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# Why is Representative Brain Donation Important for Research on Aging and Dementia?

Julie A. Schneider, M.D.

Breakout Session: The Diversification of Brain Tissue: Why and Ways Forward

Fall ADRC Meeting

October 21, 2022

# Alzheimer's disease

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- First thought to be presenile dementia because the brain investigated was that of a person in 50s.

- Until autopsies studies of older persons proved otherwise….

› Nature. 1966 Jan 1;209(5018):109-10. doi: 10.1038/209109a0.

**Correlation between scores for dementia and counts of 'senile plaques' in cerebral grey matter of elderly subjects**

M Roth, B E Tomlinson, G Blessed

PMID: 5927229 DOI: 10.1038/209109a0

# Plaques/Tangles

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- Then, plaques/tangles in persons with memory loss/dementia = Alzheimer's disease …opened floodgate of research….

- Discovery of Amyloid Beta Protein
- Discovery of Paired Helical Filament Tau
- Amyloid Precursor Protein, alpha, beta, gamma secretase
- Apolipoprotein E, Autosomal Dominant Dx (APP, presenilin)
- Mouse and other models of AD
- Anti – amyloid for in-vivo biomarkers/ treatment

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# Brain Donation propelled our Understanding of Alzheimer's Dementia

Continued enrollment of more older persons in longitudinal studies

→

More Clinical Information

→

More well characterized brains

# Prob AD more than plaques/tangles…

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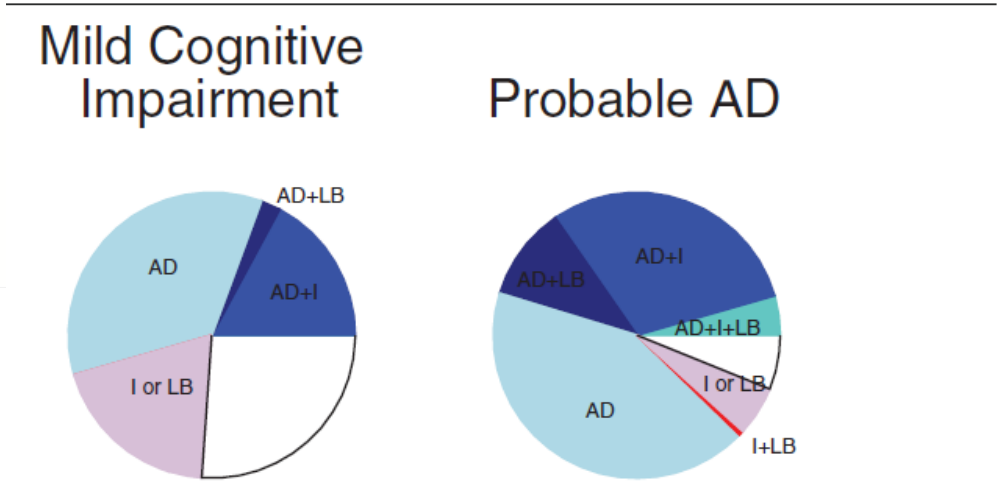
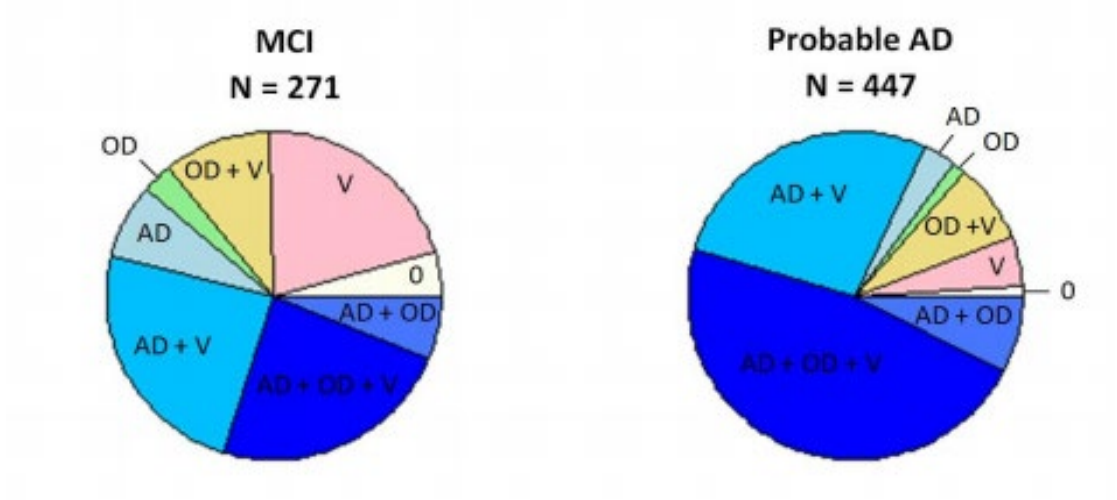



Schneider JA et al. *Ann Neurol* 2009;66:200–208.

+ macroscopic infarcts

+ Lewy bodies




**Kapasi A et al. Acta Neuropathologica 2017**

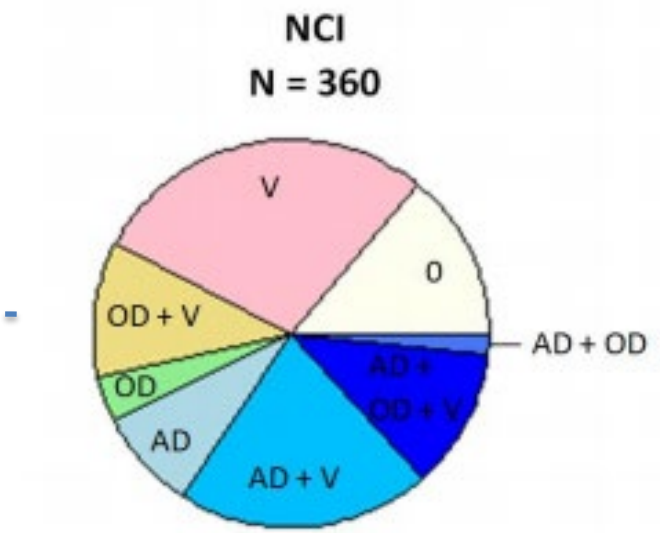
+ microinfarcts
+ arteriolosclerosis
+ amyloid angiopath
+ atherosclerosis

+ TDP/HS (LATE-NC)

# More Brains (no cognitive impairment) propelled us further …

- About 1/3 of older persons have pathologic AD pathology
- Research pivoted to “RESILIENCE”
  - Genetics, Education
  - Cognitive, Social, physical activities
  - Well-being/purpose in life
  - Diet, Exposome
  - Lesser (OR BETTER) inflammation
  - Better repair mechanisms
  - Compensation via other pathways

**Kapasi A et al. Acta Neuropathologica 2017**



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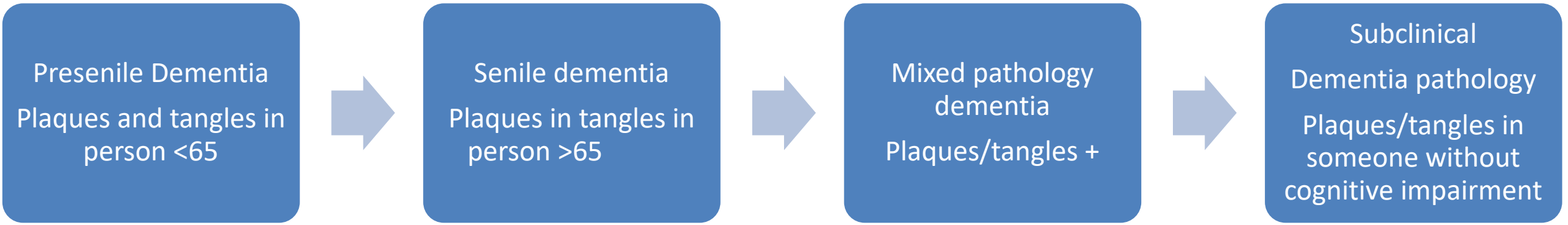
# Who and What We See Changes The Way We Think About Disease

## "What is "Alzheimer's Dementia"



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# Brains from the Community vs. Clinic

Demographics [mean (SD)] and distribution [number (%)] of pathology in two comm

| | Religious orders study | Memory and aging project | Clinical cohort |
|---|---|---|---|
| **Number** | **386** | **195** | **392** |
| Age at death (yrs) | 86.2 (SD = 7.0) | 88.0 (SD = 5.7) | 78.6 (SD = 10.4) |
| Education (yrs) | 17.9 (SD = 3.6) | 14.7 (SD = 3.0) | 14.9 (SD = 12.2) |
| MMSE | 21.0 (SD = 9.1) | 21.9 (SD = 8.8) | 7.3 (SD = 9.3) |
| No cognitive impairment | 124 (32.1%) | 64 (32.8%) | 14 (3.6%) |
| Mild cognitive impairment | 87 (22.5%) | 54 (27.7%) | 9 (2.3%) |
| Probable AD | 130 (33.7%) | 64 (32.8%) | 280 (71.2%) |
| Possible AD | 33 (8.5%) | 9 (4.6%) | 46 (11.7%) |
| Other dementia | 12 (3.1%) | 4 (2.0%) | 43 (10.9%) |
| Infarct (any) | 189 (49.0%) | 89 (45.6%) | 109 (27.8%) |
| FTLD or other atypical pathology | 1 (0.25%) | 2 (1.0%) | 36 (9.2%) |

Schneider et al.

*J Alzheimers Dis*. 2009 November ; 18(3): 691–701.

# Brains from Old vs. Oldest Old

**Pathology and dementia in the oldest old**
(age 90+ vs. <90)

James BD et al., JAMA. 2012 May 2;307(17):1798-800.

| Characteristic | Total (n=804) | Age 65-89 (n=503) | Age 90 + (n = 301) | P value |
|---|---|---|---|---|
| Age at death, yrs(SD) | 87.7 (6.7) | 83.8 (4.8) | 94.3 (3.3) | <0.001 |
| Dementia[a], no. (%) | 304 (37.8%) | 143 (28.4%) | 161 (53.5%) | <0.001 |
| AD[c] | 493 (61.3%) | 279 (55.5%) | 214 (71.1%) | < 0.001 |
| Infarcts[d] | 272 (33.8%) | 147 (29.2%) | 125 (41.5%) | < 0.001 |
| **Single path** | **374 (46.5%)** | **238 (47.3%)** | **136 (45.2%)** | **0.56** |
| **Mixed path** | **225 (28.0%)** | **113 (22.5%)** | **112 (37.2%)** | **<0.001** |
| AD + LB | 41 (5.1%) | 25 (5.0%) | 16 (5.3%) | 0.83 |
| AD + Infarcts | 162 (20.2% | 79 (15.7%) | 83 (27.6%) | <0.001 |

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Review > Brain Res. 2019 Sep 15;1719:11-16. doi: 10.1016/j.brainres.2019.05.028. Epub 2019 May 22.

## Sex differences in mixed neuropathologies in community-dwelling older adults

Lisa L Barnes [1], Melissa Lamar [2], Julie A Schneider [2]

Affiliations + expand

PMID: 31128096 PMCID: PMC6636678 DOI: 10.1016/j.brainres.2019.05.028

# Most research in men; what about women? Are their Brains different?

**Table 4:**

Results from logistic regression models indicating odds of mixed pathology in men compared to women

| Pathology | Sample size | OR | 95% CI | p-value |
|---|---|---|---|---|
| AD + TDP/HS | 1553 | 0.82 | 0.63, 1.08 | 0.16 |
| AD + CVD | 1558 | 0.76 | 0.60, 0.96 | 0.02 |
| AD + LBD | 1556 | 1.09 | 0.82, 1.44 | 0.57 |
| Parkinson's disease | 1556 | 1.37 | 1.07, 1.75 | 0.01 |
| Pure Lewy Body Disease | 1556 | 1.48 | 0.99, 2.21 | 0.05 |

Footnote: The reference group in the models is female; e.g. Males have a higher risk of Parkinson's disease pathology

Published in final edited form as:
*Alzheimers Dement.* 2016 August ; 12(8): 900–908. doi:10.1016/j.jalz.2016.04.006.

# Microinfarcts are common and strongly related to dementia i the oldest-old: The 90+ Study

María M. Corrada, ScM, ScD[a,b], Joshua A. Sonnen, MD[c], Ronald C. Kim, MD[d], and Clau H. Kawas, MD[a,e]

RESEARCH ARTICLE

# Association of Cognition and Dementia With Neuropathologic Changes of Alzheimer Disease and Other Conditions in the Oldest Old

Thomas J. Mc
Lon R. White,

*Neurology*® 2

JAMA Network Open
View Article

JAMA Netw Open. 2020 Jun; 3(6): e207559.
Published online 2020 Jun 11. doi: 10.1001/jamanetworkopen.2020.7559
PMCID: PMC7290421
PMID: 32525547

## Association of Neighborhood-Level Disadvantage With Alzheimer Disease Neuropathology

W. Ryan Powell, PhD,[1,2] William R. Buckingham, PhD,[1,2] Jamie L. Larson, PhD,[1,2] Leigha Vilen, BS,[1,2] Menggang Yu, PhD,[3] M. Shahriar Salamat, MD, PhD,[4,5] Barbara B. Bendlin, PhD,[1,6,7,8] Robert A. Rissman, PhD,[9,10] and Amy J. H. Kind, MD, PhD[1,2,6,7]

JAMA Network

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Acta Neuropathologica (2018) 136:873–885
https://doi.org/10.1007/s00401-018-1908-x

ORIGINAL PAPER

CrossMark

# Sex and age interact to determine clinicopathologic differences in Alzheimer's disease

Amanda M. Liesinger[1] · Neill R. Graff-Radford[2] · Ranjan Duara[4] · Rickey E. Carter[3] · Fadi S. Hanna Al-Shaikh[1] · Shunsuke Koga[1] · Kelly M. Hinkle[1] · Sarah K. DiLello[1] · McKenna F. Johnson[1] · Adel Aziz[2] · Nilufer Ertekin-Taner[1,2] · Owen A. Ross[1] · Dennis W. Dickson[1] · Melissa E. Murray[1]

Received: 18 May 2018 / Revised: 8 September 2018 / Accepted: 9 September 2018 / Published online: 15 September 2018


# Frequency of LATE neuropathologic change across the spectrum of Alzheimer's disease neuropathology: combined data from 13 community-based or population-based autopsy cohorts

Peter T. Nelson[1], Carol Brayne[2], Margaret E. Flanagan[3], Erin L. Abner[1], Sonal Agrawal[4], Johannes Attems[5], Rudolph J. Castellani[3], Maria M. Corrada[6], Matthew D. Cykowski[7], Jing Di[1], Dennis W. Dickson[8], Brittany N. Dugger[9], John F. Ervin[10], Jane Fleming[2], Jonathan Graff-Radford[11], Lea T. Grinberg[12,13], Suvi R. K. Hokkanen[2], Sally Hunter[2], Alifiya Kapasi[4], Claudia H. Kawas[6], Hannah A. D. Keage[14], C. Dirk Keene[15], Mia Kero[16], David S. Knopman[11], Naomi Kouri[8], Gabor G. Kovacs[17,18,19,20], Sydney A. Labuzan[8], Eric B. Larson[21], Caitlin S. Latimer[15], Renata E. P. Leite[13], Billie J. Matchett[8], Fiona E. Matthews[5], Richard Merrick[2], Thomas J. Montine[22], Melissa E. Murray[8], Liisa Myllykangas[16], Sukriti Nag[4], Ruth S. Nelson[23], Janna H. Neltner[1], Aivi T. Nguyen[11], Ronald C. Petersen[11], Tuomo Polvikoski[5], R. Ross Reichard[11], Roberta D. Rodriguez[13], Claudia K. Suemoto[13], Shih-Hsiu J. Wang[10], Stephen B. Wharton[24], Lon White[25], Julie A. Schneider[4]

# Few Brains representing the diversity of Race, Ethnicity, SES

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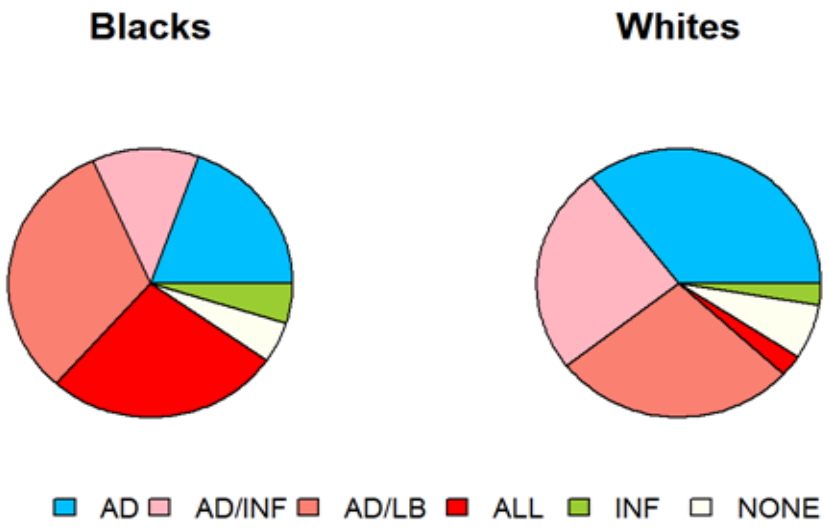
Neurology. 2015 Aug 11; 85(6): 528–534.
doi: 10.1212/WNL.0000000000001834

PMCID: PMC4540250
PMID: 26180136

## Mixed pathology is more likely in black than white decedents with Alzheimer dementia

Lisa L. Barnes, PhD,✉ Sue Leurgans, PhD, Neelum T. Aggarwal, MD, Raj C. Shah, MD, Zoe Arvanitakis, MD, Bryan D. James, PhD, Aron S. Buchman, MD, David A. Bennett, MD, and Julie A. Schneider, MD



Comparative Study > Arch Neurol. 2006 Jan;63(1):87-90. doi: 10.1001/archneur.63.1.87.

# The neuropathology of Alzheimer disease in African American and white individuals

Consuelo H Wilkins [1], Elizabeth A Grant, Sarah E Schmitt, Daniel W McKeel, John C Morris

Affiliations + expand

PMID: 16401740 DOI: 10.1001/archneur.63.1.87

> Alzheimers Dement. 2016 Jun;12(6):669-77. doi: 10.1016/j.jalz.2016.03.004. Epub 2016 Apr 16.

# Neuropathologic differences by race from the National Alzheimer's Coordinating Center

Neill R Graff-Radford [1], Lilah M Besser [2], Julia E Crook [3], Walter A Kukull [2], Dennis W Dickson [4]

Affiliations + expand

PMID: 27094726 PMCID: PMC4903907 DOI: 10.1016/j.jalz.2016.03.004

> J Alzheimers Dis. 2019;68(1):145-158. doi: 10.3233/JAD-180992.

# Neuropathological Diagnoses of Demented Hispanic, Black, and Non-Hispanic White Decedents Seen at an Alzheimer's Disease Center

Teresa Jenica Filshtein [1], Brittany N Dugger [2], Lee-Way Jin [2 3], John M Olichney [4], Sarah T Farias [4], Luis Carvajal-Carmona [5], Paul Lott [6], Dan Mungas [4], Bruce Reed [7], Laurel A Beckett [8], Charles DeCarli [4 9]

Affiliations + expand

PMID: 30775996 PMCID: PMC7286069 DOI: 10.3233/JAD-180992

Free PMC article

> Neurobiol Aging. 2001 Mar-Apr;22(2):169-75. doi: 10.1016/s0197-4580(00)00236-0.

# The prevalence of the neuropathological lesions of Alzheimer's disease is independent of race and gender

G Sandberg [1], W Stewart, J Smialek, J C Troncoso

> Free Neuropathol. 2022;3:10.17879/freeneuropathology-2022-3795. doi: 10.17879/freeneuropathology-2022-3795. Epub 2022 Mar 10.

# Neuropathology Studies of Dementia in US Persons other than Non-Hispanic Whites

My-Ie Nguyen [1], Emily Z Huie [1], Rachel A Whitmer [2], Kristen M George [2], Brittany N Dugger [1]

Affiliations + expand

PMID: 35425946 PMCID: PMC9007571 DOI: 10.17879/freeneuropathology-2022-3795

Free PMC article

ARTICLE

# Limbic-predominant age-related TDP-43 encephalopathy in Black and White decedents

Sukriti Nag, MD, PhD, Lisa L. Barnes, PhD, Lei Yu, PhD, Robert S. Wilson, PhD, David A. Bennett, MD, and Julie A. Schneider, MS, MD

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Dr. Nag
Sukriti_Nag@rush.edu

*Neurology*® 2020;95:e2056-e2064. doi:10.1212/WNL.0000000000010602

# Diversity within Diversity

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- Just like not all white people are alike
- Not all Black, Latino, Asian people are alike
  - Clinic vs. community; old vs. oldest old, male vs. female
  - Socioeconomic Status, Environment, Medical illness, etc., etc.
- Within race studies

BEHAVIORAL AND BRAIN SCIENCES (2010), Page 1 of 75
doi:10.1017/S0140525X0999152X

# The weirdest people in the world?

**Joseph Henrich**
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**joseph.henrich@gmail.com**
**http://www.psych.ubc.ca/~henrich/home.html**

**Steven J. Heine**
*Department of Psychology, University of British Columbia, Vancouver V6T 1Z4, Canada*
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**Ara Norenzayan**
*Department of Psychology, University of British Columbia, Vancouver V6T 1Z4, Canada*
**ara@psych.ubc.ca**

They found that people from **Western, educated, industrialized, rich and democratic** (WEIRD) societies — who represent as much as 80 percent of study participants, but only 12 percent of the world's population — are not only unrepresentative of humans as a species, but on many measures they're outliers. May 1, 2010

# WEIRDER BRAINS

## (WEIRD + Even Rarer)

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If most clinical research participation is WEIRD, and

donation of Brains is even rarer….

then BRAIN RESEARCH IS WEIRDER

…and who we study propels

diagnosis/medical/basic research/treatment/public health…

# THANK YOU!