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Role of TDP-43 in Non-Alzheimer's and Alzheimer's Neurodegenerative Diseases

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13th Annual Mild Cognitive Impairment (MCI) Symposium:
Alzheimer and Non-Alzheimer's Causes of MCI and Dementia

January 17th 2015

DISCLOSURES

- I do not have any financial disclosures

- I receive funding from the NIA (PI: R01 AG037491), NIDCD (PI: R01 DC010367) and the Alzheimer's Association (PI: Whitwell)

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Historical background

- Frontal lobe degeneration of non-Alzheimer type

  Brun 1987

- Dementia lacking distinctive histology

  Knopman et al. 1990

- Motor neuron disease dementia

  Cooper et al.1994

- TDP-43 is associated with FTLD & ALS

  Neumann et al. 2006

- TDP-43 is present in Alzheimer's disease

  Amador-Ortiz et al. 2007

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The TAR DNA binding protein of 43 kDa (TDP-43)

- TDP-43 is a highly conserved nuclear binding protein involved in the regulation of DNA transcription, for example, transcription repression and exon skipping
- TDP-43 is cleaved by caspases to generate C and N terminal fragments, both of which are cytotoxic
- Normal TDP-43 is found in the nucleus of the cell, while abnormal TDP-43 is observed in the cytoplasm in most instances

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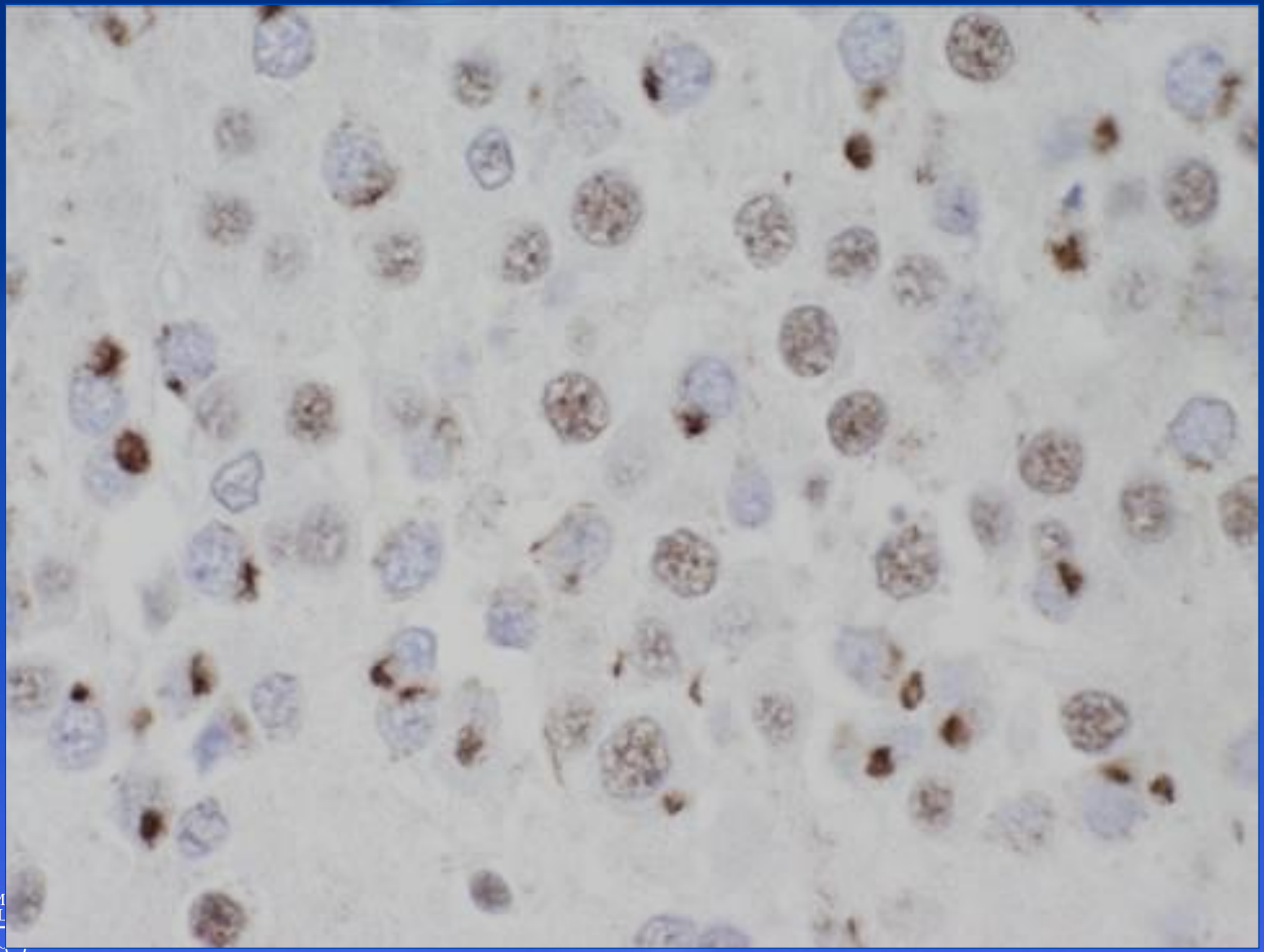

TDP-43 in FTLD and in ALS

- TDP-43 can be identified in a subset of cases of frontotemporal lobar degeneration (FTLD-TDP)
- Four subtypes of FTLD-TDP are defined based on the morphological characteristics and distribution of TDP-43
  - FTLD-TDP type A
  - FTLD-TDP type B
  - FTLD-TDP type C
  - FTLD-TDP type D

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Sampathu et al. Am J Pathol. 2006
Mackenzie et al. Acta Neuropathol. 2006, 2011

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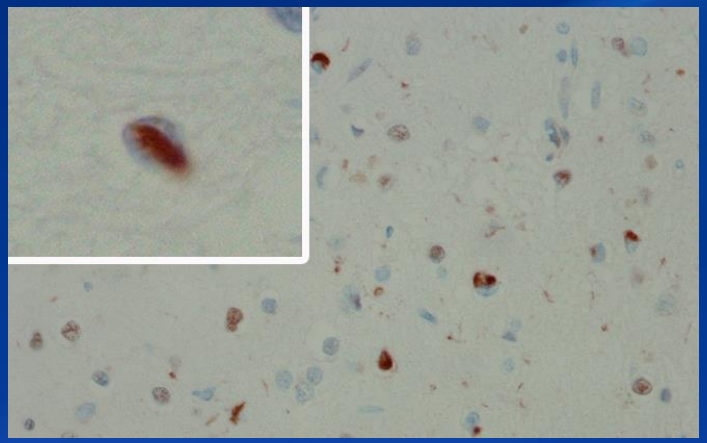
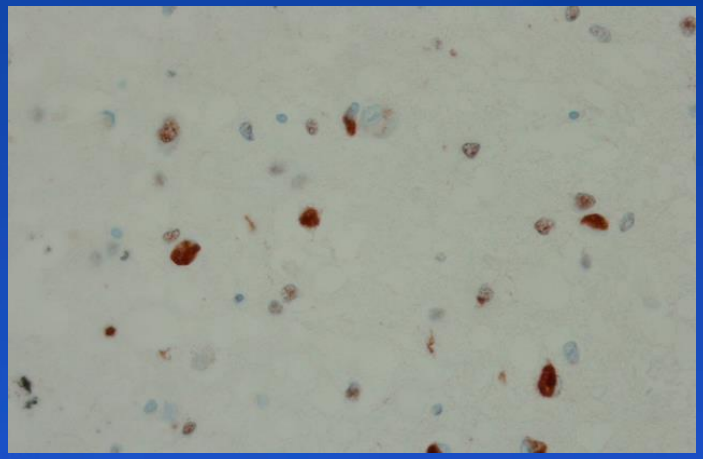
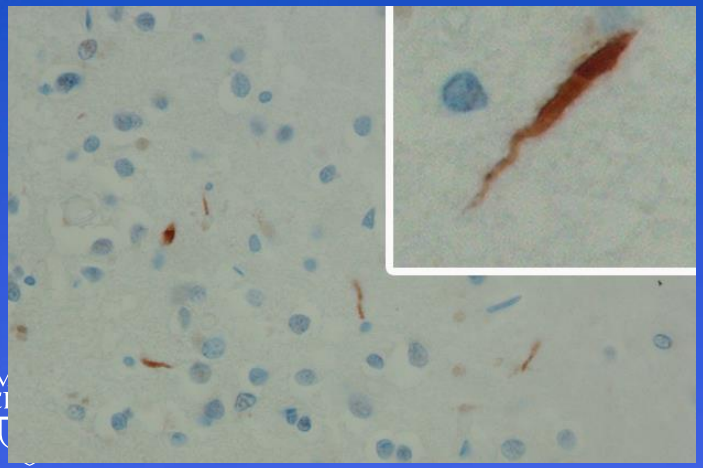


Type A: In neocortex there is a combination of neuronal cytoplasmic inclusions, dystrophic neurites and intranuclear inclusions



Type B: In neocortex there is a predominance of neuronal cytoplasmic inclusions



Type C: In neocortex there is a predominance of long thick dystrophic neurites

Clinical features of FTLD-TDP types

Clinical features	Type A	Type B	Type C
Sex M:F	Equal	Equal	Equal
Disease Duration	Average (7yrs)	Short (3yrs)	Long (10yrs)
Most common clinical diagnosis	bvFTD	FTD-MND	Semantic dementia
Others			
PPA (non-semantic)	+++	+/-	-
Corticobasal syndrome	+++	-	-
GRN mutations	+++	-	-
C9ORF72 repeat expansions	+	+++	+/-

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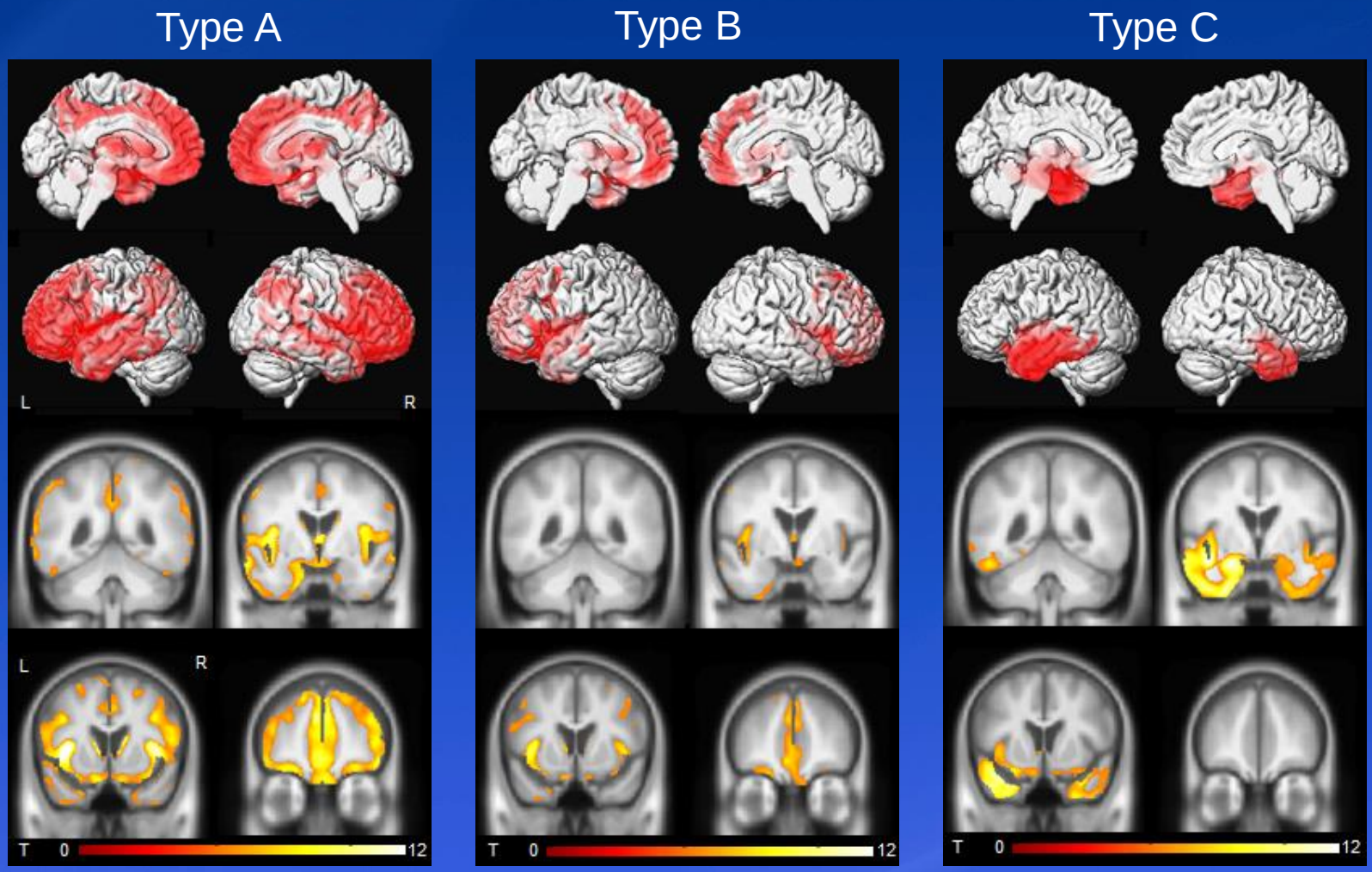
Josephs et al. Acta Neuropathol 2009

Imaging signatures of FTLD-TDP types



Whitwell et al. & Rohrer et al. Neurology 2010

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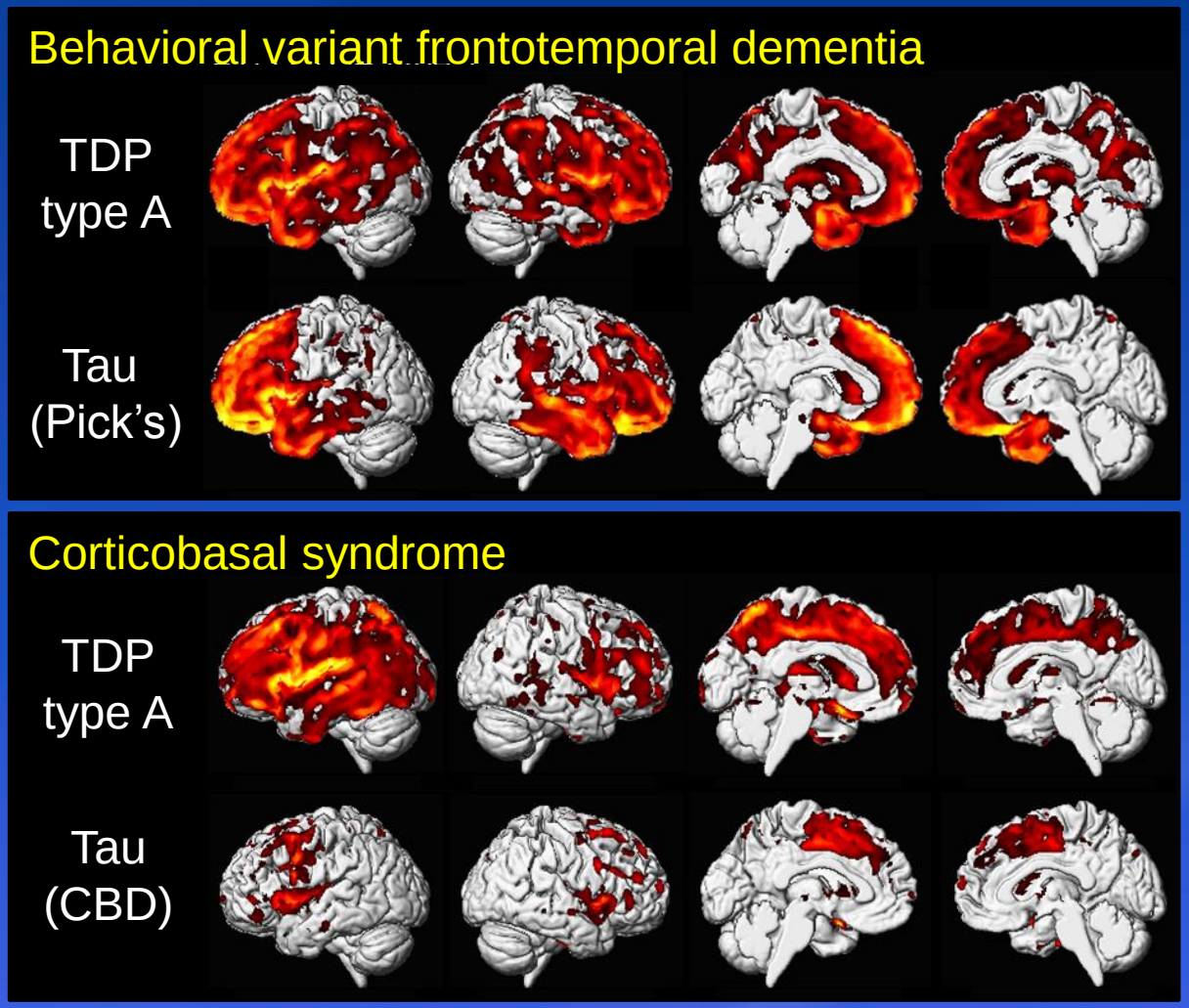
TDP-43 signatures across clinical phenotypes



Whitwell et al. Neurology 2010; Whitwell et al J Mol Neurosc 2011

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Summary

- Histological characteristics of TDP-43 in FTLD and ALS are not arbitrary
- There are strong associations between TDP-43 characteristics and clinical features
  - e.g. semantic dementia and long thick dystrophic neurites in neocortex
- TDP-43 type appears to have signature patterns of grey matter atrophy which likely drive the clinical phenotypes

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TDP-43 in Alzheimer's disease (AD)

- How common is TDP-43 in AD?
- Does it's deposition in AD occur in a stereotypic manner similar to beta-amyloid deposition in senile plaques or tau deposition in neurofibrillary tangles?
- Does it play any role in the clinical or imaging characteristics that have been associated with AD?

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How common is TDP-43 in AD?

Study Origin	USA-MN	USA-FL	Germany/ USA-PA	Japan/ Canada	USA-IL	UK-Manchester	All studies
Antibody	MC2085	Protein tech	Protein tech	pTDP-43	Protein tech	pTDP-43	Mixed
Total # cases	342	167	182	78	53	180	1,002
Percent female	62%	54%	59%	44%	49%	51%	56%
Age at death, yrs	87.1	81.7	77.5	79.3	74.4	72.9	80.6
Disease duration, yrs	9.1	NR	8.9	NR	10.6	8.6	9.0
Braak stage, range	IV-VI	IV-VI	V-VI	IV-VI	V-VI	V-VI	IV-VI
Screening region	Amygdala	Hippo	Hippo	Amygdala	Amygdala	Hippo	Mixed
# TDP+ cases	195 (57%)	61 (36%)	47 (26%)	33 (42%)	17 (32%)	34 (19%)	387 (39%)
Percent female	64%	52%	66%	42%	NA	NA	60%
Age at death, yrs	88.0	84.5	79.8	82.1	NR	NR	85.6
Disease duration, yrs	10.0	NR	10.4	NR	NR	NR	10.1

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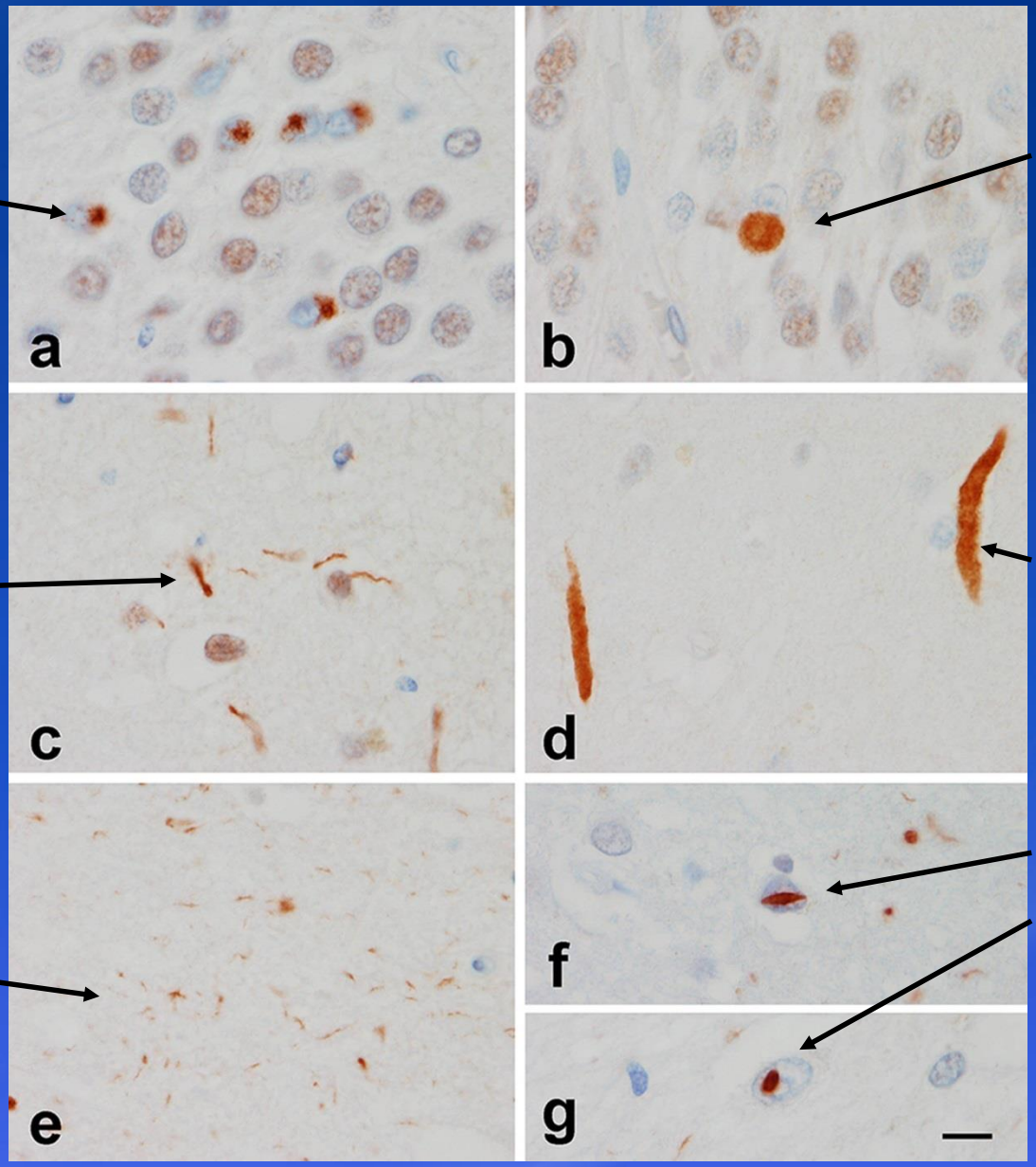
Amador-Ortiz, 2007; Higashi, 2007; Aria, 2009; Bigio, 2010; Davidson, 2011, Josephs 2014

TDP-43 inclusions

Small, asterik-like neuronal cytoplasmic inclusions

Thin, thread-like dystrophic neurites

Fine neurites in CA1



Larger, round, neuronal cytoplasmic inclusions

Large, thick dystrophic neurites

Cat-eye or rounded neuronal intranuclear inclusions

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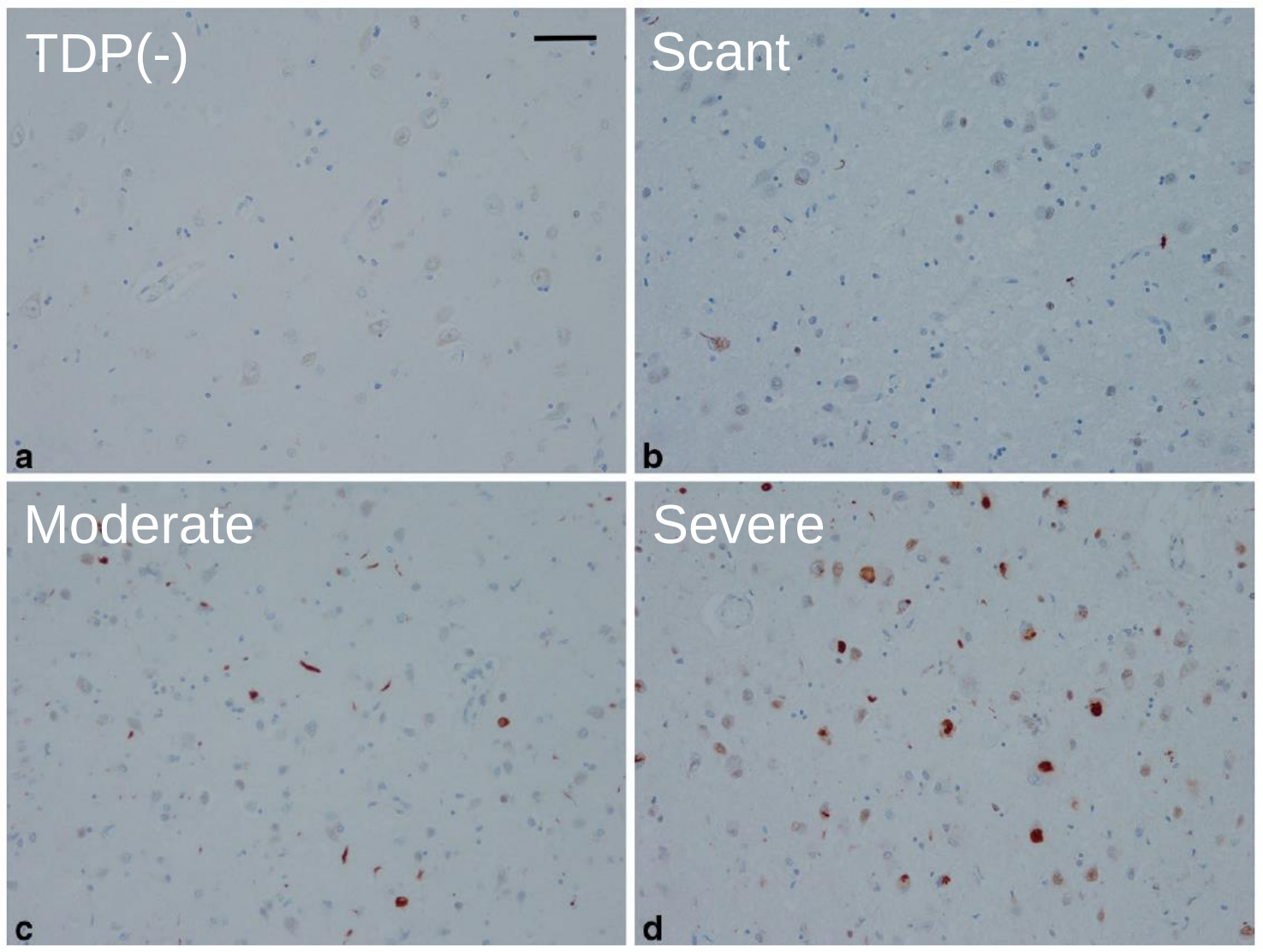
Range of TDP-43 in the amygdala



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Important questions regarding TDP-43 in AD

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TDP-43 in AD (TAD) staging scheme

TAD STAGE	Amygdala	Entorhinal/ subiculum	Dentate/ occipital-temporal	Inferior temporal	Frontal/ basal ganglia
I	■				
II	■	■			
III	■	■	■		
IV	■	■	■	■	
V	■	■	■	■	■

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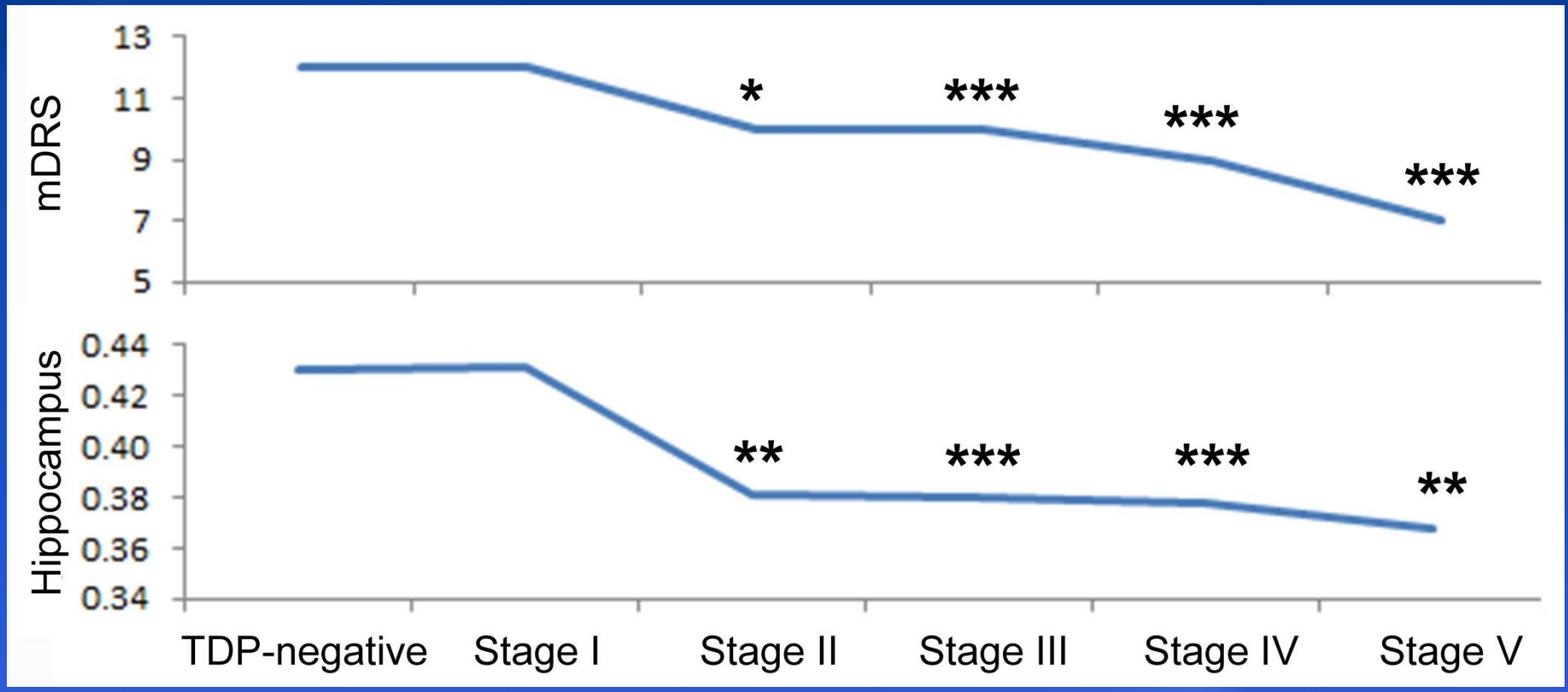
Josephs et al. Acta Neuropath. 2014

Clinical correlates of TAD staging scheme



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Is TDP-43 associated with behavioral features in AD?

- Identified all AD cases with TAD stages IV and V (temporal and/or frontal/BG TDP-43 deposition) (n=51)
- Reviewed the clinical features of all 51 cases
- There was no evidence of early behavioral features in these cases
- There was also no evidence of early parkinsonism
- None of the 51 cases were diagnosed as a frontotemporal dementia prior to death

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Jung et al. J Neurol. 2014

What is the role of TDP-43 in AD?

- 342 brains from Mayo's ADRC/MCSA brain bank
  - Intermediate-high probability AD (NIA-Reagan)
  - Braak stage IV-VI
  - Clinical evals. & neuropsychological testing
  - Were cognitively normal or impaired at death
- Screened amygdala for TDP-43 (polyclonal antibody MC2085 that recognizes a peptide sequence in the 25-kDa C-terminal fragment)
- TDP(+): Any case showing any amount of TDP-43 immunoreactivity in the amygdala
- TDP(-): Cases showing no TDP-43 immunoreactivity

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Josephs et al. Acta Neuropath. 2014

Demographic and clinical features

Characteristic	TDP (-) (n=147)	TDP (+) (n=195; 57%)	Age-adjusted p value
Female sex, no (%)	87 (59%)	125 (64%)	0.66
Age at onset, years	71 (12)	77 (9)	0.06
Age at clinical eval., years	80 (11)	85 (8)	0.45
Age at death, years	83 (12)	87 (8)	0.47
Disease duration, years	5.6 (3.2)	6.0 (3.5)	0.09
APOE e4 carriers (%)	67 (46%)	117 (62%)	<0.001
Clinical features			
Cognitively impaired, no.(%)	119 (81%)	189 (98%)	<0.001
Mini-Mental State Exam	17 (±8)	15 (±7)	<0.001
Clinical Dementia Rating Scale	9 (±7)	12 (±6)	<0.001
Boston Naming Test	40 (±13)	32 (±14)	<0.001
Dementia Rating Scale memory	13 (±6)	11 (±5)	<0.001

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Pathological and imaging features

Characteristic	TDP (-) (n=147)	TDP (+) (n=195; 57%)	Age-adjusted p value
Pathological			
Braak Stage IV\V\VI (%)	26/34/40%	17/29/54%	<0.001
Frequent CERAD, no. (%)	83 (56%)	123 (63%)	0.53
Lewy bodies, no. (%)	35 (24%)	66 (34%)	0.01
Hippocampal sclerosis , no. (%)	8 (5%)	78 (40%)	<0.001
Infarctions, no. (%)	31 (21%)	54 (28%)	0.53
Brain volumes as percentage of total intracranial volume			
Hippocampus	0.43 (0.06)	0.38 (0.07)	<0.001
Entorhinal cortex	0.18 (0.03)	0.16 (0.03)	<0.001
Amygdala	0.124 (0.01)	0.116 (0.02)	<0.001
Fusiform cortex	1.10 (0.14)	1.06 (0.13)	0.02
Lateral temporal cortex	4.08 (0.61)	4.03 (0.54)	0.71
Lateral parietal cortex	2.09 (0.39)	2.15 (0.36)	0.71
Lateral frontal cortex	3.57 (0.57)	3.64 (0.56)	0.63

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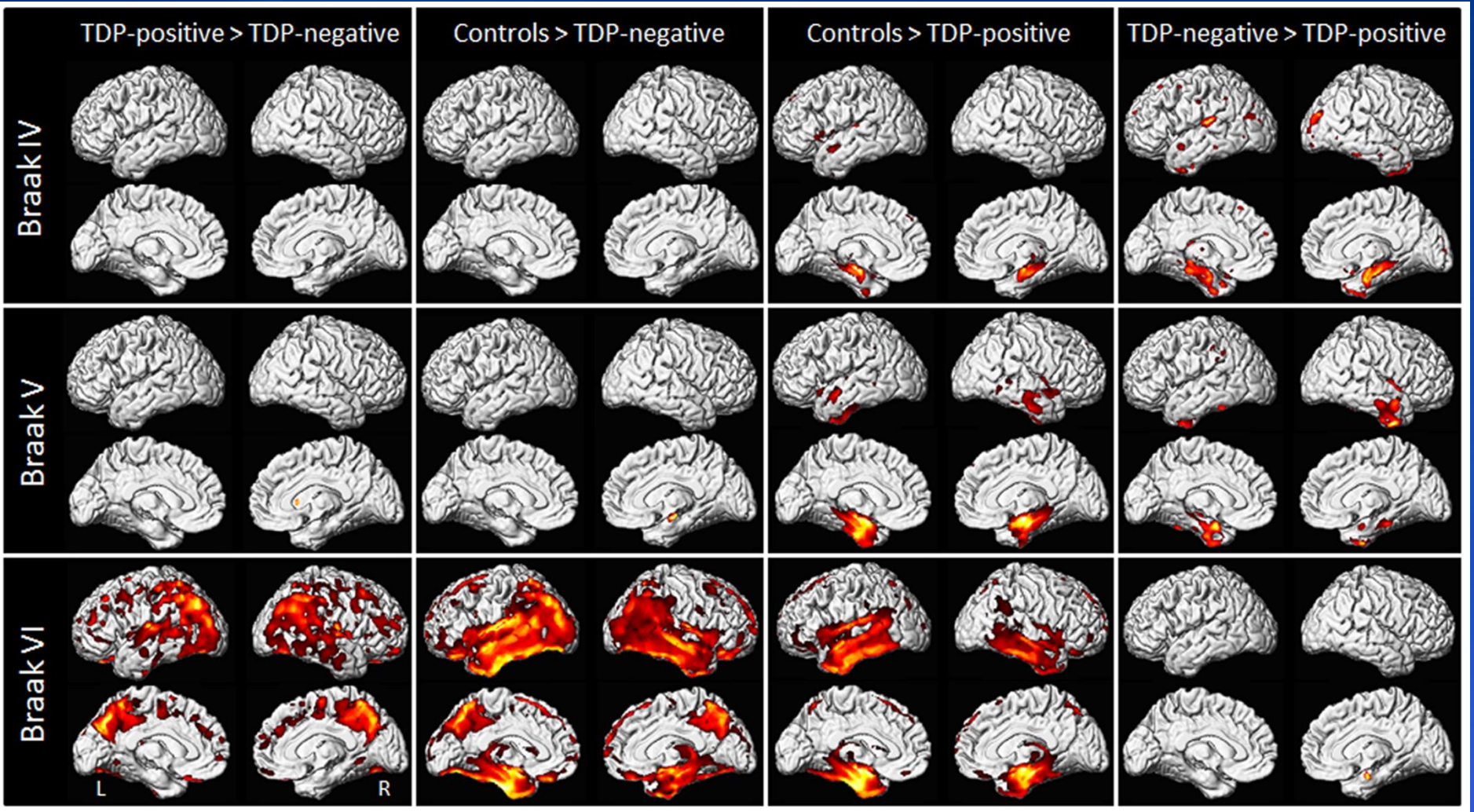

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Statistical analysis

- Linear, binary logistic and ordinal logistic regression models were used to estimate associations between outcome variables and the presence/absence of TDP-43
- Our models were stratified by Braak stage to allow us to account for any confounding effects of Braak stage and to allow us to assess additive associations and interactions between TDP-43 and Braak stage
- We extended this analysis in two ways:
  1. Age, APOE, infarctions, CERAD, Lewy bodies as covariates
  2. Mediation analysis to assess whether the results are mediated by hippocampal sclerosis (HpScl)
     - HpScl is strongly associated with TDP-43

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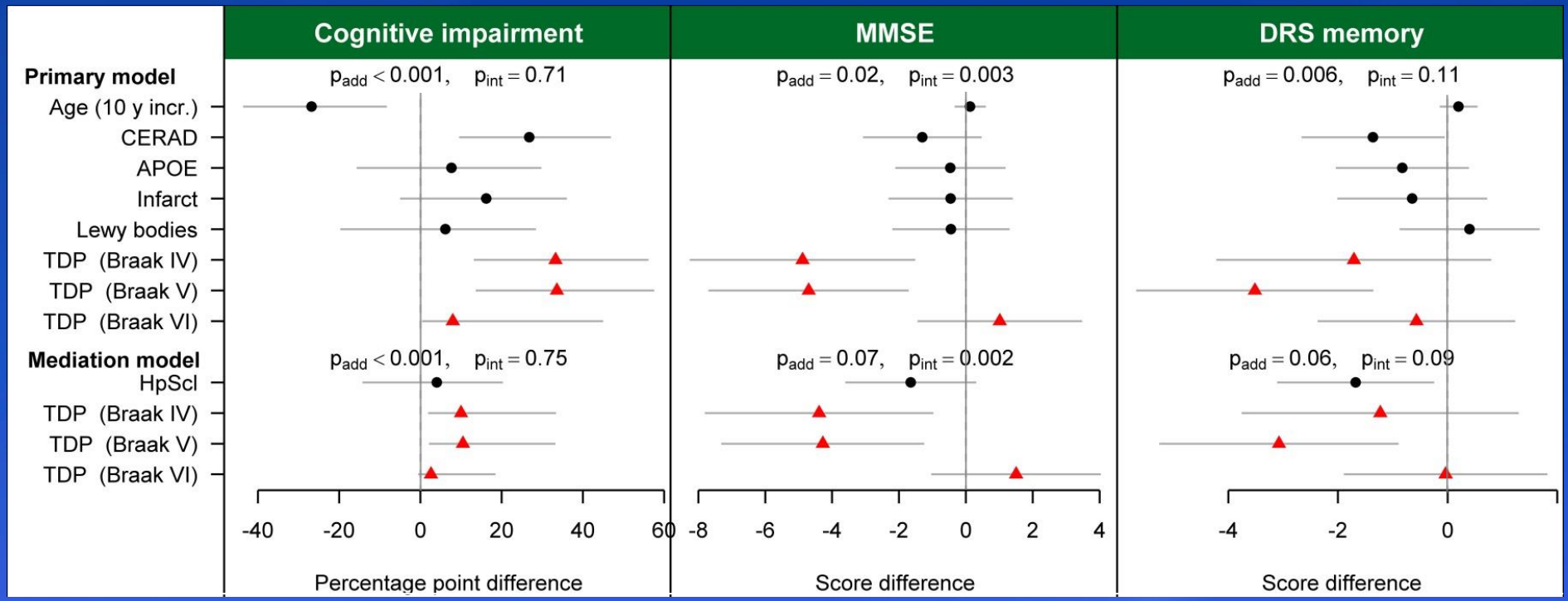
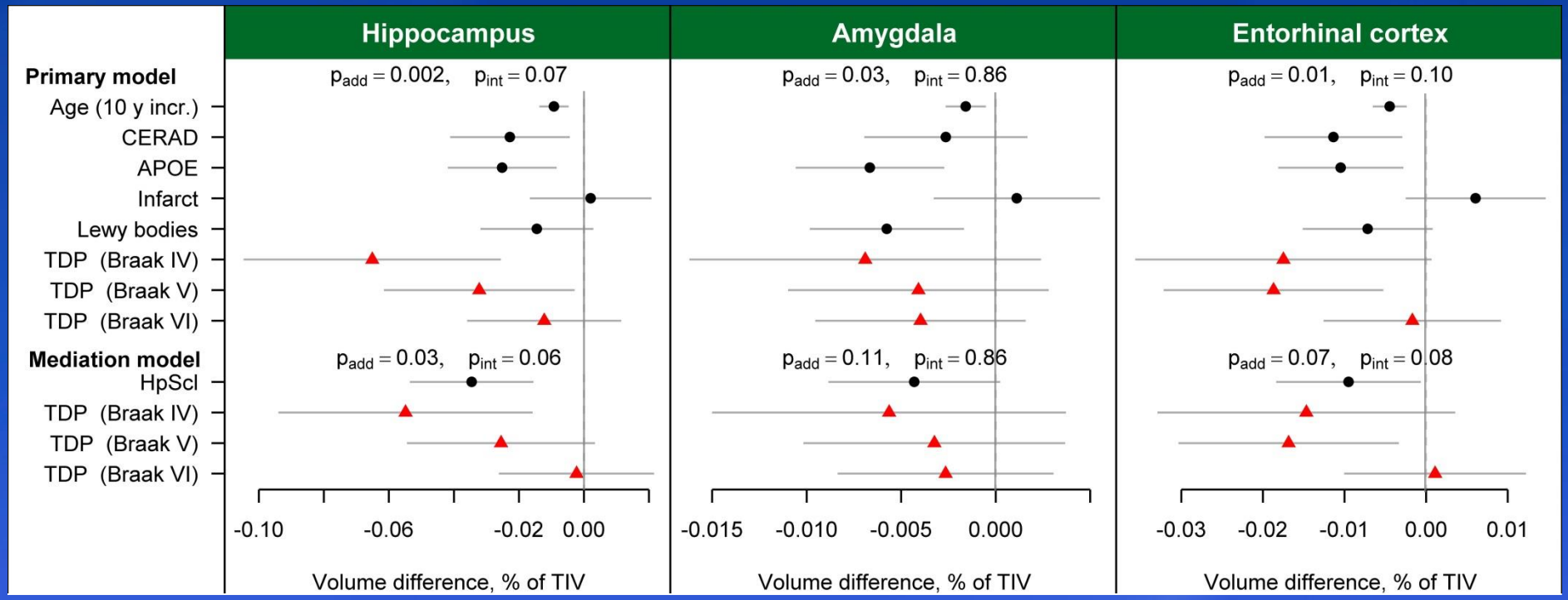
Models for the clinical variables



Josephs et al. Acta Neuropath. 2014

Models for medial temporal volumes



Josephs et al. Acta Neuropath. 2014

Summary 2

- TDP-43 appears to be playing a role in the clinical & imaging features associated with AD
- TDP-43 should be added to the list of proteins associated with the AD neurodegenerative process
- TDP-43 should be considered a potential target for the treatment of AD
- How does TDP-43, tau and beta-amyloid interact to trigger/generate neurodegeneration in AD?

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Acknowledgements

- **Investigators**

- Dennis Dickson, MD
- Jennifer Whitwell, PhD
- Bradley Boeve, MD
- Tania Gendron, PhD
- Clifford Jack, Jr, MD
- David Knopman, MD
- Amanda Liesinger, MS
- Melissa Murray, PhD
- Joseph Parisi, MD
- Ronald Petersen, MD, PhD
- Leonard Petrucelli, PhD
- Matthew Senjem, MS
- Glenn Smith, PhD
- Nirubol Tosakulwong, BS
- Stephen Weigand, MS

- **Grants**

- NIA R01-AG037491
- NIA P50-AG016574
- NIA R01-AG011378

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