ADC Directors' Meeting,
Vancouver, BC, 2016

Population Neuroscience:
"Looking at Life From Both Sides Now"

Mary Ganguli, MD, MPH
Professor of Psychiatry, Neurology, and Epidemiology,
University of Pittsburgh
Pittsburgh, PA

What is Epidemiology?

- ❑A. the study of the distribution and determinants of disease in the population.
- ❑B. a way of thinking about “life.”
- ❑C. a specific kind of sample/sampling method.
- ❑D. A and B.
- ❑E. A and C
- ❑F. all of the above.

What is Epidemiology?

- ❑ A. the study of the distribution and determinants of disease in the population.
- ❑ B. a way of thinking about “life.”
- ❑ C. a specific kind of sample/sampling method.
- ✓ D. A and B.
- ❑ E. A and C
- ❑ F. all of the above.

7 Uses of Epidemiology
(Morris, 1957)

1. Completing the clinical picture.
2. Community diagnosis.
3. Delineating new syndromes.
4. Computing individual morbid risk.
5. Charting historical trends.
6. Evaluating health services in action.
7. Identifying causal / risk factors.

Completing the Clinical Picture of Alzheimer's Disease:

- *Alois Alzheimer, 1907:*

On an Unusual Illness of the Cerebral Cortex

- Single case report.
- Rare disease of middle-aged.
- (pre-senile dementia)

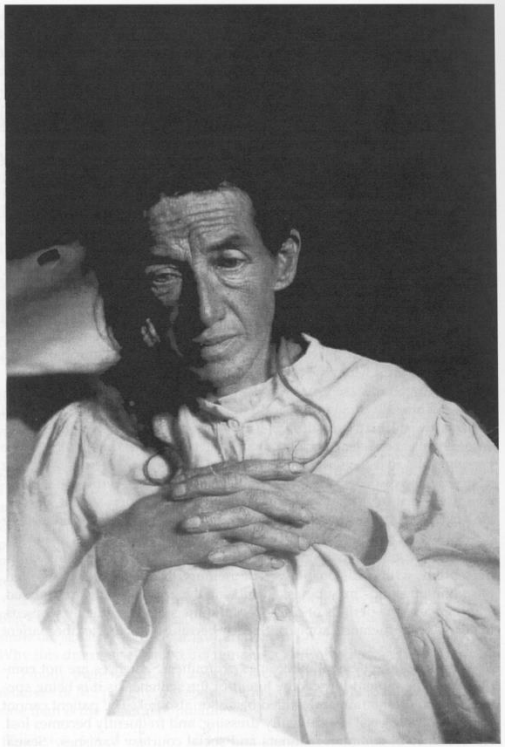


Figure 13.4. Alois Alzheimer's Patient Auguste D. Auguste D. was a 51-year-old woman with dementia who became one of Alzheimer's patients in 1901. Auguste was demented and remained under Alzheimer's care in a Frankfurt hospital for the remaining 5 years of her life. An autopsy of her brain, performed in 1906, revealed an abundance of neurofibrillary tangles and plaques that uniquely identify Alzheimer's disease. Alzheimer based his description of the disorder on her case, but her case file had been lost for nearly a century. But in December 1995, the file was found in the hospital's archive. It was in pristine form and included this photograph of Auguste, looking worried and helpless. (By permission of Prof. Dr. K. Maurer, Goethe–Universität, Frankfurt am Main. This image was first published in *Lancet*, 1997, 249: 1546-1549.)

Alzheimer's Disease:

- *Alois Alzheimer, 1907:*

On an unusual illness of the cerebral cortex.

- Single case report.
- Rare disease of middle-aged.
- (pre-senile dementia)

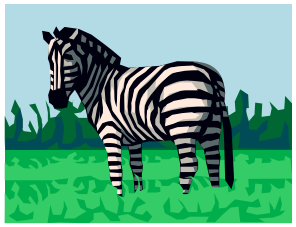
- *Martin Roth and colleagues, 1964*:

Old-age mental disorders in Newcastle-Upon-Tyne.

- Community survey.
- Fairly common disease of elderly.
- (senile dementia)

Alzheimer's Disease: *zebra or horse?*

- *Alois Alzheimer, 1907:*
  - Single case report
  - Rare disease of middle-aged
  - (pre-senile dementia)

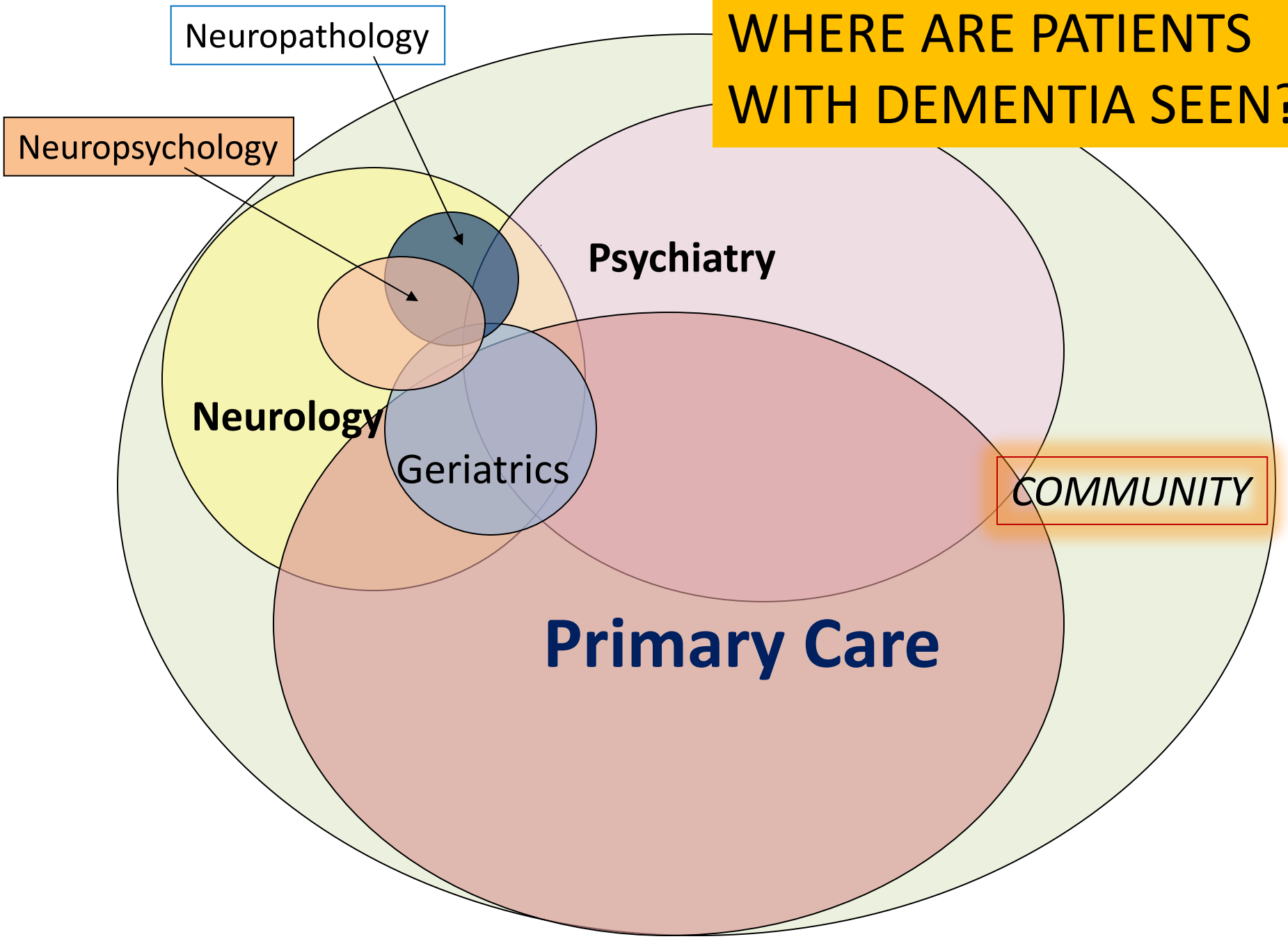


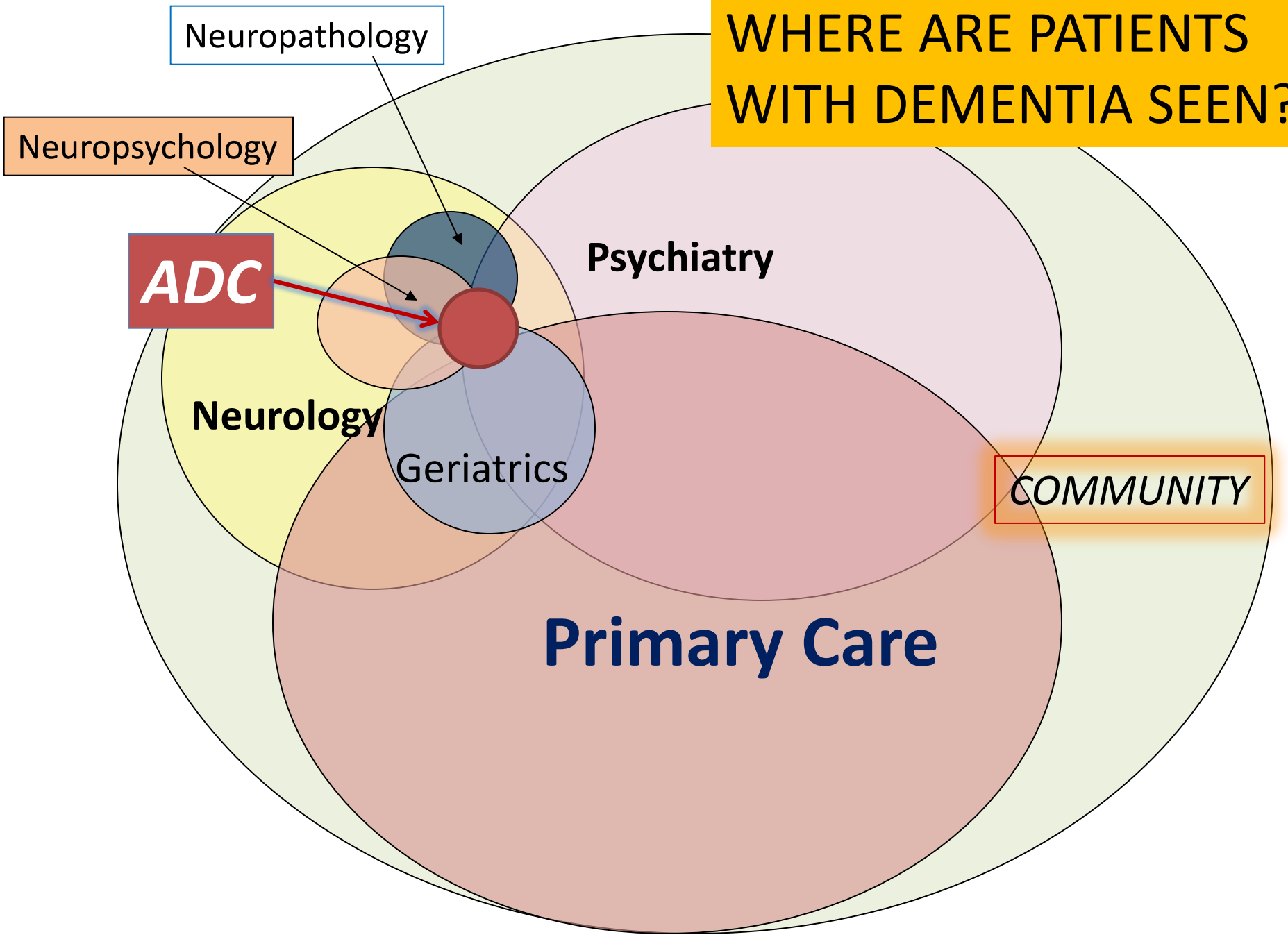
- *Martin Roth and colleagues, 1964*:
  - Community survey
  - Fairly common disease of elderly
  - (senile dementia)

Challenges in Epidemiology

Psychiatric Disorders generally *(Susser, Bresnahan, and Link, 2002)*	**Applicable to AD**
Diagnostic criteria vary across studies and over time.	Yes
No "gold standard" definitive diagnostic test .	*Yet*
Diagnosis may require an expert, or extreme standardization sacrificing validity for reliability.	Yes
Precise time of disease onset is uncertain.	Yes
Long latency period before diagnosis.	Yes
Intermittent signs and symptoms in some diseases.	(?)
Not reportable in most jurisdictions, and few if any disease registries.	Yes

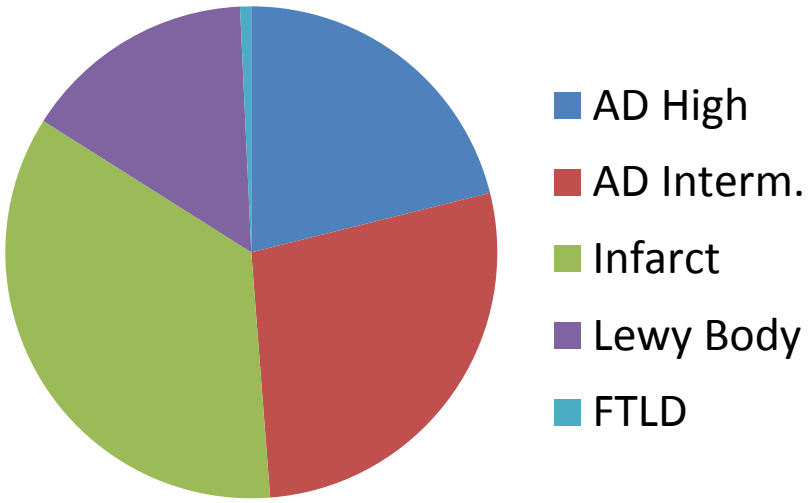
WHERE ARE PATIENTS WITH DEMENTIA SEEN?



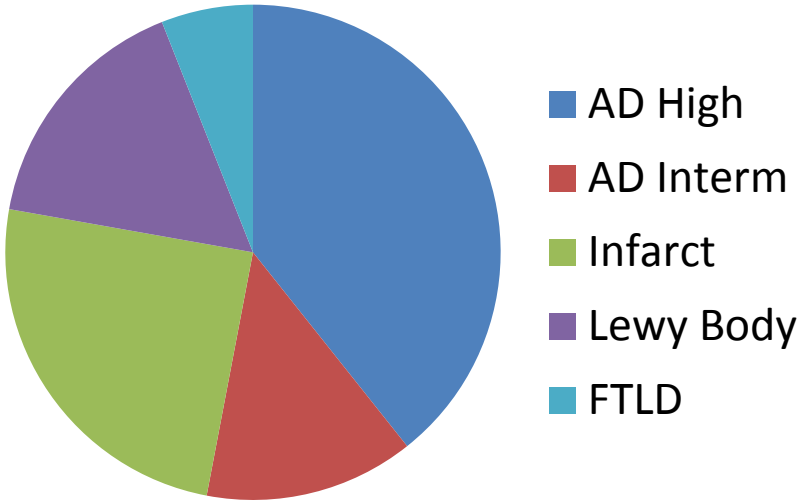

WHERE ARE PATIENTS WITH DEMENTIA SEEN?
Neuropathology
Neuropsychology
ADC
Psychiatry
Neurology
Geriatrics
COMMUNITY
Primary Care

Neuropathological Diagnoses in all individuals with clinical dementia

Community Samples



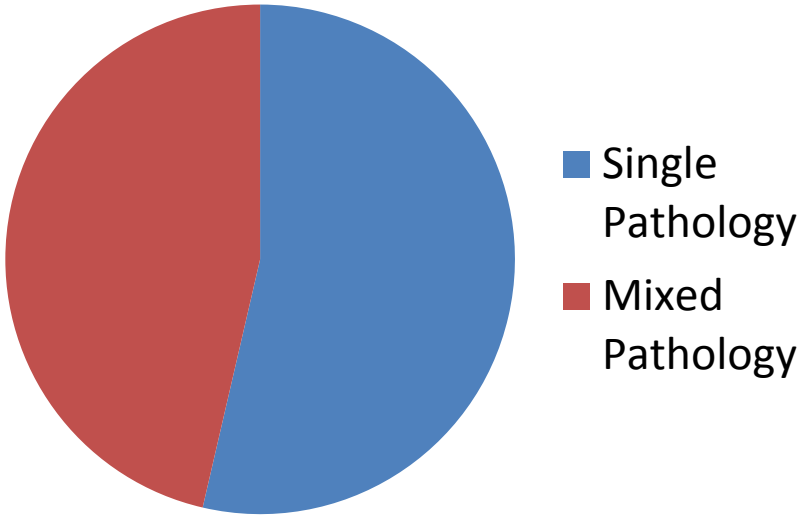
Clinic Sample



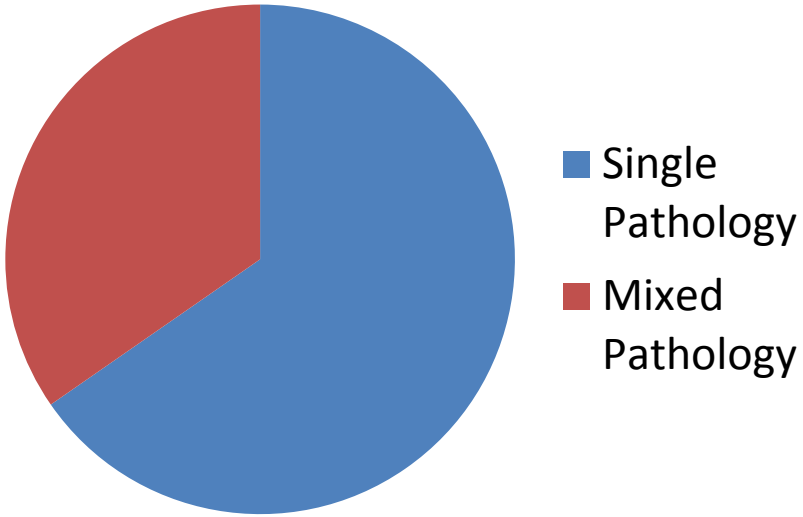
Schneider JA et al., J. Alz. Disease 2009

Single vs. Mixed Neuropathology (all clinical dementias)

Community Samples



Clinic Sample



Schneider JA et al., J. Alz. Disease 2009

The Resilient Brain

The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

ORIGINAL ARTICLE

Age, Neuropathology, and Dementia

George M. Savva, Ph.D., Stephen B. Wharton, F.R.C.Path., Paul G. Ince, M.D., Gillian Forster, B.Sc., Fiona E. Matthews, Ph.D., and Carol Brayne, M.D., for the Medical Research Council Cognitive Function and Ageing Study

N Engl J Med 2009; 360:2302-2309 | May 28, 2009 | DOI: 10.1056/NEJMoa0806142

Association between AD pathology and dementia attenuates with age; older "resilient" adults can remain free of dementia despite pathology.

Savva et al., 2009

Embrace the Heterogeneity !!

- The world is a diverse and heterogeneous place.
- Epidemiology helps us address and understand the heterogeneity.

Two Sides of Epidemiology

- The better-known macro/environment/public health side.
- The increasingly molecular side.

Goal:

For the two sides to converge and integrate to facilitate primary and secondary prevention.

Epidemiology serves Population Health

Epidemiology can:

- serve as a bi-directional bridge between clinical and basic research.
- develop frameworks and models for generating and testing hypotheses across basic and clinical research.
- provide tools for translational medicine.

Callahan, Foroud, Saykin, Shekhar, Hendrie 2014

How will Epidemiology Accomplish These Lofty Goals?

We will have a 10-point program!

You're gonna love it!

It will be Yuuuuge!

1. Deeper/denser phenotypes : incorporate biomarkers

- Combine clinical and cognitive measures with fluid and imaging biomarkers in longitudinal population studies

  -if costs come down and resources are provided.

(Someone please come up with a valid plasma marker!)

2. Deeper/denser phenotypes: add "behavioral" measures

- *Auguste D was not dragged to the mental hospital to see Professor Alzheimer because she was forgetful.*
- We must broaden the dementia phenotype to include behavioral manifestations;

  these are not mere epiphenomena.
- Behavioral and psychological symptoms often precede cognitive symptoms in dementia and are more distressing.
- "*Mild behavioral impairment*" (MBI) concept is gaining ground.

Behavioral Phenotype (example)

- First, clinical epidemiology to study behavioral phenotypes of AD (e.g., depression, apathy; possibly investigate apathy using dopamine PET, as we use amyloid PET to study MCI.)
- Then investigate the behavioral phenotypes in the population to identify preclinical/subclinical forms.

3.Molecular epidemiology: ***Omics!!***

- Move beyond clinical case-control studies into the larger community, identify AD cases at all disease stages – full disease spectrum.

- "The convergence of striking developments in biotechnology, increasing availability of biobanked samples, and advances in biostatistics and bio-informatics allow an optimistic outlook for epidemiological research."

Bonasi et al., 2003

4. Life-Course Epidemiology

Studies should enroll young adults and follow them into late adulthood to:

- Capture critical timing and duration of exposures that might influence risk of late-life diseases.
- Capture trajectories of cognitive and behavioral change over time.
- Capture evolution of biomarkers.

5. Investigate cohort effects

- Studies conducted in one generation /birth cohort should not be assumed to establish truth for all time;
- Preceding and subsequent cohorts have different experiences and exposures; thus, may have different associations and rates of outcomes.
- Declining incidence rates of stroke and dementia demonstrate this and must be investigated carefully.

6. New Generations

- Large national or regional registries like the Europeans have may never be possible in the US because of fragmented data collection, lack of a national health program, and distrust of "government."
- Coming generations may possibly be recruited and followed through social media and be willing to share the kinds of data which earlier generations would not.

  Capitalize on information-sharing habits of newer generations!

7. Inadequately studied populations

- Populations of low and middle-income countries;
- Ethnic/racial/social minorities in high-income countries;

-in whom exposures and epigenetics and secular trends may be very different and shed new light on mechanisms.

Ebola! Zika! Lead! Methane!

- Given increasing travel and migration patterns, local factors can have global impact.

8. Interventional Epidemiology?

- Use epidemiological principles to design trials and analyze/interpret results, minimizing and/or correcting for different types of bias.
- Embed certain trials in population-based studies:
- Recruit RCT participants from population-based observational studies, e.g. FINGER (*FINNISH GERIATRIC INTERVENTION STUDY*).

Epidemiology Enhances Trials

- The heterogeneous population comprises more homogeneous subgroups which epidemiology can help identify.
- Associations vary across subgroups.
- Causal mechanisms likely vary also.
- Trials should test specific interventions

directed at specific causal mechanisms

in specific subgroups/ subtypes.

One size will likely not fit all.

Challenge the Hierarchy

- Draw appropriate inferences re potential interventions from observational studies where RCTs are not feasible/practical (smoking? head trauma?parachutes?)
- The dominance of RCTs is neither universally appropriate nor universally helpful.
- Steps can be taken to enhance the reliability and validity of non-randomized research.
- Clinicians, basic researchers, policymakers need credible assessments of non-randomized data .
- “Evidence needs to be translated, whether or not complete.”

Dacks, Bennett, and Fillit 2014

9. Judicious Mining of Big Data

- *Approach with caution!* Identify appropriate Big Dataset for given research question.
- Epidemiological principles and validated methods must guide data mining.
- May be best for variables that are recorded reliably and uniformly in the EHR, e.g.,
  - medications and serious adverse effects:

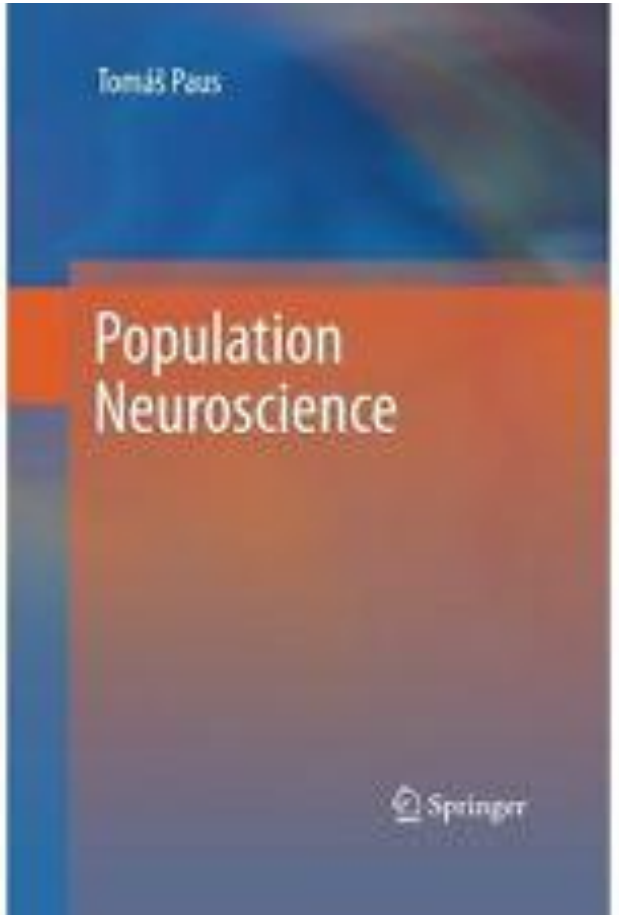
    pharmaco-epidemiological approaches may allow post-marketing surveillance to ask questions for which RCTs cannot be employed.
  - agnostic digital image data, like MRIs and retinal scans, may provide more fertile ground for data mining.

10. Data pooling

- Judicious analyses of pooled data to increase reach and power to detect small to medium size effects.
- Shared core methods to facilitate data pooling without stifling innovation /local strengths.
- Greater sharing of uniformly collected data and specimens.
- Harmonization of data where not identically collected.

Population Neuroscience (Tomas Paus, 2013)

Combining the approaches of neuroscience and population science will enable us to answer questions that we previously could not. E.g., leverage rapidly developing 'omic' technologies and methods.



PERSPECTIVE

What is a representative brain? Neuroscience meets population science

Emily B. Falk[a,b,c,1], Luke W. Hyde[d,e,f,1], Colter Mitchell[e,g,1,2], Jessica Faul[e,3], Richard Gonzalez[b,d,h,3], Mary M. Heitzeg[i,3], Daniel P. Keating[d,e,i,j,3], Kenneth M. Langa[e,k,l,3], Meghan E. Martz[d,3], Julie Maslowsky[m,3], Frederick J. Morrison[d,3], Douglas C. Noll[n,3], Megan E. Patrick[e,3], Fabian T. Pfeffer[e,g,3], Patricia A. Reuter-Lorenz[d,e,o,3], Moriah E. Thomason[p,q,r,3], Pamela Davis-Kean[b,d,e,f,4], Christopher S. Monk[d,e,f,i,o,4], and John Schulenberg[d,e,f,4]

Departments of [a]Communication Studies, [d]Psychology, [h]Statistics, [i]Psychiatry, [j]Pediatrics and Communicable Diseases, [k]Internal Medicine, [n]Biomedical Engineering; [o]Neuroscience Graduate Program; [b]Research Center for Group Dynamics, [e]Survey Research Center, and [g]Population Studies Center of the Institute for Social Research; and [f]Center for Human Growth and Development, University of Michigan, Ann Arbor, MI 48109; [c]Annenberg School for Communication, University of Pennsylvania, Philadephia, PA, 19104; [l]Veterans Affairs Center for Clinical Management Research, Ann Arbor, MI 48105, [m]Robert Wood Johnson Foundation Health and Society Scholars Program, Population Health Sciences, School of Medicine and Public Health, University of Wisconsin–Madison, Madison, WI 53706; [p]School of Medicine Pediatrics and [q]Merrill Palmer Skillman Institute for Child and Family Development, Wayne State University, Detroit, MI 48202; and [r]Perinatology Research Branch, National Institutes of Health, Detroit, MI 48202

Proceedings of the National Academy of Sciences, 2013, 110: 17615-17622

The representative brain

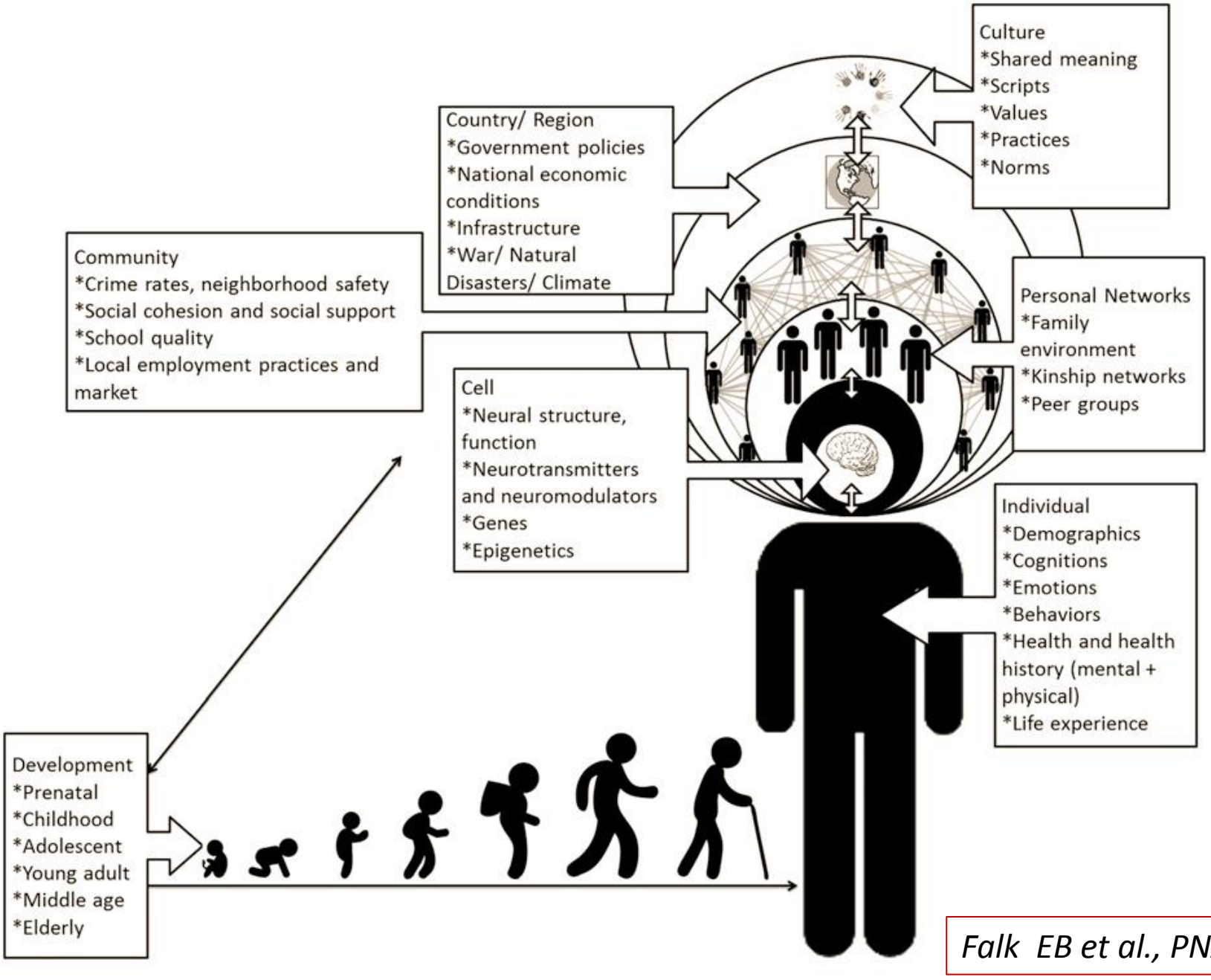
- Great strides in neuroscience (social, cognitive, clinical, affective, economic, communication, developmental).
- But most findings based on small samples of convenience.
- Unrepresentative samples:
  - distort understanding of individual differences;
  - undermine findings regarding brain-behavior relationships.

Falk et al., PNAS 2013

Population Neuroscience

- Leverages interdisciplinary expertise;
- *For neuroscientists*, more clearly defines relevant populations and sampling strategies needed when applying neuroscience methods;
- *For population scientists*, deepens understanding of neural mechanisms.
- Changes the cultures of both neuroscience and population research.
- Emphasizes developmental, ecological, and interactional models.
- Enhances generalizability of findings.

Falk et al., PNAS 2013



Falk EB et al., PNAS 2013

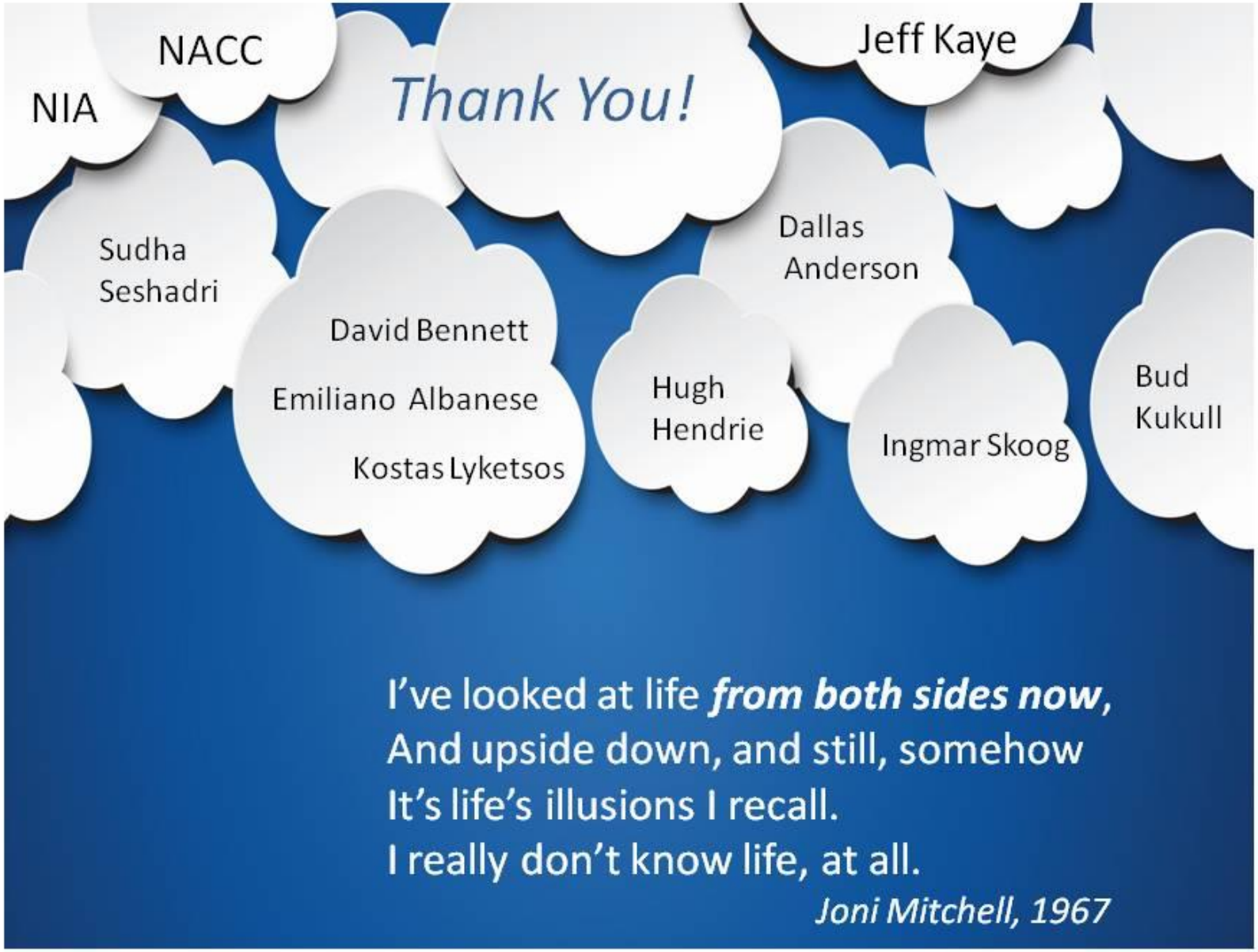
Some Goals of Population Neuroscience

- Integrate brain imaging/biomarkers into existing representative sub-samples.
- Develop methods to scale up neuroimaging /biomarker studies to larger and more representative samples.
- Use strategic samples when recruiting for stand-alone imaging/biomarker studies.
- Explore moderators of brain-behavior links and neural predictors of relevant outcomes.

Adapted from Falk et al., PNAS 2013

The Future of AD Epidemiology is in Population Neuroscience

1. Deepen/widen the phenotype under study: incorporate biomarkers.
2. Deepen/widen the phenotype under study: incorporate behavioral measures.
3. Incorporate Omics into population studies.
4. Conduct life-course studies starting in early adulthood.
5. Investigate birth cohort effects to understand time trends.
6. Capitalize on information-sharing habits of younger generations
7. Extend investigations to inadequately studied populations.
8. Inform trial design, and address questions that cannot be addressed by RCTs.
9. Judiciously mine Big Data, especially EHRs.
10. Increase sharing/pooling of data across studies.



GanguliM@upmc.edu