BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA

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U of T NEUROLOGY

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OBJECTIVES

- Behavioural variant FRONTOTEMPORAL DEMENTIA
  - New criteria: brain-behavior
  - Pathology
  - Genetics
  - Symptoms
  - Management

DEMENTIA CRITERIA

Cognitive and behavioral symptoms that:

- Interfere with work or usual social activities +
- Represent a decline from prior levels of functioning +
- NOT explained by delirium nor major psychiatric disorder +
- Cognitive impairment is detected & diagnosed – on history & objective cognitive assessment. Involves at least two
  - Impaired ability to acquire and remember new information
  - Impaired reasoning and handling of complex tasks, poor judgment
  - Impaired visual spatial and abilities
  - Impaired language functions
  - Changes in personality/usual character impaired motivation, initiative

NOT A DIAGNOSIS

DEMENTIA

ALZHEIMER'S DISEASE

PARKINSON'S DISEASE DEMENTIA

FRONTOTEMPORAL DEMENTIA/FRONTOTEMPORAL LOBAR DEGENERATION

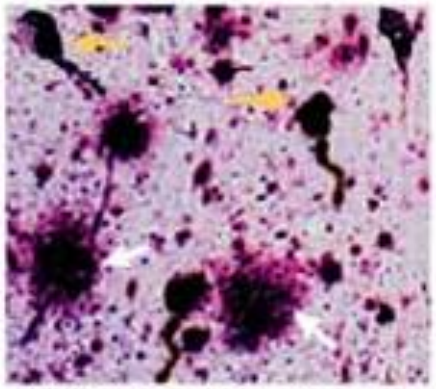
PRIMARY PROGRESSIVE APHASIA

HUNTINGTON'S DISEASE

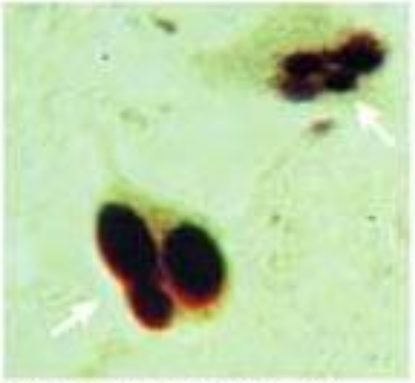
LEWY BODY DISEASE

VASCULAR DISEASE

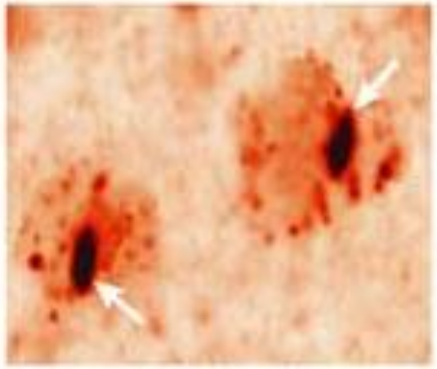
CREUTZFELD JACOB DISEASE



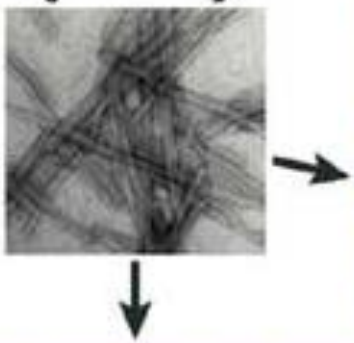
Alzheimer's plaques and tangles

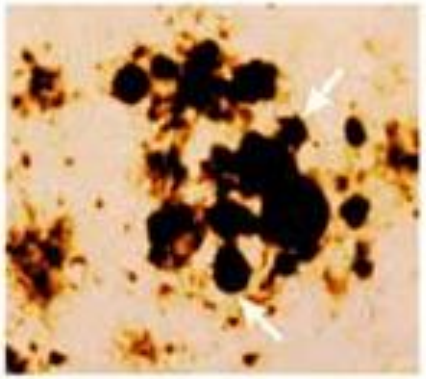


Parkinson's Lewy bodies

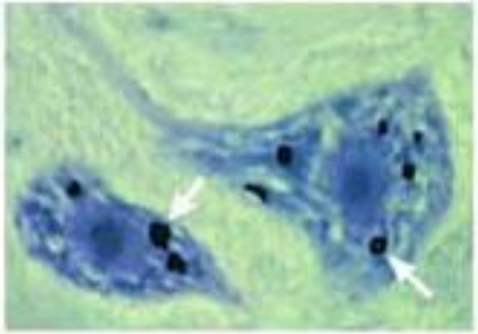


Huntington's intranuclear inclusions



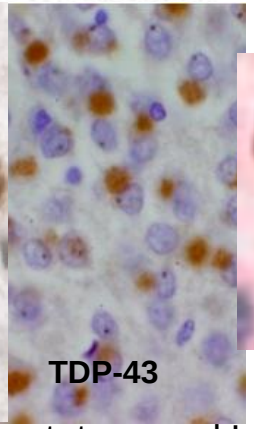


Prion amyloid plaques

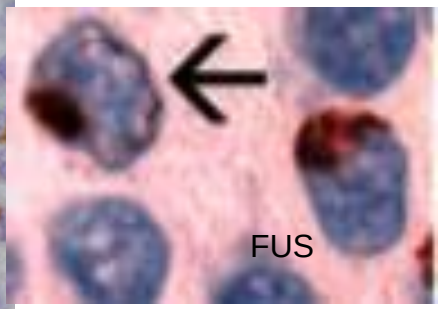


Amyotrophic lateral sclerosis aggregates

Tau



TDP-43



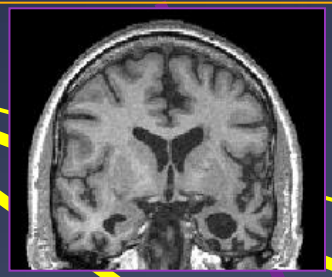
FUS

Frontotemporal Lobar Degeneration

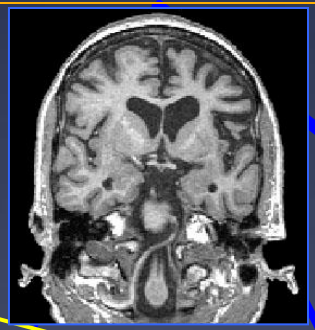
FRONTOTEMPORAL LOBAR DEGENERATION

Behavioral variant FTD

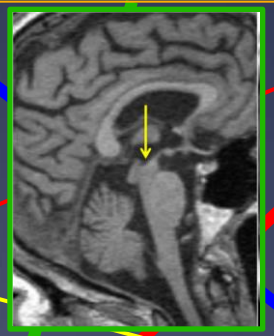
Semantic Dementia



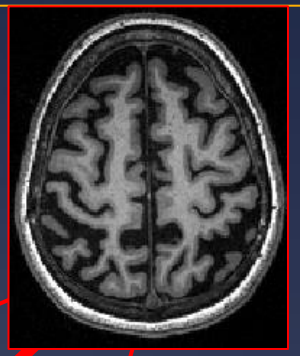
Progressive Nonfluent Aphasia



Progressive Supranuclear Palsy



Corticobasal Syndrome



FUS

TDP-43

Tau

Amyloid/tau

FTD-MND

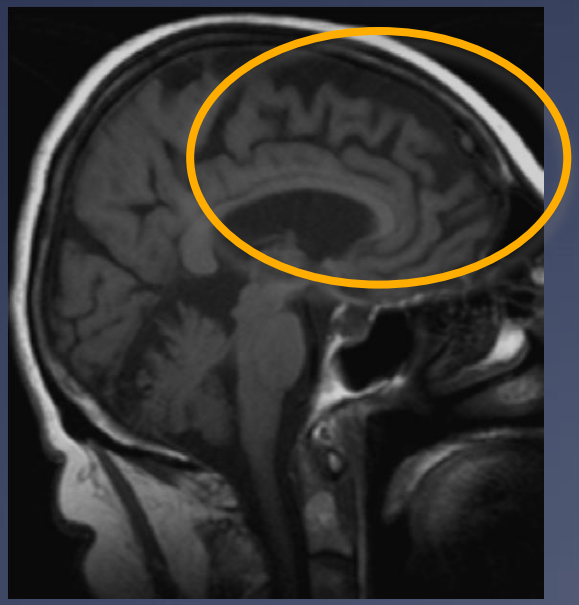
Prevalence of FRONTOTEMPORAL DEMENTIA

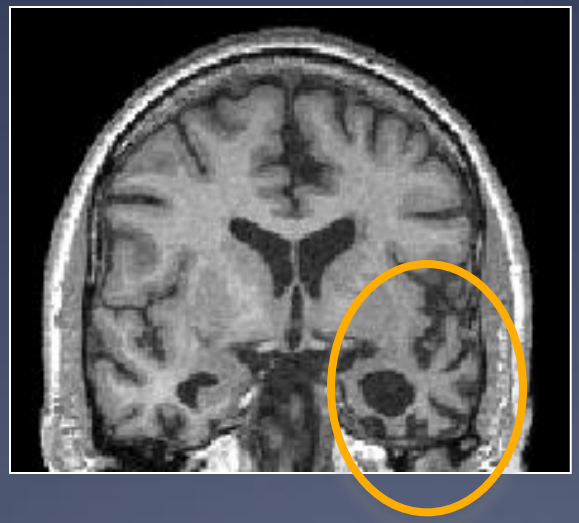
- Unknown (Lund, Manchester 16%)
- Common cause pre-senile dementia
  - Ratnavalli 1:1 with AD 45-64 years (Neurology 2002)
  - Knopman more common than AD < 60 years (Neurology 2004)
  - Knopman 20-30000 in US (J Mol Neuroscience 2011)
  - Broader spectrum even more common (PSP, CBD, ALS/MND)

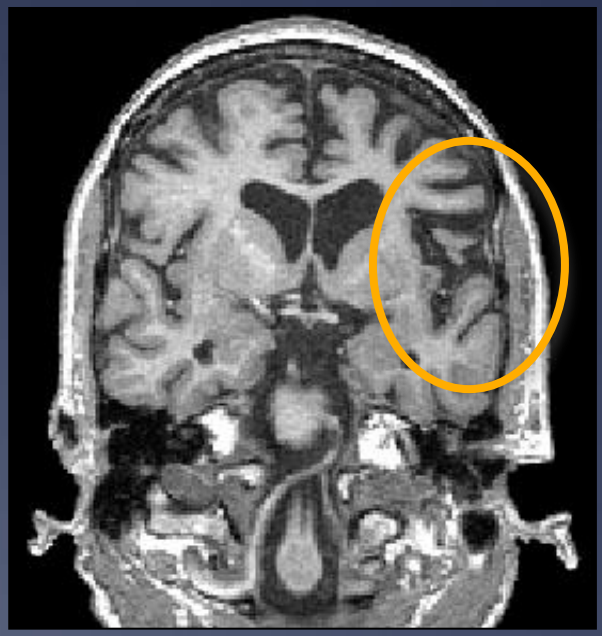
FRONTOTEMPORAL LOBAR DEGENERATION

- A family of syndromes

Behavioral variant FTD (bvFTD) AKA Pick's Disease Frontal variant FTD	Semantic variant Primary Progressive Aphasia (svPPA) (Semantic Dementia)	Non-fluent variant Primary Progressive Aphasia (nfvPPA) (Progressive Nonfluent Aphasia)







EXTENDING TERM FTLD

- Originally FTD = bvFTD, svPPA and nfvPPA
- Added to the fold:
  - FTD-with motor neuron disease (FTD-MND)
  - Corticobasal syndrome (CBS)
  - Progressive supranuclear palsy (PSP)

Behavioral variant FTD

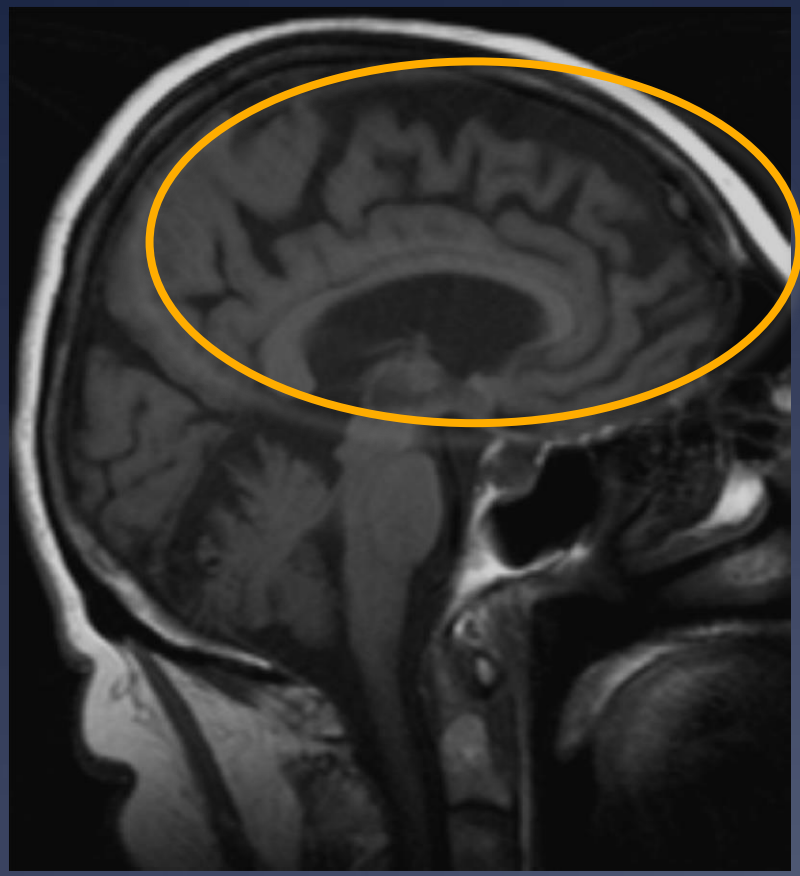
BEHAVIORAL SYNDROME – CHANGE IN PERSONALITY

Possible (3/6)

1. Early (2-3 yrs) behavioral disinhibition: *talking to strangers, touching, walking naked, blurting out offensive statements etc*
2. Early (2-3 yrs) apathy or inertia: *giving up hobbies, work, family gatherings, staying in bed or chair all day*
3. Early (2-3 yrs) loss of emotional reactivity/sympathy/ empathy: *flat, no sadness, euphoric*
4. Perseverative, stereotyped or compulsive/ritualistic behavior: pacing, *hitting thinhs, picking at skin*
5. Hyperorality and dietary changes: *increased sweets; food fad; increased intake*
6. FTD neuropsychological profile: Executive

Rascovky. Brain 2011

Behavioral variant FTD



Planning, Organizing, Sequencing,
Inhibition, Judgment, Abstraction,
Categorization, Problem-Solving

Verbal Fluency
Speech Output

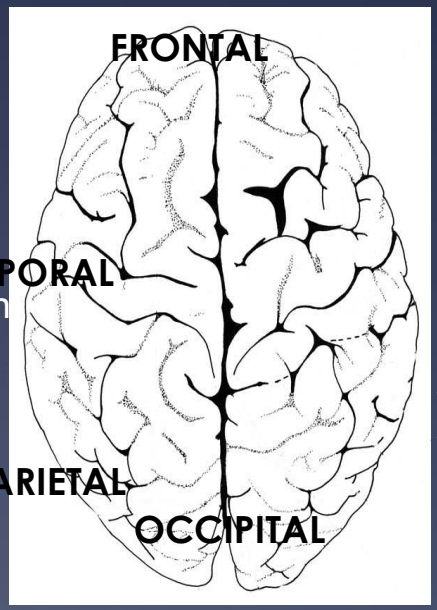
Design Fluency
Social Skills

Verbal Memory
Language
Comprehension
Word-Finding

Nonverbal Memory
Nonverbal Sound
Comprehension

Visuospatial
Visuoperception
L Praxis

Arithmetic
Reading
R Praxis



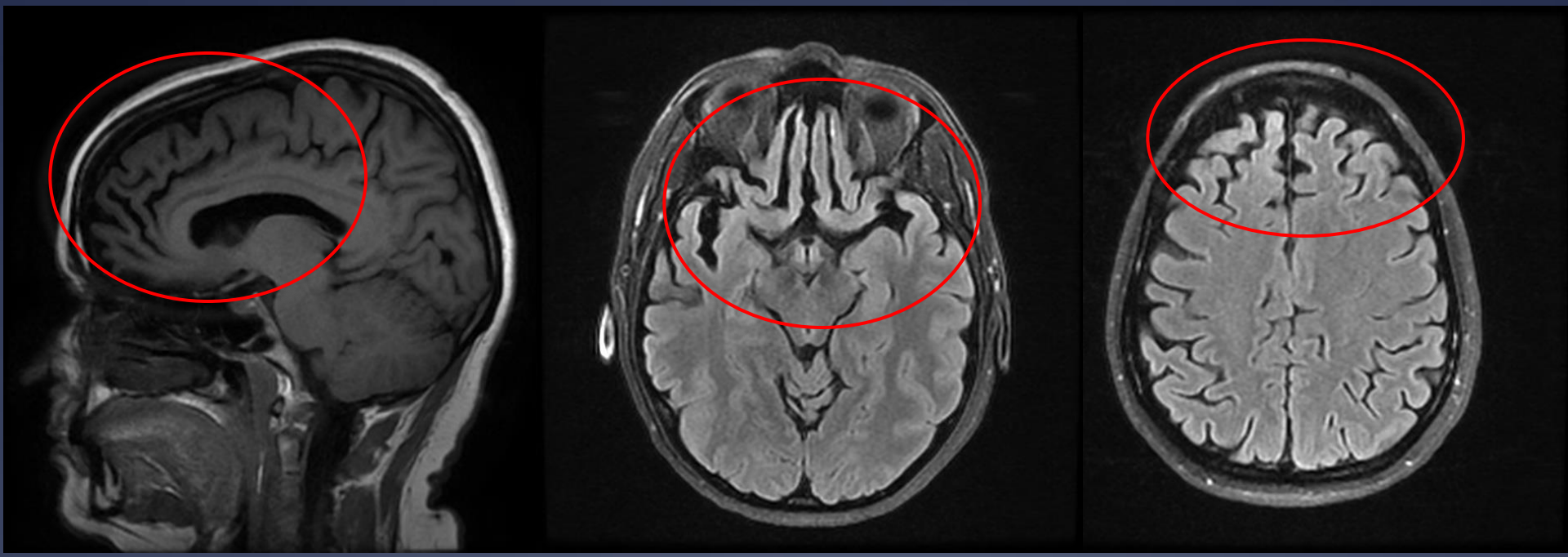
Visual Processing

Rascovky. Brain 2011

Behavioral variant FTD

Probable

1. Frontal and/or anterior temporal atrophy on MRI
2. Presence of known genetic mutation

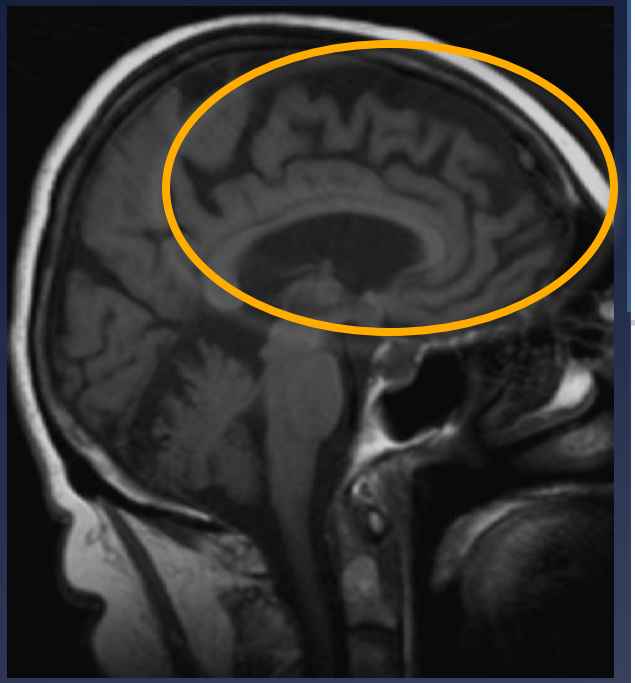


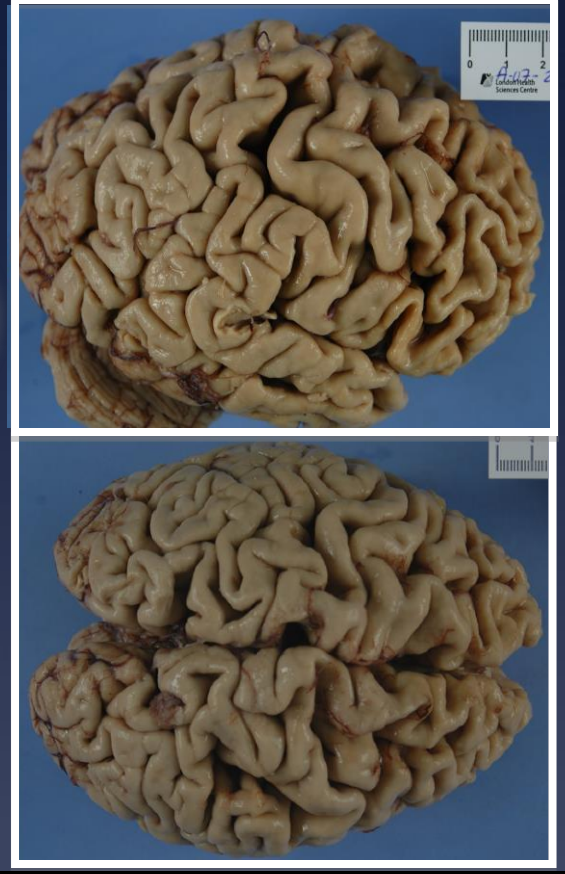
Rascovky. Brain 2011

Behavioral variant FTD

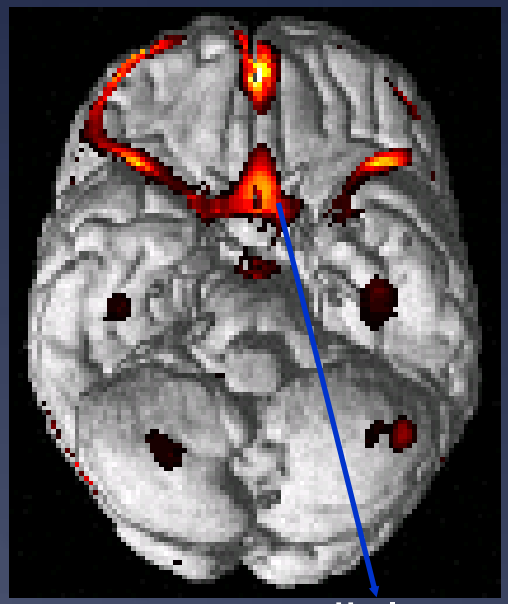
- Most common of 3 clinical syndromes (56% of all FTD cases)
- M:F = 2:1
- Earliest age of onset (58y): 35-75
- Progresses most rapidly (3.4y): slower if no MND
- Highest genetic susceptibility: family history 20-40%
- Strongly associated with ALS/MND

Rascovky. Brain 2011

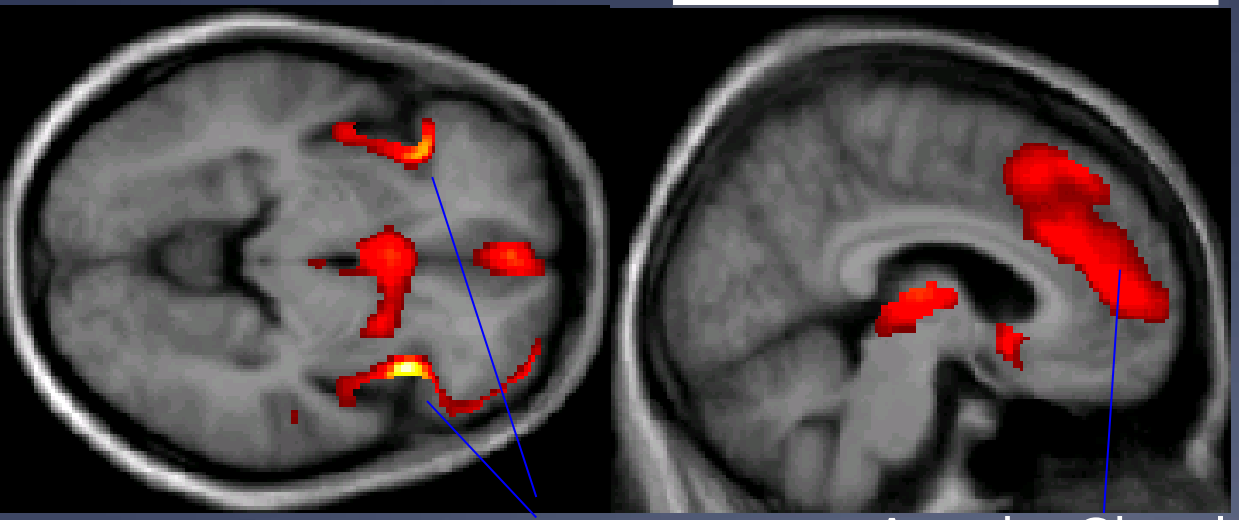




FTD vs. Controls



Ventromedial Frontal

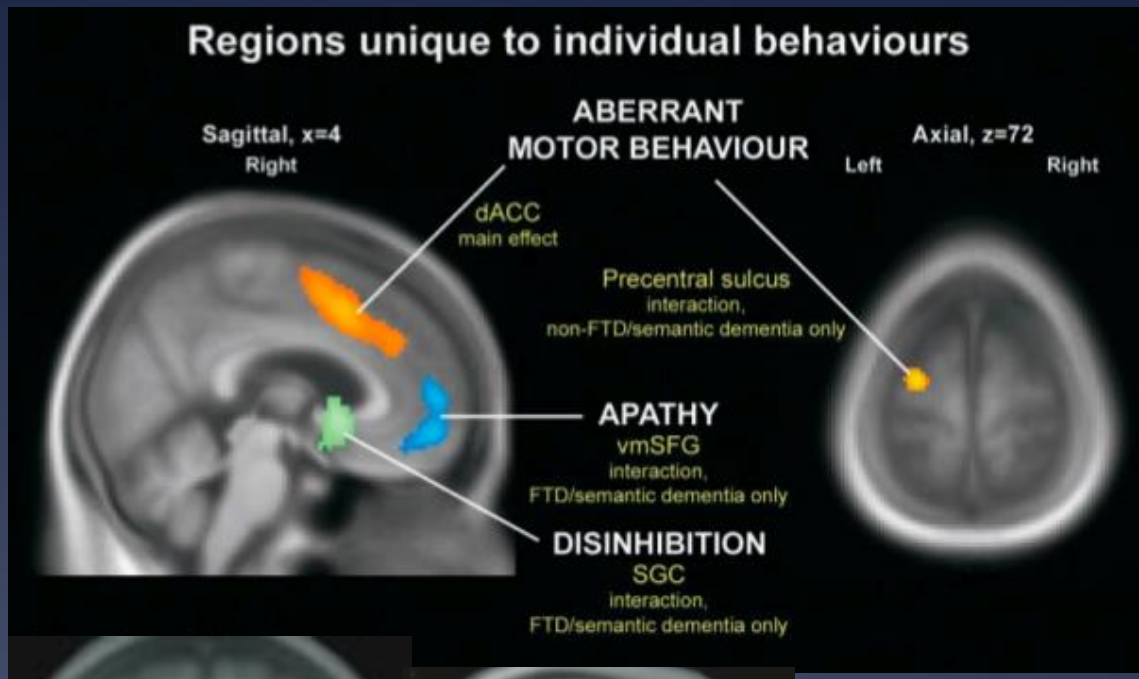


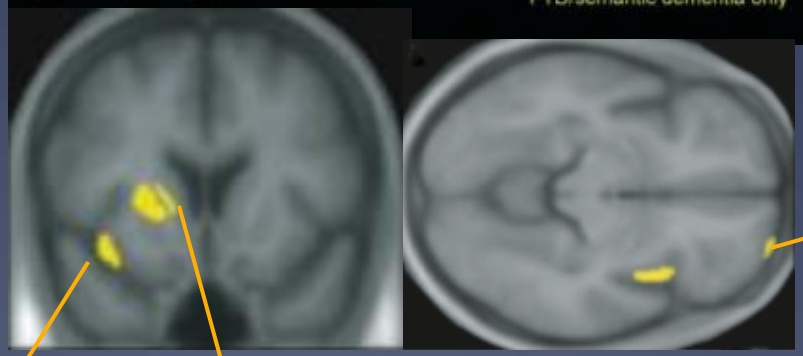
Ant Insula

Anterior Cingulate

Behavioral deficits & GM atrophy

- Apathy – atrophy right vmSFG
- Disinhibition – atrophy right subgenual Cg gyrus
- Aberrant motor behaviour - atrophy right dorsal anterior Cg & left PM cortex
- Overeating – atrophy right ventral insula, striatum, and orbitofrontal cortex





R OFC

R ventral Insula

R Striatum

Rosen Brain 2005
Wooly Neurology 2007

Frontotemporal dementia with motor neuron disease (FTD-MND/ALS)

- 40% of FTLD cases have measurable motor dysfunction; up to 15% ALS (Burrell et al., 2011)
  - MND most common with bvFTD-like symptoms
  - less with sv or nfvPPA
- 52% of MND patients MET criteria for FTD syndrome
  - Up to ½ of ALS/MND patients -functional loss in frontal lobe tests; 15% have FTLD (Ringholz et al., 2005)
  - ~Incidence of FTD in patients with bulbar onset ALS has been reported as high as 48%
- FTD precedes ALS/MND OR ALS/MND precedes
- FTD & MND have overlapping genetics & neuropathology

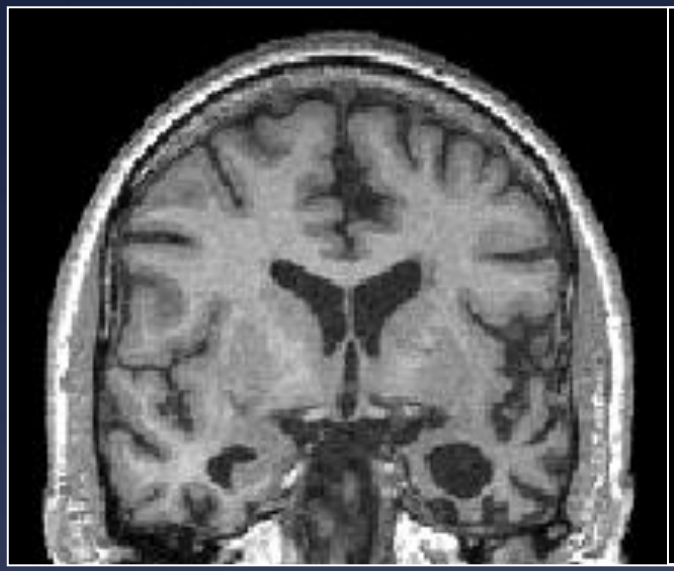
Loemen-Hoerth et al 2002
Callister et al, 2014
Swinnen, B. & Robberecht, W. 2014

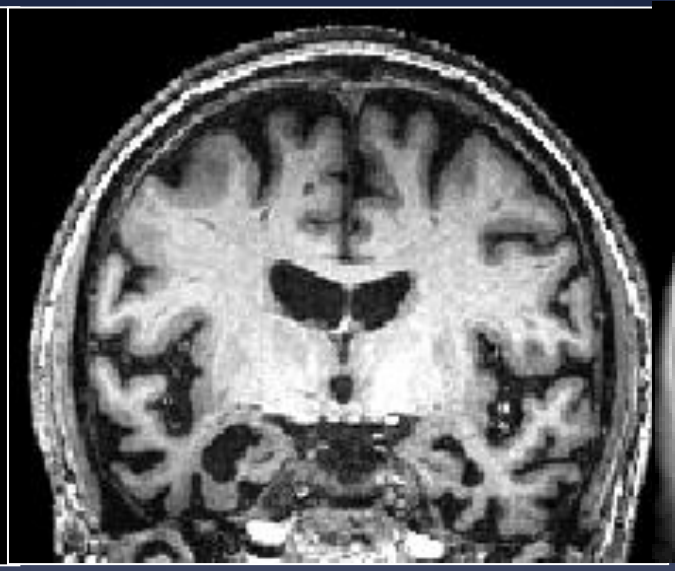
Semantic variant PPA

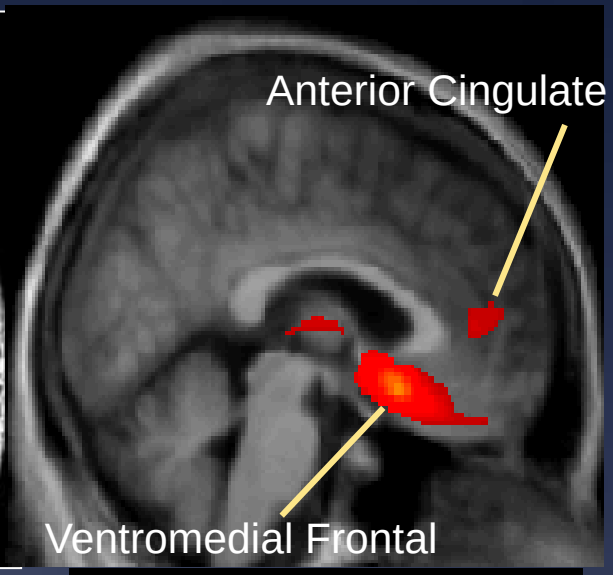
Hemisphere affected determines presentation

- Left-sided atrophy
  - loss of meaning for words, objects, & emotions
- Right-sided atrophy
  - behavioral syndrome; alterations in social conduct
  - loss of person-based semantic knowledge
  - loss of empathy/ ability to recognize emotions
- <20% of all FTD cases
- shares earlier age of onset with bvFTD
- slowest progression (5.2 yrs from diagnosis to death)

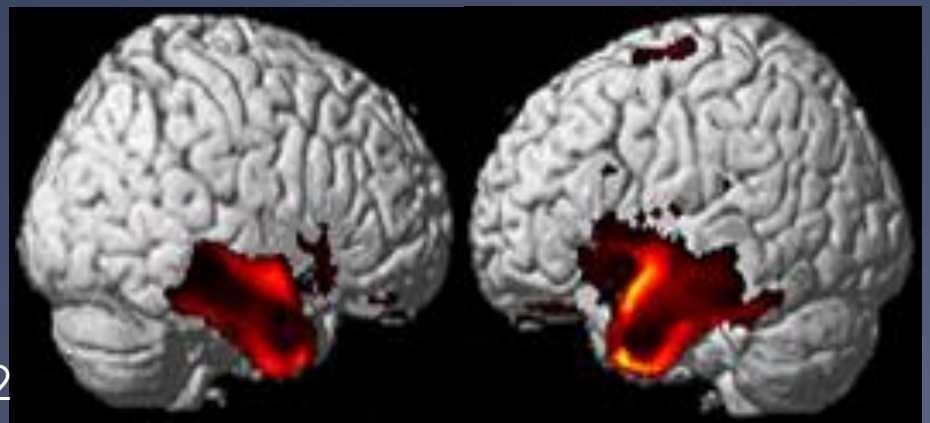
Semantic Variant

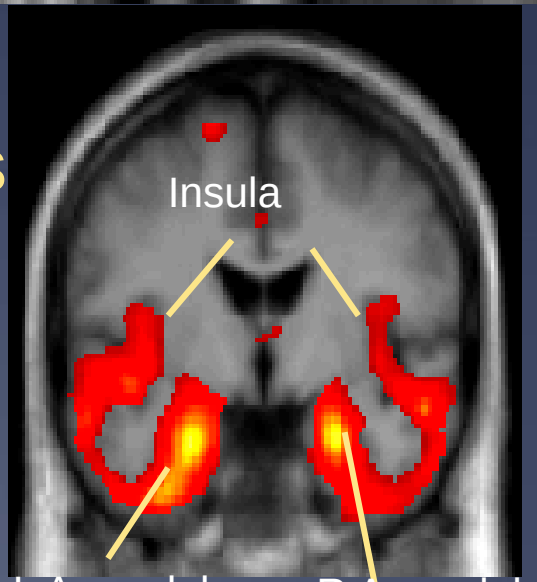






Semantic variant vs. Controls



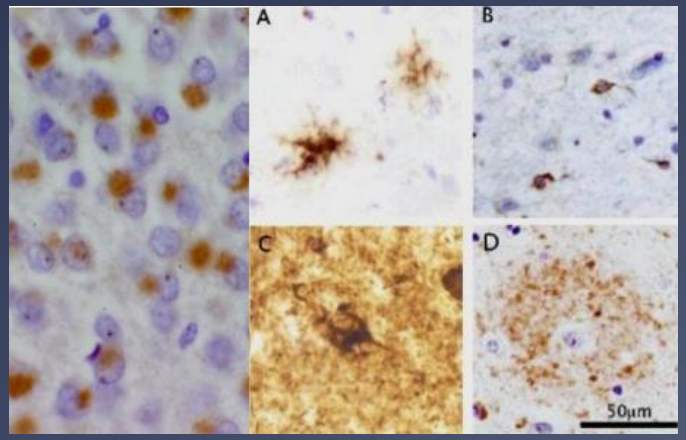


Rosen, Brain 2002

PATHOLOGY

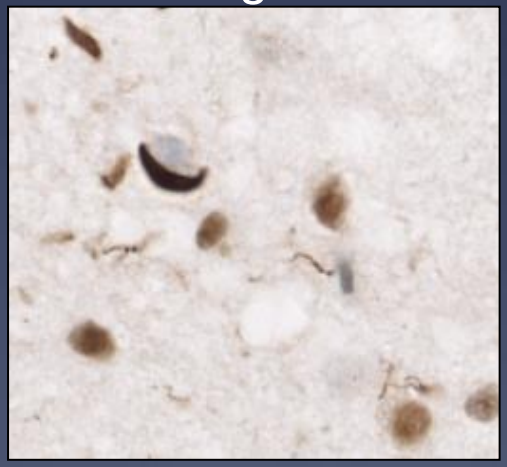
TAU

- MT-associated protein TAU (MAPT)
- Tau proteins interact w/ tubulin - stabilize MT / promote tubulin assembly into MT



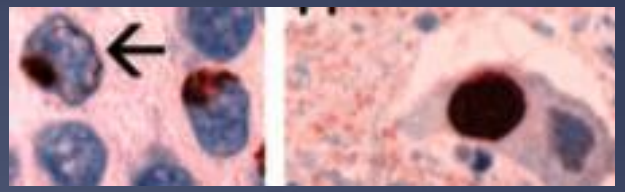
TDP-43

- TAR DNA binding protein
- nuclear protein- binds DNA & RNA
- Nuclear - cytosolic shuttling mRNAs



FUS

- Fused in Sarcoma
- bvFTD, FTD-MND, fALS type 6, sALS
- ubiquitously expressed protein
- Binds RNA & DNA
- multiple cellular functions: DNA repair & RNA transport



AMYLOID

GENETICS

- Most FTLD cases (tau or ubiquitin inclusions) are sporadic
- FTLD - strong genetic component
  - 40% - 50% of cases diagnosed as genetic
  - 10% autosomal dominant pattern of inheritance
  - BvFTD & FTD-ALS are most strongly familial

FTLD GENETICS

- MULTIPLE GENES:
  - C9ORF72 – Chr9
  - Microtubule associate protein tau (MAPT)- Chr 17
  - Progranulin- Chr 17
  - *Fused in sarcoma (FUS)- Chr 16*
  - CMPB2 gene-chromosome 3 - FTD, FTD-ALS, ALS-pathology unknown
  - VALOSIN-Containing Protein (VCP) gene - chromosome 9 - associated with autosomal dominant condition: inclusion body myopathy + Paget disease of bone (PDB) and/or FTD (IBMPFD)

GENETIC TESTING

- Who should be tested?
  - Strong family history
  - 3 or more generations
- Why get tested?
  - To know
  - Family planning
  - Possible treatment options in future
  - What do test results mean for other family members?
    - Their risk of getting disease
    - ? Insurance
- Genetic counselling before getting genetic testing if asymptomatic

DIAGNOSIS

Exam begins during History:

Appearance

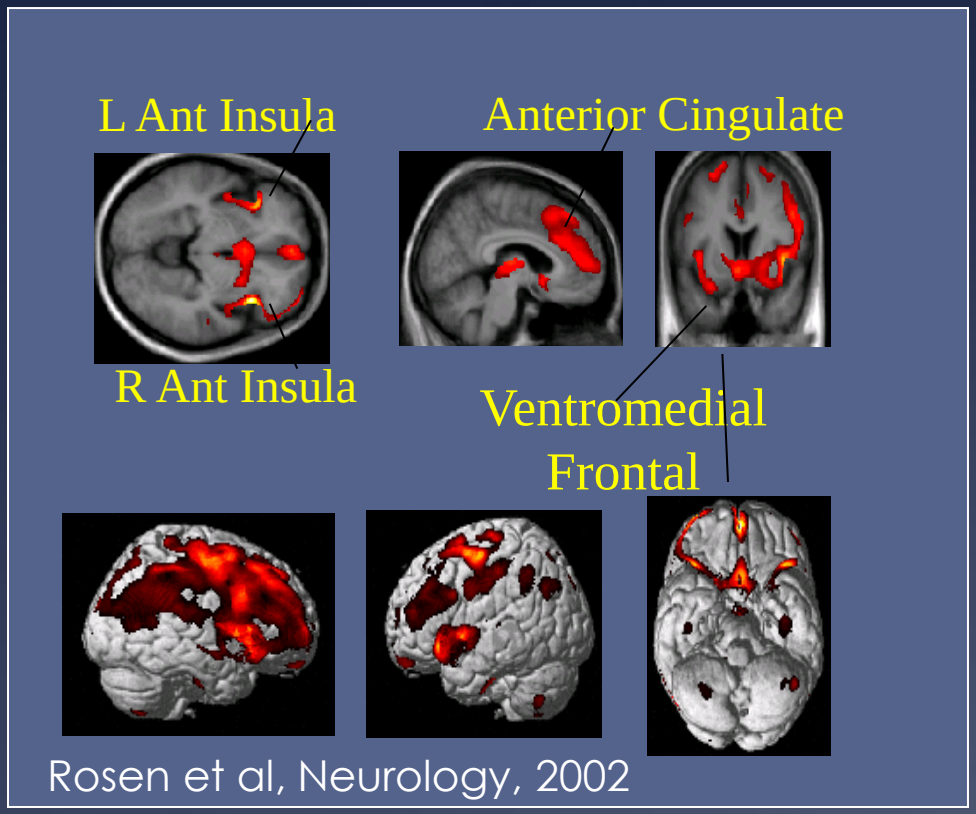
Patient's chief complaint, education, work history

- **Attention**
- Speech and **Language**
- Orientation
- Insight

Informant's chief complaint

- Social Interaction (BEHAVIOR)

Frontotemporal Dementia



Rosen et al, Neurology, 2002

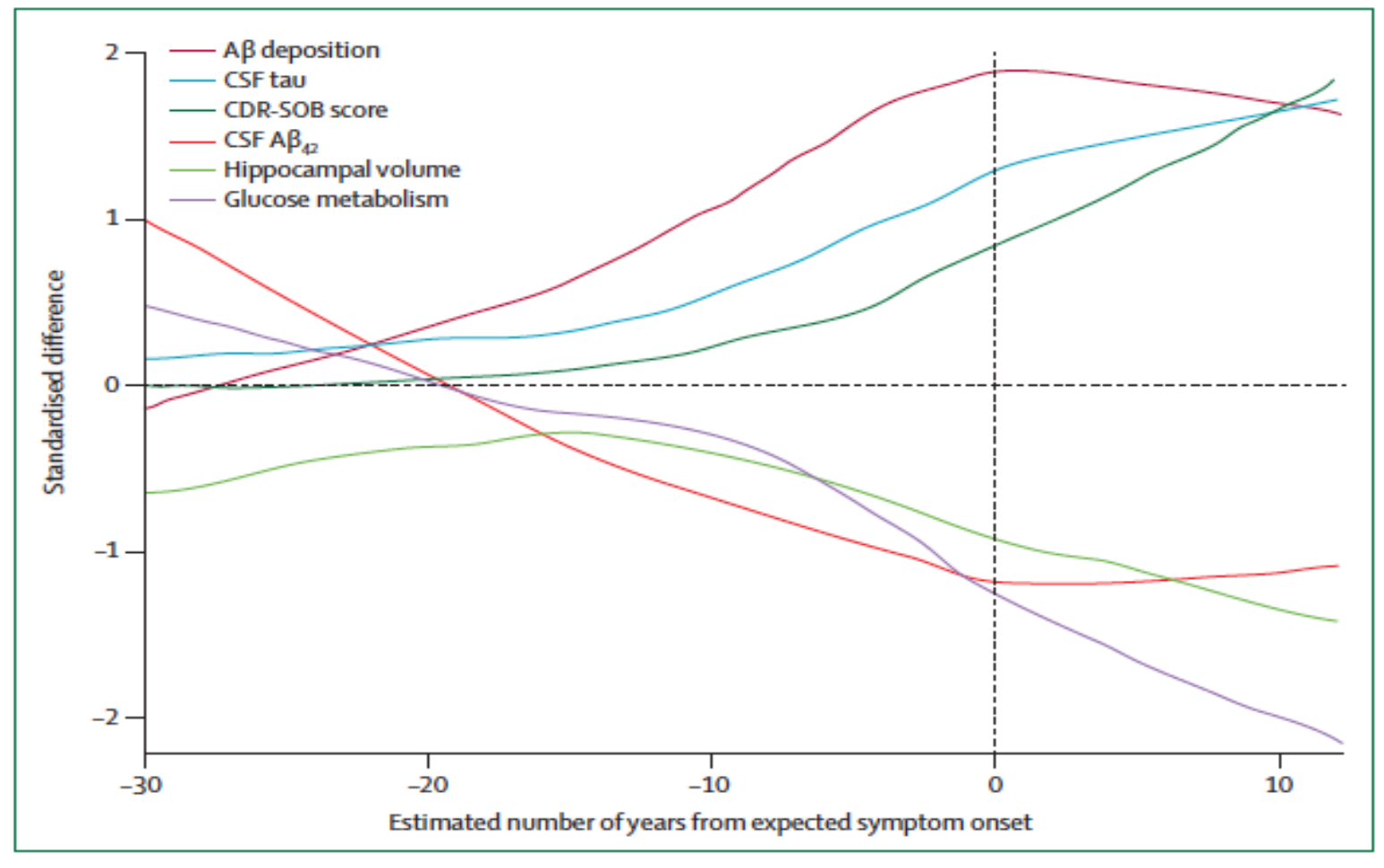
FTD begins in anterior cingulate, insular, and ventral prefrontal cortex

1ST Symptoms in FTD are

- Disinhibition
- Personality change
- Lack of concern for others
- Overeating
- Apathy

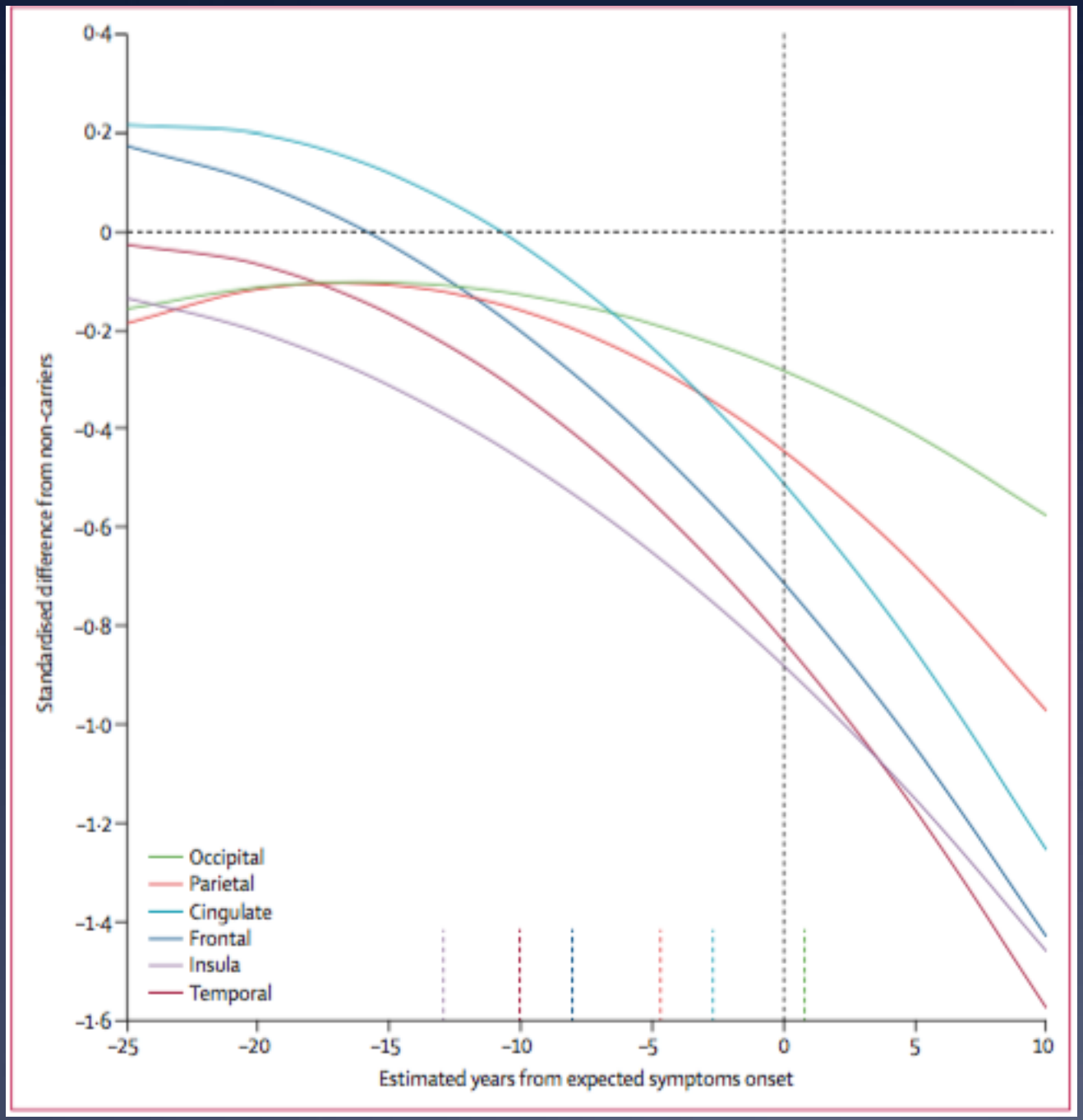
Rascovsky et al, 2011

DISEASE ONSET BEFORE CLINICAL SYMPTOMS



- Increasing evidence that this model is true
- Proof in AD and FTD

Jack, Lancet 2013



GENETIC FTLD

Rohrer, Lancet, 2015

TREATMENT

- No meds available to cure or delay progression of FTD, but meds for symptomatic relief
- Treat concomitant medical conditions including infections, parkinsonian symptoms, seizures, pain and improve nutritional status
- Review all meds (incl alternative)

NON-PHARMACOLOGICAL

- EDUCATION:
  - tolerance for disruptive but non-dangerous behavior
- medical alert bracelet / note or card to be given to strangers explaining disease
- providing distraction so patient diverts attention or alters behavior, and mild forms of bribery with favorite snacks.
- support groups for caregivers and family for information and advice, and possible respite care
- need for a POA
- behavioral symptoms often cause of institutionalization so need to be addressed and adequately treated

NON-PHARMACOLOGICAL

- Individualized exercise programs
- Adequate sleep may reduce behavioral problems
- No evidence for any herbal/alternative remedies
- Speech pathology assessment and intervention: for swallowing & for communication in SV & NFV
- PT/OT

PHARMACOLOGICAL

1. Selective serotonin reuptake inhibitors (SSRIs): Patients with FTD show serotoninergic deficits
   - used to treat compulsions, ritualistic behaviors, carbohydrate cravings, anxiety and behavioral symptoms
   - paroxetine decreased or eradicated repetitive, ritualistic behavioral in a large proportion of patients (Chow & Mendez, 2002); improved behavioral symptoms (Moretti et al, 2003)
   - Trazodone in controlling behavior in patients with FTD (Lebert et al, 2004)
   - svPPA have many compulsions that can sometimes respond to SSRI
   - nfvPPA - depression and social withdrawal common

PHARMACOLOGICAL

2. Atypical antipsychotics
   - Low doses of atypical antipsychotics such as quetiapine, olanzepine or risperidone can be used for agitation, aggression or psychotic behavior.

3. Others:
   - Valproic acid
   - Gabapentin

Acetylcholinesterase inhibitors (AChEIs)

- In FTD, relative preservation of cholinergic neurons thus no *a* priori reason to expect a benefit from cholinesterase inhibition (Huey 2006, Sparks 1991, Hansen 1988)
- not effective in FTD and have been reported to cause agitation (Perry & Miller, 2001)- cholinergic system e.g. nucleus basalis of Meynert relatively spared in FTD
- dangerous in FTD-MND as cause increased oral secretions

EXPERIMENTAL TREATMENTS

- INTERFERE WITH FORMATION AND ACCUMULATION OF TOXIC SUBSTANCES
- REMOVE TOXIC SUBSTANCES

In CLINICAL TRIALS

- Abb-8E12: binds to abnormal tau aggregates, prevent spread from neuron to neuron
- BIIB092 anti-tau antibody & BMA-986168: binds eTau that may be the cause of neuronal dysfunction directly and may be partially responsible for spread of tau
- Oxytocin (intranasal): in bvFTD for empathy and apathy
- TPI-287 (abeotaxane): microtubule stabilizer
- stereopure antisense oligonucleotide: designed to target the pathogenic allele of the *C9ORF72* gene for the treatment of ALS and FTD

FTLD ISSUES

PREVALENCE OF APATHY

- Apathy was the most prevalent symptom: 90.5% mild FTD and 100% in moderate and severe FTD (Schmid JD 2006)
- Apathy is the most common neuropsychiatric symptom reported in AD and FTD patients (Ortiz 2006, Shinagawa 2006)
- Apathy is one of the primary neuropsychiatric manifestations of frontal system dysfunctions (Landes A 2001, Boyle P 2004)

DEFINITION

Affective apathy - indifference or lack of empathy.

Behavioral apathy - indolence and requirement for prompts to initiate physical activity.

Cognitive apathy - inactivation of goal-directed cognitive activity, requiring assistance in initiating mental activity or speech.

APATHY

- Apathy - frustrating for caregivers; misinterpreted as sign of emotional disturbance, withdrawn, insensitive, uninterested, uncaring or purposeful oppositional behavior. (Politis AM. 2004, Landes A. 2001)
- Caregivers - distressed by lack of interactiveness and engagement apathy causes. (Thomas 2001)
- Burdened by increased impairment in ADLs related to apathy
- Differentiating apathy from depression - distinct pathophysiology and pharmacological and psychological interventions suitable for the two syndromes. (Allan M. 2005)
- Information about the nature of apathy can profoundly alter caregiver's perception of patients and dramatically improve their ability to provide appropriate care and engage patients with rehabilitation.

TREATMENT OF APATHY in FTD

- **Antidepressant**
- **Combined pharmacologic-behavioral interventions may optimize functioning among patients and their caregivers (Boyle 2004).**
- methylphenidate

Occupational issues

- May be the first sign of trouble
- Poor judgment; relationships strained
- Work becomes overstimulating and difficult
- Source of conflict at home: what's wrong?
- Financial, legal risks, and consequences

Driving

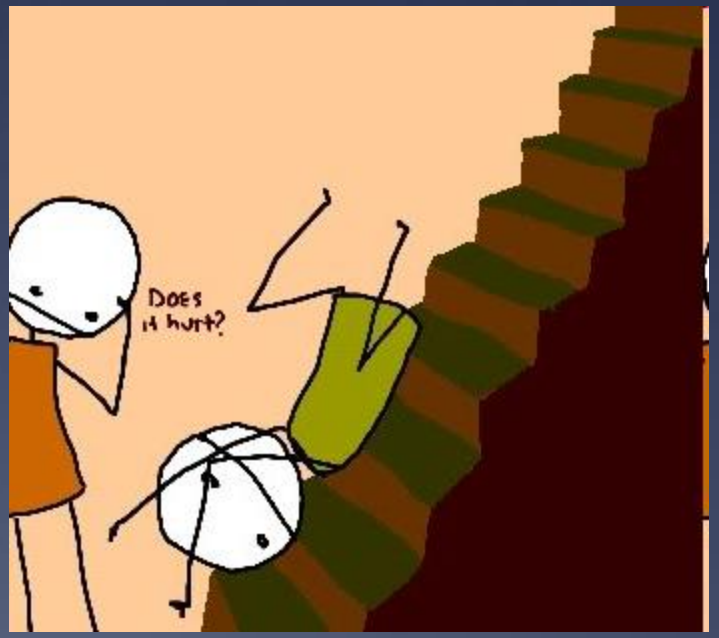
- Many patients with FTD show disregard for rules
- Lack judgment

Treatment:

- Report to MOT
- Ask family to limit access to car keys/car
- Provide transportation alternatives

Falls-prevention

- Shoes in the house!
- Hazard modifications and decisions about remodeling
- Stairs
- Hand rails
- Use of aids like walkers
- Awareness of impulsivity:
  - predict needs,
  - 1:1 supervision, helmet



Other safety hazards

- Choking-overstuffing mouth
- Sunburns

Financial vulnerability/Scams

- Legal protection: decisions regarding competency and capacity

Treatment:

- Educate families
- Divert mail to PO Box rather than to the home
- Electronic barriers- passwords and other access-blockers
- “Broken” computers

Shoplifting & criminal behavior

Treatment

- Identification bracelet, pre-program cell phone to call family member
- 1:1 supervision
- Letters for store owners, arrange an account
- Notification of local law enforcement
- Avoid tempting environments

Caring for children

- May compete with small children
- Disinhibited behavior around teens
- May lack judgment creating unsafe situations

Treatment:

- Provide supervision and allow for positive interactions with low level of responsibility
- Divert when necessary
- Aim for activities that are pleasing to all e.g. music, non-competitive games, outdoor activities

Marriage and relationships

- Sexual and intimacy changes- too much or too little?
- Dynamics are altered- no longer equal partners
- Embarrassing sexual behavior in public
- Lack of engagement or caring in relationships

Treatment:

- Counseling and support groups

Getting lost

Treatment

- Safe Return bracelet
- 1:1 supervision
- “Neighborhood watch”

CAREGIVING

Challenges of FTD vs Alzheimer's

Caregiving for person with dementia can be physically & emotionally exhausting.

FTD- specific challenges:

- Personality changes & behaviors very distressing
- Diagnosis often delayed
- Little public awareness about FTD, so less resources
- Patients affected usually younger than AD
- Language problems develop earlier, communication more difficult
- genetics

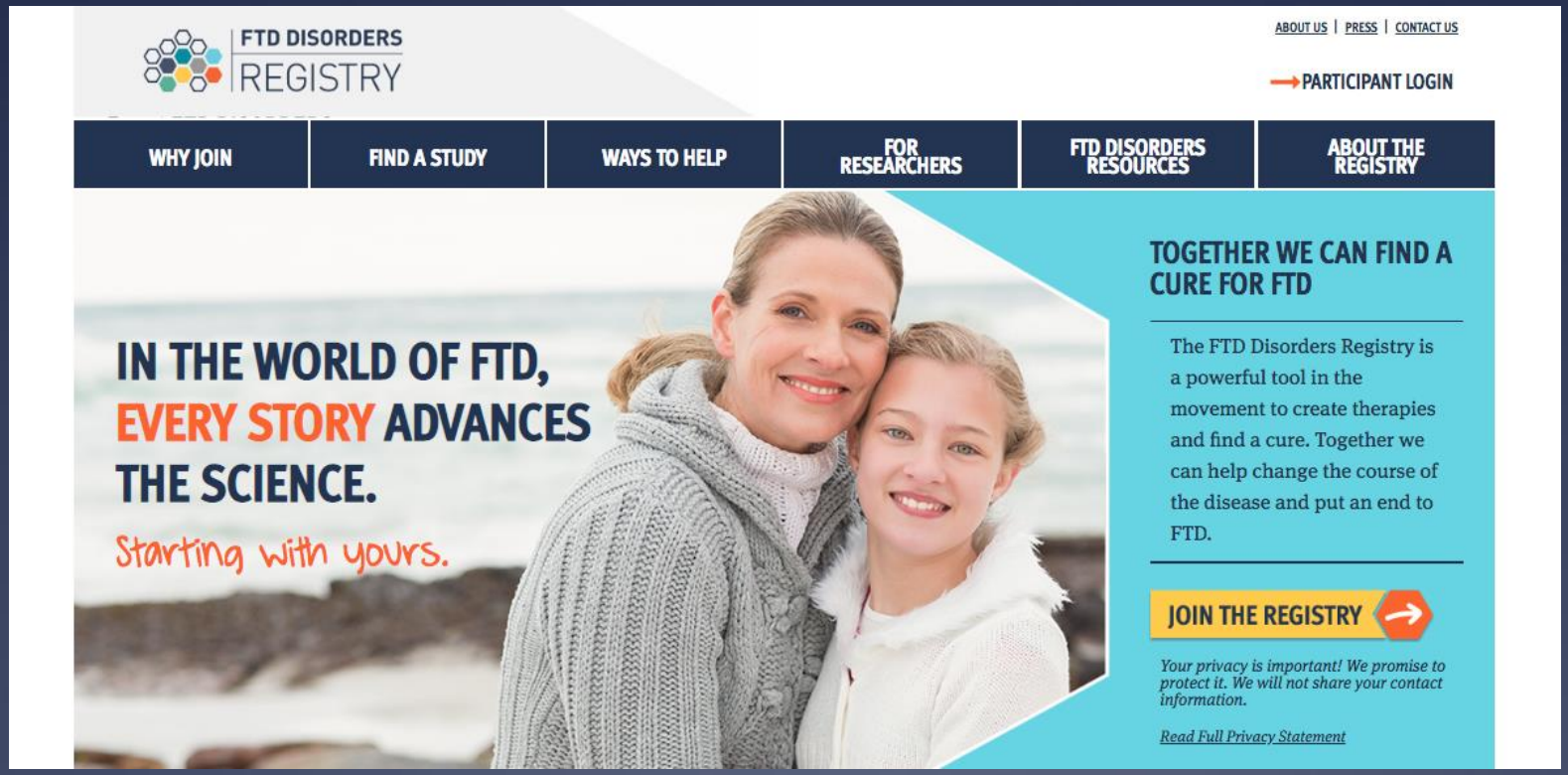
CARING FOR CAREGIVERS

- Depression
- Medical illness
- ENCOURAGE:
  - Protect your health
  - Watch out for signs of depression
  - Take charge of your life
  - Acknowledge where you are and work from there
  - Ask for help
  - Ask for financial help to pay for professional care.
  - Utilize community groups that provide caregiver respite
  - Learn everything you can about your loved one's condition
  - Seek support from other caregivers

https://ftdregistry.org/

FTD REGISTRY

- online database - collects info from those affected by all types of FTD; Persons diagnosed, (current/former) caregivers, family, and friends can join.



help advance science & move faster toward finding treatments and cures

A·R·T·F·L

Advancing Research & Treatment for Frontotemporal Lobar Degeneration

Longitudinal Evaluation of Familial FrontoTemporal Dementia Subjects

LEFFTDS

GENFI

GENETIC FTD INITIATIVE

SUMMARY

- bvFTD – a behavioral syndrome
  - Cognition can be preserved early on so standard testing won't detect
  - Changes on the MRI
  - Heterogeneous syndrome
  - Heterogeneous pathology and genetics
  - No disease modifying therapy yet
    - Some clinical trials
  - TREATMENT: Support for patient, for caregiver

THANKS FOR LISTENING

Questions

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