Brain donation: Final diagnosis and relevance

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Why is brain donation important?

Diagnosis, Research, Education
Brain donation: Final diagnosis

- Make a **definitive diagnosis** of neurodegenerative disease with 100% certainty
- **Grade the severity** of the neuropathological changes
- In most cases, reveal **mixed pathologies** and comorbidities
Brain donation: Final diagnosis

Causes of dementia

- Mixed pathologies in brains with dementia are more prevalent than we thought:
  - Vascular + Neurodegenerative
  - Mixed Neurodegenerative
Alzheimer’s disease

Amyloid-β

Tau

Lewy Body Disease

α-Synuclein

TDP43

FTD

Mixed pathologies: Prevalence

- Increasingly recognized to be frequent, particularly in older people

Alzheimer

Lewy Body Disease

Robinson et al., Brain 2018
Mixed pathologies: Relevance

- Can impact the progression of disease (more rapid course)
- Knowledge needed to evaluate the efficacy of clinical trials and the response to therapies
Healthy donors are needed to study normal aging

Resilience: Brains of cognitively normal older people often have pathology. Why people with Alzheimer’s disease pathology have no dementia?
  - Initial stages of the disease?
  - Slow progression?
  - Compensatory/adaptative mechanisms

Brain donation: Healthy individuals
Brain donations are helping dementia research

MARVL lab: We are using artificial intelligence and computer vision to improve pathology diagnosis and link the pathology to blood, CSF, and radiology images to allow earlier diagnosis.

Hippocampus from patient with dementia (left) and schematic artificial neural network (right).
Brain donations are helping dementia research.

Cobos Lab: Why are some neurons more vulnerable or resistant to disease?

Cobos Lab
https://med.stanford.edu/coboslab.html

Neurons with and without tangles in advanced dementia
Studying neurons with and without tangles at single-cell resolution

Frozen tissue
Alzheimer’s Disease

Single-cell isolation

Innovative technologies:
single-cell RNA sequencing

Identify the precise neuronal subtypes that are vulnerable or resistant

Measure gene expression in thousands of individual neurons

ADRC
for healthy brain aging

Neurons with tangles
(~ 5–8%)

Tau+

cell type 1
cell type 2
cell type 3
cell type 4
cell type 5

Tau−

Pacific Udall Center
NIH Center of Excellence for Parkinson’s Disease Research
Data analysis using bioinformatics

Combined data from 29 donors (healthy controls and full spectrum of AD) 
~ 90,000 cells

*Each dot*: one cell  
*Each color*: one type of cell

**Data available for each cell:**
- Demographic (age, sex, race)  
- Clinical data  
- Neuropathologic data  
- Gene expression levels

Inma Cobos, MD,PhD
Single-cell studies in human brains can help us to:

• Identify the earliest pathogenic events in dementia
• Identify mechanisms that can contribute to the protection and repair of neurons
• Identify novel therapeutic strategies

Inma Cobos, MD, PhD
Thank you!

Brain donor program at Stanford:

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