Clinical Correlations with Post-Mortem Findings: Clues to Identifying the Prodrome for AD - Age Matters

The Mount Sinai School of Medicine

PERC (Prevent, Enhance, Restore Cognition) Studies Team

Collaborators

Mount Sinai & Bronx VA
- **Michal Beeri**
- **Jeremy Silverman**
- **Giulio Pasinetti**
- **Pavel Katsel**
- **Samuel Gandy**
- **Patrick Hof**
- **Dushyant Purohit**
- **Daniel Perl**

- Ramit Ravona-Springer (Sheba Medical Center, Israel)
- Michael Rapp (Humbolt U. Berlin)
- Joseph Buxbaum
- Richard Mohs
- Kenneth Davis

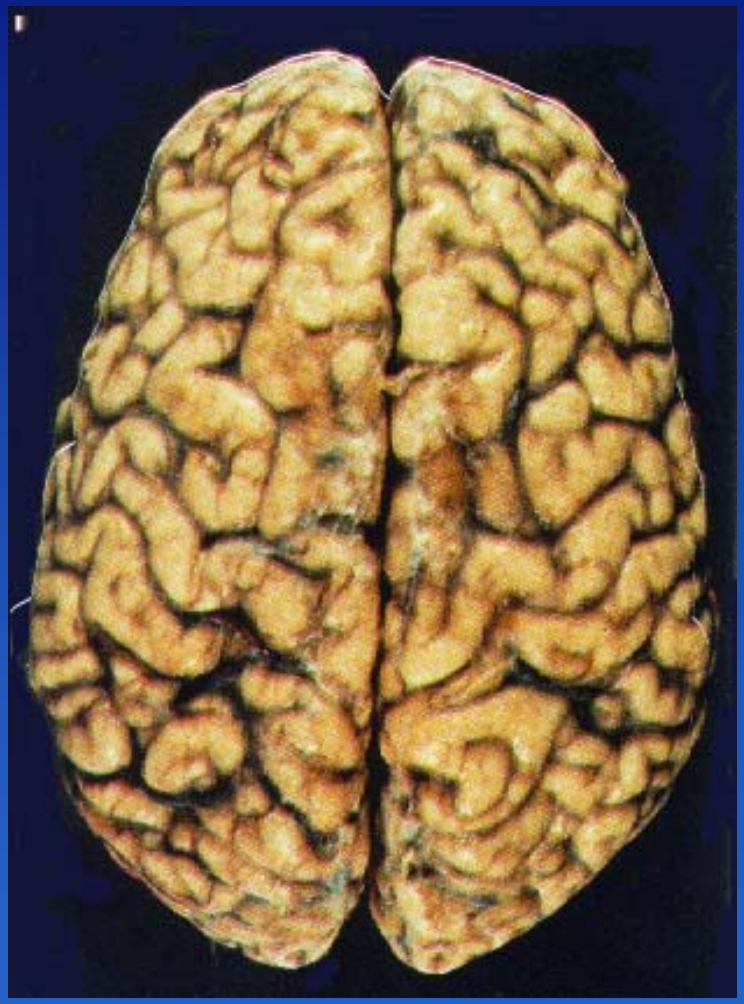
Post-Mortem
- **Afia Akram**
- **Stella Dracheva**
- **Gregory Elder**
- Peter Fam
- And many others

Clinical Assessment
- **Hillel Grossman**
- **Maria Maroukian**
- **Michael Wysocki**
- Jimmy Akivos
- And many others

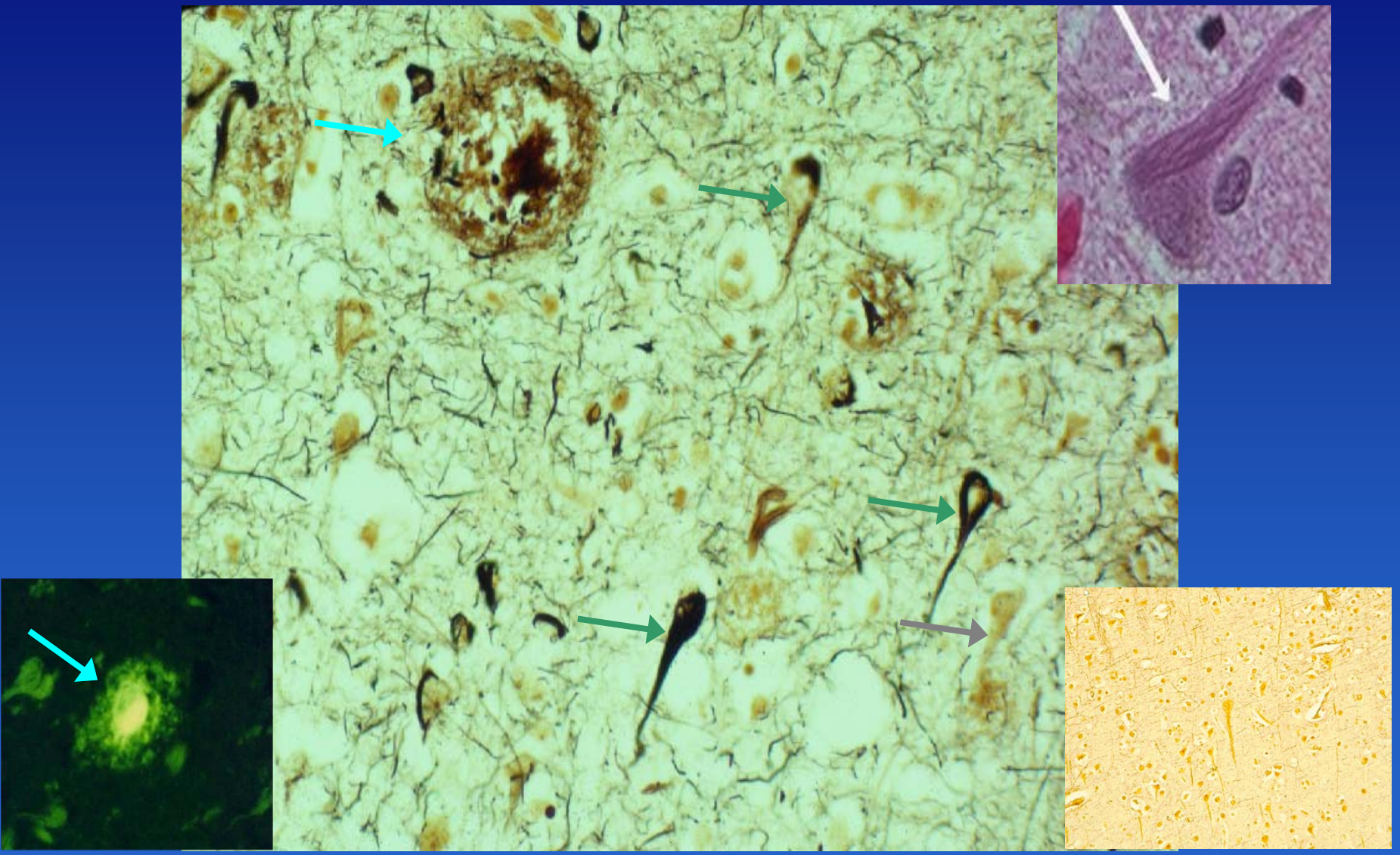
Jewish Home Lifecare System
- **Leslie Libow**
- **Gerson Lesser**
- And many others

Support:
NIH: P01-AG02219
Berkman Trust

Gross Pathology of the Brain in Alzheimer's Disease



Neuritic Plaques and Neurofibrillary Tangles in AD



Summary of Findings of Neuropathological Changes Associated with the Progression of Dementia

CDR - Cognition

Neuritic Plaques

Diffuse Plaques

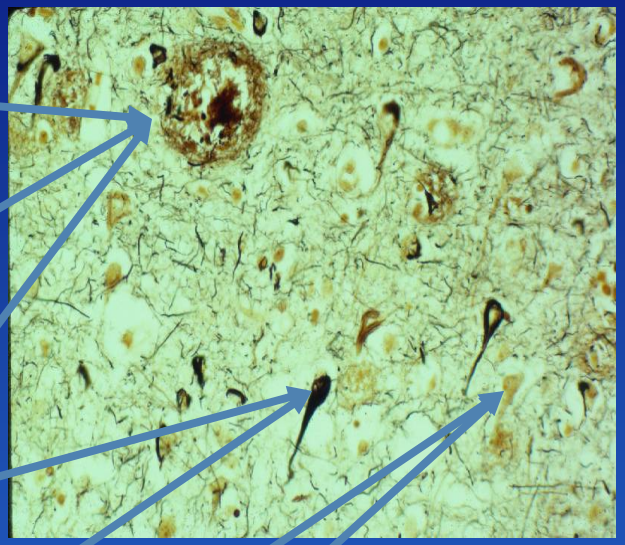
β-Amyloid

Neurofibrillary Tangles

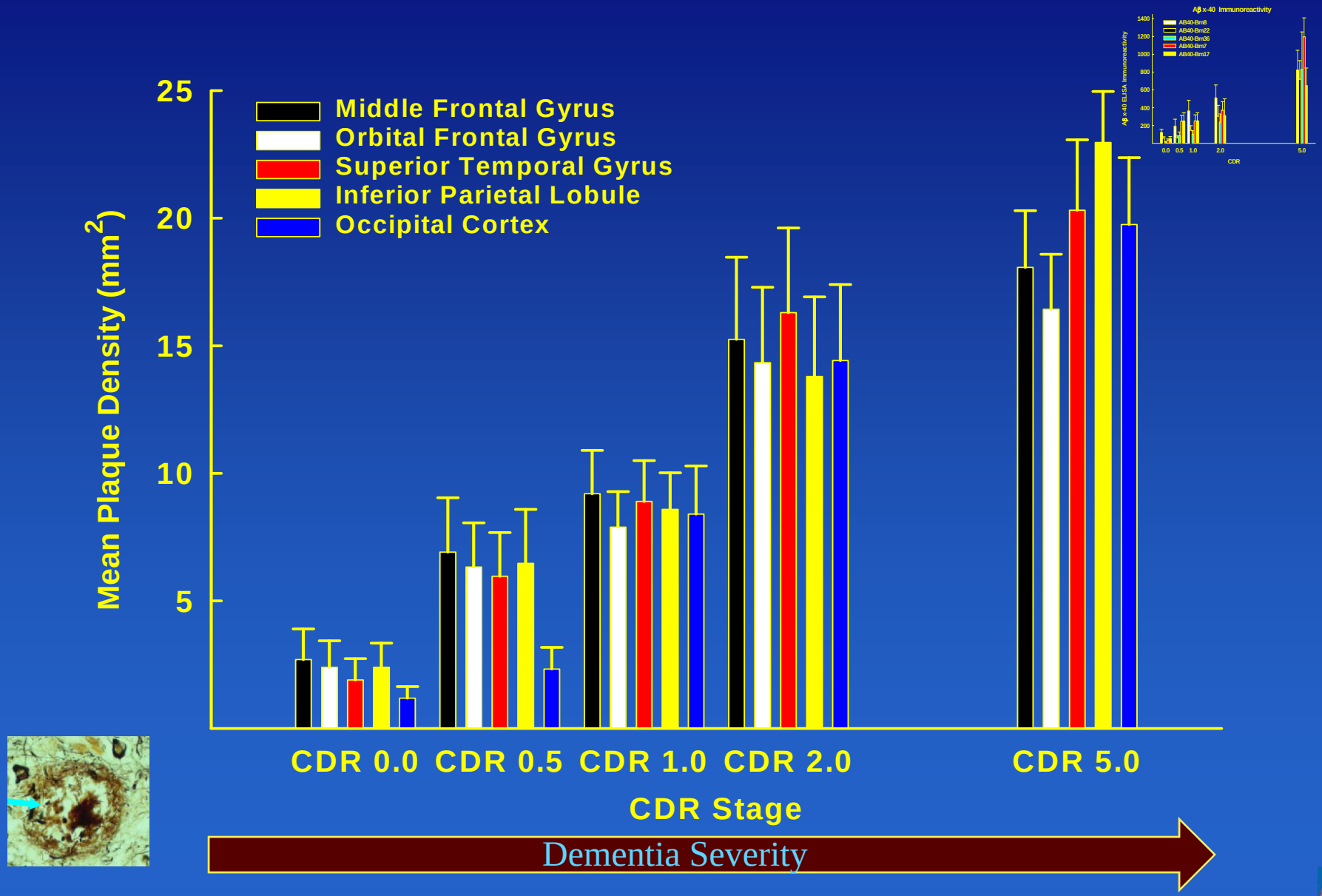
Tau Protein

Neuropeptides

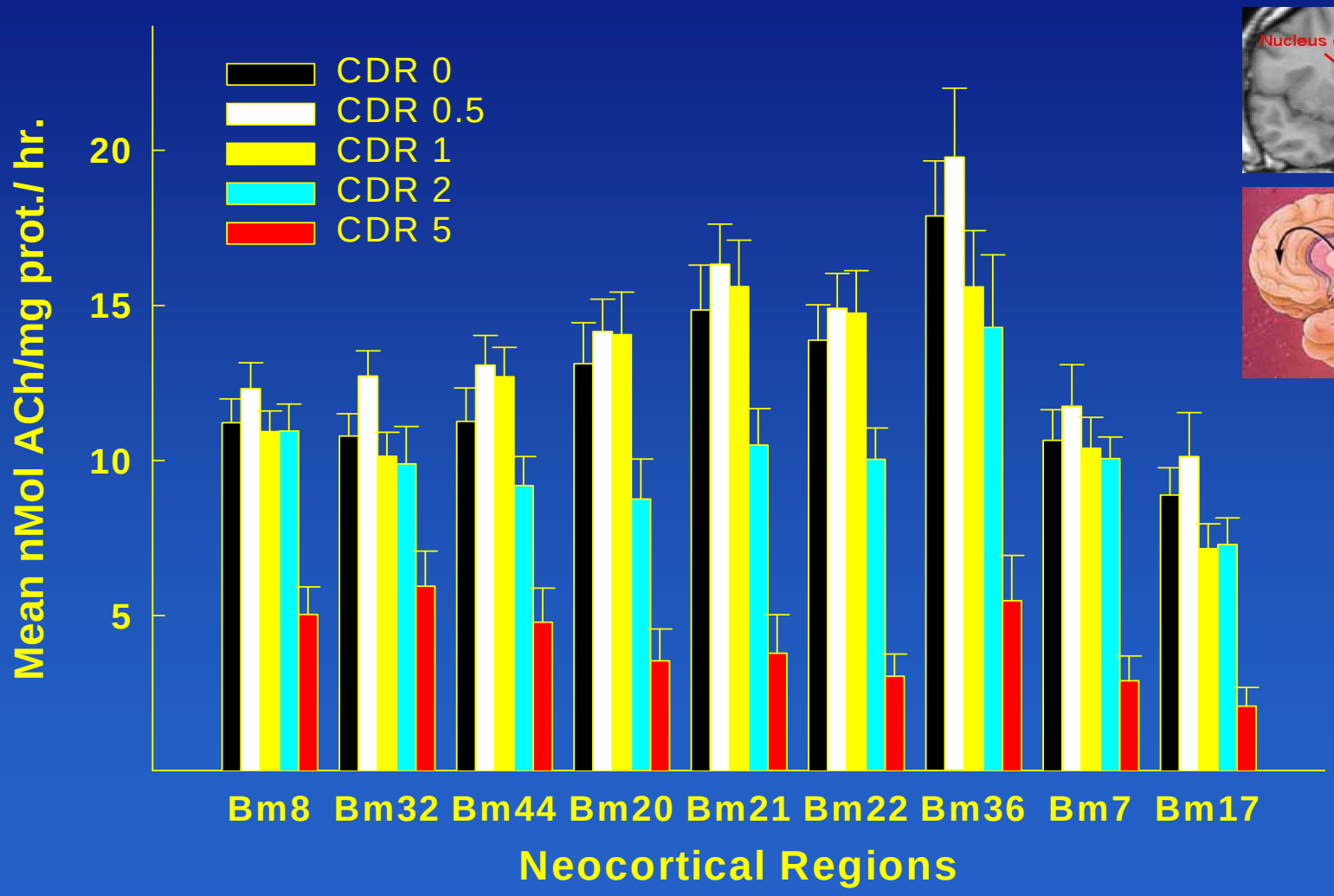
Cholinergic

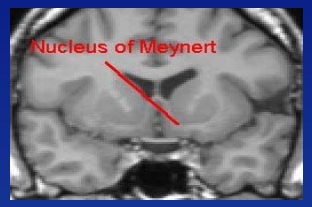


Density of Senile Plaques in Neocortical Regions as a Function of Increasing Dementia Severity.

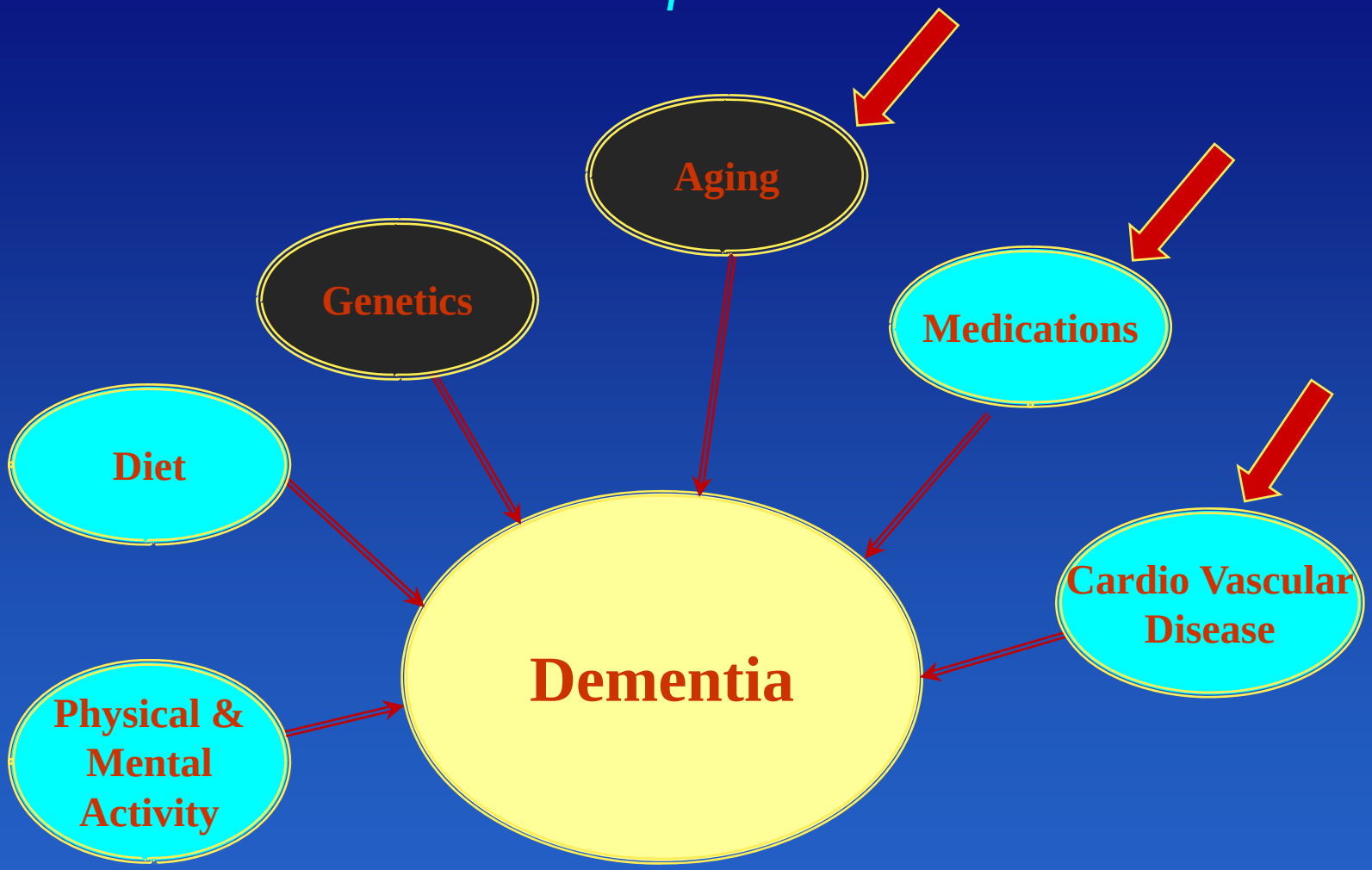


ChAT Activity, a Marker for Acetylcholine, in Neocortical Regions as a Function of Increasing Dementia Severity .





Risk Factors for Dementia

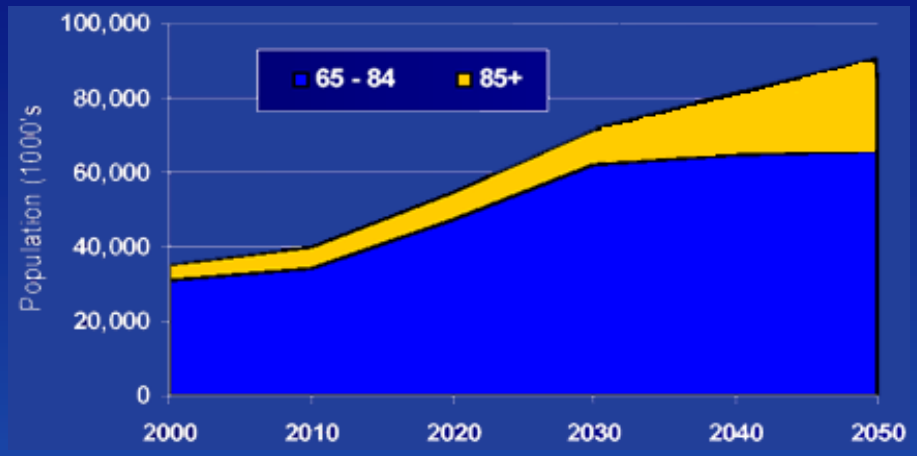


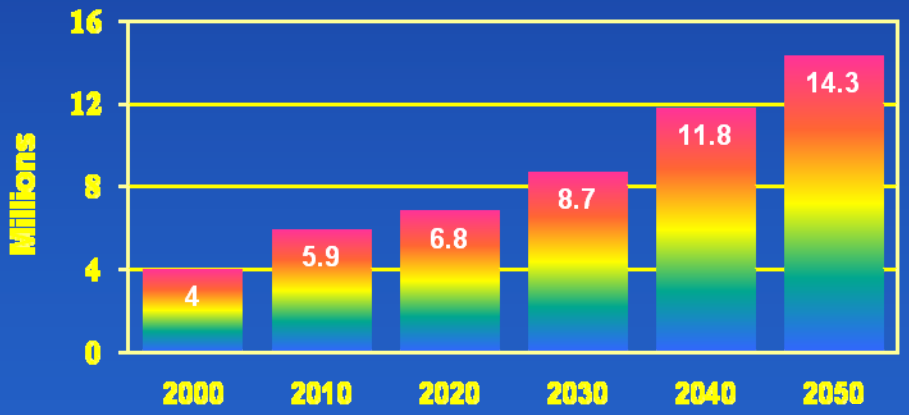
But The Neurobiology of Dementia Is More Complicated

- Age matters
  - Although we have long recognized that age is overwhelmingly the biggest risk factor for dementia and AD,
  - We have only given this gorilla in the room lip service -
    - We have often treated age above 65 or 75 years uniformly, or have at best added it into our statistical models as one of many covariates in an attempt to “decontaminate” our data and be “rid of this troublesome” pest.

Dementia and Oldest-Old

- Dementia in the oldest-old (>85 or >90) is a stronger predictor of mortality than cardiovascular disease, cancer or male sex.
- The 85+ population is the fastest growing segment of the population.
- By 2050 the number of Americans over the age of 85 will quadruple to 14 - 19.3 million.
- 9 million of these 19.3 million will be demented.
- The inflation un-adjusted cost of care will be $33-100 billion.

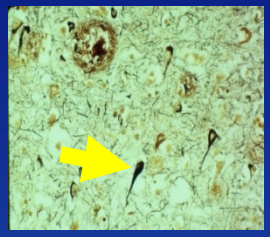


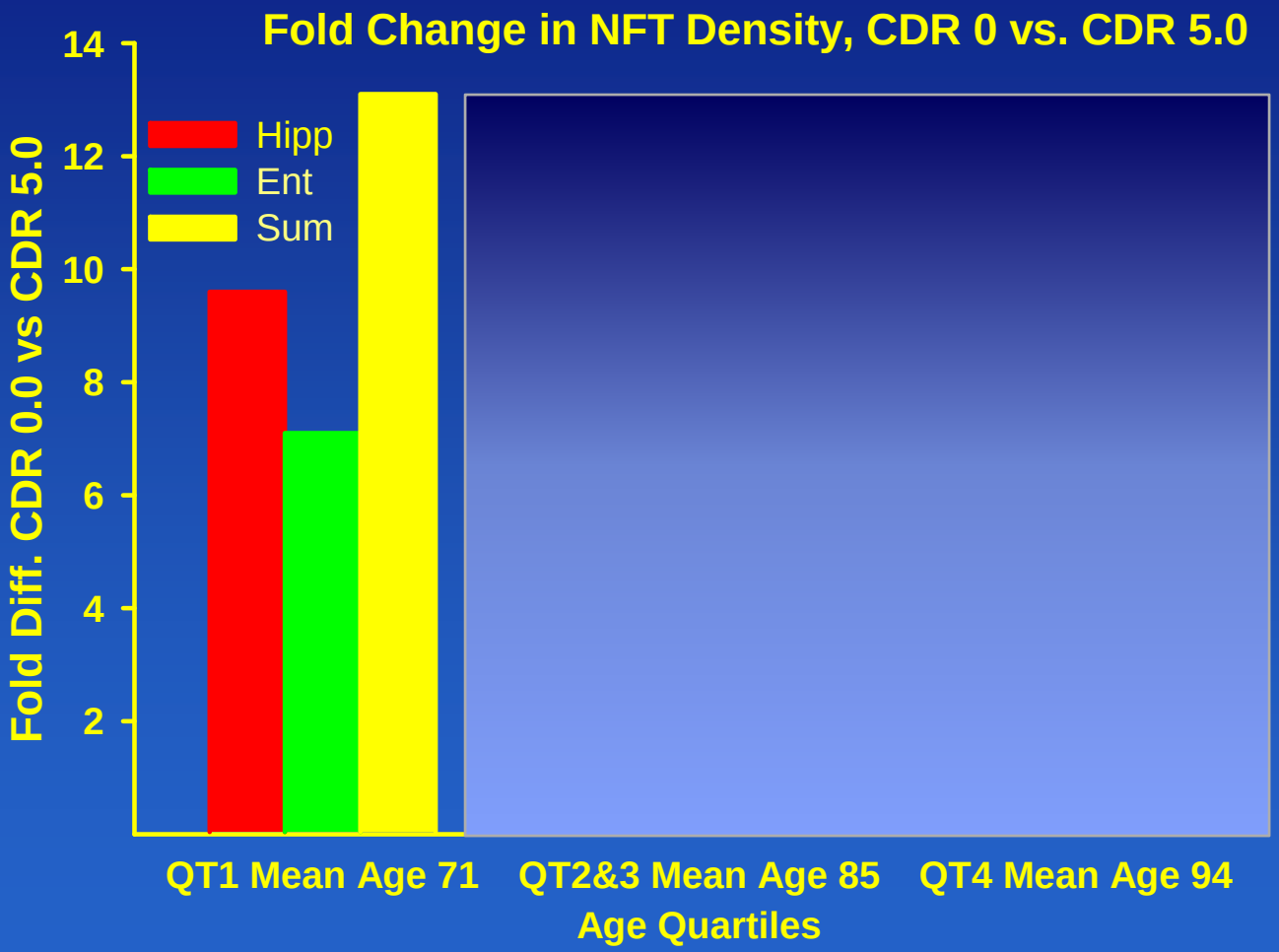


Study of the Oldest-Old

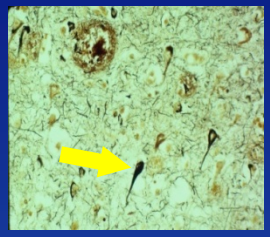
Demographic characteristics of the study cohort				
CDR	**N**	**Age**	**Male / Female**	**PMI**
Young-old group (age range 60 – 80 years)				
0.0	35	69.4 ± 0.96	18 / 17	19.0 ± 2.5
0.5	9	70.8 ± 2.15	5 / 4	8.1 ± 2.6
1.0	7	74.3 ± 1.64	2 / 5	8.8 ± 2.9
2.0	6	76.3 ± 1.69	4 / 2	18.9 ± 9.1
3.0	17	76.1 ± 1.07	7 / 10	11.3 ± 2.7
4.0	6	67.3 ± 1.26	4 / 2	16.7 ± 5.8
5.0	15	69.1 ± 1.48	12 / 3	7.8 ± 1.8
All	**95**	**71.9 + 1.46**	52 / 43	12.3 +3.92
Middle-old group (age range 81 – 89 years)				
0.0	11	84.7 ± 0.85	1 / 10	8.4 ± 1.7
0.5	9	85.7 ± 0.78	3 / 6	12.8 ± 5.4
1.0	12	84.7 ± 0.84	6 / 6	8.5 ± 2.5
2.0	12	83.9 ± 0.51	3 / 9	12.1 ± 3.8
3.0	23	85.1 ± 0.48	4 / 19	9.8 ± 2.7
4.0	18	84.0 ± 0.52	8 / 10	11.2 ± 3.8
5.0	21	86.0 ± 0.48	4 / 17	3.9 ± 0.5
All	**106**	**84.8 ± 0.64**	29 / 77	9.5 ±2.9
Oldest-old group (age range 90 – 107 years)				
0.0	7	96.4 ± 1.36	2 / 5	8.3 ± 2.3
0.5	8	92.7 ± 0.59	4 / 4	7.7 ± 2.6
1.0	10	95.8 ± 1.49	1 / 9	11.6 ± 5.0
2.0	16	94.1 ± 1.07	3 / 13	10.8 ± 2.9
3.0	36	93.4 ± 0.60	6 / 30	7.2 ± 1.3
4.0	21	94.1 ± 0.67	4 / 17	12.5 ± 4.9
5.0	18	96.6 ± 0.78	2 / 16	5.7 ± 1.0
All	**116**	**94.7 ± 0.94**	22 / 94	9.1 ±2.9
All Ages and CDRs	317	84.4 ± 0.58	103 / 214	10.5 ± 0.7

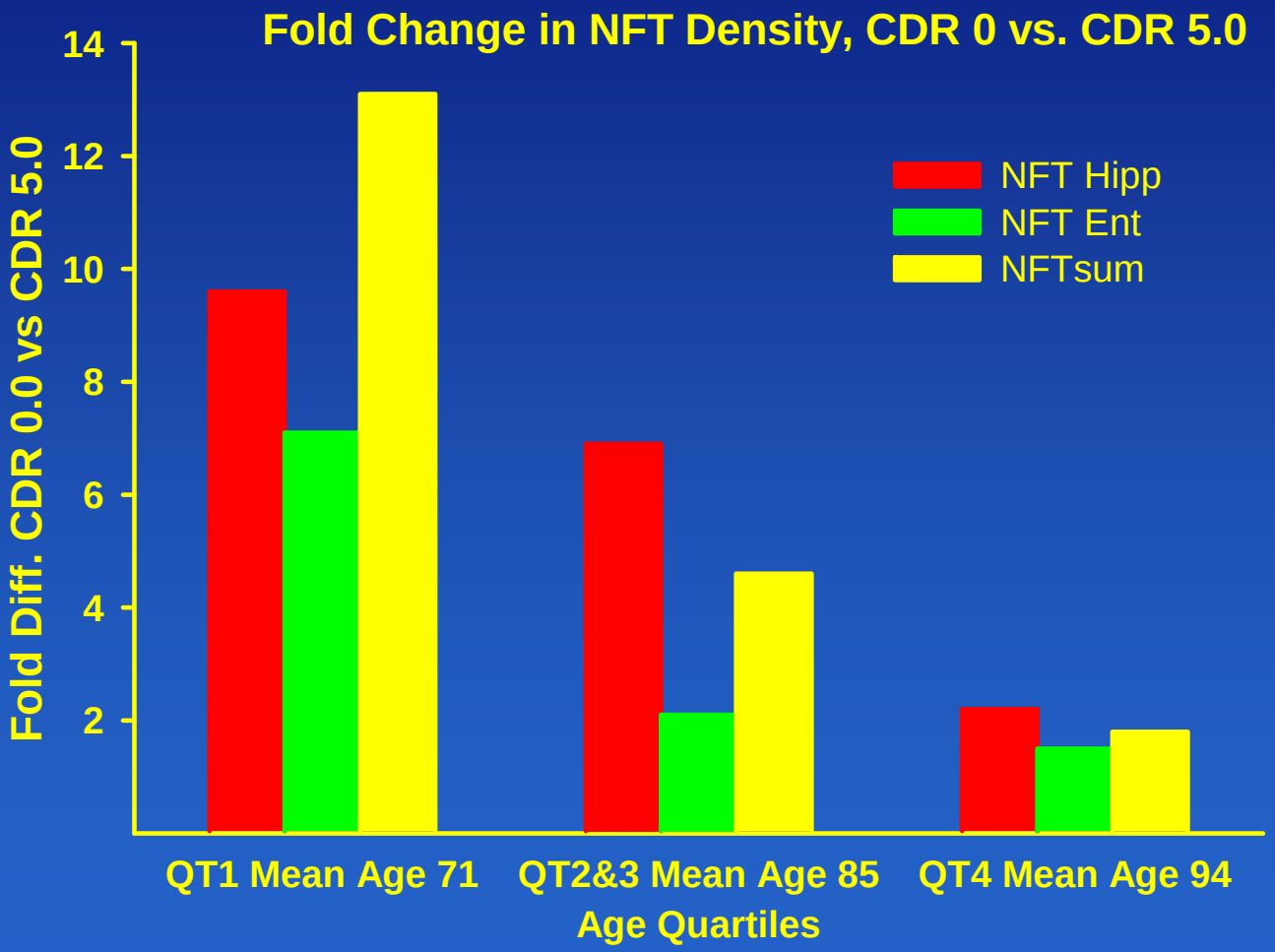
What we know may be less than what we think we know: Effect of age on the relationship of NFTs to cognition



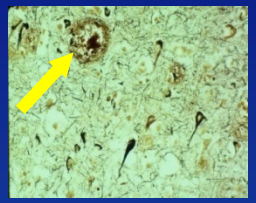


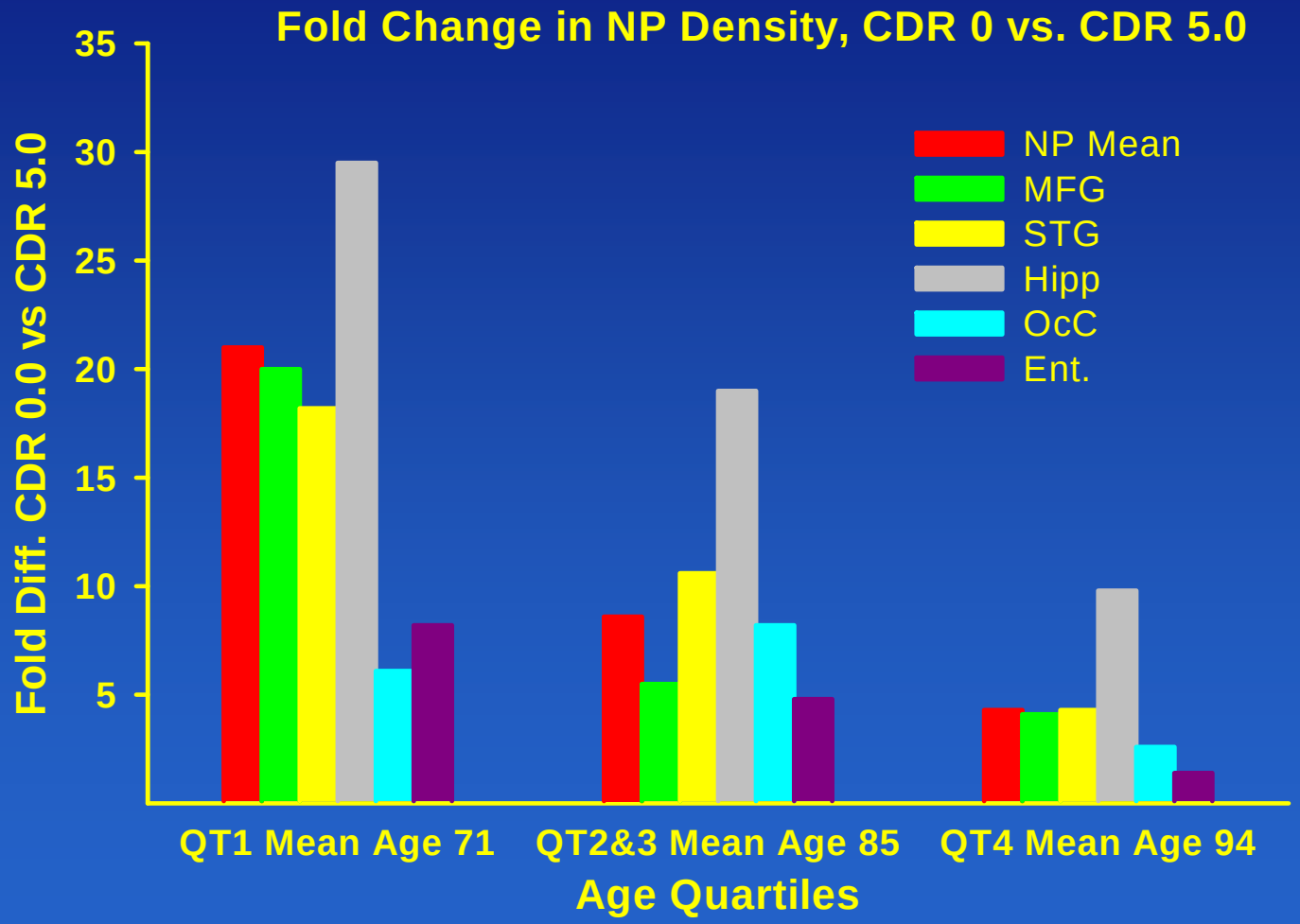
What we know may be less than what we think we know: Effect of age on the relationship of NFTs to cognition



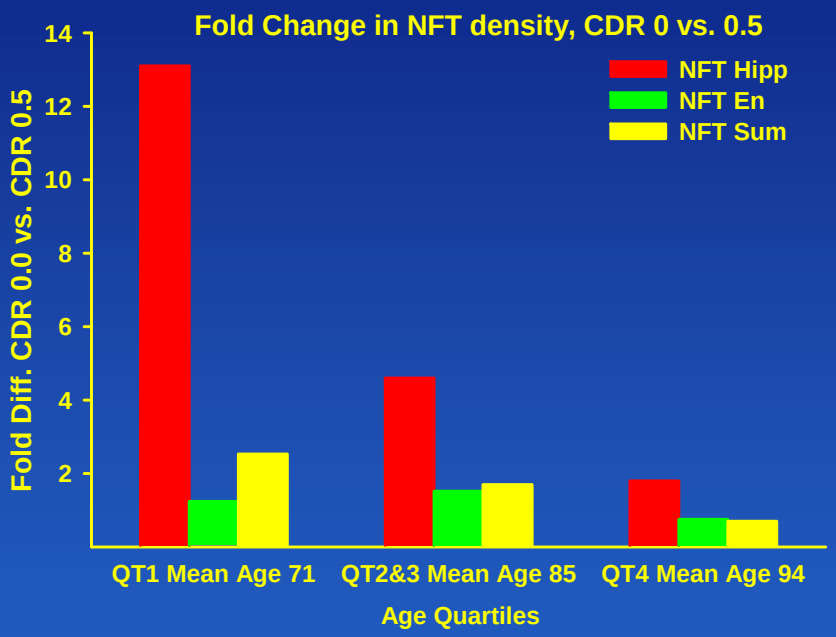


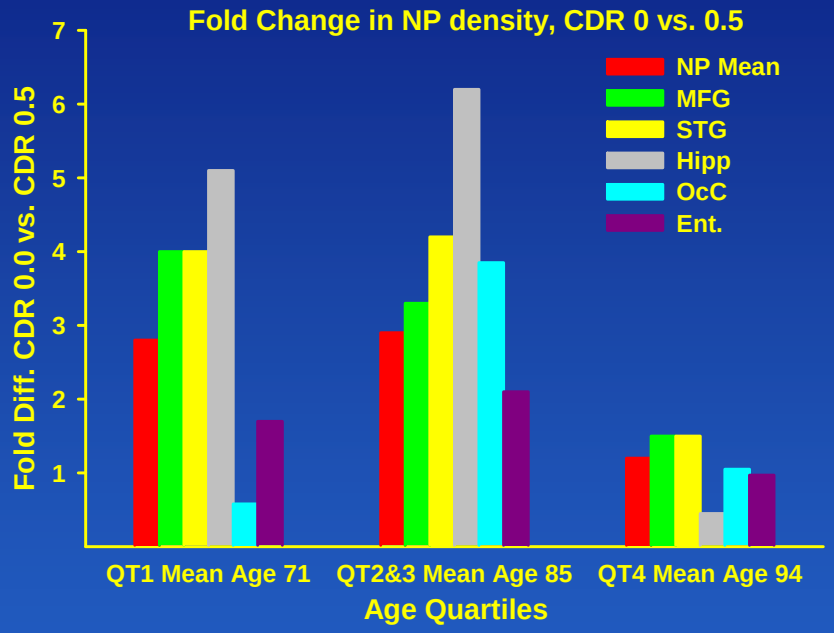
What we know may be less than what we think we know: Effect of age on the relationship of NPs to cognition

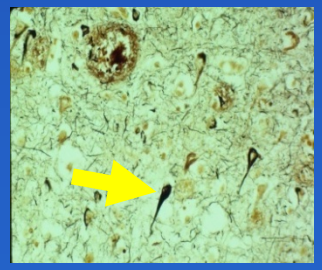


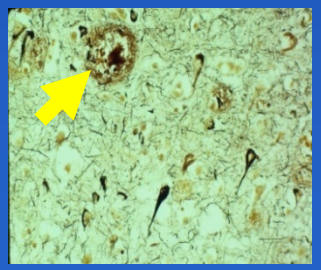


What we know may be less than what we think we know: Effect of age on the relationship of NFTs & NPs in MCI







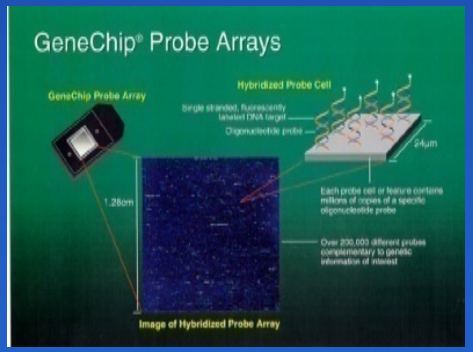


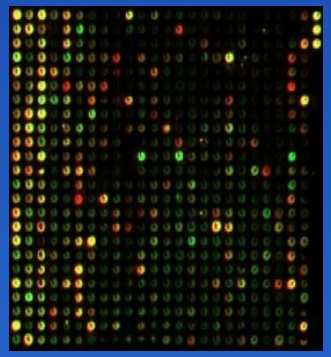
Transcriptional Vulnerability & Disease Mechanism:

Microarray studies of gene expression in AD and dementia

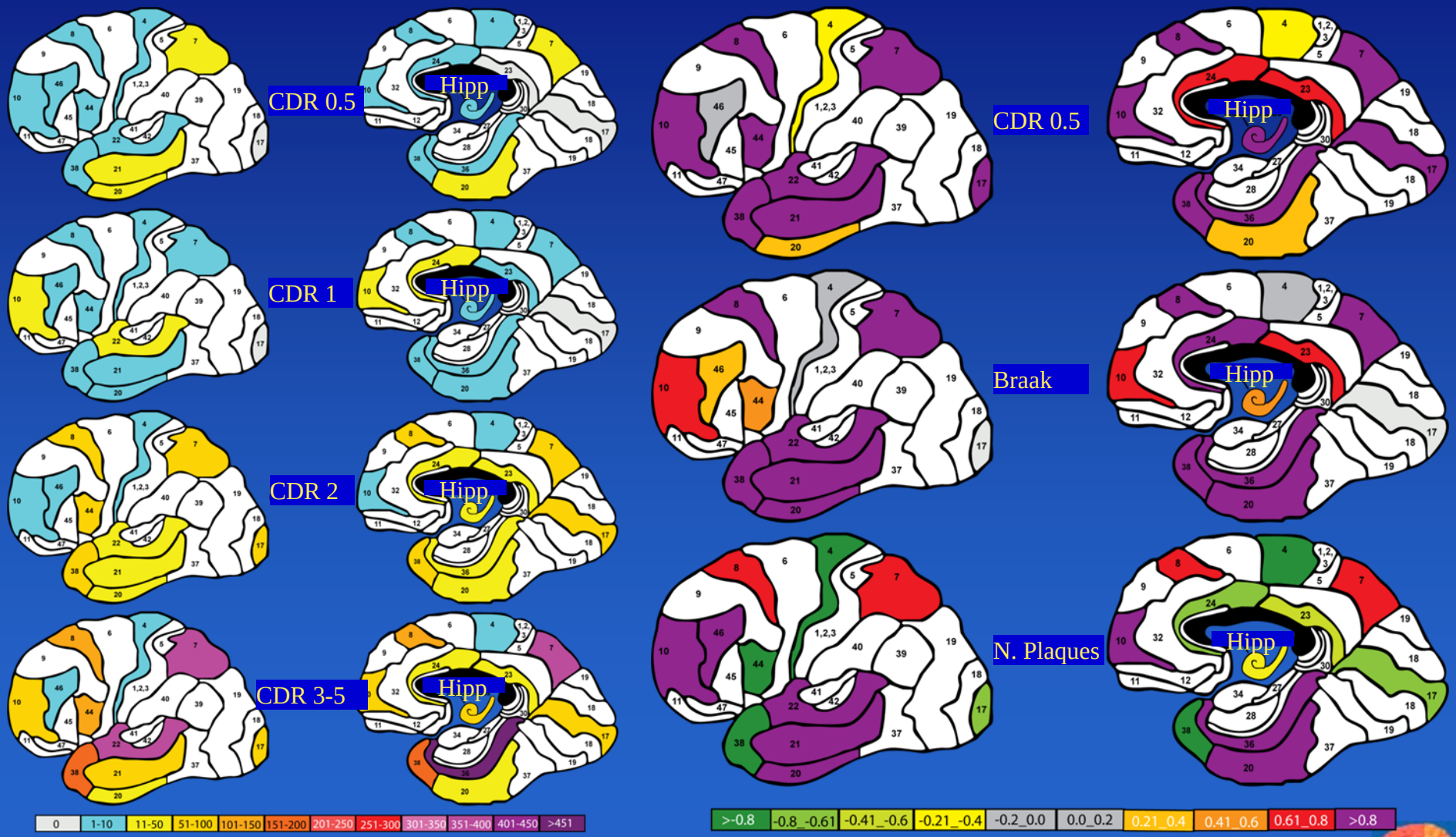
DNA ⟶ RNA ⟶ Protein

- Assessment of RNA expression using Gene-Chips.
- Large sample size (>80) permitted stratification by:
  - dementia severity groups (CDR)
  - *Age X Dementia severity groups*

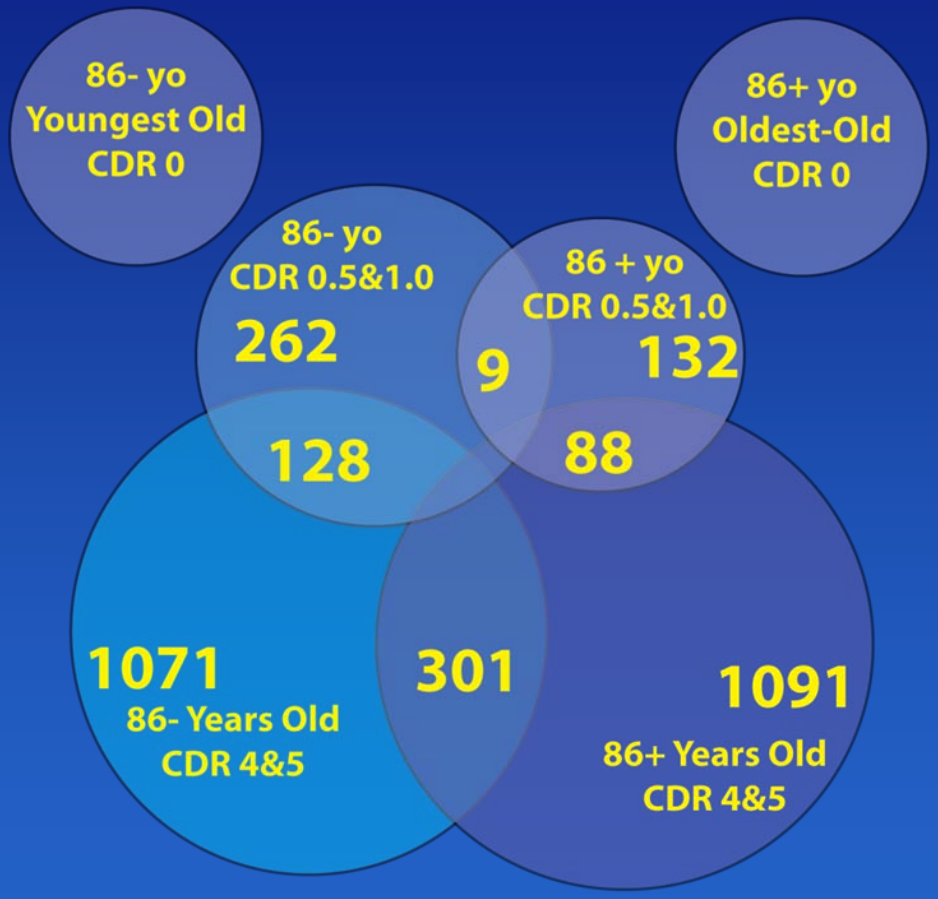




Molecular and Cellular Biological Approaches for Understanding of Disease Mechanism: *Progression of Gene Expression Abnormalities with Increasing Dementia Severity*



Gene Expression Profiles Across 15 Different Brain Regions in Young-Old vs. Old-Old



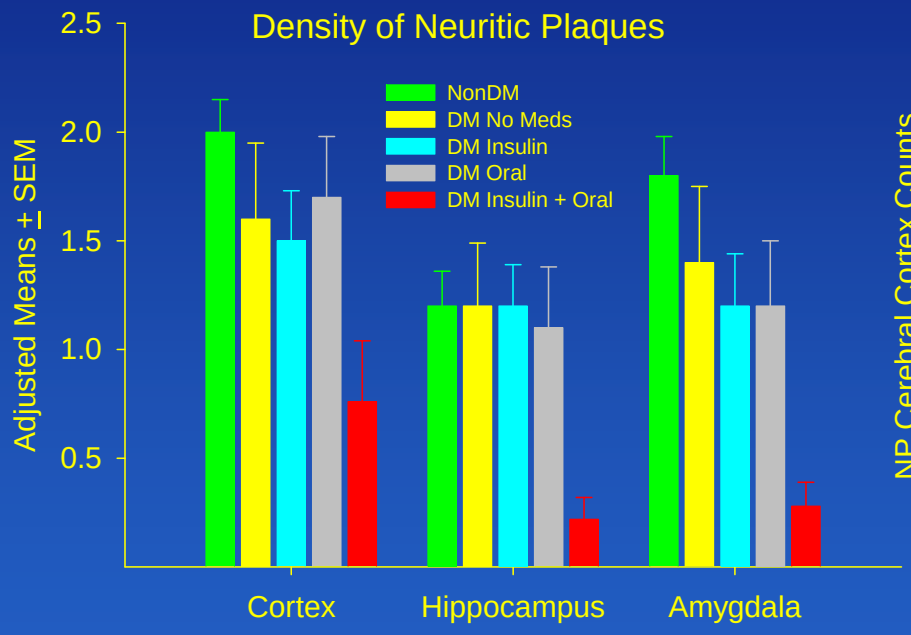
Fold Change > 1.3, ps<0.05

But The Neurobiology of Dementia Is More Complicated

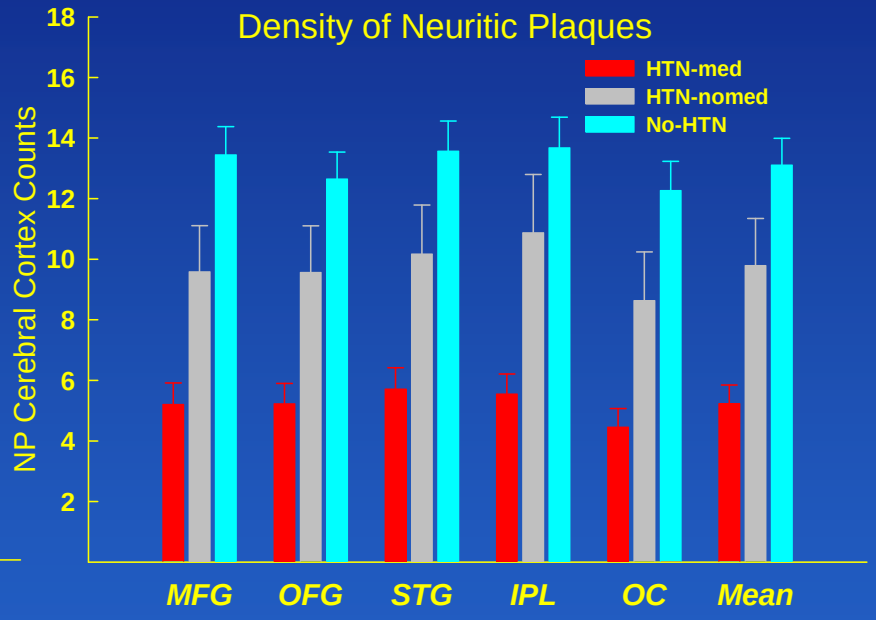
- What we know may be less than what we think we know.
  - Phenotype matters to the neurobiology of the disease.
  - And because phenotype matters to neurobiology, it will matter to therapeutic response.
    - Medical illnesses like diabetes and hypertension, their treatments are but a few of the phenotypic variables that we have examined.

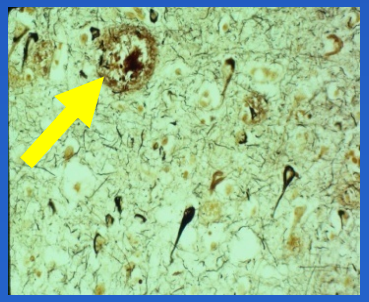
Cardiovascular Risk Factors: Type II Diabetes and Hypertension

Diabetes



Hypertension

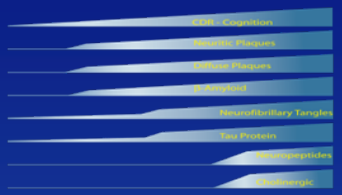




What we have learned: Age and phenotype are crucial to dementia neurobiology and potentially to therapeutic outcome.

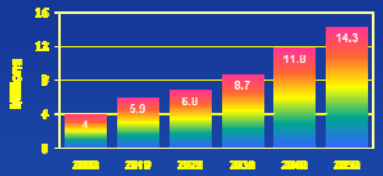
Basics of Dementia

- *Neurobiological progression relative to Dementia*

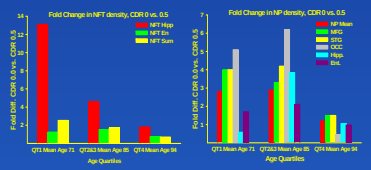


What we know may be less than what we think we know

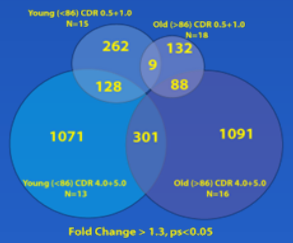
- *Is Old just Old?*



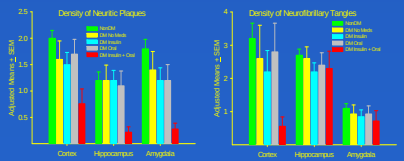
- *Neuropathology of Young-Old vs. Oldest-Old*



- *Molecular Neurobiology of Young-Old vs. Oldest-Old*



- *Risk factors and potential modifiable contributors*



THANK YOU !

We are most appreciative of the generosity of all those who have selflessly given so much to help present and future generations by participating in our studies.