The Neurobiology, Genetics & Neuropsychology of Neurodegenerative Disorders, Part 2

Lewy Body, Frontal Temporal , Vascular Diseases

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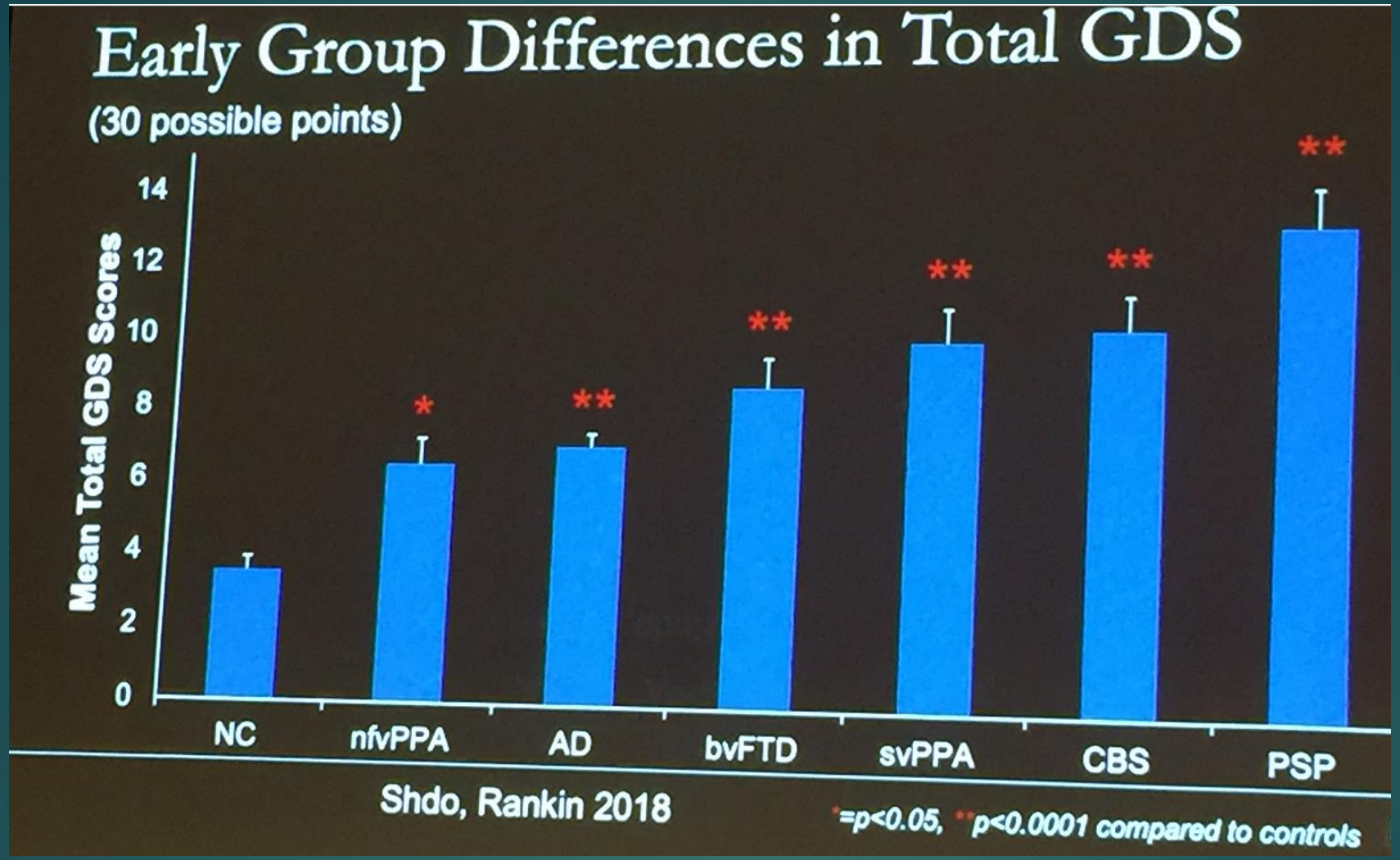
Psychiatric manifestations of Neurodegeneration (ND)

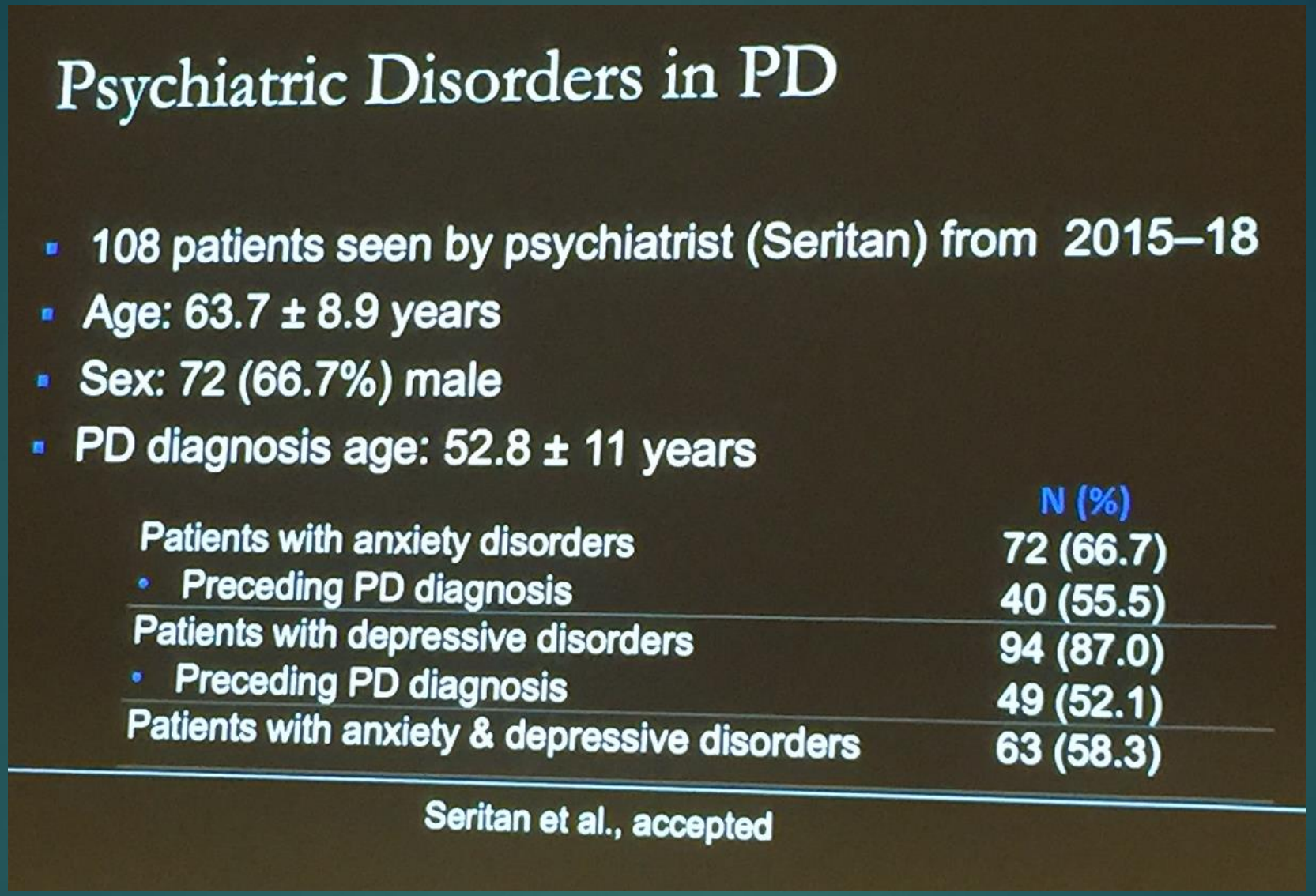
- Bruce Miller: Every ND disorder begins with psychiatric symptoms: MDD, Anxiety, Neuroticism. Belief that mood disorder is a reaction to ND disorder is wrong; MDD reflects the onset of disease, i.e. Huntington's = 2x depression & suicide
- Psych & ND: Not 2 boxes, not either-or diagnosis
- Late life depression is often a product of Vascular or AD dementia
- AD does not start with memory disorder
- MD begins before awareness of ND
- Miller: ND is roadmap for understanding of Psych. Disorders
- Need to treat both psych. Sxs and ND: use antidepressants

Bruce Miller, UCSF, 2019



GDS = Geriatric Depression Scale

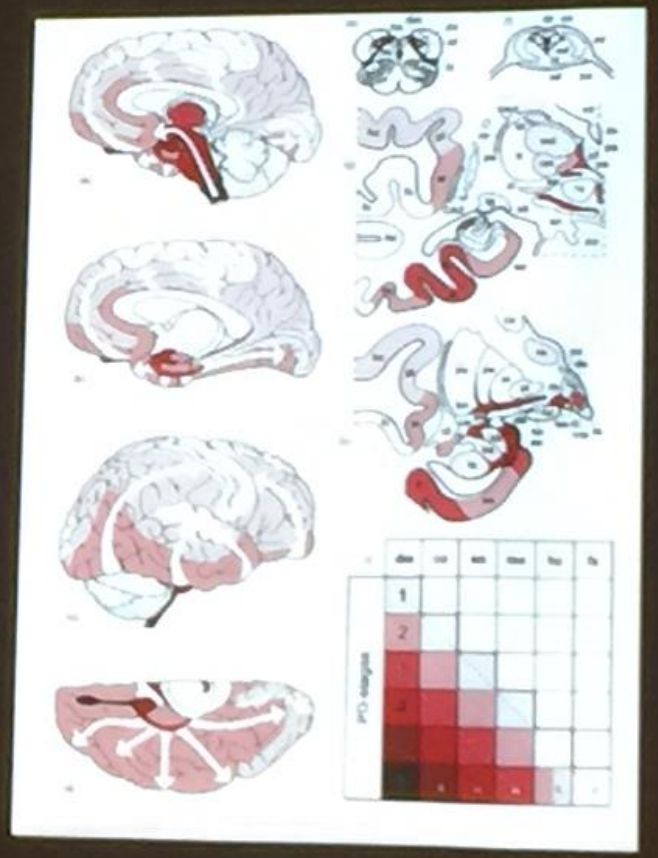
Psych manifestations are the disease, not the reaction to it;
above = mood disorder increase in AD & 5 tauopathies



Parkinsonism: anxiety and depressive disorders are initial sxs in more than 50% of PD pts; PD: can have most ferocious depression and anxiety syndromes prior to movement disorder

Hypothesis

- Early changes in brainstem reticular core (Braak stages 1–3): serotonergic, noradrenergic, and cholinergic systems disrupted → anxiety, depressive symptoms
- Amygdala sensitive to brainstem projection changes → anxiety, depressive symptoms appear earlier than motor dysfunction

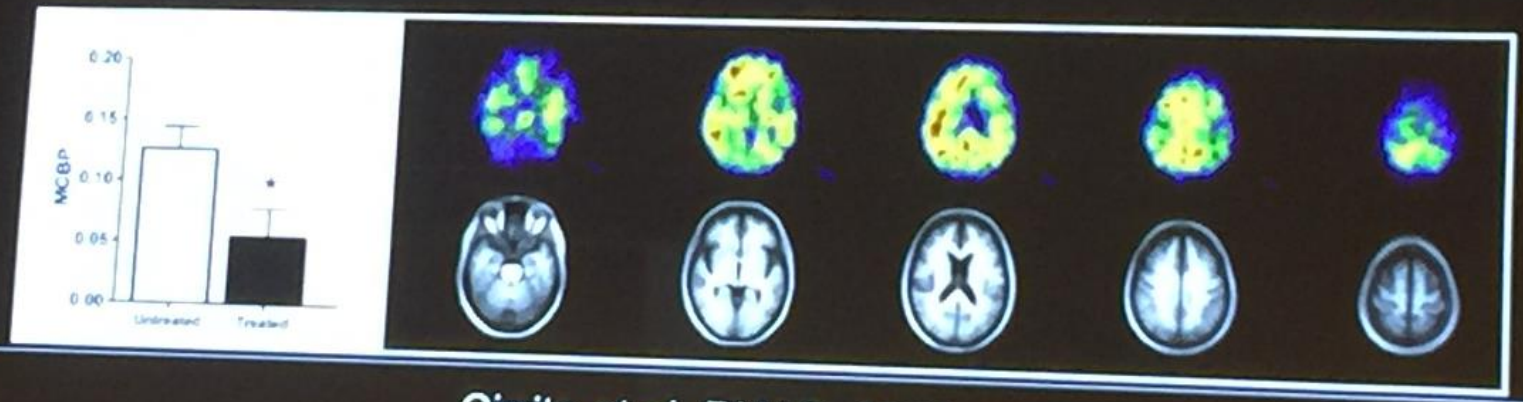


Braak et al., 2003

Early changes in brainstem reticular core is probable cause of psychiatric sxs in ND disorders

Antidepressant Use Associated with Lower Amyloid-β in Humans

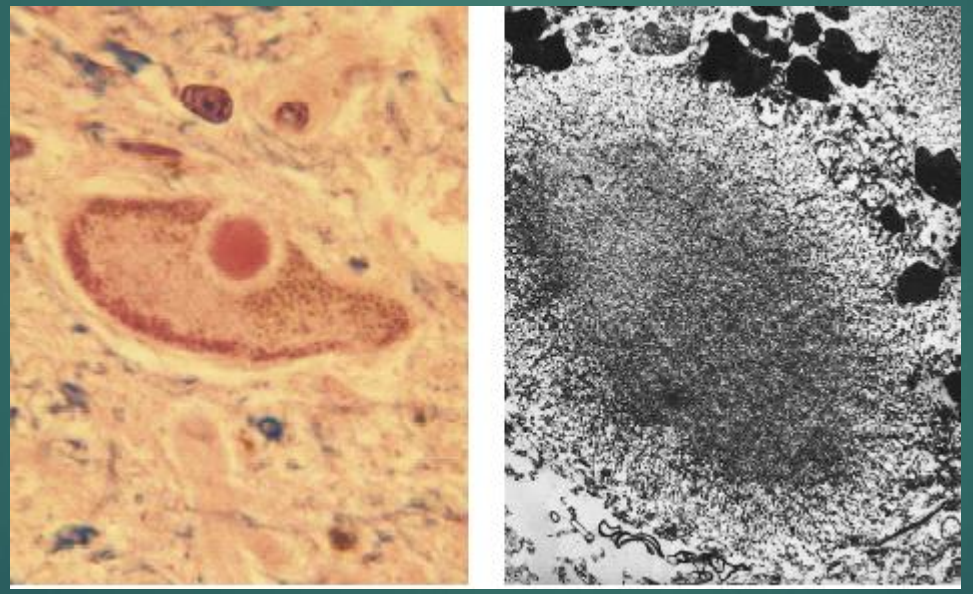
- Retrospective analysis of PET scans
- Older adults with antidepressant treatment in the past 5 years showed less amyloid-β accumulation
- Longer treatment time correlated with lower amyloid-β burden



Cirrito et al, PNAS, 2011

Lewy Body Dementia (LBD)

Lewy bodies:
Hallmark of PD, but not cause



Lewy Body Disease (LBD)

- Dr. Frederick Lewy described Lewy body in 1912.
- Smooth round lumps in neuron.
- Lewy Bodies present in Parkinsonism & LBD subcortically, but can be present diffusely.

Heyman A et al., Neurology. 1999, 52:1839-1844
Ballard CG et al. Dement Geriatr Cogn Disord. 1999, 10:104-108
Barber R et al., Neurology. 1999, 52:1153-1158.

DSM-5: Major or Mild NCD with Lewy Bodies

- Meet criteria for major or mild NCD
- Insidious onset & gradual progression
- Probable: meets 2 core features or 1 suggestive
- Possible: meets only 1 core or suggestive feature
- Core diagnostic features:
- Fluctuating cognition with pronounced variations in attention & alertness
- Recurrent well formed & detailed visual hallucinations
- Spontaneous features of parkinsonism (be it slowness of movement, tremor, or rigidity), with onset after cognition decline
- REM Sleep Behavior Disorder

2017 Updated LBD Cognitive criteria

- **Major NCD/Dementia is required.**
- In early DLB memory may be relatively normal in comparison to AD
- Attentional deficit
- Executive function deficit
- Visuospatial skills deficit

- Diagnosis and management of dementia with Lewy bodies (Fourth consensus report of the DLB Consortium - Ian G. McKeith, et al., 2017

Updated Criteria 2

- **At least two of the following core clinical symptoms are required**:
  - Delirium-like fluctuating cognition: unpredictable changes in thinking, attention and alertness
  - Repeated visual hallucinations (80%)
  - REM sleep behavior disorder (75%) (which may appear long before the dementia)
  - Parkinsonism (85%), specifically slowed movements, tremor when limbs are at rest, and muscle rigidity

- Additional criteria: the loss of smell and excessive daytime sleepiness.

Updated Criteria

- **Dementia plus one of the core clinical symptoms** (fluctuating cognition hallucinations, REM sleep behavior disorder, parkinsonism)

- **At least one of the following biomarker test results:**

  - Brain scans (SPECT or PET) indicates a reduction in brain cells that produce dopamine
  - MIBG myocardial scintigraphy reveals reduced communication of the cardiac nerves
  - A formal sleep study confirms the presence of REM sleep behavior disorder

Pathology of LBD

- Presence of neuropathology of both AD and Parkinsonism
- Presence of increased Lewy Body (intraneuronal cytoplasmic) inclusions in cortical regions and substantia nigra; NCD possible without AD pathology
- Causation: alpha-synuclein and beta amyloid
- Neurotransmitter: profound deficits in:
  - Acetylcholine (Nucleus Basilis) ↓
  - Dopamine (Substantia Nigra) ↓
- Onset ~55, duration 12-13 years

Core pathology in LBD: Dendritic loss

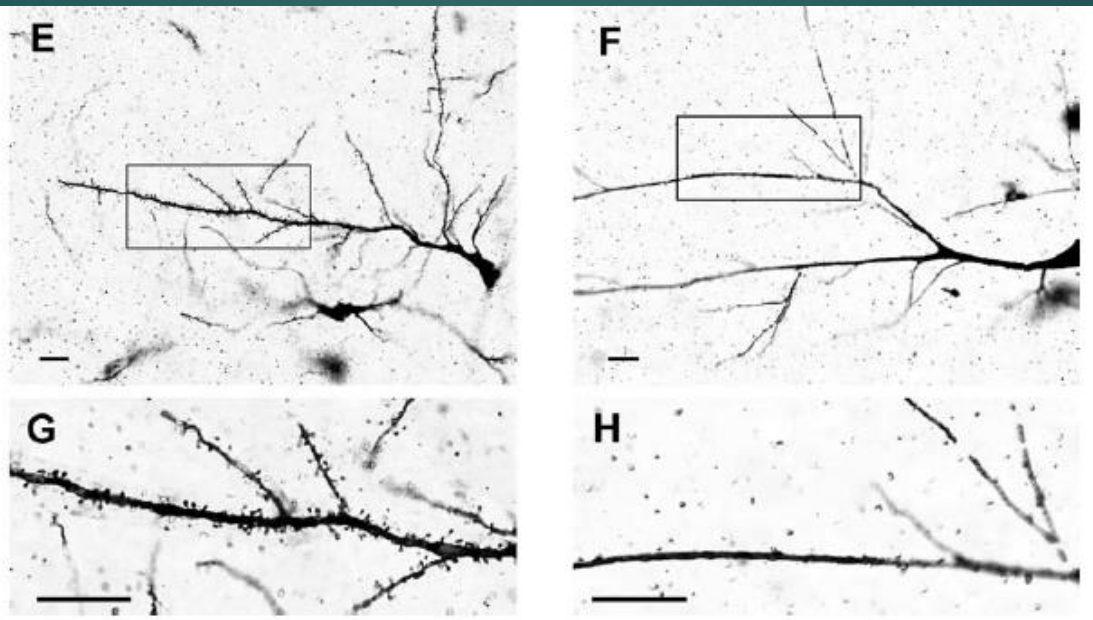


Figure 4. Pathophysiological changes at synapses in DLB. ***A–D***, Brain homogenates of six confirmed DLB cases (D1–D6) are compared with age-matched non-dementia controls (C1–C6). ***A***, ***C***, Western blot analysis for presynaptic markers (***A***) synaptophysin (SPH; SY38) and syntaxin (STX; HPC-1) and postsynaptic markers (***C***) postsynaptic density protein (PSD95, rabbit anti-PSD95) and drebrin (Dreb.; M2F6), including the loading control β-actin (β-Act.). ***B***, ***D***, Plot of the β-actin normalized average intensities for presynaptic marker (***B***) and postsynaptic marker (***D***) proteins of non-dementia controls (black bars) and DLB cases (gray bars) ± SE. ***E–H***, Golgi–Cox–Davenport staining of brain slices for visualization of dendrites and their spines in non-dementia control (***E***, ***G***) and DLB (***F***, ***H***). ***G*** and ***H*** show the magnification of the black boxes in ***E*** and ***F***. Scale bars, 50 μm.

Pre-synaptic α-synuclein aggregates causes dendritic loss

Lewy Body NCD

- ~15% of all NCD, 1 in 7, 800T in US; only 1 in 3 diagnosed
- Causes significantly greater functional disturbance than AD; Care costs 2x that of AD
- 25% of LBD caregivers rate LBD as worse than death
- 80% of people with LBD received a diagnosis for a different cognitive, movement or psychiatric disorder before ultimately learning they had Lewy Body NCD (LBD)
- Robin Williams, Ted Turner: Neurology, September 27, 2016; 87 (13) - **The terrorist inside my husband's brain by** Susan Schneider Williams

Bostrom, 2007, Alz Dis Ass

EPS symptoms (rigidity, bradykinesia)

- Extrapyramidal Sxs:
  - rigidity
  - bradykinesia (slow movement)
  - gait
  - release signs
  - myoclonus are common in moderate to severe AD (use Klonopin)

- Early EPS symptoms means it is not AD

- If Early EPS = either LBD, PD, CBD

LBD predictors

- Male
- Any EPS (resting tremor, bradykinesia)
- Cognitive fluctuation
- Visual Hallucination
- Neuroleptic sensitivity
- Depression
- Sleep disturbance
- Myoclonus
- Auditory Hallucinations
- REM sleep disorder

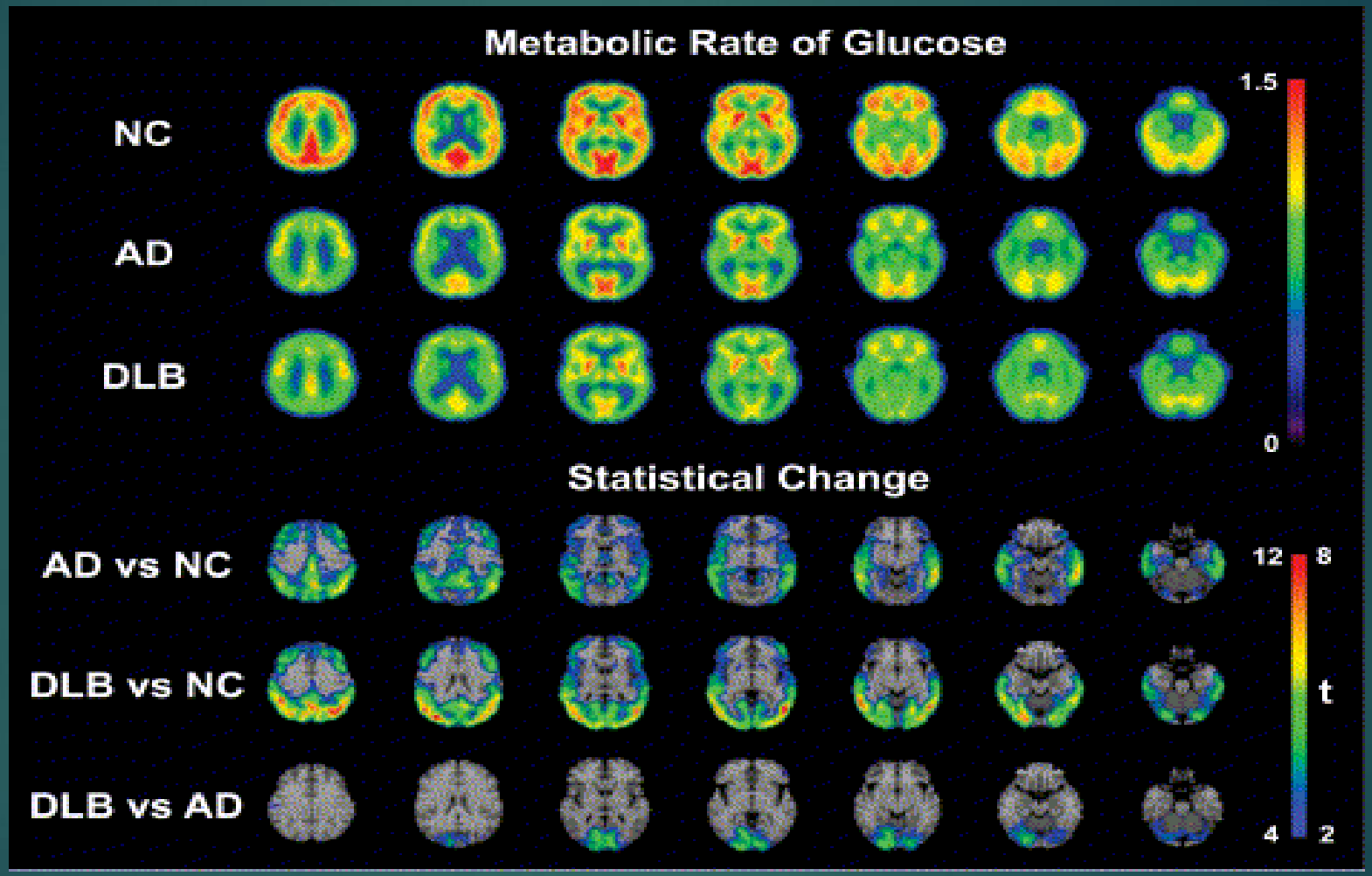
LBD Clinical Presentation

- Increased anticholinergic sensitivity (delirium)

- Severe neuroleptic medication sensitivity (potentially fatal):
  - induce Parkinson-like side-effects or Neuromalignant syndrome (high fever, sweating, unstable blood pressure, stupor, muscular rigidity, and autonomic dysfunction)

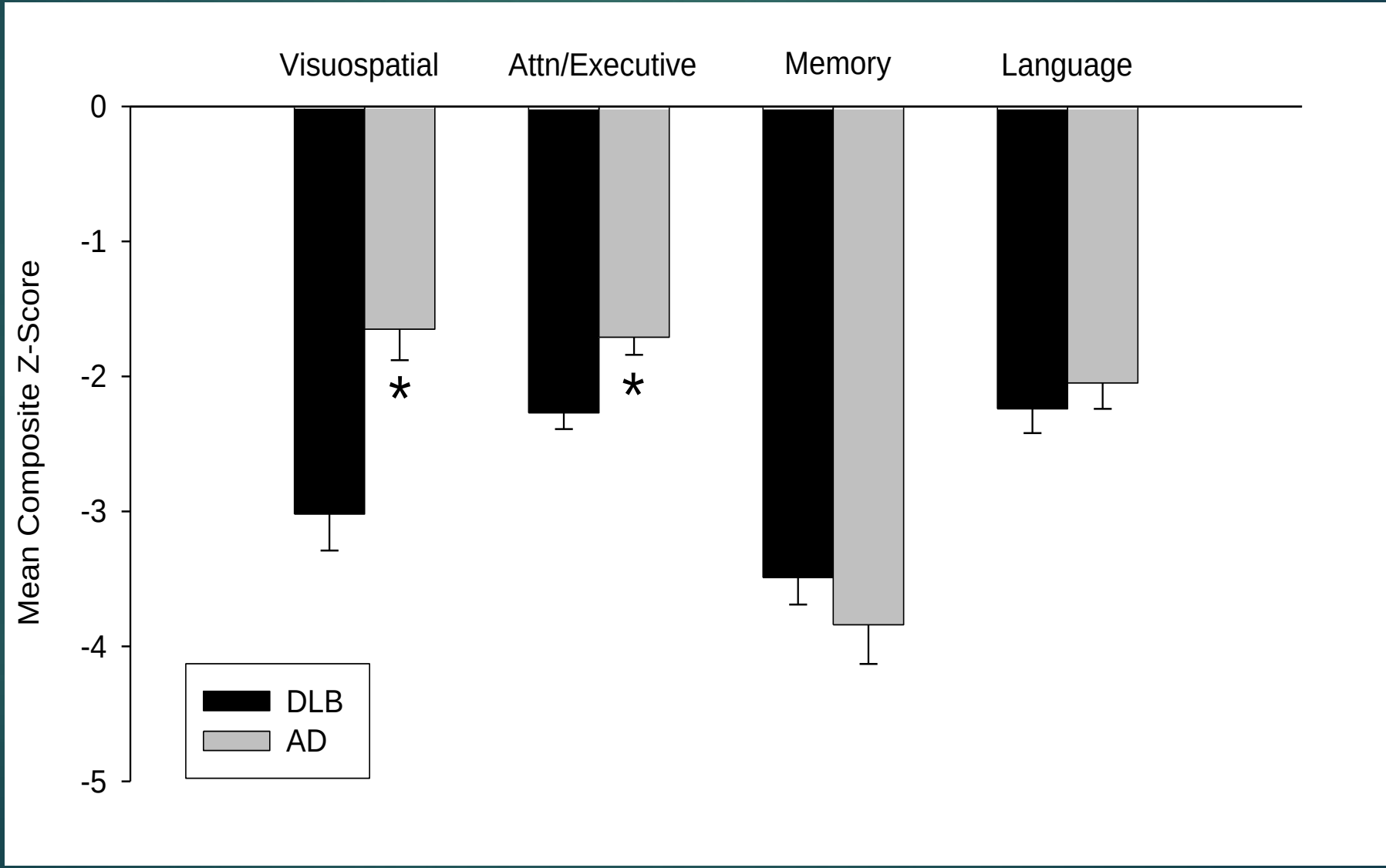
- Underdiagnosed: Clinical diagnosis of LBD in only 49% of cases confirmed at autopsy

Occipital cortex hypometabolism is worse in LBD than in AD



Gilman et al., 2007

Cognitive Profiles in AD vs. LBD: VS ↓ & EF ↓



Visuospatial Deficits: Harbinger of Bad News?

Visuospatial Deficits:

- May predispose patients for visual hallucinations (Mosimann et al., 2004; Hamilton et al., 2009)
- Can differentiate LBD from AD with 80% sensitivity and 90% specificity (Ferman et al., 2006)
- May predict the rate of cognitive decline in LBD patients (Hamilton et al., 2008)

ADHD →→ Lewy Body NCD: only 2 studies

• 2010 Argentina study: 360 patients with degenerative NCD and 149 healthy controls, matched by age, sex and education. The NCD patients comprised 109 people with NCD with Lewy bodies (LBD) and 251 with Alzheimer's.

• Adults who suffer from attention-deficit and hyperactivity disorder (ADHD) are three times more likely to develop LBD; 48 per cent of patients with LBD had previous adult ADHD. More than three times the 15 per cent rate found in both the control group and the group with Alzheimer's.

• Impulsivity and hyperactivity were significantly higher in the LBD group than the Alzheimer's group and the control group (measuring 14.7, 5.9 and 6.4 respectively on the Wender Utah Rating Scale).

• 2017 Taiwan insurance study: Adults with ADHD have a 3.4-fold risk of developing dementia

Angel Golimstok, 2010; Tzeng NS, et al., 2017

Visuospatial Deficits Add to Clinical Differentiation of LBD and AD

	DLB n = 24	AD n = 94
Visual Hallucinations	22 %	1 %
EPS	26 %	16 %
Visuoconstructive Impairment	74 %	45 %

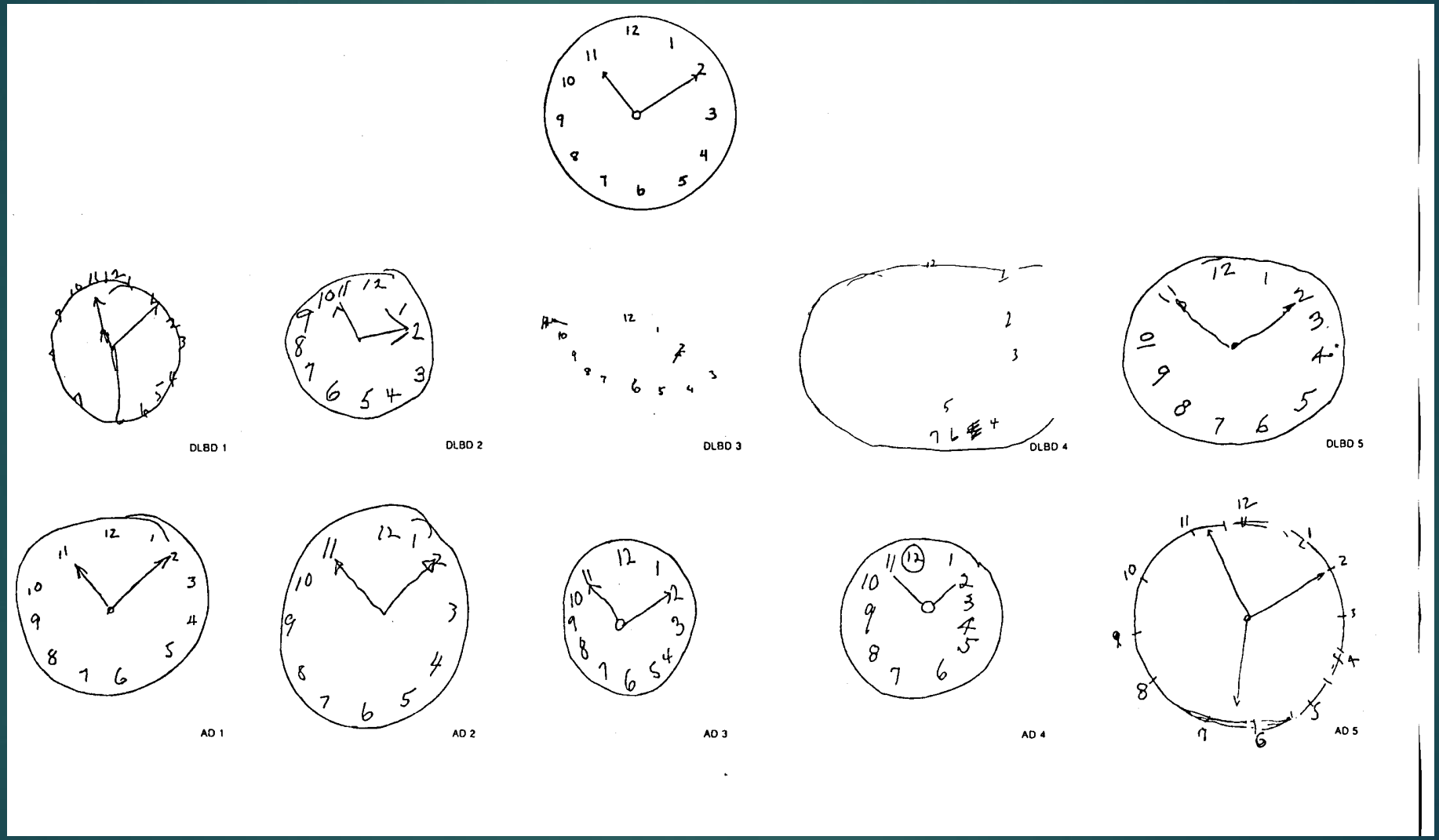
Block Design & Clock Drawings

Tiraboschi et al., 2006

LBD (top) vs. AD Clock copy: LBD worse

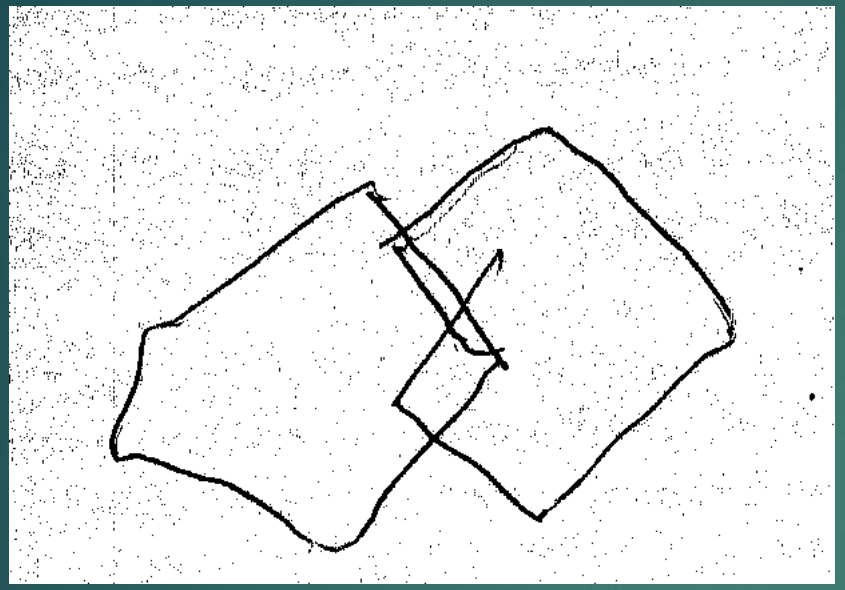
LBD

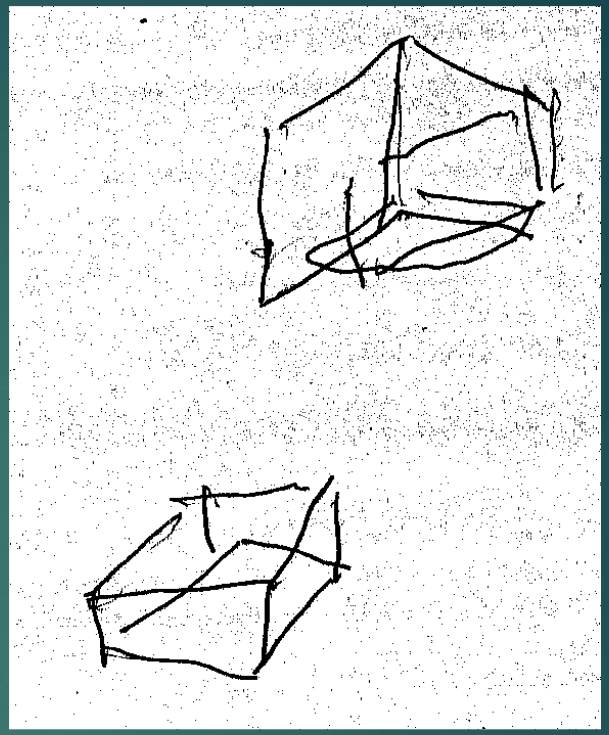
AD



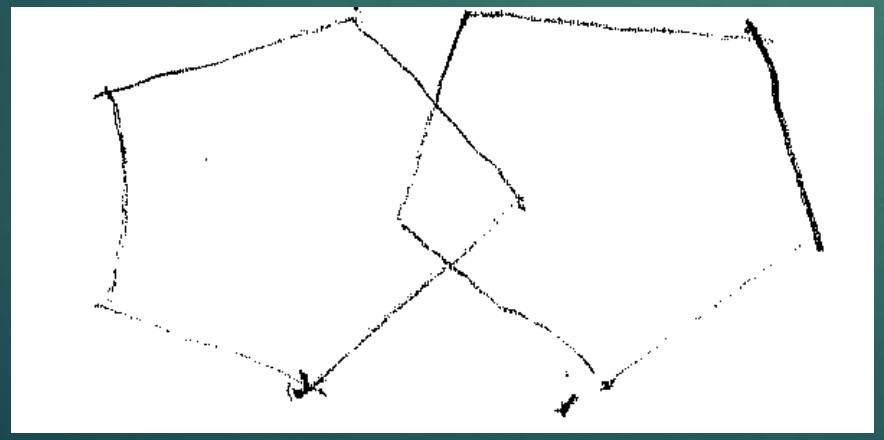
Pentagon and cube copy

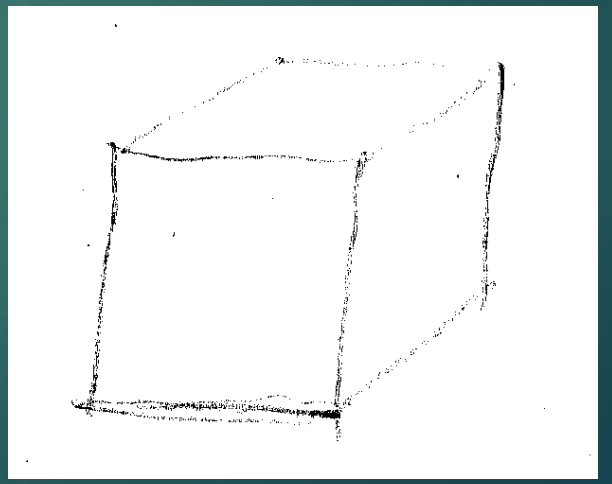
LBD





AD





Hallucinations in AD

- Normals: 6% experience a hallucination or delusion

- Alzheimer's:
  - hallucinations in 20% at 1 year and 51% at 4 years;
  - visual hallucinations in 30%
  - delusions in AD: 36%
  - severity of cognitive decline a major predictor of above

- VHs in AD: later onset & and occur with greater cognitive impairment and a more advanced stage of the dementia.

Visual Hallucinations in LBD

- LBD has significantly higher sxs:
  - visual hallucinations (70%)
  - delusions (56%)
  - delusional misidentification (50%)

- PD:
  - hallucinations in 40% of patients
  - sensation of a presence (person), a sideways passage (commonly of an animal) or illusions were present in 26%
  - formed visual hallucinations in 22%
  - auditory hallucinations were present in 10%

Visual Hallucinations in LBD

- VHs onset earlier in LBD compared to AD.
- If VHs in first 5 years: odds are 4-5 times greater for autopsy-confirmed LBD and that it is not AD.
- Types of VH images:
  - fully formed adults or children in 84%,
  - animals or insects in 37%,
  - objects in 39%,
  - unformed images, such as fire, smoke, water and designs occurred in less than 12% in both LBD and AD.

T.J. Ferman, et al., 2012

Visual Hallucinations in LBD

- Small Animals
- Little People
- Dwarves
- Odd Creatures
- Animals with hats
- Well-formed landscapes

Cases with well-formed visual hallucinations had high densities of LB in the amygdala and parahippocampus, with early hallucinations relating to higher densities in parahippocampal and inferior temporal cortices.

Delusions in LBD and AD

- In LBD, misperceptions and family misidentification are more common & and had significantly earlier onset than in AD.

- Delusions In LBD: Visual delusion
  - Capgras syndrome or reduplicative paramnesia (i.e. belief that a relative is a duplicate impostor) is common = Visual delusion (Disconnected fusiform and amygdala).

- Delusions in AD:
  - Family substitution phenomena (i.e., belief that one relative is a different relative, such as an adult child mistaken for a parent) more frequent in AD.

- Cortical NF tangle burden was associated with an earlier onset of misidentification and misperceptions in LBD and AD, but only with earlier visual hallucinations in AD.

Charles Bonnet Syndrome: an eye problem

Pts with visual loss

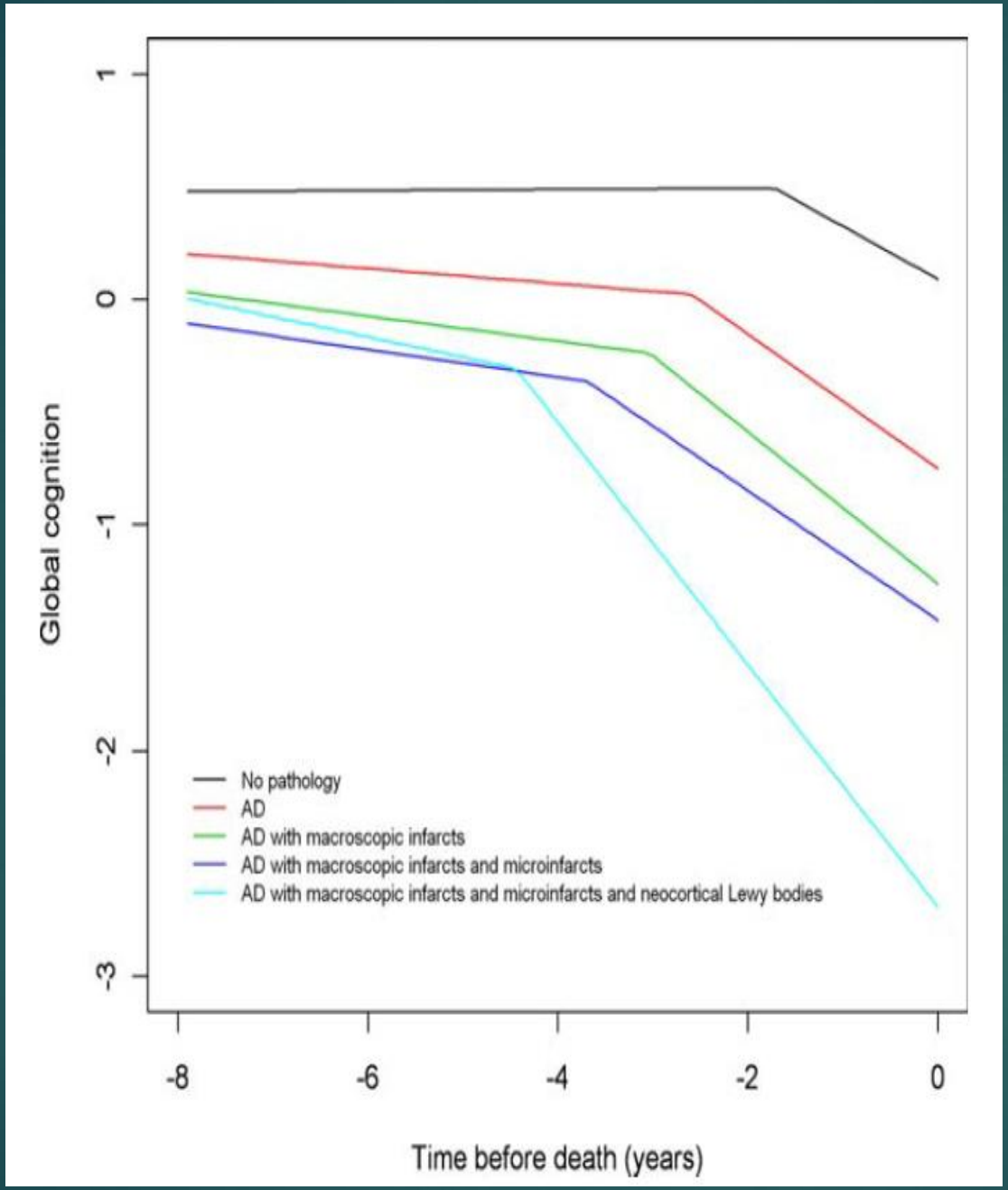
- Experience of complex visual hallucinations in ~17% of patients with visual loss (cataracts, central vision loss due to macular degeneration or peripheral vision loss from glaucoma)
- First described by Charles Bonnet in 1760 in his 89-year-old grandfather
- Usually are "lilliputian" (everything smaller).
- The most common hallucination is of faces or cartoons; sudden appearance & disappearance
- They know that the hallucinations are not real
- Reassure that they are not crazy; SSRIs may help
- Also an auditory version of this syndrome

PD vs LBD: motor 1st vs VHs 1st

- Patients with Parkinson's hallucinate due to the side-effects of ***medication***
- Hallucinations are the early signs of DLB.

- In a nutshell:
  - people who present motor difficulties before cognitive impairment are diagnosed with Parkinson's
  - those that hallucinate before motor symptoms often have dementia with Lewy bodies.

More Pathologies = Worse cognition



Normal

AD

AD + VaD

AD & LBD

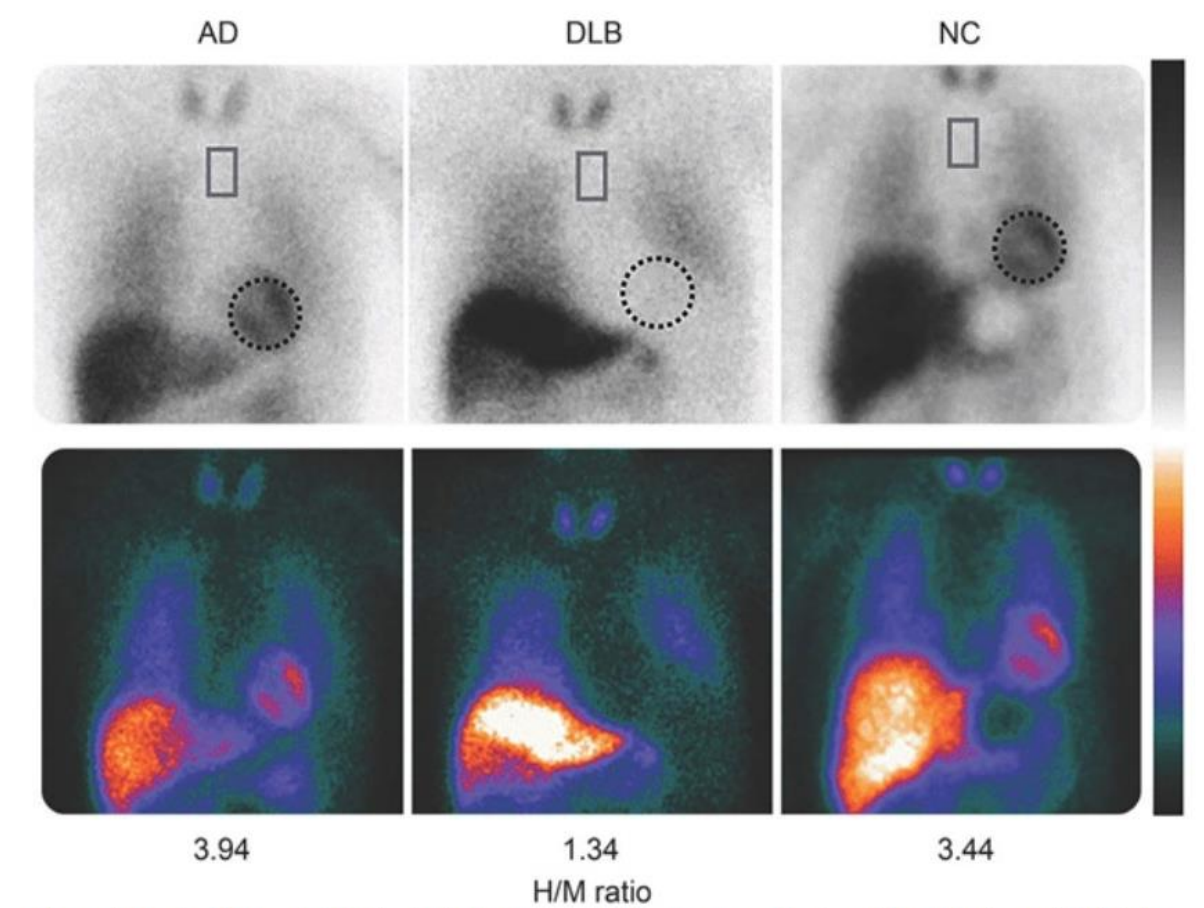
P. Boyle et al., 2013

LBD NCD: Faster decline

- 226 autopsied, community based : 126 had LB pathology (56%), 44% in neocortex
- Cognitive decline:
  - LBD alone > AD > AD with LBD
- LDB has more rapid cognitive decline
- Worse on TMTB, Story memory

Leverenz, 2008

Decline in heart signal in LBD – request nuclear medicine consult



***Heart Loses Its Nerve**: In MIBG scintigraphy, researchers measure the signal from the heart (circle). It drops off in DLB compared with normal controls and people with AD. The rectangle encloses the reference chest space, the mediastinum. [McKeith et al., 2017; CC4.0.]*

- Now a core feature: iodine-123-metaiodobenzylguanidine (MIBG) myocardial scintigraphy;
- This type of imaging visualizes the amount of postganglionic sympathetic innervation to the heart, which plummets in LBD
- sensitivity and specificity of 69 and 87 percent for distinguishing LBD from AD

LBD biomarkers

- 1 - postganglionic sympathetic innervation to the heart decline in iodine-123-metaiodobenzylguanidine (MIBG) myocardial scintigraphy;

- 2 - reduced dopamine transporter uptake in the basal ganglia in SPECT or PET,

- 3 - polysomnography confirmation of REM sleep without the usual temporary muscle paralysis.

2017: Neurology diagnosis recommendations

- LBD patients respond differently to medications used in AD and PD
- LBD tends to progress and lead to death faster than AD or PD, so a correct diagnosis helps families plan.
- Cholinesterase inhibitors appear to improve LBD patients' cognition & VHs, activities of daily living, and global function
- Avoid prescribing antipsychotics to these patients, as they can have severe adverse reactions.
- Avoid dopaminergic drugs, used widely and effectively in PD, can cause psychosis in LBD patients, though some may tolerate minimal doses.
- L-dopa was generally well tolerated in DLB but produced a significant motor response in only about 30% of patients; concerns of exacerbating neuropsychiatric symptoms.

LBD Clinical Presentation 1

- Progressive NCD
- "One year rule" between onset of NCD and PD sxs:
  - If NCD in 1st year, dx LBD;
  - If NCD later, dx PD;
  - Idiopathic PD takes 5-10 years before NCD develops
- Day to day fluctuations in attention; episodic confusion; easy to tip into sudden delirium
- Changes in arousal (sleep 20-30 hours)
- PD symptoms: axial (head and neck), not tremor

LBD Clinical Presentation 2

- Parkinsonism actually begins with a loss of smell (see Robin Williams)

- REM Behavior Syndrome years before NCD
  - Loss of motor paralysis in REM: move in dreams, physically act out their dreams by kicking, screaming and even harming themselves and others lying next to them); (see **Mike Birbiglia – "**Sleepwalk with me" film)

- RBD is common in LBD; 75% patients act out their dreams while sleeping (compared to AD, 2%), often years before the onset of other symptoms. RBD now is a core clinical feature- of LBD

R. Postuma , Neurology, 2008

LBD Clinical Presentation 3

- People diagnosed with REM sleep disorder are 18% more likely to develop a neurodegenerative disease like NCD or Parkinson within five years of their diagnosis, and 52% more likely after 12 years.

Bizket: REM Sleep Disorder

Neuropsychology of LBD

- Severe visuospatial and visuoconstructional deficits > AD
- Executive and attention deficits > AD
- Severely impaired verbal fluency (both semantic & phonemic)
- Relatively intact memory: poor retrieval rather than rapid forgetting

Memory & VS ability: AD vs. LBD

- Memory deficits precede diagnosable AD by two or more years:
  - Earliest AD symptoms: memory loss with rapid forgetting

- AD: Loss of semantic knowledge measured by tests such as confrontation naming and category fluency occurs early in the course

- Short-term memory tends to be better in LBD, especially with Aricept or Exelon.

- Severe early visuospatial dysfunction is suggestive of LBD

Differences between LBD & AD

- PD motor symptoms are LBD, not AD
  - greater rigidity and fewer tremors;
  - falls more common with LBD.
- Cognitive fluctuations are LBD, not AD.
- LBD: more severe visuospatial, visuoperceptual, and visuoconstructive problems.

Differences between AD and LBD 2

- More men seem to have LBD, while more women are prone to AD.
- Rapid Eye Movement (REM) sleep disorder is more common in LBD
- LBD: more hypersensitive to medications than either AD or PD patients.
  - Anti-psychotics drugs may work or may cause irreversible damage; could be fatal in long term.

Use Aricept for Visual Hallucinations in LBD

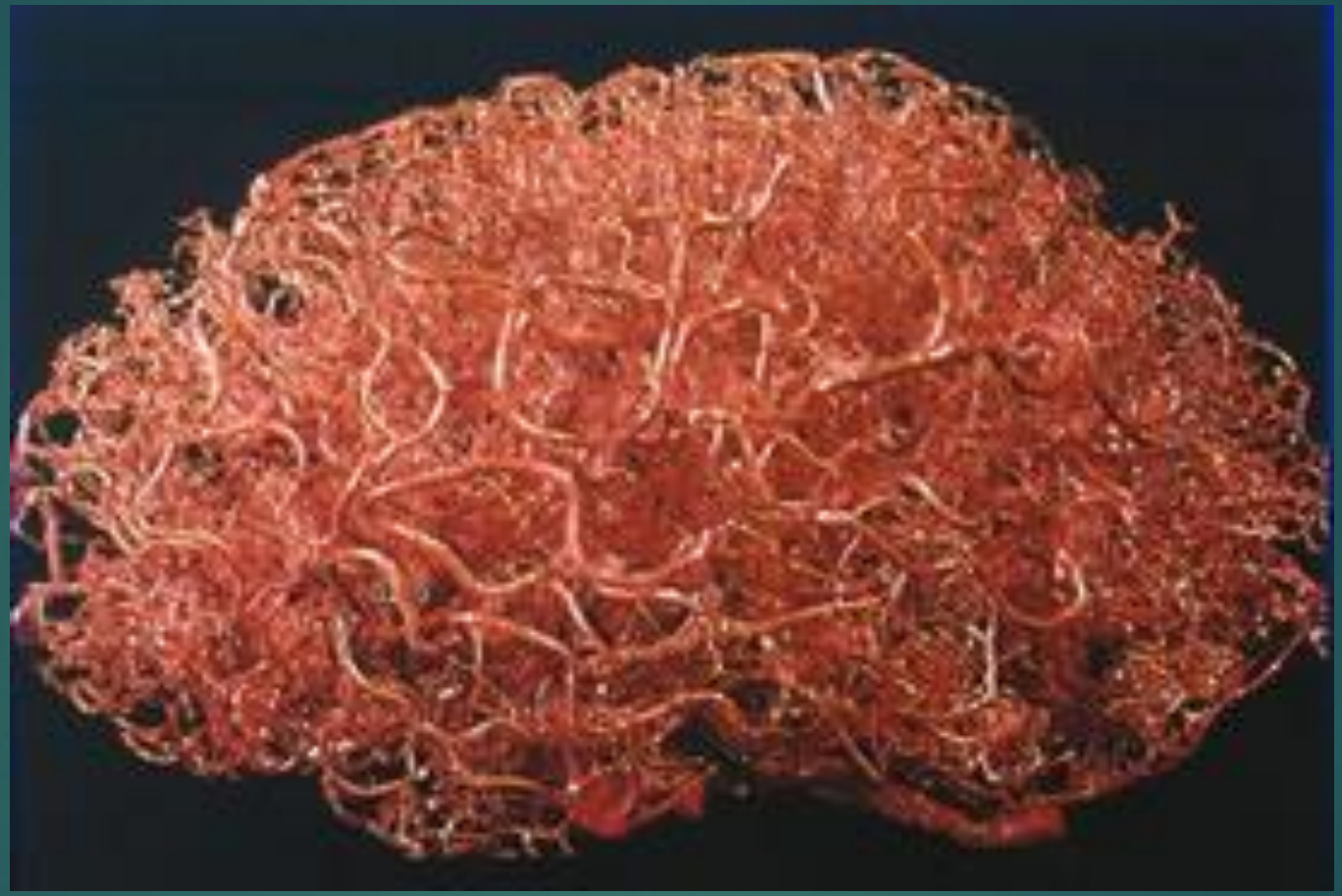
- Acetylcholinesterase inhibitors, such as donepezil (Aricept) and Namenda, are licensed to treat mild to moderate Alzheimer's disease.

- They can also be used to treat people with dementia with Lewy bodies, and can be particularly effective at treating visual hallucinations.

- They work by delaying the breakdown of the neurotransmitter acetylcholine by inhibiting the enzyme acetylcholinesterase.

Vascular NCD

Small and Large Vessel Vascular Supply



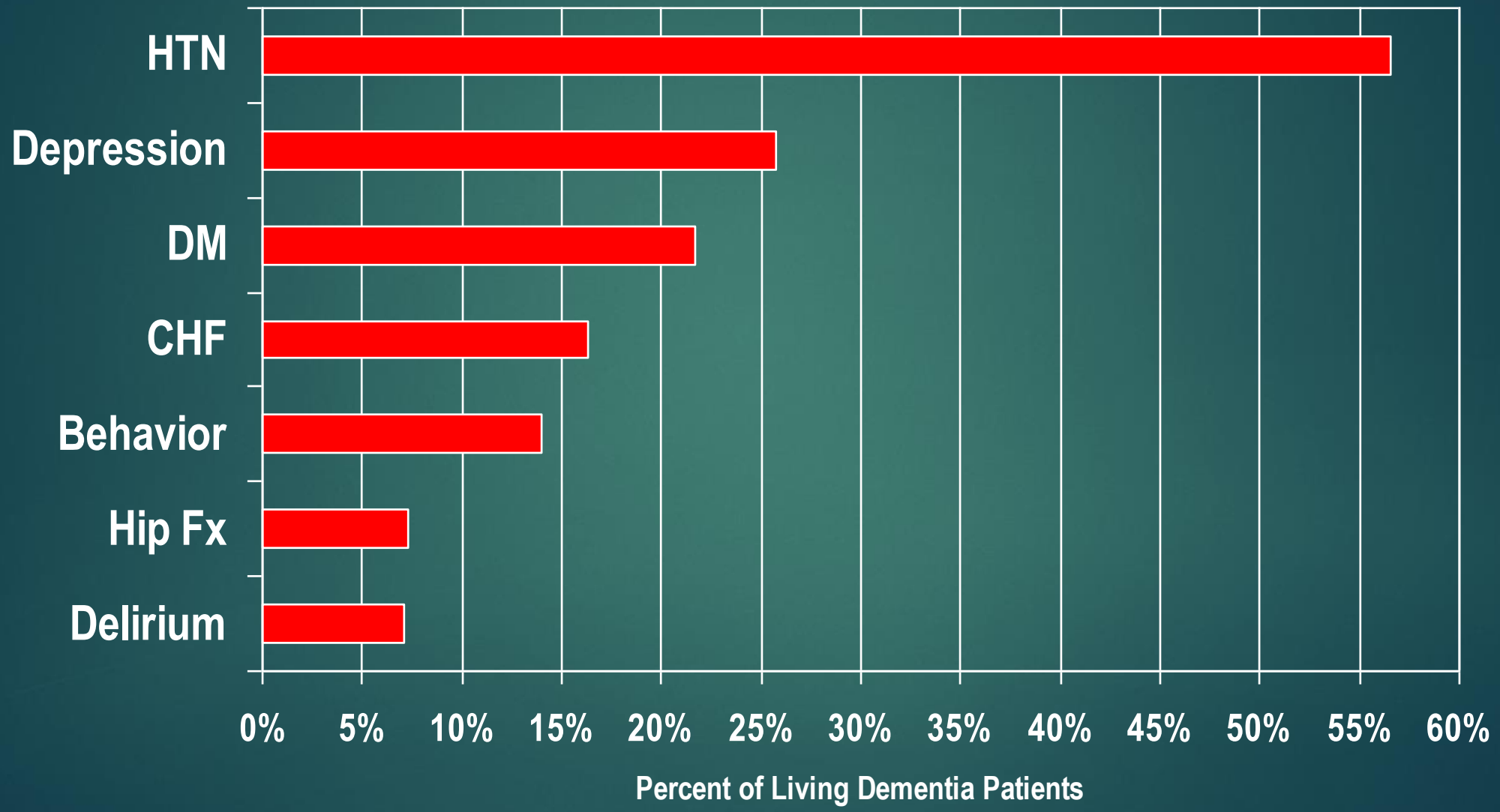
Why what is good for the heart is good for the brain:
400 miles of blood vessels

Zlokovic & Apuzzo, Neurosurgery, 43(4):877-878, 1998.

Vascular NCD

- A. Meet NCD criteria
- B. Clinical features consistent with vascular etiology:
  - Onset of cognitive deficits temporally related to 1 or more CV events
  - Evidence for decline is prominent in complex attention, processing speed, and frontal-executive function
- C. Evidence of the presence of CV disease from history, physical exam, or neuroimaging
- D. Not better explained by other syndrome

Co-Morbidities of NorCal NCD Pts

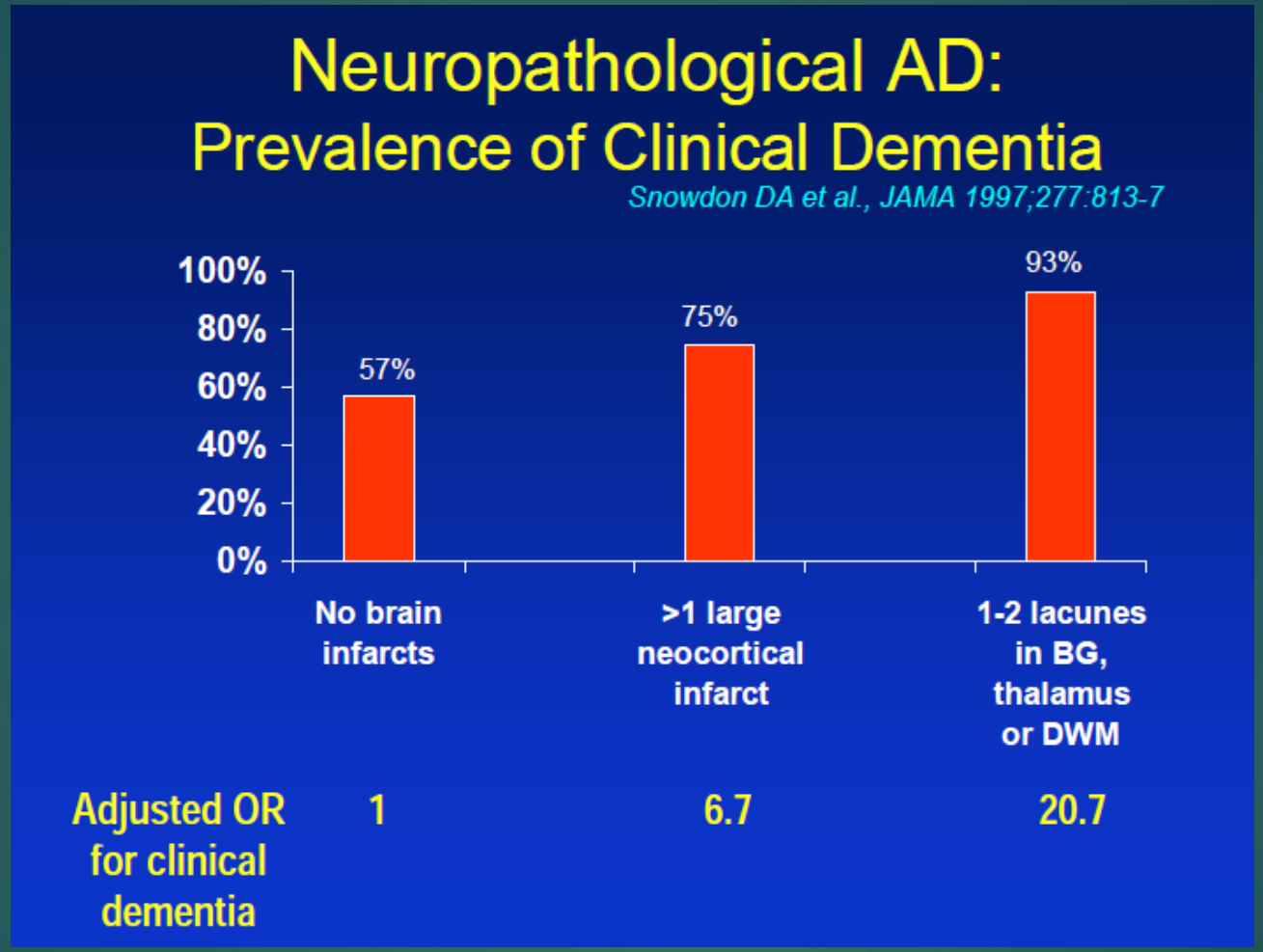


Medicare Data: NCD Comorbidities

Medicare Data for NCDs:

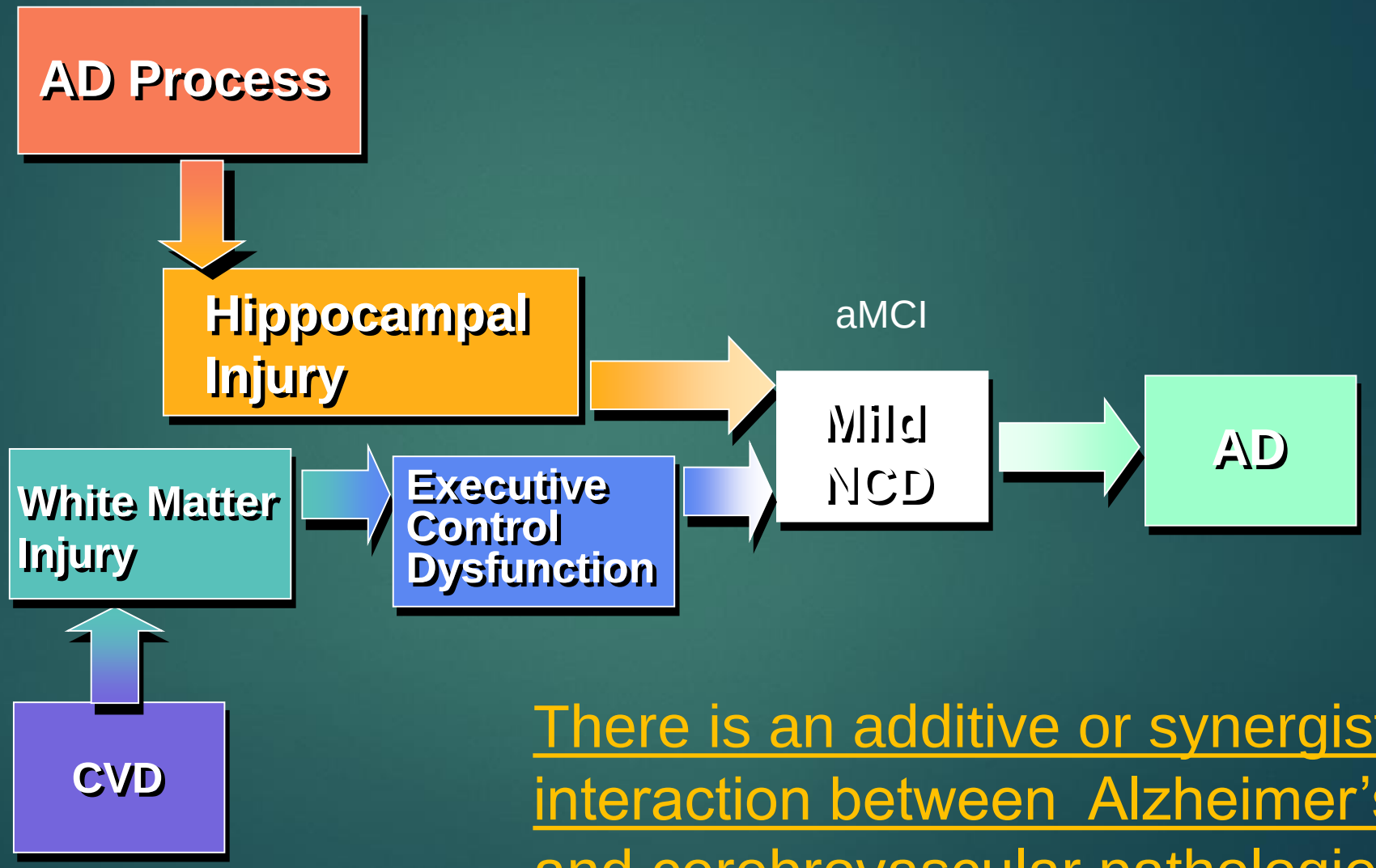
- Hypertension: 60%
- Coronary Heart: 26%
- Diabetes: 23%

Vascular Infarcts: More strokes, more NCD



50 percent of the elderly having pathologic evidence of vascular dementia (infarcts).

Combined Role of AD and CVD in Mild NCD and NCD Risk



There is an additive or synergistic interaction between Alzheimer's disease and cerebrovascular pathologies

Hypertension is the curse of the brain

- Hypertension slowly disables the brain's micro vessels, rendering them unfit to adjust blood flow to suit the brain's needs; reduces vessel autoregulation
- It exposes the brain to hypertension pressing in from the periphery, raising the risk of stroke.
- And it impairs the brain's ability to locally increase perfusion where the brain is most active, leading to cognitive decline.
- Reduced cerebrovascular blood flow is directly related to mortality—it is as if the brain is running out of breath

Concept of NCD

- VD is comorbid with most AD
- Vascular disease is largest risk factor for NCD after age
- The earliest cognitive manifestations of CV disease are changes in executive function
- MMSE systematically biased the literature in favor of the finding of Alzheimer disease and to the exclusion of vascular disorders.

Diagnostic features of VaD

- History of TIAs
- History of vascular risk factors (HTN, CAD, CHF, DM, hyperlipidemia, carotid stenosis, lupus, obesity)
- Two types:
  - Multi-infarct – ischemic (Ox blockage), large vessel infarcts
  - Subcortical white matter disease – white matter lesions, small vessel infarcts (Binswanger's)

Diagnostic features of VaD

- Presence of new gait disturbance, incontinence, speech changes, hemiplegia

- New focal neurological signs/symptoms (exag. deep tendon reflexes, extensor plantar (Babinski) response, pseudobulbar palsy, gait abn's, extremity weakness)

- Ethnicity: 2 x higher rates in African Americans and Hispanics

Meta-analysis: Vascular Mild NCD

- The most common cause of vascular cognitive impairment is cerebral small vessel disease leading to diffuse subcortical white matter lesions.
- The greatest impairment was in processing speed, and the least affected being working memory and visuospatial construction.
- VD MCI show greater deficits in processing speed & executive functioning, while those with nv-MCI exhibited a greater relative deficit in delayed memory.

Brandon P. Vasquez & Konstantine K. Zakzanis, 2014

Subcortical Vascular WM disease

Progressive Subcortical NCD Profile

but no dominant motor symptoms (not PD like)

- EF issues: Difficulty sustaining set; switching difficulty
- Learning and memory is compromised by attention disturbance, is not a pure anterograde amnesia, like AD.
- Mood disturbances are minimal – including depression.

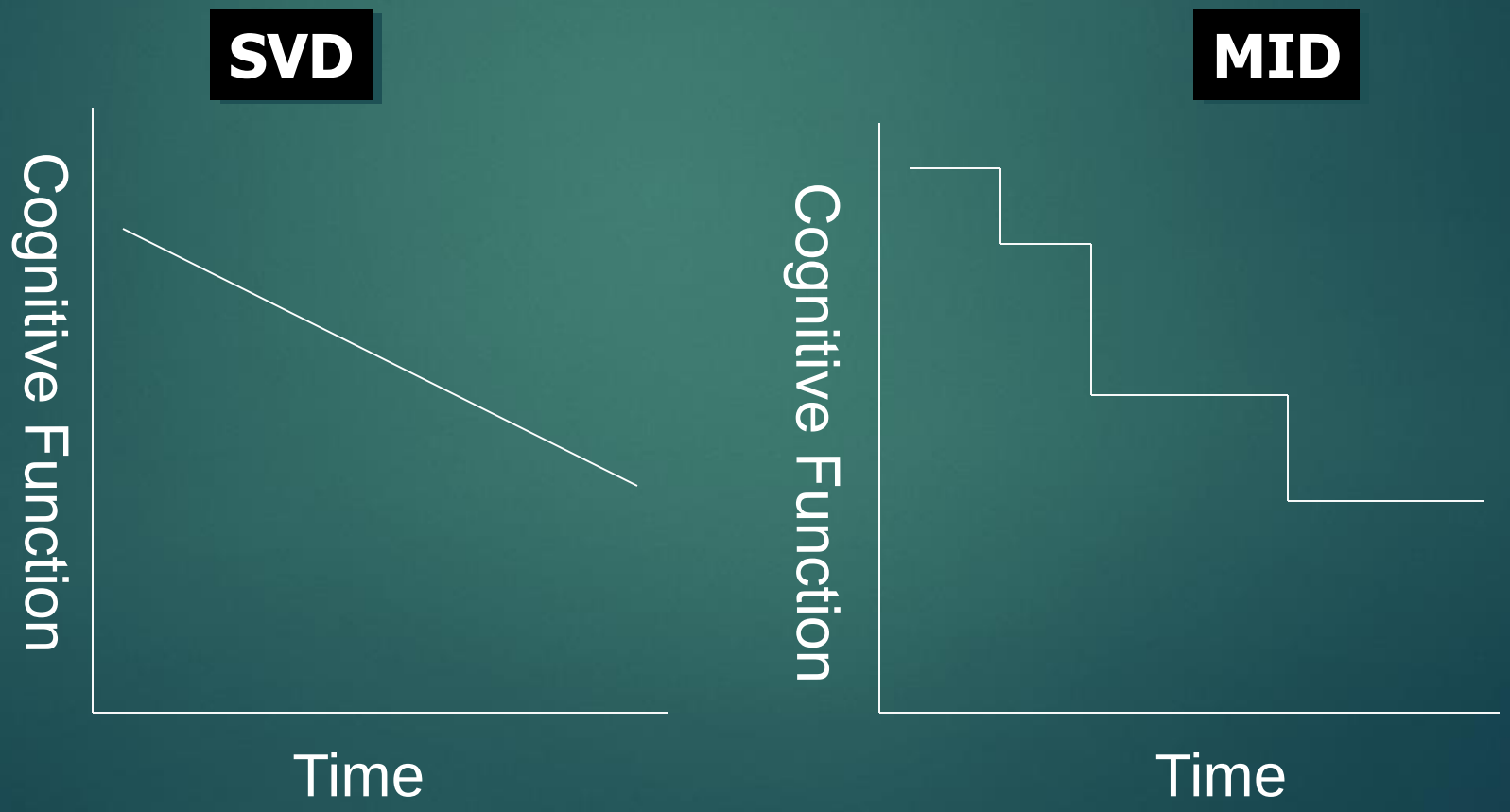
- MRI demonstrates white matter abnormalities and no focal strokes

Multi-Infarct NCD

Cognitively:

- Step-wise decline via strokes
  - Decline occurs with each successive stroke
  - Cognitive abilities typically involve frontal symptoms, but can also include other cognitive difficulties depending on stroke region.
  - MRI demonstrates focal strokes – multiple lacunes within the subcortical (BG) and even cortical regions

Subcortical vs. Multi-Infarct Vascular disease



Neuropsychology of Vascular Dementia

- ** Slowed processing speed
- ** Executive dysfunction
- Memory deficits not necessarily prominent; marked by poor retrieval, normal recognition (subcortical memory pattern)
- Intact confrontational naming
- Intact visuospatial skills
- Relative to AD, VD patients show:
  - poorer verbal fluency,
  - better free recall,
  - fewer intrusion errors
  - better recognition memory.

Cognitive Changes Post-Cardiac Surgery

- Post Cardiac Surgery: Stroke (1%-5%), neurocognitive changes (30-79% at 2 weeks and 24-57% at 6 months), depression, encephalopathy, delirium, and confusion (approximately 10%)
- 53% post-surgical confusion at discharge (delirium); 42% impaired 5 years later (NCD)
- May occur in those patients who would have developed NCD anyway (? genetic risk); In patients undergoing CABG, 20–46% have some degree of preoperative cognitive impairment.
- Causes of POCD post-cardiac surgery are most likely multi-factorial, and could be related to a variety of surgical, anesthetic, and patient factors. Age is major risk.

Newman et al., 2001, NEJM

Frontotemporal Dementia (FTD)

FTD

- A mysterious set of neurodegenerative diseases
- It can start with:
  - theft by a previously law-abiding citizen,
  - sexual misconduct by a hitherto faithful spouse
  - halting speech or a blank stare at a simple sentence,
  - overeating,
  - odd misperceptions of pain or cold
- Frontotemporal dementia (FTD) usually ends in the mute, bed-bound misery of advanced dementia, and death.

The Varieties of FTD

- FTD is an umbrella term for a diverse set of diseases that are all marked by atrophy starting somewhere in the frontal or temporal lobe of the brain, often unilateral.

- But, FTD is heterogeneous at every level—the clinical presentations, the underlying neuropathology, the neural networks that become dysfunctional, and the genes that cause the havoc.

- FTD is a spectrum of diseases that stretches toward parkinsonian symptoms on one end and amyotrophic lateral sclerosis (ALS) on the other.

7 Current FTD subtypes

- bvFTD: behavioral variant FTD
- svPPA: Semantic Progressive Primary Aphasia
- nfvPPA: Nonfluent variant PPA
- lvPPA: Logopenic variant PPA
- FTD-MND: FTD Motor Neuron Disease
- CBS: Corticobasal Syndrome
- PSP: Progressive Supranuclear Palsy

Frontotemporal NCD

- A. NCD criteria met;
- B. Insidious and gradual progression
- C. Either 1 or 2:
  - 1. Behavioral variant
    - A. 3 or more of following behavioral sxs:
      - 1 Behavioral disinhibition
      - 2 Apathy or inertia
      - 3 Loss of sympathy or empathy
      - 4 Perseverative, stereotyped or compulsive/ritualistic behavior
      - 5 Hyperorality and dietary changes
    - B. Prominent decline in social cognition and/or executive abilities

Frontotemporal NCD

- 2. Language variant
  - A. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension

- D. Relative sparing of learning & memory and perceptual-motor function

- E. Not better caused by another syndrome

Frontotemporal NCD

- Probable FT NCD: if either of following is present; otherwise Possible FTNCD
  - 1 Evidence of causative FT NCD genetic mutation, from either family history or genetic testing
  - 2 Evidence of disproportionate frontal and/or temporal lobe involvement from neuroimaging

- Possible FT NCD: if no evidence of genetic mutation, & no neuroimaging

Frontotemporal NCD (FTD)

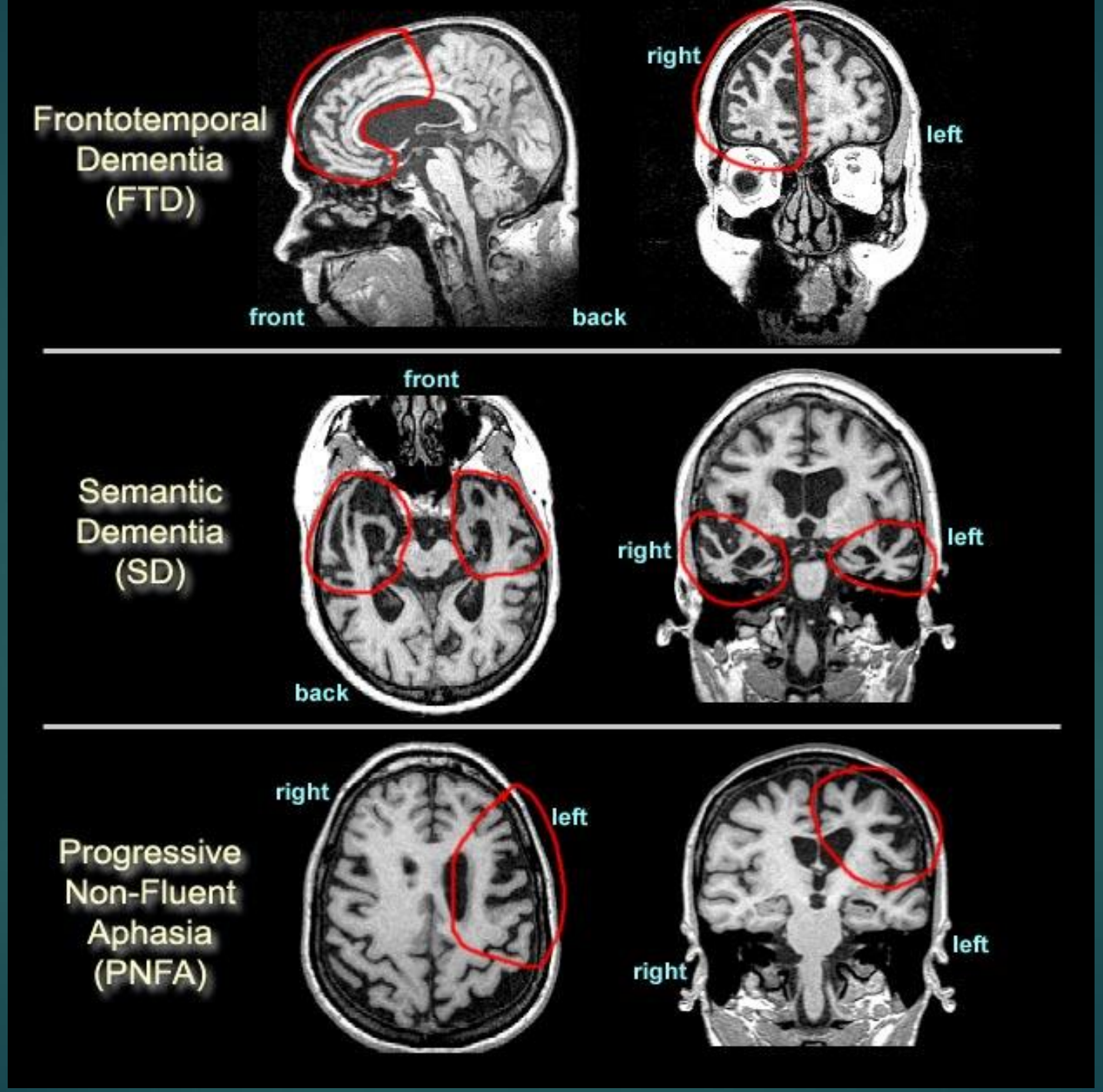
- Prevalence: 4th most common cortical NCD, (10% of NCDs)

- Deficits in behavior and cognition began to show five to 10 years after brain atrophy, a few years prior to the estimated age of onset.

- Pathology: progressive often unilateral, degeneration of:
  - the anterior cingulate (apathy, empathy, beh. initiative),
  - dorsolateral frontal (executive deficits),
  - orbital basal frontal (disinhibition),
  - temporal lobes (language)

  - frontal atrophy & hypoperfusion, 80% gliosis, bilateral amygdala degeneration
  - tau inclusions in tangles
  - Serotonin ↓

Miller B L, Cummings J L, et al., Neurology 41:1374-1382, 1991


Frontotemporal Dementia (FTD)
front
back
right
left
Semantic Dementia (SD)
front
back
right
left
Progressive Non-Fluent Aphasia (PNFA)
right
left
right
left

Prevalence

- FTD affects an estimated 250,000 Americans
- About 40% of patients have a clear-cut family history.
- Mean onset = age 60 +/- 10 years; 50% < 60

Demographics

- Of all FTD pts:
  - bvFTD: 56%
  - Sem var PPA: 19%
  - PNFA: 25%
- 65% male
- FTD+ALS (37% autosomal dominant; 59% family hx)

B. Miller, 2007

Demographics 2

- 15% of FTD develop:
  - MND (motor neuron disease) (amyotrophic lateral sclerosis)(i.e. Stephen Hawkings)
  - PSP (progressive supranuclear palsy),
  - CBS (corticobasal syndrome)

- Survival post dx:
  - FTD – 3.1 years
  - Sem var PPA – 5. 3 years

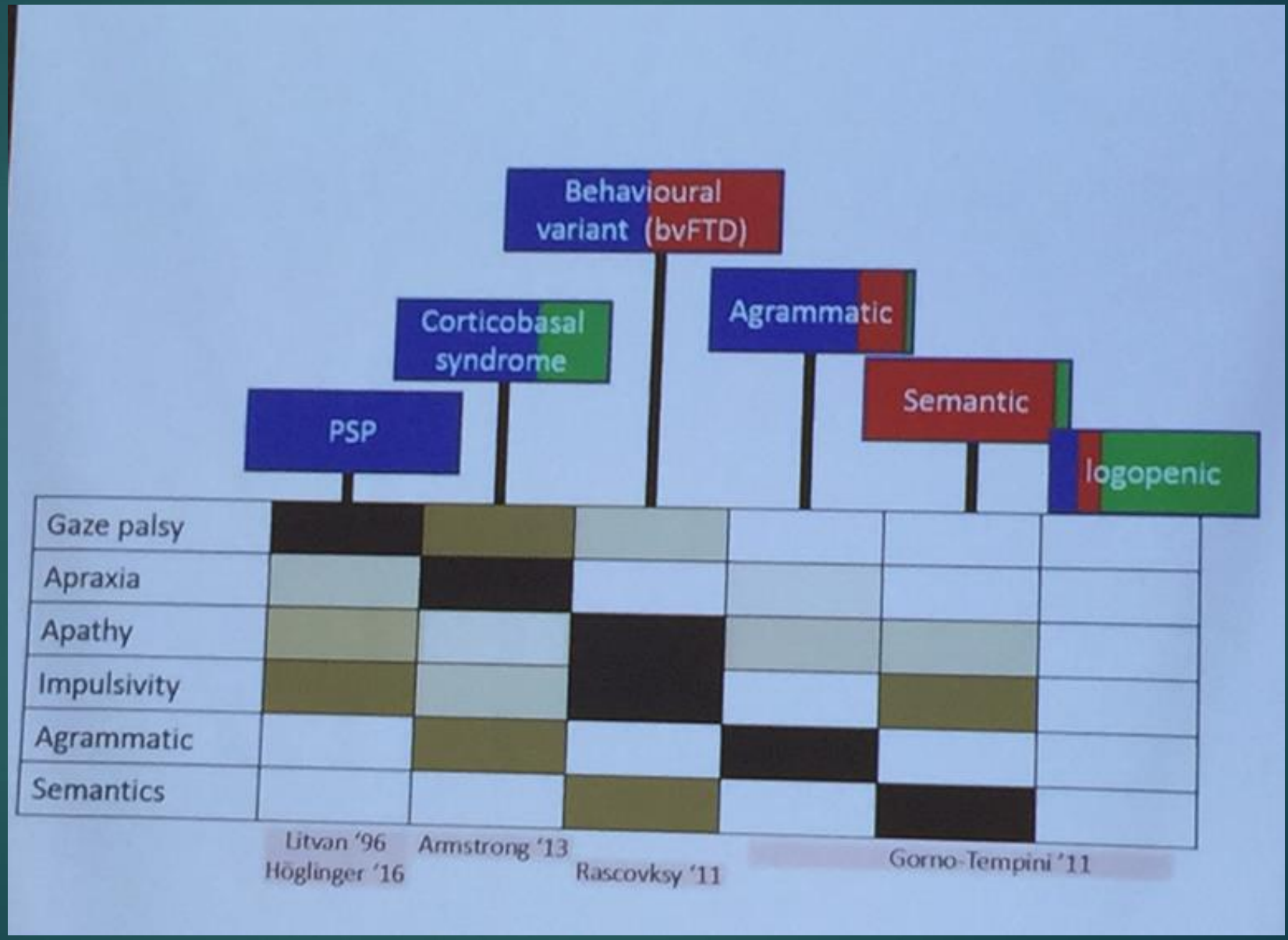
FTD is genetic

- FTD is 50% genetic
- Up to 50 percent of all cases have a family history
- 10 to 30 percent are autosomal-dominant.
- Mutations in the genes for MAPT (tau), progranulin, and C9ORF72 (40%) account for a majority of familial cases
- But more genes continue to be implicated in FTD overall, i.e. VPS13C, Hox

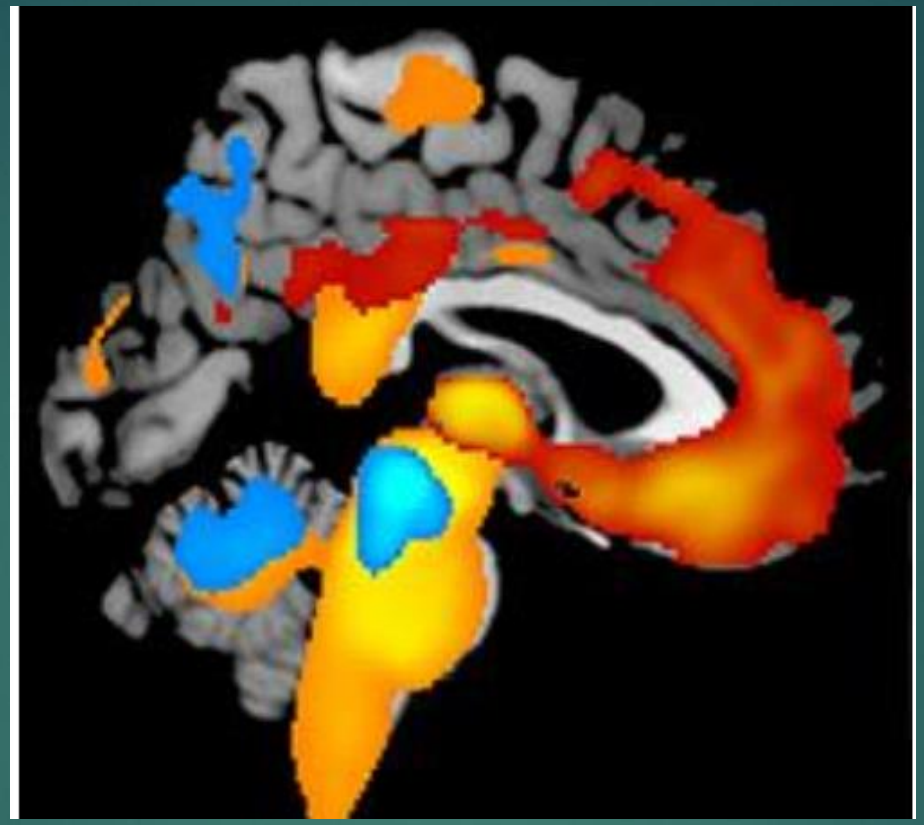
Beyond diagnostic categories toward domains of disease and phenotype

Symptom Overlap

Apathy & Impulsivity common in all



Atrophy Patterns

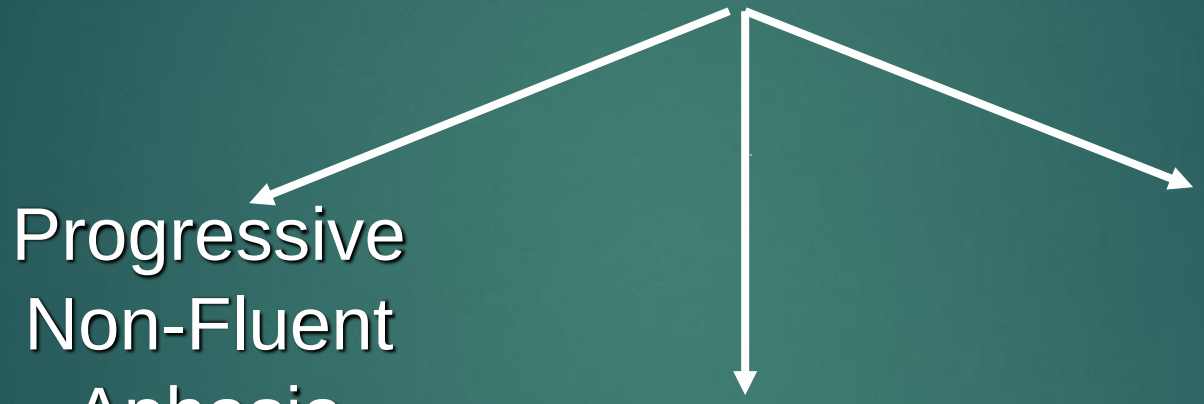


- bvFTD: Red-yellow areas indicate the relative severity of
- PSP - progressive supranuclear palsy: Yellow-orange-blue areas show annual tissue loss in

Misdiagnosis of FTD

- 28% of patients with a neurodegenerative disease received a prior psychiatric diagnosis.
- Depression is the most common psychiatric diagnosis in all groups.
- BvFTD patients received a prior psychiatric diagnosis significantly more often (51%) than patients with Alzheimer's disease (23%), semantic NCD (24%), or progressive nonfluent aphasia (12%)
- Often misdiagnoses as bipolar disorder or schizophrenia

Frontotemporal NCD
Unilateral Localization



Progressive Non-Fluent Aphasia

(nfvPPA)

Social/Executive (bvFTD)

svPPA

Left Frontal

Right Frontal

Left Temporal

Frontal NCD Types

- **Right** Frontal Variant (orbitofrontal):
  - bvFTD: Frontotemporal NCD

- **Left** Frontal/Temporal Variants: Language variants
  - nfvPPA: Primary Progressive Aphasia (Non Fluent)
    (Left Perisylvian Fissure of Frontal)

  - svPPA: Semantic Aphasia (Progressive Fluent)
    (bilateral Temporal Pole & Inferocortex)

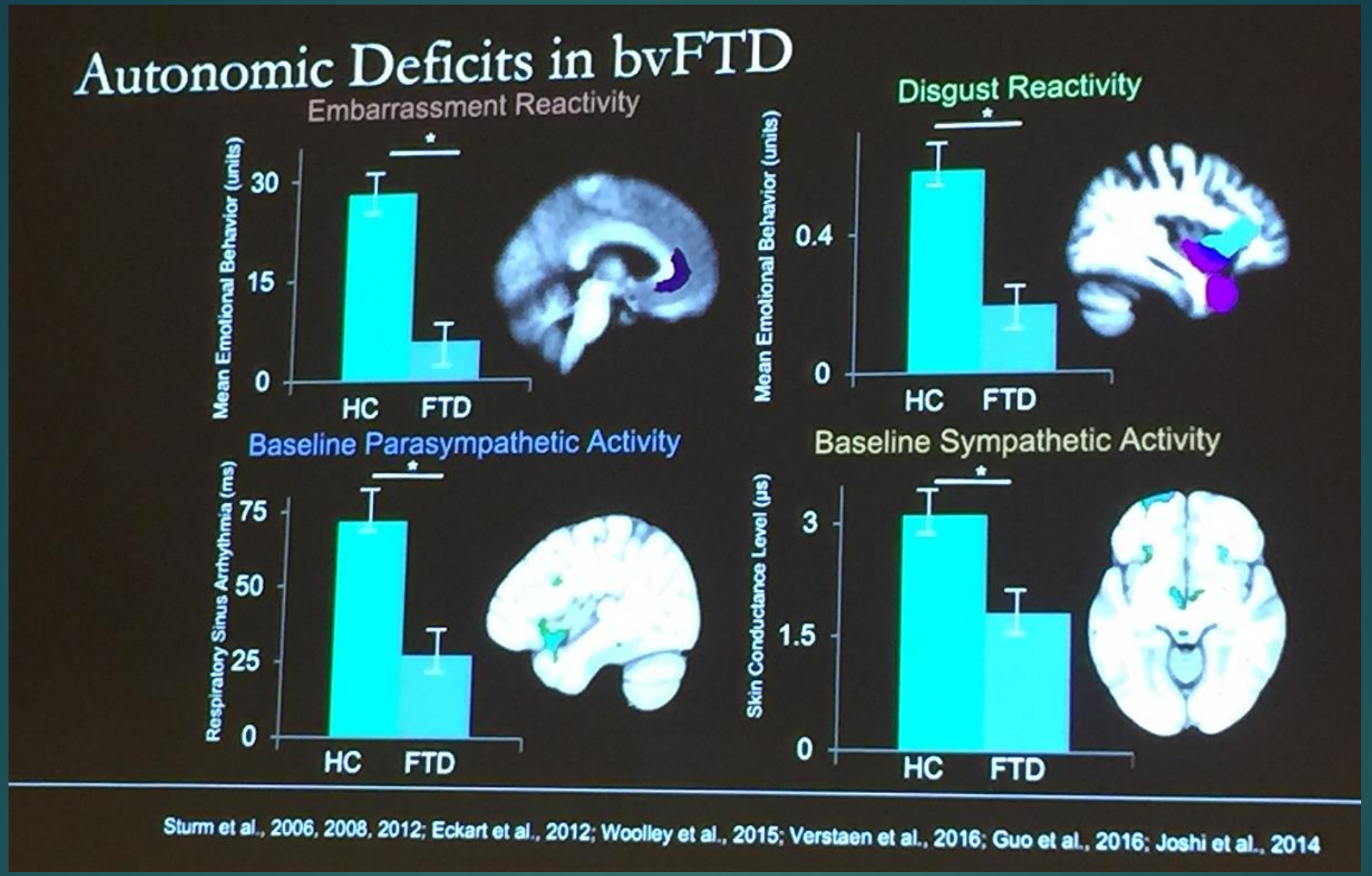
  - lvPPA: Logopenic progressive aphasia (parietal)

bvFTD: A Social Disease

- Loss of empathy
- Inappropriate touch, familiarity
- 50% arrested or do antisocial behavior
- Silly antisocial: take off clothes, urinate in public
- At work: Embezzlement, insults
- Compulsions: need to touch, shoplift, counting ants
- Alienation from family
- Divorce
- Legal & financial problems
- Addiction

Social deficits in FTD

- Wear slippers with fancy evening clothes
- Ordering 3 different dinners because they all taste good
- Walking into traffic without concern
- Spending $700T on credit cards and not know what you spent it on
- Void of emotions
- Current moment is all important
- Changes in a person’s sense of humor may be an early warning sign of FTD
- No embarrassment (ACC↓↓)



Autonomic response decline: embarrassment ↓↓, disgust ↓↓,
Parasympathetic activity ↓↓
R anterior, insula, OFC ↓↓

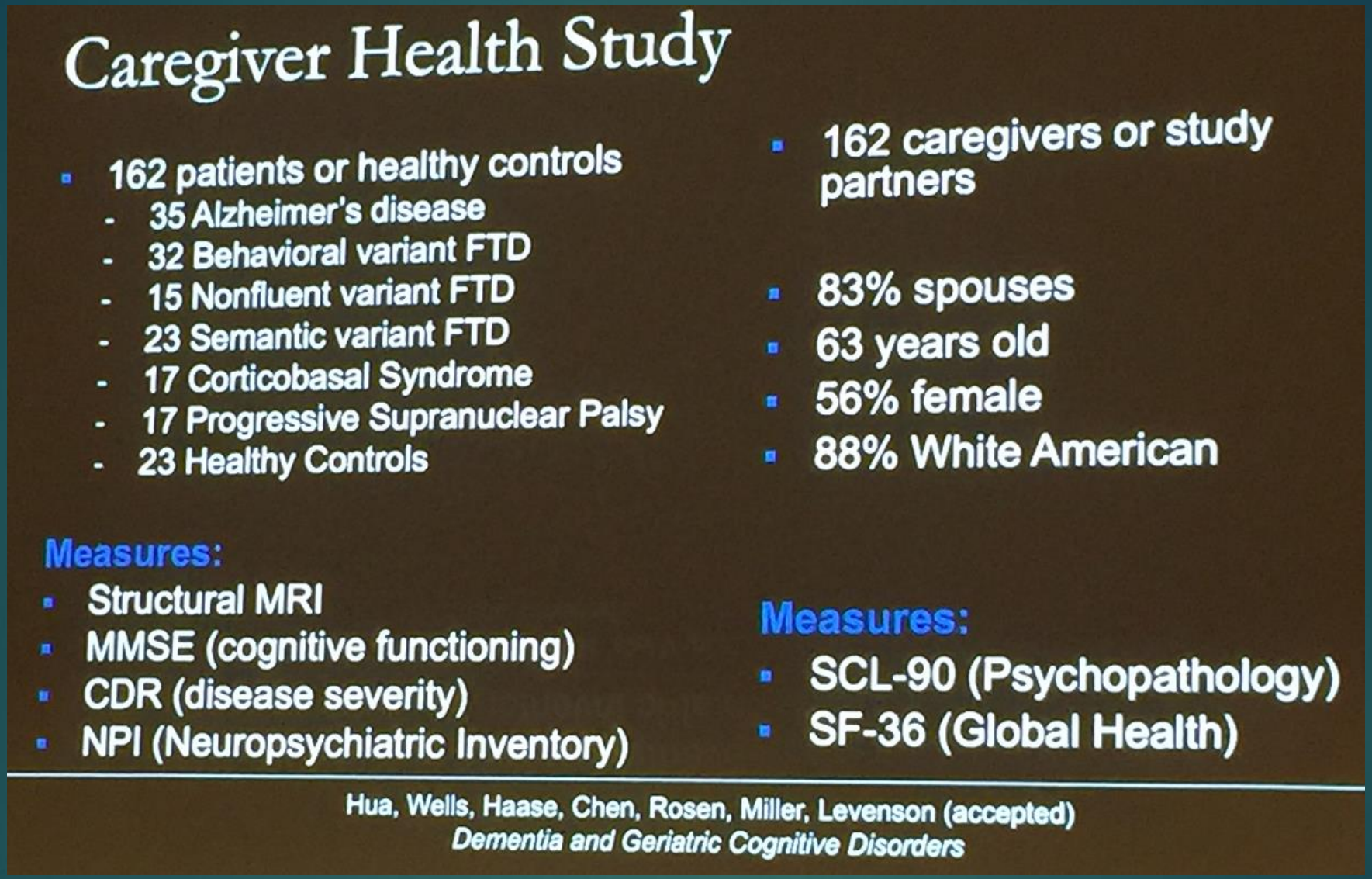
Relationship Turmoil and Empathy in FTD

- Marital dissolution and infidelity significantly greater in the bvFTD group than nfvPPA, svPPA, CBS, PSP and AD

- Across all patients, empathy loss was associated with marital dissolution

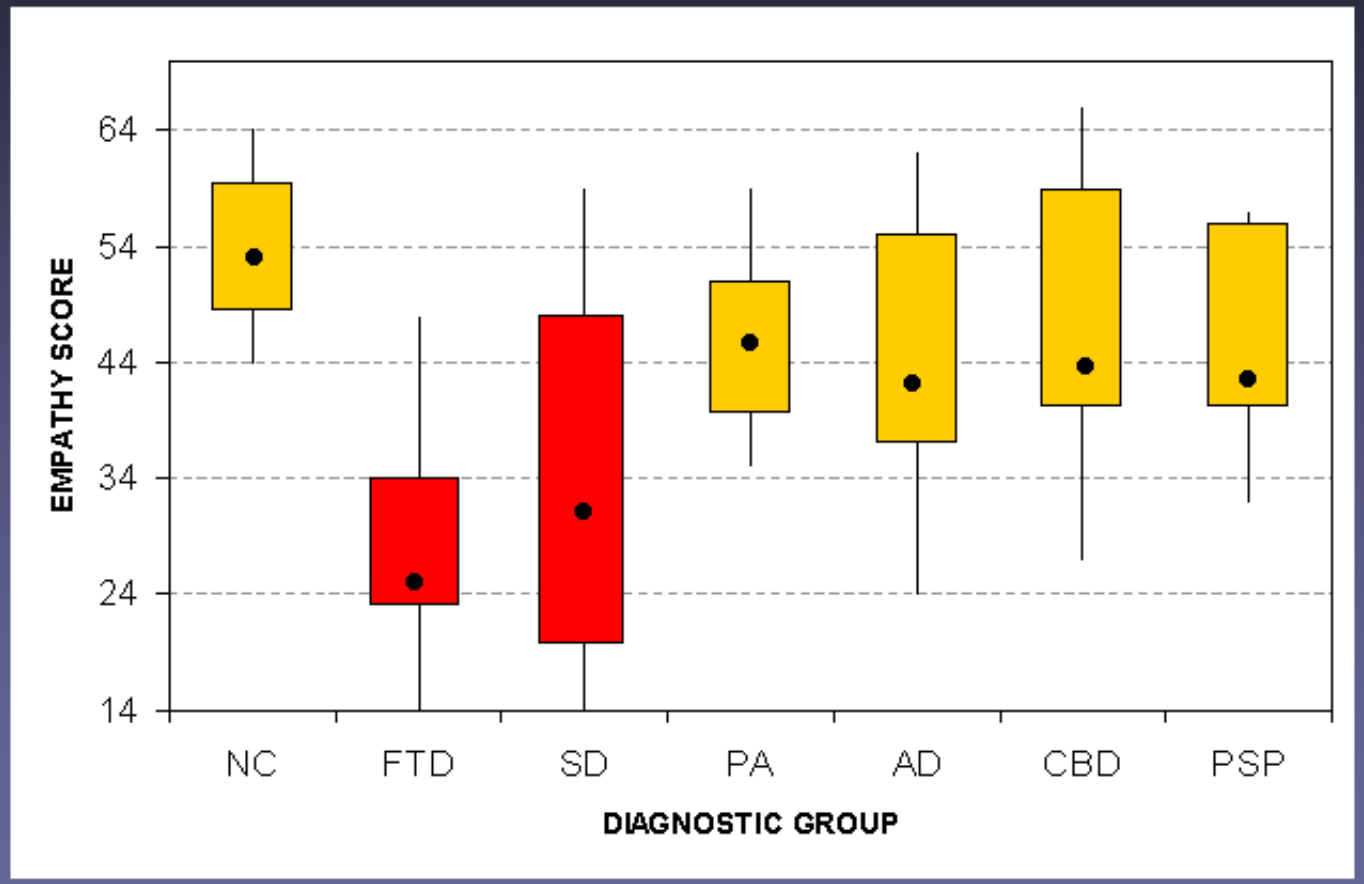
- bvFTD patients who experienced marital dissolution or infidelity had significantly lower empathy scores than those who did not
- Right anterior frontal atrophy: Divorce!

Takeda & Perry et al, in preparation



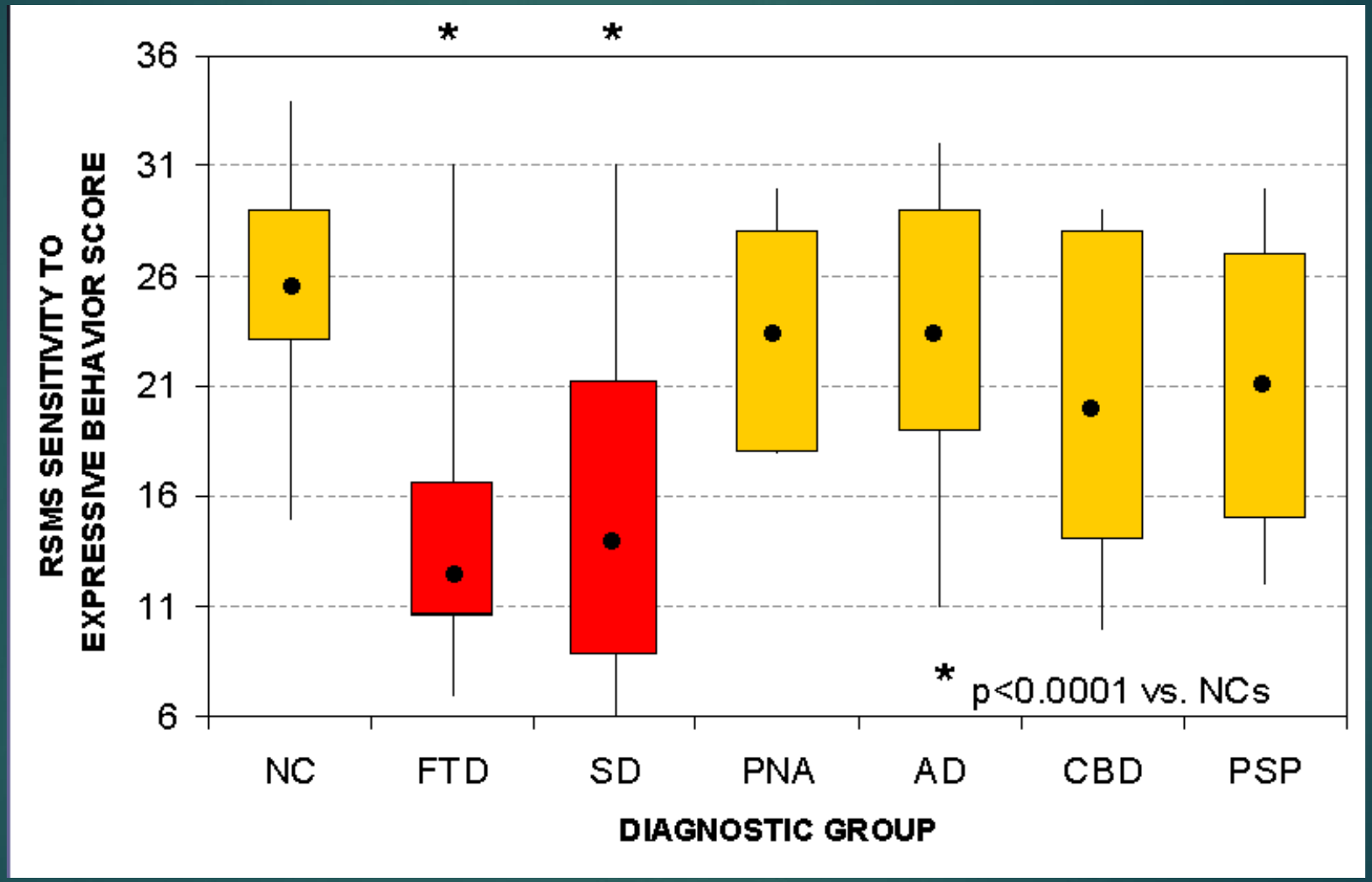
Caregiver psych. burden predicted by bvFTD anatomy in patient;
Lower empathy in ND pts associated with greater depression in caregivers

Measuring social cognition: empathy



(Rankin et al., Brain, 2006)

Self Monitoring Scale

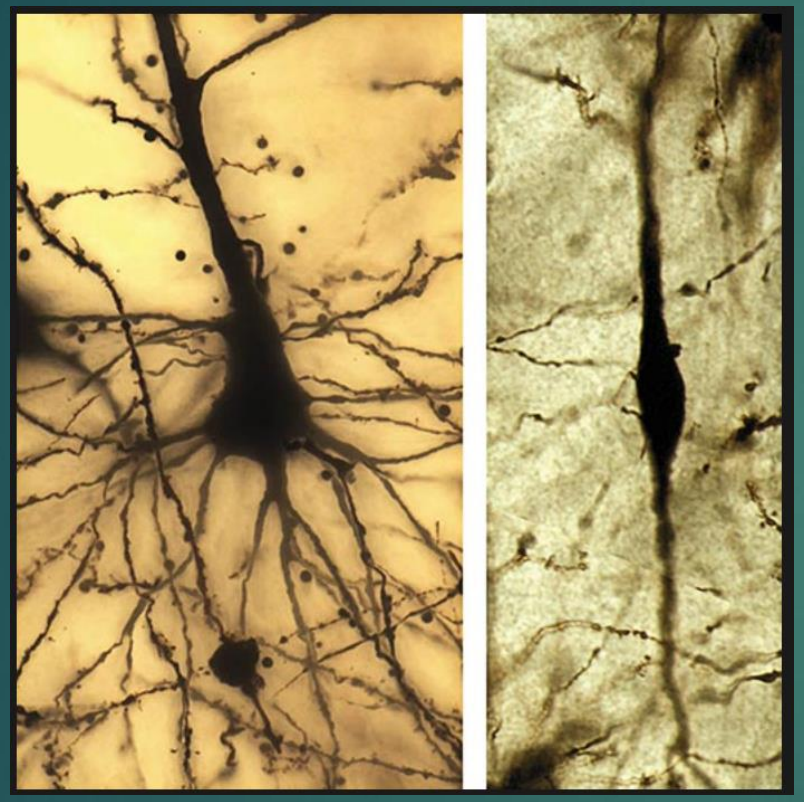


Frontal Temporal NCD

- All FTD phenomena share:
  - Presenile presentation
  - Incipient course of degeneration of the frontotemporal lobes
  - Normal EEG
  - No pronounced white matter alterations

B. Miller, 2007; Seeley, 2008

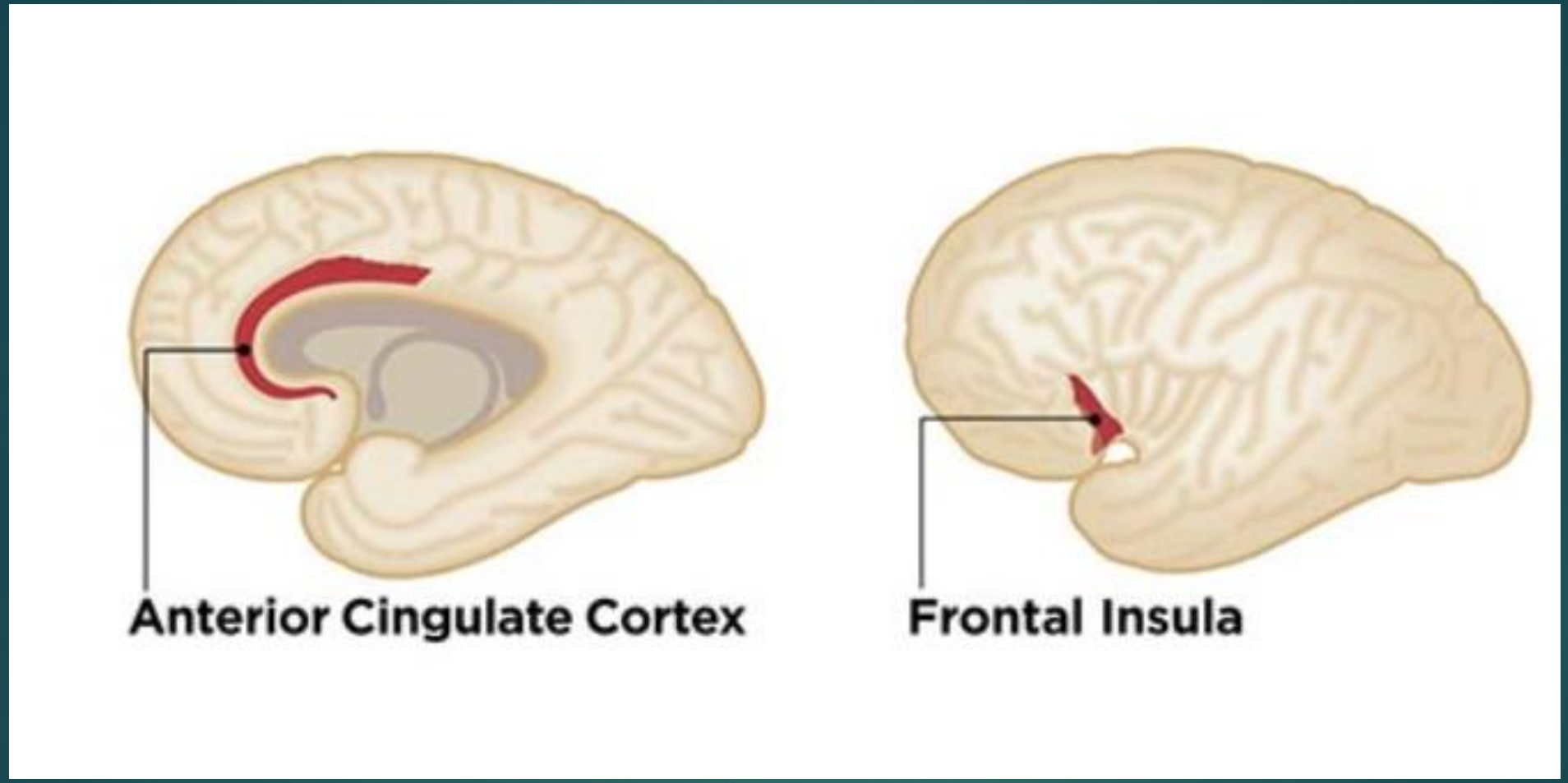
Von Economo Neurons:
Brain Cells for Socializing?



A focal concentration of VENs in ACC and frontal insula (FI) distinguishes large-brained, highly social mammals (primates, elephants, cetaceans) from other mammalian species.

(Allman et al., 2010; Hakeem et al., 2009; Hof and Van der Gucht 2007; Nimchinsky et al., 1999; Rose 1928)

Location of VENS: ACC & FI

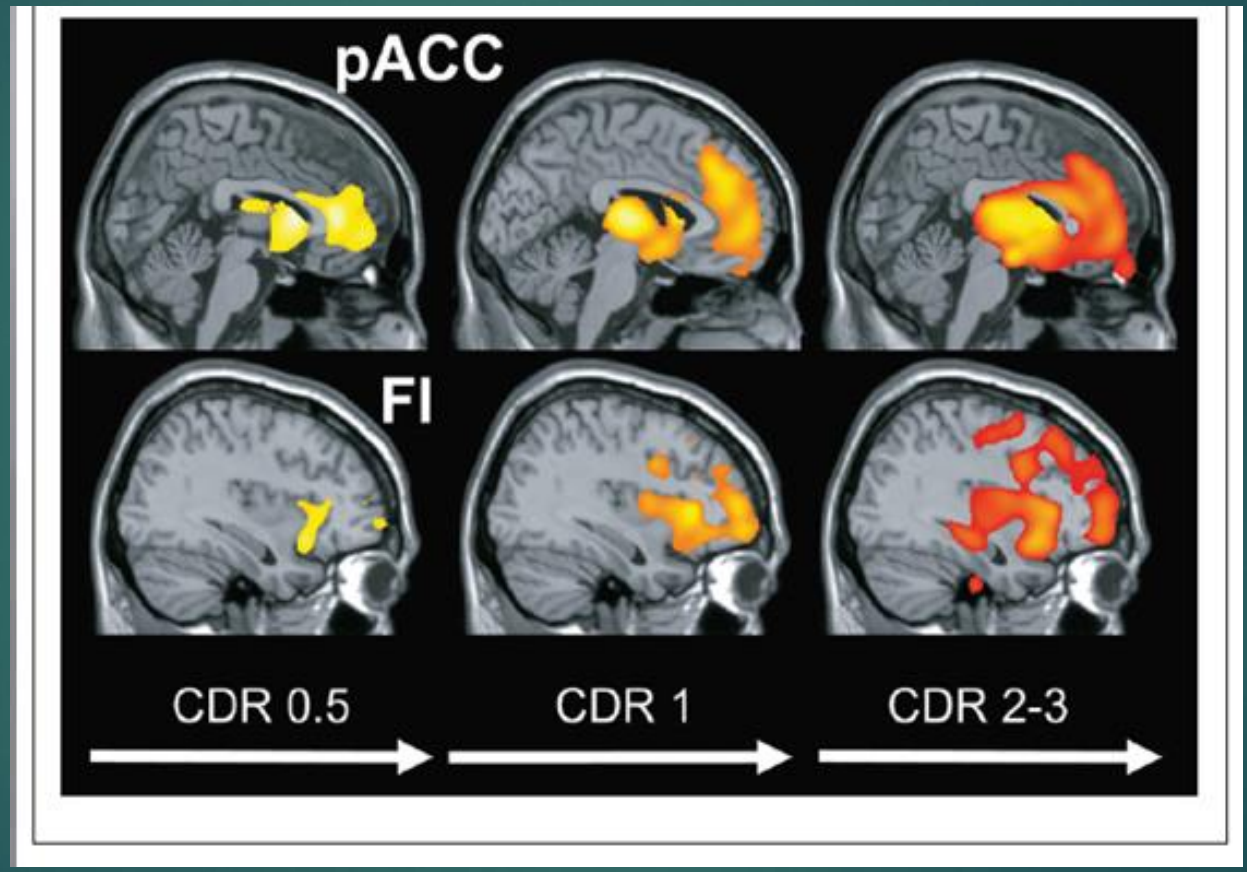


The FI features the other layer 5 neuron, the fork cell, which is scarcely seen in ACC.

Location of FTD degeneration

- Von Economo & Fork neurons are primary site of degeneration in pACC and frontal Insula
- FTD: 70 percent of VENs destroyed
- VEN & Fork neuron degeneration predicts overall behavioral symptom severity in FTD & NPI (Neuropsychiatric Inventory) impulsivity
- More R than L

bvFTD degeneration: (emotional) Salience Network (Right pACC and FI)



W. Seeley, J. Zhou, and E. Kim, 2011

Pain & Temperature & Insula

- FTD respond to music, humor, art, and even sarcasm, in an off manner.
- Early abnormalities in their ability to feel or process pain or changes in temperature: All patients with disturbed temperature or pain awareness had atrophy in their right posterior insula
- People with semantic dementia tended to have exaggerated responses, often complaining of cold or pain, for example.
- bvFTD pts tended to have dulled responses

Sarcasm & Reading Emotions ↓↓

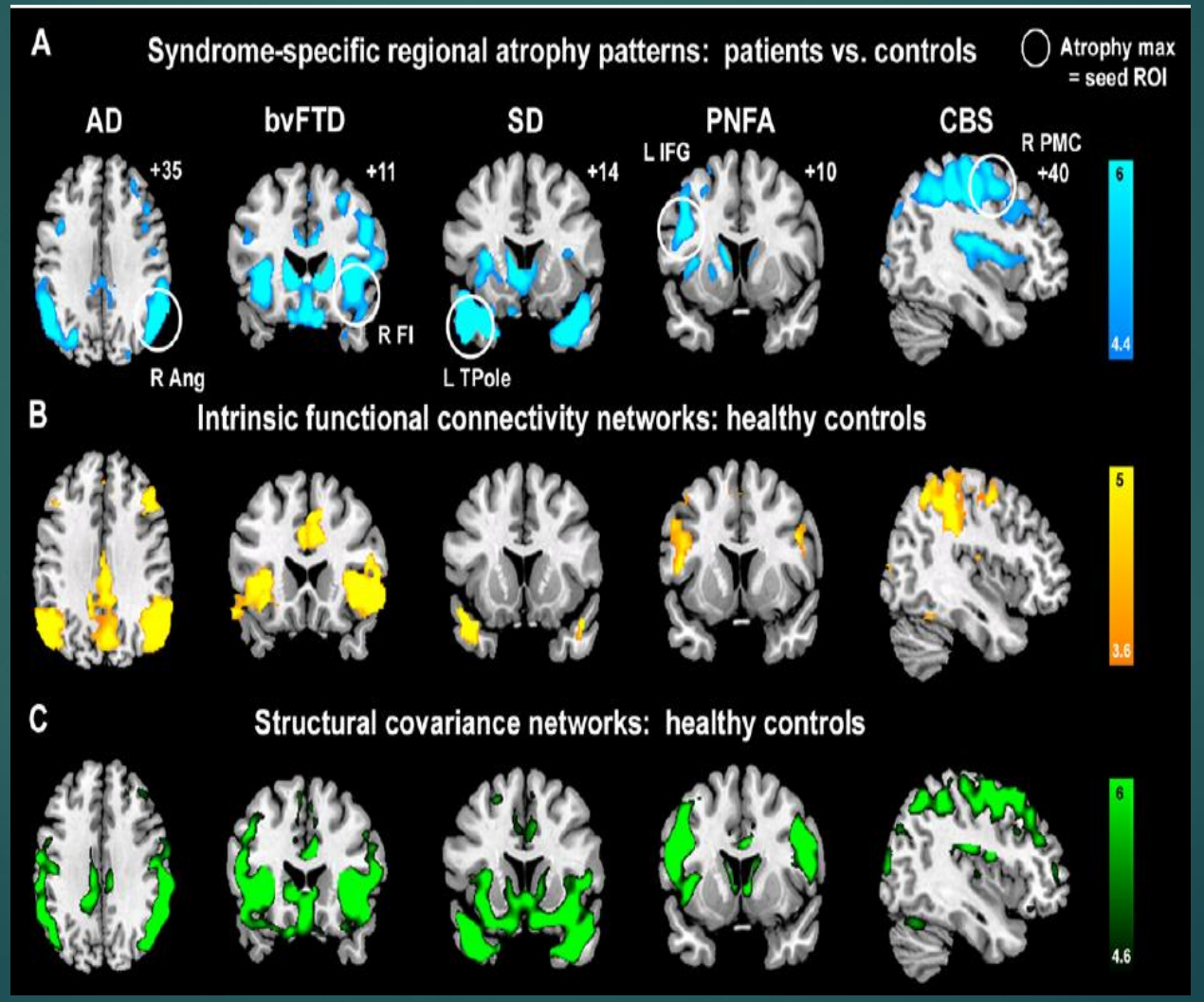
- A defunct “sarcasm radar” correlated with decreased integrity of the uncinate fasciculus, a white-matter tract that connects regions of the limbic system to those in the cortex.

- A patient’s inability to read emotions in others correlated with an erosion of white-matter tracts emanating from the thalamus and the fornix.

AD & 4 FTD+: Diagnosis by Syndrome-Specific Regional Atrophy Patterns

Atrophy location

Normals



1st & 2nd Networks: SN and DMN

- Salience Network (FI & dorsalACC); correlates with anxiety
- DMN inversely related to SN: lesion of either one affects other
- AD decreases DMN & increases SN connectivity (tight connectivity = impairment)
- The right Salience Network targeted in bvFTD: linked to emotional salience processing capacities; lost in early bvFTD

SN and DMN Networks

- Loss of contextual appropriateness of a behavior
- Know social norms, but can’t follow them; acquired sociopathy, social dysdecorum
  - Pick nose publicly, ask age, massage in church, inappropriate jokes, tell end of movie, tell you are fat

3rd Network: semantic variant Progressive Primary Aphasia

- Semantic var PPA affects left semantic network; shows progressive atrophy in early-stage PPA language disorder

- Loss of what things are: loss of word and object meaning, i.e. what is a cat

4th Network: PNFA – Progressive nonfluent aphasia

- Nonfluent, effortful, and agrammatic speech
- The PNFA-targeted left language network
- Language and motor systems that enable speech fluency

5th Network: CBS – Corticobasal Syndrome

- Prominent, asymmetric sensorimotor impairment, with akinesia, rigidity, apraxia, and cortical sensory loss or other cortical cognitive deficits

- CBS (Corticobasal Syndrome): prominent skeletal and ocular motor abnormalities

Early FTD symptoms

- FTD starts with behavioral decline long before NP/EF decline
- Early bvFTD affects social ability/Salience Network:
  - Insula, Anterior Cingulate, VM Orbital Frontal, Frontal Pole
- But not DLPF (until much later); NP tests look normal in early bvFTD
- Become socially ostracized
- Loss of facial recognition

FTD Syndromes Progression: Similar end

- In most patients, first symptoms involved semantics, behavior, or both.
  - Semantic loss begins with anomia, word-finding difficulties, and repetitive speech,
  - Early behavioral syndrome is characterized by emotional distance, irritability, and disruption of physiologic drives (sleep, appetite, libido).
  - After an average of 3 years, patients also develop whichever of the two initial syndromes--semantic or behavioral--that they lacked at onset.

(Rascovsky et al., 2011; Khan et al., 2012).

FTD Common Features

- Onset before age 65 (35-70)
- Positive family history of similar disorder in 1st degree relative in 50%
- Show up in Psychiatry not medicine; decline in social conduct; most difficult for families
- Presentation of a progressive language or behavioral disorder
- No amnesia or marked visuospatial deficit
- Later alteration in attention, initiation, executive functioning
- Often anatomically asymmetrical
- Apathy, change in eating habits, and disinhibition are great distinguishing factors between psychiatric disease and bvFTD

FTD Neuropsych Profile

- F.1. Deficits in executive tasks eventually

- Patients with bvFTD often present with deficits in executive function. Demonstrate cognitive impairment on at least one standardized test of executive ability (at or below the 5th percentile).

- May perform within normal limits on traditional executive function tests (e.g. Wisconsin Card Sorting Test, Stroop), but they consistently fail verbal and non-verbal generation tasks,

FTD NP Profile

- F.2. Relative sparing of episodic memory
  - Preservation of episodic memory relative to executive dysfunction;
    - observed in both verbal and non-verbal domains,
    - most evident when memory tests lack a heavy retrieval or executive burden (e.g. long list of words, reproduction of complex figures).
- F.3. Relative sparing of visuospatial skills
  - retain the ability to navigate their environment, copy simple and complex line drawings, assemble blocks and judge spatial positions until very late in their disease .
  - When evaluating patients with known executive impairments, care should be taken to avoid complex constructional tasks with heavy executive demands.

Functional Decline

- B. Exhibits significant functional decline
  - Patients with bvFTD typically present with moderate to severe disability, even at early stages of the disease.
  - Even though formal neuropsychological testing may reveal little cognitive difficulty, these patients cannot maintain gainful employment or live independently.

Evidence

- C. Imaging & genetic results consistent with bvFTD
  - Frontal and/or anterior temporal atrophy on MRI or CT
  - Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT
  - Autosomal dominant bvFTD may be caused by genetic mutations in several genes, including
    - microtubule-associated protein tau (MAPT),
    - charged multi-vesicular body protein 2B (CHMP2B),
    - valosin-containing protein (VCP)
    - progranulin (PGRN).

Sxs Progression

- bvFTD: addictive behaviors, personality change (submissive or disagreeable), decrease concern for others, overeating, apathy

- svPPA:
  - Left sided: word finding (often names)
  - Right sided: recognition of facial emotion, familiar faces, empathy decreased

FTD and Overeating

- Compulsively binged/carbo loading, consuming large quantities of food after reporting appropriate satiety.

- The **overeating** patients with FTD have significantly more atrophy in the right ventral insula, striatum, and anterior orbitofrontal

FTD vs. Alzheimer's

Atrophy	Specific	Diffuse
Apraxia	Late	Early
Personality Change	Marked, Early **	Subtle
Memory ↓↓	Late	Early **
ACHase Inhibitors	Little Response ?	Good Early Response
Inclusions	Pick Inclusion bodies	Neuritic Plaques & Neurofibrillary Tangles

Proportion of First Symptoms

Behavior	62%
Memory	11%
Language	12%
Executive	11%
Motor	4%

Use of Profanity in FTD on FAS letter fluency test

- Words produced during FAS letter fluency testing were reviewed, and instances of the use of “fuck,” “ass,” and “shit” and other words felt to be inappropriate were sought.

- 19% patients with FTD generated the word “fuck” during the “F” trial as opposed to none of 38 patients with AD

- Patients who said “fuck” had diagnoses of either behavioral variant FTD (3/15), progressive nonfluent aphasia (2/8), or semantic variant PPA (1/3).

Ringman, et al., 2010

Neuropsychology of FTD

- Memory: semantic ↓, intrusions & false + ↑
- Attention: ↓
- Executive: ↓
- Boone: unilateral Right vs. Left FTD (82% asymmetry):

  Right ↓: emotional klg ↓, PIQ ↓,
  Design Fluency ↓, WCST ↓,
  Facial emotion. ↓

  Left ↓ : VIQ ↓, FAS ↓, BNT ↓, Stroop ↓

Treatment of FTD

- No drugs approved specifically for FTLD exist.
- Rather, some patients with behavioral symptoms take antidepressants with modest success
- Patients with parkinsonian symptoms often are prescribed levodopa, but typically do not respond to it.

Criminality in NCDs

- 2397 NCD patients: 8.5% had a history of criminal behavior that emerged during their illness. Of the major diagnostic groups:
  - 8% with AD, 37% with bvFTD,
  - 27% with semantic variant of primary progressive aphasia,
  - 20% with Huntington disease exhibited criminal behavior.

- 14% of patients with bvFTD were statistically significantly more likely to present with criminal behavior compared with 2% of patients with AD; 6.4% were more likely to exhibit violence vs 2% of patients with AD

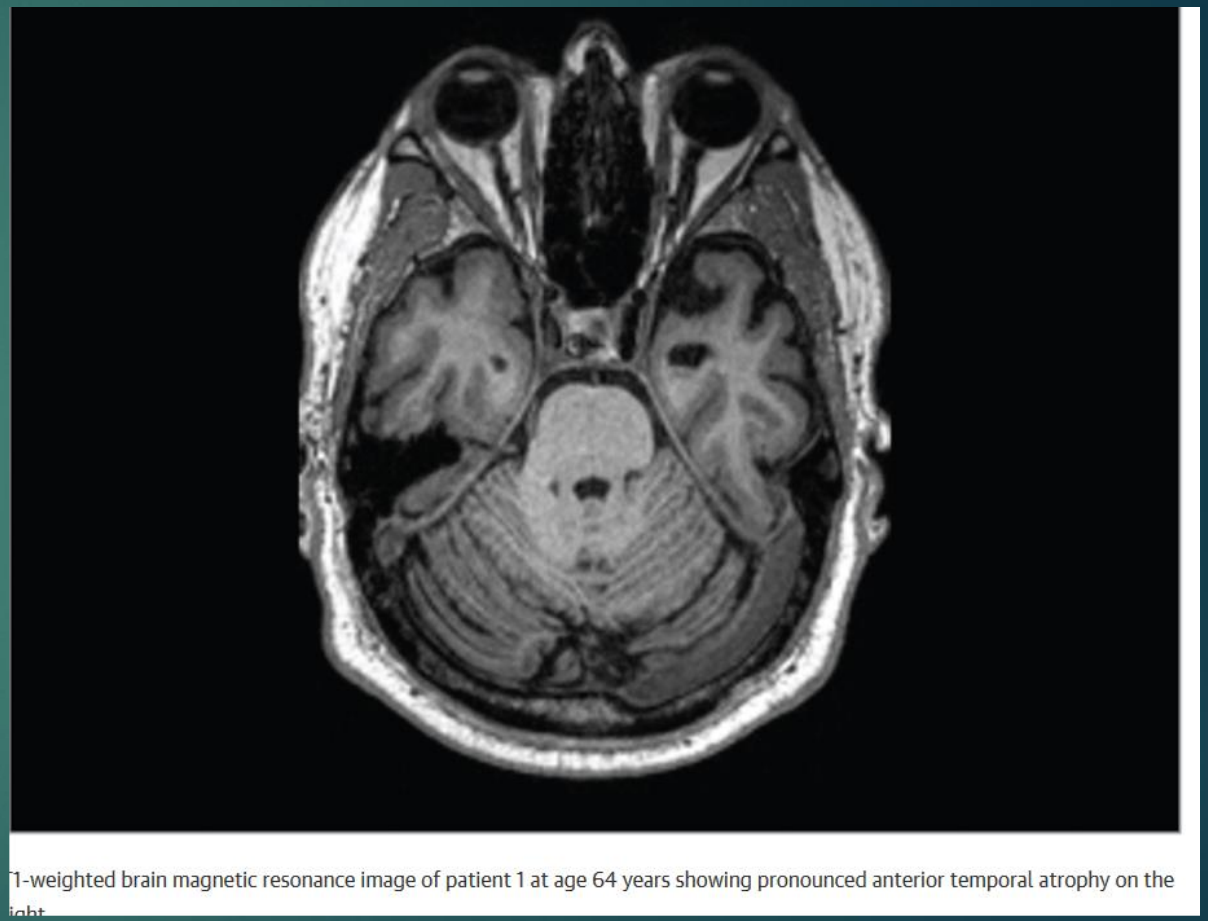
Madeleine Liljegren, et al., 2015

Criminality

- Common manifestations of criminal behavior in the bvFTD group
  - bvFTD: theft, traffic violations, sexual advances, trespassing, and public urination
  - AD: commonly committed traffic violations, often related to cognitive impairment.

- The appearance of new-onset criminal behavior in an adult should elicit a search for frontal and anterior temporal brain disease and for dementing disorders.

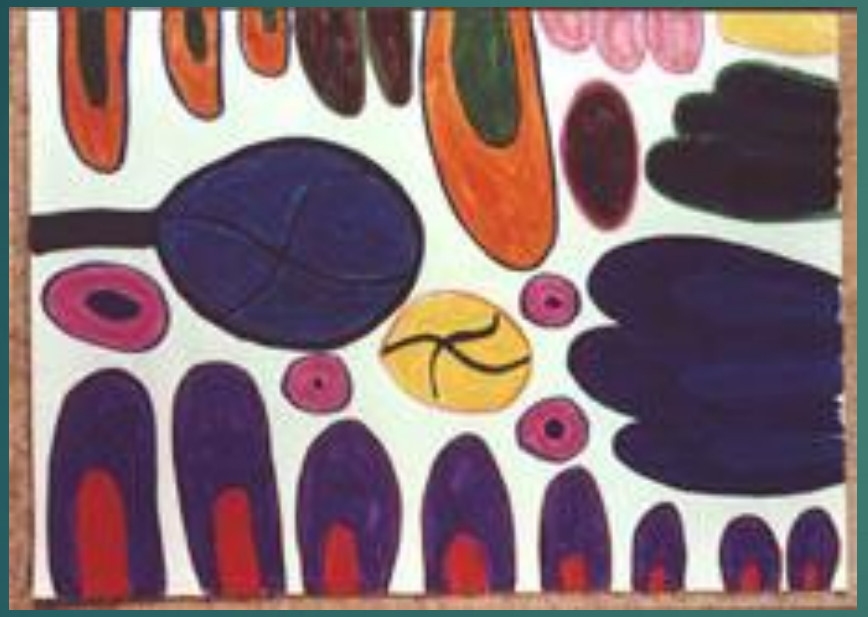
Artistic flowering: patients with FTD who experience a sudden onset increase in artistic creativity



T1-weighted brain magnetic resonance image of patient 1 at age 64 years showing pronounced anterior temporal atrophy on the right

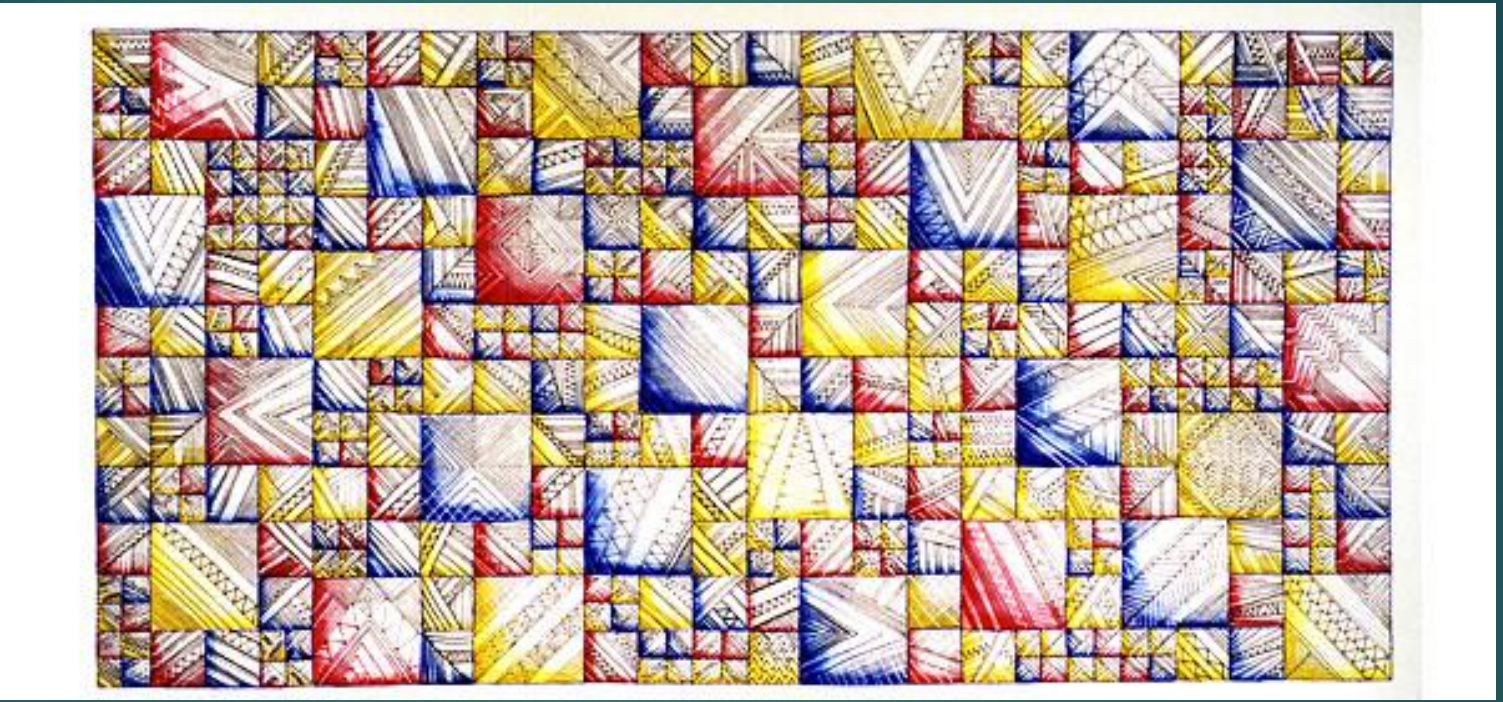
Michael G. Erkkinen, et al., JAMA, 2018

Left-sided PPA and New Artistic Ability



http://72.9.98.98/Art/gallery.htm

FTD and Art



Dr. Anne Adams:
Cell Biologist

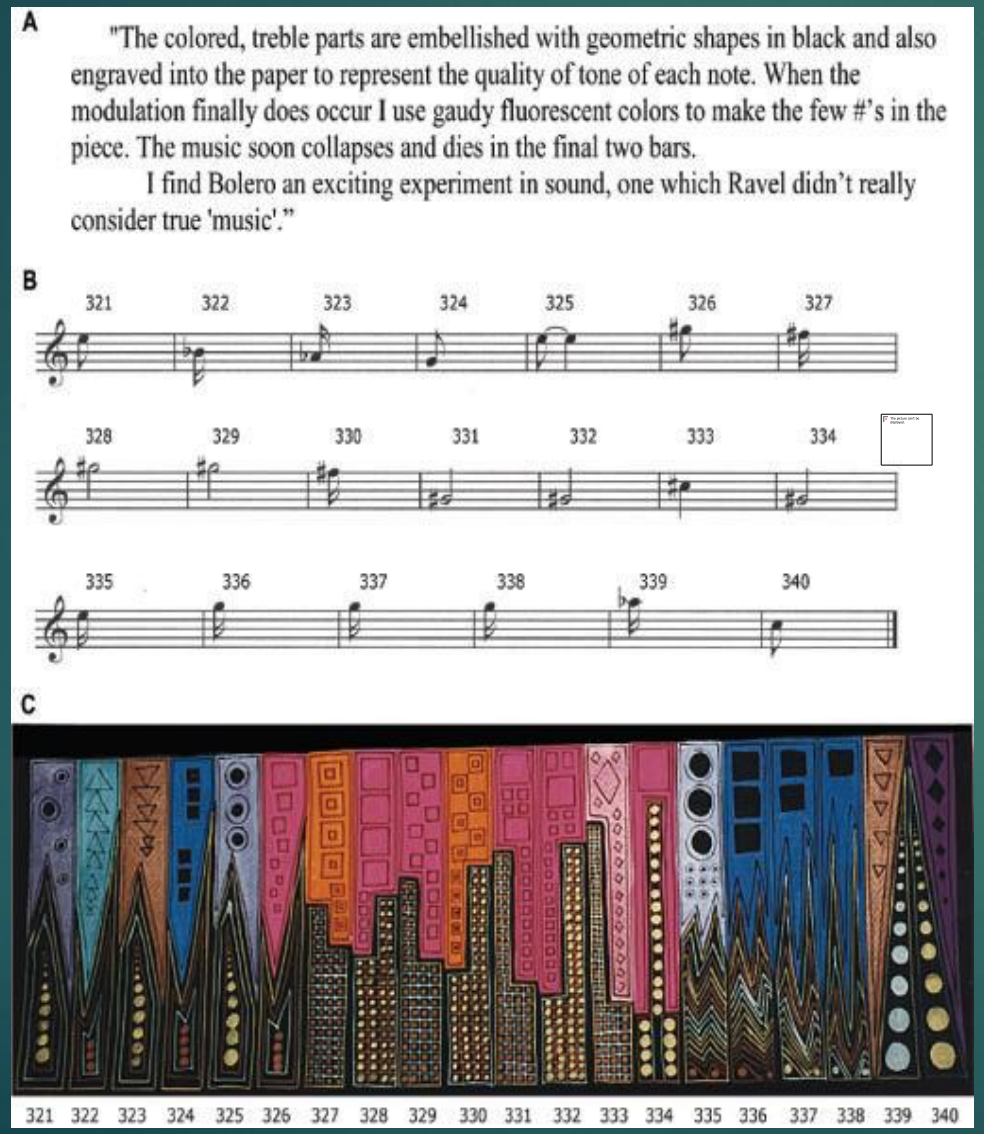
FTD and Art 2

Dr. Adams: Pi (each number colored)

FTD and Art 3

Dr. Adams: Pebbles

A. A. : Unraveling Bolero

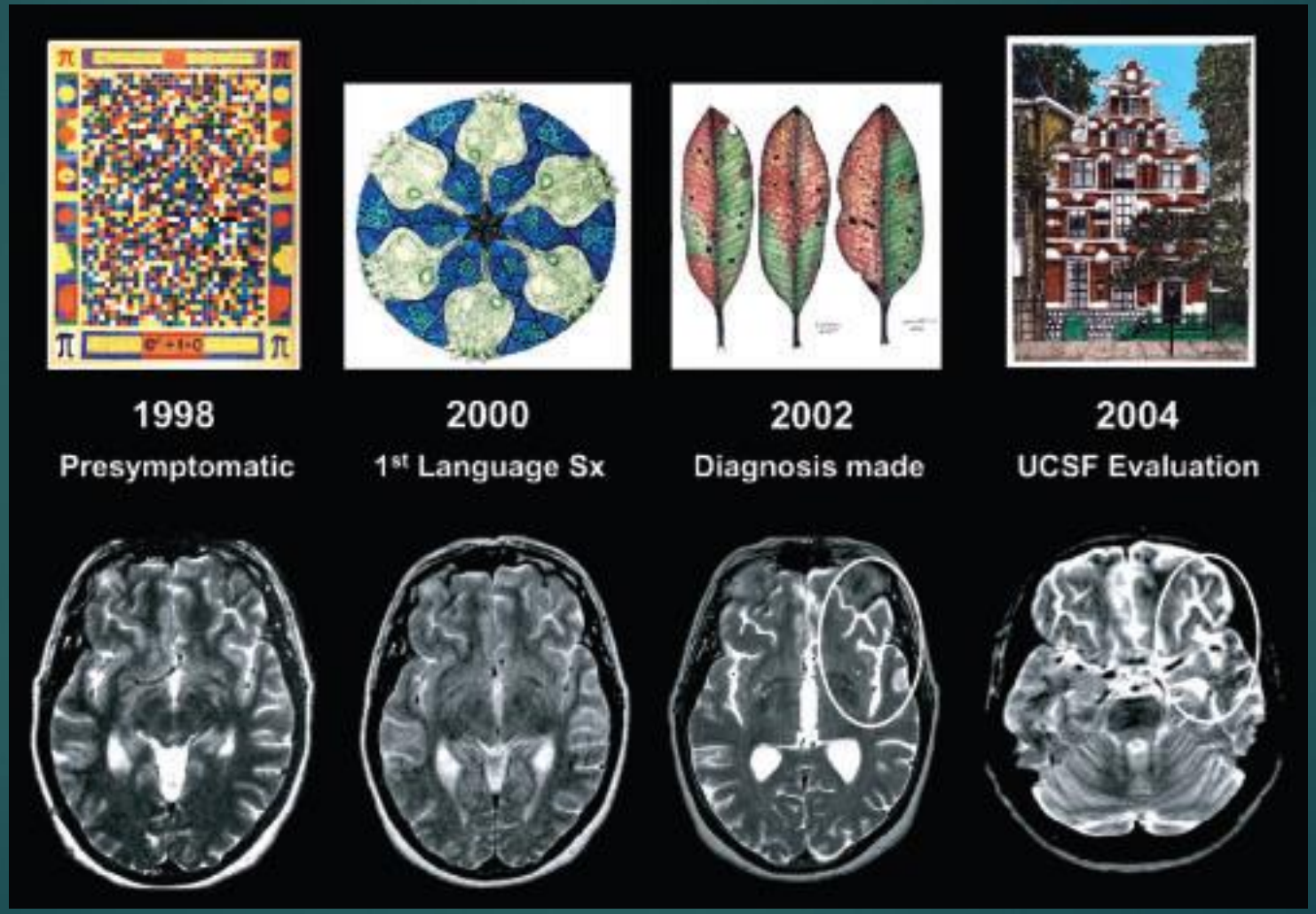


Dr. Adams was Obsessed with Ravel's Bolero

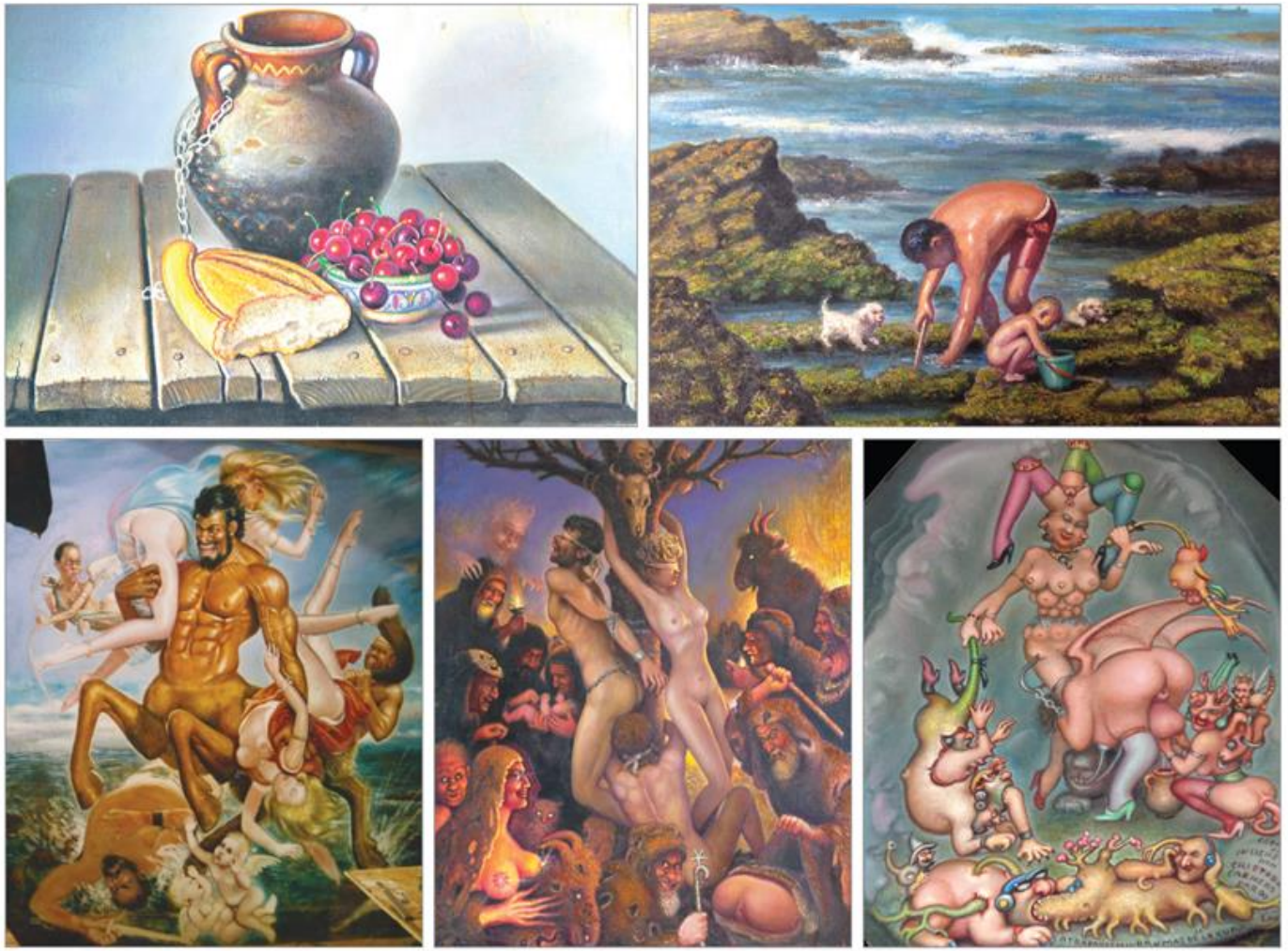
Both had PPA

FTD and Art

FTD and Art: A.A. had PPA



Case 2, age 65-72



Progressive shift in aesthetic style by patient 2: 1980s (top left), 1980s (top right), 2002 (bottom left), 2008 (bottom center), 2017 (bottom right).

Photos courtesy of the artist

Magnum opus: a 6-square-meter wooden relief painting of demons engaged in sexual acts

Treatments

Current AD Drug Therapies

Medication	Dose	Common Adverse Side Effects	Comments
Donepezil (Aricept)	5 mg/day at bedtime with or without food for 4 to 6 weeks; 10 mg/day there-after, if tolerated	Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, muscle cramps, insomnia and vivid dreams	Available in a single daily dose
Rivastigmine (Exelon)	3 mg daily, split into morning and evening doses with meals; dose increased by 3 mg/day every 4 weeks as tolerated, with a max-imum daily dose of 12 mg	Nausea, vomiting, loss of appetite, weight loss, diarrhea, indiges-tion, dizziness, drowsiness, headache, diaphoresis, weakness	Available as a patch
Galantamine (Razadyne)	8 mg daily, split into morning and evening doses with meals; dose increased by 4 mg every 4 weeks, as tolerated, with a maximum daily dose of 16 to 24 mg	Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, headache, fatigue	Available as an extended-release capsule
Memantine (Namenda)	5 mg/day with or without food; dose increased by 5 mg every week, with a maximum daily dose of 20 mg	Constipation, dizziness, headache, pain (nonspecific)	Often used as an adjunct to cholinesterase inhibitors; not recommended alone for treatment of early disease

NCD Treatments

- Cholinesterase inhibitors (acetylcholine deficit; cholinergic enhancers) – Aricept, Exelon, Reminyl
- Inhibitors basically increase the availability of intrasynaptic acetylcholine; improves attention, ADLs
- Aricept or Exelon if hallucinations in AD or LBD
- Aricept: 1 year sig. diff. from placebo; no diff. at 3 years; prefrontal activation on SPECT; cost = generic Aricept, Donepezil, for $110 a year; good for APOe4 with MCI
- Memantine (Namenda): Glutamate channel blocker; only for AD
- Combination of Aricept & Namenda appears to work best

Aricept: Possible Negative Sxs

- Side effects: diarrhea, muscle
- Hospitalized for fainting almost twice as often as people with NCD who did not receive these drugs.
- Slowed heart-rate (bradycardia) was 69 per cent more common amongst cholinesterase inhibitor users.
- 49 per cent increased chance:
  - having permanent pacemakers implanted
  - 18 per cent increased risk of hip fractures.

NCD Treatments 2

- All medications for treatment of behavior problems in AD are off label usage
- Avoid anticholinergics; benzos (cog ↓↓, hip fx, falls = shot of whiskey)
- All antipsychotics in AD have black box warning: increase CVA, stroke, death; all are sedative; Risperidone for behavioral agitation
- Best for agitation: Dextromethorphan (in cough syrups) – glutamate inhibitor
- No meds for hypersexuality (except for pillow clothes; zipper in back)

NCD Treatments 2

- VD:
  - Tx of underlying vascular disease (HTN, hyperlipidemia, diabetes)
  - HTN medications; aspirin only if Vas. hx
  - Be careful with Aricept (11 deaths in n=974 study of vascular NCD)

- LBD:
  - no neuroleptics (induce Parkinsonian sxs; sudden death)
  - Avoid anticholinergics (induce delirium)
  - Use anti-cholinesterase (reduces visual halluc.)
  - SSRIs help reduce hallucinations
  - Pimavanserin (Nuplazid) (1st non dopaminergic antipsychotic)– for PD or LBD psychosis

NCD Treatments 3

- FTD: serotonergic deficit (marked loss of postsynaptic serotonin)
  - Avoid Aricept (agitates) or Namenda
  - SSRIs or Trazodone: reduces irritability & compulsions
  - Behavioral management
  - PNFA: speech therapy, SSRI for depression

- The long-term use of antipsychotic medications in patients with Alzheimer's disease - appears to nearly doubles rate of death after one year
- No FDA approval for any antipsychotic in major NCD, except LBD
- No current medication that treats AD progression

Risk & Protective Factors for NCD

Increase risk

- Low exercise
- High blood pressure
- High cholesterol, low HDL
- Type II diabetes
- High saturated fat
- Inflammation
- Low fish/DHA
- High Homocystine

Possible Protection

- Exercise (walk; 150 min week)
- Statins-Lipitor trial positive
- Coffee
- Folate
- Curcumin (Turmeric)?
- Polyphenols: High Fruits & Veggies, Juices
- Red wine & modest alcohol

Major or Mild NCD due to Multiple Etiologies **

- Criteria met for major or mild NCD
- Evidence that NCD is consequence of more than 1 etiological process

Unspecified Neurocognitive Disorder **

- NCD but Not full criteria

Chronic Traumatic Encephalopathy

Chronic Traumatic Encephalopathy

- TBI is risk factor for NCD
- Long term effects of sports related brain trauma
- Historically dementia pugilistica among boxers
- Caused by Tau & TDP-43 abnormal proteins
- Professional, football players, 50% of boxers, wrestlers, military veterans (blast injuries)
- Repeated trauma early in life, end of career; 8-year latency period, then personality & mood & cognitive changes over 17 years, then NCD
- Motor neuron disease (ALS) in some
- NFL now requires a baseline NP evaluation of all professional football player.

Ann Mckay, New England VA Neuropathology Lab

CTE starts in high school

- 60,000 concussions per year in high school football
- Owen Thomas, 21 yo; suicided; 12 years of hs and college football; no concussions; CTE visible on slide
- 2009 Purdue study: 2 hs football teams; helmet sensors; no concussions in 1-year season
  - Subconcussive syndrome: more hits, more (50%) cognitive decline during season
- 2017 Jama (Mez, et al.,): CTE in 87% of donated brains (177/202) (48/53 college; 111/112 NFL); retrospective; sickest NFL players
- Major research problem: no normative data; comorbidities (opiates, Etoh, growth hormones, etc.)
- Need prospective studies

CTE: just head impact required for tau trigger

- Girls soccer players have been found to be about as likely to suffer concussions as boy football players—and three times more likely than boys soccer players.

- 2019 study: The concussion is really irrelevant for triggering CTE;
  - The same tau brain pathology that is observed in teenagers after head injury was also present in head-injured mice. The brain pathology was unrelated to signs of concussion, including altered arousal and impaired balance, among others.
  - Findings provide strong causal evidence linking head impact to TBI and early CTE, independent of concussion.
  - 20 percent of athletes with CTE never suffered a diagnosed concussion

Subcortical NCDs

Subcortical NCDs

- Severe Depression
- Huntington’s
- Parkinson’s
- Progressive Supernuclear Palsy
- HIV
- Multiple Sclerosis

Cortical vs. Subcortical NCDs

Cortical	Subcortical
Alzheimer's	**Parkinson's, Huntington's, HIV**
Storage/Encoding Memory Deficit	Recognition > Spontaneous Recall Retrieval problem
Rapid rate of forgetting	Normal rate of forgetting
Intrusions	Normal
Semantic Knowledge decreases Animal worse than Letter fluency	Normal Letter fluency worse than Animal
Procedural/Implicit Memory WNL	Impaired

Neuropsychology of Subcortical NCDs

- Retrieval memory pattern: normal recognition memory
- Reduced processing speed
- Executive dysfunction
- Motoric deficits
- Impaired procedural memory

Depressive Behavioral Symptoms in Testing

- Use symptom validity test (Word Memory Test) to assess effort in depressed; if ok WMT, ok NP profile
- Lack of congruence between behavioral capabilities and cognitive deficits
- Lack of dressing apraxia; aphasia, agnosia, topographic disorientation
- Reversibility of cognitive deficits

Depression vs. NCD

Test Feature	Depression	NCD
Frequent task reminder	Unusual	Needed
Memory complaint	Extreme *	Infrequent
Rate of forgetting	Normal	Rapid
Incidental Memory	Intact	Impaired
Task effort	Poor *	Good
Memory cueing	Helpful	Unhelpful
“Don’t Know” comment	Usual *	Unusual
Recognition Memory	Intact	Impaired
Digit Span	>5	<5

Resources

- UCSF Memory Clinic & Research

- Alzheimer's Association

- Family Caregiver Alliance:

  180 Montgomery St, Ste 1100,
  San Francisco, CA 94104

  phone: (415) 434.3388
  (800) 445.8106
  fax: (415) 434.3508
  info@caregiver.org

Charles J. Vella, PhD

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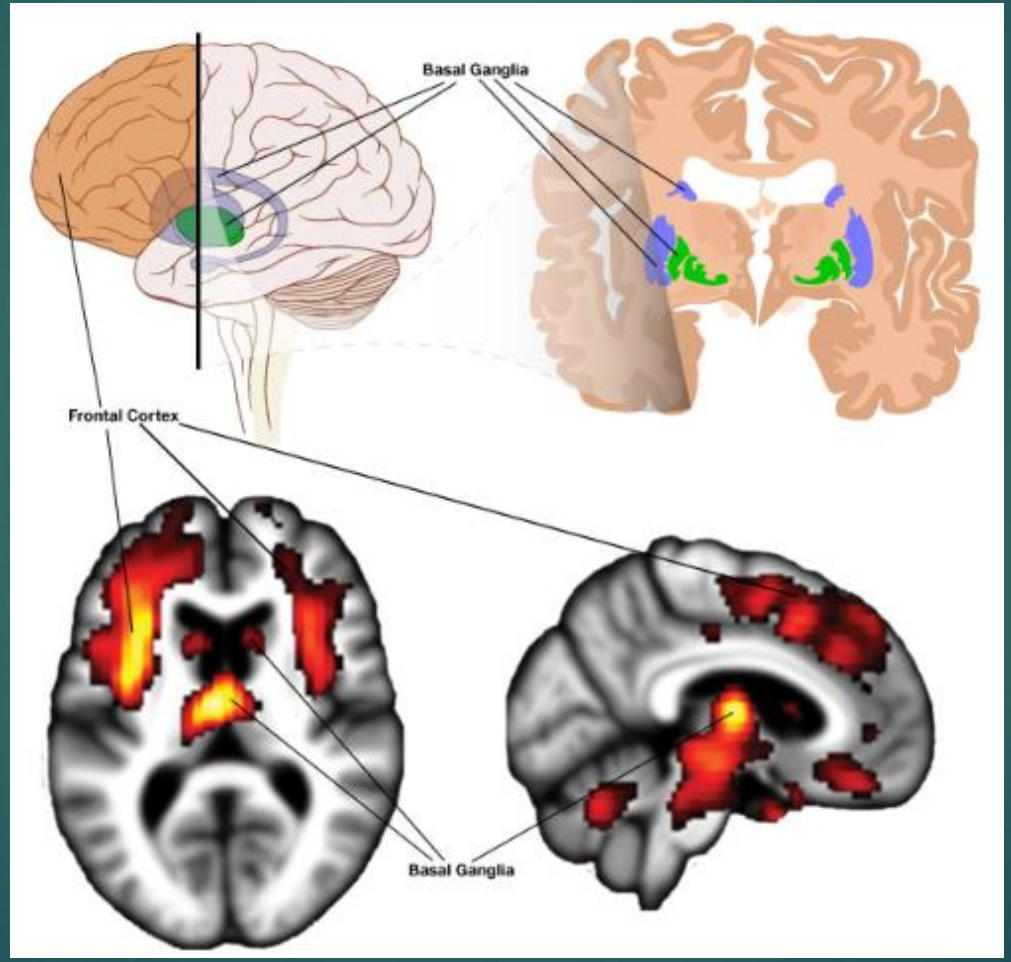
Next 100 slides

- Subcortical Dementias
- Language variants of FTD

Corticobasal degeneration



Basal Ganglia & Frontal Effects

Corticobasal Degeneration

- Causation: focal degeneration of 1 parietal or frontal lobe; absence of plaques/tangles
- Symptoms: alien hand, apraxia, profound visual spatial ↓; dystonias, progressive Parkinsonian sxs; can be indistinguishable from FTD; visual neglect is best predictor
- CBD is caused by abnormal accumulations of the protein tau
- Nearly two-thirds of the patients diagnosed with CBD during life turned out to have another condition at autopsy, esp. AD

Corticobasal Degeneration

- Corticobasal degeneration (CBD) is a progressive neurological disorder first described in 1968 by Rebeiz, Richardson and Kolodny.
- Sxs that best predict CBD: progressive non-fluent aphasia, apathy, disinhibition with poor judgment or problems with leg movement.
- The MRI finding most suggestive of CBD was tissue loss in the frontal lobes and basal ganglia

Progressive Supranuclear Palsy

- Extrapyramidal disorder, often with NCD

- Progressive supranuclear palsy (PSP) is a degenerative brain disease leading to difficulties with walking and balance, problems with eye movements (gaze palsy), changes in behavior and executive control, difficulty with speech and swallowing, and NCD; a tauopathy
- The presence of applause sign? with the classical oculomotor findings, the presence of a dysexecutive syndrome, parkinsonian features and delayed verbal and motor responses makes the diagnosis of Progressive Supranuclear Palsy (PSP) highly probable.

- Causation: tangles with abnormal tau in substantia nigra, globus pallidus, dorsal midbrain, dorsal frontal; hypometabolism; can be asymmetric

- Symptoms: apathy, executive ↓, falls increase, axial rigidity, slowing, falls, swallowing and ocular difficulties (gaze palsy)

Applause test

- In the “three clap test”, the patient is asked to clap three times as quickly as possible, but only three times after demonstration by the examiner
- The performance of the subject is normal when he or she claps only three times or abnormal when he or she claps more than four times or when he or she initiates a program of applause that he or she cannot stop.
- Patients with CBD, MSA, and PSP showed significant differences in clap scores compared with normal controls.
- The test differentiated patients with CBD from those with PD and HD, but failed to discriminate patients with PSP from other parkinsonian groups.
- The specificity of the applause sign is 100% in distinguishing parkinsonian patients from normal subjects with the highest sensitivity in CBD patients.
- We concluded that the applause sign is highly specific for parkinsonian disorders but it is not a specific sign for PSP; it appears to be most sensitive for CBD.
- Rules out FTD

Posterior Cortical Atrophy

PCA

- Form of gradually progressive brain disorder due to neurodegeneration in the back parts of the brain, usually involving the parietal and/or occipital lobes.

- PCA was originally described by Dr. Frank Benson and colleagues in 1988 and is sometimes referred to as Benson's syndrome or the visual variant of Alzheimer's disease because a substantial portion of patients studied so far harbor underlying Alzheimer pathology in the brain, although there are other causes as well.

(Benson DF, et al., Arch Neurol 1988; 45:789-793),

PCA 2

- Gradually progressive syndrome involving changes in vision, including navigation in space, reaching to objects, construction, and the tendency to "see the trees instead of the forest" (individual details of a scene instead of the big picture).
- There can also be difficulties recognizing objects by looking at them, even though they can be understood by touching them or hearing sounds associated with them.
- Balint's syndrome: inability to perceive the visual field as a whole (simultanagnosia), difficulty in fixating the eyes (oculomotor apraxia), and inability to move the hand to a specific object by using vision (optic ataxia)
- Neglect/hemianopsia
- This is usually a result of the AD related gradual shrinkage of the right parietal and/or occipital lobes.

PCA 3

- There are several forms of PCA, including a form that mainly involves language, calculation, and sometimes complex movement. This form usually involves the left parietal lobe.

- Can also be due to other diseases including dementia with Lewy bodies and Creutzfeldt–Jakob disease.

- Affects people at an earlier age than typical cases of Alzheimer's disease, with initial symptoms often experienced in people in their mid-fifties or early sixties. This was the case with writer Terry Pratchett (1948-2015)

PCA Symptoms

- Decrease in visuospatial and visuoperceptual capabilities
- The atrophy is progressive; early symptoms include difficulty reading, blurred vision, light sensitivity, issues with depth perception, trouble navigating through space, and hemispatial neglect
- Apraxia, alexia, and visual agnosia
- As neurodegeneration spreads, more severe symptoms emerge, including the inability to recognize familiar people and objects, trouble navigating familiar places, and sometimes visual hallucinations. In addition, patients may experience difficulty making guiding movements towards objects, and may experience a decline in literacy skills including reading, writing, and spelling

PCA vs AD

- Early stage PCA patients will show brain atrophy more centrally located in the right posterior lobe and occipital gyrus, while AD brain images show the majority of atrophy in the medial temporal cortex. Later similar.

- Loss of grey matter in the posterior and occipital temporal cortices within the right hemisphere

- Presence of neurofibrillary tangles and neuritic plaques in affected brain regions; this eventually leads to major NCD in both diseases

- PCA tends to impair working memory and anterograde memory, while leaving episodic (personal) memory intact, whereas AD patients typically have damaged episodic memory.

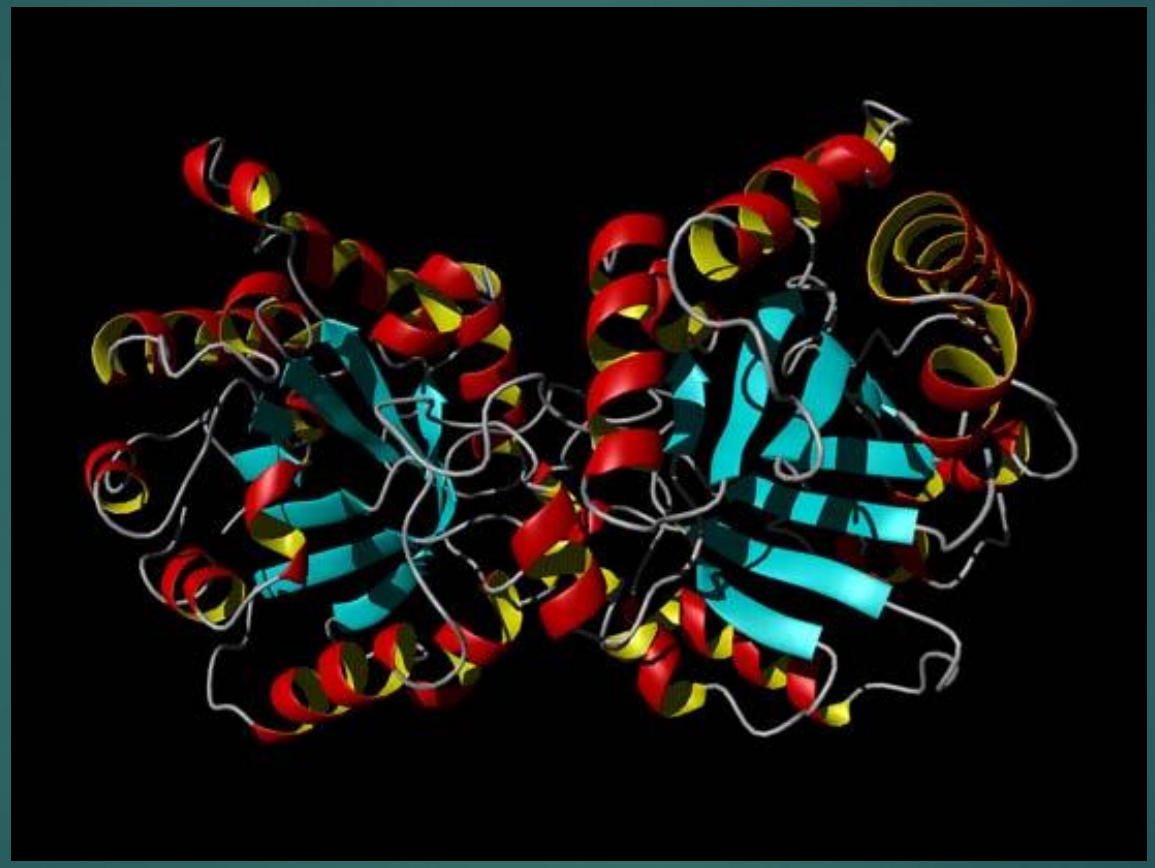
Prion Disorders:

Transmissible Spongiform Encephalopathy (TSE)

&

Creutzfeldt-Jakob NCD (CJD)

Prion: abnormally folded protein



Normal function of prions is memory consolidation

NCD Due to Prion Disease

- A. NCD criteria met
- B. Insidious onset & rapid progression of impairment common
- C. Motor features of prion disease present (myoclonus, ataxia, or biomarker evidence)
- D. NCD not due to another condition

Transmissible Spongiform Encephalopathy (TSE)

- Prion:
  - The normal form of the protein is called **PrP^{C}**,
  - the infectious form is called **PrP^{Sc}** ;
  - normal function helps Schwann cells create myelin, and creation of permanent memory

- Prion Disease: proteinaceous infectious particle, prion

- Prion diseases can be divided into two groups:
  - those with plaques that destroy brain blood vessels: cerebral amyloid angiopathy, that damages brain arteries.
  - those without plaques that lead to the sponge-like damage to nerve cells.

TSE

- Non-Human:
  - Scrapie in sheep, Mink, Deer/Elk (Wasting Disease)
  - Cattle (Bovine Spongiform Encephalopathy = Mad Cow Disease)

- Human (same polypeptide; shape determines which neurons killed):
  - Kuru (New Guinea, endocannabilism, wives cook brain; eye infections)
  - Creutzfeldt-Jacob Disease (CJD) (Slovakia, Sephardic Jews) (cortex)
  - Gerstmann-Straussler-Scheinker Disease (GSS) (cerebellum)
  - Fatal Familial Insomnia (FFI) (thalamus)

Transmissible Spongiform Encephalopathy (TSE) 2

- Varieties: sporadic, inherited, environmentally acquired
- **Sporadic:** 90% of TSE
- Stanley Prusiner of UCSF: amyloidogenic prion protein (modified form of the prion protein (PrP) designated PrPSc), misfolding of protein produces amyloid plaques; very infective; GABA ↓
- Random distribution, 1 case per million, not catchable
- Onset 55-70; equal male-female; gradual onset over weeks to months in 86%

Transmissible Spongiform Encephalopathy (TSE) 3

- Pattern sequence:
  - memory deficit,
  - cerebellar sxs, visual-ocular,
  - then pyramidal/extrapyramidal,
  - then involuntary movements, esp. myoclonus,
  - terminating in mutism and global NCD,
  - death within 6 months (10% 2 years); median duration 4.5 months

- Can initiate with stuttering, MS, Wernicke-Korsakoff, bulbar palsy, Parkinsonism, ALS

- Diagnosis:
  - 1- EEG: 1-2 cycle per second slow wave triphasic spiking of.5-2 Hz
  - 2- CSF: 14-3-3 kinase inhibitor protein
  - 3- MRI: basal ganglia hyperintensities
  - 4 – Biopsy

Transmissible Spongiform Encephalopathy (TSE) 4

- Use Universal Precautions
- **Iatrogenic:**

- Infection via: corneal transplant, neurosurgery, dura mater graft (cadaver), growth hormone (cadaver), gonadotrophin, EEG needles

- Onset: 9-16 years post infection; 15 year onset for subcutaneous injection

- Hard to kill: ineffective: steam autoclave, benzene, ethanol, formaldehyde, radiation

- **Familial (10% of TSEs):**
  - Creutzfeldt-Jacob Disease (CJD) (Slovakia, Sephardic Jews)
  - Gerstmann-Straussler-Scheinker Disease (GSS)
  - Fatal Familial Insomnia (FFI)
  - Chromosome 20

Creutzfeldt-Jakob NCD (CJD)

- Prevalence: 1% of NCD, 1 in a million
- Causation: infectious prion disorder (abnormal shape changing protein) (Posner, UCSF); very infective (heat does not kill; corneal transplant, human growth factor transmission); gaba ↓
- Creutzfeldt-Jakob: Historically Eastern European Jewish disorder, in 50's, very rapid (1 year); any age (20-90); 5-15% familial
- Mad Cow Disease (Bovine Spongiform encephalitis): CJD in humans; meat consumption; related, younger (in England: 2 million cows; 156 human cases currently)

CJD

- DWI and FLAIR images are highly sensitive and specific for CJD: cortical white ribbons (Young, 2005), basal ganglia
- Spontaneous (85%), Genetic (15%), Transmitted/Acquired (>1%)
- “Alzheimer’s in fast forward”
- Great mimicker, depending on where it hits

Symptoms of CJD

- Triad of symptoms:
  - NCD,
  - Involuntary movements (esp. myoclonus),
  - Specific EEG activity (periodic sharp, often triphasic, discharges of .5-2 Hz)

- Prodromal: fatigue, anxiety, appetite/sleep/concentration ↓; then incoordination, altered vision, abnormal gait, rapid NCD
- Proportion of First Symptoms:

Motor	30%
Memory	25%
Executive	15%
Language	10%

Variant CJD (vCJD): Mad Cow Disease

- First DX in UK in 1996, 10 year after BSE epidemic: 2 million cows; 156 human cases

- Prevalence: 20 per year, 20 year course;
- Onset: average age 27

- Duration: 14 months post onset (2x faster than Sporadic rate)

- Beef products (Mad Cow Disease): originally spinal column, brain extracts)

- Symptoms: first psychiatric and sensory (limb pain)

Parkinson's Disease

- Prevalence: 1% of > 65; males > females
- Causation: Lewy bodies in substantia nigra are pathologic hallmark
- Symptoms: akinesia (loss of motor initiation), tremor (resting, pill rolling), rigidity, paucity of movement,

  bradykinesia (slow), postural instability,

  gait abnormal
- NCD: 18-41% of PD; later the motor onset, higher NCD
- Often die of problems related to swallowing
- TX: Carbidopa/Levodopa (Sinemet®)

Parkinson’s Cognitive Decline

- The disease begins on average around age 60 and the risk of Parkinson's increases with age.
- About one-third to one-half of Parkinson's sufferers exhibit some signs of cognitive impairment at the time they are diagnosed, but over time virtually all patients will experience substantial cognitive decline.
- The motor symptoms of Parkinson's appear to be caused by decreased amounts of dopamine.
- Deficits in planning, making decisions and controlling their emotions, and often exhibit changes in personality as a result; not necessarily memory.

Parkinson's Disease:

- Over treatment of PD with dopamine agonists is known to induce abnormal economic decision-making, including compulsive gambling.
- Typical Cognitive Profile:
  - Retention of Problem Solving Abilities with only fluctuations in attention and processing speed
  - Intact learning and memory, although rapid retrieval is compromised
  - Visuoperceptual abilities may be variable
- Typical Emotional Profile:
  - Depressive symptoms reported or may appear
  - May appear apathetic or report apathetic symptoms.

Parkinson’s Disease 2

- Motor disability: uncorrelated with cognition; correlated with depression
- Classic picture: facial expressiveness ↓, depression, cognitive slowing, VS & executive ↓, impaired free recall/normal recognition
- Memory: subcortical profile

  impaired free recall and normal recognition

  List learning < story learning

  Semantic coding ↓

  Mixed procedural memory: ok mirror reading; poor temporal order

Huntington's Disease

- Genetics: 50% autosomal dominant (chromosome 4 gene); 2 per 100 thousand
- Causation: atrophy of neostriatum (esp. caudate nucleus)
- Disruption of frontal-striatal circuits
- Onset: late 30-40s; 15-20 years duration
- Symptoms: behavioral and personality changes first; choreoform movements, mood ↓, subcortical cognitive decline
- Xenazine: 1st Treatment: shown to decrease chorea in the short-term, it also showed slight worsening in mood, cognition, rigidity, and functional capacity in clinical trials

Neuropsychology of Huntington’s

- Severe executive deficit
- Attention deficit
- Free recall deficit; normal recognition
- Procedural memory impaired

Normal Pressure Hydrocephalus

- Caused by impaired reabsorption of cerebrospinal fluid and the consequent build-up of fluid in the brain, increasing pressure in the brain.
- The classic triad consists of abnormal gait, urinary incontinence, and NCD. (NPH) presents with a gradually progressive disorder.
- The gait disturbance is typically the earliest feature noted and considered to be the most responsive to treatment. The primary feature is thought to resemble an apraxia of gait. True weakness or ataxia is typically not observed. The gait of NPH is characterized as bradykinetic, broad based, magnetic, and shuffling.
- The urinary symptoms of NPH can present as urinary frequency, urgency, or frank incontinence.
- People with a history of brain hemorrhage (particularly subarachnoid hemorrhage) and meningitis are at increased risk.
- Can sometimes be corrected with surgical installation of a shunt in the brain to drain excess fluid.

Normal Pressure Hydrocephalus 2

- Patients commonly present with a gait disorder and NCD. On neurologic examination, pyramidal tract findings may be present in addition to the above findings.
- The NCD of NPH: prominent memory loss and bradyphrenia (slow thinking).
- Frontal and subcortical deficits are particularly pronounced. Such deficits include forgetfulness, decreased attention, inertia, and bradyphrenia.
- The presence of cortical signs such as aphasia or agnosia should raise suspicion for an alternate pathology such as Alzheimer disease or vascular NCD.
- However, comorbid pathology is not uncommon with advancing age. In one study, more than 60% of patients with NPH had cerebrovascular disease.
- In another similar study, more than 75% had Alzheimer disease pathology at the time of shunt surgery.

Language variants of FTD

Next 54 slides

Progressive Primary Aphasia: PPA

- The other main form of FTD, primary progressive aphasia (PPA), starts with:
  - problems understanding speech (the semantic variant)
  - Or deficit in generating speech (the nonfluent or agrammatic form).

- Certain developmental language disabilities may render the brain's language network less resilient. Childhood dyslexia may make the brain more prone to logopenic subtype of PPA later in life.

Primary Progressive Aphasia

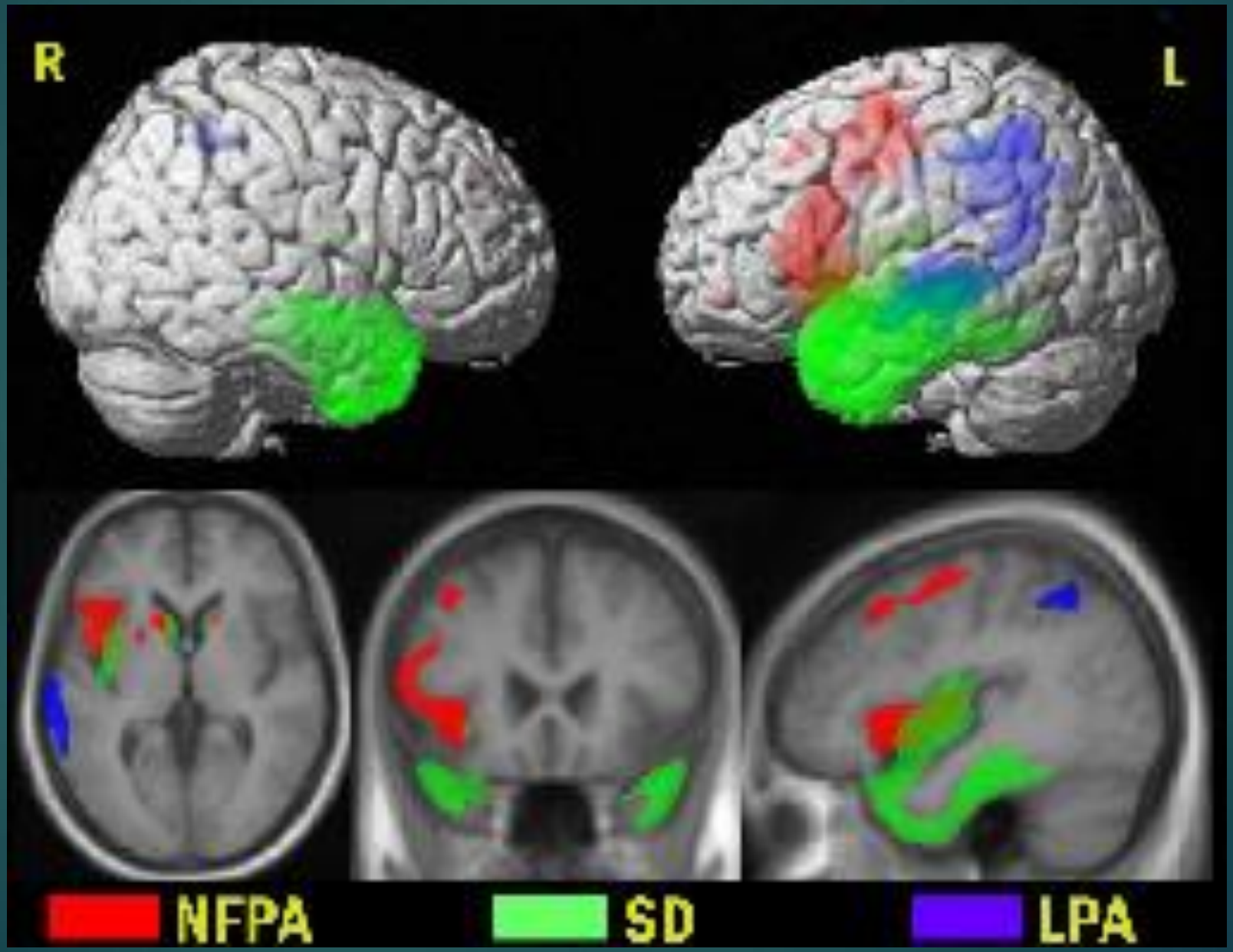
3 Subtypes of Primary Progressive Aphasia (PPA)

- Nonfluent/Agrammatic PPA
  - Formerly Progressive Non-Fluent Aphasia
- Semantic Variant PPA
  - Formerly Semantic Dementia
- Logopenic Progressive Aphasia

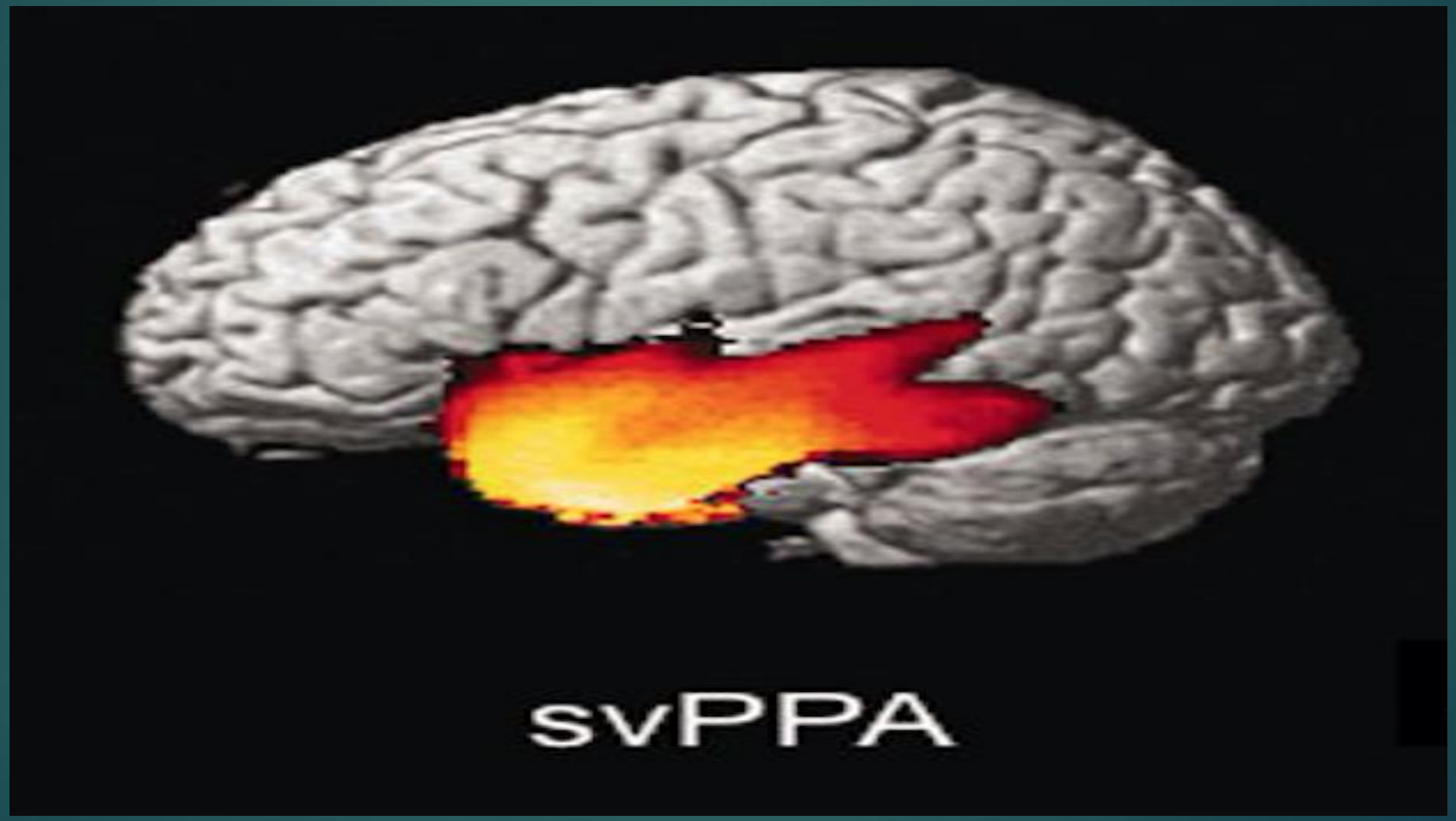
PPA: 3 varieties

- svPPA: Loss of semantic meaning
- nfvPPA: Nonfluent PA: speech apraxia, processing complex syntax deficit → FTD type pathology (L inferior F, insula)
- Logopenic: phonologic paraphasias -- AD

FMRI: NFPA, Sem var PPA, LPA



svPPA = temporal lobe



Neary Criteria for Semantic variant PPA

- Progressive fluent language disorder
- Loss of word meaning
- Semantic paraphasias
- And/or progressive perceptual disorder with prosopagnosia or visual agnosia

Asymmetric degeneration of R or L temporal

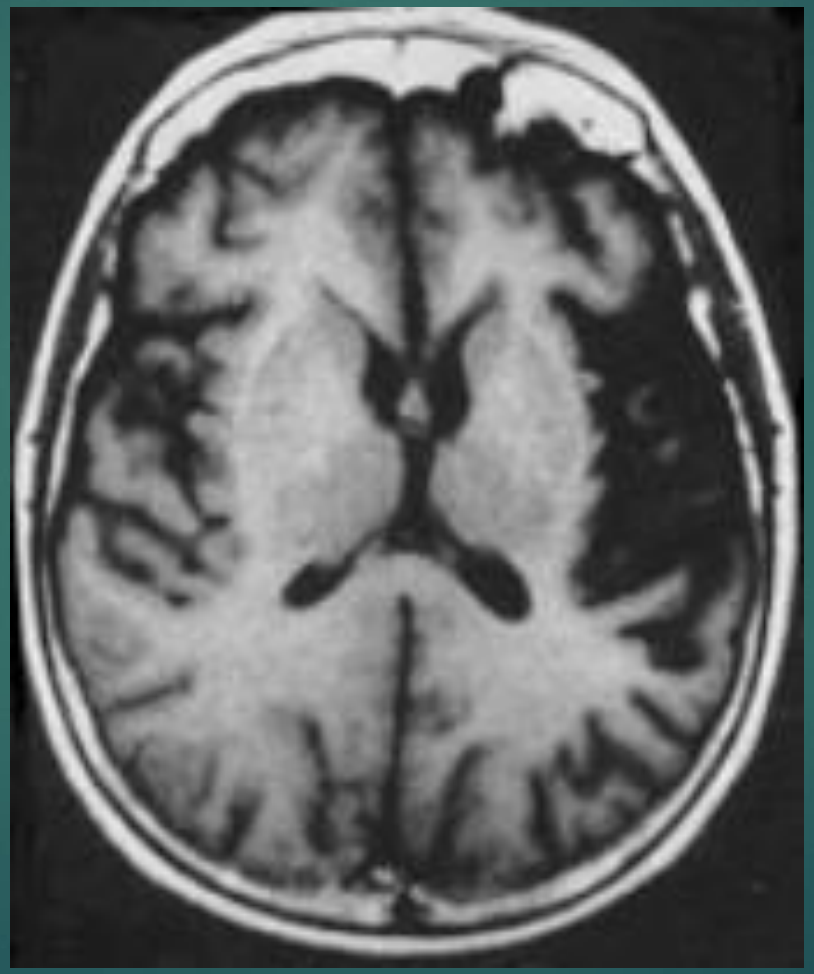
Semantic variant PPA (svPPA) 1

- Language disorder: impaired understanding of word meaning, object identity (visual agnosia), picture meaning
  - progressive, fluent, empty spontaneous speech
  - loss of word meaning: poor naming and comprehension
  - semantic paraphasias
- Anomia 1st, then word meaning loss, klg of what things are (recognition of sounds, smells) ↓ ↓ ↓

Semantic variant PPA 2

- Perceptual disorder
  - Prosopagnosia (inability to recognize faces)
  - Associative agnosia (visual object agnosia; inability to recognize, with intact perception) i.e. tennis ball
- Memory intact
- Focal anterior, bilateral temporal atrophy, > L
- Ubiquitin-positive but tau-negative inclusions. Identical to those in amyotrophic lateral sclerosis (motor neuron disease), but none in brainstem or spinal cord motor neurons.

Primary Progressive Aphasia



Left

Semantic variant PPA 3

- Left anterior temporal FTD:
  - dissociation between marked single-word and object knowledge deficits,
  - but sparing of phonology and fluency

- Semantic meaning loss → comprehension ↓
- Severe word finding ↓ (BNT, fluency)
- Loss of word recognition on Picture Vocabulary
- Memory ↓, long sentence memory ↓

Semantic Variant PPA 3

- General knowledge ↓
- Surface dyslexia (cannot recognize a word as a whole), poor object klg
- Spared repetition, motor speech
- Speech is fluent; awareness of deficit

- If R Temp, face recognition ↓

- Damage to the major superior and inferior temporal white matter connections of the left hemisphere (inferior longitudinal fasciculus. & arcuate and uncinate fasciculi) with relative sparing of the fronto-parietal superior longitudinal fasciculus.

NP Testing of Semantic variant PPA

- BNT (15 item): < 5
- Draw a word ↓, i.e. cat, duck
- Color in animal picture ↓, i.e. brown frog
- Echoic memory buffer ↓
- Digits Backwards ↓
- Trails, design copy ok

svPPA

- Anomia = Defining feature of svPPA
  - Unavailable content words (specific nouns, verbs, adjectives) are replaced and surrounded by speech that is correctly pronounced and has normal grammatical structure.
  - Syntax is often simplified

- Word retrieval deficit not a word finding problem; rather a loss of semantic knowledge.

- Lower-frequency words are replaced by more general and higher-frequency words
  - Zebra becomes “horse,” “animal,” and eventually “thing”

svPPA

Anomia

- Simple Test
  - Ask patient to repeat a long, unusual word such as “hippopotamus” or “chrysanthemum” and then to define it
    - Repetition is almost always normal and rapid
    - Definition will be generalized, lacking detail, and sometimes completely uninformative
- Object use is also impaired, although not initially
  - Patients typically function normally with everyday objects at home, but show impairment on formal tests

svPPA

Behavior and Personality Change

- Degraded social functioning
  - Emotional Withdrawal
  - Depression
  - Disinhibition
  - Apathy
  - Irritability
  - Difficulty understanding the things people do and say

svPPA

Behavior and Personality Change

- Changes in Eating Behavior
  - Restriction of food preferences rather than the overeating in bvFTD
  - Exacerbation of a sweet tooth
- Loss of physiological drives is common
  - Poor appetite
  - Weight Loss
  - Decreased Libido
- New sense of religiosity and/or eccentricity of dress have been reported

svPPA

- Stereotyped interests often looking similar to obsessions are prominent but delayed feature
  - Patients with left-predominant svPPA often become fixated on objects like coins or buttons or visual arts
  - Patients with right-predominant svPPA often become fixated on letters, words, and symbols (e.g. word puzzles, writing notes, poetry)

svPPA

- Deficits in person recognition often occur at some stage in the disease (Thompson et al., 2003)
- Right predominant may *present* with a profound difficulty in recognizing and naming people
- Regardless of side dominance there is a cross-modal loss of person knowledge involving face, name, and/or voice recognition

svPPA

Maintained Skills

- Orientation
- Recall of recent life events
- Visuospatial and topographical abilities
- Complex hobbies (e.g. sports games)

svPPA: Neuropsychological Findings

- Impaired semantic memory
  - Object/Picture Naming
  - Category Fluency
  - Generation of verbal definitions to words and pictures

- Progression of anomia
  - Substitution of similar category coordinate
    - Zebra -> Giraffe
  - Then higher-familiarity member of category
    - Zebra -> Horse
  - Then superordinate category name
    - Zebra -> Animal
  - Then vague circumlocution, often with personal content
    - Zebra -> It's one of those things, I saw them on the television last night
  - Then inability to say anything
    - Zebra -> I don't know

svPPA

Neuropsychological Findings

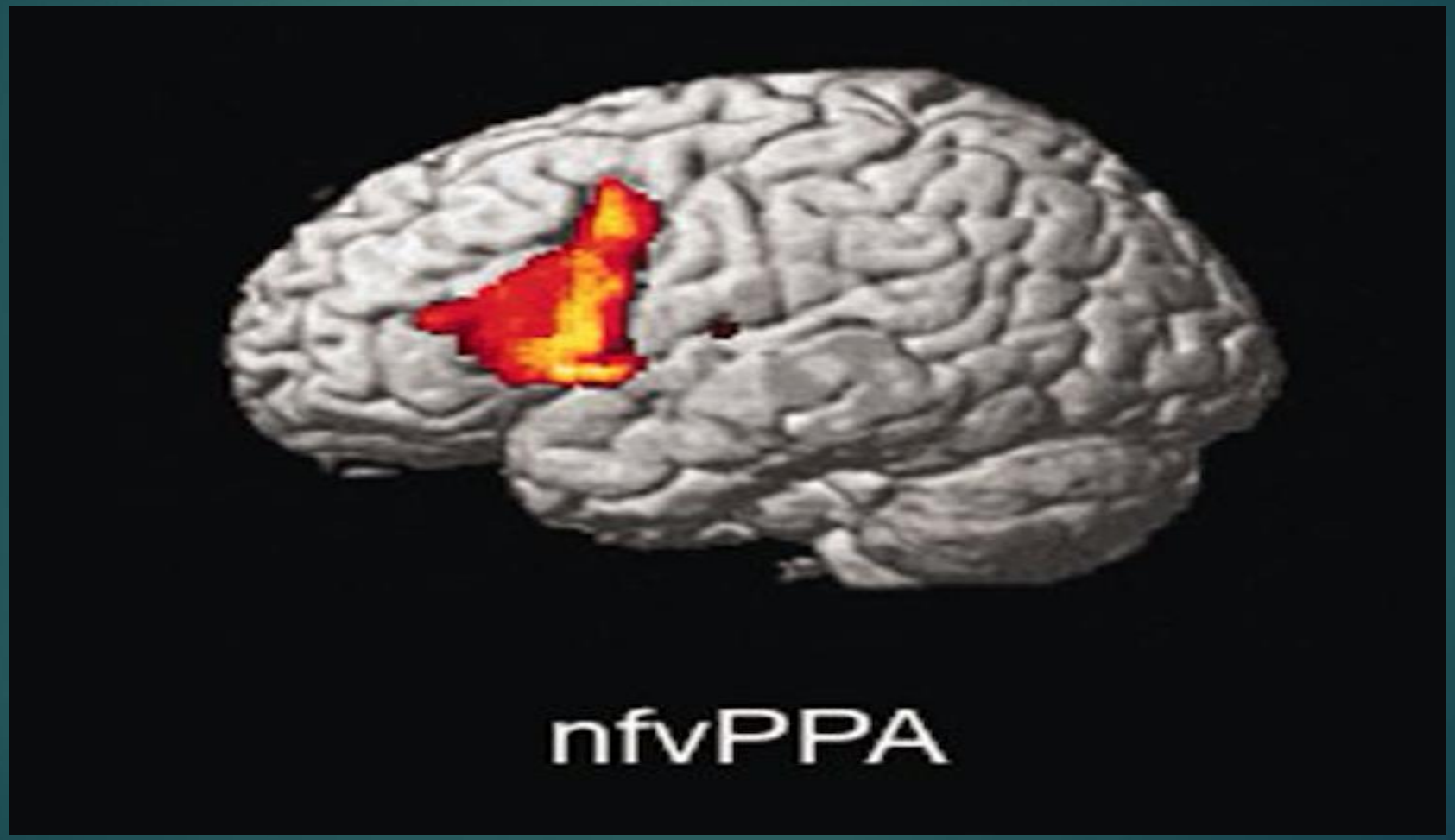
- Verbal anterograde memory (story memory, list learning) is impaired as a result of poor semantic knowledge that can't be encoded

- Differential between Alzheimer's Disease:
  - Autobiographical memory
    - AD - impaired memory for recent life events but preserved autobiographical memory for earlier phases of their lives (Nestor et al., 2002)
    - svPPA - memory for remote autobiographical events is most vulnerable (Piolino et al., 2003; Westmacott et al., 2004)

svPPA: Structural and Functional Imaging

- Focal, often asymmetric (L>R) atrophy of the anterior temporal lobe (Hodges et al., 1992)
- Temporopolar and perirhinal cortices most affected (Rosen et al., 2002)
- Degree of anterior temporal atrophy correlates with extent of semantic impairment (Davies et al., 2004)
- Left hippocampus is typically as atrophied as AD if not more when matched for disease duration (Davies et al., 2004)
- Amygdala is consistently involved and linked to emotional recognition impairments

Nonfluent PPA



Nonfluent Primary Progressive Aphasia

- Disorder of speech production ↓ (expressive language deficit)
- Language disorder is primary deficit for first 2 years
- Non-fluent spontaneous speech with 1 of the following:
  - Phonemic paraphasias - errors in which the incorrect sound is used within a word (e.g. ‘tittle’ for ‘little,’ or ‘label’ for ‘table’)
  - Anomia - naming deficits that cause long pauses during spontaneous speech or the selection of a word
  - Agrammatism - omission or inappropriate use of grammatical words such as articles, prepositions, and auxiliary verbs
- Relatively spared word comprehension
- Other possible features: stuttering, oral apraxia, impaired repitition, alexia, agraphia, early preservation of word meaning, late mutism
- Focal Left Temporal atrophy, hypometabolism

Mesulam, Annals of Neur., 1986

Nonfluent PPA

Clinical Features

- Nonfluent speech - hesitant, effortful production with reduced speaking rate; Speech is generally slow, halting, and effortful
- Patients often complain of articulation or word-finding problems
- Memory, visuospatial, and judgment spared, at least initially
- It is the most common PPA (Mesulam & Weintrob, 1992; Mesulam et al., 2003)
- CBD is most common pathology (Gorno-Tempini et al., 2004; Kertesz 2005)
- Nonfluent PPA more likely to be female and isolated language problems will occur for 4 years before other symptoms begin

Nonfluent PPA

Clinical Features

- Often starts with anomia and progresses to non-fluency
- “Broca’s-like-aphasia”
- Patients will use a simplified sentence and decreased phrase length
- Speech is slow and apraxia of speech and/or stuttering are common complaints
- Anomia thought to be a problem of speech production rather than semantic loss

Nonfluent PPA

Clinical Features

- As the disease progresses patients can show symptoms of executive dysfunction
  - Poor thought organization
  - Severe frustration
  - Depression
  - Mild disinhibition

Nonfluent PPA: Neuroimaging

- Left frontal hypometabolism as measured by PET (Grossman et al., 1998; Nestor et al., 2003)
- Atrophy found in the left inferior and middle frontal gyri, motor cortex, premotor cortex, and anterior insula regions (Nestor et al., 2003; Gorno-Tempini et al., 2004)
- Left greater than right atrophy is well documented, bilateral damage is common (Westbury & Bub, 1997)

Nonfluent PPA

Neurological Evaluation

- Mild motor symptoms are present usually in the right hand or right side of the body (Kertesz et al., 2003; Kertesz & Munoz, 2004)
- Diffuse motor slowing
- Reduced dexterity
- Mild Rigidity

Nonfluent PPA

Neurological Evaluation

- Limb apraxia (deficits when carrying out purposeful movement) is common and along with acalculia can be present early in the disease (Neary et al., 1998)
- Impaired ideomotor apraxia (inability to correctly imitate hand gestures and voluntarily mime tool use) is consistent with disruption to a left parietofrontal network (Joshi et al., 2003)
- Buccofacial apraxia and dysarthria can be present (Grossman et al., 1996)

Nonfluent PPA

Pathology

- Tauopathies are the most common: CBD, FTLD, PSP, argyrophilic grain disease (Kertesz et al., 2005; Josephs et al., 2006; Knibb et al., 2006)

- Despite distinct clinical presentation, a growing number of reports suggest that as much as 30% of nonfluent PPA caused by AD pathology (Knibb et al., 2006)

Nonfluent PPA

Demographics

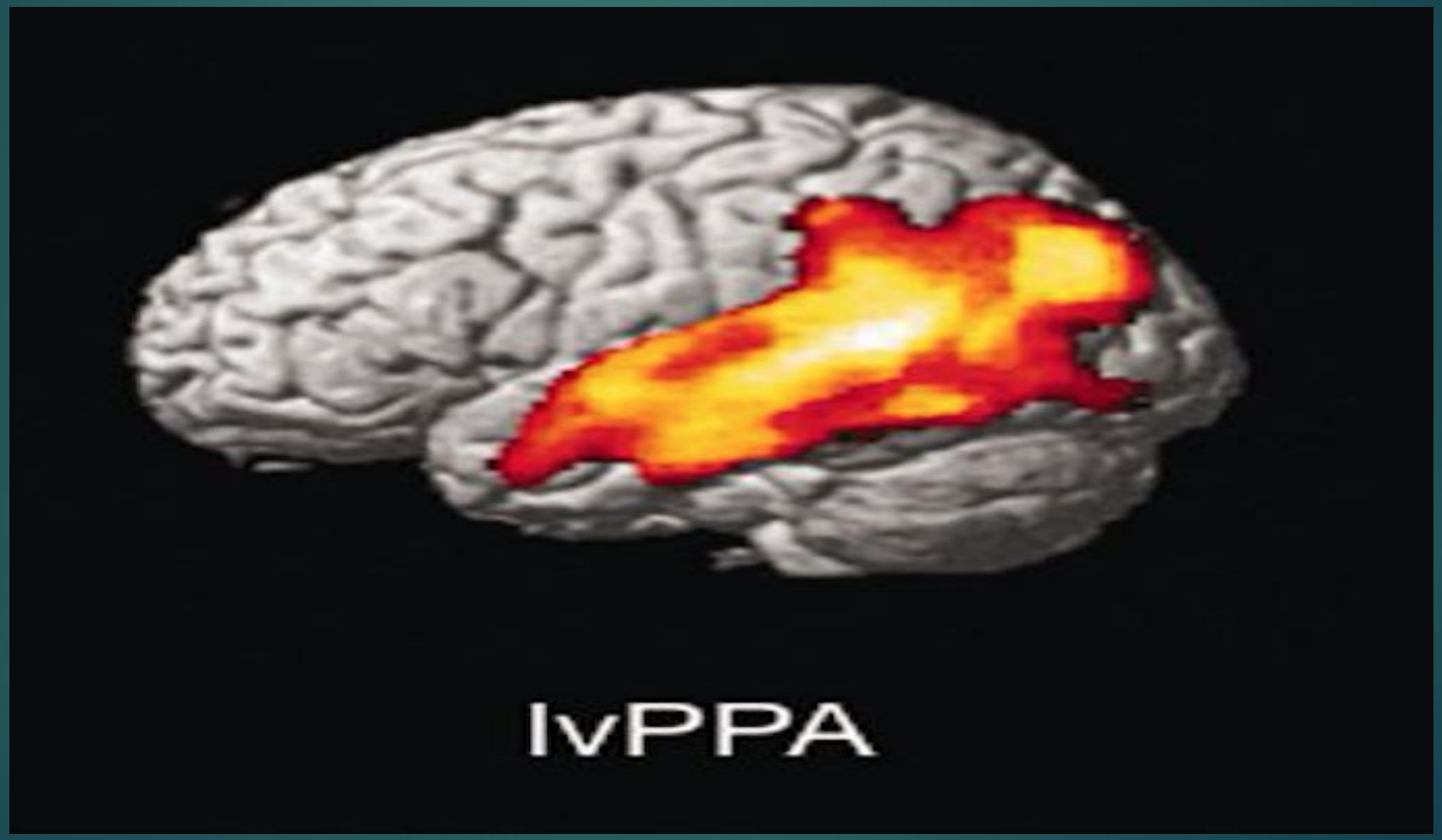
- Nonfluent PPA have a later age of onset (ave. 63 y) than svPPA and bvFTD

  - Nonfluent PPA - 63-years-old
  - bvFTD - 58-years-old
  - svPPA - 59-years-old

Treatment Options

- Work with a speech-language pathologist
- Use of augmentative/alternative communication devices (e.g. talking computers)

Logopenic PPA



Logopenic PPA: Word Finding deficit

Clinical Features

- The presenting feature in people with logopenic PPA is deterioration in their ability to retrieve words.
- Spontaneous speech is at slow rate with frequent pauses due to significant word-finding problems; hesitant and nonfluent, with islands of good speech
- No agrammatism; good articulation
- Confrontation naming impairment is usually less severe than svPPA and errors are phonological in nature (Gorno-Tempini et al., 2004)

Logopenic PPA

- **Word retrieval or word-finding;** retain the underlying meaning of words.
- **A slow rate of speech** with frequent pauses due to difficulty finding the right words; the mechanics or motor skills needed to produce speech are not affected.
- **Sentence and phrase repetition is impaired**, but **repetition of single words is spared.**
- **Reading and writing abilities** may be preserved longer than speech, but these eventually decline, as well.
- Over time, **impaired comprehension** of long or complex verbal information, due to problems with working memory (auditory attention span).
- **Mutism** eventually develops with progression.
- **Difficulty swallowing** may develop late in the course of illness.

Logopenic PPA

Clinical Features

- Sentence and phrase repetition is characteristically impaired while reproduction of short, single words can be spared
- This can also cause problems with sentence comprehension, which is influenced by length than grammatical complexity
- Phonologic paraphasias in spontaneous speech and naming
- Sound substitutions are usually well articulated, without distortions
- Lack of agrammatic errors, preservation of articulation, and prosody

Logopenic PPA

Neuroanatomy

- Left temporoparietal junction area (i.e. posterior temporal, supramarginal, and angular gyri)

- AD pathology most common underlying pathology

- ApoE4 Haplotype
  - LPA - 67%
  - svPPA - 0%
  - Nonfluent PPA - 20%

Verbal Fluency in FTD vs AD

- FTD: worse on both letter and semantic category fluency
- AD: diminished semantic/category fluency where letter fluency is intact.
- Letter fluency (FAS/Cowat): more frontal executive process for organized lexical search strategy.
- Semantic fluency: accesses more temporal semantic/factual neural networks

K. Rascovsky, 2010