SINGLE-CELL TRANSCRIPTIONAL ANALYSIS AS A FRAMEWORK FOR DISSECTING RESILIENCE MECHANISMS

AGS/NIA R13 Conference
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March 4, 2024

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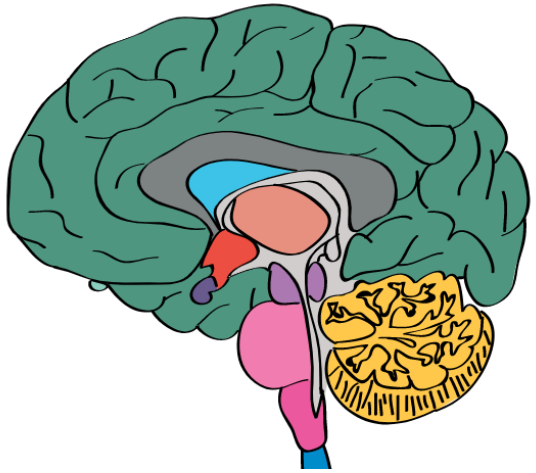
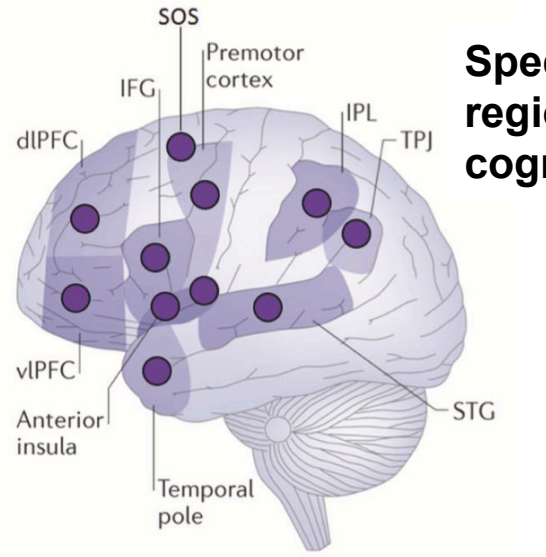
Understanding cognitive resilience requires us to dissect the complex, heterogenous landscape of the brain

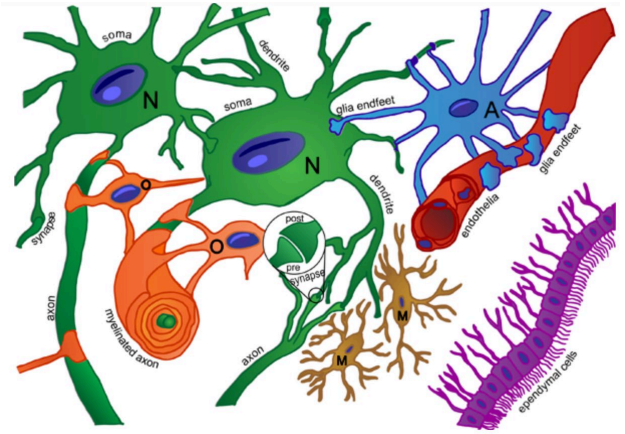
Regional (Anatomic) Contributions

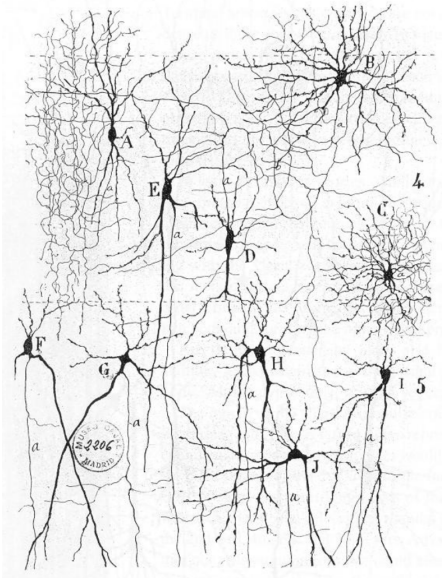




Specific cortical regions involved in cognition

Cellular Contributions

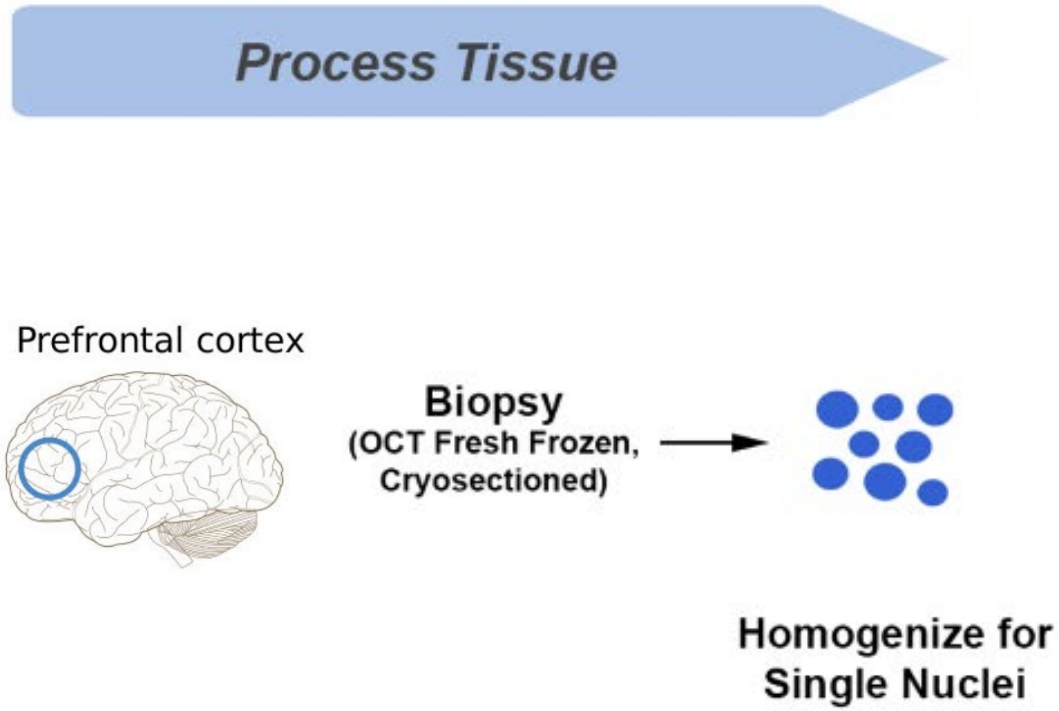




Neuronal heterogeneity recognized > 100 years ago

Human Protein Atlas
Lanooij SD et al. *Mol Psych* 2023
Santiago Ramón y Cajal

The single-cell revolution



Numerous studies have leveraged single cell technology to study neurodegeneration

Table 1 | Single-cell transcriptomic and epigenetic datasets from postmortem Alzheimer's disease tissue

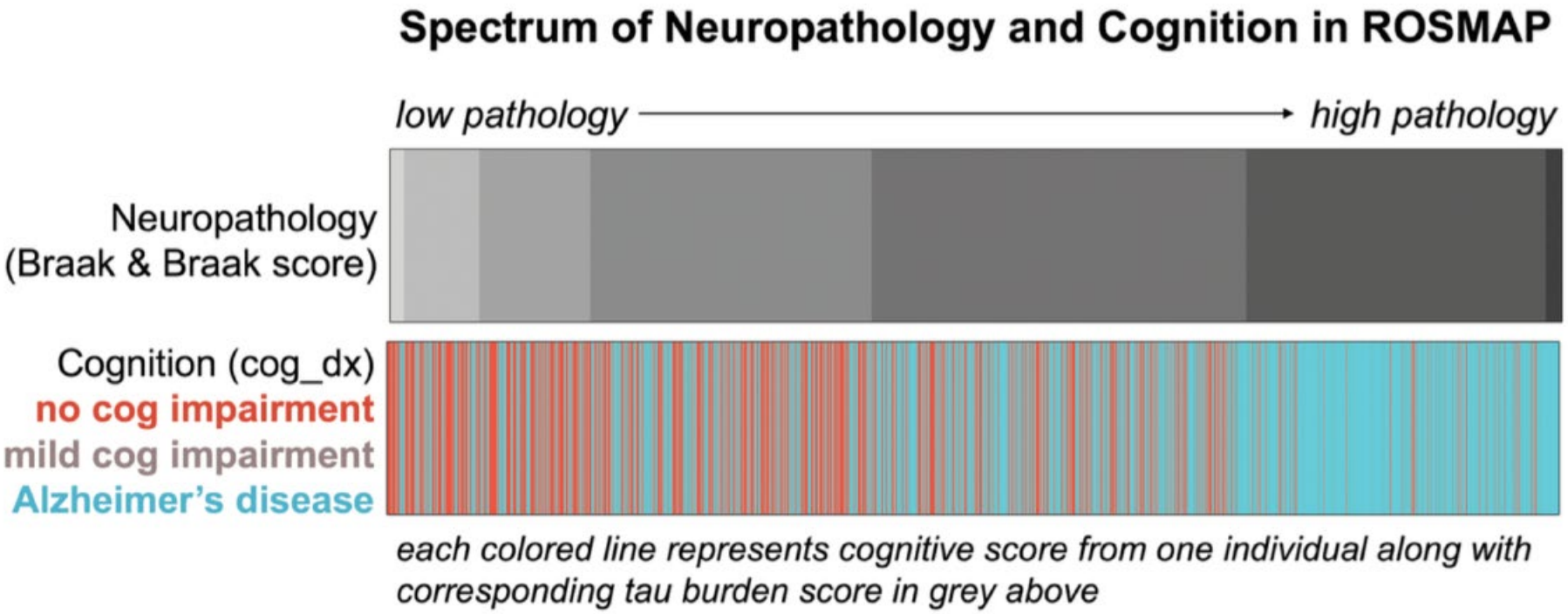
Study	Data ID	Participant cohort	Brain region	Sequencing strategy	Total nuclei
[a]Mathys et al.[8]	syn18485175	48	PFC (BA10)	snRNA-seq	80,660
Davila-Velderrain et al.[13]	NA	112	Hippocampus	snRNA-seq	489,558
			Entorhinal cortex		
[a]Grubman et al.[7]	GSE138852	12	Entorhinal cortex	snRNA-seq	13,214
[a]Leng et al.[18]	GSE147528	10	Caudal entorhinal cortex	snRNA-seq	42,528
			Superior frontal gyrus	snRNA-seq	63,608
Zhou et al.[9]	syn21125841	32	Dorsolateral prefrontal cortex	snRNA-seq	66,311
Lau et al.[14]	GSE157827	21	PFC (BA6, BA8, and BA9)	snRNA-seq	169,496
Otero-Garcia et al.[12]	GSE129308	8	PFC (BA9)	AT8 and MAP2 FACS	63,110
Alsema et al.[127]	GSE146639	27	Superior parietal lobe Superior frontal gyrus	CD11/CD45 FACS; bc-Smart-seq2	
Marinaro et al.[128]	NA	12	PFC (BA9)	FACS neurons and glia; snRNA-seq	89,325
[a]Yang et al.[116]	GSE163577	17	Hippocampus	Vascular enriched fraction then snRNA-seq	143,793
		8	Superior frontal cortex		
Gerrits et al.[129]	GSE148822	18	Occipitotemporal cortex and fusiform gyrus	$NEUN^-/OLIG2^-$ FACS, then snRNA-seq	482,472 nuclei
Del-Aguila et al.[130]	http://ngi.pub/snuclRNA-seq/	3	Parietal lobe	snRNA-seq	26,331
Olah et al.[131]		14	Dorsolateral prefrontal cortex	$CD11b^+/CD45^+$, snRNA-seq	16,242
		3	TNC		
[a]Morabito et al.[77]	syn3219045	20	PFC	snATAC-seq and snRNA-seq	191,890
Xu et al.[132]	GSE181279	5	PBMCs	CD45 selection, then TCR-seq	36,849
Gate et al.[133]	GSE134578	18	Peripheral $CD8^+$ TEMRA; CSF cells	TCR-seq	21,267
Smith et al.[134]	GSE160936	12	Entorhinal and somatosensory cortex	$NEUN^-/SOX10^-$	52,706 astrocytes and 27,592 microglia

NA, not applicable; PBMCs, peripheral blood mononuclear cells; PFC, prefrontal cortex; TCR-seq, T cell receptor sequencing. [a]Signifies a particularly noteworthy study.

Murdock et al. *Nat Neurosci* 2023

Fewer studies have looked at phenotypic variation within a disease state

RUSH

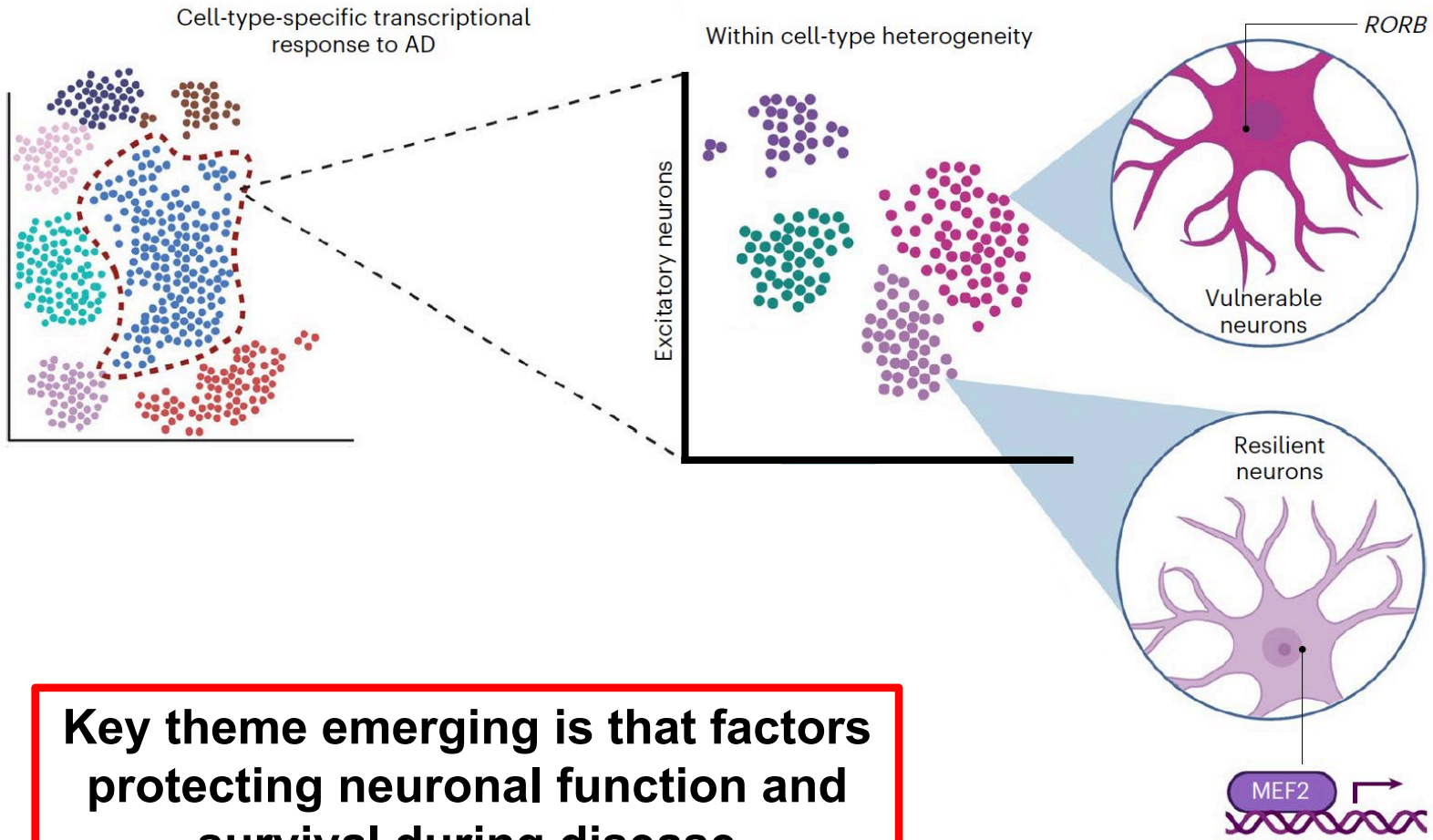


Bennett DA et al. *J Alzheimer's Disease* 2018
Barker SJ*, Raju RM* et al. *Science Transl Med* 2021

Finding cognitively resilient patients in the ROSMAP cohort

Patient ID	Sex	Race	Cog Dx	Global cog at last visit	Age of death (yrs)	Global pathology	Amyloid	CERAD score	Braak score	Neurofibrillary tangles	PMI (hrs)
Resilient											
	F	W	1.00	-0.10	87.62	0.98	2.78	1.00	5.00	1.05	6.28
	F	W	1.00	-0.41	97.55	1.66	11.68	1.00	4.00	1.38	
	F	W	1.00	-0.40	90.29	1.11	4.35	1.00	4.00	0.63	5.53
	F	W	1.00	0.40	88.80	0.16	0.29	4.00	3.00	0.40	19.50
	F	W	1.00	0.03	93.25	0.14	0.39	4.00	4.00	0.43	5.00
	F	W	1.00	0.52	85.89	0.87	11.05	1.00	4.00	0.30	11.50
	F	W	1.00	0.83	87.94	0.14	0.00	4.00	3.00	0.22	20.00
	F	W	1.00	-0.24	83.69	0.27	0.00	4.00	4.00	0.76	3.93
	F	W	1.00	-0.19	95.61	0.52	6.22	2.00	4.00	0.54	7.28
Non-resilient											
	F	W	4.00	-1.19	95.29	1.91	14.47	1.00	5.00	1.68	6.17
	F	W	4.00	-1.29	82.70	2.43	7.33	1.00	5.00	2.82	6.75
	F	W	4.00	-1.52	88.65	0.32	0.12	4.00	4.00	0.96	24.00
	F	W	4.00	-0.88	96.80	0.75	4.66	1.00	4.00	0.64	13.17
	F	W	4.00	-0.71	82.28	0.77	10.62	1.00	5.00	0.82	11.42
	F	W	4.00	-1.81	85.24	1.07	17.53	2.00	4.00	0.58	17.42
	F	W	4.00	-0.21	99.35	0.98	2.47	2.00	4.00	0.35	7.93
	F	W	4.00	-3.86	93.57	0.13	0.19	4.00	3.00	0.29	2.33
	F	W	4.00	-3.62	85.67	0.13	0.00	4.00	4.00	0.39	19.25
P-value	1.00	1.00	0.00	0.001	0.77	0.37	0.32	0.91	0.17	0.29	0.45

Identifying the neuronal genes associated with resilience at single cell resolution



Science

Neuronal Activity-Dependent Cell Survival Mediated by Transcription Factor MEF2

Zixu Mao,[1]* Azad Bonni,[1] Fen Xia,[2] Mireya Nadal-Vicens,[1] Michael E. Greenberg[1]†

Key theme emerging is that factors protecting neuronal function and survival during disease progression facilitates resilience

Barker SJ et al. *Science Transl Med* 2021
Murdock et al. *Nat Neurosci* 2023
Leng K et al. *Nat Neurosci* 2021
Udeochu JC et al. *Nat Neurosci* 2023

Larger scale dissection of genes and cell types associated with resilience

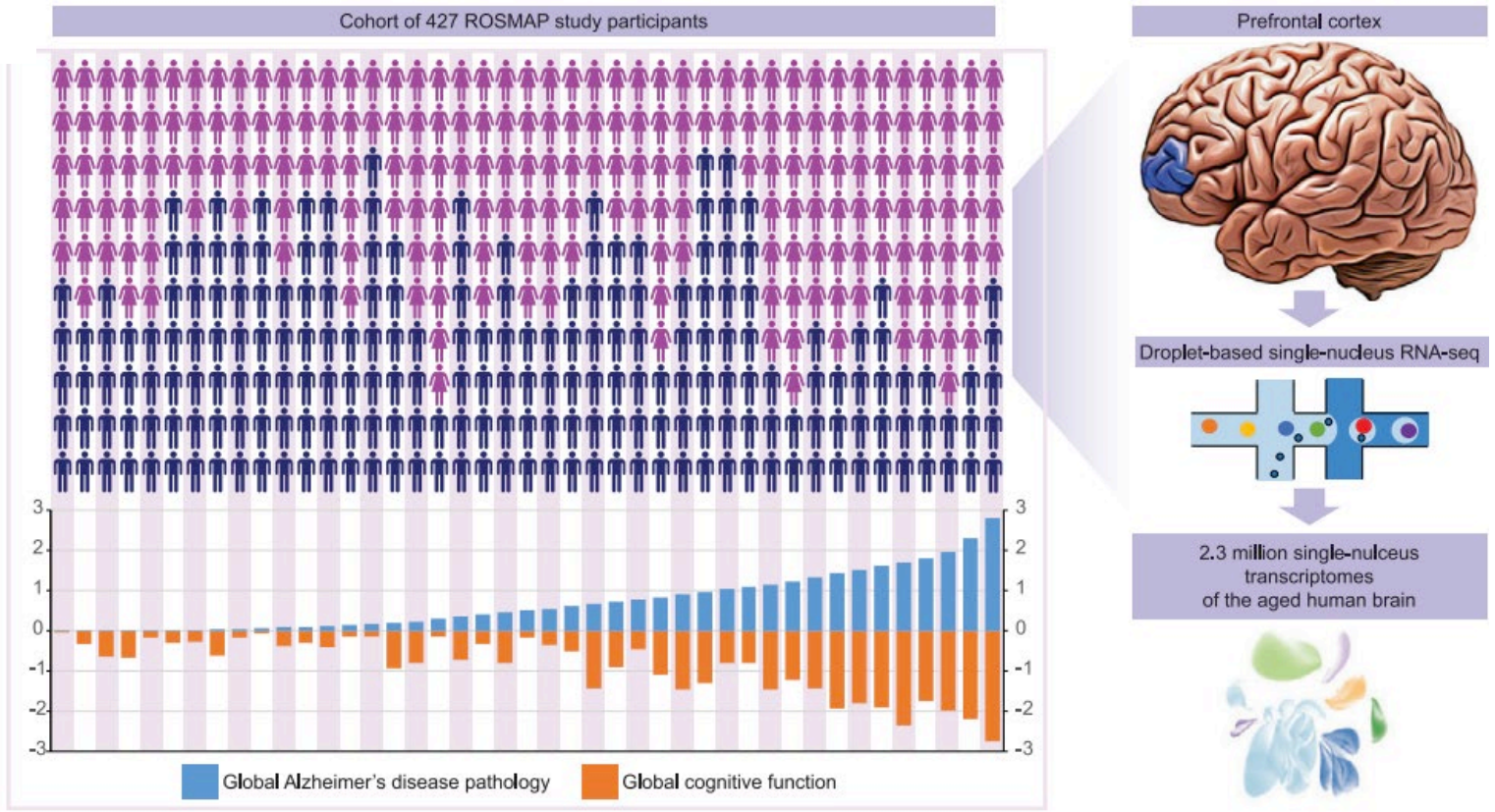
Cell

CellPress
OPEN ACCESS

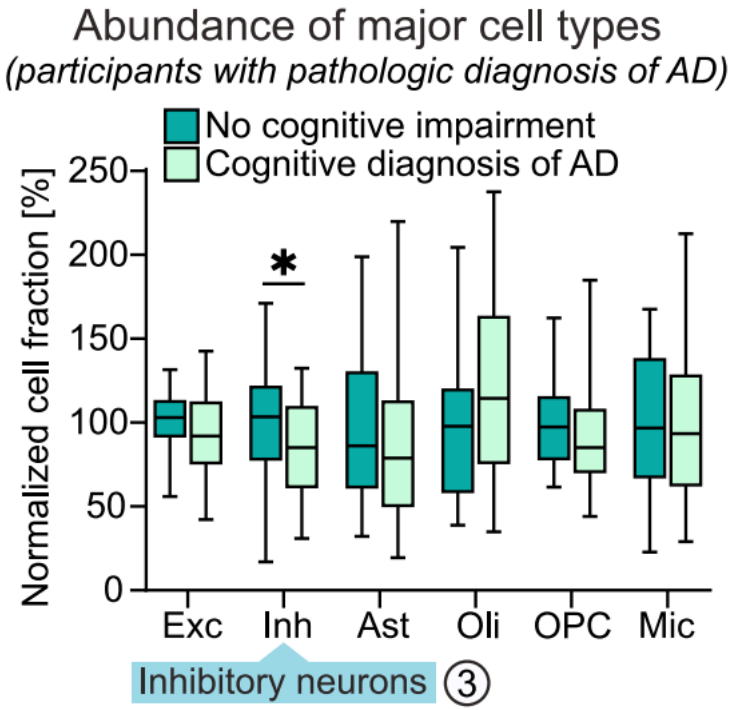
Article

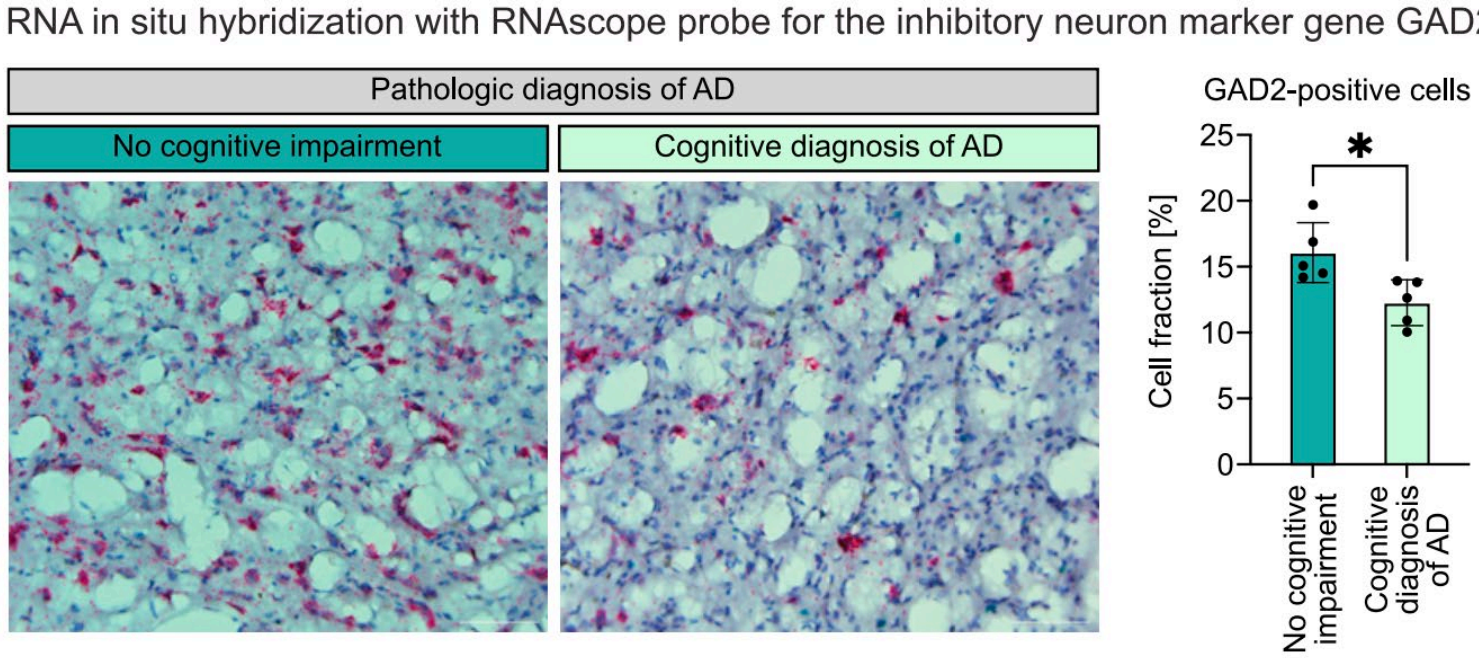
Single-cell atlas reveals correlates of high cognitive function, dementia, and resilience to Alzheimer's disease pathology

Hansruedi Mathys,[1,2,3,7,8,*] Zhuyu Peng,[1,2,8] Carles A. Boix,[4,5,8] Matheus B. Victor,[1,2] Noelle Leary,[1,2] Sudhagar Babu,[3] Ghada Abdelhady,[3] Xueqiao Jiang,[1,2] Ayesha P. Ng,[1,2] Kimia Ghafari,[3] Alexander K. Kunisky,[3] Julio Mantero,[4,5] Kyriaki Galani,[4,5] Vanshika N. Lohia,[3] Gabrielle E. Fortier,[3] Yasmine Lotfi,[3] Jason Ivey,[3] Hannah P. Brown,[3] Pratham R. Patel,[3] Nehal Chakraborty,[3] Jacob I. Beaudway,[3] Elizabeth J. Imhoff,[3] Cameron F. Keeler,[3] Maren M. McChesney,[3] Haishal H. Patel,[3] Sahil P. Patel,[3] Megan T. Thai,[3] David A. Bennett,[6] Manolis Kellis,[4,5,7,*] and Li-Huei Tsai[1,2,5,7,9,*]



Inhibitory neuron survival is associated with preservation of cognition in the presence of pathology





What are the molecular regulators of interneuron survival in resilient patients?

Mathys et al. *Cell* 2023

No studies to date have assessed other domains of resilience in aging or aging-related disorders

INVITED COMMENTARY

WILEY

Molecular underpinnings of physical activity and resilience: A brief overview of the state-of-science and research design needs

Jennifer N. Baumgartner[1] | Bramaramba Kowtha[1] | Gabriela Riscuta[2] | Anil Wali[3] | Yunling Gao[4]

RUSH

The role of epigenetics in psychological resilience

Demelza Smeeth, Stephan Beck, Elie G Karam, Michael Pluess

Readouts of physical resilience →

Motor function	Motor function composite - Average of 10 tests
Motor dexterity	Motor function partial composite: Dexterity
Motor gait	Motor function partial composite: Gait
Motor hand strength	Motor function partial composite: Hand strength
Average total daily activity	Actical activity measure - Average total daily activity (MAP only)
Average daily activity per active hour	Actical activity measure - Average activity per hour of activity (MAP only)
Average daily inactivity	Actical activity measure - Average percentage of day without activity (MAP only)
BMI	Body mass index
Physical activity (5 items)	Hours of physical activity in late life - Sum of 5 items

Readouts of psychological resilience →

Clinical depression	Diagnosis of major depressive disorder made by clinician based on clinical review
Depressive symptoms	Measure of depressive symptoms (Modified CES-D)
Neuroticism	Neuroticism from NEO Five-Factor Inventory - Sum of 12 items
Extraversion	Extraversion from NEO Five-Factor Inventory - Sum of 6 items
Openness	Openness from NEO Five-Factor Inventory - Sum of 12 items (ROS only)
Agreeableness	Agreeableness from NEO Five-Factor Inventory - Sum of 12 items (ROS only)
Conscientiousness	Conscientiousness from NEO Five-Factor Inventory - Sum of 12 items

Challenges and limitations to translating insights from single-cell studies

- Limited definition of resilience in post-mortem tissue
  - Cognitive testing prior to death, with variable timing of last testing to tissue harvesting
  - Pathological burden determined post-mortem
- Variable definitions of resilience across multiple studies
  - Some transcriptional studies define resilience and non-resilience as binary states
  - Others define it as a continuous spectrum
- RNA is unstable in post-mortem tissues (combination of degradation and ischemia-induced changes)
- High technical variability in methodologies, platforms and analytical pipelines employed all result in different biological conclusions being made in different studies
  - We need more meta-analysis-esque studies that integrate data
- Translating post-mortem discovery into diagnostic and therapeutic interventions

Acknowledgements

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

- Environmental and Social Epigenetics (EASE) group, past and present
  - Alexis Davison
  - Juan Santoyo
  - Ying Zhou
  - Erica McNamara
  - Karim Abdelaal
  - Scarlett Barker
  - Fatima Gunther-Rahman
  - Noah Milman
- Professor Li-Huei Tsai
- Professor Stuart Lipton (Scripps)
- Professor Manolis Kellis (MIT)
  - Carles Boix
- Professor David Bennett (Rush)
- Division of Newborn Medicine
  - Stella Kourembanas
  - Kristie Leeman
  - Admin Team (Sarah, Steph, Brianna, Aleshia, etc..)
- Boston Medical Center, Department of Pediatrics
  - Vincent Smith
  - Kate Michelson
- The mice and patients that enable our research
- The families and children that inspire our work

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