

25th Annual Southern California Alzheimer's Disease Research Conference

New Guidelines and Importance of Brain Donation

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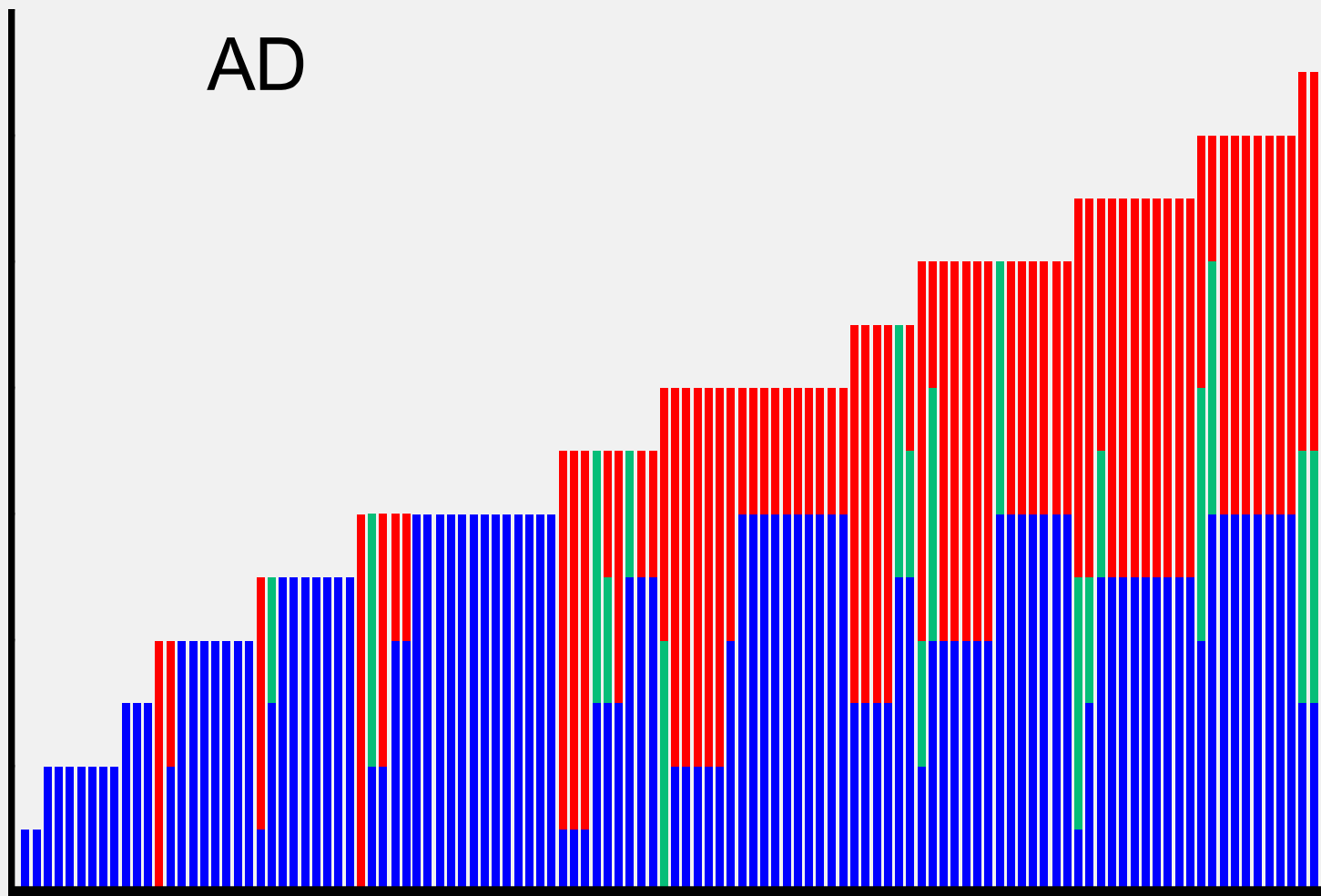


National Alzheimer's Project Act (NAPA)

- **Signed into law by President Obama**
 - **January 2011**
- **National Plan to Address Alzheimer's Disease**
 - **“Preventing and effectively treating Alzheimer's disease, including Alzheimer's disease–related dementias, by 2025”**

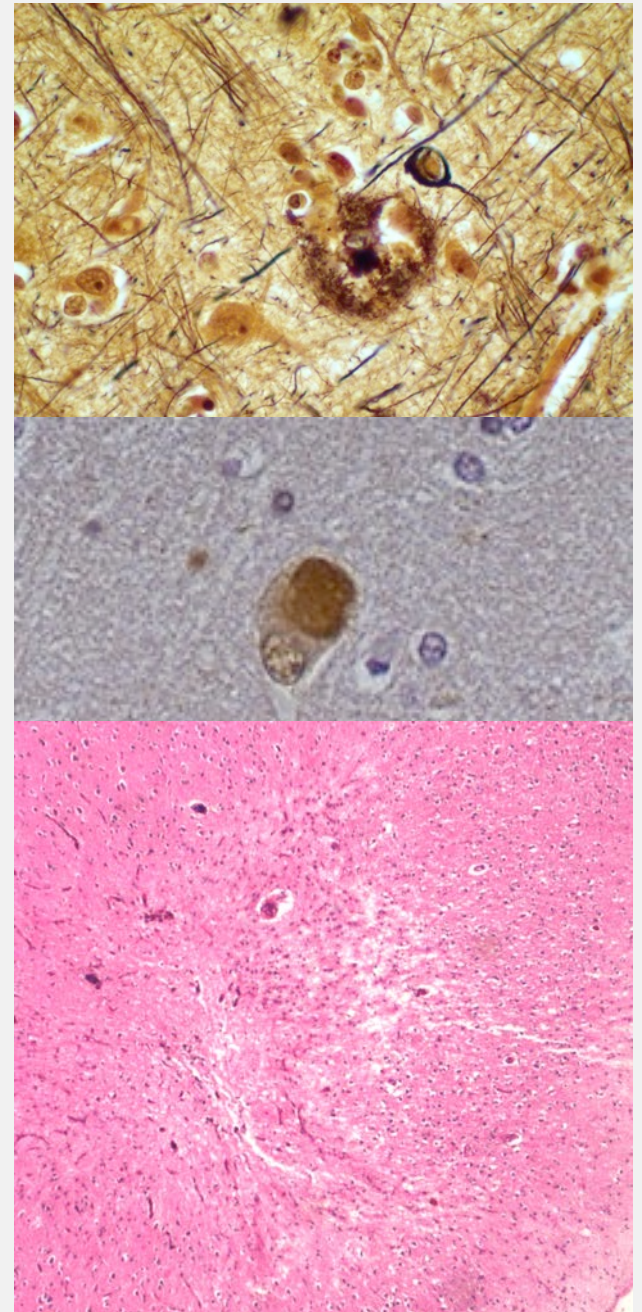
Scientific and Medical Input to NAPA

- ***Alzheimer's Disease Research Summit 2012:
Path to Treatment and Prevention***
 - <http://www.nia.nih.gov/about/events/2012/alzheimers-disease-research-summit-2012-path-treatment-and-prevention>
- ***Alzheimer's Disease–Related Dementias:
Research Challenges and Opportunities***
 - <http://www.ninds.nih.gov/ADRD2013>
 - ***Neurology, 2014***



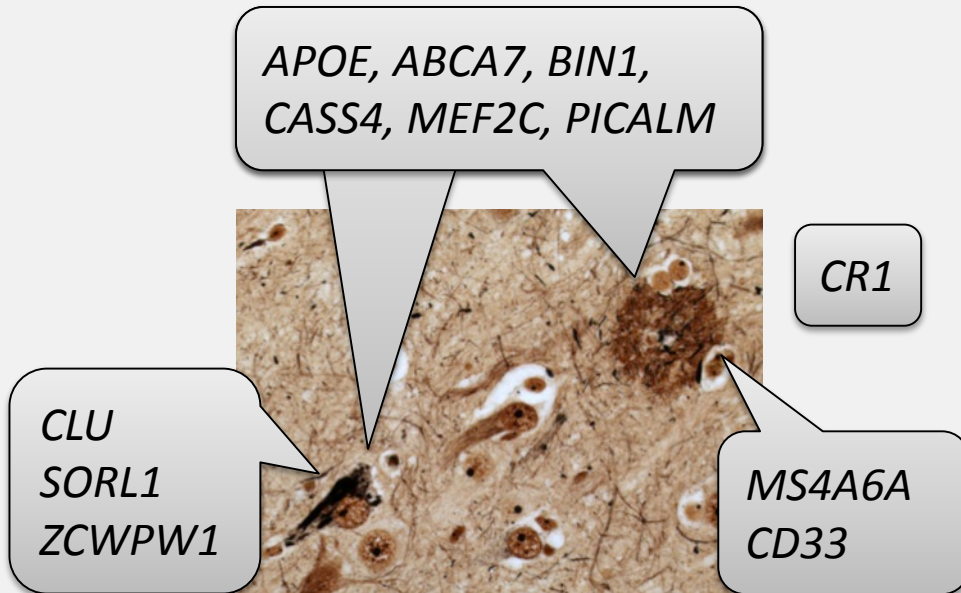
Cognitive Impairment and Dementia

- **Syndrome**
- **In older adults ...**
 - An idiosyncratic convergent trait
 - AD, VBI, LBD, HS
 - Caused by chronic diseases
 - Dementia
 - Prodrome
 - Latency
- **In middle-aged adults**
 - Less co-morbidity
 - AD, FTD, LBD



Molecular Complexity

- 22 IGAP loci



- **GWAS:** Cases & Controls
 - VBI – none
 - CAA - *APOE* 10^{-23}
 - LBD - *APOE* 10^{-12}
 - HS - *KCNMB2* 10^{-8}
- **Future**
 - Molecular phenotype
 - Brain
 - CSF

AD Research Summit 2012 (NIA)

- **AD dementia**
 - G. McKhann
 - Alzheimer's & Dementia 2011;7:263-269
- **Mild Cognitive Impairment due to AD**
 - M. Albert
 - Alzheimer's & Dementia 2011;7:270-279
- **Toward defining preclinical stages of AD**
 - R. Sperling
 - Alzheimer's & Dementia 2011;7:280-292
- **Guidelines for neuropath assessment of AD**
 - B. Hyman and T. Montine
 - Alzheimer's & Dementia 2012;8:1-13. 165 citations
 - Acta Neuropathol. 2012;123:1-11. 139 citations

AD-Related Dementias 2013 (NINDS & NIA)

- **Fronto-temporal dementia**
- **Lewy Body Disease**
- **Vascular Brain Injury**
- **Multi-etiology dementia**
- **Health Disparities**
 - **T. Montine**
 - ***Neurology*, August 2014**

Parkinson's Disease 2014 (NINDS)

- **Motor and non-Motor symptoms (including dementia)**
 - **T. Montine**
 - ***Annals of Neurology*, September 2014**

2012 Guidelines for neuropath assessment

- Thomas G. Beach
- Eileen H. Bigio
- Nigel J. Cairns
- Dennis W. Dickson
- Charles Duyckaerts
- Matthew P. Frosch
- Bradley T. Hyman
- Eliezer Masliah
- Suzanne S. Mirra
- Thomas J. Montine
- Peter T. Nelson
- Creighton H. Phelps
- Julie A. Schneider
- Dietmar Rudolf Thal
- John Q. Trojanowski
- Harry V. Vinters

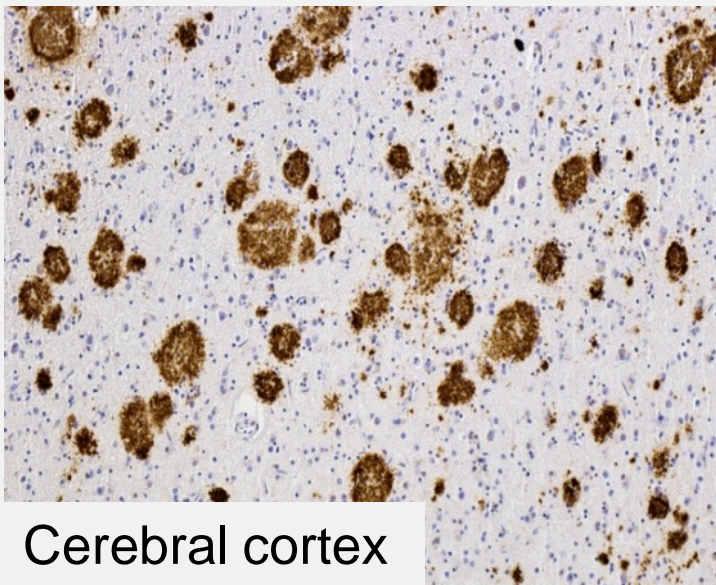
Major Changes to NP Assessment

Issue	1997	2012
Dx of dementia required for NP AD	Yes	No
NP assessment	Braak stage and CERAD score	These plus Thal phase
Common co-morbid diseases	Little guidance	Explicit
Minimum regions	Silent	Explicit
Reporting and CPC	Silent	Guidelines

AD Neuropathologic Change

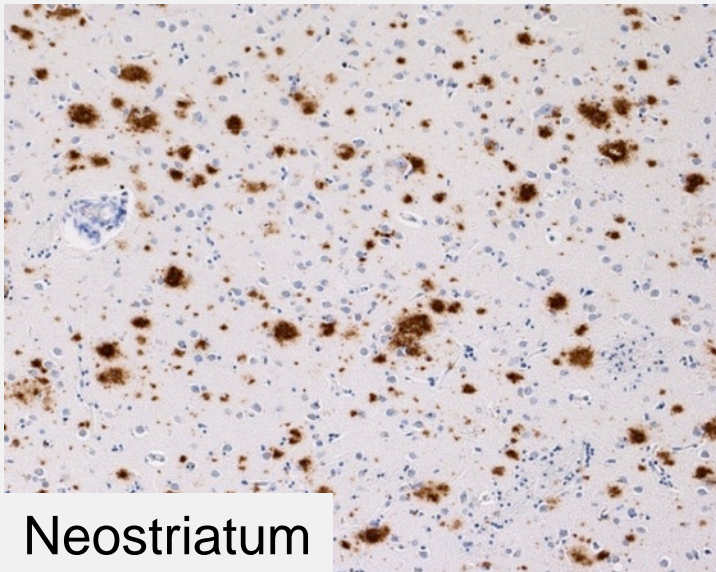
"A"	Thal Phase for A! plaques [57]	"B"	Braak and Braak NFT Stage [14,15]	"C"	CERAD neuritic plaque score [41]
0	0	0	None	0	None
1	1 or 2	1	I or II	1	Sparse
2	3	2	III or IV	2	Moderate
3	4 or 5	3	V or VI	3	Frequent

AD Neuropathologic Change		B ¹		
A ²	C ³	0 or 1	2	3
0	0	Not ⁴	Not ⁴	Not ⁴
1	0 or 1	Low	Low	Low ⁵
	2 or 3 ⁷	Low	Intermediate	Intermediate ⁵
2	Any C	Low ⁶	Intermediate	Intermediate ⁵
3	0 or 1	Low ⁶	Intermediate	Intermediate ⁵
	2 or 3	Low ⁶	Intermediate	High

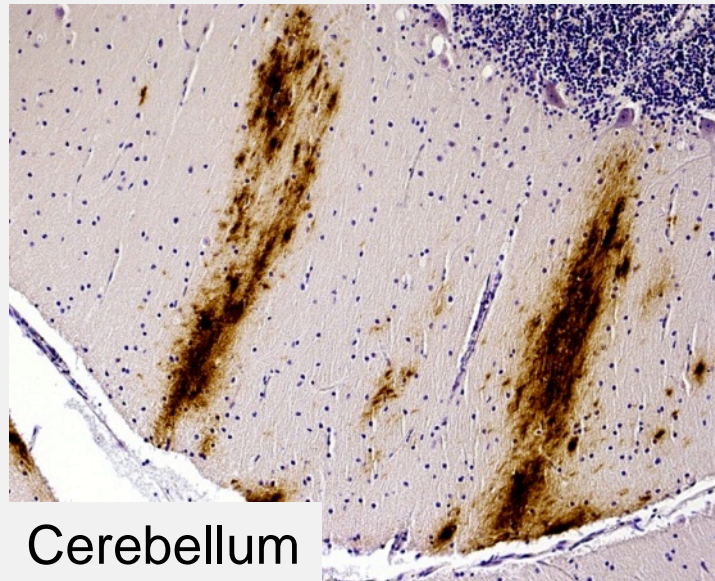


Cerebral cortex

A (amyloid) Score

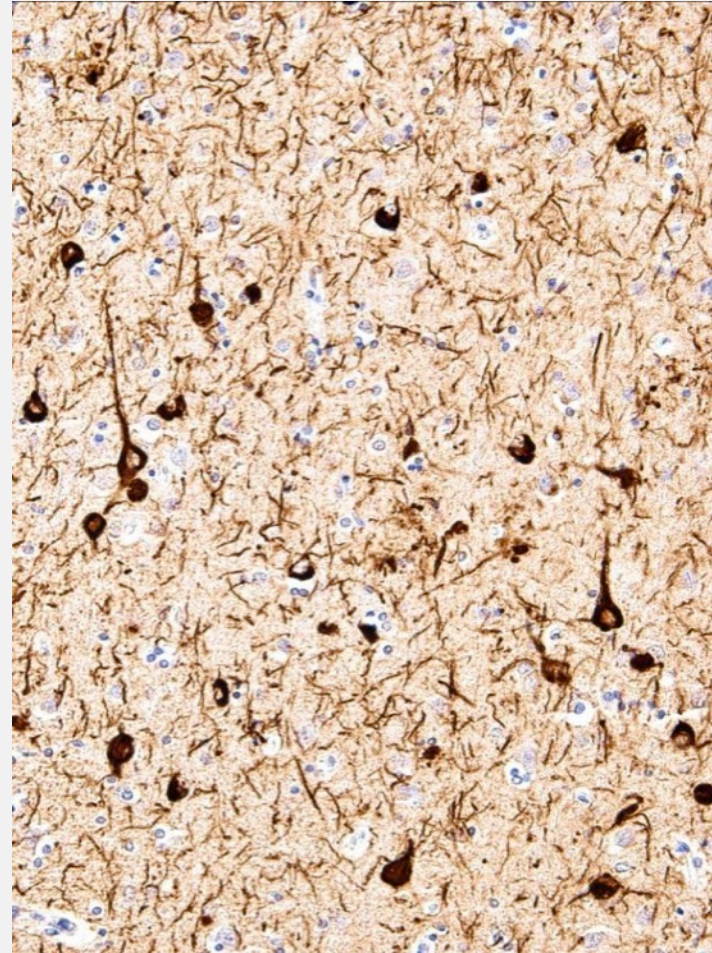
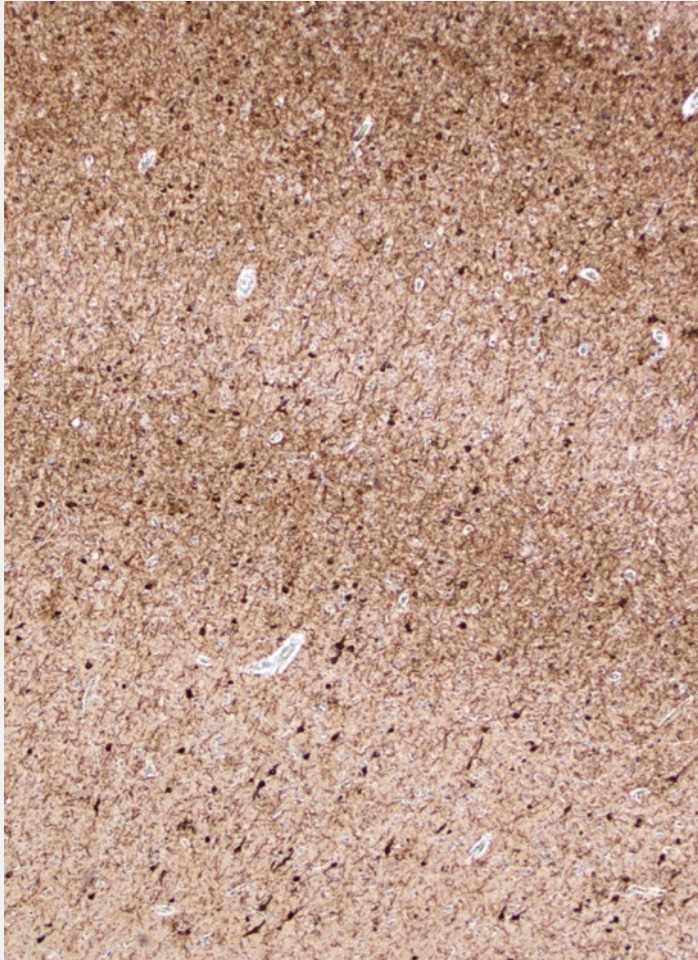


Neostriatum



Cerebellum

B (Braak) Score in primary visual cortex

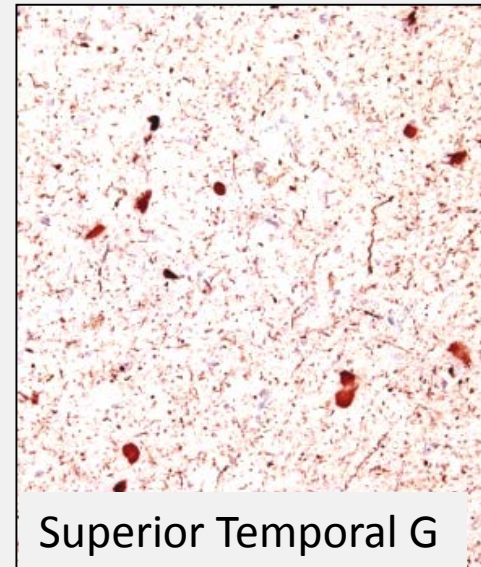
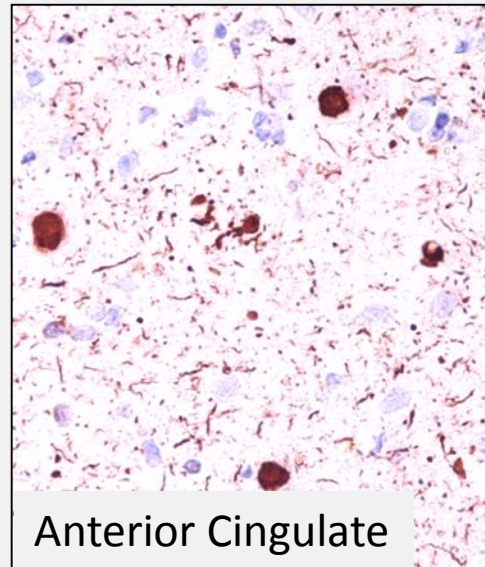
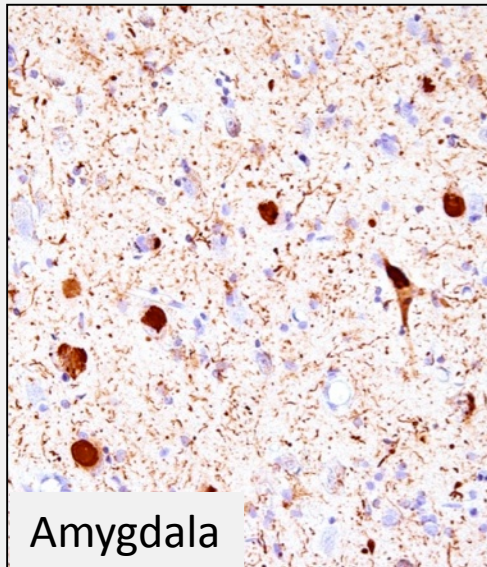
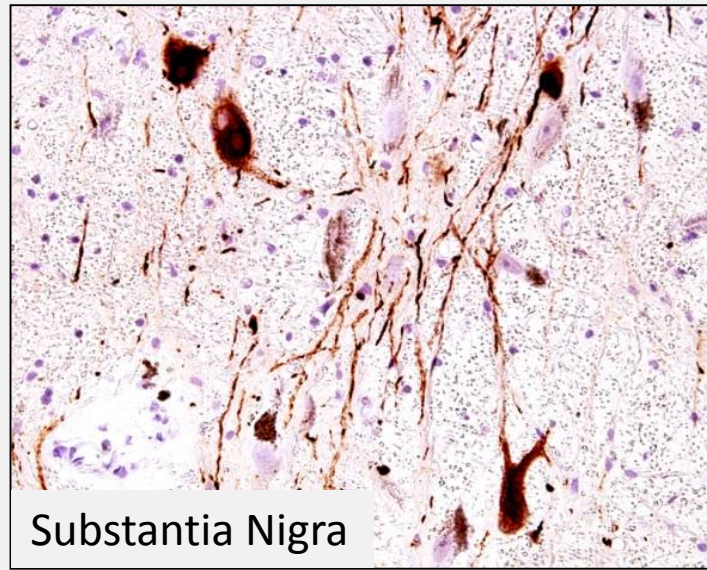
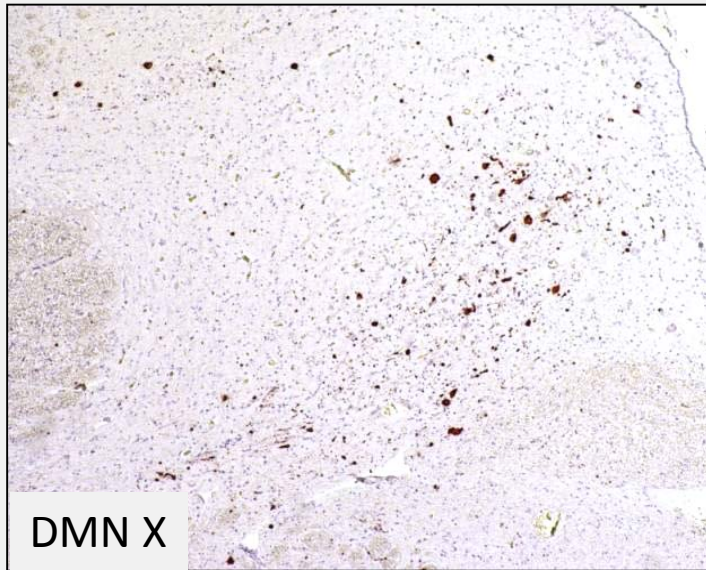


PHF-1 antibody was generously provided by Dr. Peter Davies

Lewy Body Disease

None	No LBs or related changes in IHC for α -synuclein
Brainstem-predominant	LBs in medulla, pons, or midbrain
Limbic (Transitional)	LBs in cingulate or entorhinal cortices, usually with brainstem involvement
Neocortical (Diffuse)	LBs in frontal, temporal, or parietal cortices usually with involvement of brainstem and limbic sites, which may include amygdala
Amygdala-predominant	LBs in amygdala with paucity of LBs in the above regions

Lewy Body Disease



Anti-alpha-synuclein antibody KM51 (Novocastra, Newcastle, United Kingdom)

Cerebrovascular Disease and Vascular Brain Injury

- **CVD**

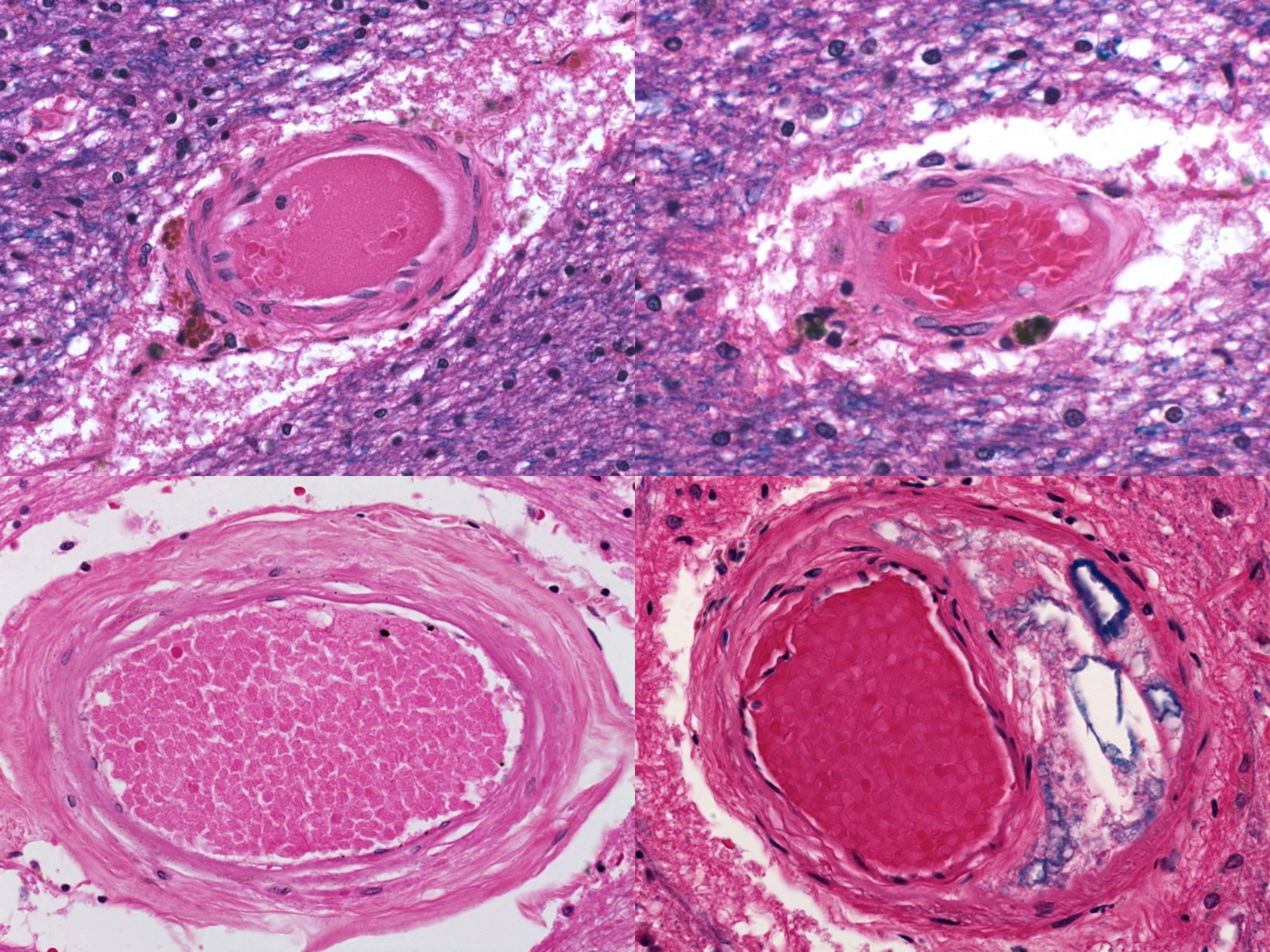
- **Report using standardized approach**

- **VBI**

- Record size and location of gross infarcts

- Enumerate microinfarcts in standard screening sections

- > 2 sufficient to explain cognitive impairment



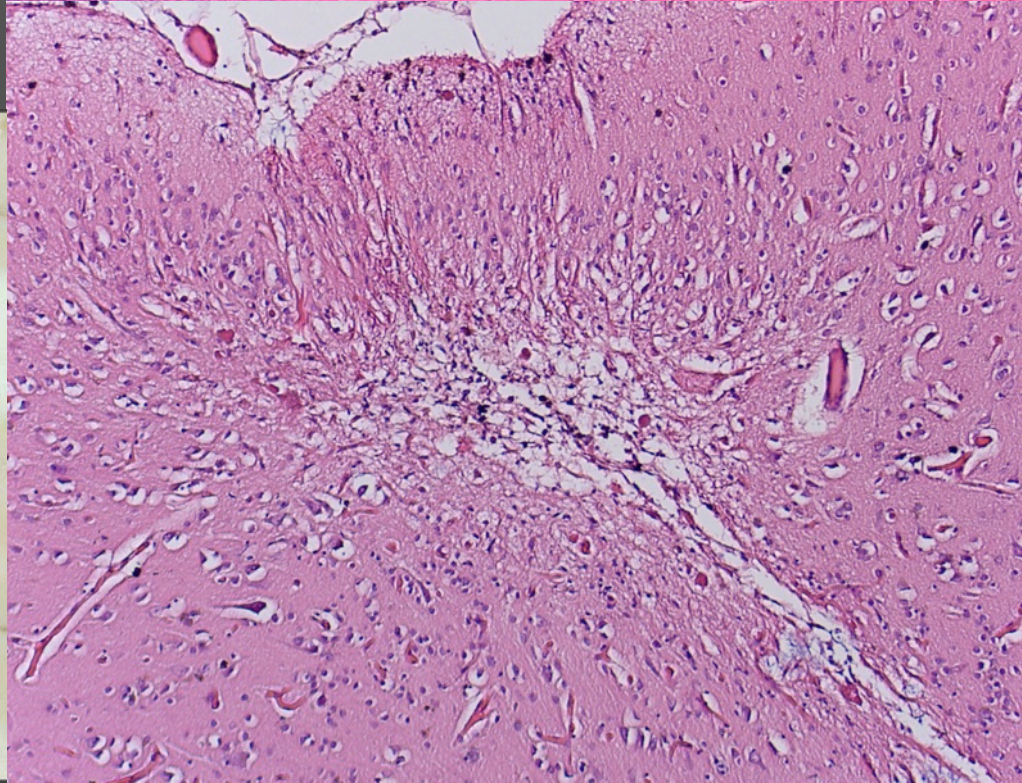
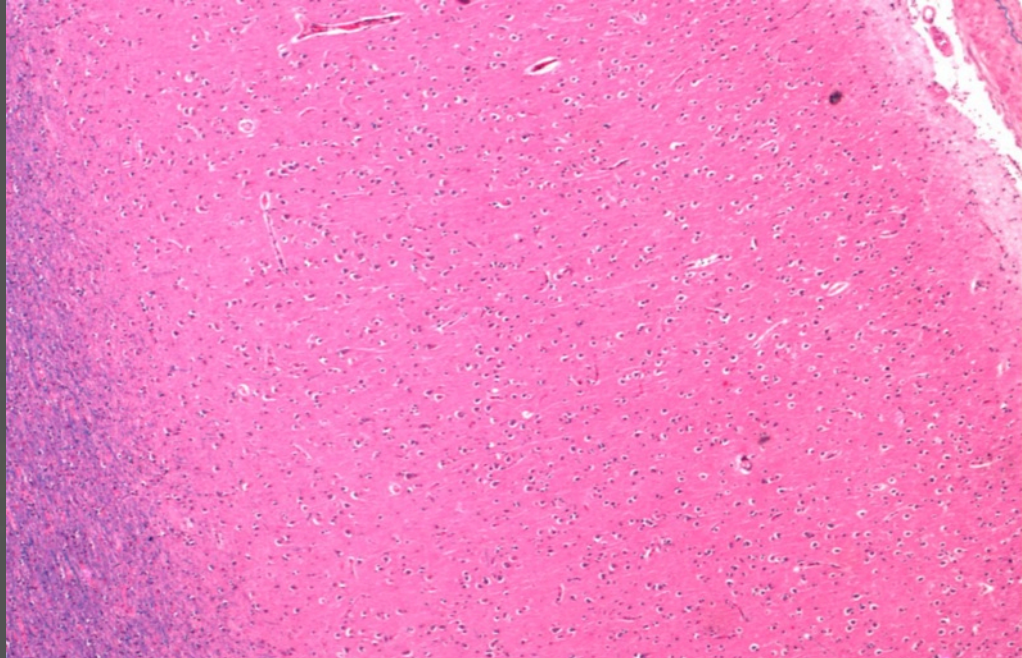
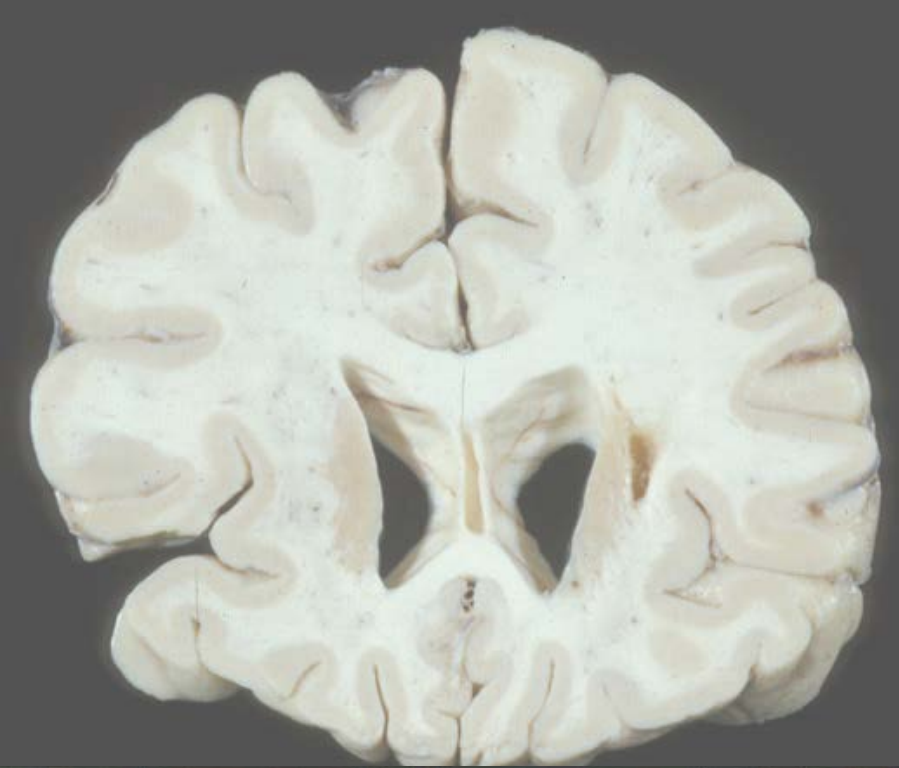
Cerebrovascular Disease and Vascular Brain Injury

- CVD

- Report using standardized approach

- VBI

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Major Challenges Remain

- Almost all of our knowledge about dementia in the US comes from people of European decent
- Incomplete knowledge about disease mechanisms
 - Knowledge about potential interactions is very limited
 - AD VBI meeting held by NINDS and AA in 2014
- Representative experimental models are needed to fuel therapeutic discovery

Next Steps ...

- **Fall 2014**
 - Updated milestones
- **9-11 February 2015**
 - AD Research Summit II
- **Winter 2016**
 - ADRD II
- **2025**
 - “Preventing and effectively treating Alzheimer’s disease, including Alzheimer’s disease–related dementias”, NAPA

Thank you