2nd Annual Frontotemporal Degeneration
Caregiver Education Conference
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FTD:
Improving
Outcomes & Outreach

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Acknowledgements

- Alzheimer North Carolina, Inc.
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- Bruce Miller, MD / UCSF
- FTD patients and families

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Objectives

- Clinical overview of FTD vs. AD
- Clinical care: diagnosis and treatment
- UNC-CH Memory Disorders Program:

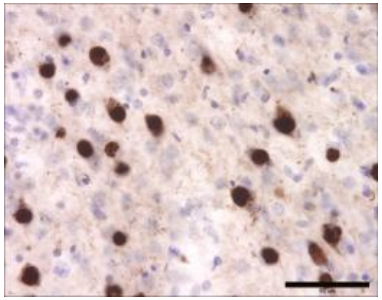
  Partners & Networks:

  - Clinical care
  - Research
  - Education / Outreach

Once upon a time, FTD was just Pick's disease

- 1892: Pick described case of lobar atrophy affecting frontal and/or anterior temporal lobe

- 1911: Alzheimer describes pathological association to silver-staining "Pick bodies"



A lot has changed in 120 yrs, mostly in the last few

AD vs FTD

	AD	FTD
First Reported	1906	1892
US Prevalence	5,000,000+	30,000
Onset (most):	65-85 yo	55-75 yo
Primary Clinical Change	Memory	Personality/ Language
Pathology:	Amyloid + Tangles (Tau)	Tau/TDP-43 other proteins

Compared to AD, FTD is:

- >100x less prevalent, much more variable:
  - clinically
  - pathologically
  - genetically

  Often associated with motor signs:

  - parkinsonism
  - motor neuron disease (ALS)

  that may occur early or late in the course

FTD Diagnostic Criteria

- 1970-80s: Pick's disease
  Frontal Lobe Dementia w/o Pick bodies
- 1994: Lund-Manchester FTD Criteria
  - Pick's disease
  - Frontal Lobe Degeneration (w/o Pick bodies)
  - Motor Neuron Disease type
- 1998: Neary Criteria for Frontotemporal Lobar Degeneration (FTLD):
  - Frontotemporal Dementia (bvFTD)
  - Primary Progressive Aphasias (language)

2011: A New Era Begins

- FTD Consortium Criteria–bv FTD(Rascovsky et al, 2011):
  - Multicenter study n=176 autopsy-proven bvFTD subjects
  - ***Possible*** : 3/6 of:
    - disinhibition / apathy / loss of empathy/ repetitive behaviors / hyperorality/ dysexecutive syndrome
  - ***Probable***: above + functional disability and characteristic MRI/PET brain imaging

FTD Diagnostic Criteria are Multi-dimensional

- Emotional/Personality Changes
  - Apathy / Inertia*
  - Disinhibition (e.g. impulsive, socially inappropriate)*
  - Loss of sympathy or empathy
- Motor/Vegetative Changes
  - Repetitive, compulsive, ritualistic behaviors*
  - Dietary changes (sweets), binge-eating*
- Cognitive
  - Executive cognitive deficits

*Assessed on the NPI-Q

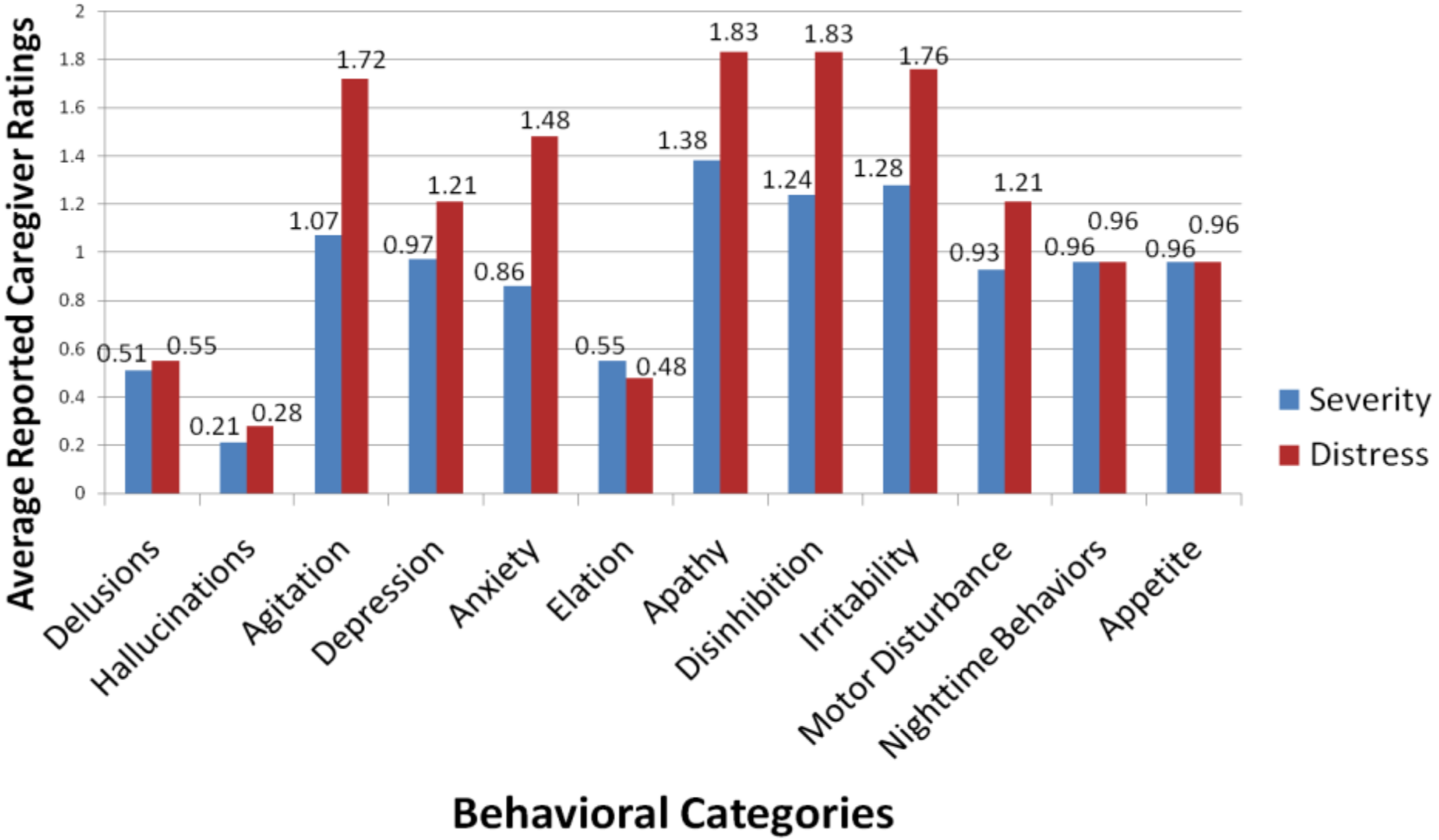
Clinical Assessment of Behavioral Symptoms

- Neuropsychiatric Inventory (NPI) Cummings et al, 1994): caregiver interview of 12-behavioral symptoms in dementia
- NPI Distress Scale (Kaufer et al, 1998): measure of caregiver distress for each behavioral symptom present
- NPI-Questionnaire (NPI-Q): (Kaufer et al, 2000): short-form of NPI designed for clinical practice

NPI-Q Symptoms in FTD

UNC Memory Disorders Clinic

Apathy / Disinhibition / Irritability most prominent and most distressing



Possible Mimics of FTD

- Early Alzheimer's disease
- Subcortical cerebrovascular disease
- Chronic excessive alcohol use
- Traumatic brain injury(s)
- Normal-pressure hydrocephalus
- Cerebellar degeneration
- Obstructive sleep apnea? (untreated)

FTD – Treatment

- No proven therapies, empiric symptomatic Rx
- Cholinesterase-inhibitors? (? AD or FTD)
- Trazadone for agitation (Lebert et al, 2004)
- SSRIs (e.g. sertraline) for obsessive-compulsive behaviors (sweet craving, ritualistic behavior)
- Open-label trial of memantine suggests possible therapeutic benefit on behavior

A 26-week, multicenter, randomized, double blind, placebo controlled trial of memantine for behavioral variant frontotemporal dementia (bvFTD) and semantic variant primary progressive aphasia (SD)

Adam Boxer, David Knopman, Dan Kaufer, Murray Grossman, Chiadi Onyike, Neill Graf-Radford, Mario Mendez, Jill Shapira, Diana Kerwin, Alan Lerner, Chuang-Kuo Wu, Mary Koestler, Kathryn Sullivan, Robert Nicholson, Jerin Ullah, Scott Fields, John Neuhaus, M. Marsel Mesulam and Bruce Miller

Primary Outcomes: behavioral symptoms (NPI)
global assessment of change

Data presented July 2012 at AAIC, Vancouver, Canada

Social Cognition

- "Emotional intelligence"
  - Empathy / Sympathy vs Sociopathy
  - Self / social awareness
- Perceiving other's emotional state: SD and bvFTD subjects have difficulty recognizing sarcasm (Rankin, 2009)
- Social affiliation / bonding: oxytocin as a possible treatment for bvFTD

Measuring Relevant Clinical Outcomes (Caregiver Assessment of Clinical Change)

Informant:_____ **Caregiver Assessment of Clinical Change** **Relationship to Patient:**_____

Patient Name:_____ **Date:**_____

Instructions: Place a check in the appropriate column for items 1-20 to indicate ***changes*** observed in the patient **since your last visit**. If unsure how to answer, circle the number. If the problem is new, please indicate with a check in the appropriate box.

- Marked Change- Very marked or prominent, a dramatic change
- Moderate Change- Significant, but not a dramatic changeC
- Minimal Change- Noticeable, but not a significant change

Patient's Rating	Decline				Improvement		
Function	Marked	Moderate	Minimal	No Change	Minimal	Moderate	Marked
1. Bathing, toileting							
2. Grooming, dressing							
3. Eating habits, manners							
4. Sleep pattern							
5. Doing household tasks							
6. Motivation to do things							
7. General mood (happy, sad)							
8. Suspiciousness or false beliefs							
9. Anxiety level							
10. Restlessness, agitation							
11. Participating in conversation							
12. Involvement with family or friends							
13. Cooperation							
14. Awareness of others feelings							
15. Interest in hobbies/leisure activity							
16. Remembering names and events							
17. Ability to find appropriate words							
18. Keeping track of time							
19. Awareness of environment							
20. Ability to follow instructions							

Functional Abilities (1-5)

Behavioral Symptoms (6-10)

Social Behavior (11-15)

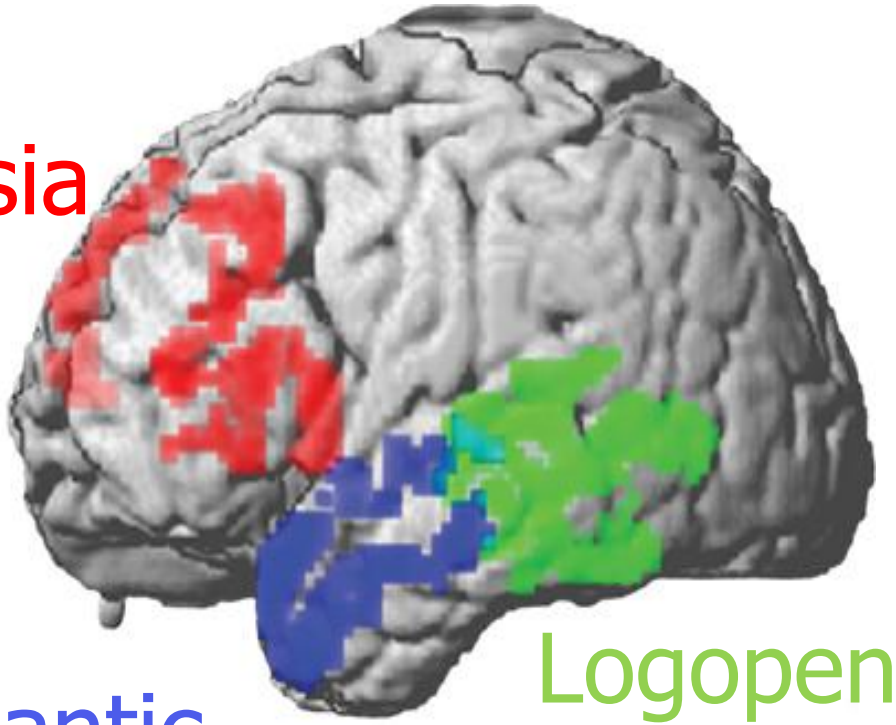
Cognitive Functions (16-20)

FTLD – Clinical Syndromes

- Frontotemporal dementia (bv FTD) – prominent behavior and personality changes *(right temporal-insular region)*
- Progressive nonfluent aphasia (PNFA) – early speech and language dysfunction *(left prefrontal cortical region)*
- Semantic dementia (SD) – loss of word and object meaning *(L>R anterior temporal region)*

Classification of Progressive Aphasia

Progressive Nonfluent Aphasia (PNFA)



Semantic Dementia (SD)

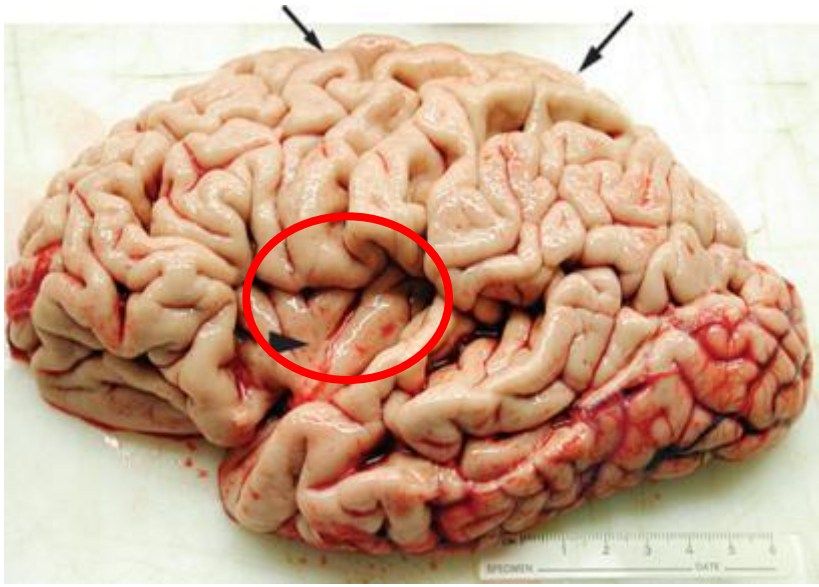
Logopenic Phonological Aphasia (LPA)

(Gorno-Tempini, 2010)

Progressive Nonfluent Aphasia

Mesulam, 1982

- Hesitant, effortful speech
- Speech 'apraxia'
- Stuttering
- Phonemic paraphasia
- Agrammatism
- Dec. letter> category fluency



Grossman, Nat Neurosci, 2010

Pathology: Tau 50%. “AD” 25%, TDP-43 20%

Semantic Dementia
(Snowden 1989, Hodges, 1992)

- Poor confrontation naming
- Impaired word comprehension
- Poor object / person knowledge
- Poor naming
- Surface dyslexia
- Dec. category > letter fluency

Pathology: TDP-43 70%, “AD” 25% , Tau 10%

Logopenic Phonoloigcal Aphasia

(M. Gorno-Tempini, 2004)

- Impaired single word retrieval
- Impaired repetition
- Slow speech with sound errors
- Grammatical, intact motor speech
- Spared single word comprehension
- Dec. category = letter fluency

Pathology: "AD" 50%. TDP-43 40%, Tau 10%

Treatment of PPA

-Bromocriptine 15-week double-blind study – no effect (Reed et al Ann Neurol, 2004)

-Galantamine double-blind study in PPA and FTD showed trend effect favoring treatment (Kertesz et al, 2008)

-Memantine open-label 26 week study (N=43) showed benefit in bvFTD and SD, but not PNFA (Boxer et al, Alz Dis Assoc Disord 2009)

-Memantine double-blind crossover study (18->9) showed a trend for less decline on language tests (Johnson et al, Alz Dis Assoc Disord, 2010)

Degenerative Dementia as a Dynamic Process

Abnormal proteins accumulate over time:

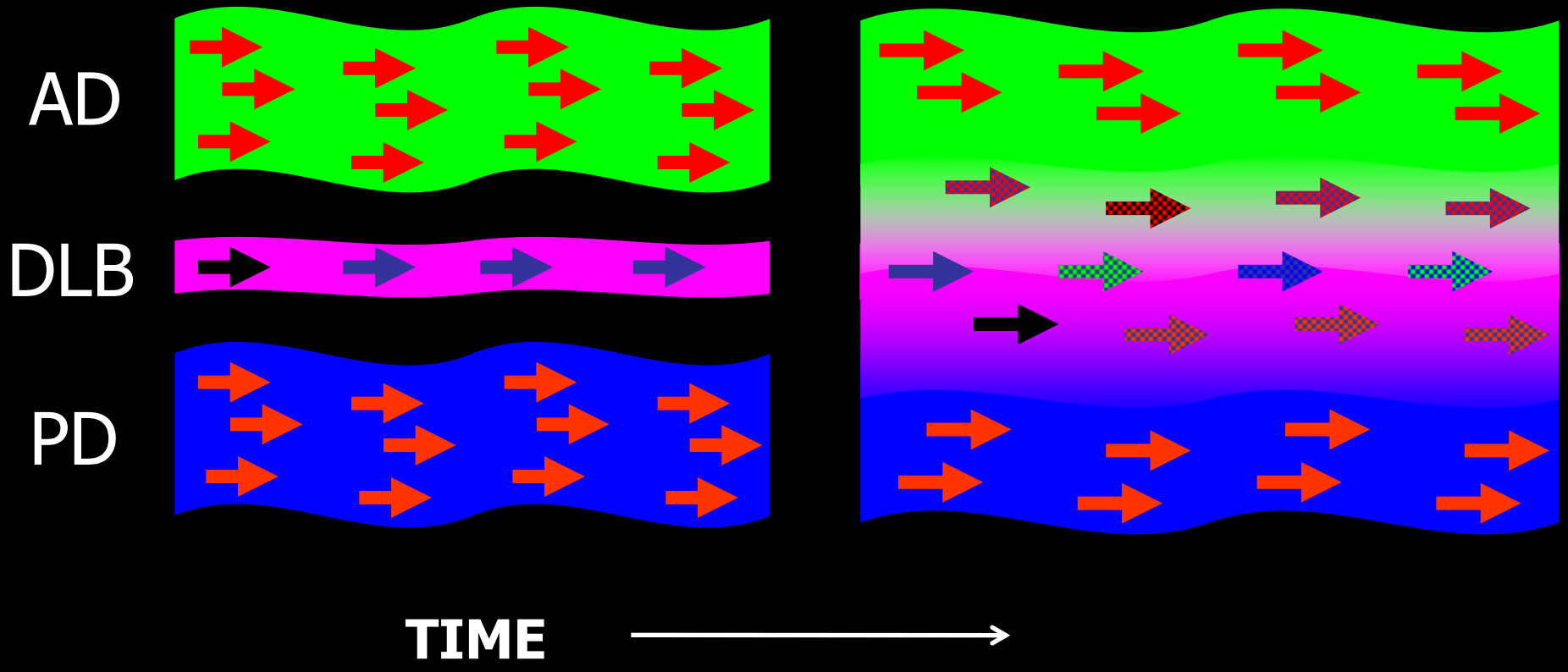
example: Alzheimer (AD), Parkinson (PD), and Lewy Body Dementia (DLB / PDD)

AD: amyloid + tau
PD: alpha-synuclein (Lewy body)
DLB/PDD:alpha-synuclein +/- amyloid

Clinical syndromes evolve over time (cognitive / motor / behavioral)

"Three Rivers" Model of AD-PD

Alzheimer's and Parkinson's also form
a clinical-pathological spectrum



Relative cognitive / motor signs vary over time

FTLD – Pathology

- Two major pathological subtypes:

  - FTLD-tau: tau protein inclusions (40%)
  - FTLD-TDP-43: (ubiquitin inclusions) (55%)
  - FTLD-FUS (5%)
  - Other rare forms (VCP, CHMP2B)

FTLD – Tau

- Tau-positive inclusions (40% of FTLD)
- Includes:
  - Pick's disease (Pick bodies)
  - Microtubule-associated protein mutations (MAPT)
  - Progressive supranuclear palsy
  - Corticobasal degeneration
  - Argyrophilic grain disease

Progressive Supranuclear Palsy

(Steele-Olzewski-Richardson, 1964)

Key clinical features:

- Speech / swallowing difficulties
- Early postural instability / falls
- Vertical supranuclear gaze paresis

- Axial rigidity
- Subcortical dementia in most (later)
- Apathy, depression, anxiety
- Pseudobulbar affect

PSP: Pathology & Treatment

- Tau-positive neurofibrillary tangles
- Cholinergic drugs (e.g. donepezil) may help cognition, but worsen motor dysfunction
- Dopaminergic agents ± benefit
- SSRIs for mood & pseudobulbar signs
- Supportive care (PT & swallowing)

PSP Experimental Treatments

- Lithium, Valproic acid, NP031112 (GSK-3 inhibitors)
- Pyruvate / creatine / niacinamide
- Coenzyme Q
- AL-108 (davunetide)- neuroactive peptide microtubule stabilizer (Phase 2/3 trial)

Corticobasal Degeneration

- 1968: Reibez et al: “corticodentatonigral degeneration with neuronal achromasia”
- Limb dyspraxia, gait disturbance, myoclonus, “alien hand” (asymmetric)
- Corticobasal “syndrome”:
  - may begin with cognitive or motor signs, later develop the other
  - variable pathological substrates

Pick Spectrum (Tauopathy)

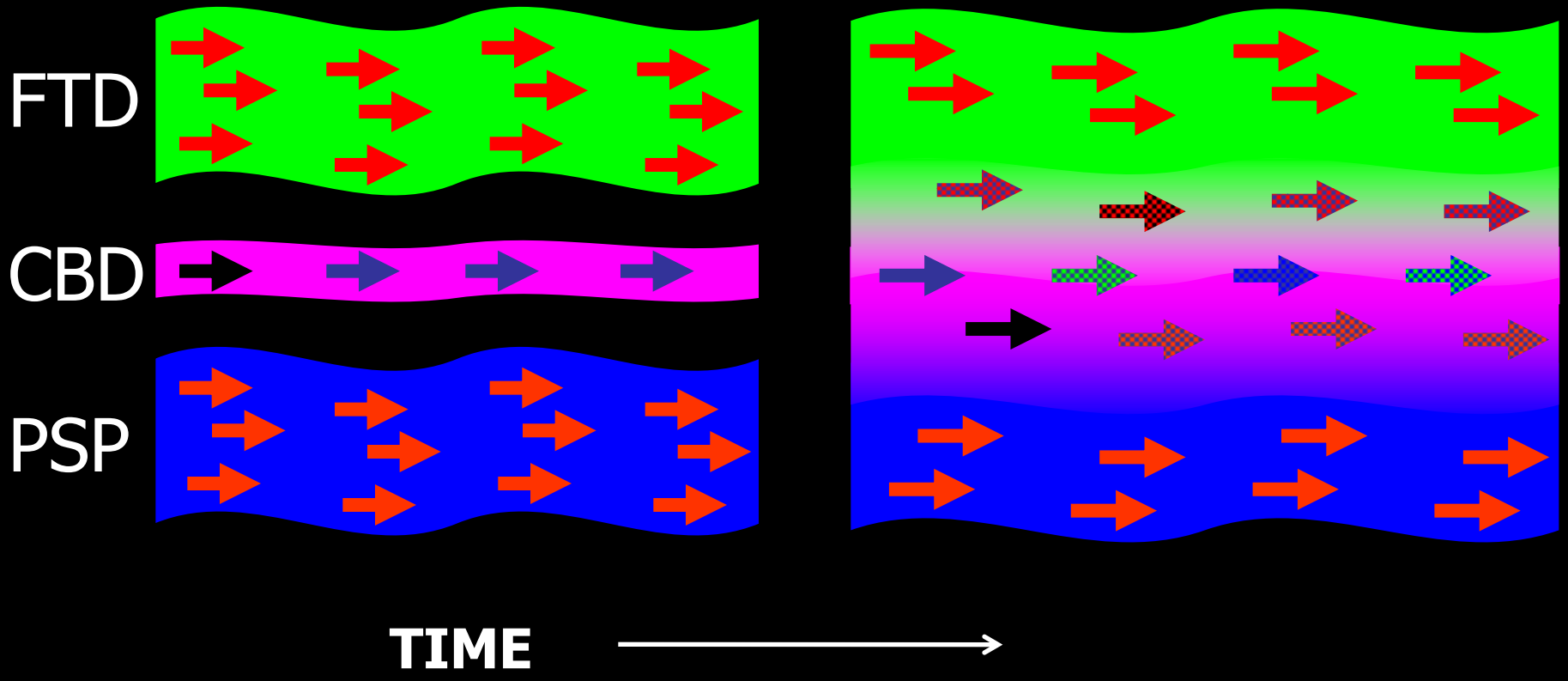
- FTLD-tau, CBD, and PSP form a spectrum of tauopathies:

- CBD may begin with PSP motor features and develop focal cortical atrophy, or vice versa

- 1/3 of bvFTD patients develop CBD

- 1/3 of PPA patients develop bvFTD or CBD

"Three Rivers" Model of FTLD-Tau

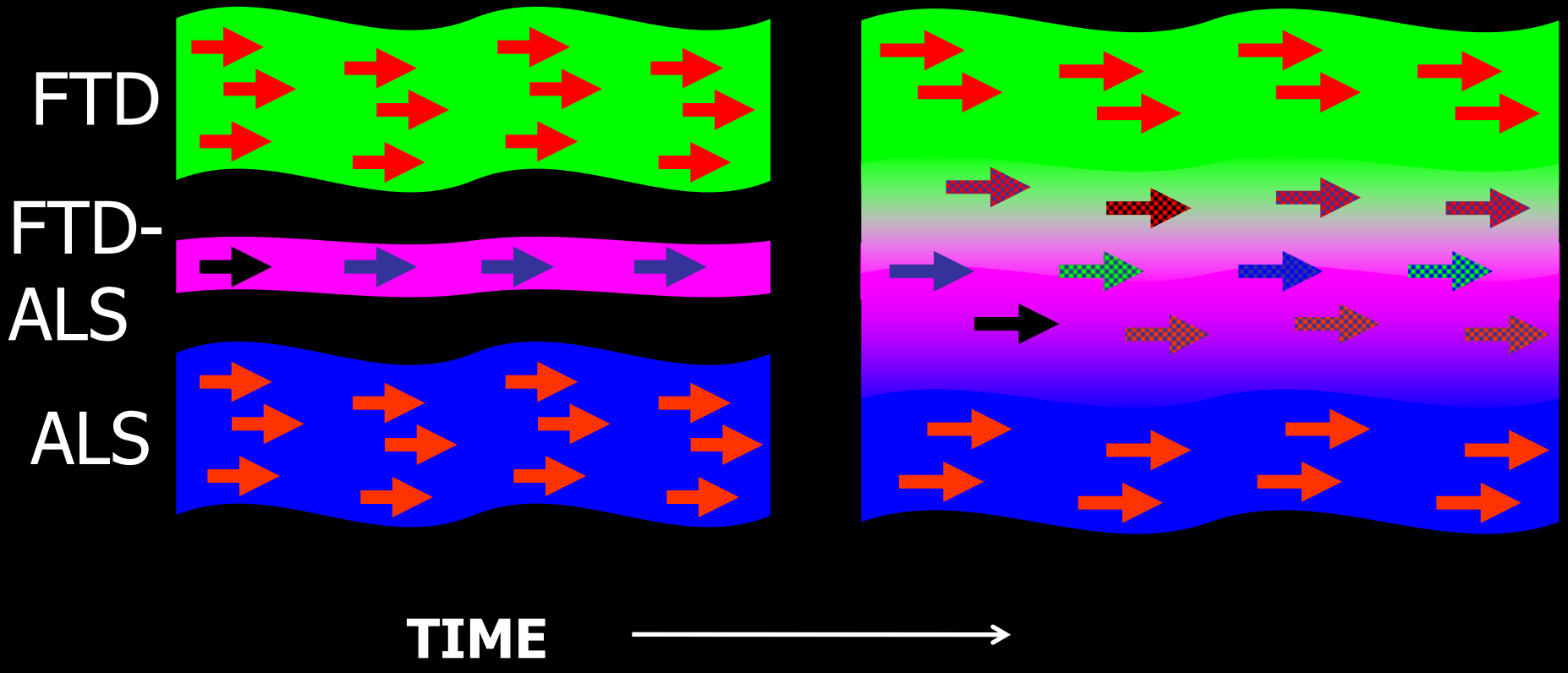


Relative cognitive / motor signs vary over time

FTLD – TDP-43

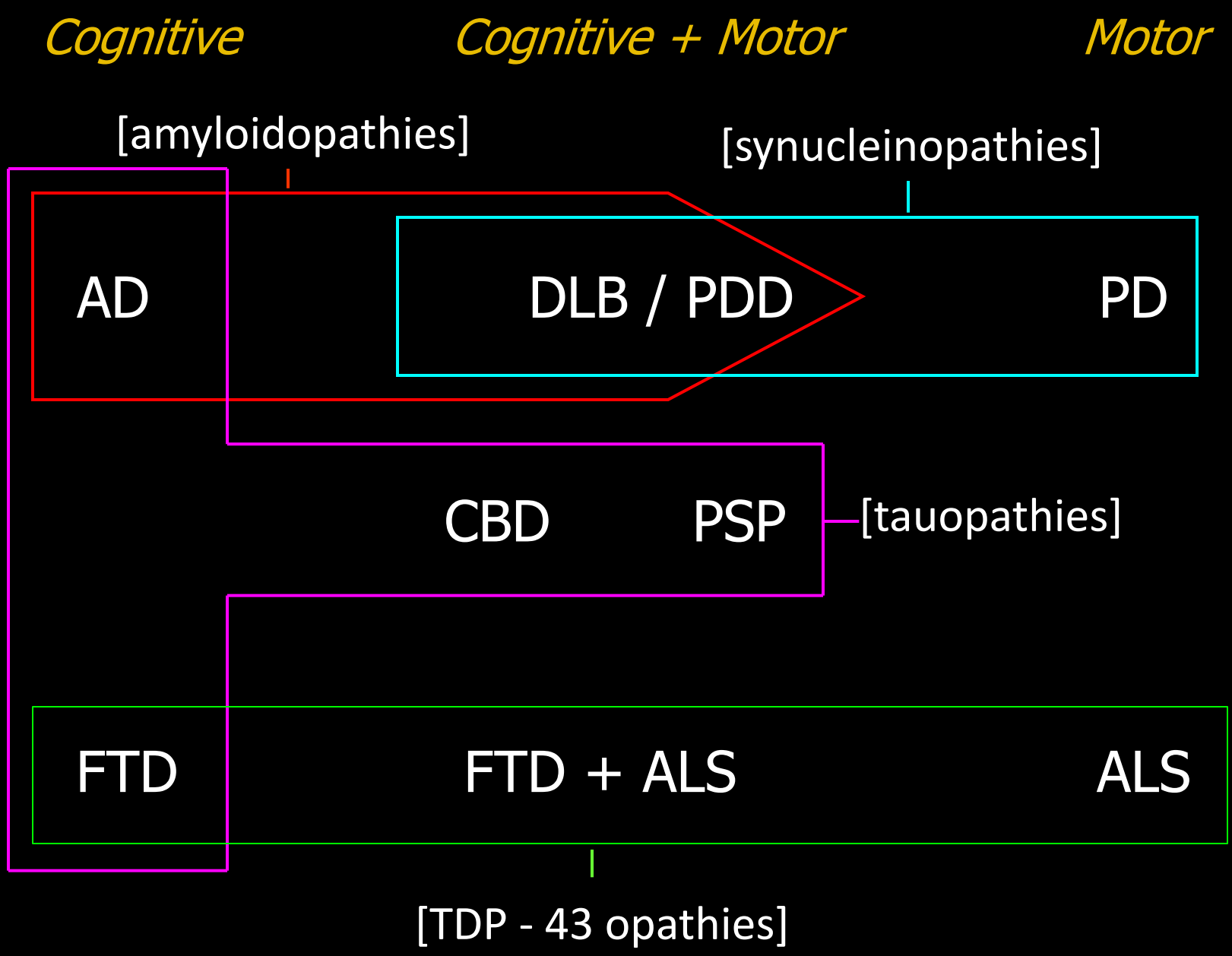
- TDP-43 (DNA-binding protein) is primary constituent of ubiquitin inclusions (formerly FTLD-U); growth factor
- 55% of FTLD
- Associated with progranulin gene mutations (chrom. 17)
  - Semantic dementia
  - FTD-motor neuron disease

"Three Rivers" Model of FTLD-U (TDP-43)



Relative cognitive / motor signs vary over time

Adapted from Kaufer & DeKosky, Dementia Classification: Relationship to the Neurobiology of Disease, *Neurobiology of Mental Illness, 2nd ed.*, 2009



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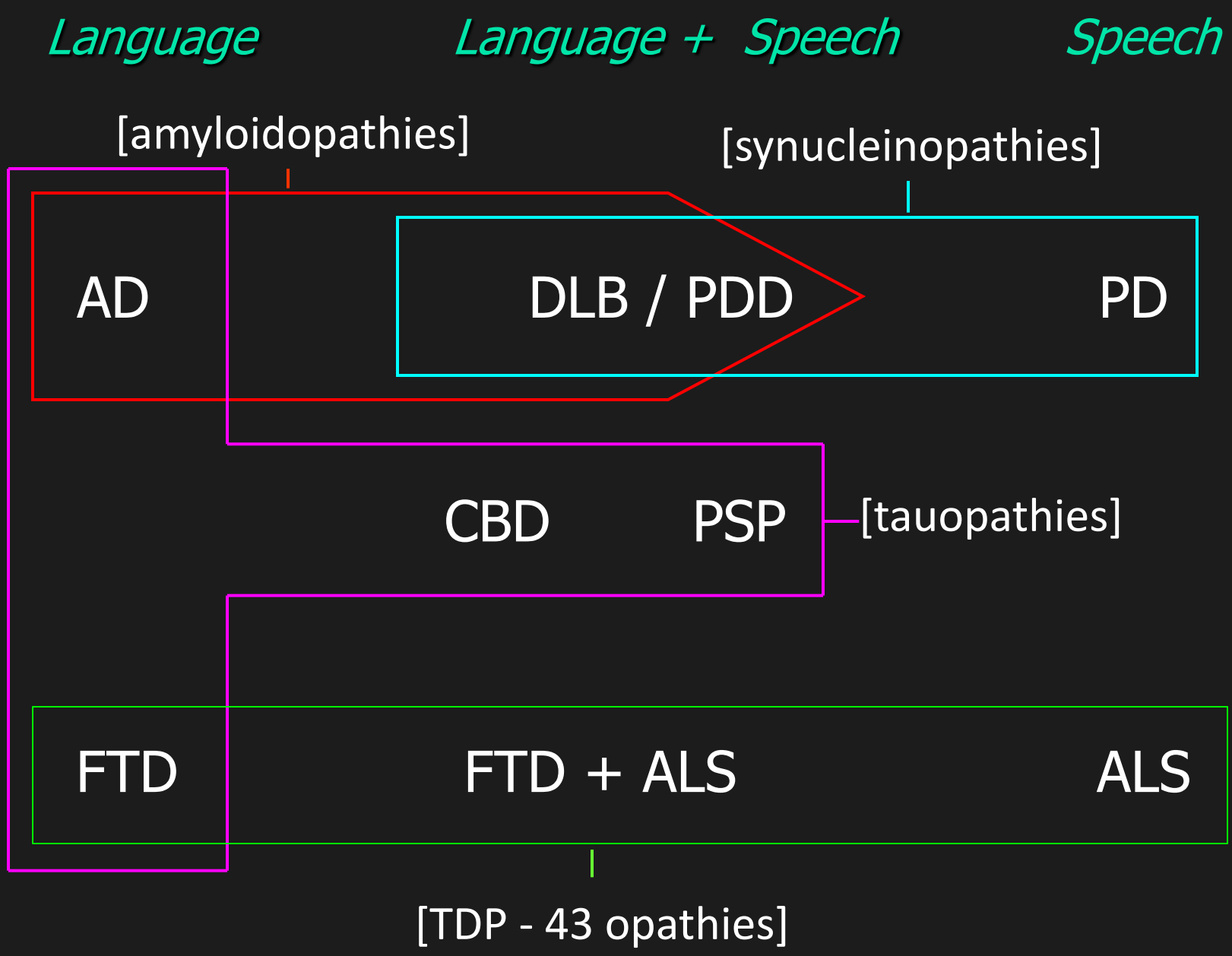

Chronic Traumatic Encephalopathy

- Associated with multiple concussions (notably in retired pro football players)
- Clinical signs: memory loss, behavioral changes, gait and speech problems, Parkinsonism
- Pathology: tau-positive tangles
- Variant of FTLD-tau?
- Research in CTE will help understanding of FTD disorders and vice versa

Improving Clinical Outcomes

- NPI-Q2 Validation Study (Guardian Angel Thrift Fund)
- NPI-Q intended for clinical practice, but used mainly by the 32 Alzheimer research centers
- Problem: measures are generic i.e. “apathy”, sleep” etc., based on NPI scoring
- NPI interview included 8 items for each domain, but tems were not scored
- NPI-Q2 adds 4 specific items for domain:
  - More like NPI
  - Easier to complete
  - More useful data (sleep to much or too little)

Dementia Performance Measurement Set

October 2011

Physician Consortium for Performance Improvement® (PCPI™)

Measure #1: Staging of Dementia

Measure #2: Cognitive Assessment

Measure #3: Functional Status Assessment

Measure #4: Neuropsychiatric Symptom Assessment

Measure #5: Management of Neuropsychiatric Symptoms

Measure #6: Screening for Depressive Symptoms

Measure #7: Counseling Regarding Safety Concerns

Measure #8: Counseling regarding Risks of Driving

Measure #9: Palliative Care Counseling and Advance Care Planning

Measure #10: Caregiver Education and Support

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FTLD Module (NACC)

- National Alzheimer centers have focused primarily on AD assessments
- Relative to FTD, like measuring the circumference of a ball with a ruler
- May 2012: expanded research assessment for FTD:
  - Executive cognition tests
  - Social cognitive assessments
  - Language assessments to characterize PPA

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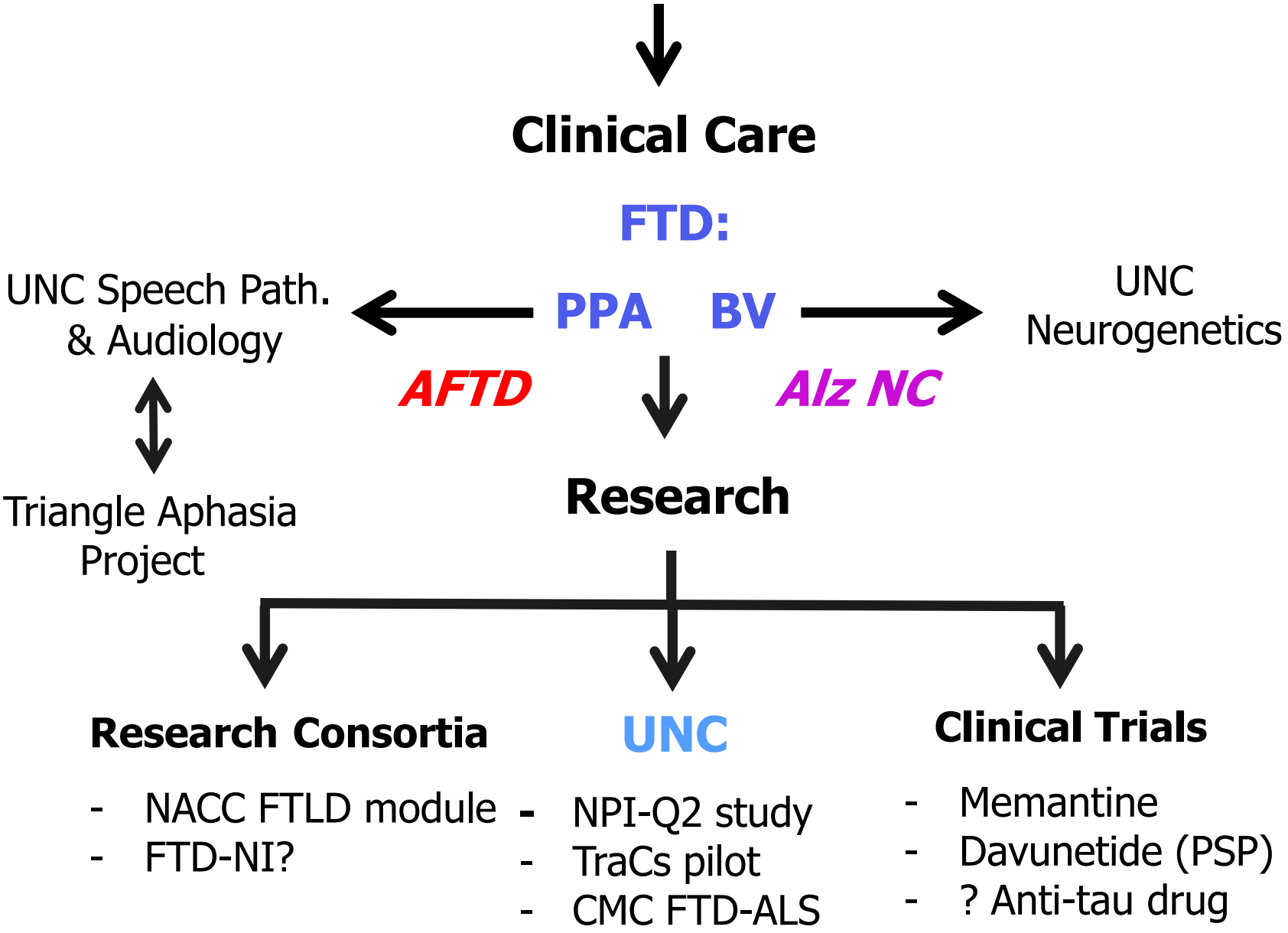

FTD /PPA Caregivers

- Behavioral, language, motor disabilities make FTD/PPA among most challenging dementia
- FTD Caregiver Survey (Chow et al, 2011):

First signs:

judgment & thinking (26%)

memory (23%)

behavior (20%)

language (12%)

Caregiving Challenges:

not realizing it's a brain problem (52%)

difficulty getting diagnosed (43%)

not knowing how to help pt. (25%)

feeling inadequate as a caregiver (24%)

FTD Outreach

- National: AFTD, PPA connection
- Regional: Alzheimer's North Carolina, Triangle Aphasia Project

- Goals:
  - establish a statewide/regional registry for FTD / PPA patients (research)
  - expand educational outreach activities and caregiver support resources throughout the state/region

Final Thoughts

- FTD is clinically & pathologically complex
- Defining robust clinical outcome measures for treatment studies is challenging
  - How do you measure “personhood?”
- Need more sensitive clinical assessments and biomarkers for early detection
- Need large-scale collaborative research and care support networks: