PET scan shows reduced uptake in medial frontal lobes
Neuropsychology testing shows retrieval-based memory deficits and variable executive dysfunction
Take-home point: repeat testing in clinically concerning cases.
59:43 / 1:04:59


Case #3
Ryan Darby
58-year-old school librarian developed profound behavioral changes.
Fired from his job for making sexual advances towards students.
Convicted twice of bank fraud, losing the majority of his family's assets.
His wife initially tried to help by obtaining control of his finances, but because he had normal performance on cognitive tasks, she was denied.
Wife ultimately filed for divorce
After bouts in prison, he was released to a homeless shelter, where he was tragically murdered after a misunderstanding with another resident.
At autopsy he was found to have FTD pathology.
1:00:29 / 1:04:59


FTD: Conclusions
Ryan Darby
Clinical Features:
Behavior: disinhibition, apathy, over-eating, OCD / repetitive behaviors
Cognitive: executive dysfunction, semantic and nonfluent language
Motor: ALS, CBS, PSP
Pathology:
Tau: 40-50 %
TDP-43: 40-50%
Genetics:
C9ORF72
MAPT
GRN
Work-up / Management
Neuroimaging: MRI, FDG-PET
Referrals: Neuropsychology, Genetics, Speech / PT / OT, Psychiatry
Medications: SSRI, mood stabilizers, anti-psychotics
Supportive: Social work, caregiver support group, patient advocacy groups
1:01:36 / 1:04:59