

Air Pollution and Parkinson's Disease

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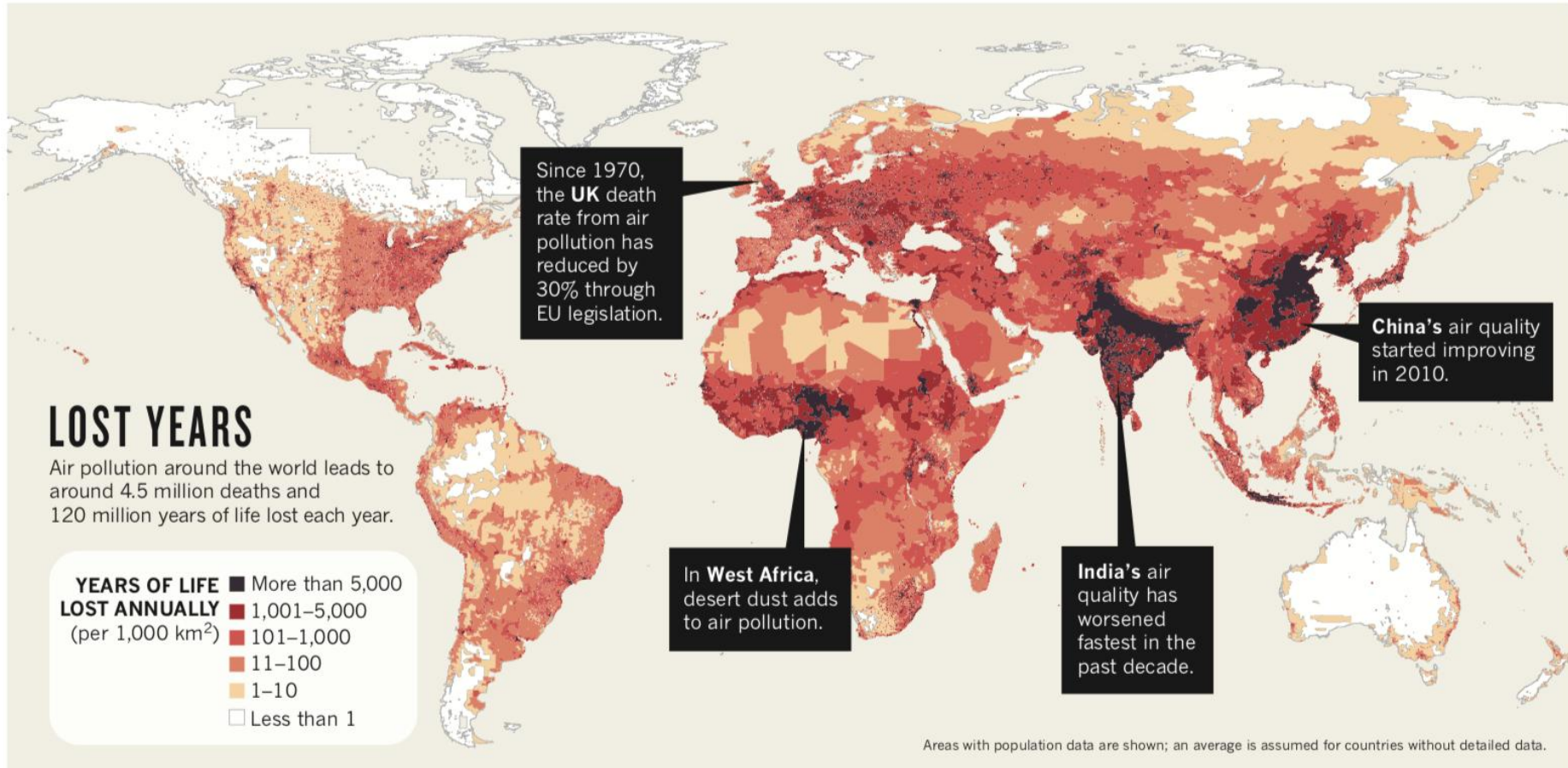
Director of Movement Disorders

Disclosures

Nothing to disclose

Air Pollution Dramatically Increases Mortality

SOURCES: WHO/REF. 5





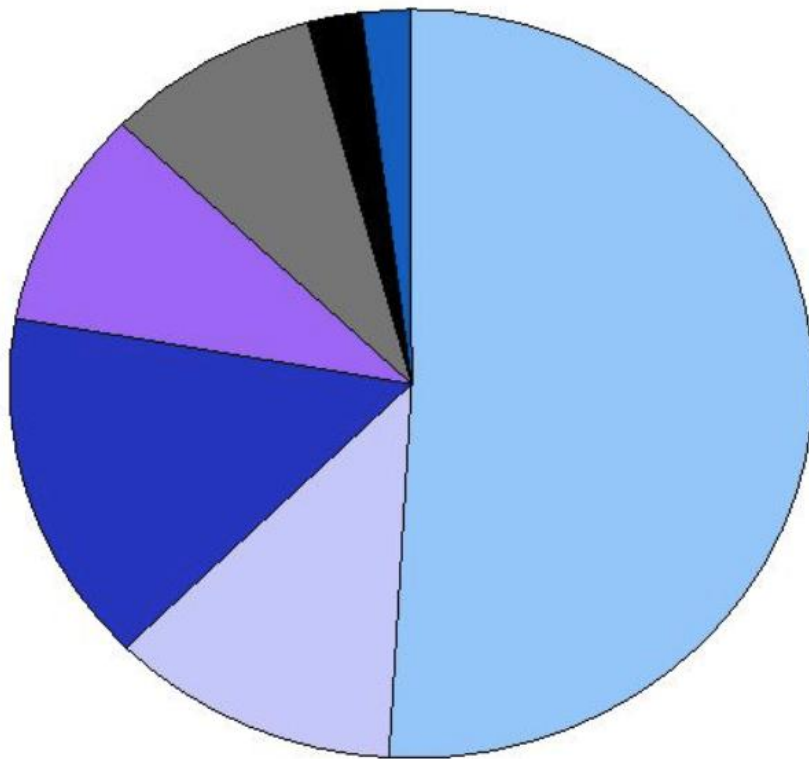
THE POLLUTED BRAIN

The microscopic particles sifting from freeways and power plants don't just harm your heart and lungs. They may also attack your brain

By Emily Underwood, in Los Angeles, California

Types and Sources of Air Pollution

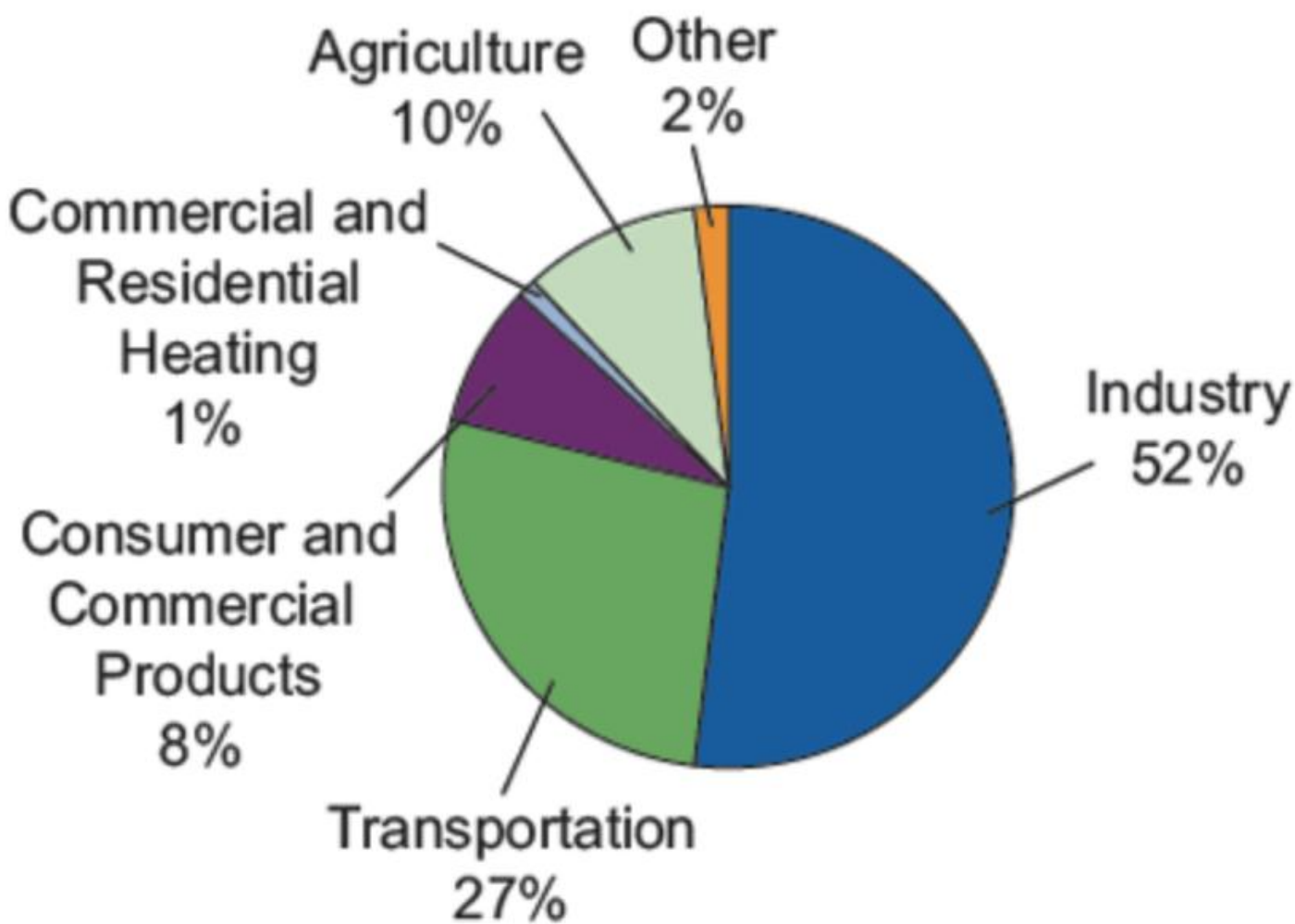
Primary Air Pollutants



- Carbon monoxide
- Nitrogen oxides
- Particulates
- Volatile organics
- Sulfur dioxide
- Ammonia
- Lead



Sources of Emissions of Air Pollutants



Air Pollution and Neurological Disorders

- Stroke: Increased incidence and mortality
 - Estimated 9% of stroke disability years and 8.5% of stroke deaths could be due to PM_{2.5} exposure.
 - Higher living near roadway.
 - 1 study showed association with ICH
- Headaches: Increased migraines
- MS: Short-term exposure exacerbation of disease activity. Unclear if it alters incidence.
- ALS: Unclear if it alters incidence
- Dementia: Likely associated with increased incidence.
- Parkinson's disease: Evidence is growing

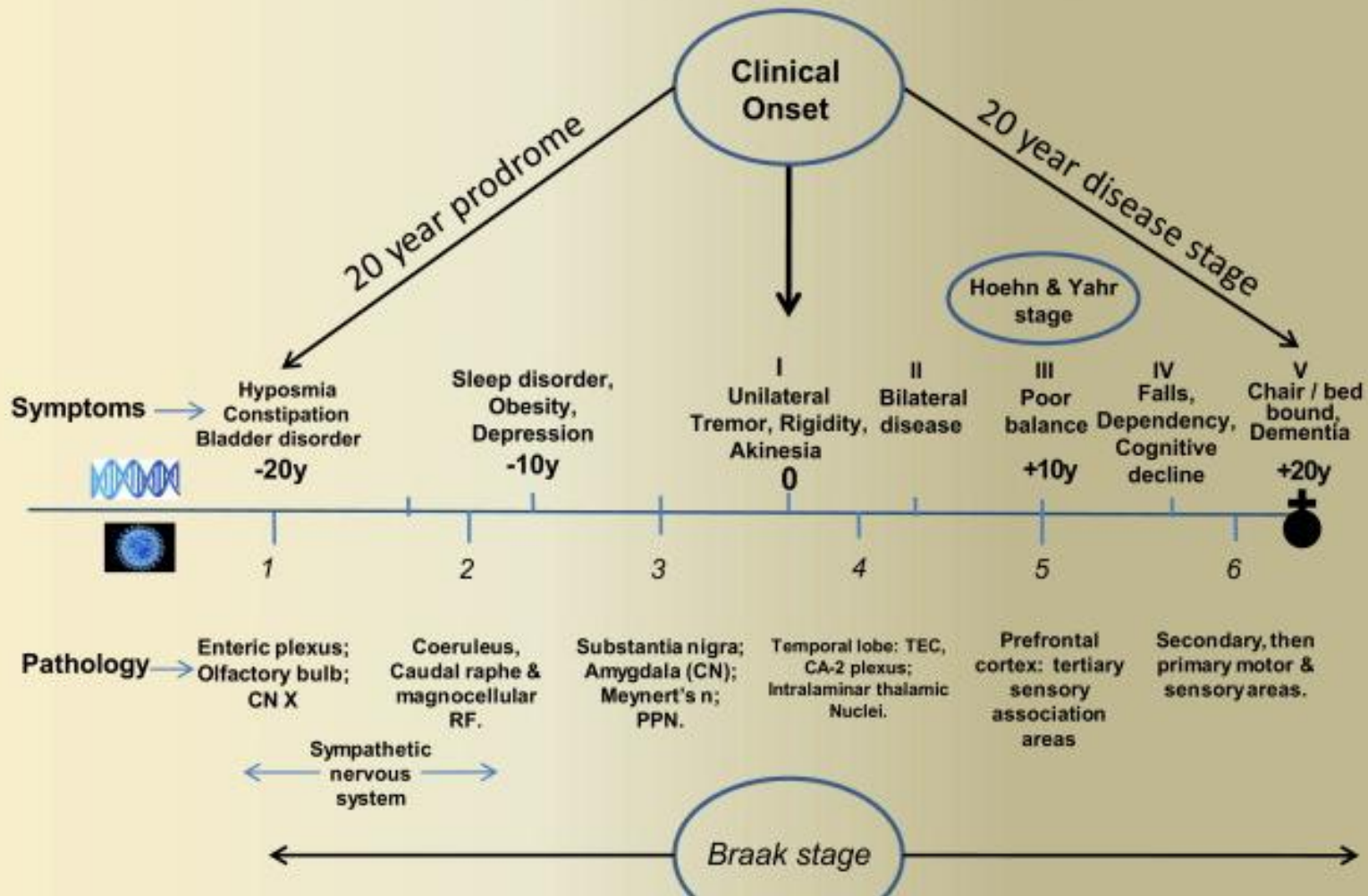
Parkinson's Disease: Why Study the Environment?

- Only approx. 30% of PD can be explained by genetics
- PD pathology starts in the gut and olfactory bulb which are entry points for environmental toxins.

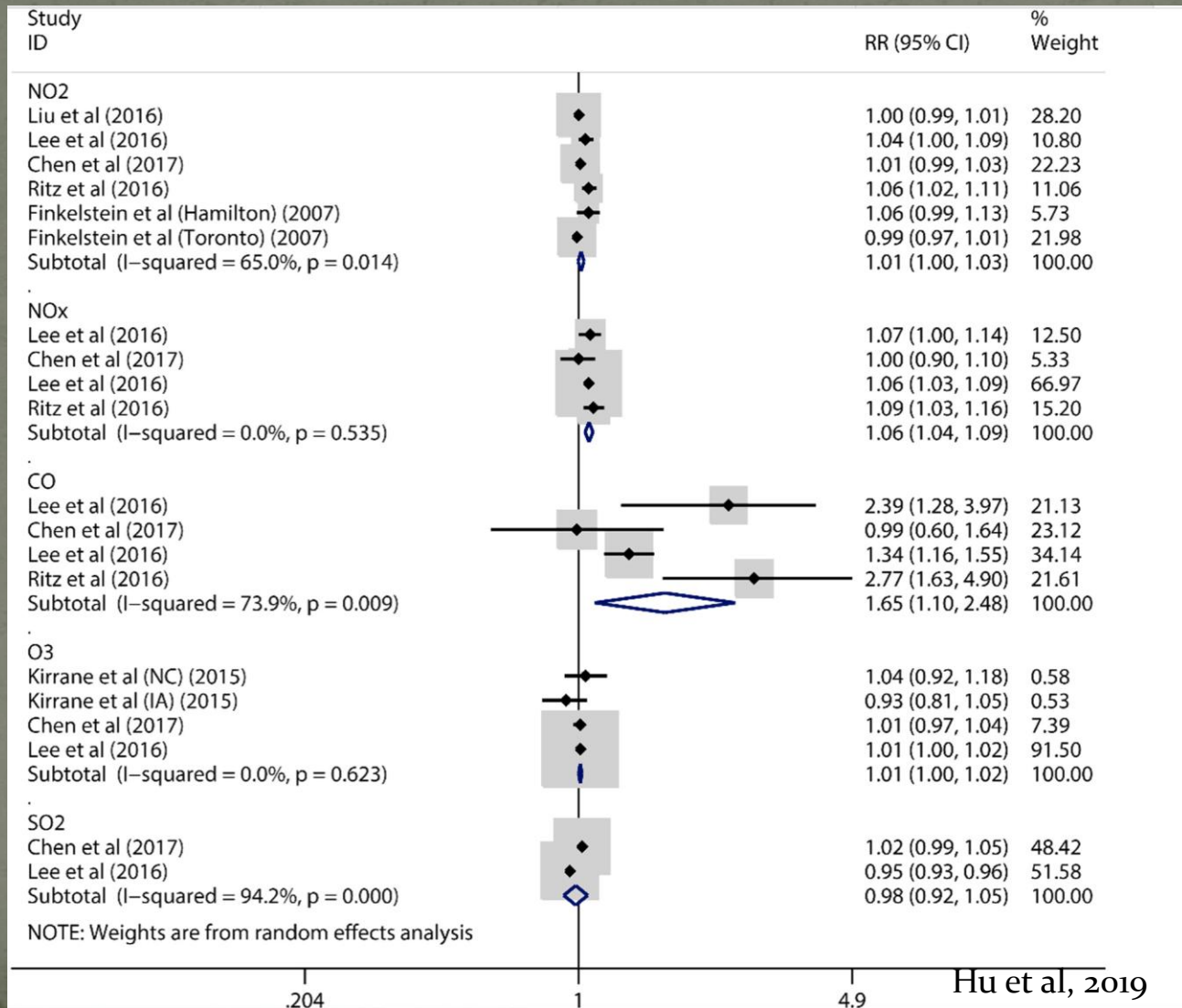
Parkinson's Disease and Air Pollution: Why is it so hard to study?

- PD is relatively rare for genetic and epidemiological studies
- Diagnosis is not always clear early in the disease and by the time you make the diagnosis, the disease process has been going on for decades.
- It is very slowly progressive so it is very difficult to model the disease in animals.

Disease Process Spans Decades



Meta-analysis of AP and PD up to 2019



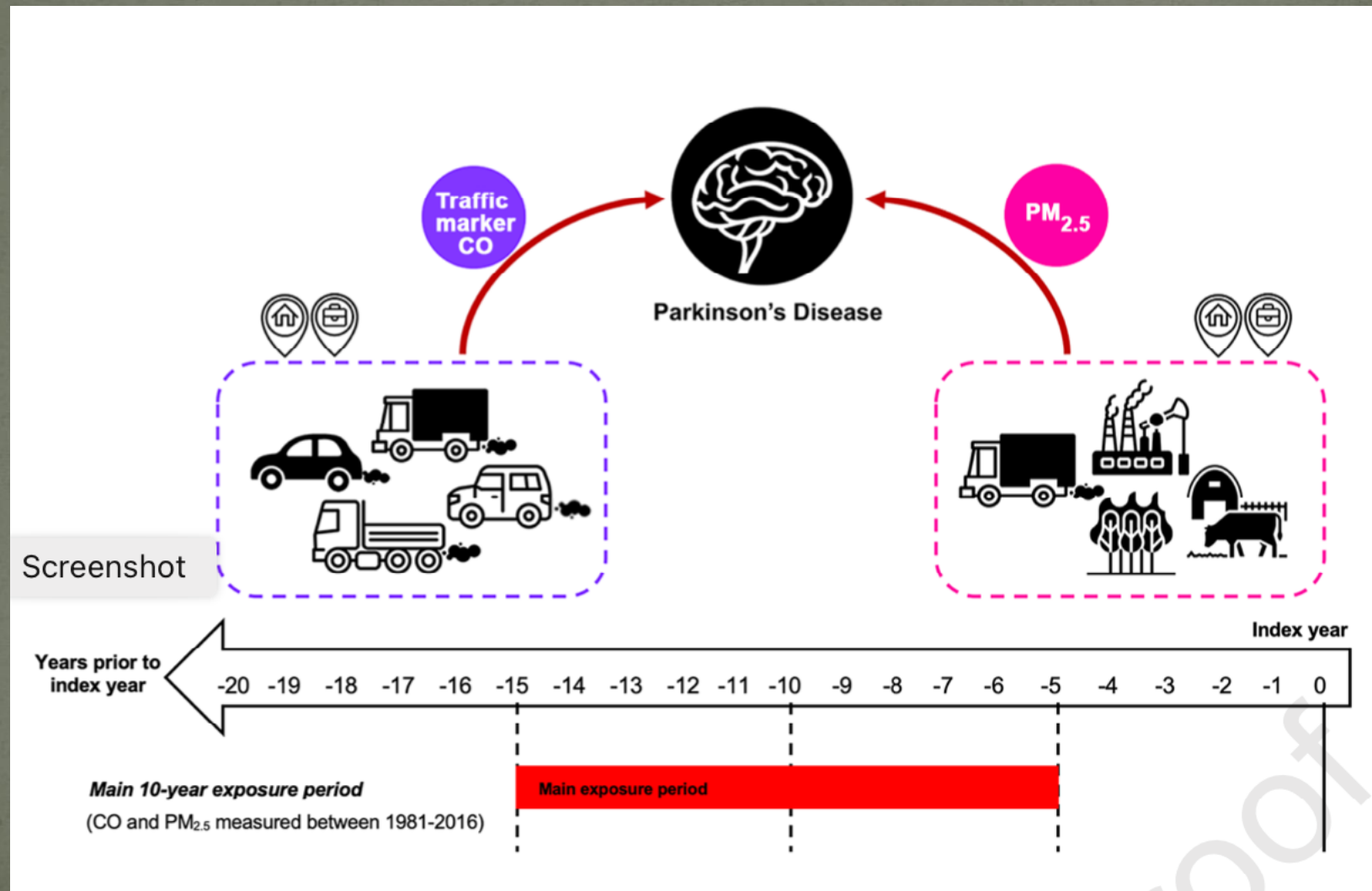
Some Recent Epidemiological Studies



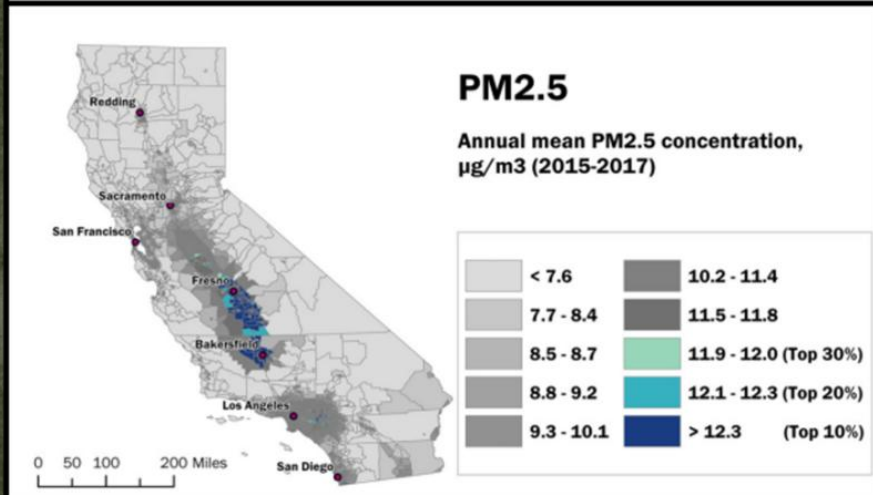
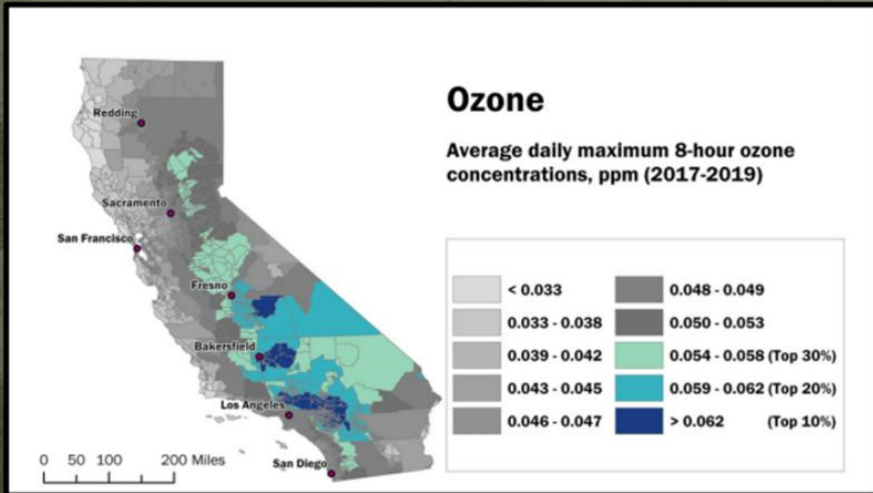
Beate Ritz MD, PhD

Author	Study Design	Population	Exposure Range	Length of Exposure/ Lag time to Ds	OR	Strengths	Weaknesses
Kirrane 2015 ⁹	Case-Control	301 cases in US	O ₃ (ppb): IA mean: 39.0, max: 41.5; NC mean 40.6; max 46.5. PM _{2.5} (µg/m ³): IA mean 8.9; max 11.5; NC mean 12.6; max 17.7	4 years	OR = 1.39 (.98-1.98) for O ₃ ; OR = 1.34 (.93-1.93) for PM _{2.5}	Adjusted for multiple variables including pesticides	Short exposure time, small population
Ritz 2016 ¹⁴	Case-Control	1696 PD cases in Denmark	NO ₂ : 9.8-43.26 µg/m ³ ; NOx: 13.46-181.55 µg/m ³ ; CO: 0.36-2.34 mg/m ³	31 years	NO ₂ : 1.09 per 2.97 µg/m of exposure; NOx: 1.06 per 7.10 ppb of exposure; CO: 1.13 per 0.12 ppm of exposure	Large population, long exposure, adjusted for multiple variables	Low air pollution in Denmark
Lee 2016 ¹⁰	Case-Control	11,117 incident PD cases in Taiwan	PM ₁₀ : 29.3-86.8 µg/m ³ ; NO _x : 5.2-77.6 ppb; O ₃ : 19.0-39.2 ppb; CO: 0.2-1.5 ppm	11 years	OR = 1.37 (1.23-1.52) for CO; OR = 1.17 (1.07-1.27) in multi-pollutant models	Large population, adjusted for age, year of Dx	Short exposure time, adjusted for only a few variables
Lee 2016 ¹¹	Case-Control	408 incident PD cases in Denmark (subset of Ritz 2016)	NO ₂ : 9.8-43.26 µg/m ³ ; NOx: 13.46-181.55 µg/m ³ ; CO: 0.36-2.34 mg/m ³	31 years	OR=3.1 for AA allele of the interleukin-1β gene with high NO exposure	Long exposure, adjusted for multiple variables, gene interaction with air pollution	Small population, low air pollution in Denmark,

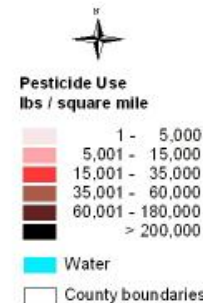
Air Pollution and PD in the Central Valley



Air Pollution in the CA Central Valley and PD



Pesticide Use



Association between 10-year average CO exposure with a 5-year lag time and Parkinson's disease

Residential	Cases/controls	Odds ratio (95% CI)		
		Unadjusted	Model1 ^a	Model2 ^b
Continuous CO (ppb) ^c	688/851	1.07 (1.01, 1.13)	1.08 (1.02, 1.14)	1.08 (1.02, 1.15)
T1 (0.01-2.87)	242/343	Reference	Reference	Reference
T2 (2.88-9.06)	242/292	1.17 (0.93, 1.49)	1.24 (0.97, 1.59)	1.26 (0.98, 1.61)
T3 (9.07-368.00)	204/216	1.34 (1.04, 1.72)	1.40 (1.07, 1.83)	1.47 (1.12, 1.94)
p-trend ^d		0.02	0.01	0.01
Occupational				
Continuous CO (ppb) ^c	336/309	1.02 (0.97, 1.08)	1.05 (0.99, 1.12)	1.05 (1.00, 1.12)
T1 (0.01-2.87)	70/73	Reference	Reference	Reference
T2 (2.88-9.06)	97/97	1.04 (0.68, 1.61)	1.21 (0.76, 1.91)	1.22 (0.77, 1.93)
T3 (9.07-368.00)	169/139	1.27 (0.85, 1.89)	1.72 (1.12, 2.65)	1.77 (1.15, 2.74)
p-trend ^d		0.20	0.01	0.01

^aAdjusted for age, race, sex, education, and study wave.

^bAdjusted as in model 1 plus smoking and pesticide exposure.

^cChange per interquartile range (IQR) of 10.27 ppb.

^dBased on linear model through the tertile medians.

Association between 10-year average PM_{2.5} exposure with a 5-year lag time and Parkinson's disease

Residential	Cases/controls	Odds ratio (95% CI)		
		Unadjusted	Model1 ^a	Model2 ^b
Continuous PM _{2.5} (µg/m ³) ^c	761/910	1.29 (1.14, 1.47)	1.39 (1.21, 1.61)	1.42 (1.22, 1.64)
T1 (0.88-14.50)	245/319	Reference	Reference	Reference
T2 (14.51-17.80)	242/316	1.00 (0.79, 1.26)	1.05 (0.82, 1.34)	1.08 (0.84, 1.38)
T3 (17.81-29.40)	274/275	1.30 (1.02, 1.64)	1.39 (1.06, 1.81)	1.45 (1.10, 1.91)
p-trend ^d		0.03	0.02	0.01
Occupational				
Continuous PM _{2.5} (µg/m ³) ^c	372/352	1.24 (1.03, 1.48)	1.50 (1.22, 1.86)	1.51 (1.22, 1.88)
T1 (0.88-14.50)	110/125	Reference	Reference	Reference
T2 (14.51-17.80)	133/107	1.41 (0.98, 2.03)	1.76 (1.21, 2.59)	1.79 (1.22, 2.65)
T3 (17.81-29.40)	129/120	1.22 (0.86, 1.75)	1.59 (1.06, 2.38)	1.64 (1.09, 2.47)
p-trend ^d		0.28	0.02	0.01

^aAdjusted for age, race, sex, education, and study wave.

Kwon et al 2023 *unpublished*

^bAdjusted as in model 1 plus smoking and pesticide exposure.

Is the Size of the Effect of AP on PD Risk Relevant?

- Since so many people are exposed to air pollution, it could account for a significant percentage of PD cases.
 - If we extrapolate the risk of PD in the Ritz study to the air pollution levels in Los Angeles CA during the 1970s and 80s (i.e. NO_2 , NO_x and CO levels), air pollution could account for up to 70% of the cases

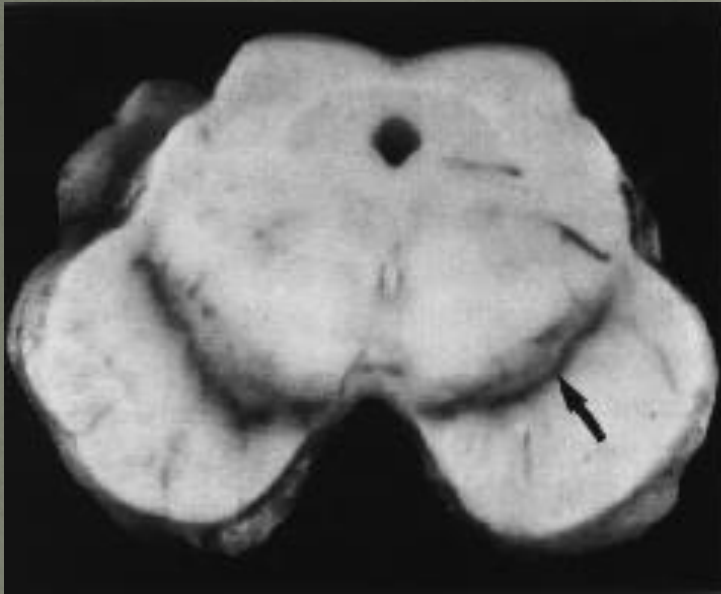
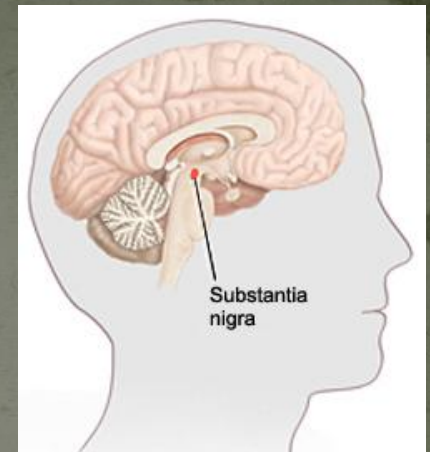
Biological Plausibility; How can AP increase risk?

- Autopsies of people and dogs in high AP regions (Mexico City) showed increased AD/PD pathology and inflammation relative to controls.
- *In vitro*, diesel exhaust extracts cause dopaminergic cell death and inflammation.
- Subacute exposure to diesel exhaust in rodents causes CNS inflammation and increased α -synuclein but does not cause dopaminergic neuronal death.

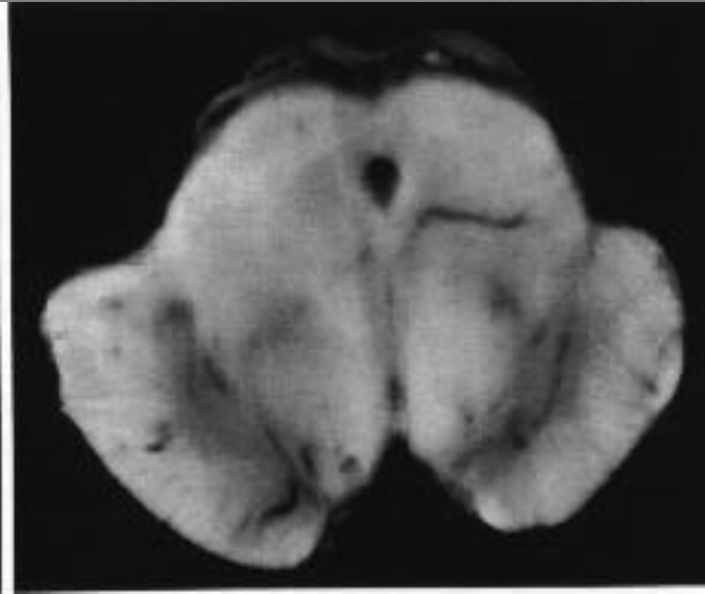
How might Air Pollution Act?

A Brief Review on the Pathophysiology of PD

PD is Characterized by Loss of
Substantia Nigra Neurons but
Pathology is Widespread



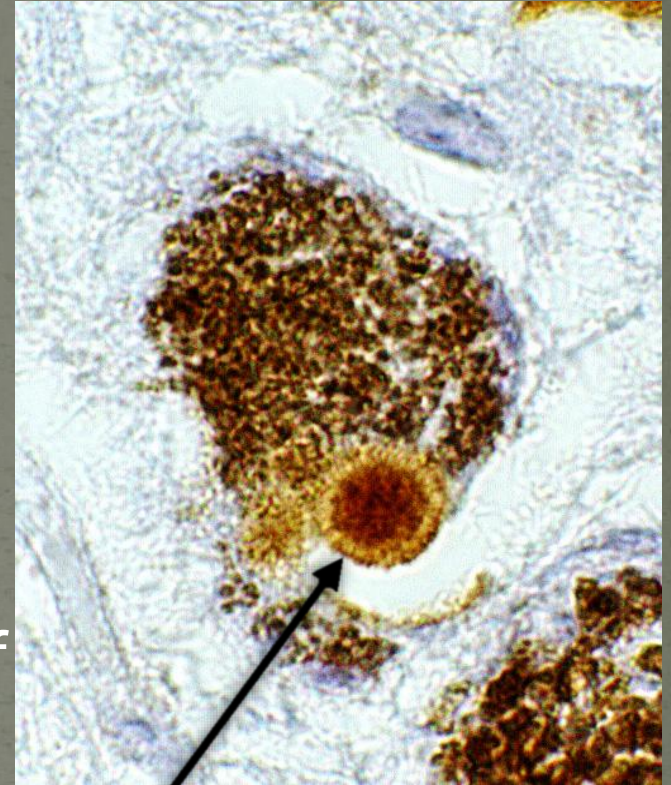
Normal Substantia
Nigra



Substantia Nigra in PD

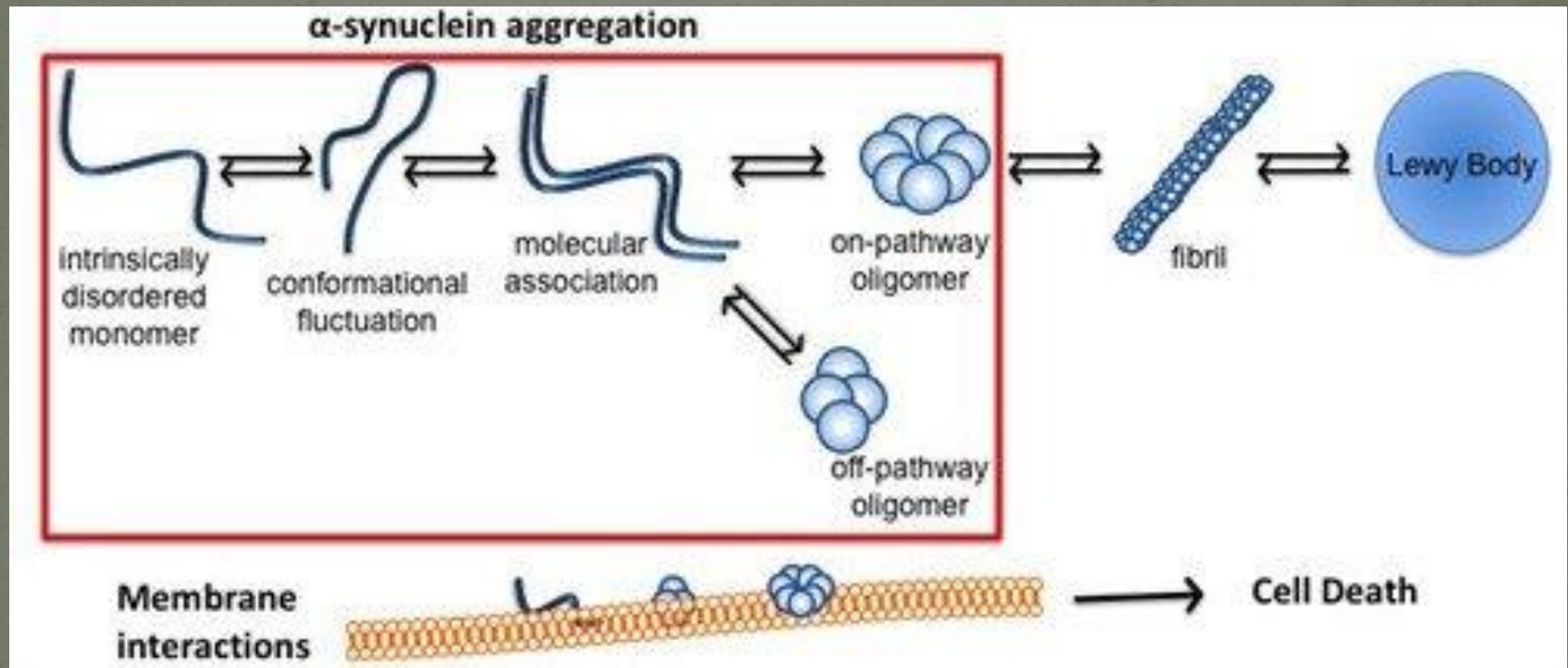
α -Synuclein is Central to PD

- 1st gene linked to PD.
- Point mutations and gene duplication cause typical PD.
- Major component of Lewy Body in sporadic PD.
- Overexpression in animals recreates many of the features of PD.

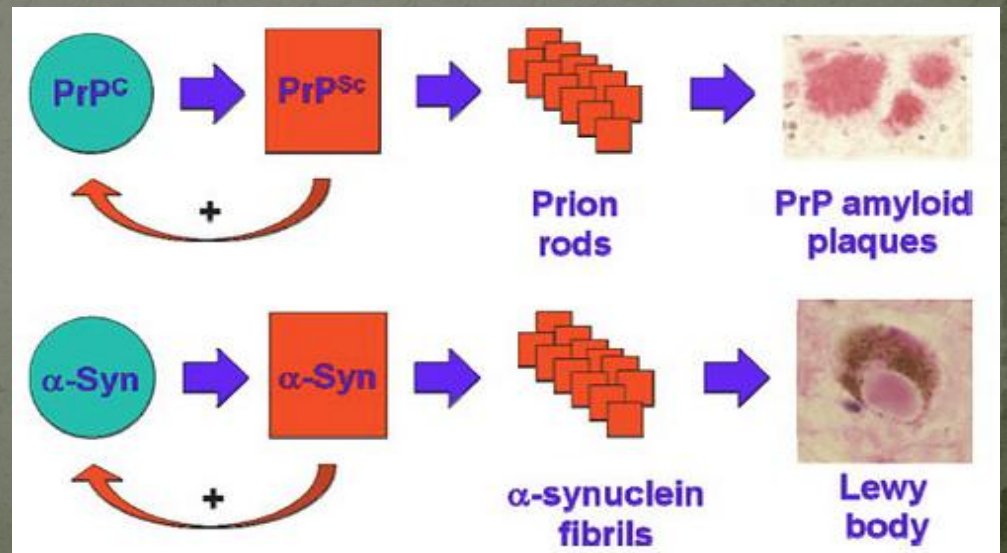
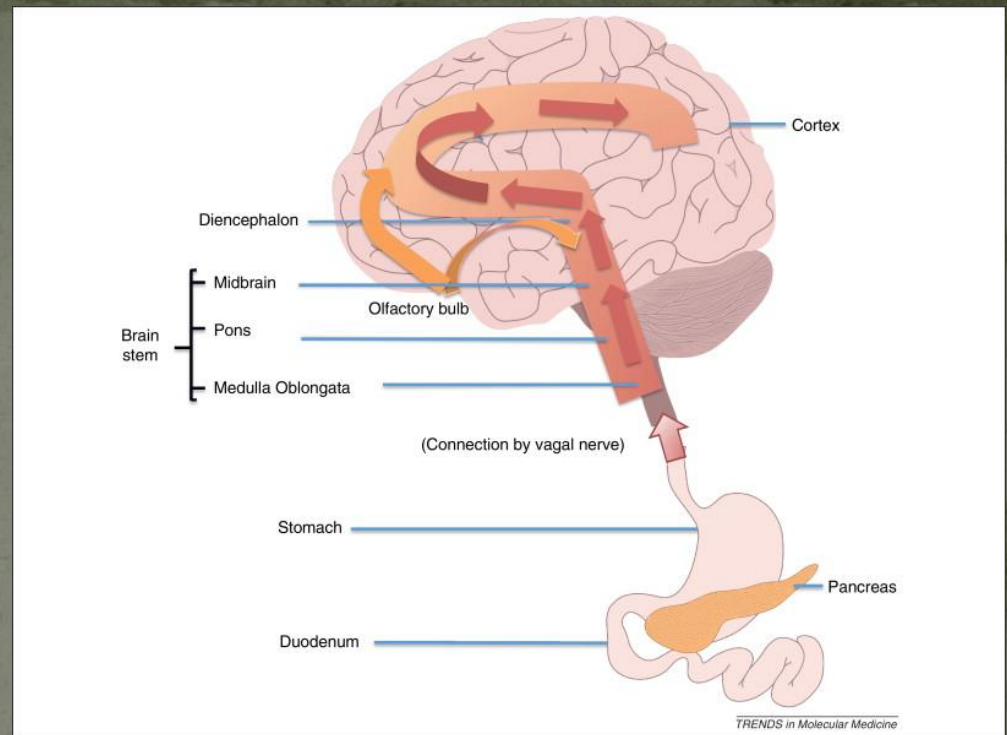


Lewy Body

α -Synuclein Oligomers Confer Toxicity

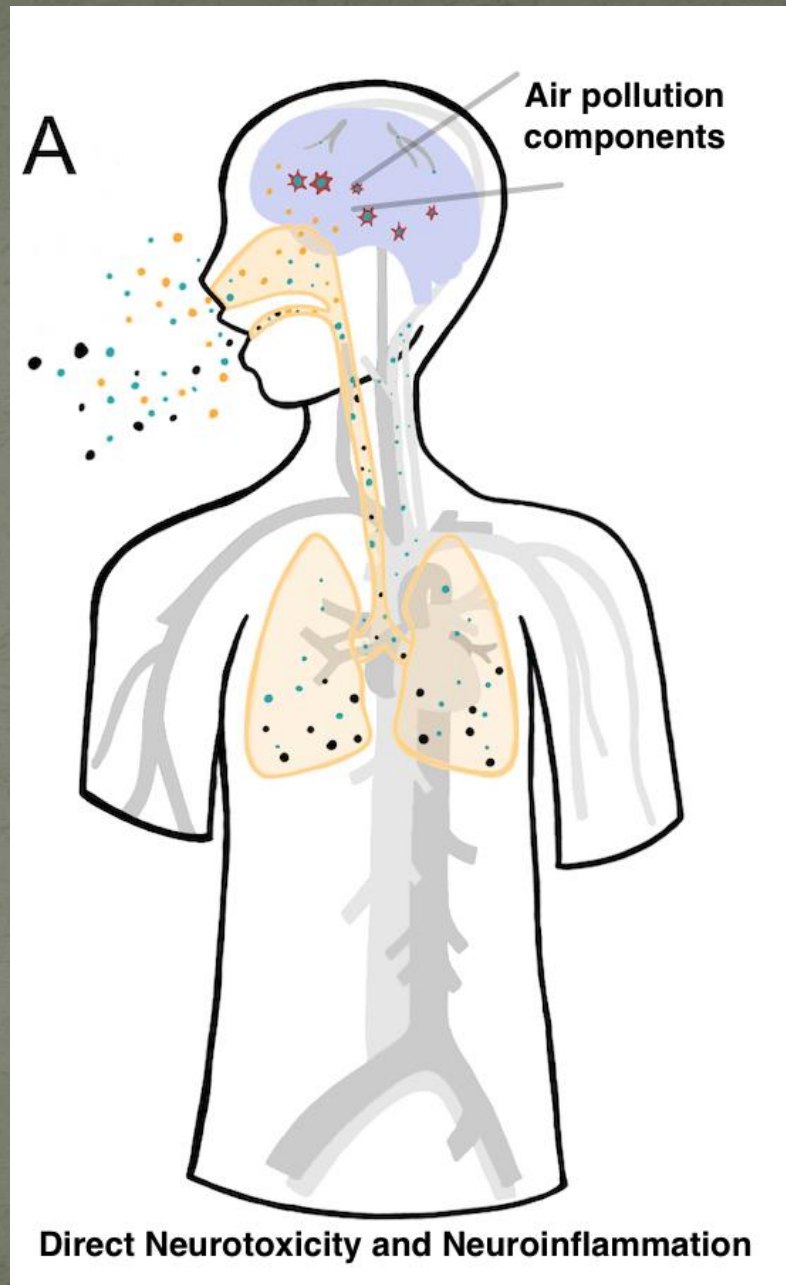


PD appears to start in the gut and/or olfactory bulb and propagate in a prion-like manner



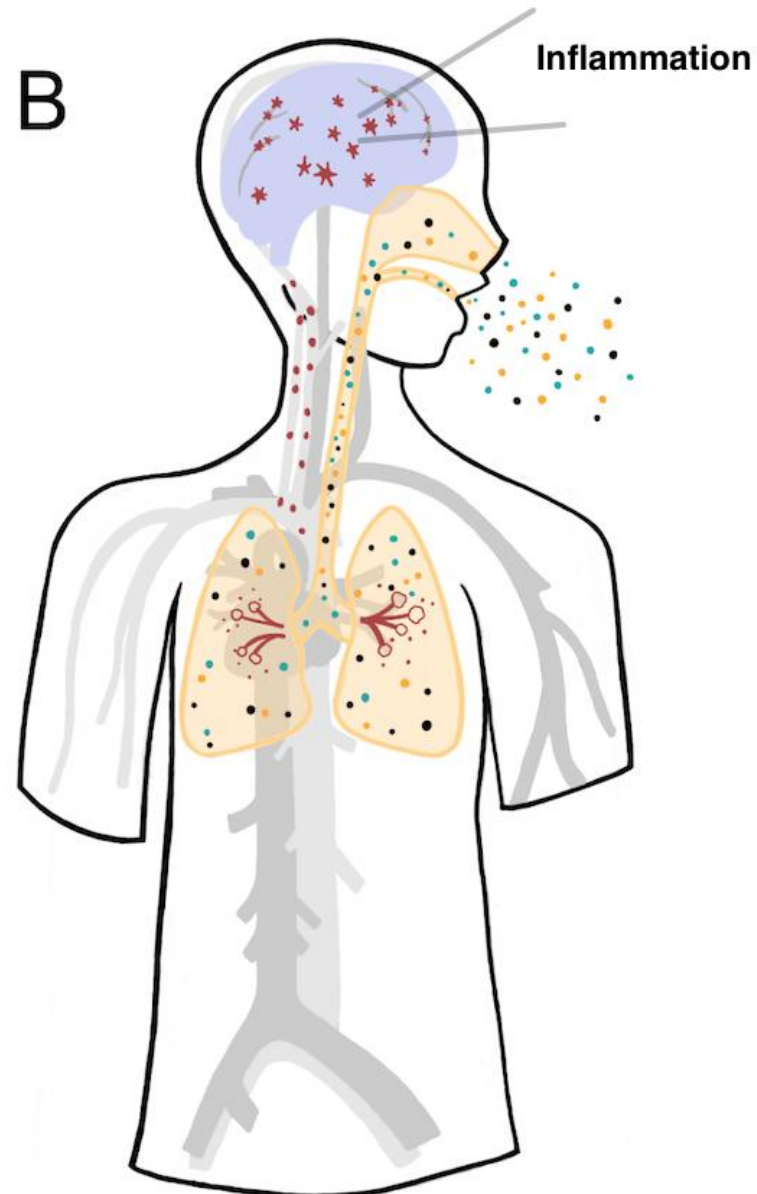
How might AP increase the risk of PD and Dementia?

- Many components of AP reach the brain and can accumulate (PAHs, metals etc.)
- These toxins can be neurotoxic and/or inflammatory



How might AP increase the risk of PD and Dementia?

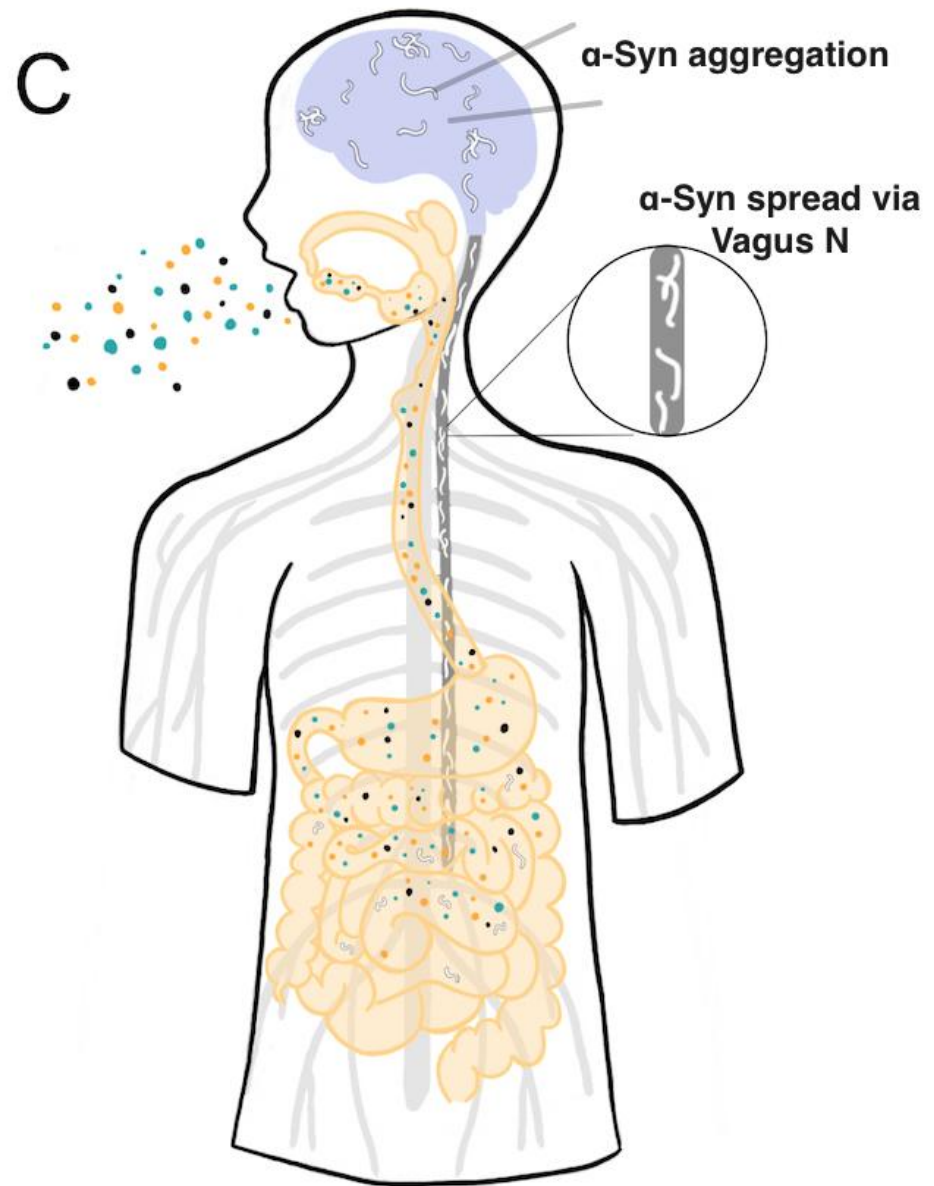
- AP causes systemic inflammation (increased TNF, IL-1 β)
- In animal models, systemic inflammation can cause loss of DA neurons.
- IBD and hepatitis associated with increased risk of PD.



Air Pollution-Lung-Brain Connection

How might AP increase the risk of PD and Dementia?

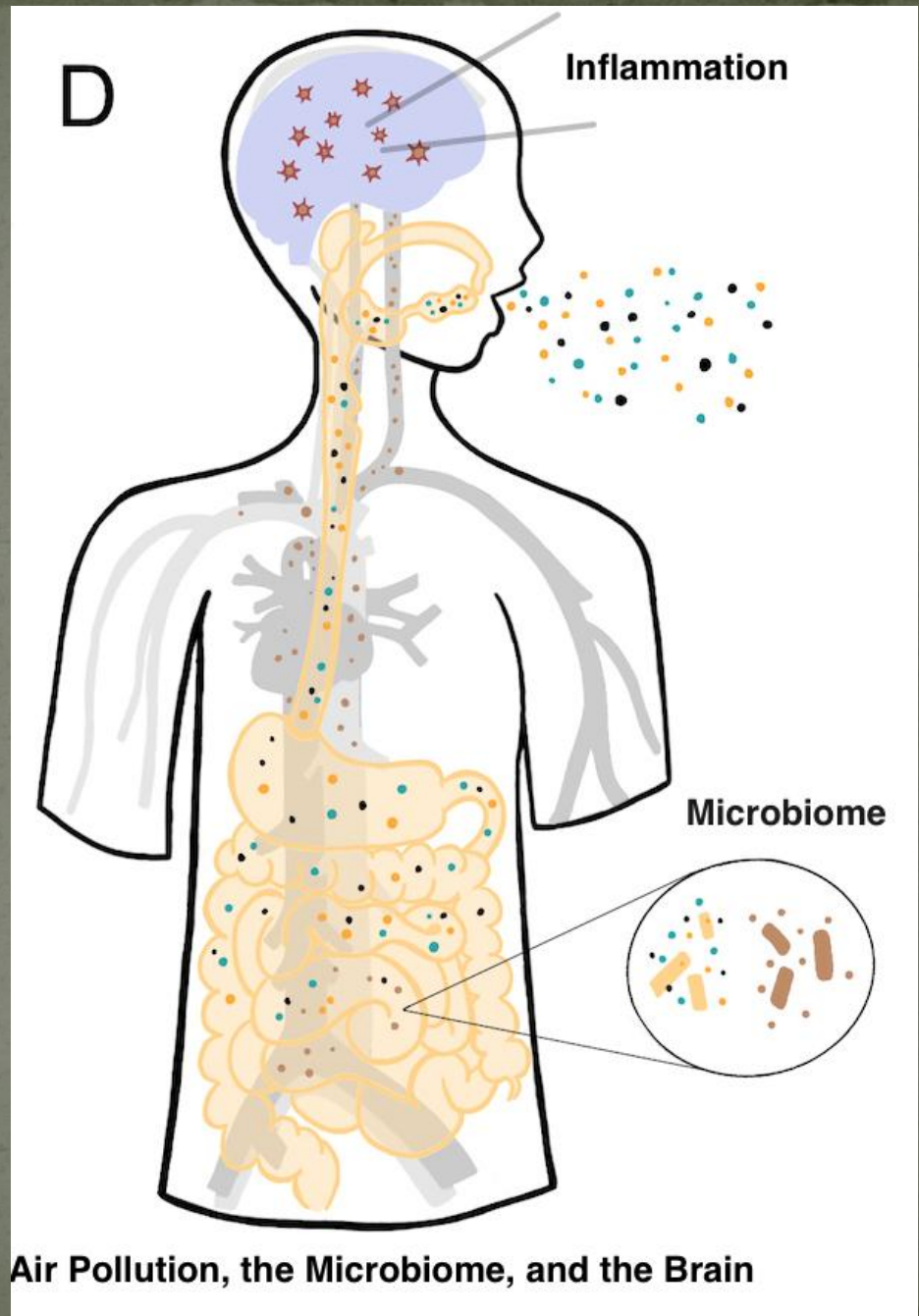
- α -Synuclein found in gut neurons and can spread via vagus.
- AP causes gut inflammation and leakiness which promotes α -synuclein pathology



Air Pollution and Gut α -Syn

How might AP increase the risk of PD and Dementia?

- AP alters microbiome
- Microbiome can be inflammatory
- PD is associated with altered microbiome

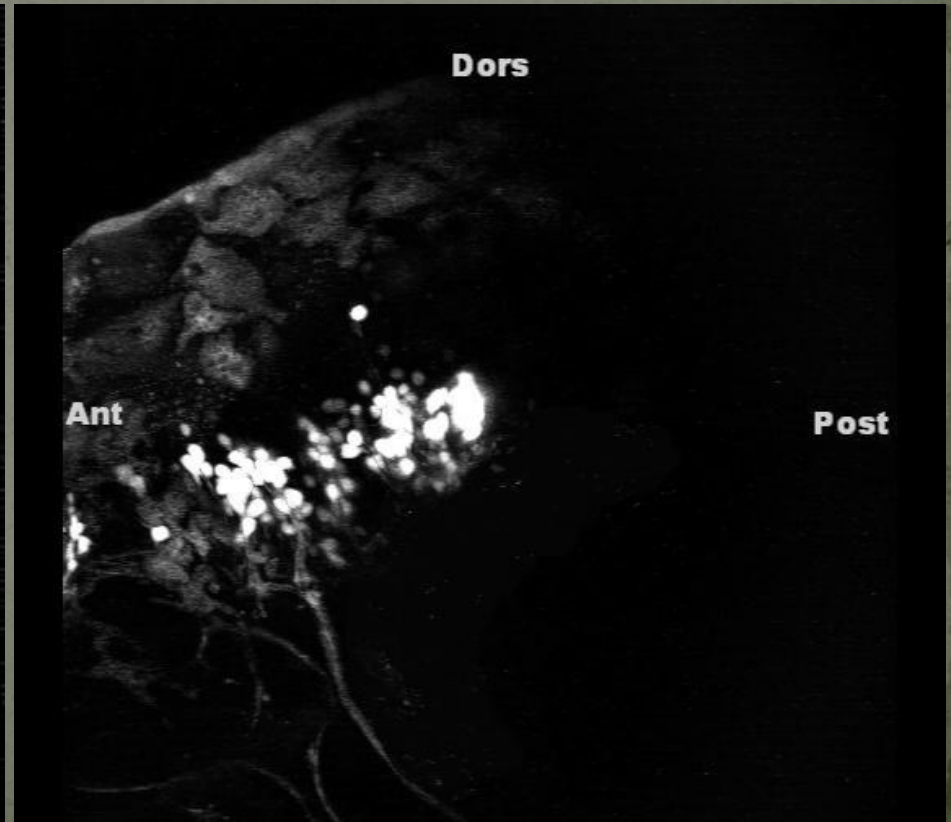
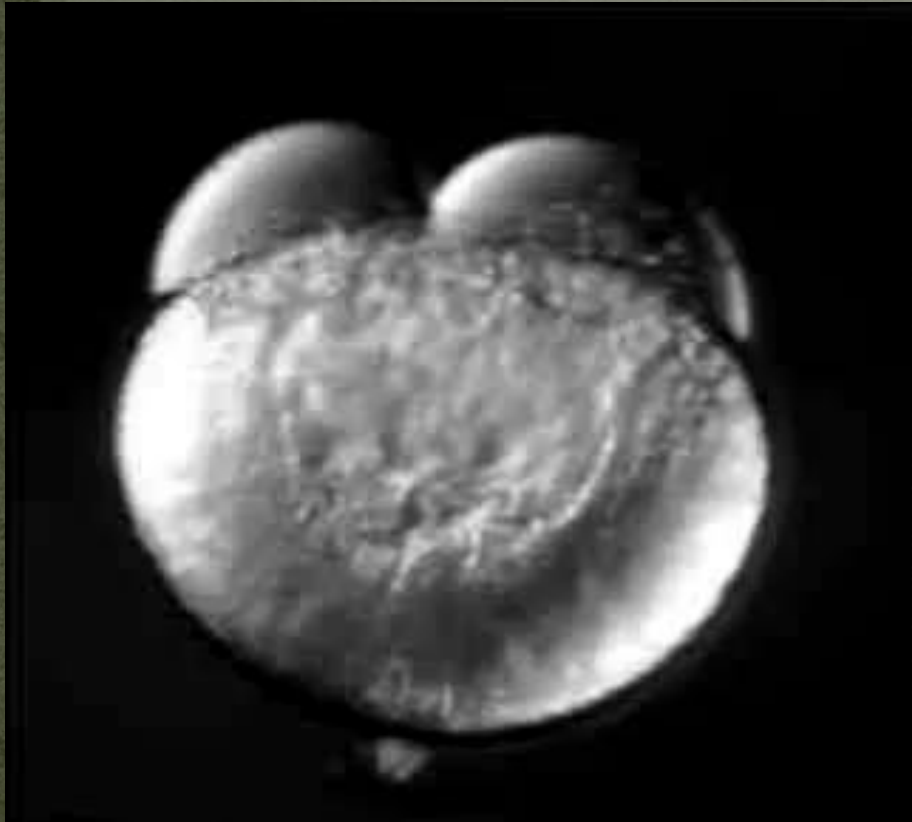


Our Studies on Direct Toxicity and Inflammation Caused by Diesel Exhaust

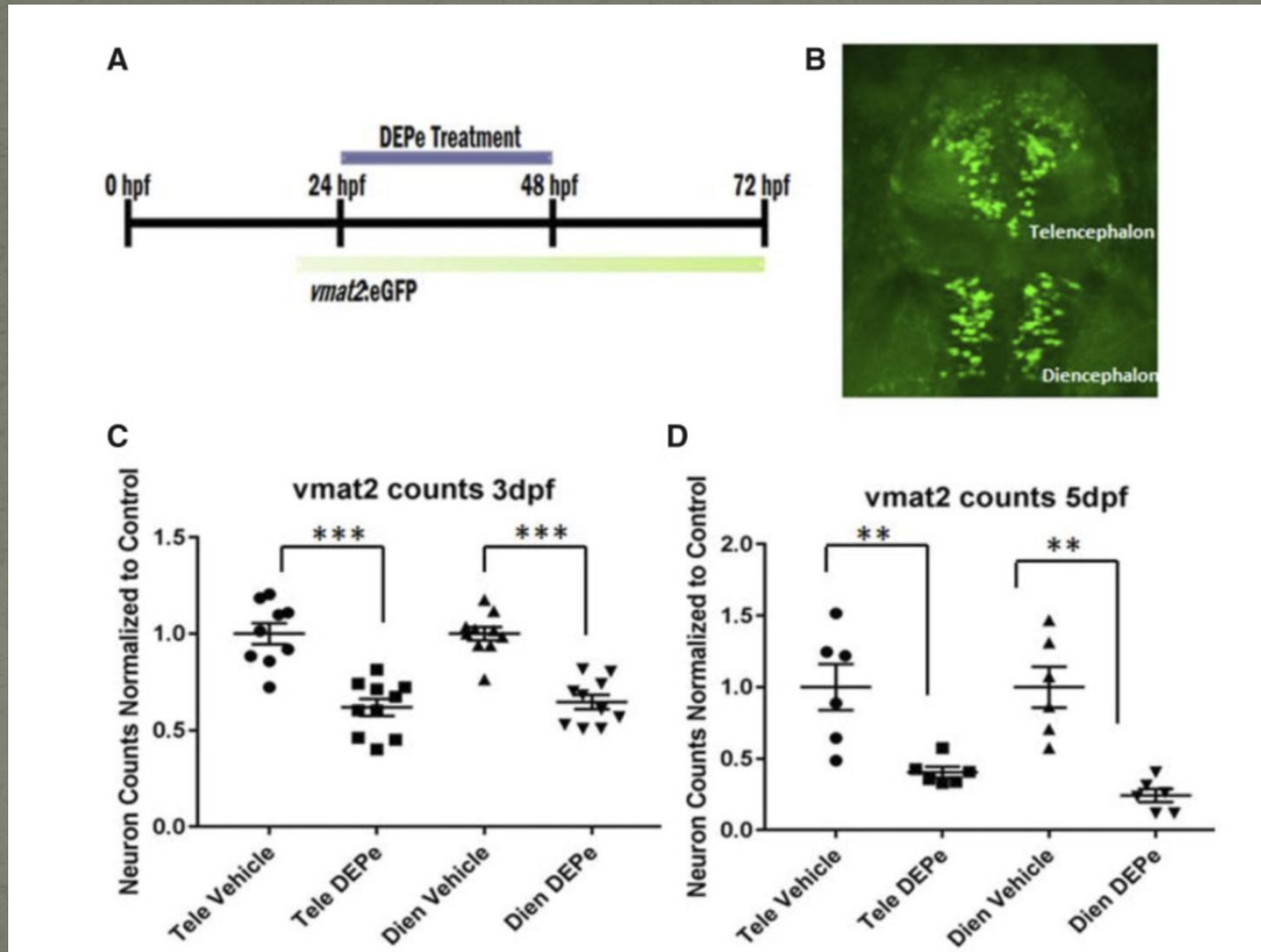
Zebrafish as a Tool to Study Molecular Mechanisms



- They develop quickly, are transparent and it is easy to modify them genetically and expose them to toxins

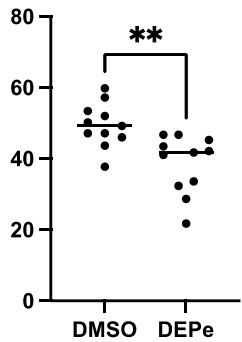


DEPe is Toxic to Aminergic Neurons

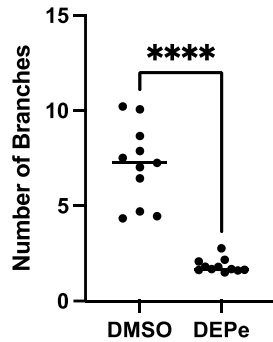


Inflammatory Response to DEPe

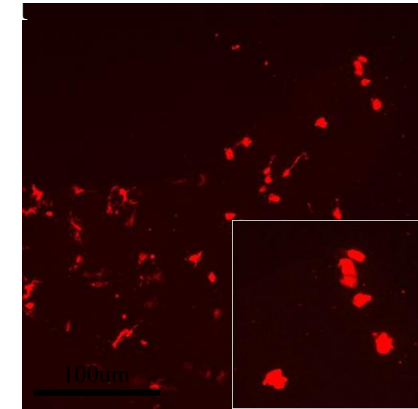
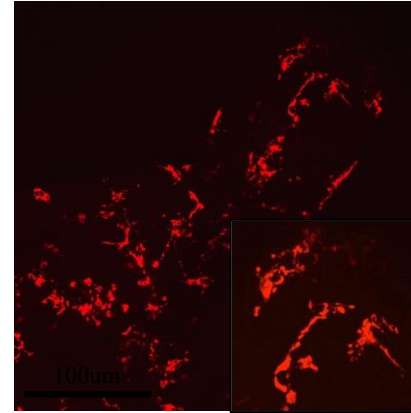
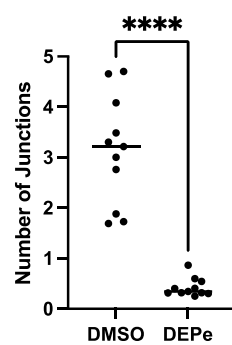
Microglial Maximum Branch Length



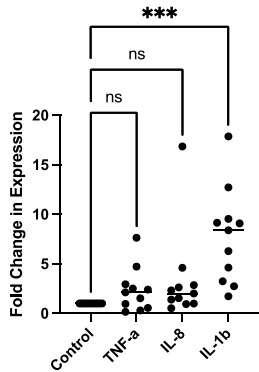
Microglial Number of Branches



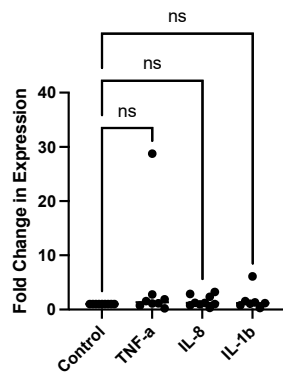
Microglial Number of Junctions



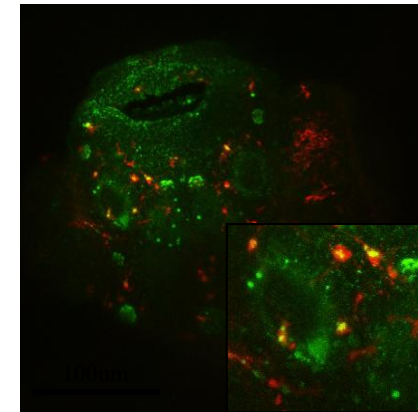
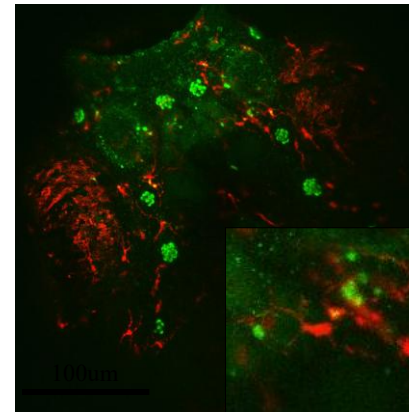
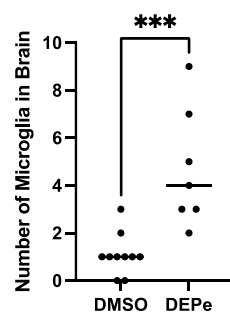
Whole Body Expression of Pro-Inflammatory Cytokines



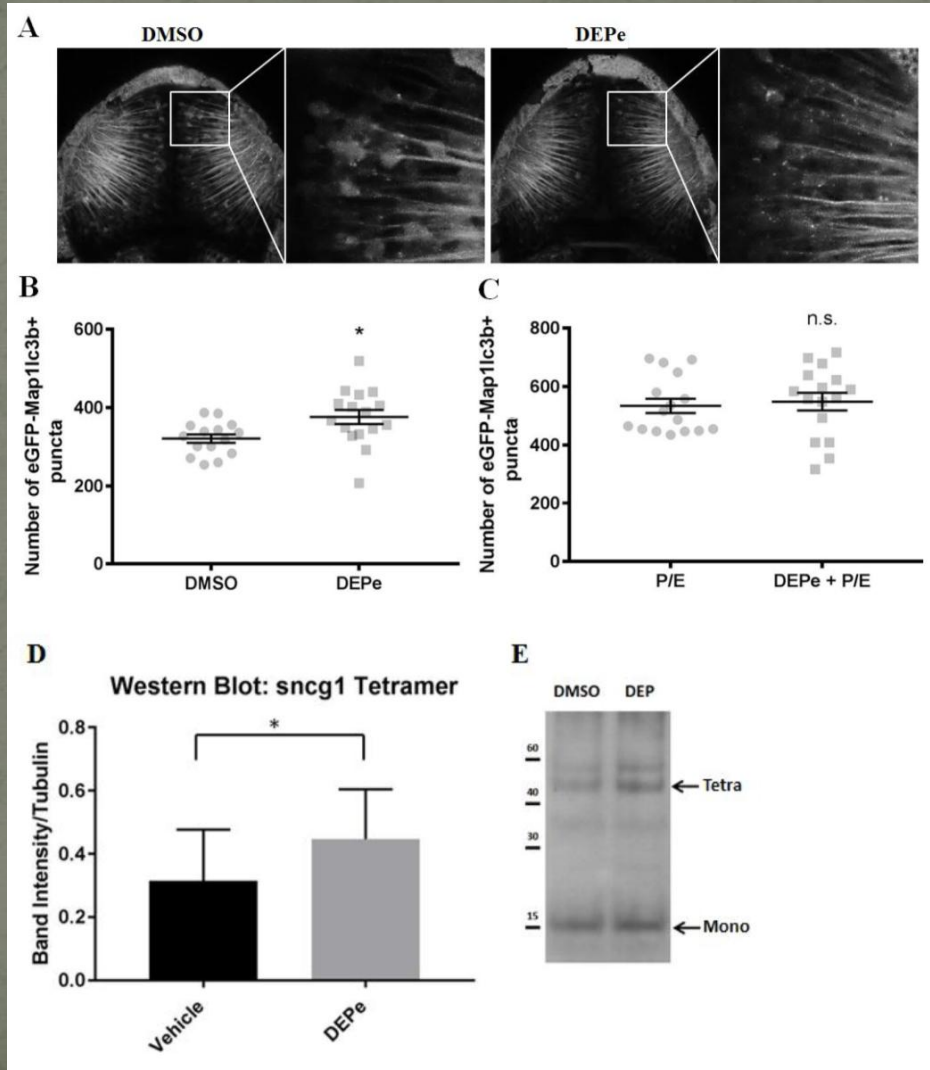
Head Expression of Pro-Inflammatory Cytokines



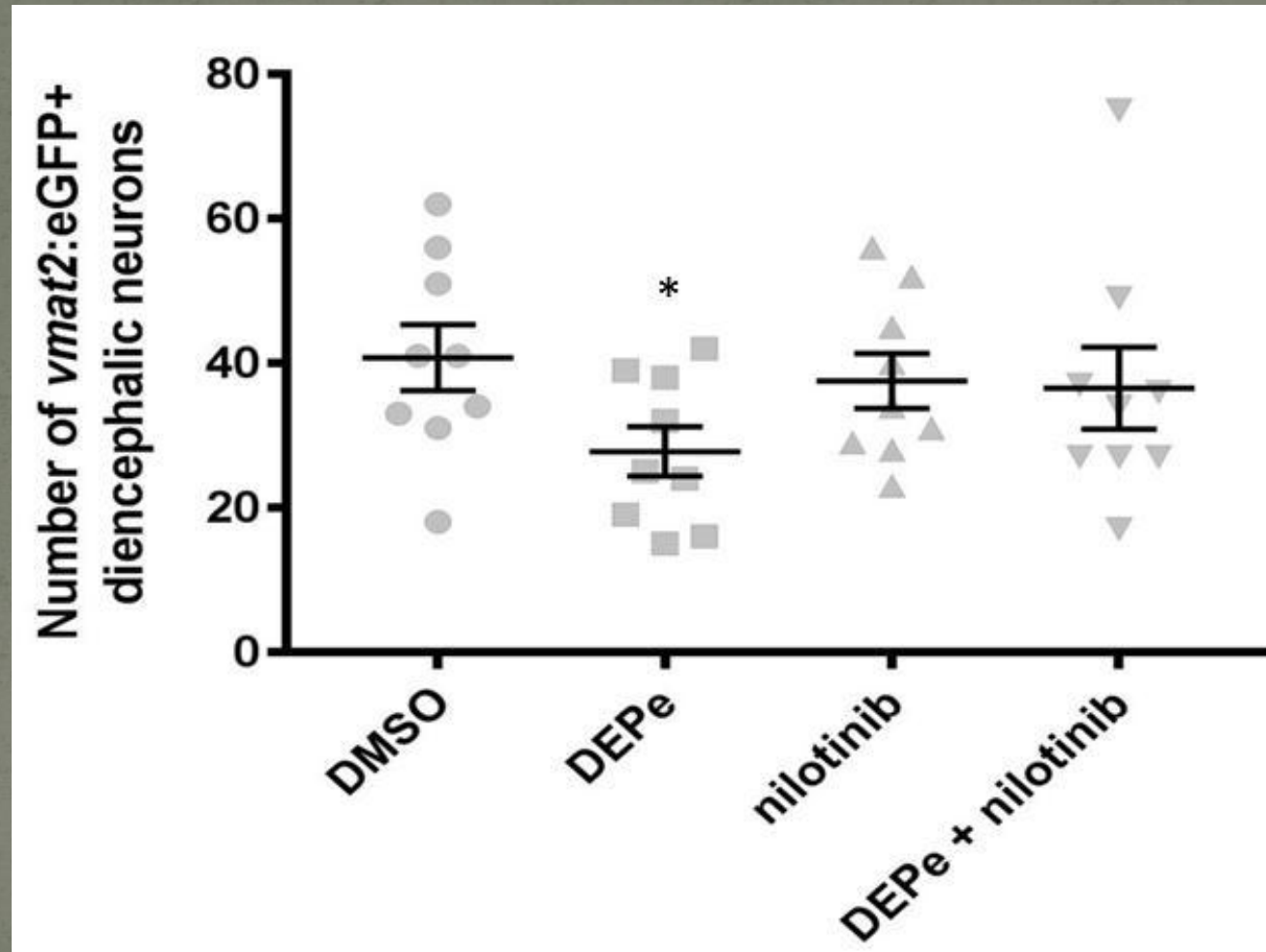
Microglia Colocalized with Lysotracker



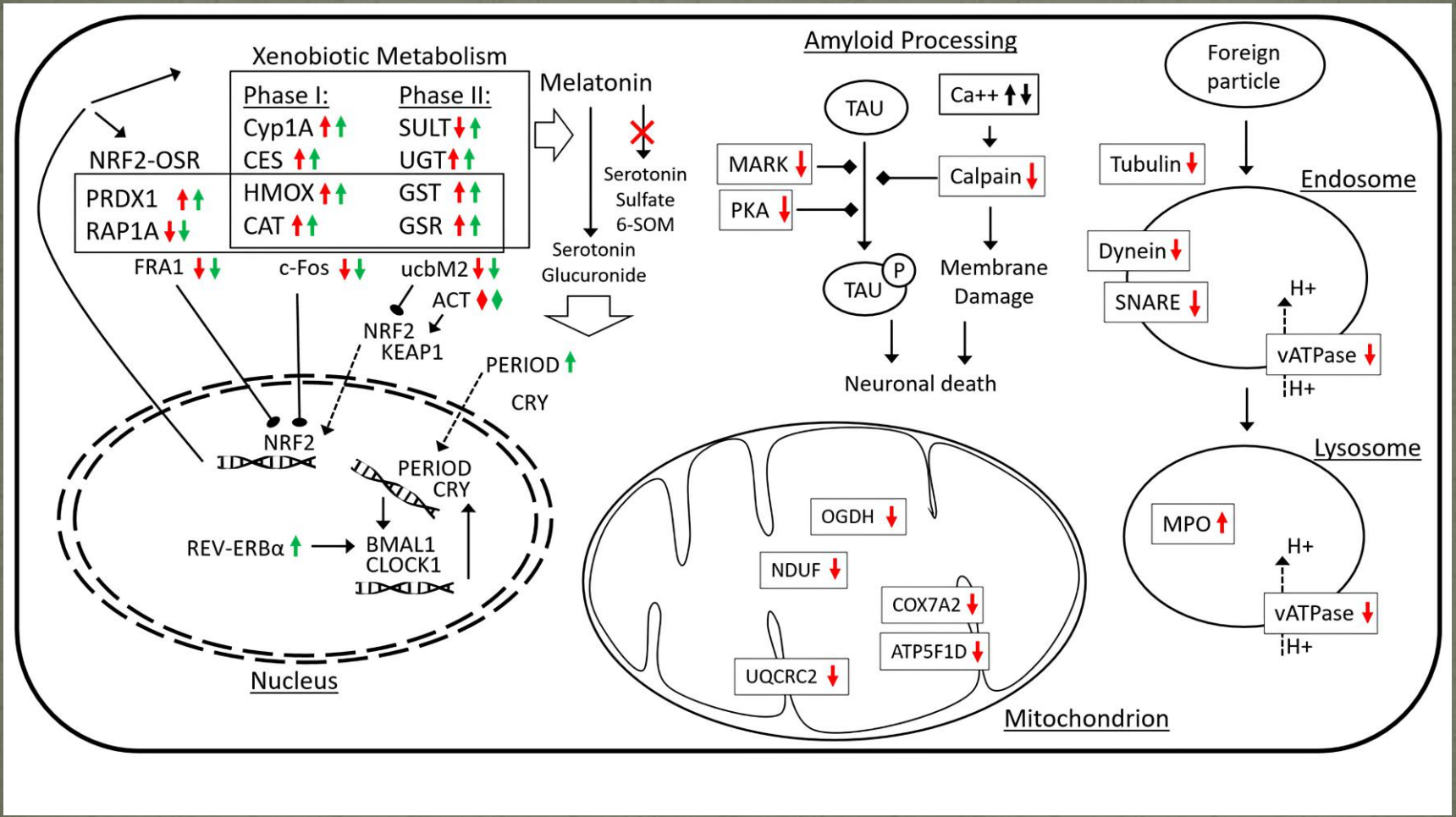
DEPe Inhibits Autophagic Flux



Stimulating Autophagy Rescues DEPe-Induced Neuronal Loss



Transcriptomics and Proteomics of ZF Brains



Overall Conclusions

- Epidemiological studies support an association of air pollution and Parkinson's disease
- Animal studies support biological plausibility
- Air pollution is likely an important risk factor for Parkinson's disease

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