Airborne Metals, Neurodegeneration, and Dementia in the Adult Changes in Thought Study

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Overall Study Aims

Examine associations & pathways: $PM_{2.5}$-metal exposure vs. dementia-associated neuropathology (DAN).

- **Aim 1 – Metals analysis:** Characterize $PM_{2.5}$ and associated metal levels within donor brains and olfactory bulbs (OBs)

- **Aim 2 – Neuropathology:** Measuring $PM_{2.5}$ metals and examining associations with DAN pathology

- **Aim 3 – Epidemiology analysis:** Assessing association between ambient $PM_{2.5}$ metals and Incident dementia and cognitive performance
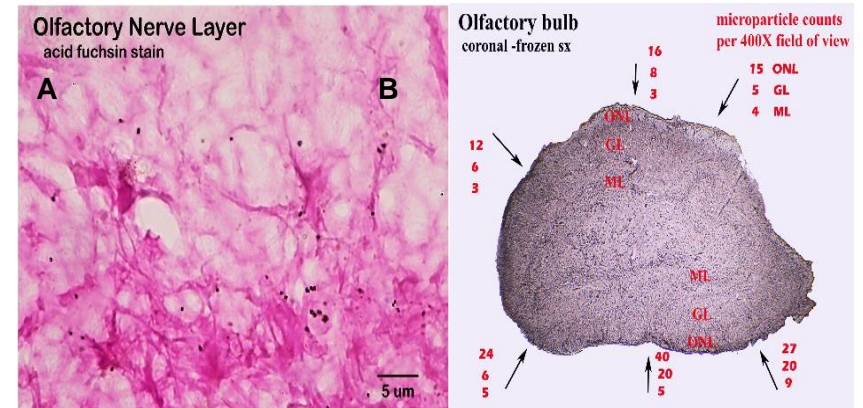
Conceptual Design
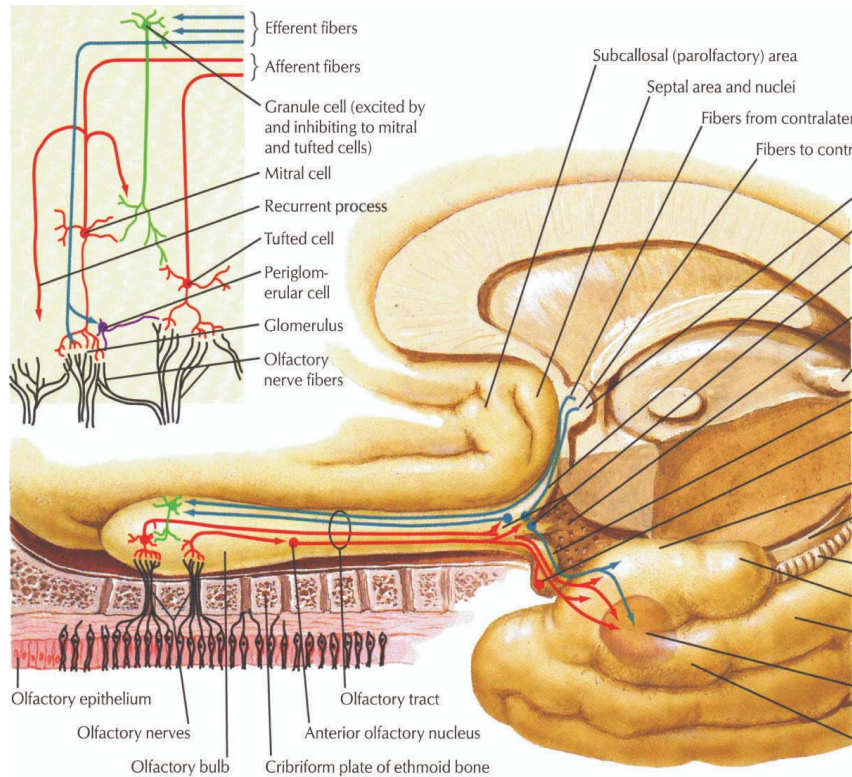
The Neurology of Olfaction. 2009, editors. CH Hawkes & RL Doty. Cambridge University Press pp 1-58.
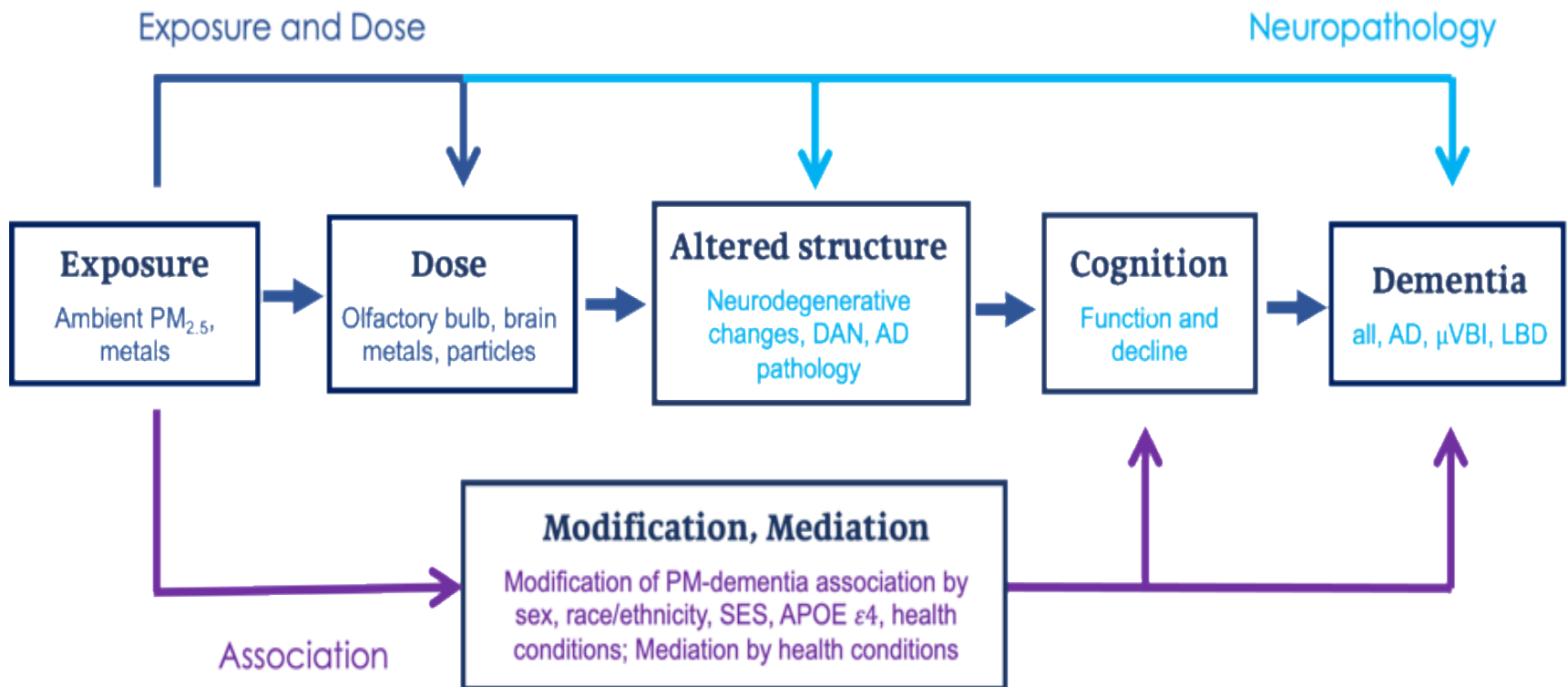
Figure 1. *Study Design*
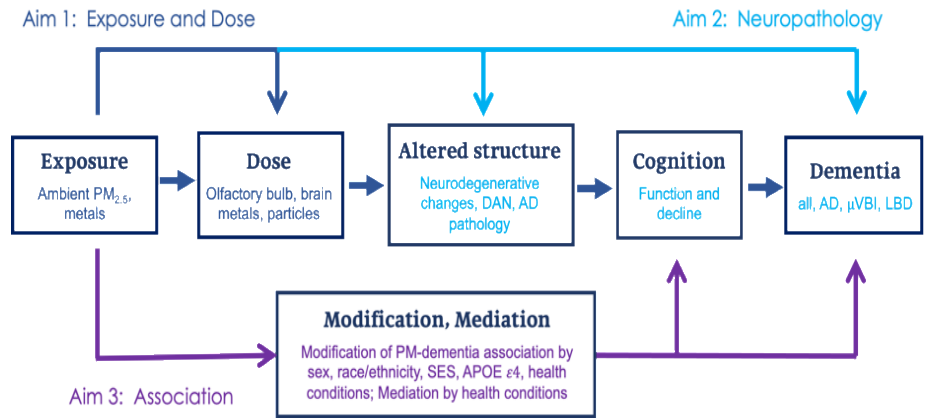
Preliminary Dara

Specific Aims and Study Design

Aim 1: Metals analysis

Frozen OBs analyzed for metals by Kurt Pennell at Brown

- **N=33 archived,140 prospective**

Projected Number Clinical and Pathological Characteristics of ACT Participants

Clinical diagnosis	n	%
Demented	66	47
Nondemented	74	53
Pathological diagnosis	**n**	**%**
Alzheimer's disease	48	34
Microinfarcts	29	21
Lewy bodies (any region)	18	13
AD + Microinfarcts	11	8

- **2 methods of measuring PM$_{2.5}$ metals in frozen tissue**

  - NexION 2000 ICP-MS system

| Location	Concentration in Tissue (ug/g)											
	Al	As	Be	Co	Cr	Cu	Fe	Ni	Pb	Se	Va	Zi
Left OB	22.8	0.85	0.08	0.03	0.85	4.04	22.9	0.16	0.07	1.03	2.81	7.21
Right DB	24.3	0.78	0.11	0.07	0.78	3.40	19.9	0.06	1.71	0.69	2.57	5.63

  - Scanning electron microscope(SEM) with energy dispersive x-ray spectroscopy (EDS)

Aim 2: Neuropathology

- RedPATH Database

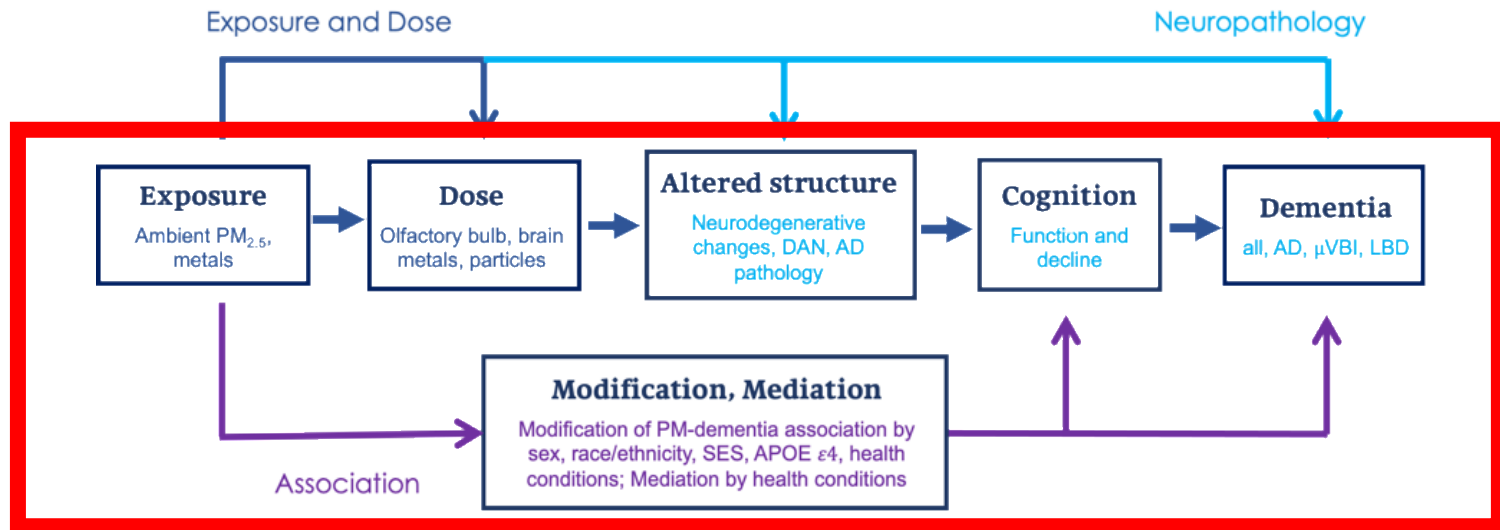|	RedPATH	ACT	Received
Demographic	24	11	52
APOE3/4	1	1	0
Diagnostic	57	7	57
Gross	12	2	24
Microscopic	446	2	1,143

- Standard NP indices
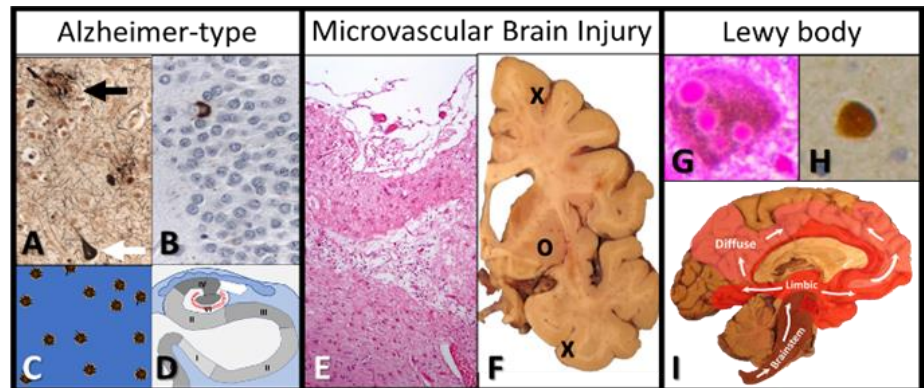
# Aim 2: FFPE - Block A13

- Blocks available: Amygdala & OB (specimens)

- Currently assessed
  - Other tau pathology
  - Other SCNA pathology

- Assessed as part of our study
  - Beta-amyloid
  - Innate immune markers

# Aim 3: Epidemiological Analyses

To quantify associations between ambient PM$_{2.5}$ and associated metals with dementia (all, subtype) and cognitive performance **for all participants**, controlling for confounders

Aim 3: Epidemiological Analyses
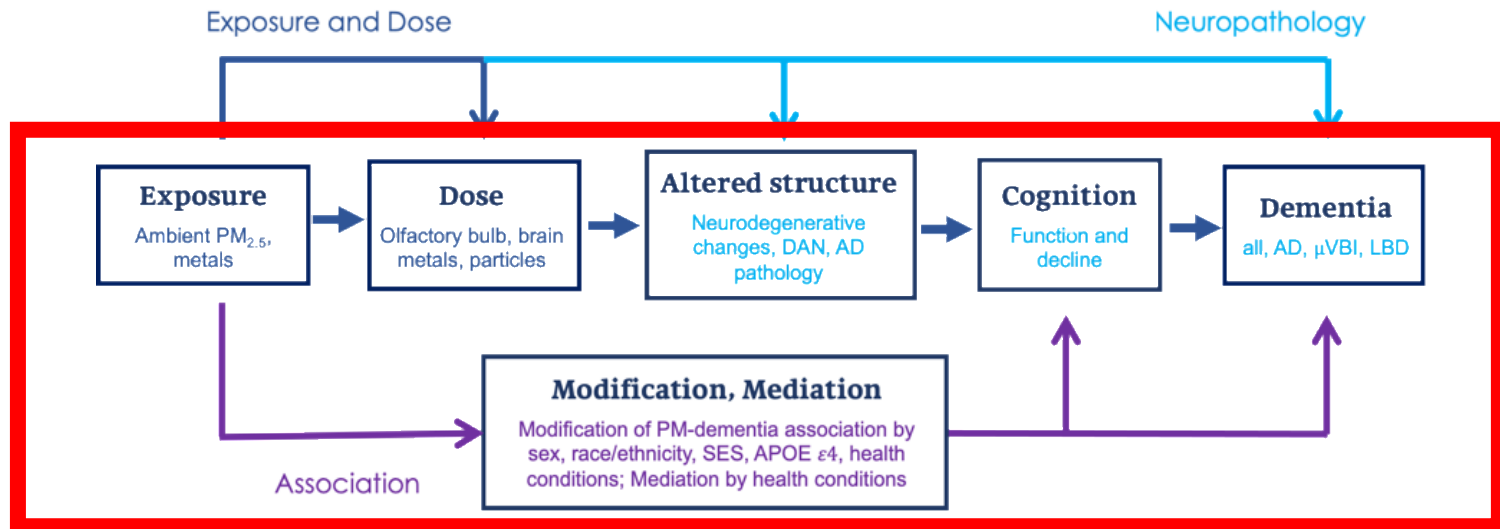
To quantify associations between ambient PM$_{2.5}$ and associated metals with dementia (all, subtype) for **subset of participants with gold standard dementia diagnoses via autopsy**

Aim 3: Epidemiological Analyses
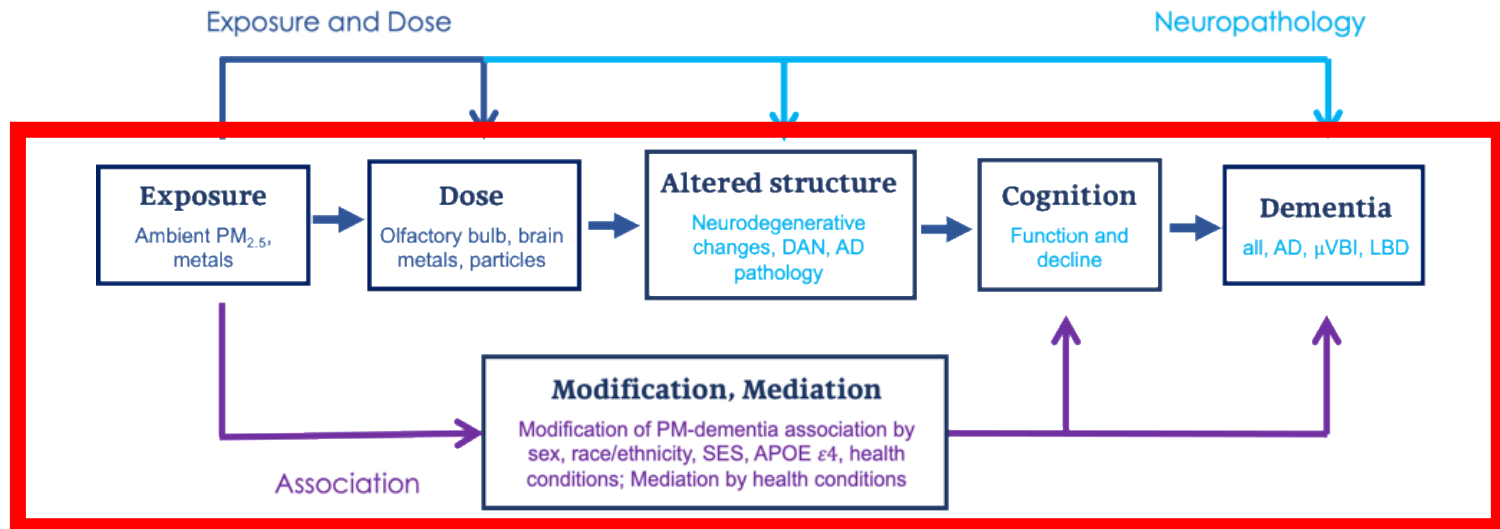
To examine **effect modification** by sex, race/ethnicity, health status, and APOE and **mediation** by prior health conditions

1st Year Activities

- **Aim 1: Analysis of olfactory bulbs (OB) for metals**
  - o OBs sent to Kurt Pennell at Brown to be analyzed for metal-specific content
  - o Sample methods evaluated and adjusted as necessary
- **Aim 2: Neuropathology**: Data obtained, analyses underway
- **Aim 3: Epidemiological analysis (Aim 3):**
  - o *Spatio-temporal modeling:* Development of models to estimate participant-specific ambient $PM_{2.5}$ component exposures underway
  - o *Data use agreement* in preparation to allow sharing of ACT data at ZIP code level
- **Coordination and Collaborations**:
  - o *OB/brain sample* retrieval and analysis (Aim 1, 2)
  - o *Data linkage*: Exposure estimates for each ACT participant based on residential address, levering previous work of Lianne Sheppard's group; preparation to allow such linkage is underway
  - o *Data sharing*: Sharing of data and results (e.g., for participant-specific exposure estimates) will be performed following standard protocols
  - o *Data coordination*: All activities will be coordinated with parent and relevant other ACT studies, such as Magali Blanco's anticipated NIH K award
- **Communications:** Monthly group meetings, smaller team meetings

Study Team

Tufts University: Helen Suh (Co-PI)

Arkana Labs & McGill MNI: Josh Sonnen (Co-PI)

Adult Changes in Thought: Eric Larsson

Brown University: Kurt Pennell

Northeastern University: Trent Honda

University of Washington: Adam Szpiro

Collaborators: C. Dirk Keene, Paul Crane, Magali Blanco