Update on the Pathological Diagnosis of CTE

Ann C. McKee M.D.
Professor of Neurology and Pathology VA Boston Healthcare System
Boston University School of Medicine
Director of the CTE Program
Associate Director, Alzheimer's Disease Center

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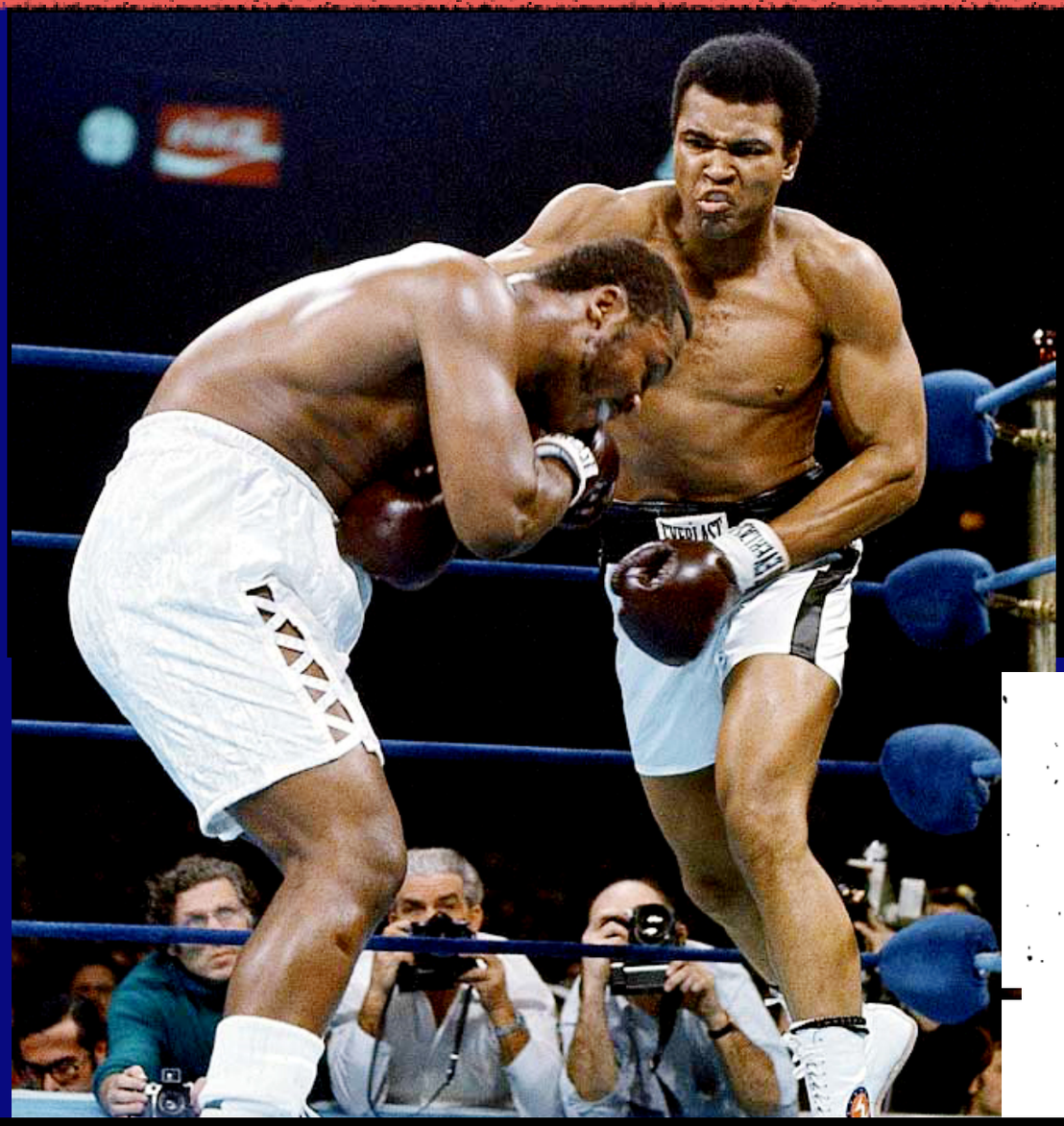
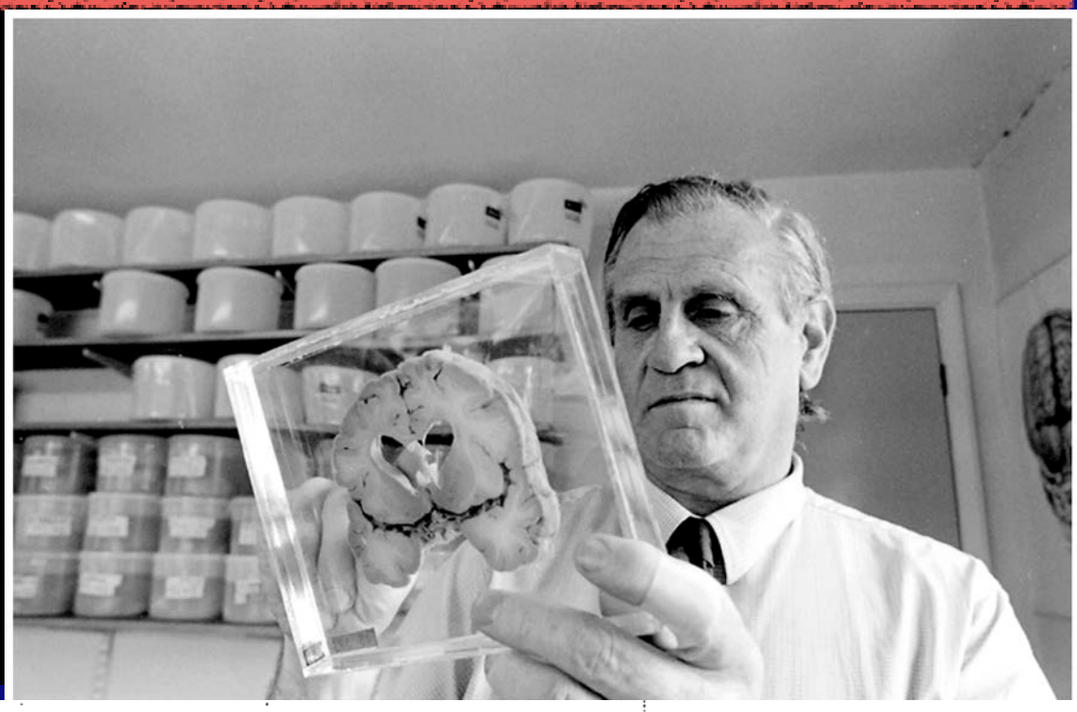
Clinicopathological Series of 15 boxers with CTE

Corsellis, Bruton, Freeman-Browne 1973





The aftermath of boxing[1]

J. A. N. CORSELLIS, C. J. BRUTON, AND DOROTHY FREEMAN-BROWNE[2]

From the Department of Neuropathology, Runwell Hospital, Wickford, Essex

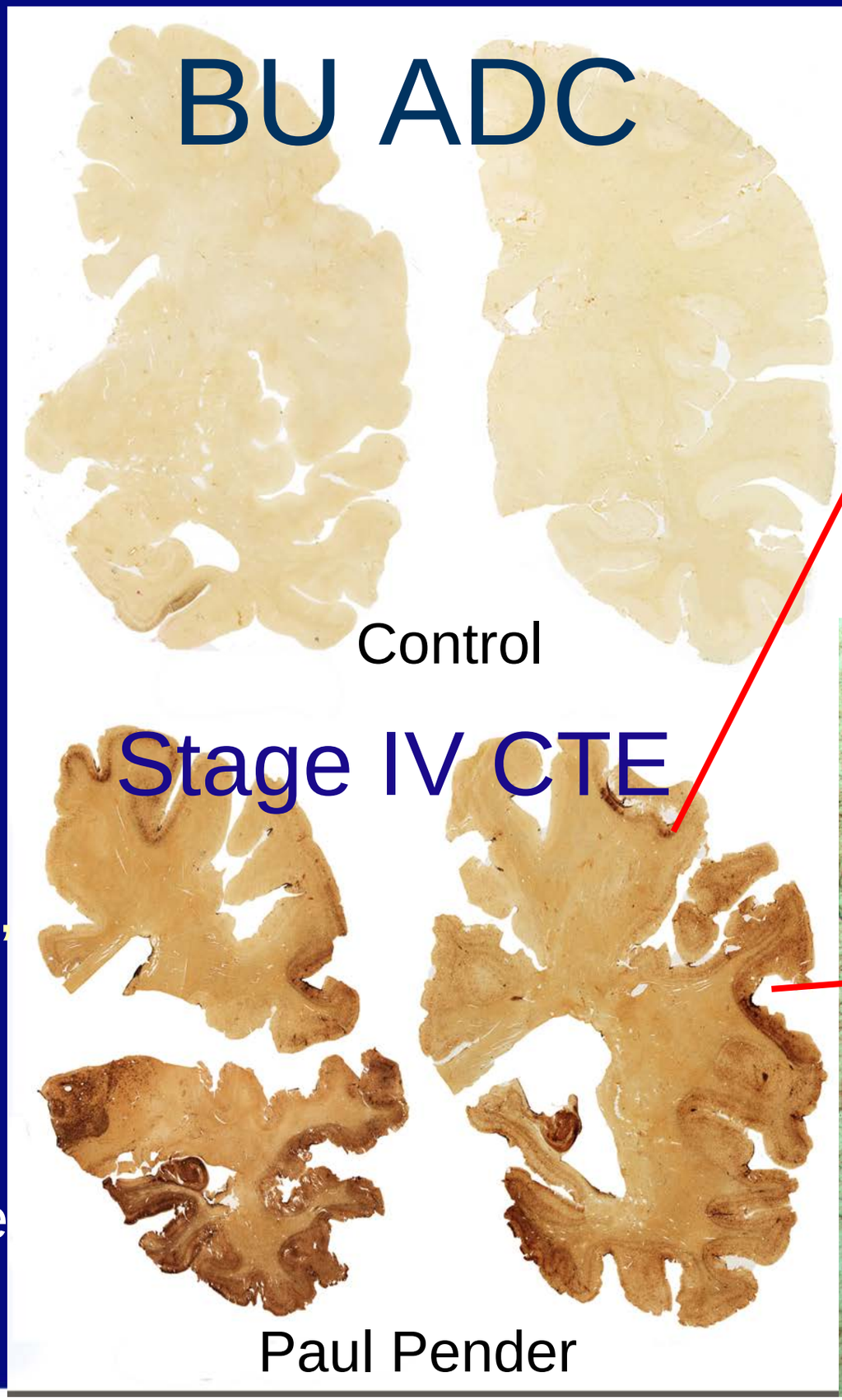
Psychological Medicine, 1973, 3, 270-303

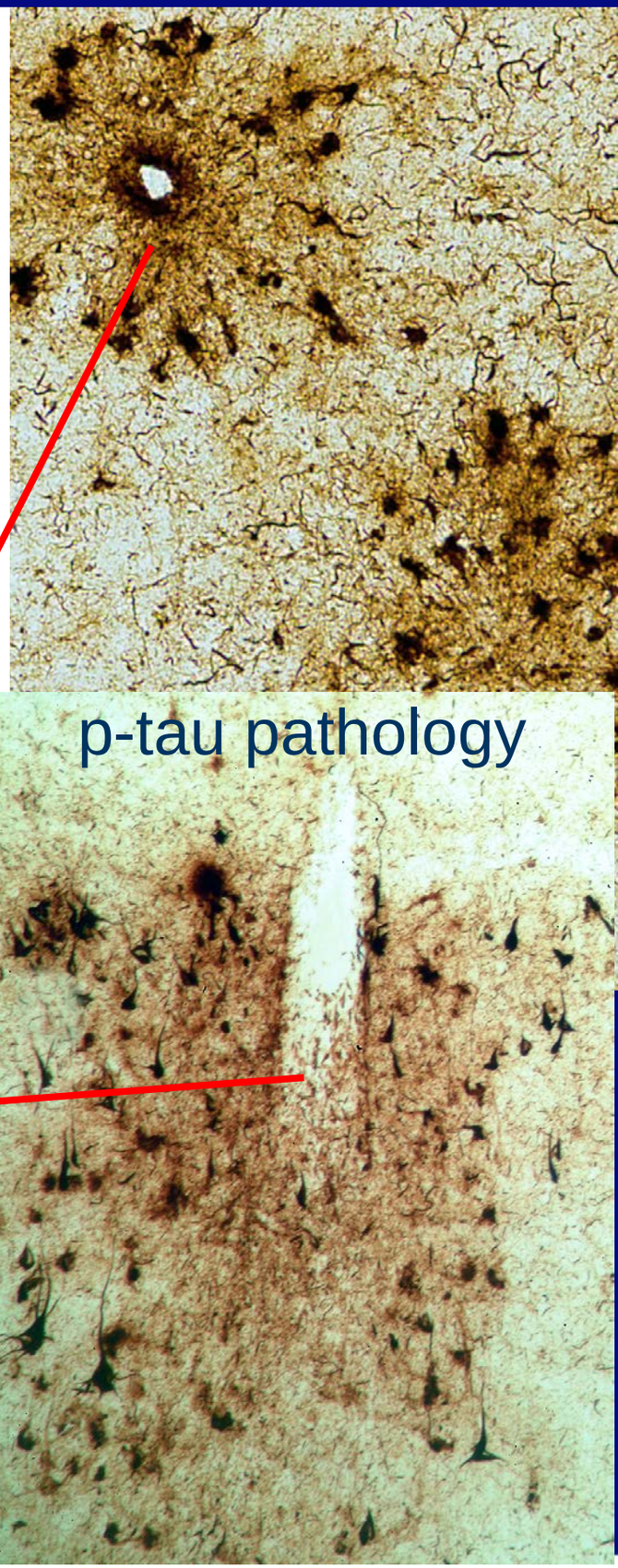
Cerebral atrophy, Enlargement of the lateral and third ventricles,
Thinning of the corpus callosum,
Cavum septum pellucidum with fenestrations,
Cerebellar scarring and
Neurofibrillary degeneration of the cerebral cortex and substantia nigra found on silver stains

Paul Pender

World Champion boxer, Marine

Died at age 73 with severe dementia





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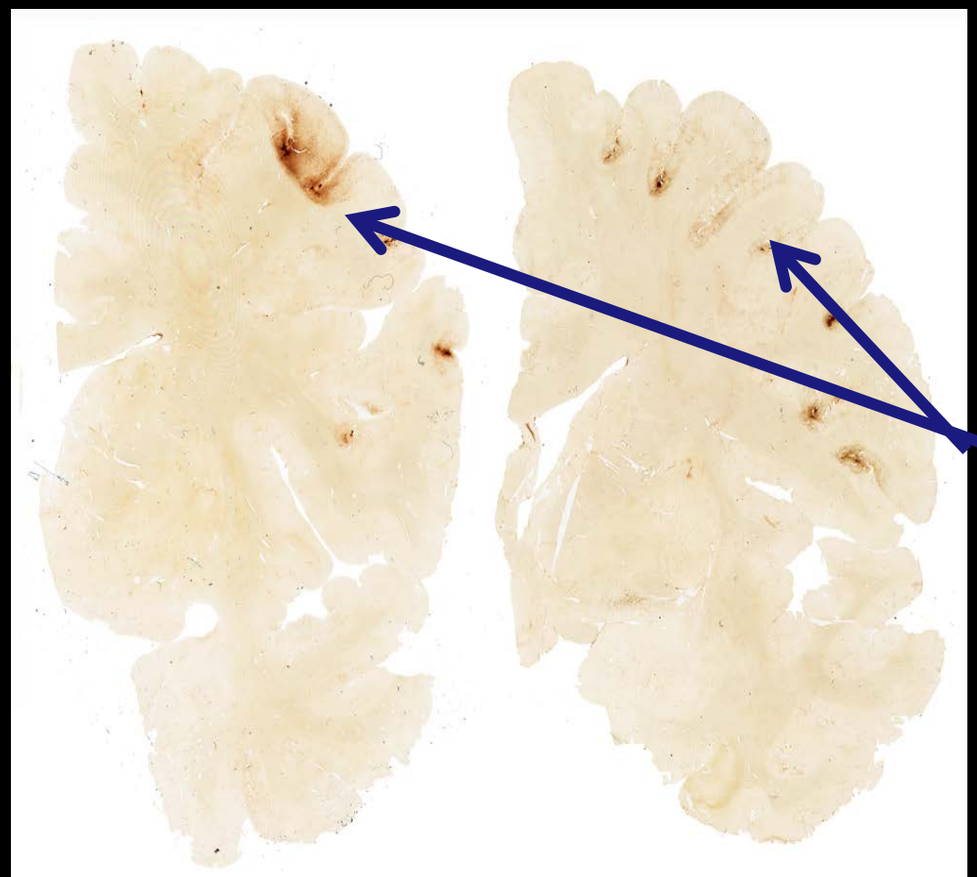
BRAIN
A JOURNAL OF NEUROLOGY

McKee et al 2013

The spectrum of disease in chronic traumatic encephalopathy

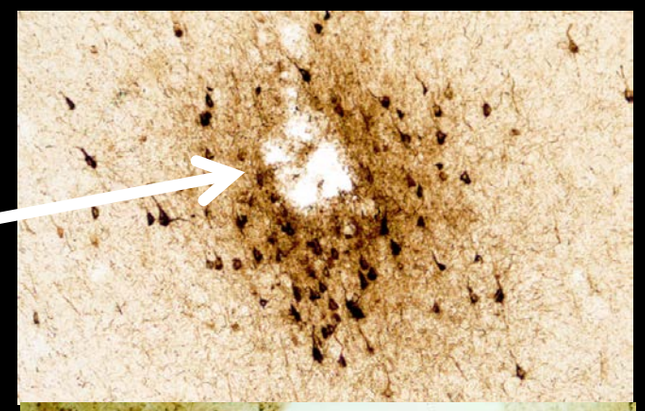
85 brains from mTBI subjects were analyzed; CTE found in 68: all males, 1 - 98 yrs, 64 athletes, 21 military veterans (86% were also athletes)

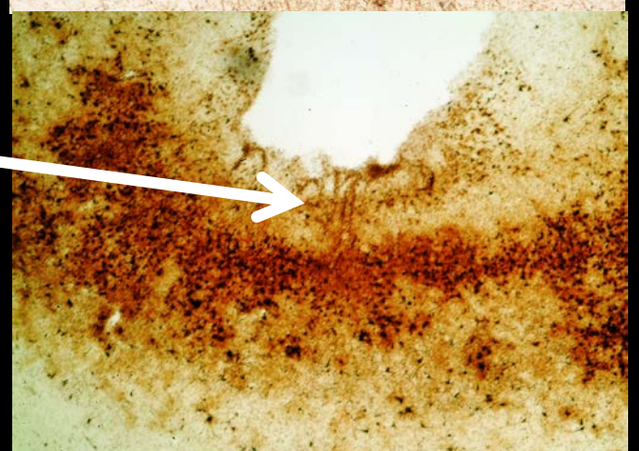
Neuropathological Criteria for CTE



P-tau lesions

1. Perivascular
2. Focal distribution at depths of sulci





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Stages of Tau Pathology

Age at Death

Stage I

mean age: 28.3 ± 13 years

Stage II

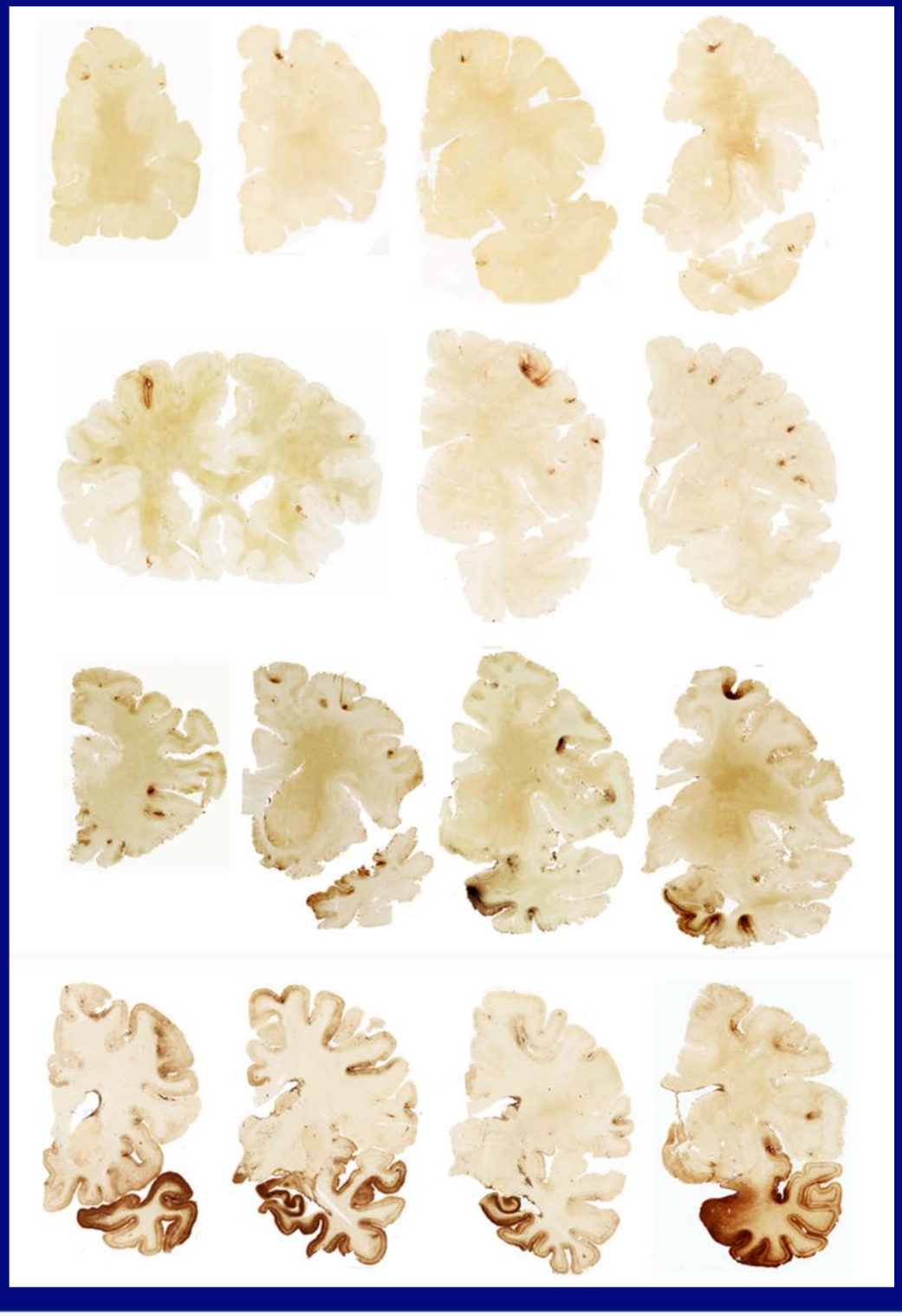
mean age: 44.3 ± 16 years

Stage III

mean age: 56.0 ± 14 years

Stage IV

mean age: 77.4 ± 12 years



McKee *et al*, 2013, *Brain*

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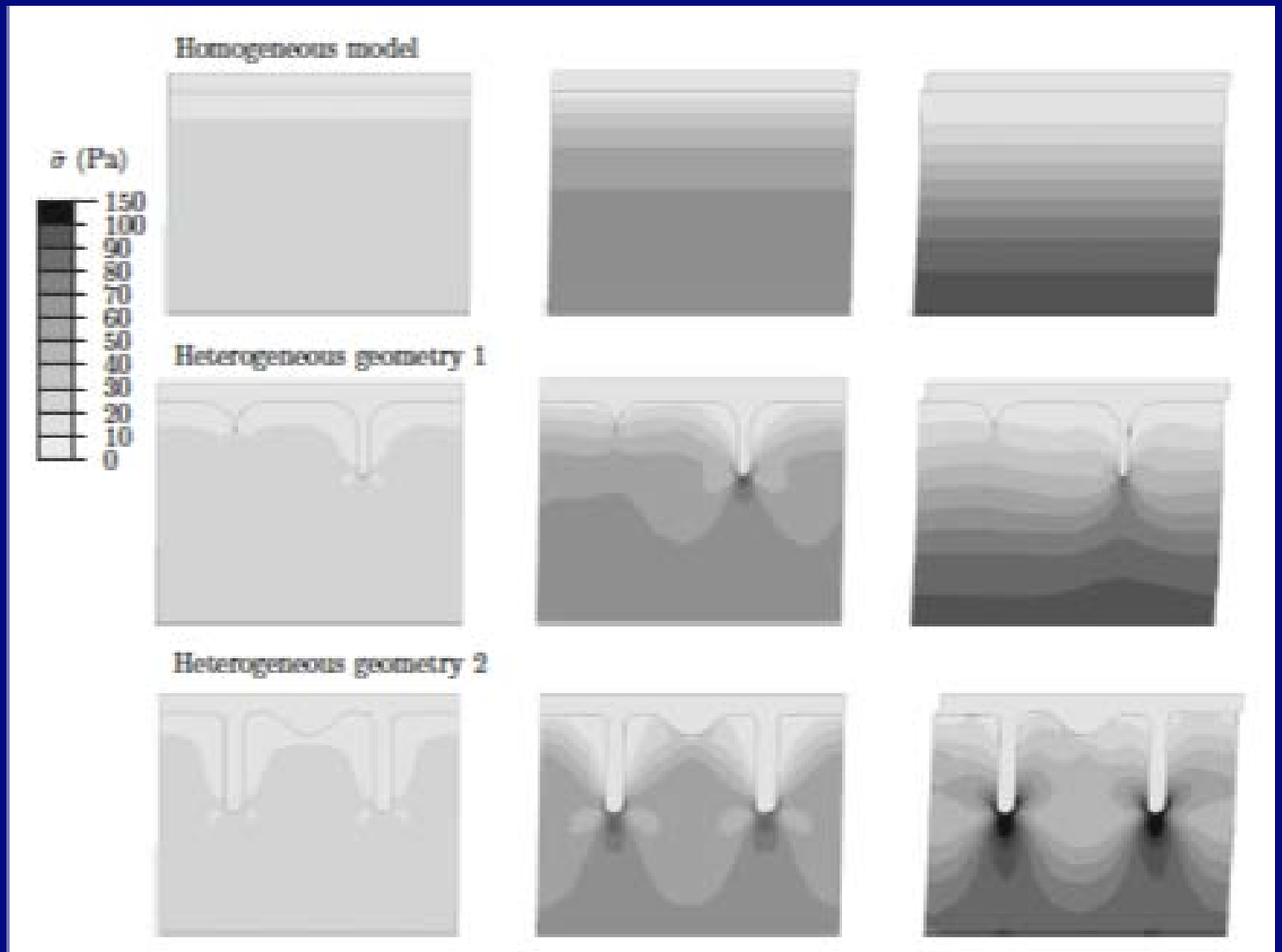
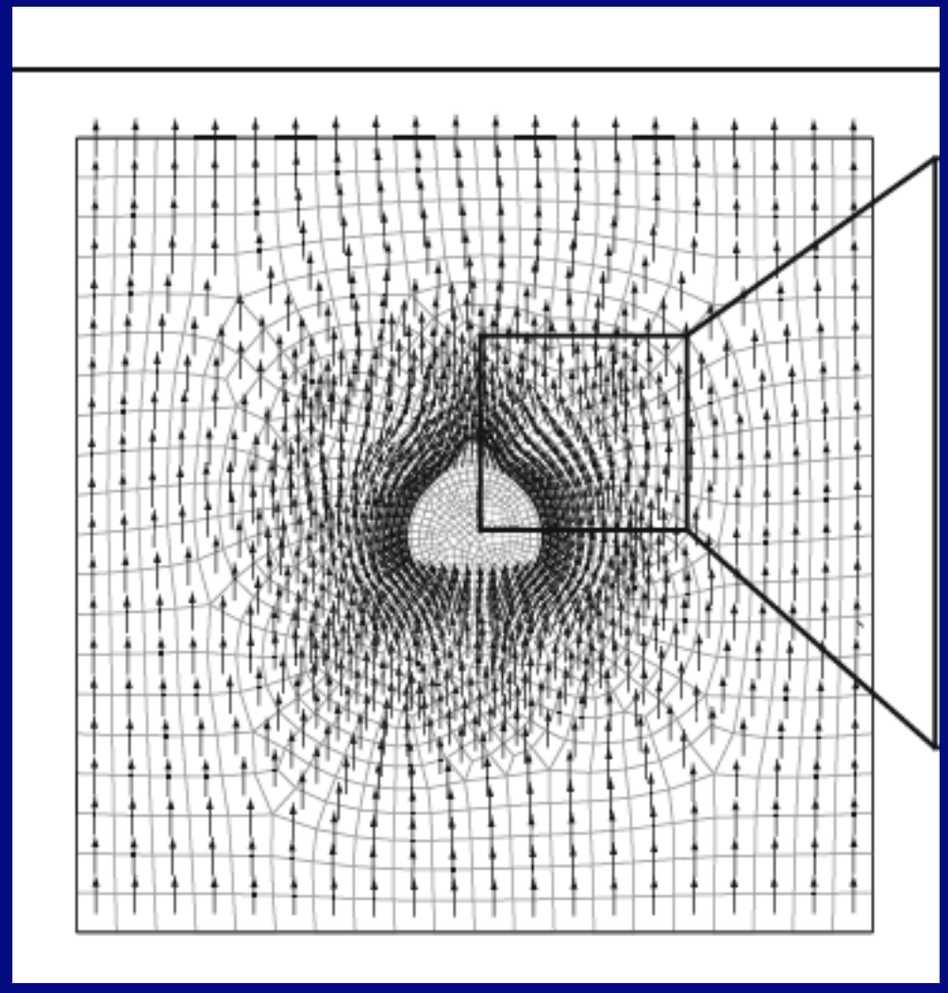
Why is tau protein deposited in those brain regions?

Sulcal depth and perivascular area are regions of physical stress concentration





Cloots et al Annals of Biomedical Engineering, Vol. 36, No. 7, July 2008

Cloots et al.J Mechanical Behavioral Biomedical Materials 2012 (41-52)

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In 2014, the NINDS/NIBIB launched a major effort to define the neuropathological characteristics of CTE.

One of the first objectives: evaluate the preliminary consensus criteria for the neuropathological diagnosis of CTE.

First consensus meeting: Is CTE is a distinct tauopathy that can be distinguished from other tauopathies?

Methods: The study design was based on previous successful NIH-sponsored consensus conferences for other tauopathies, specifically PSP and CBD

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25 cases of various tauopathies from:

Mayo Clinic Jacksonville
Columbia Presbyterian
Boston University

10 cases of CTE (with and without Aß)
5 cases of Alzheimer’s disease
2 cases of Progressive Supranuclear Palsy
2 cases of Corticobasal Degeneration
2 cases of Argyrophilic Grain disease
2 cases of Primary age-related tauopathy
2 cases of Guamanian Parkinson’s Dementia Complex

All tissue was processed at Boston University.

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12 regions from 25 cases (27 slides per case) stained with LHE, Bielschowsky silver, and immunostained for Aß, p-tau and p-TDP-43).

A 675 slides were digitally scanned using an Aperio scanner at Mayo Clinic Jacksonville

Digitized images of the 675 slides were organized into cases labeled with the case number (1-25), the brain region, and the stain.

The digitized slides were provided to the evaluating neuropathologists on portable hard drives.

No clinical or demographic information was provided to the neuropathologists– including no information regarding the subjects age, gender, clinical symptoms or athletic exposure.

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Brain region	Stains				
	LHE	AT8	Aß42	TDP43	BIEL
Superior frontal (BA 8,9)	X	X			
Dorsolateral superior frontal (BA 45, 46)	X	X	X		
Caudate, Accumbens, Putamen	X	X			
Temporal pole (BA 38)	X	X			
Superior temporal (BA 20, 21,22)	X	X		X	
Amygdala, with entorhinal cortex (BA 28)	X	X			
Hippocampus, lateral geniculate nucleus	X	X	X	X	X
Thalamus with mammillary body	X	X			
Cerebellum with dentate nucleus	X	X			

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The neuropathologists were given a tauopathy criteria guide that provided provisional criteria for CTE (McKee et al, Brain 2013) as well as published criteria for the other tauopathies.

The following criteria for the neuropathological diagnosis of CTE are proposed (McKee et al., 2013):

1. Perivascular foci of p-tau immunoreactive neurofibrillary tangles (NFTs) and astrocytic tangles (ATs) in the neocortex

2. Irregular distribution of p-tau immunoreactive NFTs and ATs at the depths of cerebral sulci

3. NFTs in the cerebral cortex located preferentially in the superficial layers (often most pronounced in temporal cortex)

4. Supportive features: Clusters of subpial ATs in the cerebral cortex, most pronounced at the sulcal depths.

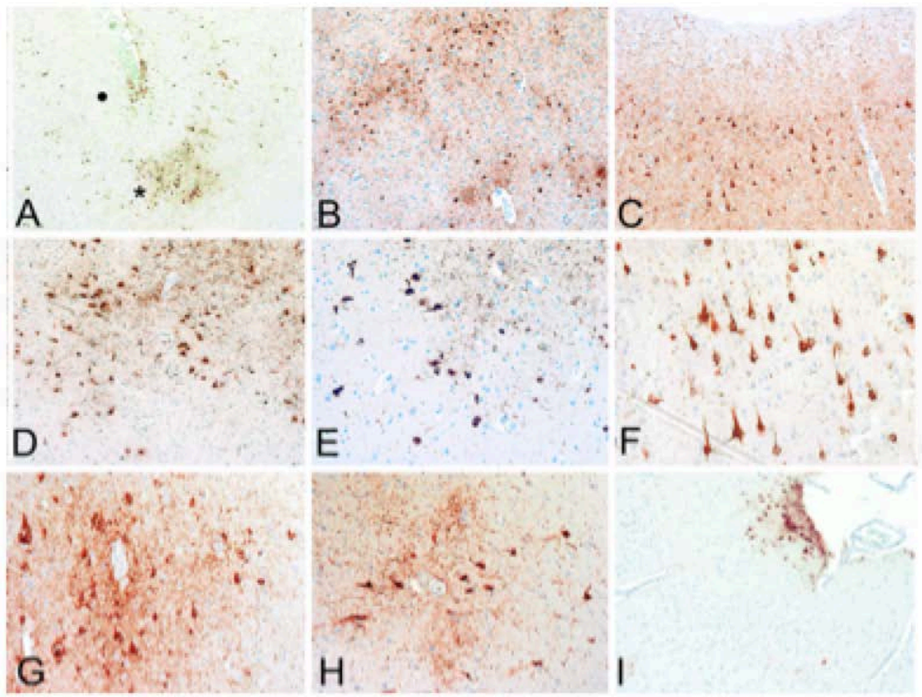

Figure 1. Microscopic CTE p-tau pathology

A. Clusters of NFTs and glial tau pathology are often found at the depths of the sulci in the frontal, insular and temporal cortices (*), often associated with clusters of subpial ATs (•).

B., D., E., G., H. There is often an accentuation of the NFTs around small blood vessels

C., F. The NFTs preferentially involve the superficial layers of cortex, a feature that is often most prominent in the temporal lobe. Clusters of subpial ATs are also common in CTE.

The neuropathologists independently luated the cases and filled out evaluation ns.

The process was extremely time-consuming, requiring on average 4 hours per case 00 hours per individual neuropathologist) lack of any other provided information ade the process quite difficult.

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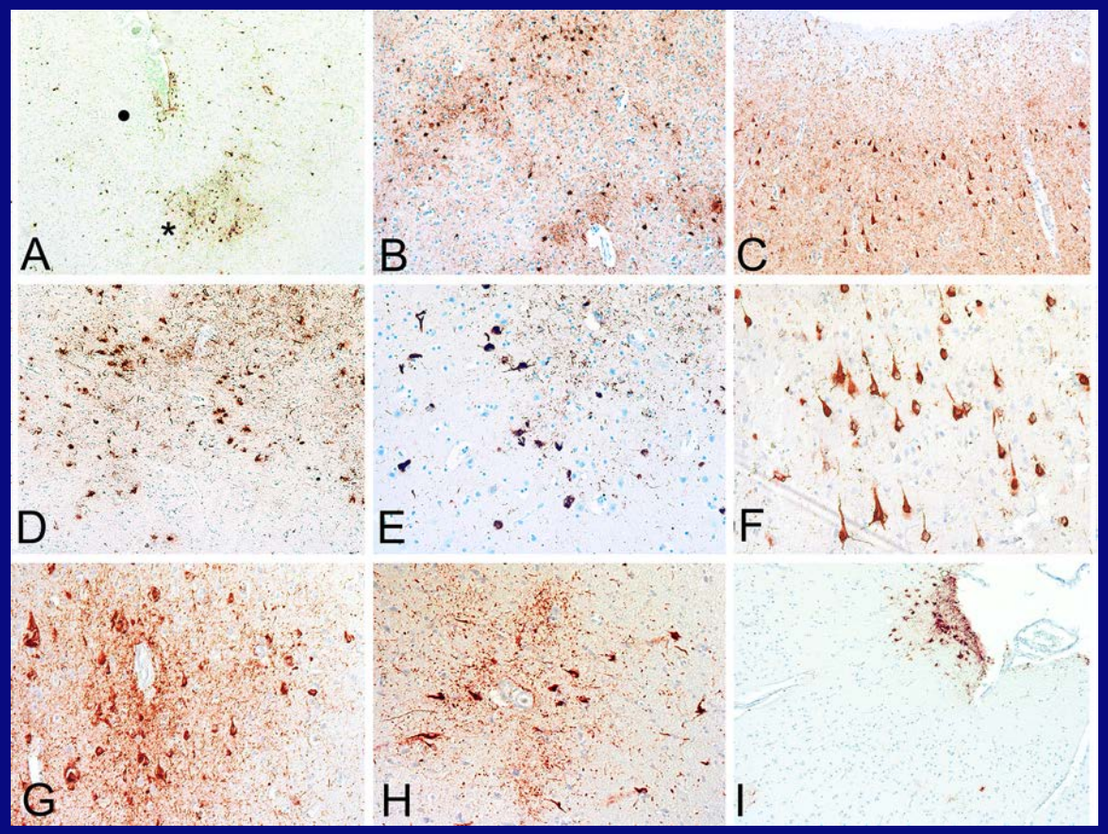
Neuropathological Criteria for CTE

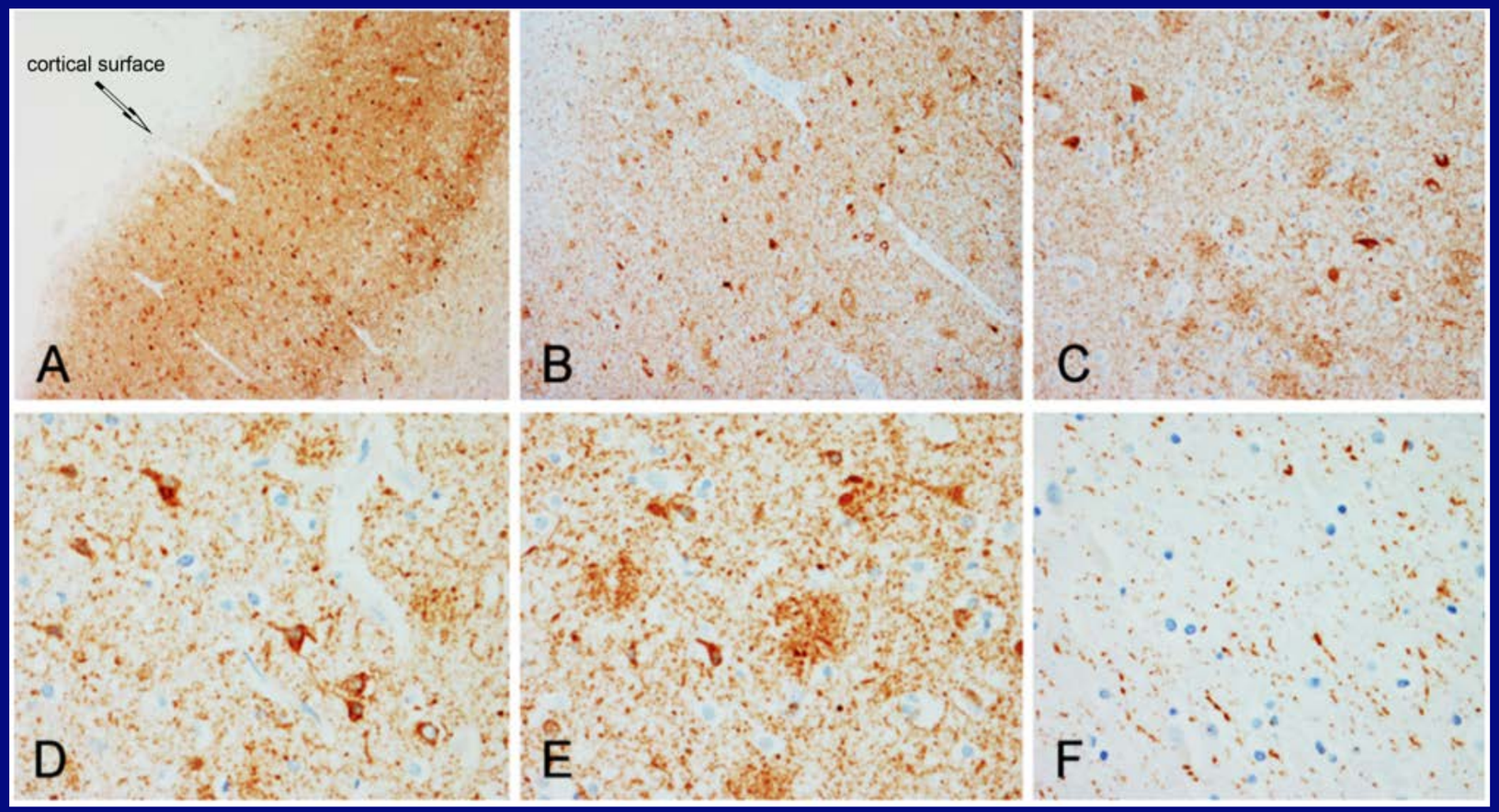
The following criteria for the neuropathological diagnosis of CTE were used (McKee et al., 2013):

1. Perivascular foci of NFTs and astrocytic tangles in the neocortex
2. Irregular distribution of NFTs and ATs at the depths of cerebral sulci
3. NFTs in the cerebral cortex located preferentially in the superficial layers (often most pronounced in temporal cortex)
4. Supportive features: Clusters of subpial ATs in the cerebral cortex.



Neuropathological Criteria for AD

Extracellular deposits of ß-amyloid (Aß) peptides, or senile plaques, and NFTs are considered essential neuropathological features of AD. The recent National Institute on Aging- Alzheimer's Association guidelines for the neuropathological assessment of AD include an "ABC" score that incorporates histopathological assessments of amyloid ß deposits (A), staging of NFTs (B), and scoring of neuritic plaques (C) (Montine et al, 2012).



Microscopic AD p-tau pathology

A. Dense tau pathology is found throughout all cortical layers, with laminar accentuation in layers III and V. There is no preferential distribution around penetrating vessels or at the pial surface. Lamina I often has a paucity of tau. **B. & C.** Phospho-tau immunohistochemistry reveals a mixture of neurofibrillary tangles (NFT), neuritic plaques (NP) and neuropil threads. **D.** Pretangles and NFT occur in affected cortices. (note: lack of association of tau pathology with blood vessel) **E.** Neuritic plaques are characteristic. **F.** There is little tau pathology in the white matter, when it occurs it consists primarily of threads immediately beneath cortical ribbon.

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Seven neuropathologists evaluated the digitized slides independently:

Nigel Cairns, Ph.D.

Dennis Dickson, M.D

Rebecca Folkerth, MD

C. Dirk Keene, M.D

Daniel Perl, M.D.

Thor Stein M.D., Ph.D.

Jean Paul Vonsattel, M.D.

and submitted their diagnostic evaluations prior to the conference.

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NINDS/NIBIB Consensus Conference

February 25-27, 2015

Neuropathological criteria for CTE:

Wayne Gordon PhD, C. Dirk Keene, MD, Daniel Perl, MD, Debra Babcock,PhD, Irene Litvan, PhD, Rebecca Folkerth, MD, Thor Stein MD, PhD, Ann McKee, MD, Walter Koroschetz, MD, Nigel Cairns, PhD., Jean Paul Vonsattel, MD, William Stewart, MD, Dennis Dickson, MD, Patrick Bellgowan, MD

Results

There was substantial agreement within the neuropathologists who reviewed the cases (Cohen's kappa: 0.67)

There was substantial agreement between reviewers and CTE diagnosis (Cohen's kappa: 0.78) using the proposed criteria for CTE

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Age	Sport	Original Dx	TDP 43	Aß	CTE	CTE plus	OTHER	%	TOTAL
61	BOX	CTE 3	+	0	6	CTE+ HS		100	**90%**
66	NFL	CTE 4	0	0	5	CTE+PART+AGD		100	
						CTE+ADC+HS			
69	NFL	CTE 3	+	0	5	CTE+HS		100	
						CTE+PART			
62	NFL	CTE 4	+	+	5	CTE+HS		100	
						CTE+AD+HS			
70	NFL	CTE 4	+	+	2	CTE+ADC 3		100	
						CTE+AD			
						CTE+AD+HS			
78	NFL	CTE 4	+	+	0	CTE+ADC 4		100	
						CTE+AD 3			
70	NFL	CTE 4 + vas	+	+	3	CTE+AGD	AGD	85	
						CTE+HS			
						CTE+ AD			
82	NFL	CTE 4	+	+	1	CTE+ADC	MSA	85	
						CTE+ADC+HS 2			
						CTE+AD+HS			
66	NFL	CTE 4	+	+	3	CTE+HS	HS	71	
						CTE+AD+HS 2	GPDC		
						CTE+ADC+HS			
75	NFL	CTE 4	+	+	0	CTE+ADC 2	PSP 2	57	
		+adc +lbd				CTE+AD+HS	GPDC		

Most common additions to CTE diagnosis (70 evals):

- Hippocampal sclerosis: 13
- Alzheimer's disease: 8
- Changes of Alzheimer's disease: 7
- PART: 2
- Argyrophilic Grain Disease: 2

Most common alternate diagnosis (6/70=9%):

- GPDC: 2
- PSP: 2
- AGD:1
- HS:1
- MSA:1

Original Dx	Dx	OTHER	%	TOTAL
AD	AD 7		100	100
AD	AD 7		100	
AD	AD 7		100	
AD	AD 6	CTE+AD	100	
AD	AD 6	CTE+AD	100	
CBD	CBD 6	CTE+CBD	100	86
CBD	CBD 5	PSP 2	71	
PART	PART 6	AGD	85	78
PART	PART 5	AGD 2	71	
PSP	PSP 3	AGD	43	43
		AD+AGD		
		GPDC		
		?		
PSP	PSP 3	CTE+AD	43	
		CTE+ADC		
		?		
		AD		
		PART		

Original Dx	Dx	OTHER	%	
AGD	AGD 2	AGD+ADC	43	36
		PART 2		
		PICKS		
		PSP		
AGD	AGD 2	AD	28	
		CTE+AD		
		PSP		
		GPDC		
		MSA		
GPDC	GPDC 3	PSP 3	43	22
		CTE+PART		
GPDC	GPDC 0	CTE+ADC	0	
		PICKS		
		AD+PSP		
		CTE+AD+HS 2		
		CTE+AD		

15 additions of CTE to another diagnosis (70 evals):

- To Alzheimer's disease: 2/35 responses (6%)
- To CBD: 1/14 (7%)
- To AGD: 1/14 (7%)
- To PSP: 2/14 (14%)
- To GPDC: 4/14 (29%)
- To PART: 0/14

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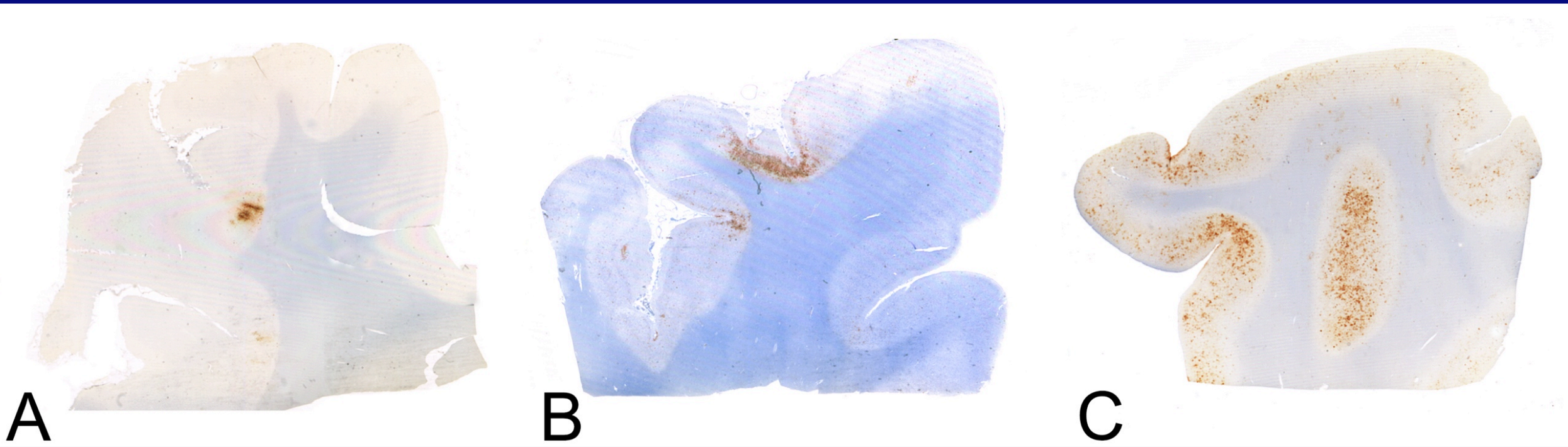
Results



Visual inspection of p-tau stained slides often revealed the irregular pathology of CTE

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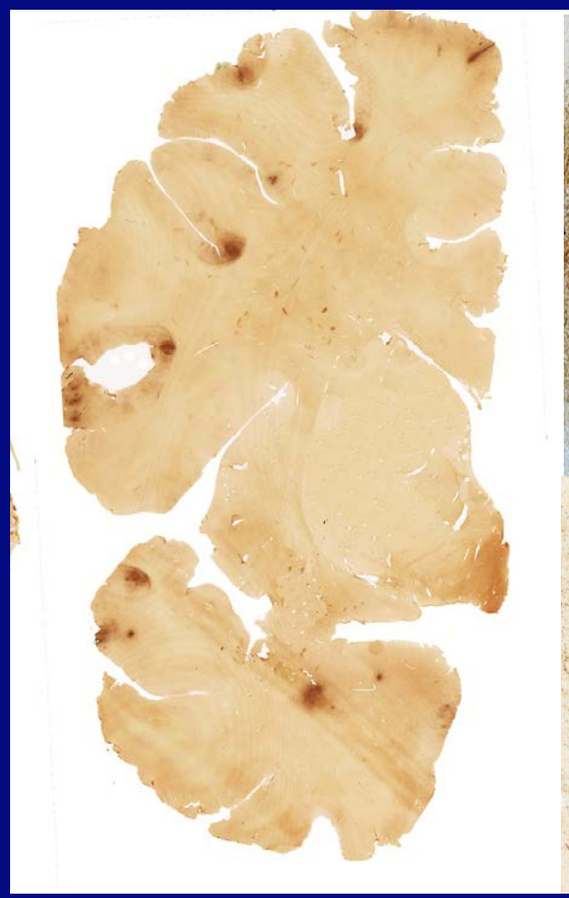
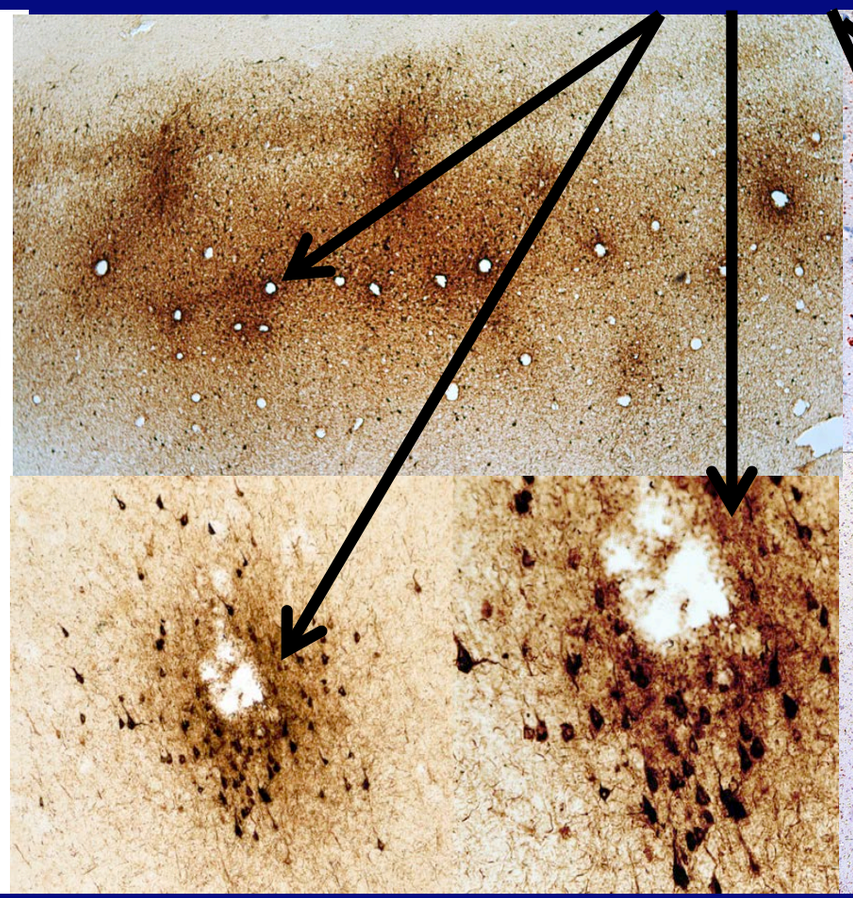
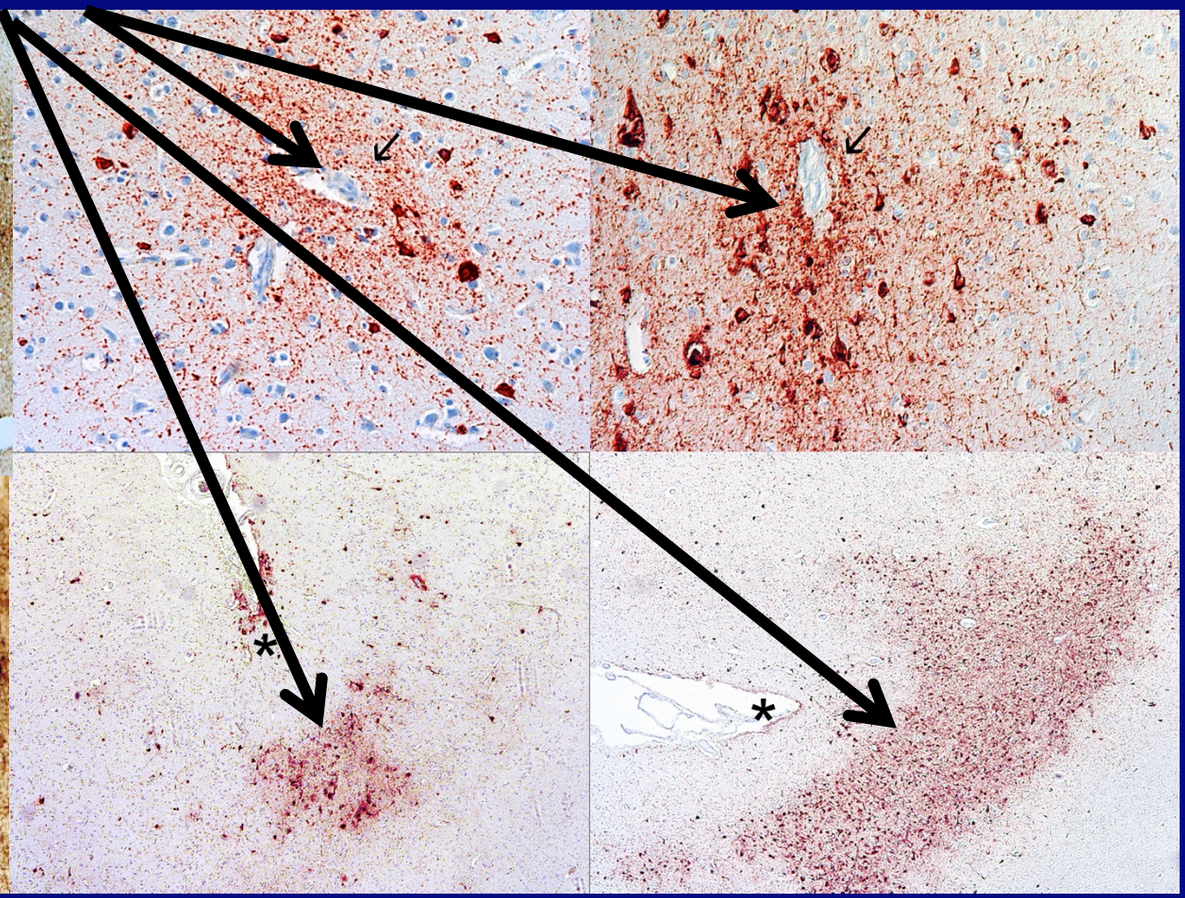
Criteria for CTE

THE PATHOGNOMONIC LESION







"In CTE, the tau lesion considered pathognomonic was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes at the depths of the depths of the cortical sulci in an irregular pattern."

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Supportive features (p-tau pathologies)

These features were commonly found in the CTE cases but were not considered diagnostic

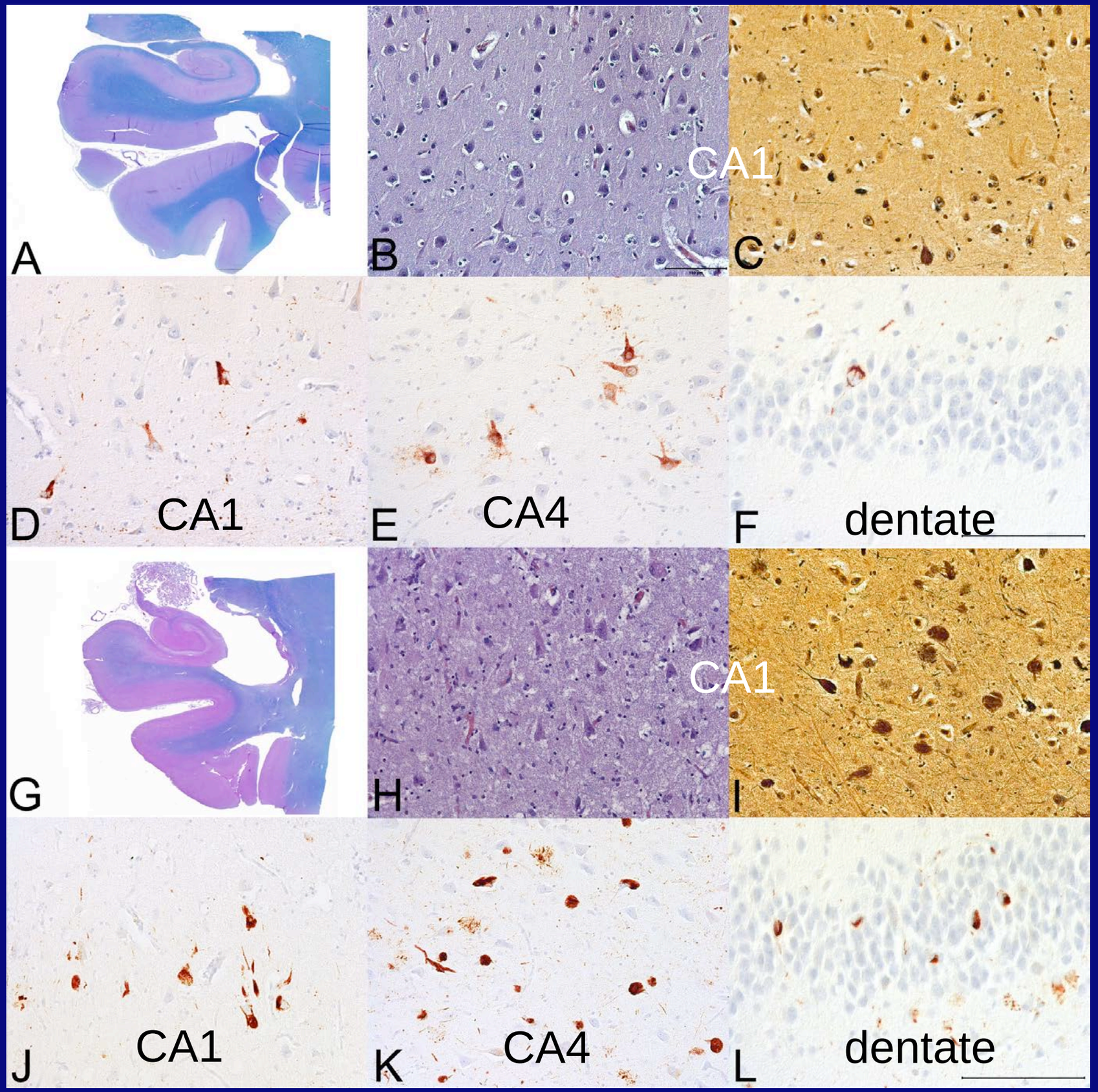
Abnormal p-tau immunoreactive pretangles and NFTs preferentially affecting superficial layers (layers II/III)

In the hippocampus, pretangles, NFTs or extracellular tangles preferentially affecting CA2 and pretangles and prominent proximal dendritic swellings in CA4.

Abnormal p-tau immunoreactive neuronal and astrocytic aggregates in subcortical nuclei.

P-tau immunoreactive thorny astrocytes at the glial limitans of the subpial region found at the depths of the cerebral sulci.

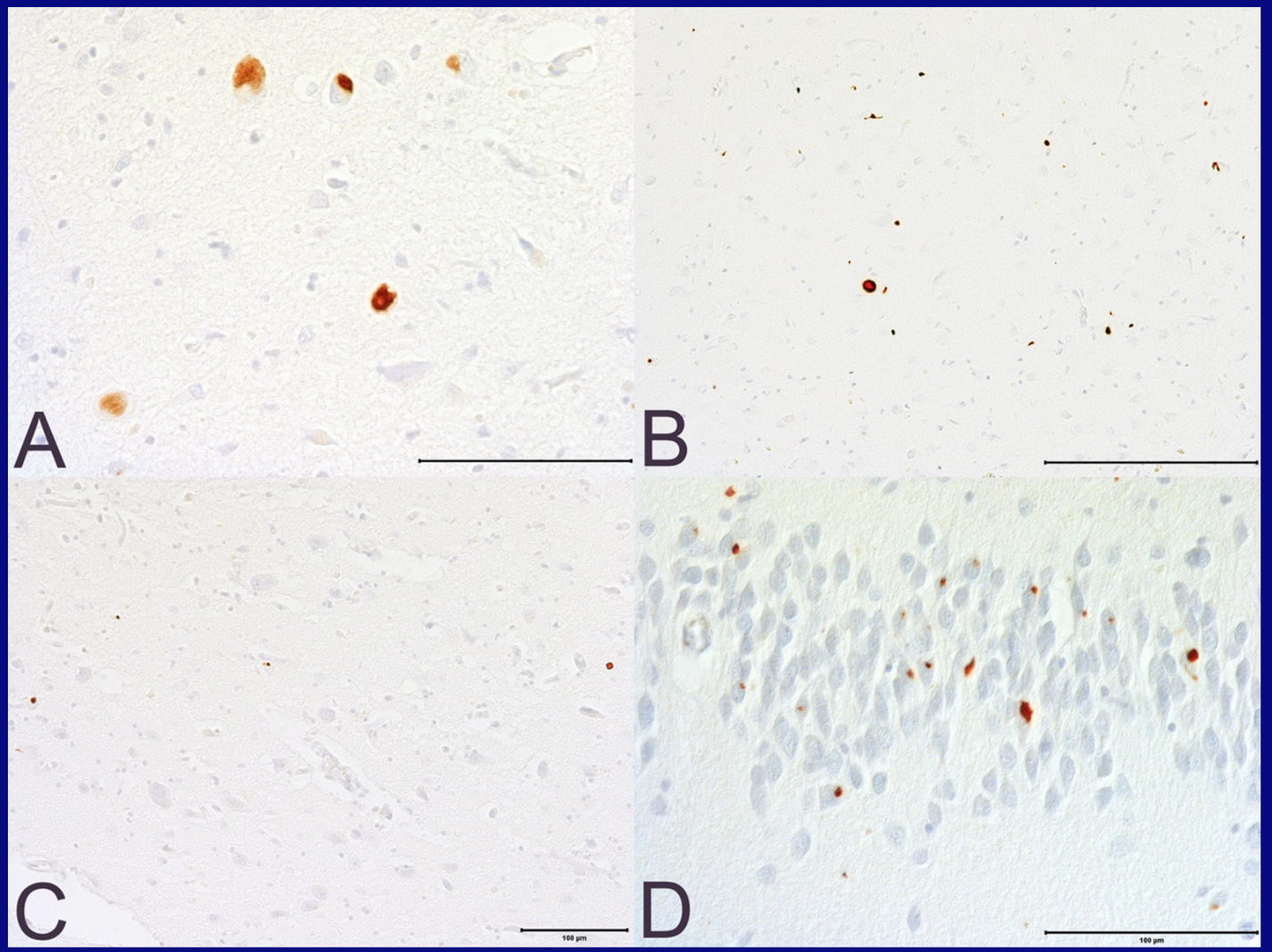
P-tau immunoreactive large grain-like and dot-like neurites (in addition to some threadlike neurites)


A
B
CA1
C
D
CA1
E
CA4
F
dentate
G
H
CA1
I
J
CA1
K
CA4
L
dentate

Supportive features (non-tau pathologies)

1. Macroscopic features: Disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and signs of previous traumatic injury.

2. TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex and amygdala



Age-related non-specific p-tau-related pathology that may be present (ARTAG)

1. Thorn shaped astrocytes in patchy subcortical white matter

2. Subependymal and periventricular, perivascular thorny astrocytes in the mediobasal regions
3. Thorn-shaped astrocytes in amygdala or hippocampus

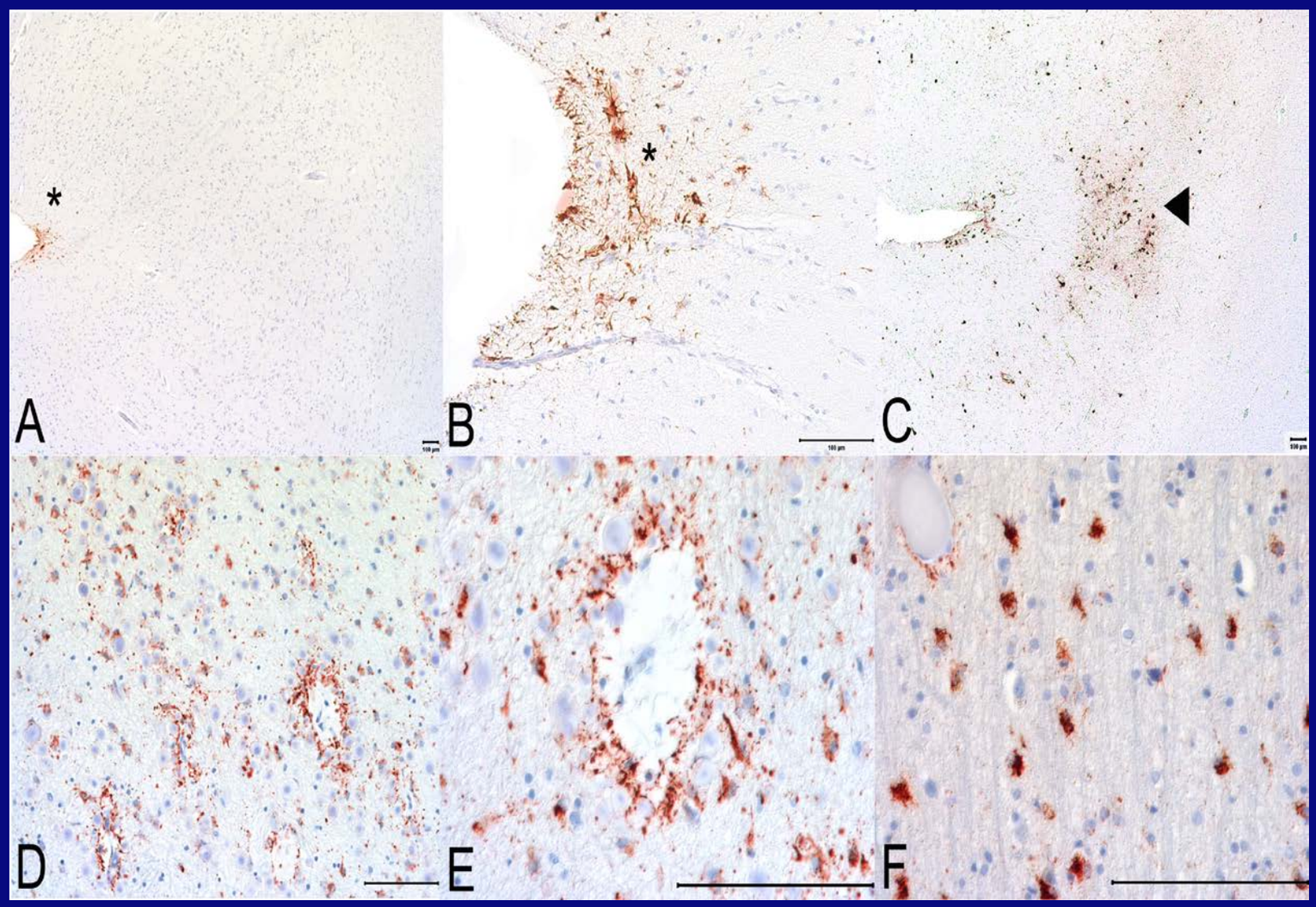


Table 2. Preliminary NINDS criteria for the pathological diagnosis of CTE

REQUIRED FOR DIAGNOSIS OF CTE	
1.	The pathognomonic lesion consists of ptau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci.

SUPPORTIVE NEUROPATHOLOGICAL FEATURES OF CTE	
Ptau-related pathologies:	
1.	Abnormal p- tau immunoreactive pretangles and NFTs preferentially affecting superficial layers (layers II/III), in contrast to layers III and V as in AD).
2.	In the hippocampus, pretangles, NFTs or extracellular tangles preferentially affecting CA2 and pretangles and prominent proximal dendritic swellings in CA4. These regional p-tau pathologies differ from the preferential involvement of CA1 and subiculum in AD.
3.	Abnormal p-tau immunoreactive neuronal and astrocytic aggregates in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, and isodendritic core (nucleus basalis of Meynert, raphe nuclei, substantia nigra and locus coeruleus).
4.	P-tau immunoreactive thorny astrocytes at the glial limitans most commonly found the subpial and periventricular regions.
5.	P-tau immunoreactive large grain-like and dot-like neurites* (in addition to some threadlike neurites).
Non-ptau-related pathologies:	
1.	Macroscopic features: Disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and signs of previous traumatic injury.
2.	TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex and amygdala.

AGE-RELATED, NON-SPECIFIC PTAU-RELATED PATHOLOGY THAT MAY BE PRESENT, NON-DIAGNOSTIC AND NON-SUPPORTIVE[18]	
1.	Thorn shaped astrocytes in patchy subcortical white matter
2.	Subependymal and periventricular, perivascular thorny astrocytes in the mediobasal regions
3.	Thorn-shaped astrocytes in amygdala or hippocampus

Future directions

- These criteria are just the beginning of the process of fully characterizing the pathology of CTE, and this was only the first of a series of consensus conferences of the investigators funded by the NINDS research initiative.

- Many important questions were not yet addressed, such as involvement of spinal cord, neuronal cell loss, gliosis, inflammation, hemosiderin deposition, specific pathologic stages of the disorder, and concurrent amyloid pathology.

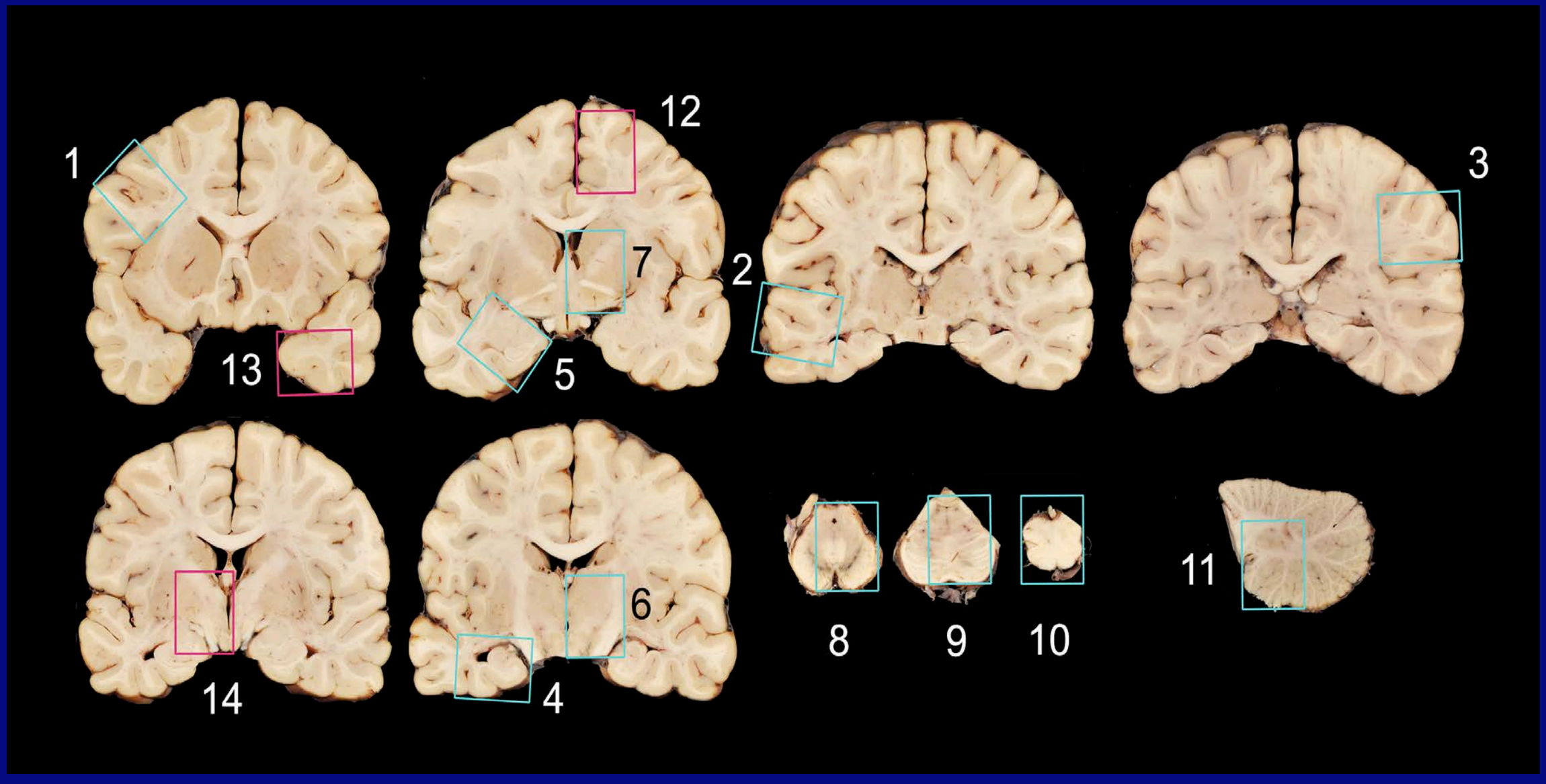
- Similar to most neurodegenerative disorders, CTE remains a diagnosis that can only be made definitively upon neuropathological examination of the brain. Because the pathological diagnosis requires p-tau immunostaining, and often, additional sampling compared to routine practices, its detection in autopsy cohorts has been limited. It is, therefore, unclear how common CTE occurs in post-mortem series. yet known.

Recommended sampling

Table 3. Recommended brain regions to be sampled and evaluated
In addition to the NIA-AA recommended regions for the evaluation of Alzheimer's disease (AD) neuropathologic change and Lewy body disease (LBD) [28], we recommend wider p-tau screening to capture CTE and other tauopathies. In addition, if there is a high index of suspicion of CTE, we recommend taking extra sections of frontal and temporal cortices, and hypothalamus including the mammillary body.

	CTE		
Region			
Middle frontal gyrus*	pTau[1]	pTDP-43	Aß[3]
Superior & middle temporal gyri*	pTau[1]		
Inferior parietal lobule*	pTau[1]		Aß[3]
Hippocampus and EC	pTau	pTDP-43[2]	
Amygdala	pTau	pTDP-43[2]	
Thalamus	pTau		
Basal ganglia with basal nucleus of Meynert	pTau		
Midbrain including SN	pTau		
Pons including LC	pTau		
Medulla including DMV	pTau		
Cerebellar cortex and dentate n.	pTau		
Additional sections if high suspicion			
Superior frontal	pTau[4]		
Temporal pole	pTau[4]	pTDP-43	
Hypothalamus including mammillary body	pTau[4]		

Recommended sampling



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Recommended sampling

- Follows the protocol recommended by NIA-AA and has been shown in pilot studies to detect 80% of CTE cases (20% of CTE cases, all early stage, are missed)
- Recommendation that all the cortical sections be taken to include the region at the depths of the cortical.
- Of note, Bielschowsky silver stain and Thioflavin do not detect the diagnostically significant focal perivascular cortical tau lesions and the panel recommended p-tau immunohistochemistry for the diagnosis of CTE using AT8 immunostaining or equivalent p-tau antibody (CP-13 or PHF-1).

Summary

Future directions will include further validation of the neuropathological criteria for CTE, including staging of the severity of p-tau pathology and characterization of early disease.

It will also be important to determine the differential hippocampal p-tau pathology in CTE compared to AD and whether the TDP-43 pathology is distinctive for CTE.

The contributions of other proteinopathies, including Aß, TDP43, and alpha-synuclein will also be important to determine.

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VA Boston/ Boston University/ SLI
Chronic Traumatic Encephalopathy Program

BU/VA CTE Program

Jason Adams
Victor Alvarez MD
Kathryn Babcoc
Alexandra Bourlas
Christine Baugh
Andrew Budson MD
Robert Cantu, MD FACS
Kerry Cormier
Dan Daneshvar, MD, PhD
Brian Frye
Matthew Jacobs
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Todd Solomon, PhD
Thor Stein, MD, PhD
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Other Institutions

David Brody, Wash U
Robert Brown MD, U Mass
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Dennis Dickson, MD Mayo Clinic
Rebecca Folkerth, MD Brigham
Garth Hall, PhD U Mass Lowell
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Dirk Keene, MD U Wash
Alexander Lin, PhD, BWH
Irene Litvan, MD UC San Diego
Thomas Montine, MD, PhD U Wash
Daniel Perl, MD USHS
Michael Strong, MD Western
William Stewart, Glasgow
Jean Paul Vonsattel, MD Columbia

BU Goldstein Lab

Andrew Fisher, PhD
Chad Tagge, PhD
Juliet Montcaster, PhD
Mark Wojnarowicz

CLF

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Chris Nowinski

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