Molecular Pathology – Part 1
LBD, FTD, ALS and More
[AlzD and EOAD in Part 2]

Final Exam: Monday - 4/26 from 1:00 to 3:00
Review Session Day/Time, extra office-hours: TBA
Final Exam Period will likely be extended to 4 hours

For my personal Top 50 List:
- why no tau mutants in AlzD?
- why is atrophy "undefined"?
- why is familial AlzD accelerated?
- why is Semantic D lateralized?
- why have all β-amyloid trials failed?

see Chapters 12, 13 -- SNCD

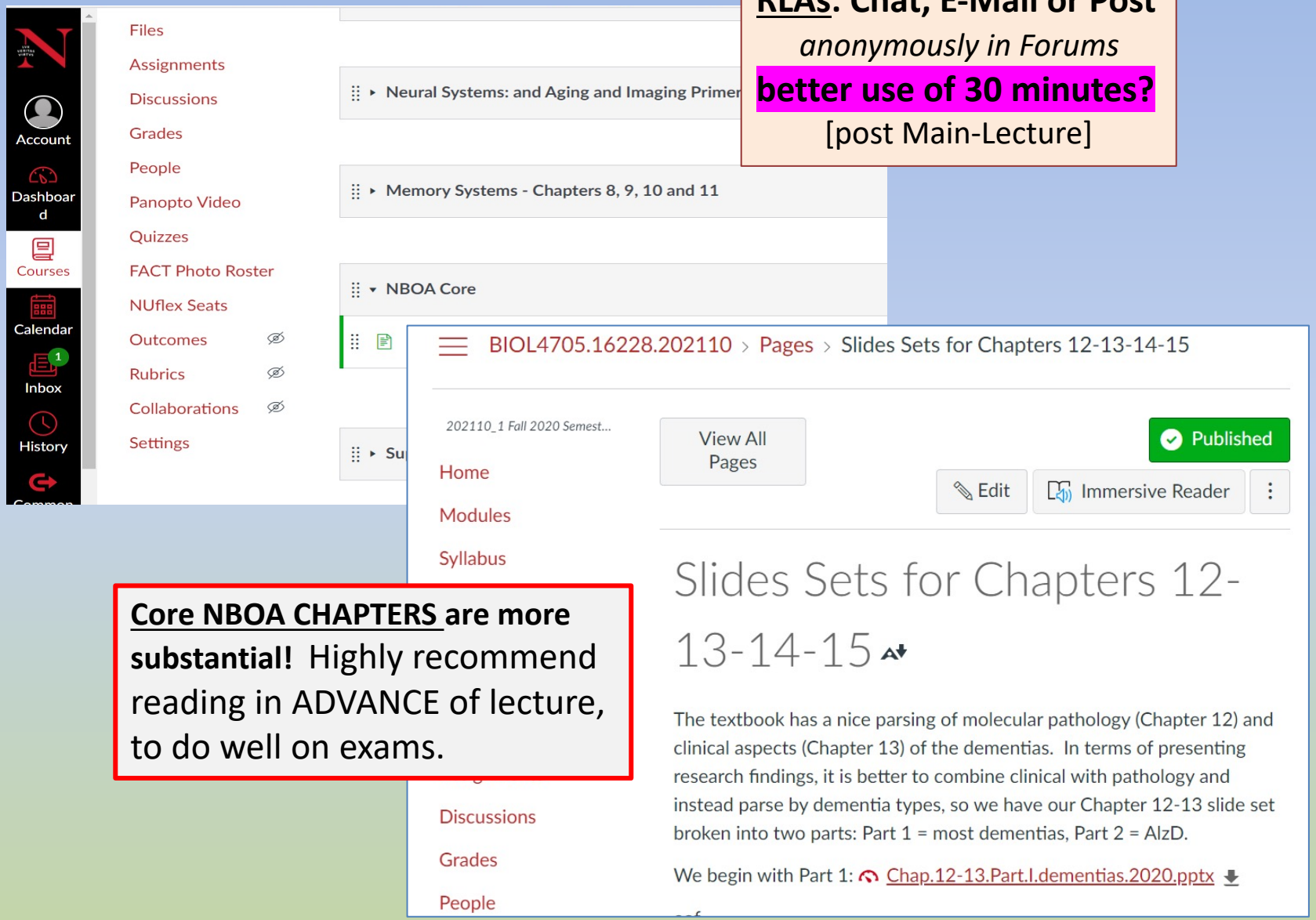
kahoot

RLAs: Chat, E-Mail or Post

anonymously in Forums

better use of 30 minutes?

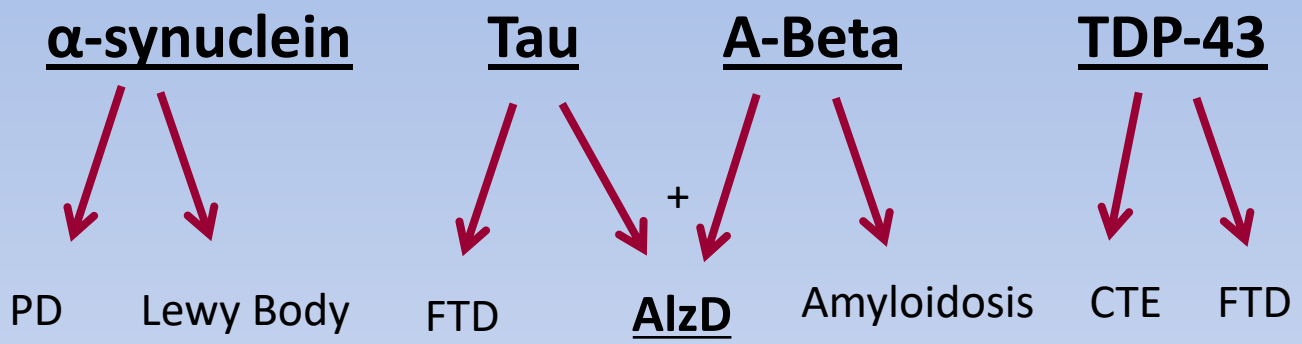
[post Main-Lecture]



Core NBOA CHAPTERS are more substantial! Highly recommend reading in ADVANCE of lecture, to do well on exams.

The Big Four
α-synuclein
TDP-43
beta-amyloid
tau
+ fus/bvFTD

Primary connections are shown!



The Cast of Bad Actors

- **Tau, A-Beta** mentioned already; much more to come on AlzD, EOAD
- **LBD / *alpha synuclein*** including Parkinson's, LB dementia
- **FTD:** includes behav. variants, semantic dementia, primary progressive aphasia
- **TDP-43** = TAR DNA-binding protein 43, transcription factor; also *fus*

Which of the above are IDPs?

fus: what about MY contributions???

EOAD: Please review Glossary and make suggestions

ALL THE DEMENTIAS THAT ARE FIT TO TWEET!

Neuropsych Consult, Feb. 28, 2018 *and* **Chapter 13 Preview**

AlzD (classic) = rapid forgetting, most common
main focus this semester, can exceed 10 years progression

Lewy Body Disease/PD = next most common contains α-synuclein
visual and REM components, visuospatial, hallucinations, attention fluctuations
w/ Parkinson symptoms; l-dopa might not help, neuroleptics bad, Aricept good
= diffuse Lewy body disease = dementia w/ Lewy bodies; can have tau, AB

FTD's = range of dementias including Picks [also next most common]
different types, can progress quickly, e.g. 5 years.

Combos – when 1 dementia is not enough
Lewy Body + AlzD symptoms
AlzD + Parkinsonian symptoms

ALSO: Semantic Dementias/SD and primary progressive aphasia/PPA
SD degrades stored knowledge, whereas PPA affects fluency, word-finding

Lewy Body Dementia: LBD and Parkinson's Disease (PD)

LBD - terminology frequency, G-Scholar
Lewy Body Disease – 36,000
Lewy Body Dementia – 28,000
Lewy Body Disorders – 4,000
…but there is another…

if you use wrong **LBD term**
you get only 4k/68k articles
i.e. only 1 of every 17 articles**

Other Terms of Endangerment:

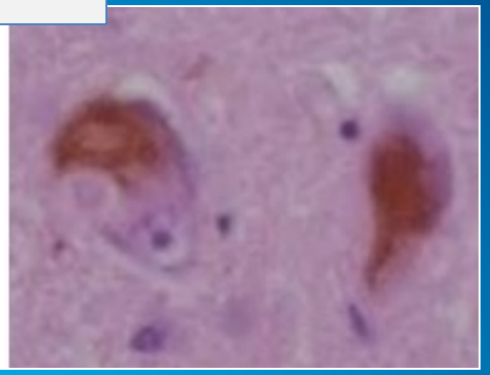
Proteinopathy = 10,000 hits*
AlzD = 1,760,000 hits
FTD = 14,000
FTLD = 19,600

*was 14,000-???

Pathology *IS* Post-Mortem

Lewy Bodies vs. Tauopathies

Lewy bodies are abnormal aggregates of protein that develop inside nerve cells in Parkinson's disease (PD), **Lewy body dementia**, and some other disorders. They are identified under the microscope when histology is performed on the brain. **[post-mortem]**

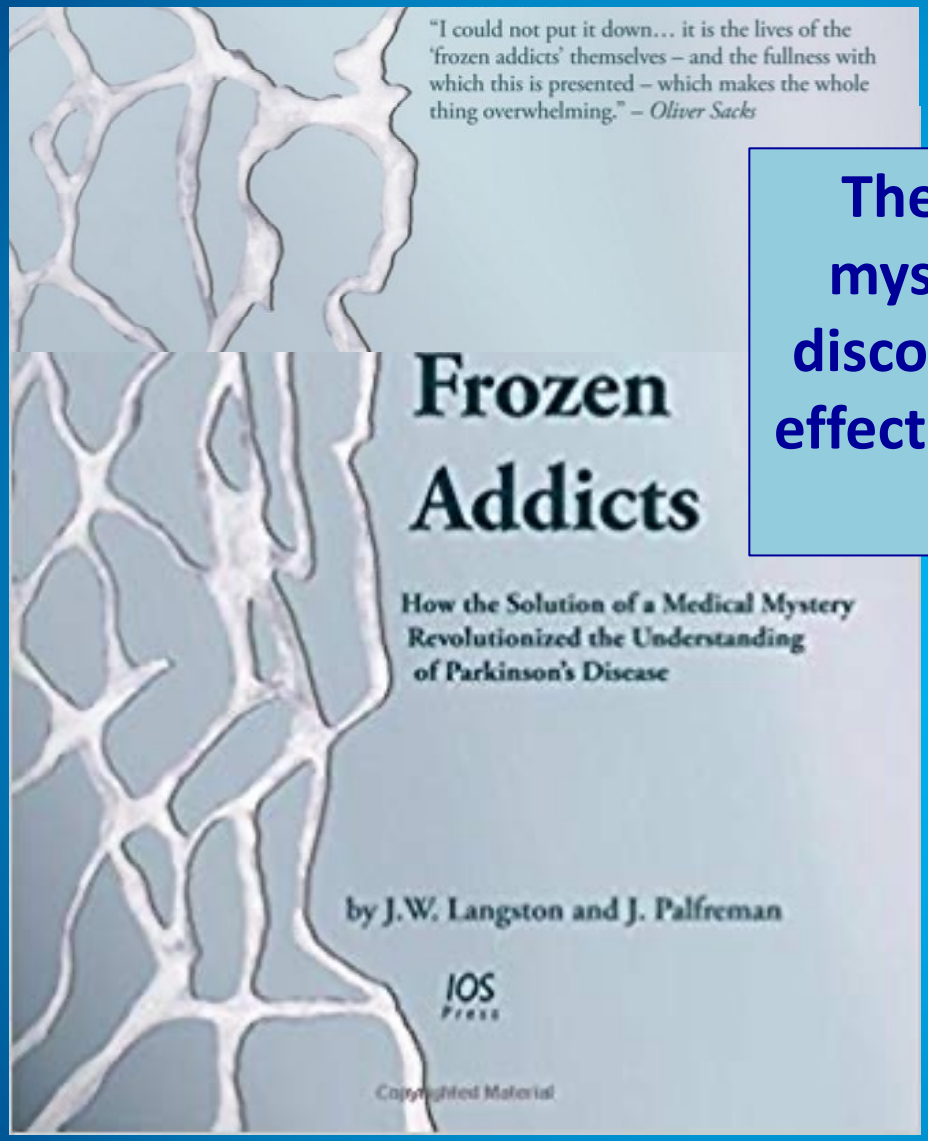


Wiki: People with LBD display an inability to plan or engage in analytical or abstract thinking; they show markedly fluctuating cognition. [remind you of anyone?] me on a good day
LBD is often associated with **Parkinson's,** but some forms of LBD can progress more rapidly than classical PD.

Parkinson's: primarily due to loss of dopaminergic cells in the substantia nigra [Lewy bodies might stem from α-synuclein (an IDP) aggregation; why this occurs specifically in SN cells is uncertain, as is its relation to the MPTP story-see Chap. 12!]

Pick's Disease: Pick's Disease is really a tauopathy, a type of pathology because it does not define any particular FTD category but is found in different subsets of FTD variants, most often the behavioral variant "bvFTD". Progresses faster than AlzD. More below.

Tau vs. Lewy Bodies: tau is a microtubule-associated protein that forms tangles. LB's contain α-synuclein aggregates: both can be considered "protein-aggregate" diseases (aka proteinopathies) but they seem to afflict different cell types.



The story of a medical mystery-- including the discovery of MPTP and its effects on the human basal ganglia.

https://www.amazon.com/Case-Frozen-Addicts-Mystery-Revolutionized-Understanding/dp/1614993319

Ulterior Query: Is Wikipedia WORSE than PNAS, *Science* and Nature?

Alpha-synuclein

From Wikipedia, the free encyclopedia

Alpha-synuclein is a protein that is abundant in the human brain.[4] Smaller amounts are found in the heart, muscles, and other tissues.[4] In the brain, alpha-synuclein is found mainly at the tips of nerve cells (neurons) in specialized structures called presynaptic terminals.[4] Within these structures, alpha-synuclein interacts with phospholipids[5] and proteins.[4] Presynaptic terminals release chemical messengers, called neurotransmitters, from compartments known as synaptic vesicles. The release of neurotransmitters relays signals between neurons and is critical for normal brain function.[4]

Although the function of alpha-synuclein is not well understood, studies suggest that it plays a role in maintaining a supply of synaptic vesicles in presynaptic terminals by clustering synaptic vesicles.[6] It may also help regulate the release of dopamine, a type of neurotransmitter that is critical for controlling the start and stop of voluntary and involuntary movements.[4]

Wiki: alpha-synuclein aggregates to form insoluble fibrils in pathological conditions characterized by Lewy bodies, such as Parkinson's disease, dementia with Lewy bodies and *multiple system atrophy*
also: alpha-synuclein is found in the nucleus, mitochondria, presynaptic terminals AND is an Intrinsically Disordered Protein! ← MORE SLIDES BELOW!

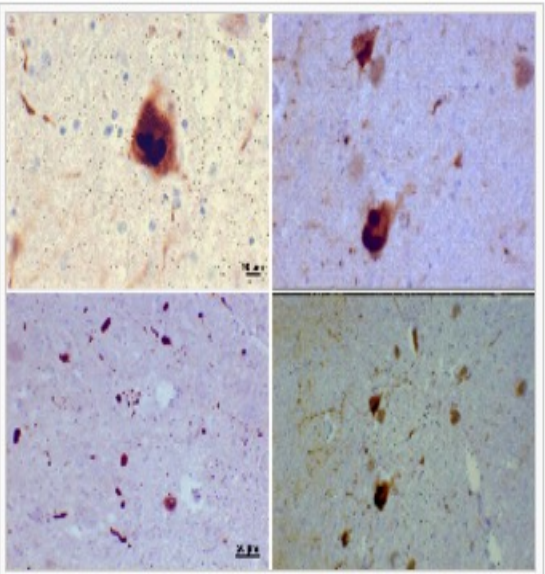
CHAT: Why are LBD's Toxic? [not a trick question, but potentially. why?]

UPDATED: ONE MORE BODY!

Lewy bodies are abnormal aggregates of protein that develop inside nerve cells in Parkinson's disease (PD), Lewy body dementia, and some other disorders. They are identified under the microscope when histology is performed on the brain.

Lewy bodies appear as spherical masses that displace other cell components. The two morphological types are classical (brain stem) Lewy bodies and cortical Lewy bodies. A classical Lewy body is an eosinophilic cytoplasmic inclusion consisting of a dense core surrounded by a halo of 10-nm-wide radiating fibrils, the primary structural component of which is alpha-synuclein. Cortical Lewy bodies are also composed of alpha-synuclein fibrils, but are less defined and lack halos. In histopathology, Cortical Lewy bodies are a distinguishing feature for dementia with Lewy bodies (DLB), but may occasionally be seen in ballooned neurons characteristic of Pick's disease and corticobasal degeneration,[1] as well as in patients with other tauopathies.[2] They are also seen in cases of multiple system atrophy, particularly the Parkinsonian variant.[3]

MSA



Photomicrographs of regions of substantia nigra in this Parkinson's patient show Lewy bodies and Lewy neurites in various magnifications. Top panels show a 60-times magnification of the alpha-

Lewy Bodies and Brain Damage

Alpha-synuclein found in multiple dementias

major component of Lewy Bodies

Q: how important for Parkinson's?

MSA might include Prion diseases

Lewy Body pathologies are in contrast with

TDP-43 and Tauopathies

not so Heavenly Bodies:

Lipofuscin – in lysosomes, cytosol
Lewy Bodies – diff. locations
RNA foci – fluoresc. dots in nucleus
RNA granules: related to dyshomeostasis
Ubiquitinylated Inclusions: TDP43-FTD
Marinesco Bodies – in catechol. nuclei
NFTs, PHFs (tau) – cytosolic
Amyloid Plaques - extracellular

Alpha Synuclein is found in Lewy Bodies and seems to play a causative role in their formation (SNCD, p. 117 -118), but we still do not know (i) WHY they are neurotoxic or (ii) why certain neurons are predisposed to them. While PD is not a big focus this semester, Lewy-body Dementia/LBD is of interest, in terms of Cognitive Decline.

The Contribution of Tau, Amyloid-Beta and Alpha-Synuclein Pathology to Dementia in Lewy Body Disorders

David J. Irwin and Howard I. Hurtig*

J. Alzheimers Disease & Parkinsonism -- 2018

NOTE: Alpha-synuclein (in Lewy Bodies) occurs in dementias **both with PD** (called PDD here) and in **"pure LBD"** i.e. patients with dementia but minimal Parkinson signs.

Abstract

Parkinson's Disease (PD) and the closely related Dementia with Lewy Bodies (DLB) are due to the accumulation of pathogenic alpha-synuclein protein in brain cells manifest by heterogeneous motor and non-motor symptoms, including cognitive impairment and dementia. The majority of patients with Parkinson's Disease develop Dementia (PDD) in late stages of the disease and have widespread neocortical distribution of alpha-synuclein pathology at autopsy, compared with PD without dementia, in which neocortical synuclein pathology is less prevalent. These three entities PD, DLB and PDD comprise a clinical spectrum, collectively known as Lewy Body Disorders (LBD). Recent investigations into the neuropathological basis of LBD have demonstrated that while synuclein pathology is the defining feature of these disorders, it is often accompanied by other age-related neurodegenerative pathologies. In particular, amyloid plaque and tau tangle pathology characteristic of Alzheimer's Disease (AD) (~50% of all LBD patients have sufficient pathology at autopsy for a secondary neuropathologic diagnosis of AD), appear to contribute to cognitive impairment in LBD, and the combination is associated with a shorter interval between

Their term Lewy Body Disorders was a distant third BUT *Dementia with Lewy Bodies* = 64,000 hits!

Literature Nomenclature
is Convoluted ***AND*** Garbled!

or Fronto-Temporal Lobar Dementia!

FTD is Fronto-Temporal Dementia
including PPA, Semantic Dementia and bvFTD

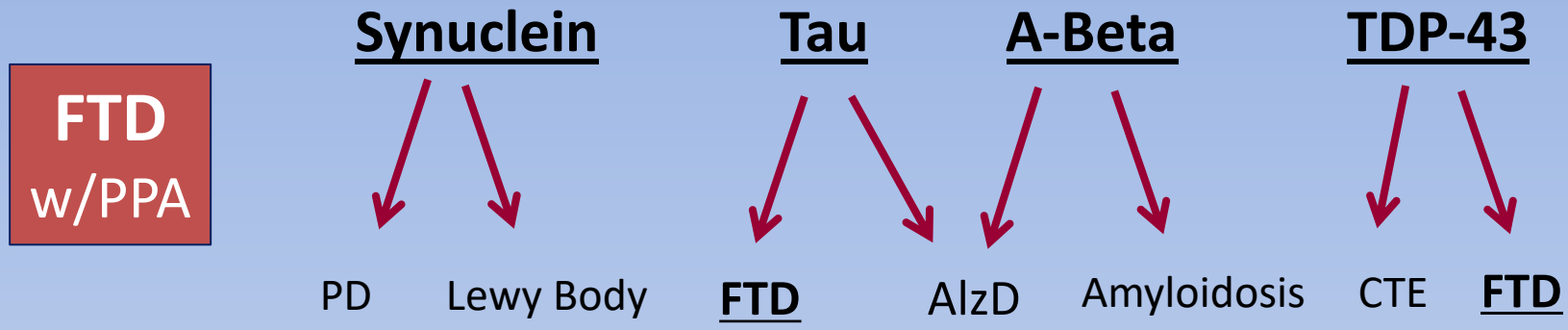
PPA = Primary Progressive Aphasia
bvFTD = behavioral variant FTD
SemD = Semantic Dementia

The Cast of Bad Actors

- **FTD:** includes behav. variants, semantic dementia, primary progressive aphasia
- **Tau Pathology** takes on multiple forms and occurs in multiple subtypes, as does:
- **TDP-43** = TAR DNA-binding protein 43, transcription factor; also ***fus***

  TDP-43 = major disease protein in ubiquitin-positive, tau-/alpha-synuclein-negative FTD

  cool fact: toxic TDP-43 is hyperphosphorylated. Implications?
- **FTLD** = pseudonym for FTD. FTLD encompasses the rat's nest of pathologies that underlie the clinical cases which go more by the FTD brand!
- **Pick's Disease** = pseudonym for Tauopathies! [*historically convoluted*, see SNCD]



More on FTD (fronto-temporal dementia) including PPA

- includes Pick's Disease and other early-onset dementias (e.g. ages 45 to 65)
- **progressive loss of spindle neurons in frontal and temporal lobes = R-Topic**
- can involve tau and TDP-43 proteins, and other proteins (**see Chap. 12**)
- "frontotemporal lobar degeneration" is the *pathology* underlying FTD *syndrome*

Primary Progressive Aphasia (PPA) is a subtype of FTD. PPA is 50% TDP-positive.

How can "a disease" be 50% TDP positive? *There are a number of possibilities:*

1. PPA is two distinct diseases with unrelated etiologies. One requires TDP.
2. TDP plays a contributory role in a multifactorial, multigenic illness, e.g.:
   e.g. 5 factors produce PPA, the presence of any 3 yields PPA symptoms, progression
3. TDP is irrelevant to etiology/symptoms of PPA (but might be relevant to other FTDs)
   - TDP might be present at same frequency in PPA as general population (prolly not true)
   - TDP might be present at higher frequencies in PPAs, yet still play no role in illness.

Table 13.1 -- *Better Version* than in your SNCD hardcopy**

Categories of FTD Dementia. Delving into neurodegeneration leads us into the *fog of dementia* with all its overlapping, fuzzy and contradictory reports. **Table 13.1** attempts to parse the major variants of FTD along with guesstimates of how much different pathologies contribute to each variant. Not that this will help, but, for a given FTD variant (e.g. bvFTD) the next 3 columns show approximate contributions of different pathologies—each of which is considered a different "FTLD"! We said it wouldn't help, but please do note that *only the far right column concerns familial cases*: we welcome contributions to help us flesh out and refine this table.

Table 13.1	**% tau-Picks**	**% TDP**	**% fus**	**useful resource**	**-- % familial**
bvFTD	55%	25%	20%	Bang et al. 2015	-- 33% *MAPT, GRN C90RF72*
SemD	20%	80%	???	Landin-Romero 2016	-- 5% [all non-TDP?]
PPA	88%	50%	???	Bang et al. 2015	-- family history ~ 25%
CBD/PSP	50%	25% - 50%	???	Kertesz et al., 2006; Bang	--

Table 13.1: Pathology underlying FTP Variants. This table attempts to provide rough / best estimates of the contributions of pathology to different FTD variants, as well as the fraction of each variant that is familial (genetically inherited). The percentages given for different pathologies concern the sporadic cases; the familial cases are a separate category and the familial % shown, for each FTD variant, is a guess as to what % of the total number of sporadic + familial cases is familial. Of the total FTD population, bvFTD is the most common variant, while SemD makes up about 1/3rd of FTD cases per Landin-Romero et al. (2016); who also note some associations between tau mutations and TDP pathology subtypes). Yokota et al. (2009) provides pathology estimates that overlap table values: all SemD cases had TDP; bvFTD was 64% "Picks" (tau); 28% TDP-43. In those bvFTD and PPA cases that showed strong motor (ALS-like) symptoms, which some classify as FTD-MND (motoneuron disease), predominantly TDP-43 pathology was reported by Vinceti et al. (2019), but see further details below. Tee and Gorno-Tempini (2019) summarize family history data for PPA and SemD.

****My only TABLE got chopped in two in the publication process. ☹**

Deeper Dive into FTD Pathologies

NOT Assigned READING for TUESDAY!

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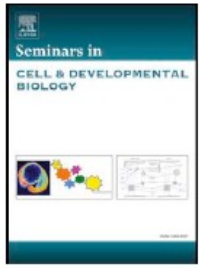
Mandrioli-2020

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb



Review

ALS and FTD: Where RNA metabolism meets protein quality control = PQC

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ARTICLE INFO

Keywords:
Amyotrophic lateral sclerosis
Frontotemporal dementia
Phase separation
Stress granules
Protein quality control
Protein aggregation

ABSTRACT

We can add another body

Recent genetic and biochemical evidence has improved our understanding of the pathomechanisms that lead to amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), two devastating neurodegenerative diseases with overlapping symptoms and causes. Impaired RNA metabolism, enhanced aggregation of protein-RNA complexes, aberrant formation of ribonucleoprotein (RNP) granules and dysfunctional protein clearance via autophagy are emerging as crucial events in ALS/FTD pathogenesis. Importantly, these processes interact at the molecular level, converging on a common pathogenic cascade. In this review, we summarize key principles underlying ALS and FTD, and we discuss how mutations in genes involved in RNA metabolism, protein quality control and protein degradation meet mechanistically to impair the functionality and dynamics of RNP granules, and how this leads to cellular toxicity and death. Finally, we describe recent advances in understanding signaling pathways that become dysfunctional in ALS/FTD, partly due to altered RNP granule dynamics, but also with stress granule-independent mechanisms and, thus could be promising targets for future therapeutic intervention.

SCIENTIFIC REPORTS

Interesting Article, Helpful INTRO

2018

OPEN

TDP43 nuclear export and neurodegeneration in models of amyotrophic lateral sclerosis and frontotemporal dementia

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Hilary C. Archbold[1], Kasey L. Jackson[2], Ayush Arora[1], Kaitlin Weskamp[1,3], Elizabeth M.-H. Tank[1], Xingli Li[1], Roberto Miguez[1], Robert D. Dayton[2], Sharon Tamir[4], Ronald L. Klein[2] & Sami J. Barmada[1,3,5]

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are progressive neurodegenerative disorders marked in most cases by the nuclear exclusion and cytoplasmic deposition of the RNA binding protein TDP43. We previously demonstrated that ALS–associated mutant TDP43 accumulates within the cytoplasm, and that TDP43 mislocalization predicts neurodegeneration. Here, we sought to prevent neurodegeneration in ALS/FTD models using selective inhibitor of nuclear export (SINE) compounds that target exportin-1 (XPO1). SINE compounds modestly extend cellular survival in neuronal ALS/FTD models and mitigate motor symptoms in an *in vivo* rat ALS model. At high doses, SINE compounds block nuclear egress of an XPO1 cargo reporter, but not at lower concentrations that were associated with neuroprotection. Neither SINE compounds nor leptomycin B, a separate XPO1 inhibitor, enhanced nuclear TDP43 levels, while depletion of XPO1 or other exportins had little effect on TDP43 localization, suggesting that no single exporter is necessary for TDP43 export. Supporting this hypothesis, we find overexpression of XPO1, XPO7 and NXF1 are each sufficient to promote nuclear TDP43 egress. Taken together, our results indicate that redundant pathways regulate TDP43 nuclear export, and that therapeutic prevention of cytoplasmic TDP43 accumulation in ALS/FTD may be enhanced by targeting several overlapping mechanisms.

Read through slides 15-16-17. This weekend: email any questions you have about the papers.

SCIENTIFIC REPORTS

OPEN

TDP43 nuclear export and neurodegeneration in models of

Interesting Article
Helpful INTRO

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease, affecting approximately 2-3 per 100,000 individuals worldwide[1–3]. Although traditionally described as a pure motor condition that spares cognition[4], up to half of those diagnosed with ALS exhibit cognitive and behavioral deficits analogous to those found in a separate disorder, frontotemporal dementia (FTD)[5,6]. Supporting a fundamental connection between ALS and FTD, mutations in several genes, including *TARDBP*, *FUS*, *UBQLN2*, *TBK1*, *VCP*, *OPTN*, and *C9orf72*, result in both diseases[7–16]. Moreover, in the majority of those with ALS and FTD, the pathologic hallmark of disease is the cytoplasmic deposition of the nuclear RNA binding protein TDP43[17], implying a common mechanism underlying these clinically-overlapping neurodegenerative disorders.

The subcellular localization of TDP43 and related RNA binding proteins is critical for the function and the survival of neurons. These proteins contain nuclear localization and nuclear export signals that facilitate rapid trafficking between the nucleus and cytoplasm. Disrupting the TDP43 nuclear localization signal enhances neurotoxicity[18–20] and, in some cases, mimics the effects of disease-associated mutations in *TARDBP*, the gene encoding TDP43[18]. Strategies that effectively reduce cytoplasmic TDP43 concentrations, including the induction of macroautophagy (one of the major catabolic pathways active within the cytoplasm)[21], prevent neurodegeneration and extend cellular survival in models of ALS and FTD. These observations underscore the physiologic importance of cytoplasmic protein deposition in the pathogenesis of ALS and FTD.

recall: IDPs, RNA-dyshomeostasis, nuclear pores (import, export)

Acta Neuropathol. 2010 Jul; 120(1): 33–41.
Published online 2010 May 20. doi: 10.1007/s00401-010-0698-6
PMCID: PMC2887939
NIHMSID: NIHMS214921

FUS pathology defines the majority of tau- and TDP-43-negative frontotemporal lobar degeneration ← FTLD ≈ FTD

FTLD is another name for FTD. sorta**
Gory Details **in Chapter 13!**

Through an international consortium, we have collected 37 tau- and TAR DNA-binding protein 43 (TDP-43)-negative frontotemporal lobar degeneration (FTLD) cases, and present here the first comprehensive analysis of these cases in terms of neuropathology, genetics, demographics and clinical data. 92% (34/37) had fused in sarcoma (FUS) protein pathology, indicating that FTLD-FUS is an important FTLD subtype. This FTLD-FUS collection specifically focussed on aFTLD-U cases, one of three recently defined subtypes of FTLD-FUS. The aFTLD-U subtype of FTLD-FUS is characterised clinically by behavioural variant frontotemporal dementia (bvFTD) and has a particularly young age of onset with a mean of 41 years. Further, this subtype had a high prevalence of psychotic symptoms (36% of cases) and low prevalence of motor symptoms (3% of cases). We did not find *FUS* mutations in any aFTLD-U case. To date, the only subtype of cases reported to have ubiquitin-positive but tau-, TDP-43- and FUS-negative pathology, termed FTLD-UPS, is the result of charged multivesicular body protein 2B gene (*CHMP2B*) mutation. We identified three FTLD-UPS cases, which are negative for CHMP2B mutation, suggesting that the full complement of FTLD pathologies is yet to be elucidated.

Keywords: FTLD, FUS, FT

Hazel Urwin,[1] Keith A. Josephs,[25] Jonathan D. Rohrer,[2] Ian R. Mackenzie,[7] Manuela Neumann,[8] Astrid Authier,[1] Harro Seelaar,[9] John C. Van Swieten,[9] Jeremy M. Brown,[10] Peter Johannsen,[11] Jorgen E. Nielsen,[11,12] Ida E. Holm,[13] The FReJA Consortium, Dennis W. Dickson,[14] Rosa Rademakers,[14] Neill R. Graff-Radford,[14] Joseph E. Parisi,[6] Ronald C. Petersen,[5] Kimmo J. Hatanpaa,[15] Charles L. White III,[15] Myron F. Weiner,[16] Felix Geser,[17] Vivianna M. Van Deerlin,[17] John Q. Trojanowski,[17] Bruce L. Miller,[18] William W. Seeley,[18] Julie van der Zee,[19,20] Samir Kumar-Singh,[19,20] Sebastiaan Engelborghs,[20,21] Peter P. De Deyn,[20,21] Christine Van Broeckhoven,[19,20] Eileen H. Bigio,[22] Han-Xiang Deng,[23] Glenda M. Halliday,[24] Jillian J. Kril,[25] David G. Munoz,[26] David M. Mann,[27] Stuart M. Pickering-Brown,[28] Valerie Doodeman,[29] Gary Adamson,[1] Shabnam Ghazi-Noori,[1] Elizabeth M. C. Fisher,[3] Janice L. Holton,[4] Tamas Revesz,[4] Martin N. Rossor,[2] John Collinge,[1,3] Simon Mead,[1] and Adrian M. Isaacs[21]

Introduction

Frontotemporal lobar degeneration (FTLD) describes a group of diseases characterised by bilateral, often asymmetric, atrophy of the frontal and anterior temporal lobes. Frontotemporal dementia (FTD), also termed behavioural variant FTD (bvFTD), is the most common clinical manifestation, but FTLD can also cause the language disorders progressive non-fluent aphasia

fus sound familiar?

= fused in sarcoma
= IDP (intrinsically disordered protein)
fus pathology ➔ bvFTD at age 41!

this is a variant of FTD that is both tau, TDP43 negative w/ few motor signs
mechanism of *fus* induced degeneration is uncertain; "variant" details not testable

TDP-43: associated w/ ALS, CTE, FTD

- binds to thousands of RNAs in neurons
- involved in splicing, transcription repression
- found in hippo. dendrites, binds neurofilament

CTE = Chronic Traumatic Encephalopathy
[stay tuned! in Chapter 13?]
chalk-talk: 1000 / 100 argument below
but I still like "League of Denial" documentary

FTD, FTLD are just two ways of looking at the same spectrum of disease**

Implications of the prion-related Q/N domains in TDP-43 and FUS

Maria Udan[1] and Robert H. Baloh[1,2,*]
[1]Department of Neurology; Neuromuscular Division; [2]Hope C ersity; St. Lou

more about ALS than FTD:

in Prion, 2011

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are clinically overlapping neurodegenerative disorders whose pathophysiology remains incompletely understood. ALS initiates in a discrete location and typically progresses in a pattern consistent with spread of the degenerative process to involve neighboring regions of the motor system, although the basis of the apparent "spread" remains elusive. Recently mutations in two RNA binding proteins, TDP-43 and FUS, were identified in patients with familial ALS. In addition to being involved in numerous events related to RNA metabolism, each forms aggregates in neurons in ALS and FTLD. Recent evidence also indicates that both TDP-43 and FUS contain prion-related domains rich in glutamine (Q) and asparagine (N) residues, and in the case of TDP-43 this is the location of most disease causing mutations. This review discusses the potential relevance of the prion-related domains in TDP-43 and FUS in normal physiology, pathologic aggregation and disease progression in ALS and FTLD.

it typically has a focal site of onset in the nervous system, i.e., begins with unilateral hand weakness. Second, progression is characterized by apparent "spread" of neurodegeneration, usually to the contralateral hand, followed by involvement of the legs. Recent detailed autopsy studies of ALS patients have confirmed that loss of motor neurons is most pronounced at the site of onset and diminishes in a gradient fashion with further distance from that site.[3] While many aberrant phenomena including excitotoxicity, oxidative stress, mitochondrial dysfunction and altered axonal transport have been implicated in ALS pathogenesis, it is not easily apparent how any of these could explain the focal initiation or the progressive spread of the disease through the motor system.[4]

While the majority of ALS occurs sporadically, approximately 5–10% of patients have a family history of the disorder, typically autosomal dominant. For nearly 15 years the only known ALS gene was SOD1, mutations in which are responsible for ~20% of familial cases. In 2006, accumulations of a RNA binding protein called TDP-43 were identified in degenerating neurons in both ALS and

TDP-43, *fus*: reprised!

- role in ALS, FTD
- mechanism of spread unknown

ALS pathology starts focal

← candidate mechanisms

SOD mutations = 1 candidate

2006: TDP-43 identified

Prion-like domains noted

accounts for spread, damage?

Udan, in Prion, 2011

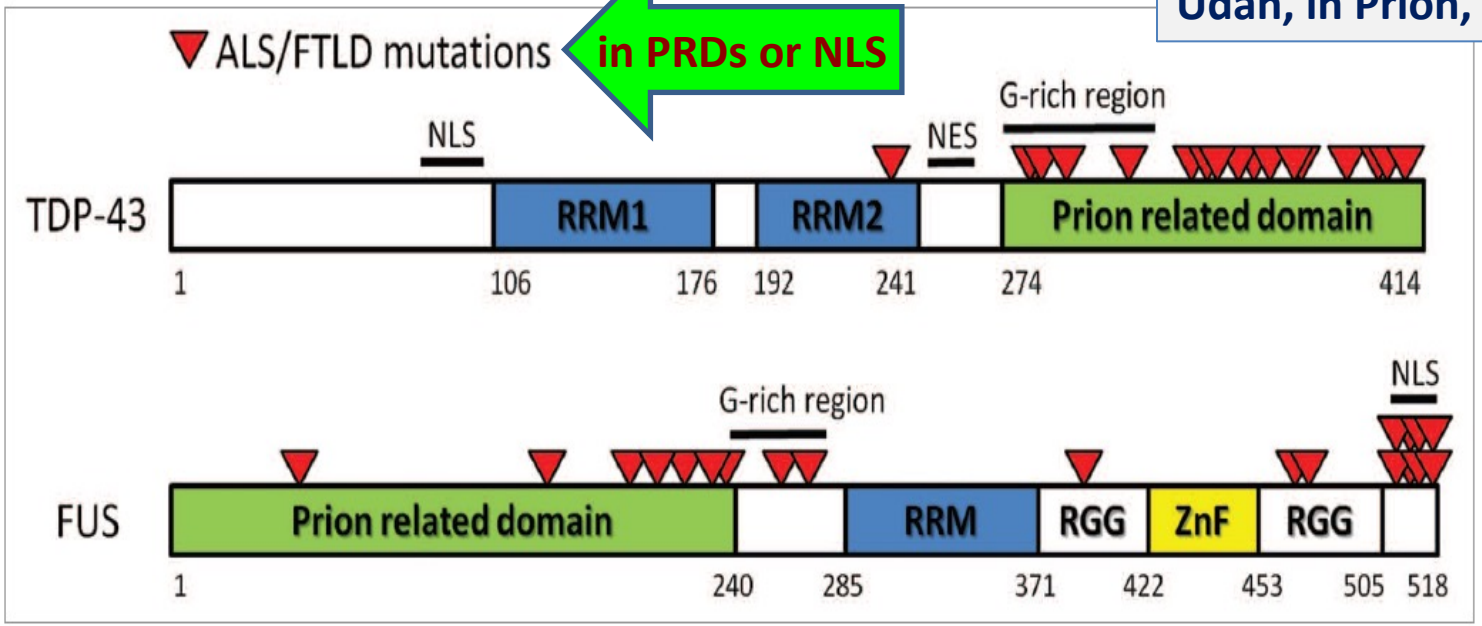

Figure 1. Line diagrams of TDP-43 and FUS showing the relationship between the prion-related domains and mutations in ALS and FTLD. The location of the prion-related domains are based on experimental findings of their interactions with polyglutamine inclusions[13,14] and a prediction algorithm based on yeast prion domains.[15] In the case of TDP-43, all but one of the ALS associated mutations are located in the prion-related Q/N rich domain. In FUS, the majority of ALS associated mutations occur in the C-terminal nuclear localization signal (NLS). However, a second cluster also occurs in or adjacent to the N-terminal prion related domain. NES, nuclear export signal; RRM, RNA binding domain; RGG, arginine, glycine, glycine repeat rich region; ZnF, zinc finger domain.

- TDP-43 and *fus*, two of the major players in FTD (and ALS) are suggested to have Prion like properties!
- AlzD *also* suggested to be prion-esque

frontiers in
AGING NEUROSCIENCE

OPINION ARTICLE
published: 02 March 2015
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Intrinsically disordered proteins and their (disordered) proteomes in neurodegenerative disorders

2015

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Table 1 | IDPs and associated neurodegenerative diseases.

Protein (number of residues)	Disease(s)	Disorder by prediction (%)[a]	Number of binding partners on BioGrid[b]
Aβ (42)	Alzheimer's disease Dutch hereditary cerebral hemorrhage with amyloidosis Congophilic angiopathy	16.9 (28.6)	1975 (for the Aβ precursor protein)
Tau (758)	Tauopathies Alzheimer's disease Corticobasal degeneration Pick's disease Progressive supranuclear palsy	77.6 (99.1)	73
Prion protein (231)	Prion diseases Creutzfeld-Jacob disease Gerstmann- Sträussler -Schneiker syndrome Fatal familial insomnia Kuru Bovine spongiform encephalopathy Scrapie Chronic wasting disease	55.8 (61.0)	60
α-Synuclein (140)	Synucleinopathies Parkinson's disease Lewy body variant of Alzheimer's disease Diffuse Lewy body disease Dementia with Lewy bodies Multiple system atrophy Neurodegeneration with brain iron accumulation type I	90.7 (37.1)	416
β-Synuclein (134)	Parkinson's disease Diffuse Lewy body disease	87.3 (52.2)	16
γ-Synuclein (127)	Parkinson's disease Diffuse Lewy body disease	100 (56.8)	26
TDP43 (414)	Amyotrophic lateral sclerosis and frontotemporal lobar degeneration	57.3 (35.8)	286

SEE NEXT SLIDE

An UPDATE on IDPs and DEMENTIA! ➔

Table 1 | IDPs and associated neurodegenerative diseases.

2015

Protein (number of residue	Number of binding partners on BioGrid[b]	Disease(s)
Aβ (42)	1975 (for the Aβ precursor protein)	Alzheimer's disease Dutch hereditary cerebral hemorrhage with amyloidosis Congophilic angiopathy
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TDP43 (414)	286	Amyotrophic lateral sclerosis and frontotemporal lobar degeneration

Quite the CAST of CHARACTERS!

We find AlzD, LBD, multiple forms of FTD and assorted lesser dementias in this table (like CBD, MSA, PSP).

… not to mention the Mad Cows and Cannibals!

Don't eat AlzD Brains!

TDP-43 pathology in anterior temporal pole cortex in aging and Alzheimer's disease

Sukriti Nag[1,2*], Lei Yu[1,3], Patricia A. Boyle[1,4], Sue E. Leurgans[1,3], David A. Bennett[1,3] and Julie A. Schneider[1,2,3]

Nag et al. Acta Neuropathologica Communications (2018) 6:33

Abstract

heard of ATPC? *heard of OFC?* **5-Stage Process!**

TDP-43 pathology was investigated in the anterior temporal pole cortex (ATPC) and orbital frontal cortex (OFC), regions often degenerated in frontotemporal lobar degenerations (FTLD), in aging and Alzheimer's disease (AD). Diagnosis of dementia in the 1160 autopsied participants from 3 studies of community-dwelling elders was based on clinical evaluation and cognitive performance tests which were used to create summary measures of the five cognitive domains. Neuronal and glial TDP-43 cytoplasmic inclusions were quantitated in 8 brain regions by immunohistochemistry, and used in ANOVA and regression analyses. TDP-43 pathology was present in 547 (49.4%) participants in whom ATPC (41.9%) was the most frequently involved neocortical region and in 15.5% of these cases, ATPC was the only neocortical area with TDP-43 pathology suggesting not only that ATPC is involved early by TDP-43 but that ATPC may represent an intermediate stage between mesial temporal lobe involvement by TDP-43 and the last stage with involvement of other neocortical areas. To better study this intermediary neocortical stage, and to integrate with other staging schemes, our previous 3 stage distribution of TDP-43 pathology was revised to a 5 stage distribution scheme with stage 1 showing involvement of the amygdala only; stage 2 showed extension to hippocampus and/or entorhinal cortex; stage 3 showed extension to the ATPC; stage 4 – showed extension to the midtemporal cortex and/or OFC and finally in stage 5, there was extension to the midfrontal cortex. Clinically, cases in stages 2 to 5 had impaired episodic memory, however, stage 3 was distinct from stage 2 since stage 3 cases had significantly increased odds of dementia. The proportion of cases with hippocampal sclerosis increased progressively across the stages with stage 5 showing the largest proportion of hippocampal sclerosis cases. Stage 5 cases differed from other stages by having impairment of semantic memory and perceptual speed, in addition to episodic memory impairment. These data suggest that of the regions studied, TDP-43 pathology in the ATPC is an important early neocortical stage of TDP-43 progression in aging and AD while extension of TDP-43 pathology to the midfrontal cortex is a late stage associated with more severe and global cognitive impairment.

not really a nag

big TDP study
1160 elderly
5 cognitive domains
immuno postmortem
curious results
ATPC ≈ Semantic Dementia

- **Anterior Temporal Pole**: in 15% of cases, ATPC was only neocortical area w/ TDP-43
- **Why/How does TDP-43 spread**? Is it often not widespread b/c "community dwelling"?
- ATPC is strongly involved in **Semantic Dementia** (not "really" PPA, imho). **5-stage --**
- **progression is**: amygdala, hippo or ERC, **ATPC**, mid-temporal/OFC, PFC more broadly

to do: check Discussion for relevance to AlzD (vs. FTD)

nice bvFTD OVERVIEW 2011

Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management

bvFTD highlighted in CHAPTER 15

Olivier Piguet, Michael Hornberger, Eneida Mioshi, John R Hodges

Lancet Neurol 2011; 10: 162–72

Published Online December 13, 2010 DOI:10.1016/S1474-4422(10)70299-4

Neuroscience Research Australia, Randwick, NSW, Australia (O Piguet PhD, M Hornberger PhD, E Mioshi PhD, Prof J R Hodges FMedSci)

Correspondence to: Prof John Hodges, Neuroscience Research Australia, Barker St, Randwick, NSW 2031, Australia **j.hodges@neura.edu.au**

Patients with behavioural-variant frontotemporal dementia (bvFTD) present with insidious changes in personality and interpersonal conduct that indicate progressive disintegration of the neural circuits involved in social cognition, emotion regulation, motivation, and decision making. The underlying pathological changes are heterogeneous and are characterised by various intraneuronal inclusions. Biomarkers to detect these histopathological changes in life are becoming increasingly important with the development of disease-modifying drugs. Gene mutations have been found that collectively account for around 10–20% of cases. Recently, criteria proposed for bvFTD define three levels of diagnostic certainty: possible, probable, and definite. Detailed history taking from family members to elicit behavioural features underpins the diagnostic process, with support from neuropsychological testing designed to detect impairment in decision making, emotion processing, and social cognition. Brain imaging is important for increasing the level of diagnostic certainty. A recently developed staging instrument shows much promise for monitoring patients and evaluating therapies, which at present are aimed at symptom amelioration. Carer education and support remain of paramount importance.

bvFTD most pathologically diverse FTD: TDP-43, tau and some fus

[vs. PPA (mostly tau), SemanticD (mostly TDP-43)]

several tau isoforms (3R, 4R) or TDP-43 inclusion bodies [w/ubiquitin]

complex genetics but stronger familial contribution than AlzD

family "history" of possible FTD contaminated by sporadic AlzD

but if multiple 1st degree "suspect" relatives ➔ screen for MAPT, GRN genes

odd behaviors is strongest indicator of bvFTD, especially at onset

but symptoms emerge gradually; care-giver details are crucial

phenocopy bvFTD: no atrophy, cogn. decline, only men, might get better

Diagnosis of bvFTD

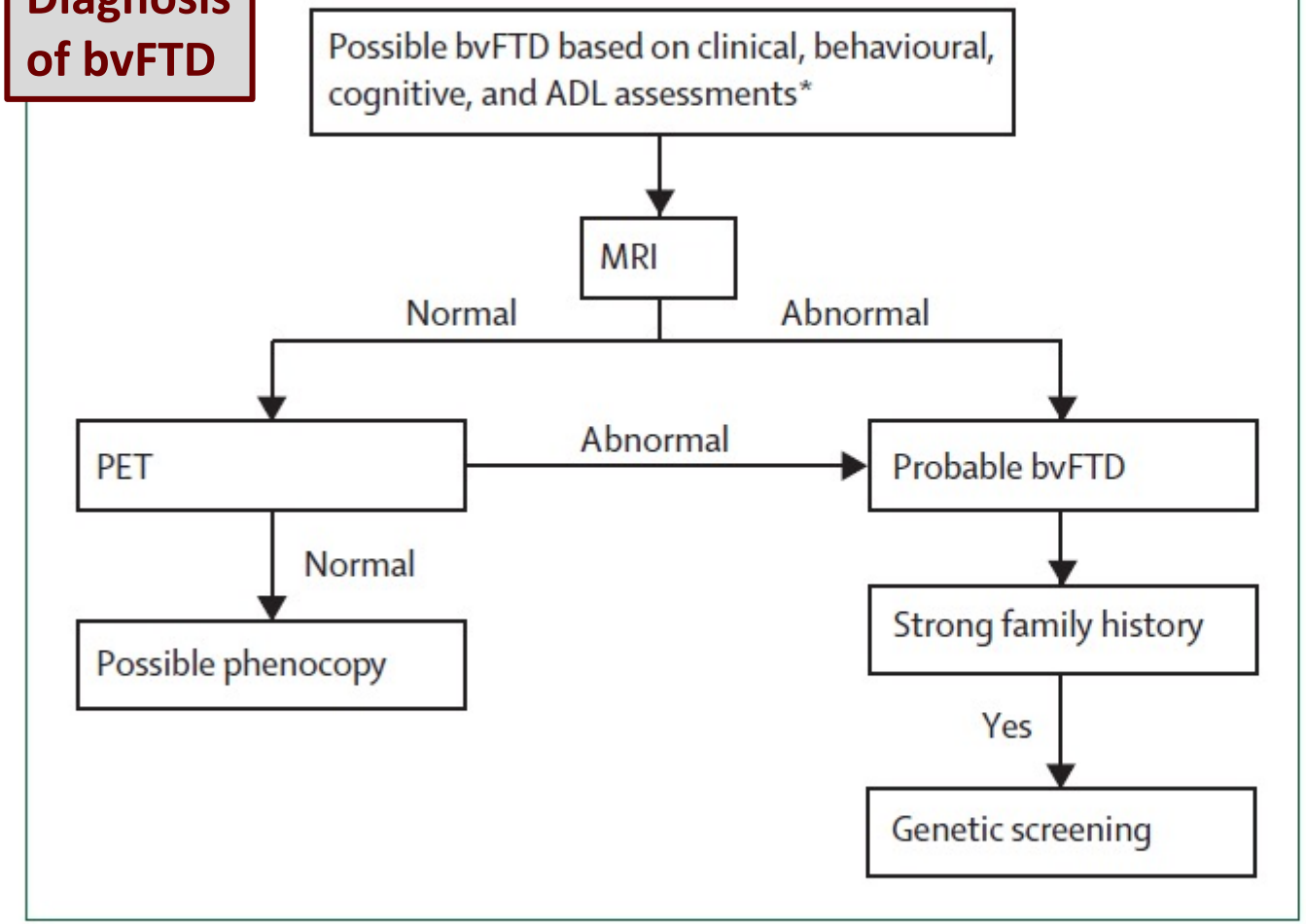


Figure 1: Possible investigations after the diagnosis of suspected bvFTD based on clinical assessment

Piguet et al., 2011 Lancet

Symptoms may include: behavioral disinhibition, (I love security, shop-lifting) hyper-orality, loss of sympathy/empathy, compulsiveness, executive function deficits with relative sparing of memory and visuospatial functions

see SNCD Chaps. 12 13

Should AlzD be *called* a tauopathy???

Tauopathy: FTD style! ignore all the AlzD details…for now

Tauopathy

Since Tauopathies have *no requirement* **for involvement of beta-amyloid,** ***but AlzD does*****, should we EXCLUDE AlzD from our DISCUSSION of tauopathy? … YES…**

…but this is NOT the approach of Wikipedia!

Tauopathies are a class of neurodegenerative diseases associated with the pathological aggregation of tau protein[1] in the human brain.

The best-known of these illnesses is Alzheimer's disease (AD), wherein tau protein is deposited within neurons in the form of neurofibrillary tangles (NFTs). They were first described by the eponymous Alois Alzheimer in one of his patients suffering from the disorder. Tangles are formed by hyperphosphorylation of a microtubule-associated protein known as tau, causing it to aggregate in an insoluble form. (These aggregations of hyperphosphorylated tau protein are also referred to as PHF, or "paired helical filaments"). The precise mechanism of tangle formation is not completely understood, and it is still controversial as to whether tangles are a primary causative factor in the disease or play a more peripheral role. AD is also classified as an amyloidosis because of the presence of senile plaques.[2]

The degree of NFT involvement in AD is defined by Braak stages. Braak stages I and II are used when NFT involvement is confined mainly to the transentorhinal region of the brain, stages III and IV when there's also involvement of limbic regions such as the hippocampus, and V and VI when there's extensive neocortical involvement. This should not be confused with the degree of senile plaque involvement, which progresses differently.[3]

Other conditions in which neurofibrillary tangles are commonly observed include:

- Progressive supranuclear palsy[4] although with straight filament rather than PHF tau
- Dementia pugilistica (chronic traumatic encephalopathy)[5]
- Frontotemporal dementia and parkinsonism linked to chromosome 17, however without detectable β-amyloid plaques.[6]

← The *REAL* tauopathies iaw SNCD

Tauopathy

MeSH D024801

[edit on Wikidata]

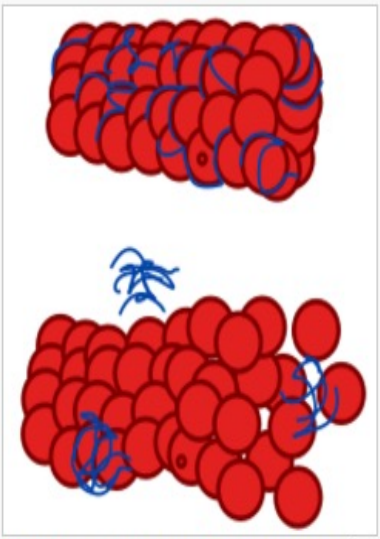


Diagram of a normal microtubule and one affected by tauopathy

Does tauopathy **always present** as NFTs? PHFs?....no… ➔

When Neuropathologists Run Wild

The Amazing Pathology of Tau and "Pick's Disease"

Pick's was once a disease and ≈ FTD

Then FTD became diverse (bvFTD, PPA, SemD)

Then Pick's became Tauopathy (which AlzD, formally, is not)

Table 13.1	% tau-Picks	% TDP	% fus
bvFTD	55%	25%	20%
SemD	20%	80%	???
PPA	88%	50%	???
CBD/PSP	50%	25% - 50%	???

REMEMBER: Tau is not a clinical diagnosis, it is a pathology (when it goes bad). Since Pick's is ≈ "tau pathology", that means it also is NOT a clinical diagnosis. AND YET it is all over the neurology literature

for future note

SemD and PPA are VERY DIFFERENT – more different from each other than from bvFTD. Should we lump them TOGETHER and EXCLUDE bvFTD? And should we then mix in an amyloid-dementia that is completely different from ALL of FTD? why?

Acta Neuropathologica (2019) 138:705–727

HIGHLIGHTS **2019**

A subset of FTD cases involves pathological accumulations of the protein Tau

- While PHFs and NFTs are emblematic of AlzD, **more varied aggregates are seen in FTD**
- Different aggregate-types relate to **isoforms of the Tau protein** (coded by MAPT gene)
- occult implications for neuroanatomical selectivity of pathology and its spread

Shelley Forrest et al.

FTD-tau and other Tauopathies

Cellular and regional vulnerability in frontotemporal tauopathies

we are SKIPPING bodies here!

Abstract

The frontotemporal tauopathies all deposit abnormal tau protein aggregates, but often of only certain isoforms and in distinguishing pathologies of five main types (neuronal Pick bodies, neurofibrillary tangles, astrocytic plaques, tufted astrocytes, globular glial inclusions and argyrophilic grains). In those with isoform specific tau aggregates glial pathologies are substantial, even though there is limited evidence that these cells normally produce tau protein. This review will assess the differentiating features and clinicopathological correlations of the frontotemporal tauopathies, the genetic predisposition for these different pathologies, their neuroanatomical selectivity, current observations on how they spread through the brain, and any potential contributing cellular and molecular changes. The findings show that diverse clinical phenotypes relate most to the brain region degenerating rather than the type of pathology involved, that different regions on the *MAPT* gene and novel risk genes are associated with specific tau pathologies, that the 4-repeat glial tauopathies do not follow individual patterns of spreading as identified for neuronal pathologies, and that genetic and pathological data indicate that neuroinflammatory mechanisms are involved. Each pathological frontotemporal tauopathy subtype with their distinct pathological features differ substantially in the cell type affected, morphology, biochemical and anatomical distribution of inclusions, a fundamental concept central to future success in understanding the disease mechanisms required for developing therapeutic interventions. Tau directed therapies targeting genetic mechanisms, tau aggregation and pathological spread are being trialled, although biomarkers that differentiate these diseases are required. Suggested areas of future research to address the regional and cellular vulnerabilities in frontotemporal tauopathies are discussed.

Neuropathological Features of FTD subtypes: *A Work of Art!*

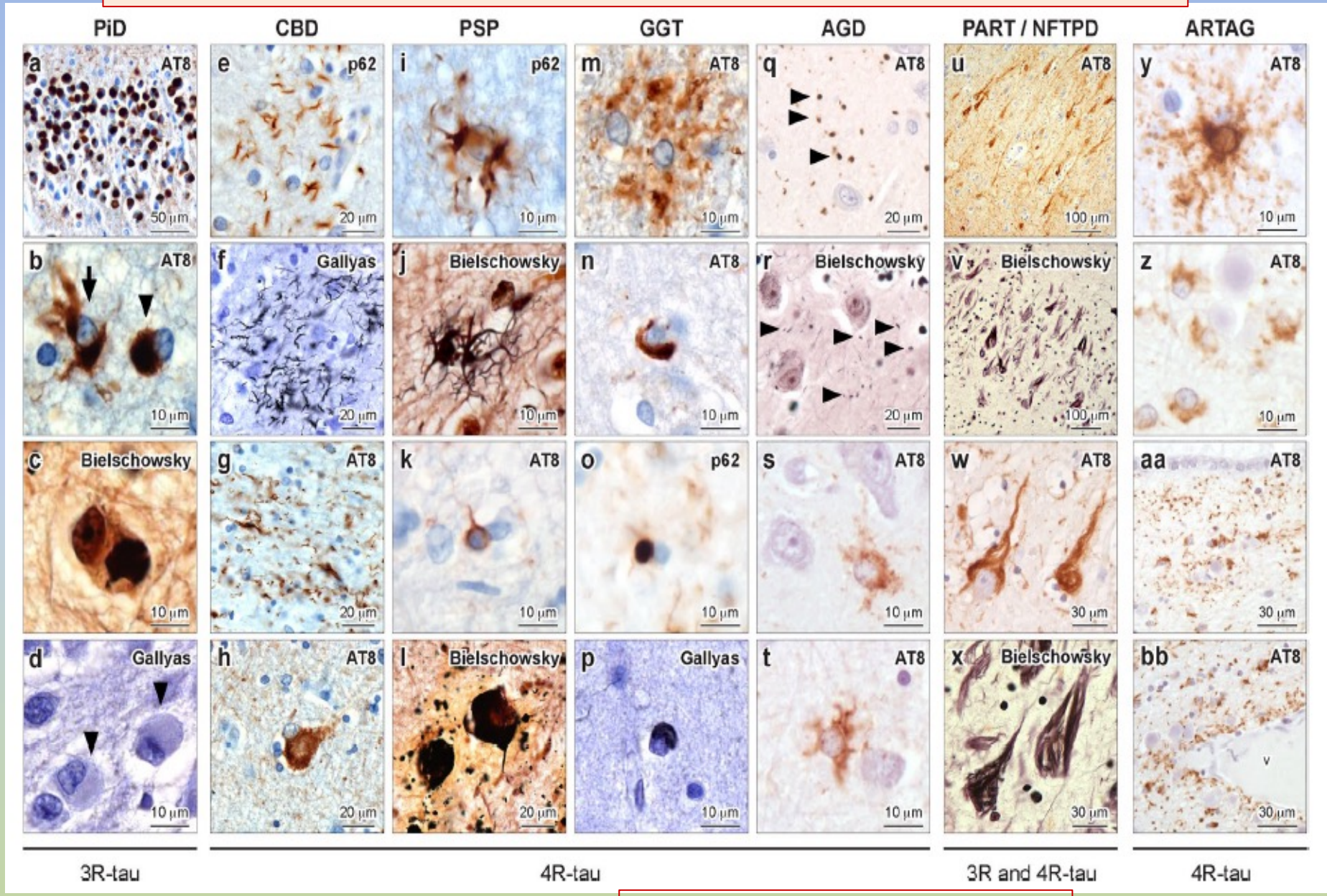


FIGURE 1 – Forrest et al. 2019

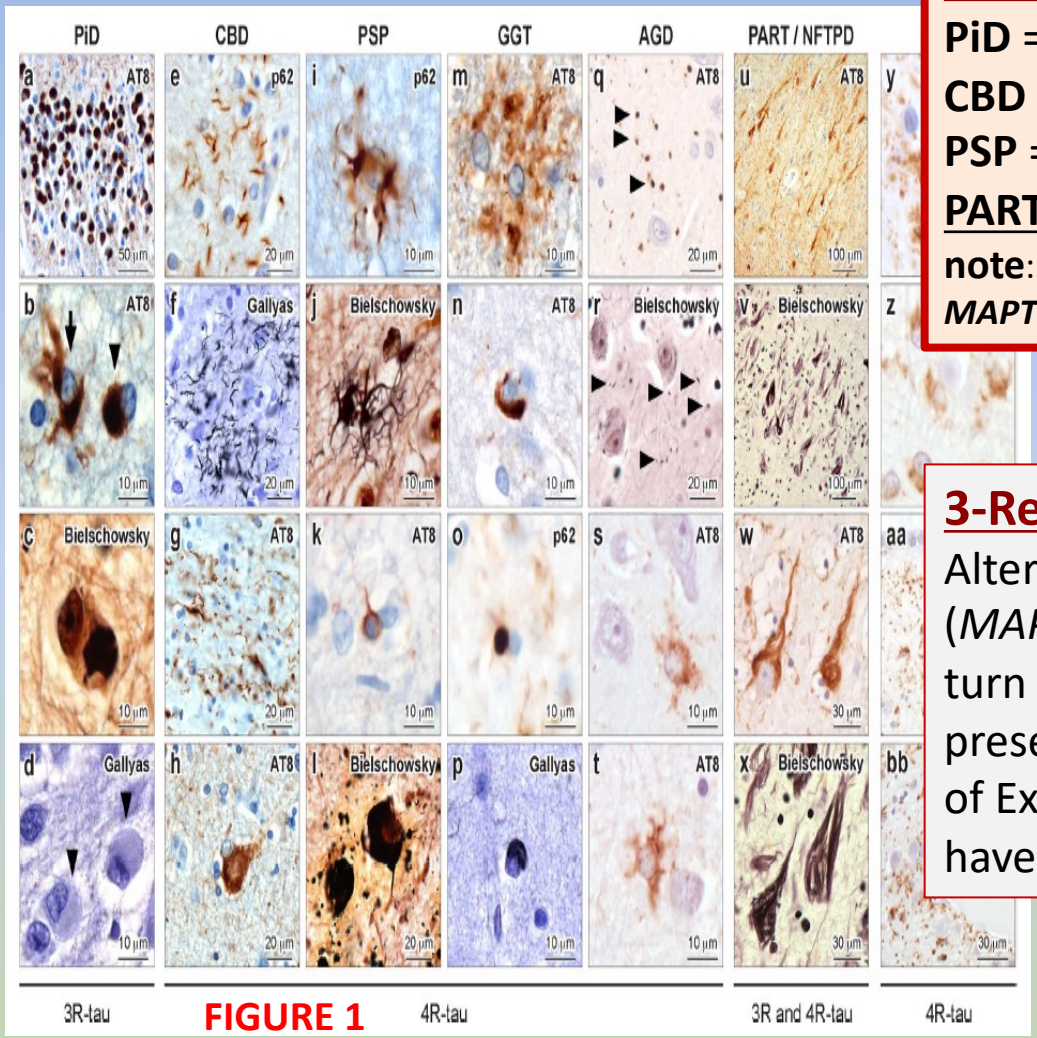


FIGURE 1

FTD variants involving tau

PiD = Pick's Disease (includes some bvFTD)

CBD = cortico-basal degeneration

PSP = progressive supranuclear palsy

PART = primary age-related tauopathy**

note: NONE of these have an amyloid component

MAPT = Microtubule Associated Protein Tau

3-Repeat and 4-Repeat Tau

Alternative splicing of the tau gene (*MAPT*) leads to 6 tau isoforms, which in turn leads to different pathologies as presented in Figure 1. Inclusion/Exclusion of Exon #10 determines if isoform will have 3 or 4 microtubule repeat domains.

In FTD, tau becomes phosphorylated at physiological and pathological sites making it unable to bind to microtubules.

FIGURE 1 – Forrest et al. 2019

Primary age-related tauopathy (PART): a common pathology associated with human aging

John F. Crary · John Q. Trojanowski · Julie A. Schneider · Jose F. Abisambra · Erin L. Abner · Irina Alafuzoff · Steven E. Arnold · Johannes Attems · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Marla Gearing · Lea T. Grinberg · Patrick R. Hof · Bradley T. Hyman · Kurt Jellinger · Gregory A. Jicha · Gabor G. Kovacs · David S. Knopman · Julia Kofler · Walter A. Kukull · Ian R. Mackenzie · Eliezer Masliah · Ann McKee · Thomas J. Montine · Melissa E. Murray · Janna H. Neltner · Ismael Santa-Maria · William W. Seeley · Alberto Serrano-Pozo · Michael L. Shelanski · Thor Stein · Masaki Takao · Dietmar R. Thal · Jonathan B. Toledo · Juan C. Troncoso · Jean Paul Vonsattel · Charles L. White 3rd · Thomas Wisniewski · Randall L. Woltjer · Masahito Yamada · Peter T. Nelson

Acta Neuropathol (2014) 128:755–766
DOI 10.1007/s00401-014-1349-0

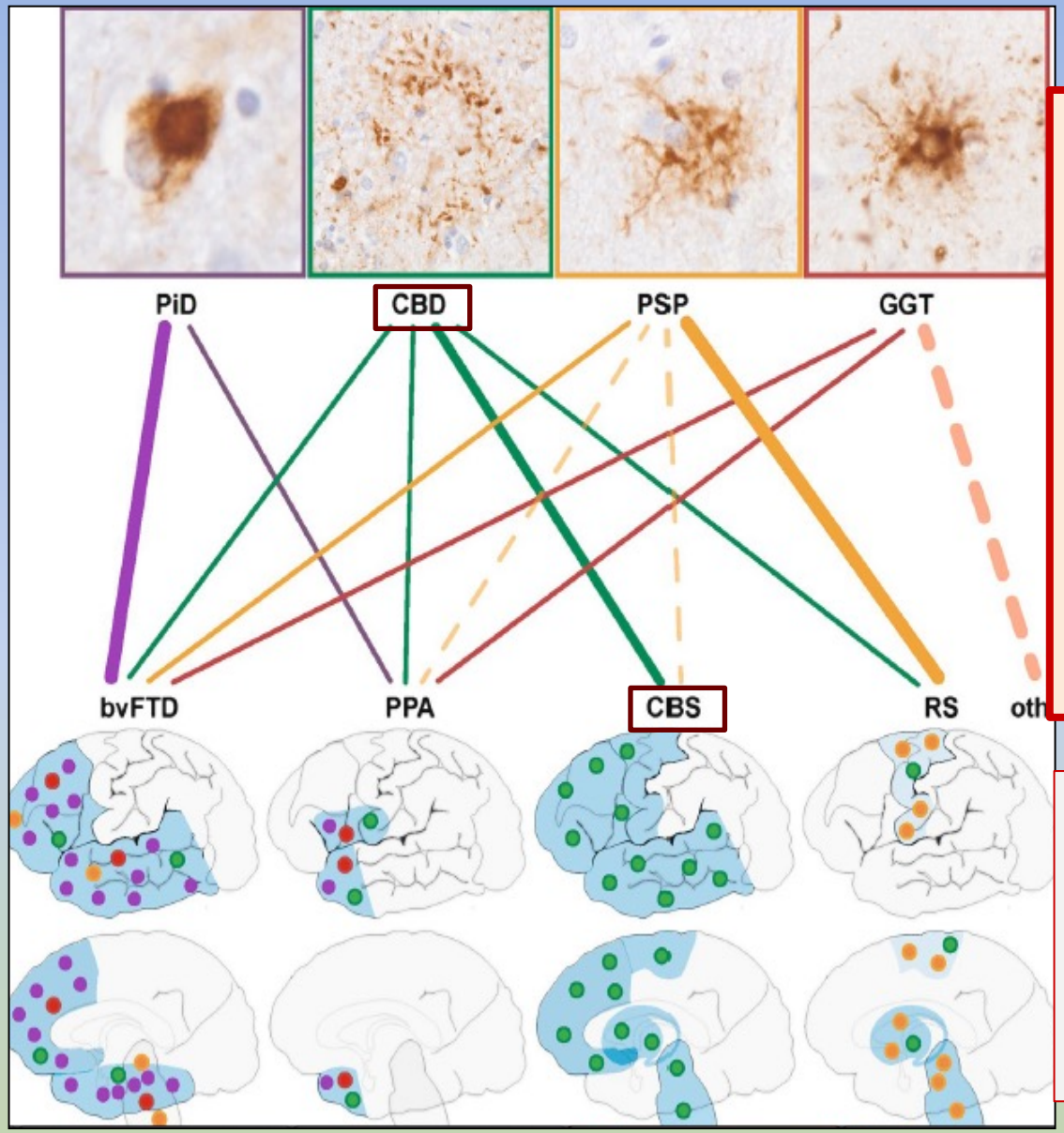
CONSENSUS PAPER

Received: 24 July 2014 / Revised: 26 September 2014 / Accepted: 28 September 2014

Abstract We recommend a new term, "primary age-related tauopathy" (PART), to describe a pathology that is commonly observed in the brains of aged individuals. Many autopsy studies have reported brains with neurofibrillary tangles (NFTs) that are indistinguishable from those of Alzheimer's disease (AD), in the absence of amyloid (Aβ) plaques. For these "NFT+/Aβ−" brains, for which formal criteria for AD neuropathologic changes are not met, the NFTs are mostly restricted to structures in the medial temporal lobe, basal forebrain, brainstem, and olfactory areas (bulb and cortex). Symptoms in persons with PART usually range from normal to amnestic cognitive changes, with only a minority exhibiting profound impairment. Because cognitive impairment is often mild, existing clinicopathologic designations, such as "tangle-only dementia" and PART is almost universally detectable at autopsy among elderly individuals, yet this pathological process cannot be specifically identified pre-mortem at the present time. Improved biomarkers and tau imaging may enable diagnosis of PART in clinical settings in the future. Indeed, recent studies have identified a common biomarker profile consisting of temporal lobe atrophy and tauopathy without evidence of Aβ accumulation.

Not FTD b/c NOT a dementia
- most cases are mild
- very common w/ old age
- role in general Cognitive Decline?

Forrest et al. 2019

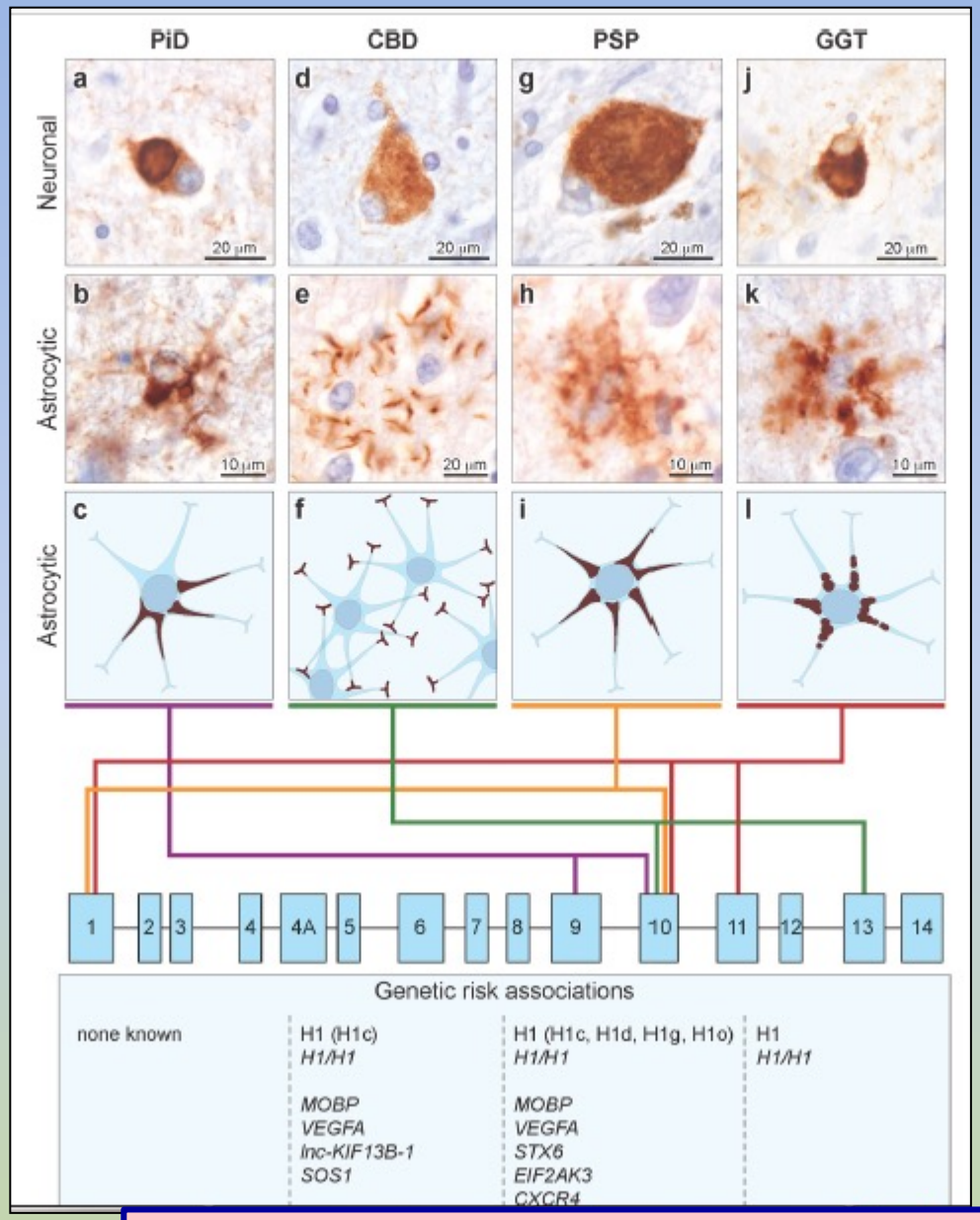


Pathology vs. Syndrome

The clinical syndromes of FTD are not "fully determined" by pathology b/c pathologies found at different neocortical locations can give rise to distinct symptoms / syndromes. For examples Pick's tau pathology (PiD) is most often in anterior PFC and associated with bvFTD, but at times w/ PPA and localized more to language centers.

CBD vs. GGT For our ltd. purposes, Cortico Basal **degeneration** / **CBS syndrome** are the same thing. This contrasts w/ Glial Globular Tauopathy which is only weakly assoc. w/ diff. syndromes and thus not diagnostic.

Figure 2 suggests that the **clinical syndrome** is determined more by the **location** of the pathology than its specific **cellular appearance** (although strong correlations can exist).



Neurons and Astrocytes

The neuronal inclusions vary across different types of FTD-tauopathy (PiD or bvFTD-tau; CBD, PSP). The same holds for astrocytes (upper row = histology; lower row = diagram of localizations in astrocytes).

Genetic Risks

A much larger fraction of FTD cases are familial (~ 50%, but varies by subtype) vs. AlzD which is only 5% familial (i.e. EOAD). In addition to familial cases (with dominant or recessive genes that directly produce the disease) there are also genetic risk-factors that might or might not lead to dementia: much more on this in Chapter 19-SNCD.

Figure 3 identifies familial / genetic risks for FTD-tauopathies and associated pathology in neurons and glia.

Forrest et al. 2019

All the FTDs that are FIT to PRINT!

bvFTD: w/ TDP-43 or fus
PPA
Semantic Dementia
other FTD tauopathies

One disease or many?

meanwhile…

In FTD, somewhere it was said that a specific, non-pyramidal, neuron type was afflicted. They are called Spindle Neurons, but, as it turns out, these are Von Economo neurons. Which is weird, possibly random. **See notes if curious**.

Primary Progressive Aphasia (PPA) is a subtype of FTD. PPA is 50% tau-positive.
How can "a disease" be 50% tau positive? we do not yet have an answer.

A Question of Individual Variation (theoretical)

There is a population of individuals with propensity for Tau "pathology" of whom ***many will never show dementia*** or substantial cognitive deficits (true).

Some "Tau Pathology", by itself, can be innocuous (tau comes in different flavors).

MAYBE **a different pathology**, that is actually causative of PPA symptoms, triggers "tau pathology" in predisposed individuals (thus increasing tau prevalence).

But: if in these same individuals w/ random tau, the tau has no influence upon:

- severity -- progression --- treatment-response

In such cases, the presence of "tau-pathology" is a red herring!

i.e. tau is maybe irrelevant in "other-pathology" FTD cases…

Another, very different, "ANSWER" (a problem really) is that some are lumping disparate diseases into a perhaps too-general:

Case in Point: "PPA category" ➔

caveat: Clinician's View & Under Protest!

Primary Progressive Aphasia (PPA)

- Three variants of the syndrome
  - Logopenic (PPA-L) ← also called **Atypical AlzD, not an FTD!**
  - Agrammatic (PPA-G) ← aka **PPA**
  - Semantic (PPA-S) ← aka **Semantic Dementia**
- Each variant dependent upon the anatomical distribution of cortical atrophy
- Caused by different neuropathologies, each which tend to be associated with specific PPA variants

This categorization of PPA conflicts with mine (in SNCD). I consider ***Semantic Dementia*** to be an ~unrelated FTD neurodegenerative disease. **MORE CRUCIALLY**: I consider **Logopenic PPA to not be a PPA or FTD at all: it is an amyloid disease unlike ALL FTDs!**

It's a rat's nest, and not any ONE's fault! PPA lecture avail.

NKM, 2019

PPA addendum: **new slide!**

69 year old patient; bladder cancer surgery many years earlier (lost 10 church members)
Info: had language problems. **Query**: agrammatic?
Info: no, hesitancy, difficulty coming up with language. **Query**: anomia, Semantic D?
Opinion: some anomia, but not SemD. **Your Call**: _____
white text: . . what next?
. .

This chat made clear the value of the clinical embrace of the three PPAs, which is fine if your clinic has no research aspirations. The alternative and widely used FTD categorization (bvFTD, PPA, SemanticD) has both clinical and research benefits. Both are important, but students should know that Atypical AlzD (aka logopenic PPA) is an amyloid-driven neuro-degenerative disease and as such distinct from every FTD case. **For monopathologies!**

next up:

The Amazing Case of Julie M.

ELSEVIER

Brain and Cognition 55 (2004) 254–261

www.elsevier.com/locate/b&c

The Unusual Story of Julie M.

The role of context in remembering familiar persons: Insights from semantic dementia

Sven Joubert,* Sandrine Mauries, Emmanuel Barbeau, Mathieu Ceccaldi, and Michel Poncet

"Julie", age 49, had no behavioral changes, but complained of memory issues. Had *Pyramids-and-Palm-Trees* task deficits and bombed the A-bomb (famous events) test and could not name celebrities (much to their dismay, sic), but could provide many details about them (i.e. she had severe *anomia*). But her autobiographical (AB) memory of familiar friends and family was stellar, including episodic details (maybe no cingulate involvement?). Most stunning: her MRI.
Misc: can anyone find ANY mention of neuronal information-storage details in ANY of these papers?

Semantic dementia (SD) is a progressive condition characterized by an insidious and gradual breakdown in semantic knowledge. Patients suffering from this condition gradually lose their knowledge of objects and their attributes, concepts, famous persons, and public events. In contrast, these patients maintain a striking preservation of autobiographical memory. The aim of the present study was to examine in a patient suffering from SD the role of context in the ability to recall knowledge of familiar persons. In an experiment, patient J.M. was asked to name and identify familiar persons that appeared on family photographs from recent and remote periods of her life. In the first experimental condition, the pictures represented personally familiar persons present in a specific spatial and temporal context. In a second experimental condition, the pictures showed personally familiar persons who were presented without any specific episodic context. Results indicate that the patient was able to name and identify familiar persons irrespective of the context of presentation (with/without context) and of the time period (recent/remote). No temporal gradient was found using family photographs. Finally, in contrast with familiar persons, J.M. presented a severe anomia for celebrities. Results are discussed in light of recent research in the field.

Brief AAN note below

Why did she NOT ask "what is broccoli?"

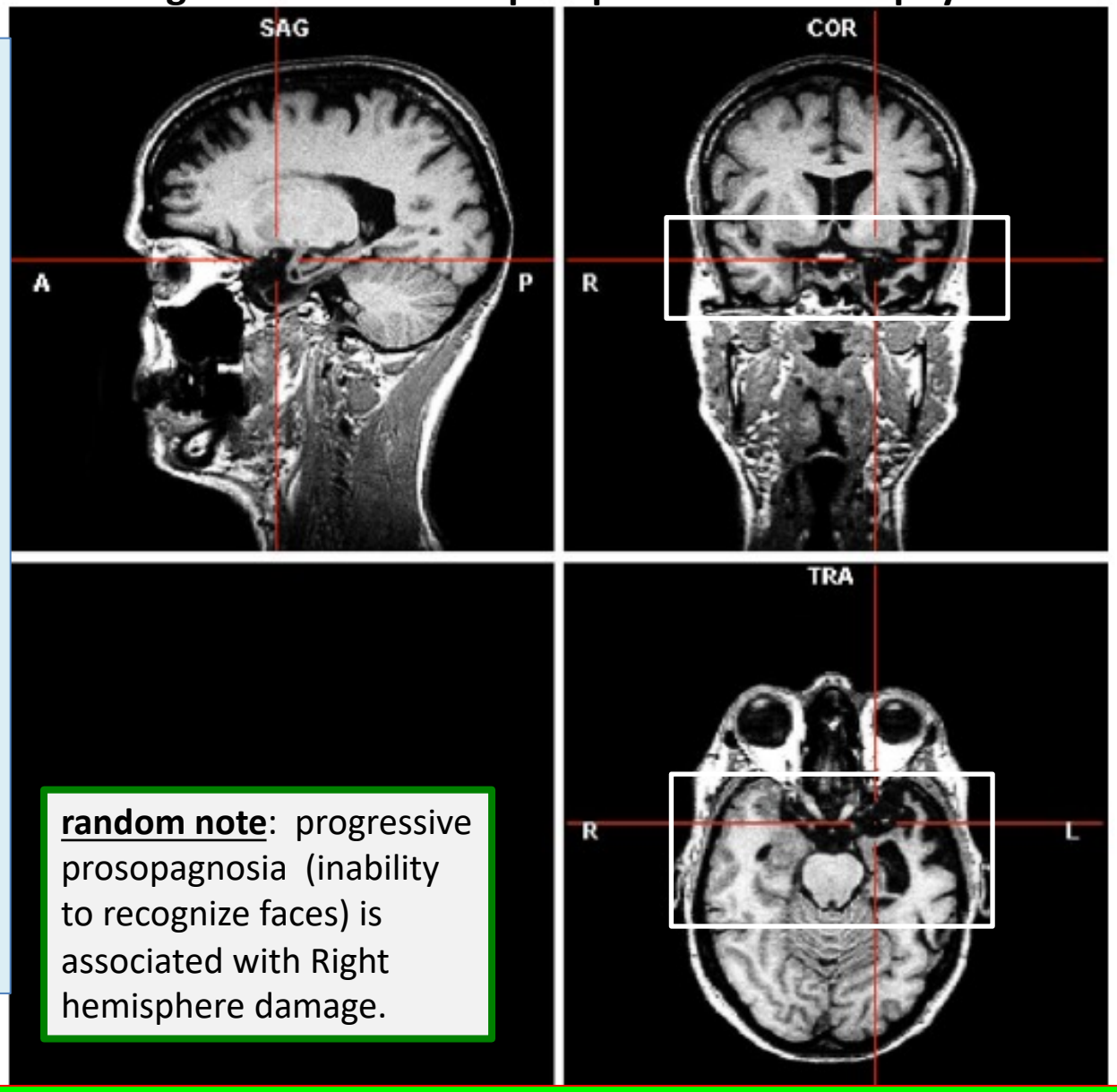
Fig. 1: Julie's left temporopolar severe atrophy.

See anything unusual here?

Discussion:
What is the nature of the damage in *Semantic Dementia?*

Why did they use both *verbal* and *visual stimuli?* [JM did fine on both for the autobiographical memory testing]. Despite her severe *anomia*, she had good language skills!

Anomia = inability to name things.



random note: progressive prosopagnosia (inability to recognize faces) is associated with Right hemisphere damage.

Julie's losses are, imho, more "*symbolic*" than *real world*, given her autobiographical abilities and her "behavioral normality", i.e. her real world efficacy. This MRI was a shocker!

Note: **Semantic Dementia** might be thought of as a "temporal lobe" version of of FTD aka Frontotemporal Dementia, which affects spindle neurons & is a tauopathy!

A number of studies have uncovered an interesting phenomenon in SD: patients show a better preservation of very recent events and semantic facts when compared with other time-periods (Graham & Hodges, 1997; Graham, Pratt, & Hodges, 1998; Graham, Simons, Pratt, Patterson, & Hodges, 2000; Nestor, Graham, Bozeat, Simons, & Hodges, 2002; Snowden et al., 1996a, 1996b). This temporal gradient, inverse to that observed in memory disorders resulting from hippocampal pathology (Alzheimer's disease notably), has been interpreted as support for the standard model of consolidation (Graham & Hodges, 1997; Hodges & Graham, 1998). According to this model, the hippocampal complex is essential for the retrieval of recent memories. Repeated activation of hippocampal–neocortical connections eventually leads, over time, to the formation of permanent neocortical connections which can be activated independently of the hippocampal formation by the event. In SD, the primary locus of atrophy concerns the temporal neocortex. According to this model of memory consolidation, the selective atrophy of the temporal neocortex in SD (at least in the early stages) will result in a progressive loss of long-term autobiographical and semantic memories, while the relative sparing of the hippocampal complex will allow

In WM stores, there is no possibility of repeated activation b/c this info is "lost in space"

Joubert - 2004

normal encoding and retrieval of recently experienced events. However, due to the disruption of the temporal neocortex and to the temporary role of the hippocampus in storing new information, the consolidation of these new memories will only be momentary. An alternative theory, the multiple traces theory (Nadel & Moscovitch, 1997), suggests that the hippocampal complex plays a permanent rather than a temporary role in the retrieval of episodic memories. According to this model, the hippocampus is involved in the storage and retrieval of recently experienced events (covering the past few years of life). After this time, episodic memories become independent of their context of acquisition and become more semantic in nature. It is assumed that the temporal neocortex plays a critical role in the storage of these semantic representations.

The locus of atrophy in SD affects predominantly the temporopolar regions of the brain (anterior and inferior temporal poles), at least in the early stages, with a highly asymmetrical pattern of atrophy affecting predominantly the left hemisphere. In a recent voxel-based morphometric study of SD patients, Mummery et al. (2000) found the temporopolar regions to be most affected in this condition, with sparing of hippocampal structures. Other volumetric MRI studies, however, have found hippocampal structures to be greatly diminished, with a gradient of severity along the antero-posterior axis affecting predominantly the anterior portions of the hippocampi. The extent of atrophy was always more important in the left hemisphere than in the right (Chan et al., 2001; Galton et al., 2001). These different findings relative to hippocampal atrophy are

why is LH is SO MUCH worse than RH?

Semantic Dementia: further tidbits Julie's family reported NO "behav." changes (i.e. not bvFTD) but she was referred for imaging / cognitive testing for **memory/word-finding complaints**. [MRI striking as were SPECT findings **and her 18/80 score naming line drawings; median = 74**]. Also had complex-sentences deficits along with "surface dyslexia" – difficulty with **irregular** (phonologically cryptic) words. At this point in her illness she **had lost much semantic knowledge**, although some non-name info could be retrieved, especially with cluing, so substantial semantic networks persisted.

Despite deficits in ABM-knowledge (distant-past events especially- see Fig. 2), she was excellent at recalling people known to her. Hippocampus is damaged in SemD (and it presumably works with ATL) which might explain older-episodic losses, but her **ABMs of people known well to her** are robustly stored.

mint is a regular word, pint is not!

***NEW TOPIC*: is Dementia a THOUSAND different diseases?**

Is BIG DATA ready for *Massively Personalized Medicine*

What is 10 Factorial? *and* **Why should you Care?**

If there are 10 genetic risk factors and the number of distinct syndromes = the number of diff. combinations then there are 10! total combinations

i.e. 1 x 2 x 3 x 4 x 5 x 6 x 7 x 8 x 9 x 10 = # different combos / diseases.

turns out, this is big freakin number: 3.6 million (or thereabouts)

This is a land of opportunity for an entrepreneur with these chops:

bioinformatics x *programming* x *molecular biology* x *NBOA*

F = Formidable! ➔ see NOTES below

resource: professional PPA slide-deck: avail. on request

Hot Off the Presses: Neuron, March 2021

1. Neuron Commentary: G&H [Gratuze & Holtzman]

2. Neuron Article: PLB [Pablo Largo-Barrientos et al.]

This **Neuron Commentary** and **Research Article** nicely bring together some key threads including a **connection** between the

FTD dementias AND some core AlzD pathology

Moreover, they get to the heart of some **essential linkages** between *pathology* and *neuronal circuits*, and also elevate the quandary that is **the relationship** between *neural inflammation* vs. the more *neuron-intrinsic* pathological processes.

First: Quick Overview by Me ... + ... Y'all can ask Questions NOW!
Chat-Rooms: Assorted Questions to Assorted Rooms [updated list below]

Neuron Commentary: G&H, Gratuze & Holtzman, 2021

Neuron

Previews

Targeting pre-synaptic tau accumulation: a new strategy to counteract tau-mediated synaptic loss and memory deficits

Maud Gratuze[1] and David M. Holtzman[1,*]
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https://doi.org/10.1016/j.neuron.2021.02.014

misc. for Don: PLB intro refs. rat WM deficits
Shi-2019: microglia w/ ApoE ➔ neurodegener.

Synaptic tau accumulation is believed to promote synaptic loss, which contributes to cognitive deficits in Alzheimer's disease and tauopathies. In this issue of *Neuron*, Largo-Barrientos et al. report that synaptic loss can be mitigated by lowering Synaptogyrin-3, a known mediator of tau binding to synaptic vesicles.

Tau is a microtubule-associated protein that is present predominantly in the axonal compartment of neurons. In physiological conditions, the main function of tau is to regulate microtubule assembly and stabilization and to modulate axonal transport. Moreover, several other physiological functions have been characterized, showing that tau influences neuronal excitability as well as diverse cellular processes including cell morphogenesis, cellular signaling, and apoptosis. Tau can become pathological when it aggregates. Its aggregation is facilitated by post-translational modifications such as hyperphosphorylation and acetylation that notably impair its ability to bind to microtubules and facilitate tau in the synapse can disrupt synaptic function and drive synaptic degeneration (Hoover et al., 2010). However, the mechanism underlying this phenomenon is not fully understood. Impairment of microtubule transport or altered synaptic structure has been suggested to drive tau-mediated synapse loss, and more recently, it has been shown that components of the complement system can tag tau-affected synapses, resulting in microglial engulfment and synapse loss. The presence of tau-pathology-mediated microgliosis and astrogliosis is a prominent hallmark of AD and other tauopathies, and recent evidence suggests that microglia are required for tau-mediated neurodegeneration (Shi aptic terminals that was previously characterized as a mediator of tau binding to synaptic vesicles (Liu et al., 2016; McInnes et al., 2018). Largo-Barrientos et al. employed a well-characterized mouse model of tauopathy harboring the P301S human tau mutation, PS19 mice. By 9 months of age, this model develops strong tau hyperphosphorylation and aggregation, neurofibrillary tangle deposition, and gliosis, as well as neuronal loss, brain atrophy, and loss of synaptic proteins in specific brain regions including the hippocampus, entorhinal cortex, and piriform cortex. The authors first confirmed in this model the pre-synaptic accumulation of tau and Synaptogyrin-3 in mossy fibers of the hippo-

➔ **Tau-mutant line w/ P301 human tau mutation**

Hyperphosphorylation – crucial step in AlzD pathology; always present in tauopathies? [≈ tau-FTLD]
mechanism of tau toxicity inside synapse was uncertain [perhaps altered transport, structure; complement-C1q]
PLB: mutant-tau binding to synaptogryin-3 ➔ synaptic loss, behavioral deficitsr
or is it: RNA dyshomeostasis & "PQC" protein quality control ➔ phase separations, stress granules. Mandrioli-2020

Updated Questions: about article and SG3 (Synaptogyrin-3)

Discussion Questions for Breakout Rooms: **re:** *PLB article* **in Neuron**

1. How does **SG3** seem to **contribute** to Tau pathology?
What evidence supports the **mechanisms proposed in Figure 1** of G&H?
[be prepared to explain Figure 1, next slide, to classmates]

2. Is this story **more about FTD** or **AlzD**?
Which **mechanisms** from **Chapter 3** SNCD might contribute to SG3 pathology?
Is PS19 a **mouse model of AlzD**?

3. Do NFTs occur in PS19? . [yes] . Does SG3 ko decr. NFTs? .[not addressed].
what causes neurodegeneration: tau path? IDPs? neuro-inflamm?

4. Is **Neuroinflammation** part of the SG3-pathology mechanism?

5. What is the **mechanism** by which neuroinfl. causes synapse loss?
Is microglial activation **synonymous** with neuroinflammation?

6. Do G&H consider AlzD to be a "**tauopathy**"?
How is the PLB story diff. from McInnes 2018? Is PLB taking their credit?

METHODS: Laundry List

note: mice don't naturally get AlzD or FTD
addition of mutant human genes ➔ mouse models

PS19 = name of mouse line with Tau P301S
mice show Tau aggregation and SG3 binding (McInnes, 2018)
binding is evident in Mossy Fibers (DG ➔ CA3 field of terminals)

SG3 Knockdown = single copy (heterozygous) knockout
k.o. in PS19 ➔ rescue of LTP, WM (but not spatial memory)
immunostain, EM of mossy fibers shows less Synapse Loss

TBD: if broader neocortical losses also reduced or n. death, atrophy

PS19: shows neuroinflammation, astro/gliosis, gene expression changes. SG3 k.o. does not alter this so has diff. mechanism

G&H, 2021

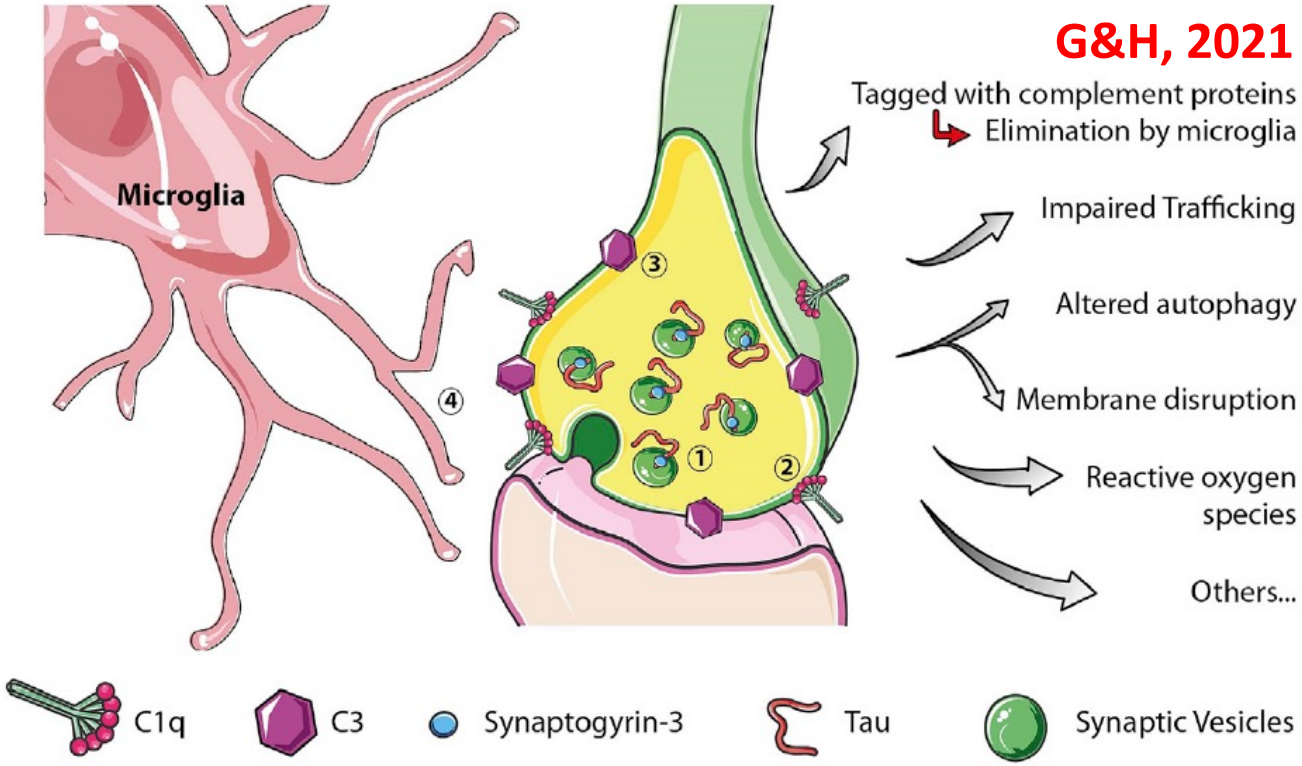

Figure 1. Possible mechanisms by which pre-synaptic tau accumulation led to synaptic loss
Interaction between Synaptogyrin-3 and tau results in tau accumulation in the synapse, which could impair trafficking, alter autophagy, disrupt the membrane, promote the production of reactive oxygen species, and induce synaptic tagging of C1q, resulting in synapse engulfment by microglia.

Neuron

Neuron: PLB Pablo Largo-Barrientos et al. 2021

Report

Lowering Synaptogyrin-3 expression rescues Tau-induced memory defects and synaptic loss in the presence of microglial activation

Pablo Largo-Barrientos,[1,2] Nuno Apóstolo,[1,2] Eline Creemers,[1,2] Zsuzsanna Callaerts-Vegh,[3] Jef Swerts,[1,2] Caitlin Davies,[4] Joseph McInnes,[1,2] Keimpe Wierda,[1,2] Bart De Strooper,[1,2,5] Tara Spires-Jones,[4] Joris de Wit,[1,2] Valerie Uytterhoeven,[1,2,*] and Patrik Verstreken[1,2,6,*]

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https://doi.org/10.1016/j.neuron.2020.12.016

SUMMARY

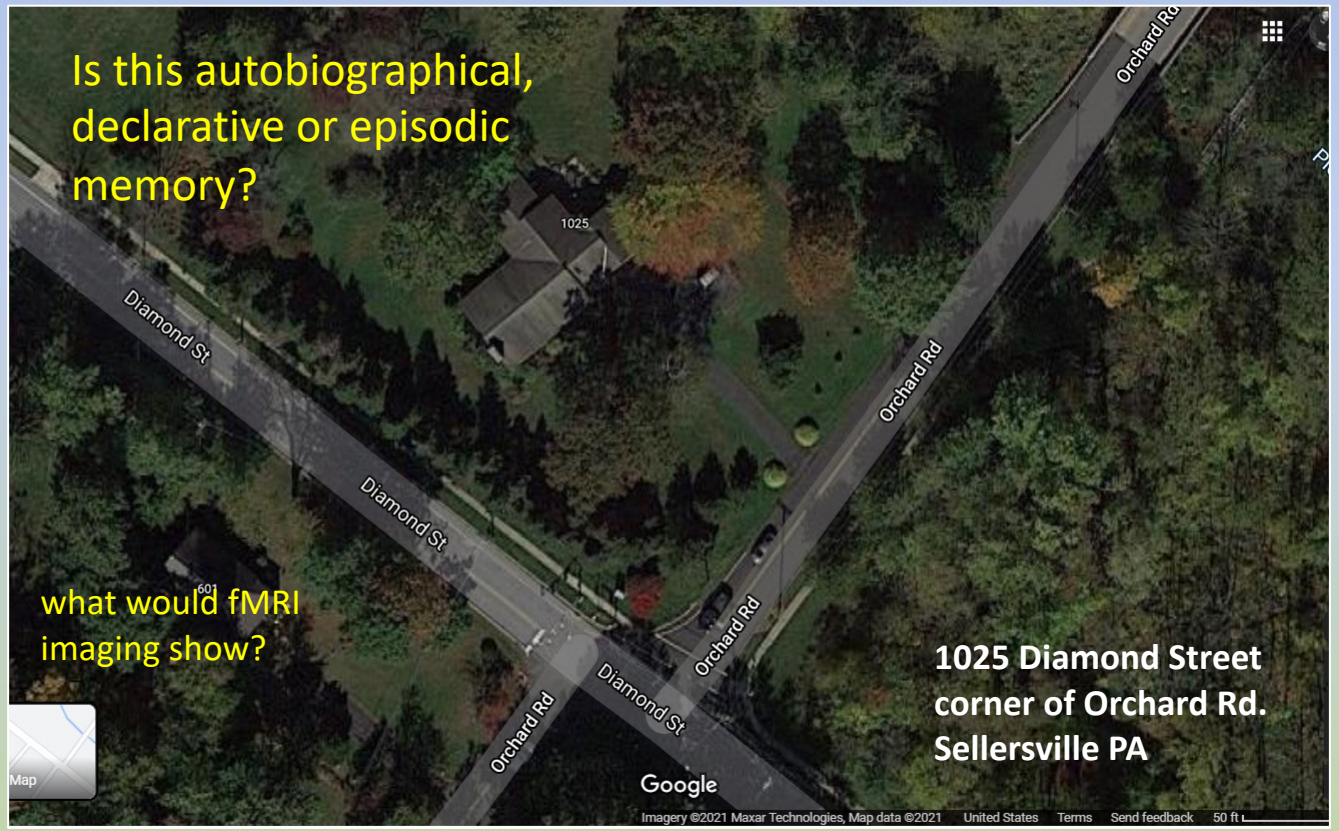
Tau is a major driver of neurodegeneration and is implicated in over 20 diseases. Tauopathies are characterized by synaptic loss and neuroinflammation, but it is unclear if these pathological events are causally linked. Tau binds to Synaptogyrin-3 on synaptic vesicles. Here, we interfered with this function to determine the role of pathogenic Tau at pre-synaptic terminals. We show that heterozygous knockout of *synaptogyrin-3* is benign in mice but strongly rescues mutant Tau-induced defects in long-term synaptic plasticity and working memory. It also significantly rescues the pre- and post-synaptic loss caused by mutant Tau. However, Tau-induced neuroinflammation remains clearly upregulated when we remove the expression of one allele of *synaptogyrin-3*. Hence neuroinflammation is not sufficient to cause synaptic loss, and these processes are separately induced in response to mutant Tau. In addition, the pre-synaptic defects caused by mutant Tau are enough to drive defects in cognitive tasks.

Peter: I can't remember, I can't recall, I got no memory of anything at all

Frank: I remember doo doo, I remember doo doo, she had a swimming pool

David: my brain hurt like a warehouse, it had no room to spare
I had to cram so many things to store everything in there

Don: so many memories of Diamond Street and Orchard Road



I went from 1025 Diamond Street to 1025 Greendale in just 35 years!

Please note main Take Home Message

of four Abstracts below

[gist of the Title mainly]

TDP-43 pathology in anterior temporal pole cortex in aging and Alzheimer's disease

2018

Sukriti Nag[1,2*], Lei Yu[1,3], Patricia A. Boyle[1,4], Sue E. Leurgans[1,3], David A. Bennett[1,3] and Julie A. Schneider[1,2,3]

Nag et al. Acta Neuropathologica Communications (2018) 6:33

Abstract

heard of ATPC? *heard of OFC?* **5-Stage Process!**

TDP-43 pathology was investigated in the anterior temporal pole cortex (ATPC) and orbital frontal cortex (OFC), regions often degenerated in frontotemporal lobar degenerations (FTLD), in aging and Alzheimer's disease (AD). Diagnosis of dementia in the 1160 autopsied participants from 3 studies of community-dwelling elders was based on clinical evaluation and cognitive performance tests which were used to create summary measures of the five cognitive domains. Neuronal and glial TDP-43 cytoplasmic inclusions were quantitated in 8 brain regions by immunohistochemistry, and used in ANOVA and regression analyses. TDP-43 pathology was present in 547 (49.4%) participants in whom ATPC (41.9%) was the most frequently involved neocortical region and in 15.5% of these cases, ATPC was the only neocortical area with TDP-43 pathology suggesting not only that ATPC is involved early by TDP-43 but that ATPC may represent an intermediate stage between mesial temporal lobe involvement by TDP-43 and the last stage with involvement of other neocortical areas. To better study this intermediary neocortical stage, and to integrate with other staging schemes, our previous 3 stage distribution of TDP-43 pathology was revised to a 5 stage distribution scheme with stage 1 showing involvement of the amygdala only; stage 2 showed extension to hippocampus and/or entorhinal cortex; stage 3 showed extension to the ATPC; stage 4 – showed extension to the midtemporal cortex and/or OFC and finally in stage 5, there was extension to the midfrontal cortex. Clinically, cases in stages 2 to 5 had impaired episodic memory, however, stage 3 was distinct from stage 2 since stage 3 cases had significantly increased odds of dementia. The proportion of cases with hippocampal sclerosis increased progressively across the stages with stage 5 showing the largest proportion of hippocampal sclerosis cases. Stage 5 cases differed from other stages by having impairment of semantic memory and perceptual speed, in addition to episodic memory impairment. These data suggest that of the regions studied, TDP-43 pathology in the ATPC is an important early neocortical stage of TDP-43 progression in aging and AD while extension of TDP-43 pathology to the midfrontal cortex is a late stage associated with more severe and global cognitive impairment.

not really a nag

If this is *neurodegeneration* why are inclusions found in glia?

Atrophy and Microglial Distribution in Primary Progressive Aphasia With Transactive Response DNA-Binding Protein-43 kDa

2018

Garam Kim, BA, BM, Kabriya Bolbolan, BS, Tamar Gefen, Ph

PPA-TDP found in language areas; assoc. w/ greater atrophy

Marek-Marsel Mesulam, MD, and Changiz Geula, PhD

lateralized reactive microglia
- correlates with atrophy
- TDP also matches atrophy but microglia ≠ TDP-43

Objective: To quantitatively determine the density and distribution of activated microglia across cortical regions and hemispheres in the brains of primary progressive aphasia (PPA) participants with pathological diagnoses of frontotemporal lobar degeneration with transactive response DNA-binding protein-43 (TDP-43) inclusions and to examine the relationships between microglial densities, patterns of focal atrophy, (TDP-43) inclusions, and clinical phenotype.
Methods: Activated microglia and TDP-43 inclusions were visualized in whole-hemisphere brain sections using immunohistochemical methods from five participants with PPA-TDP. Unbiased stereology was used to bilaterally quantify human leuckocyte antigen/D related–positive activated microglia and TDP-43 inclusions across five language-related regions. Density and distribution of both markers were compared across cortical regions and hemispheres, and their relationships to patterns of focal atrophy and clinical phenotype were determined.
Results: Activated microglia displayed asymmetric distribution favoring the language-dominant hemisphere, consistent with greater postmortem and/or in vivo atrophy in that hemisphere, in PPA-TDP. In one participant with no asymmetric atrophy, quantitative distribution of microglia also lacked asymmetry. Patterns of microglial activation also showed variation that favored areas of high atrophy in regions affiliated with language function, demonstrating concordance between patterns of microglial activation, atrophy, and clinical phenotype. TDP-43 also showed higher inclusion densities in areas of high atrophy than in regions with low atrophy, but no clear relationship with microglia density at a regional level.
Interpretation: The initial activation of microglia is most likely a response to cortical abnormalities in PPA-TDP, which contribute to atrophy. The patterns of microglial activation, TDP-43 inclusion deposition, atrophy, and clinical phenotype suggest that activated microglia may make unique contributions to cortical thinning and TDP-43 inclusion formation.

ANN NEUROL 2018;00:000–000

FTD is a FAMILY. PPA and SD are members of the family!

FTD-inclusions found in multiple diseases; translocation to cytosol; hyperP, sequestration!

Histol Histopathol. 2009 August ; 24(8): 1081–1086.

2009

Cytoplasmic Inclusions of TDP-43 in Neurodegenerative Diseases: A Potential Role for Caspases

Troy T. Rohn, Ph.D.
Department of Biology Science/N

TDP-43 is the dominant pathology in Semantic Dementia

Early take on TDP pathology: cleavage by caspase ➔ toxic fragments

Abstract

TAR DNA-binding protein-43 (TDP-43) proteinopathies are classified based upon the extent of modified TDP-43 inclusions and include a growing number of neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration with ubiquitin immunoreactive, tau negative inclusions (FTLD-U) and FTLD with motor neuron disease (FTLD-MND). In addition, TDP-43 inclusions have also been identified in a number of other neurodegenerative disorders including Alzheimer's disease, corticobasal degeneration, Lewy body related diseases and Pick's disease. Current understanding suggests that in these diseases, TDP-43 is relocated from the nucleus to the cytoplasm and sequestered into inclusions that contain modified TDP-43. Major modifications of TDP-43 have been identified as being hyperphosphorylation and proteolytic cleavage by caspases. In this review a summary of the major findings regarding the proteolytic modification of TDP-43 will be discussed as well as potential toxic-gain mechanisms these fragments may cause including cytoskeletal disruptions.

Cogn Behav Neurol. 2008 Sep;21(3):157-63. doi: 10.1097/WNN.0b013e3181864a09.

Frontotemporal dementia mimicking dementia with Lewy bodies. **2008** **TDP-43**

Claassen DO[1], Parisi JE, Giannini C, Boeve BF, Dickson DW, Josephs KA.

⊕ Author information

Abstract

BACKGROUND: Some patients with frontotemporal dementia (FTD) have concomitant extrapyramidal (motor) symptoms and psychosis and may simultaneously meet consensus criteria for FTD and for dementia with Lewy bodies (DLB). Clinicopathologic studies are helpful in understanding the underlying neurodegenerative process in such cases.

OBJECTIVE: To describe clinical and pathologic features of 6 patients with signs and symptoms suggestive of both a diagnosis of FTD and DLB at first clinical presentation, of which 2 patients have now undergone autopsy, and to compare them with autopsy-confirmed FTD and Lewy body disease patients.

RESULTS: All 6 patients met published consensus criteria for a diagnosis of both FTD and DLB (5 probable and 1 possible). Clinical symptoms of FTD included personality and behavioral changes, whereas those suggestive of DLB included Parkinsonism, fluctuating cognition, parasomnia, and hallucinations. Five patients underwent single photon emission computed tomography ((99m)Tc) imaging, which showed varying degrees of frontal lobe hypoperfusion. Magnetic resonance imaging, electroencephalogram, and electromyogram were not helpful in differentiating FTD from DLB. Histologic examination of the 2 autopsy cases was consistent with a pathologic diagnosis of TDP-43 proteinopathy; specifically frontotemporal lobar degeneration with ubiquitin-only immunoreactive changes, type 1. There were significant differences between these 6 patients and the 2 groups of autopsy confirmed FTD and Lewy body disease patients.

CONCLUSIONS: We have identified a novel group of FTD patients with clinical features that overlap with DLB, yet seem to be different from both typical FTD and typical Lewy body disease. **…perfusion ≠ hypoperfusion, yet authors do that**

Lumpers and Splitters: scientists are often described as lumpers or splitters where we might like to either group things, to better understand categories, or divide things, to focus on diversity of observations. Here the authors create a new grouping based upon 2 autopsies. This nicely reflects the down-in-the-weeds details of real gerontology. Symptoms for DLBD are present in the abstract above. REM-thrashing at night can be a harbinger of DLBD and it can respond to the AChE inhibitor aricept.

TDP-43 is a tau-negative, alpha-synuclein negative type of FTD. [reprise of *basics* in notes]

Coming Up Next:

The 900 lb Gorilla in our Midst

AlzD = Alzheimer's Disease
EOAD = Early Onset AlzD