The Role of Pesticide Exposure in Parkinson's Disease

Brain Awareness Week

March 15, 2022

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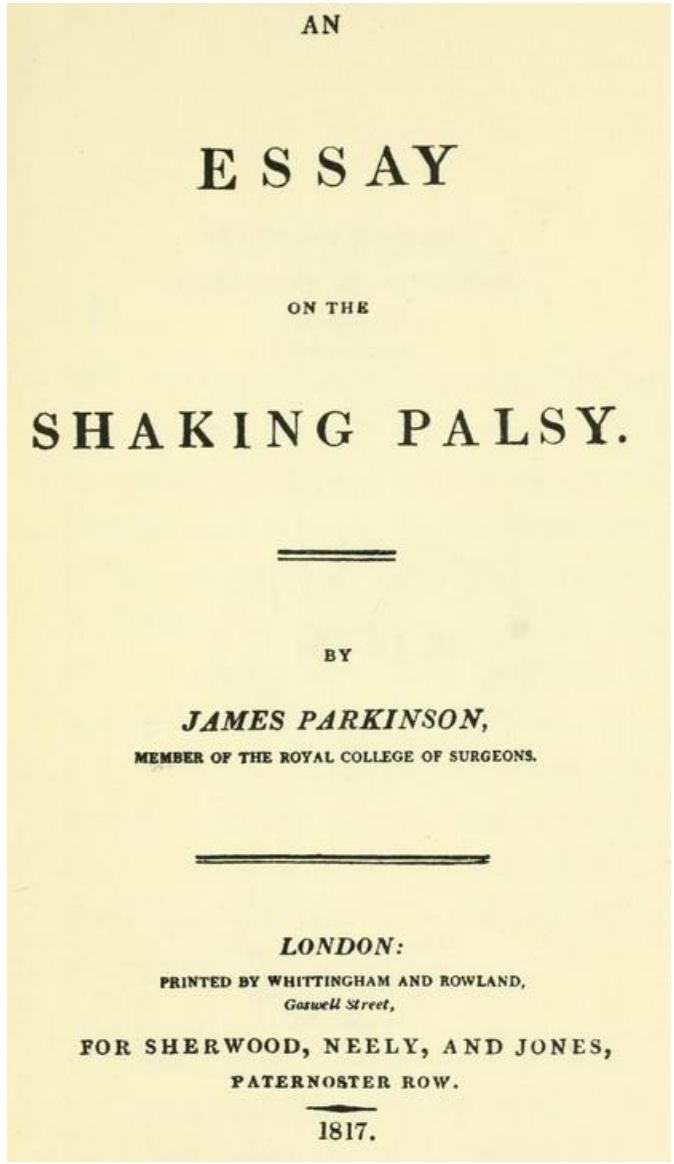
SUNY Empire State College

SUNY EMPIRE STATE COLLEGE

BRAIN AWARENESS WEEK Dana Foundation

Parkinson's Disease

- 2nd most common neurodegenerative disorder
- Primarily a movement and motor control disorder
- Progressive disease in the brain
  - Basal ganglia
- Vast majority of cases (95%) are idiopathic (not genetic)



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,

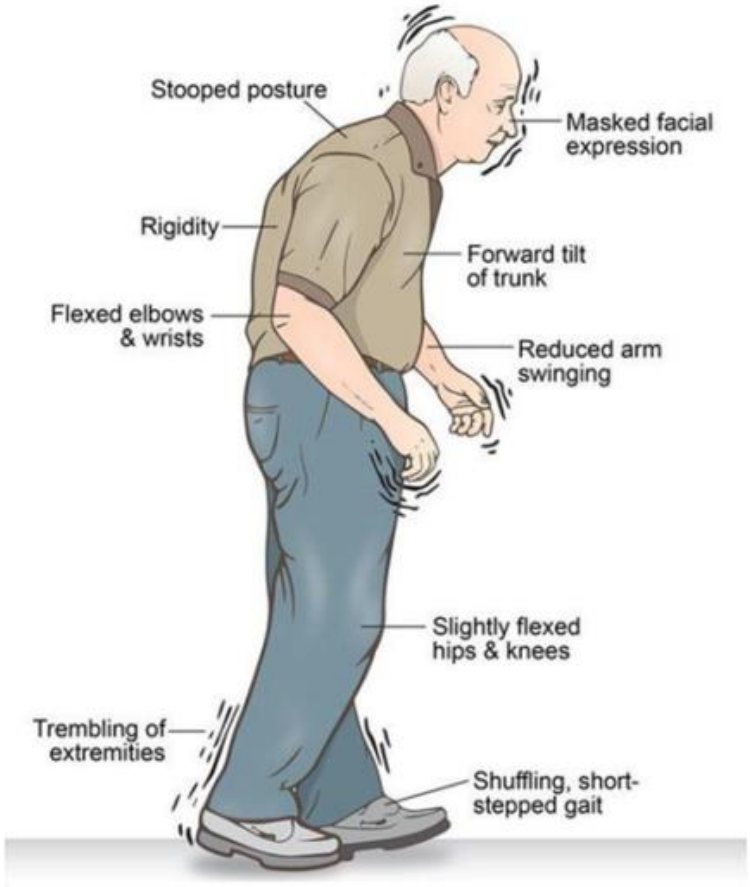
FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.

1817.

https://openlibrary.org/books/OL25167312M/An_essay_on_the_shaking_palsy

Parkinson's Disease

- Primarily a movement and motor control disorder



T Tremor: shaking, usually starting on one side

R Rigidity: stiffness of the limbs, neck, or trunk

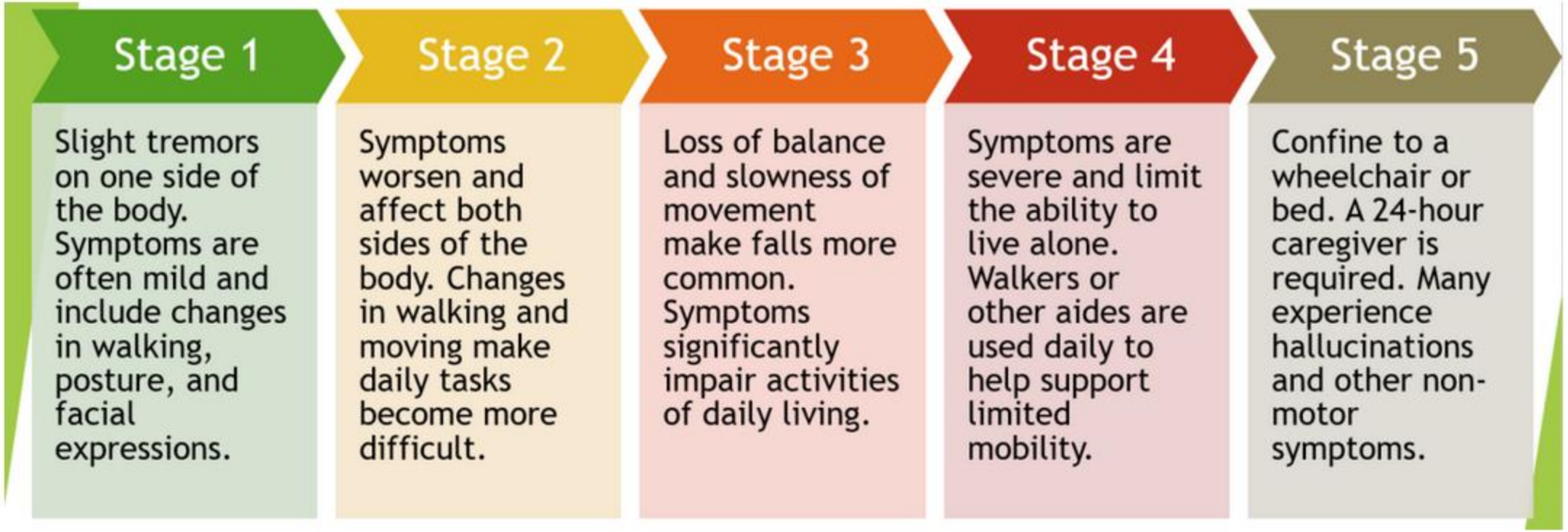
A Akinesia: loss or impairment in power of voluntary movement

P Posture and balance

https://parkinsonsnebraska.org/understanding-parkinsons-disease/

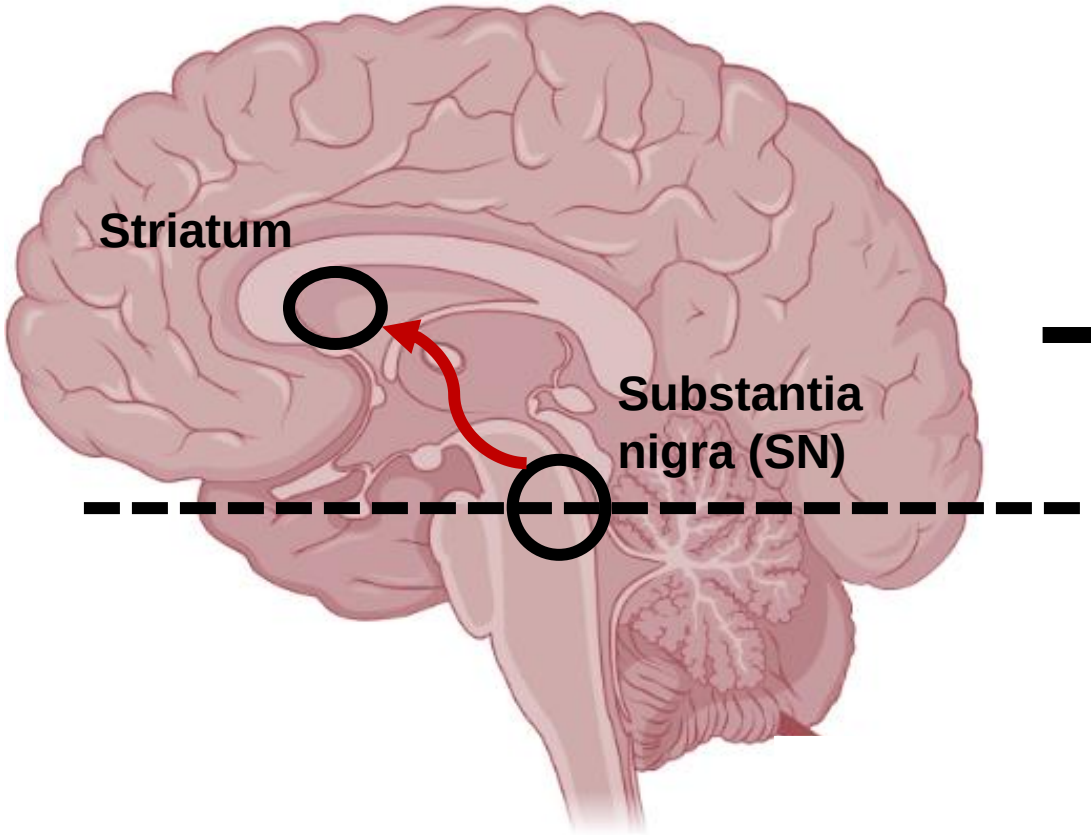
Parkinson's Disease

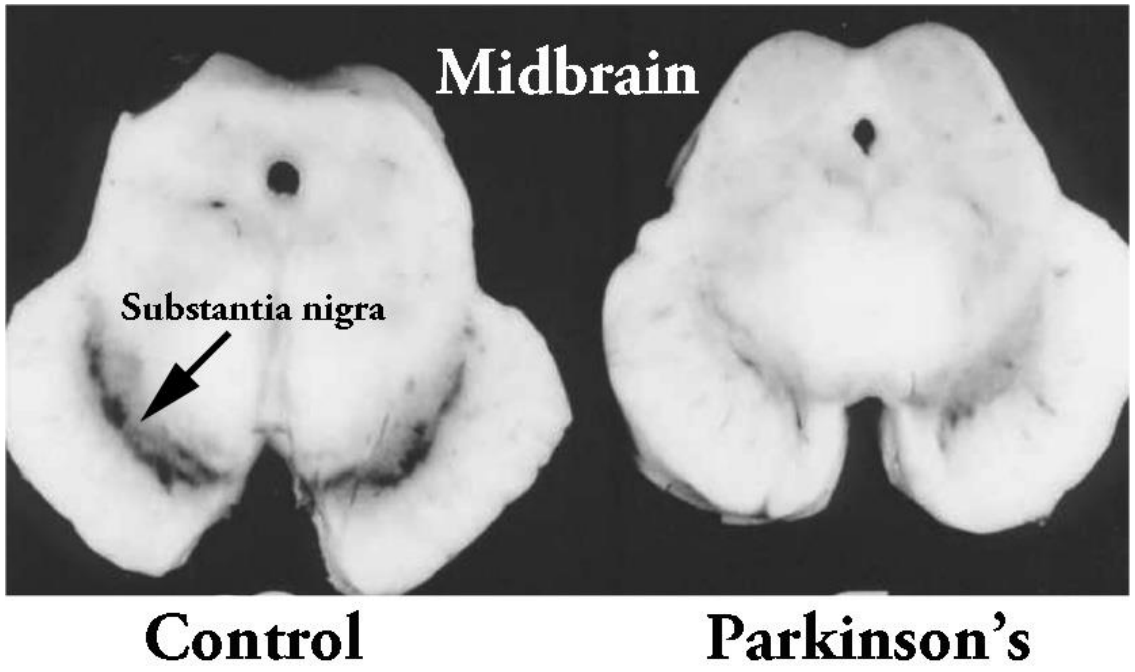
- Comprised of 5 progressive stages of severity



https://parkinsonsnebraska.org/understanding-parkinsons-disease/

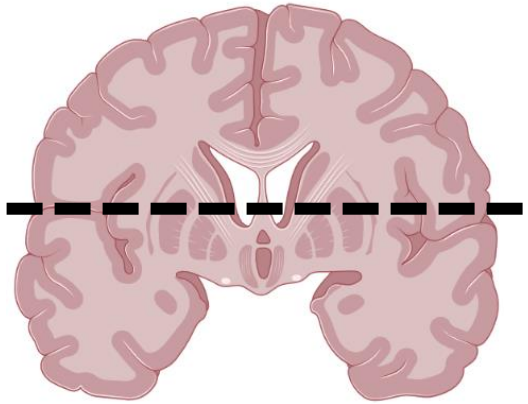
Loss of Dopamine Cells in the Brain



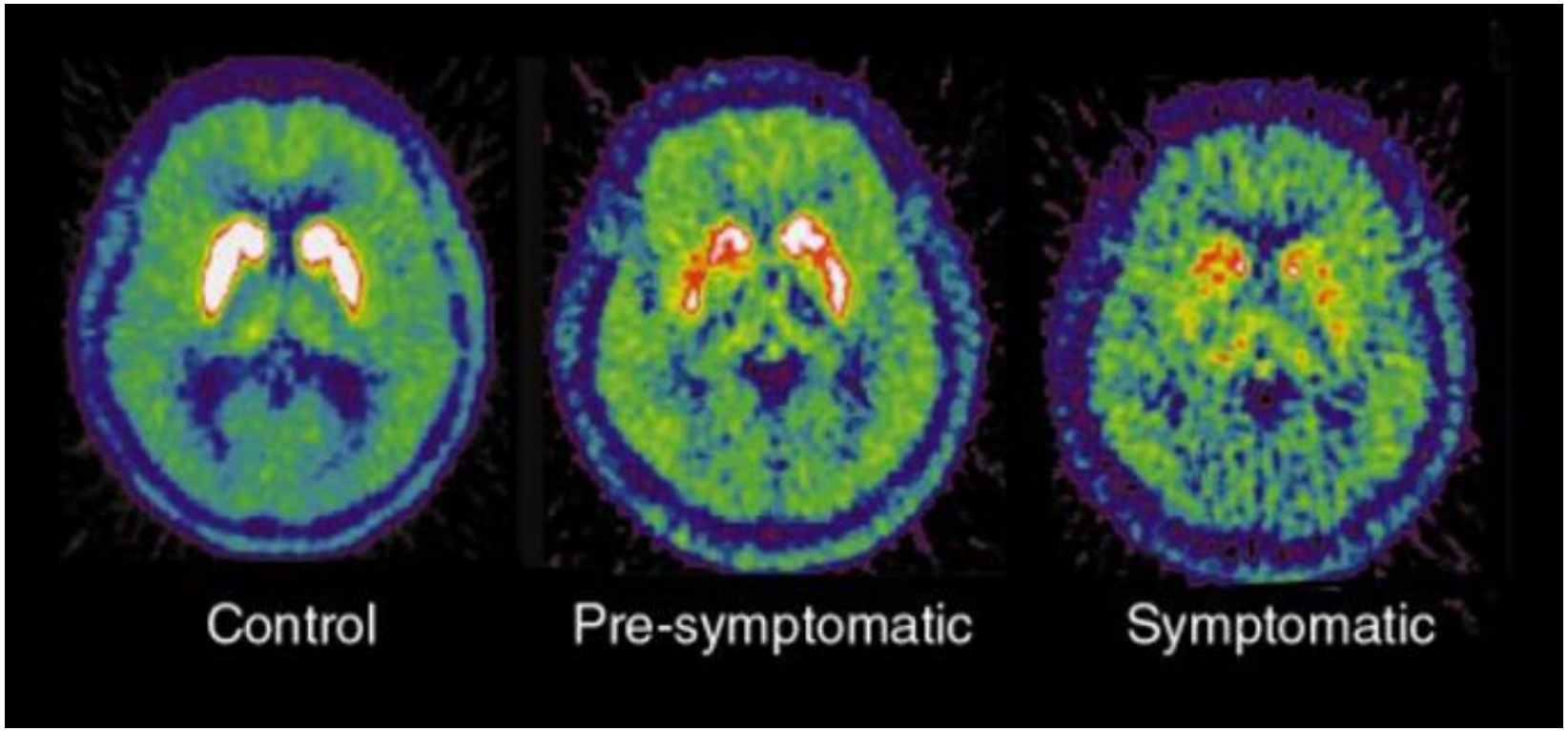


https://scienceofpd.files.wordpress.com/2018/02/midbrain.jpg

Dopamine loss in PD



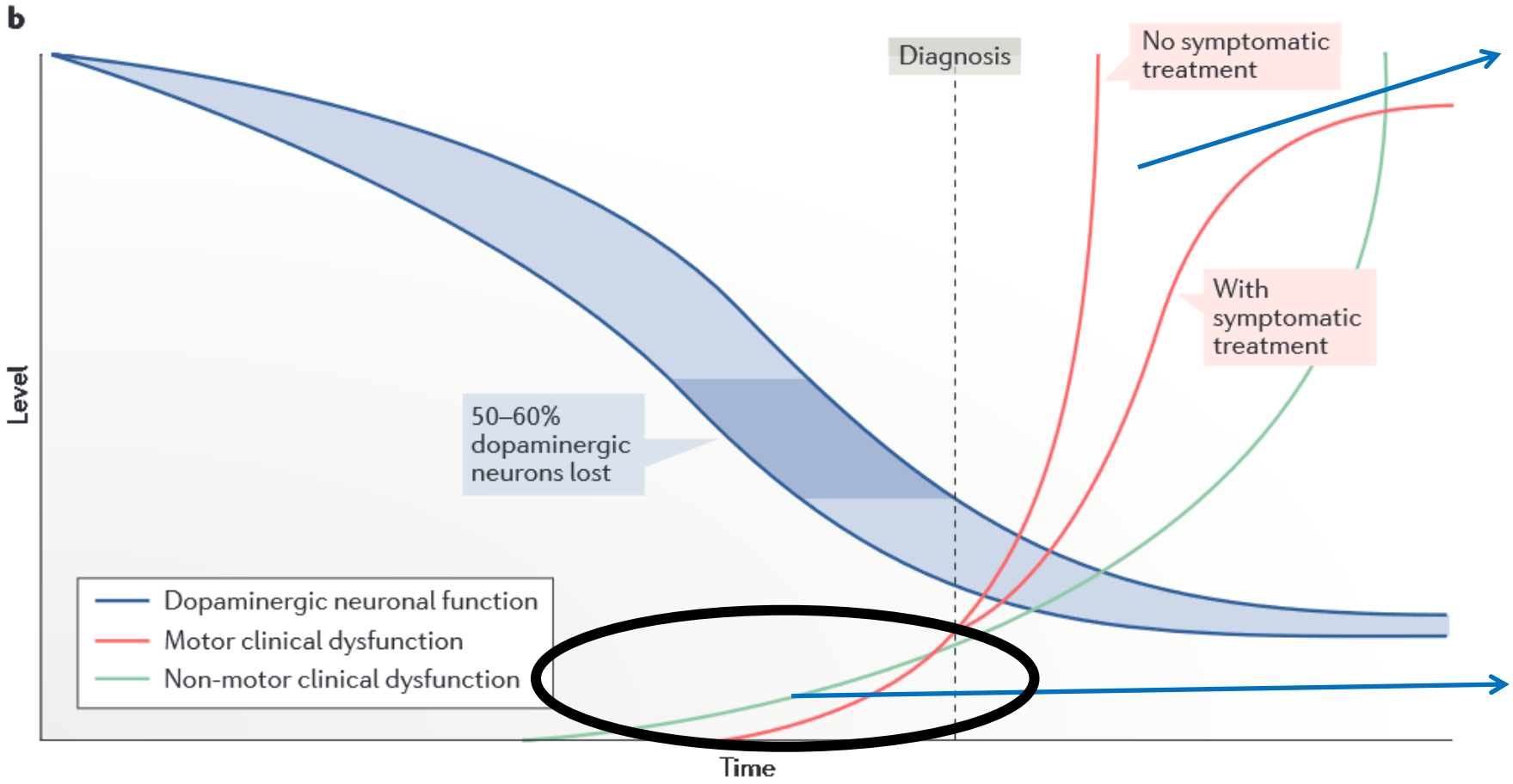
Front of brain



Back of brain

Dunnett & Bjorklund (1999) *Nature*

Progression of Parkinson's Disease



Motor Symptoms:

- Akinesia
- Rigidity
- Resting tremor
- Postural instability

Non-motor Symptoms:

- Loss of smell (Hyposmia)
- Apathy/depression
- Cognitive impairment
- Sleep disorder
- Gastrointestinal dysfunction

Schapira, Chaudhuri, Jenner (2017) *Nature Reviews Neuroscience*

Risk Factors for Parkinson's Disease

Age

- PD correlates with age

Genetics

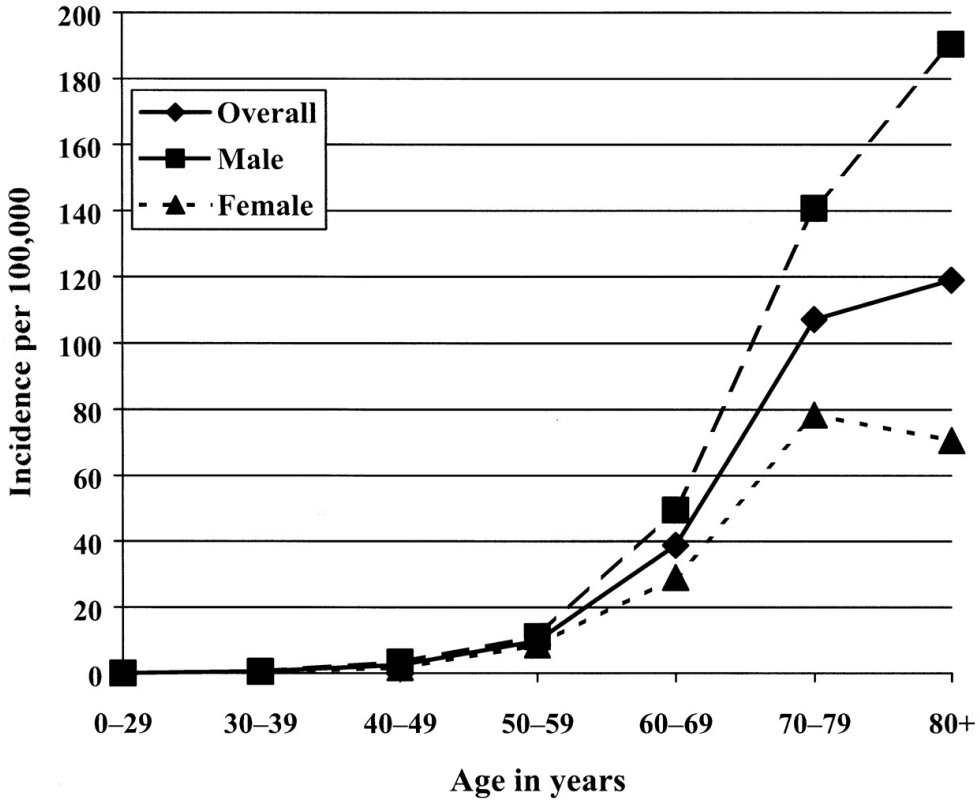
- ~5-10% of cases
- "PARK" genes

Head Trauma

- Contact sports – boxing

Environmental Factors

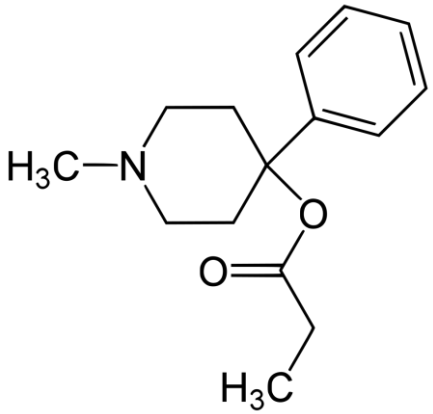
- Herbicides, air pollution, metal exposure, MPTP



Van Den Eeden et al. (2003) *Am. J. Epidemiology*

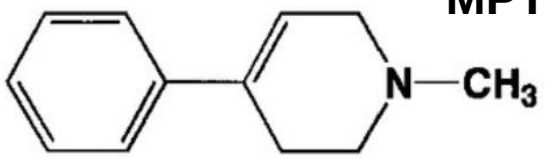
The MPTP model of PD

- Discovery of MPTP – 1982
- Heroin users (26-42 y.o.) reported to ER with acute Parkinsonism
  - Drug contaminated with MPTP
- Provided a model to study PD in the laboratory



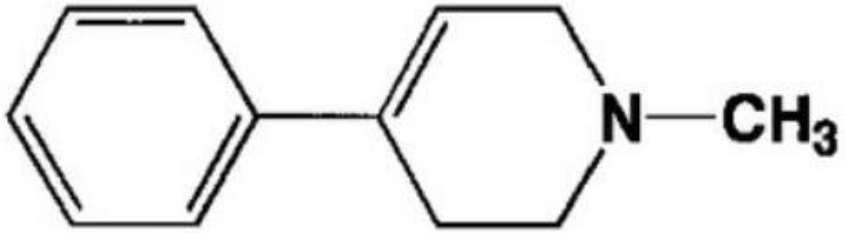
Synthetic opioid MPPP

Dopamine neurotoxin MPTP

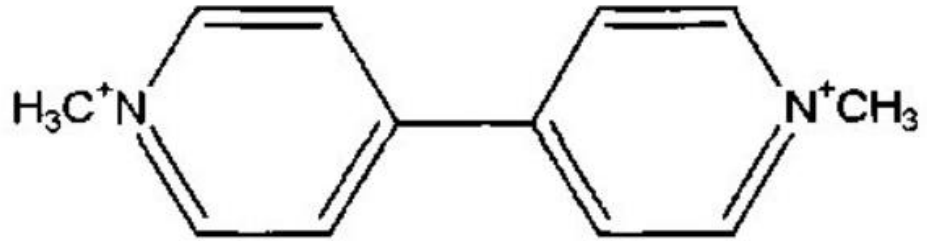


Commonly used herbicide, paraquat, resembles MPTP

MPTP



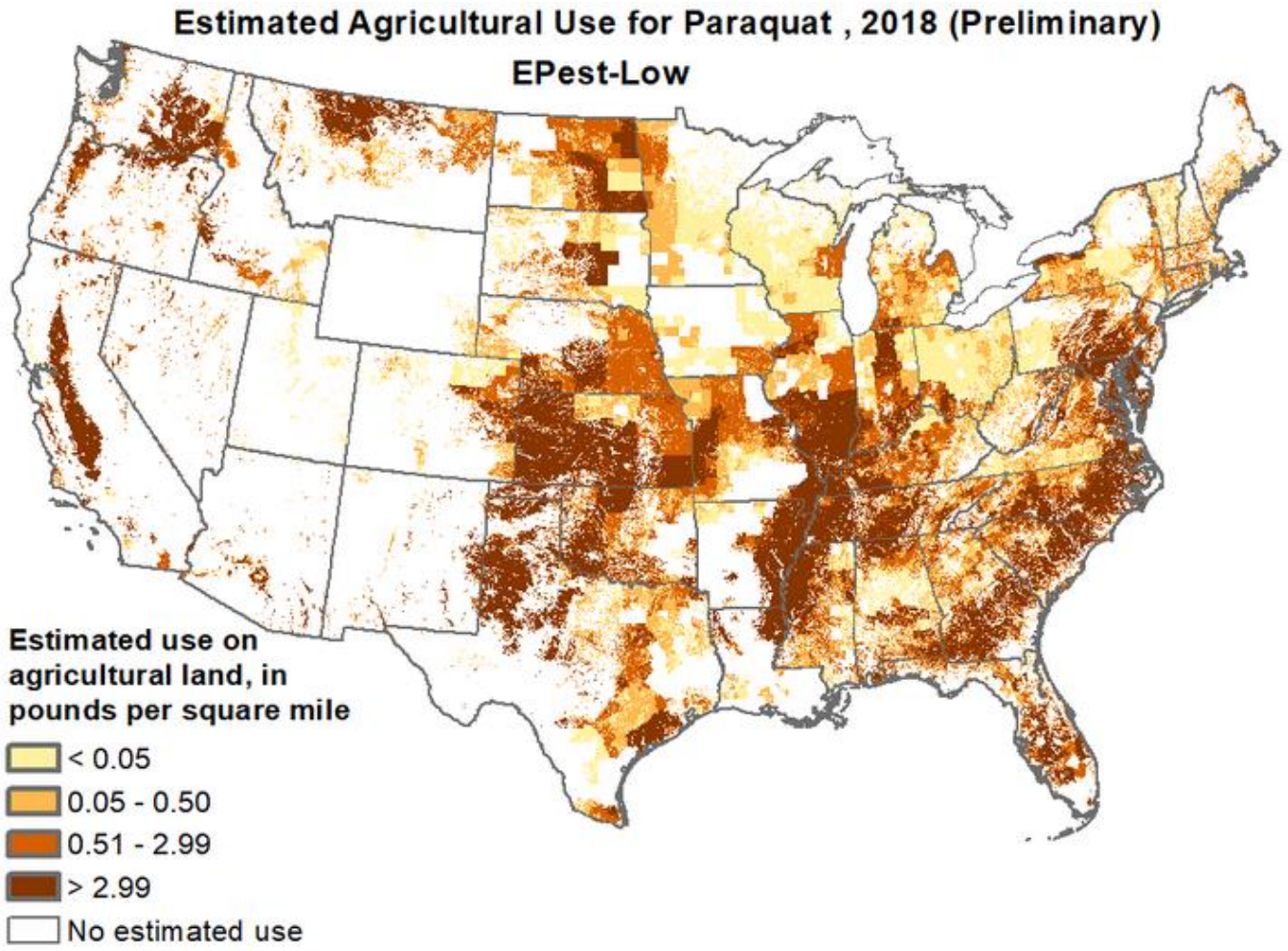
Paraquat

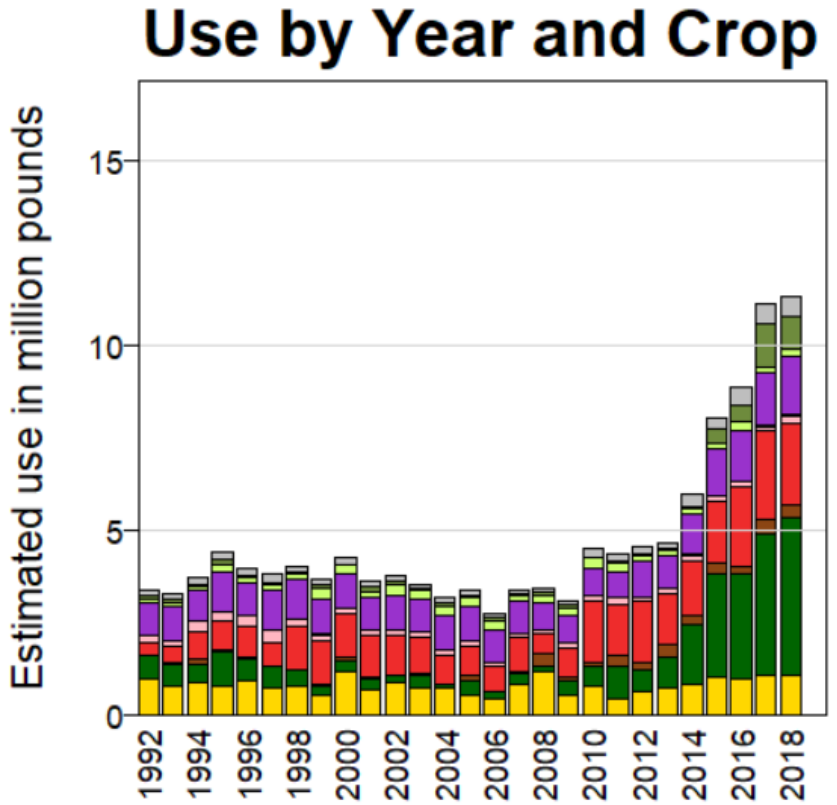


Trade name: Gramoxone

- Paraquat – broad spectrum herbicide
- Acutely toxic to humans in large doses
- Banned in every major agricultural producer except the U.S. – must be licensed applicator

Paraquat use in United States





https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2018&map=PARAQUAT&hilo=H

Paraquat is associated with PD in farmers

Table 3. Association of PD with ever use of pesticides before diagnosis or reference date by mechanism.

Pesticide	Cases ($n = 110$) [n (%)]	Controls ($n = 358$) [n (%)]	OR (95% CI)	p-Value
Oxidative stressors				
Paraquat	23 (24)	49 (14)	2.5 (1.4–4.7)	0.004
Permethrin	16 (16)	41 (12)	1.5 (0.77–2.9)	0.244
Carbon disulfide	2 (2)	3 (1)	2.6 (0.41–16)	0.313
Chloranil	1 (1)	3 (1)	1.6 (0.16–16)	0.706
Cyhalothrin	1 (1)	1 (0)	3.8 (0.22–64)	0.359
Dichlone	3 (3)	8 (2)	1.6 (0.40–6.2)	0.517
Mercury compounds	2 (2)	5 (1)	1.4 (0.26–7.5)	0.692
Pybuthrin	0 (0)	6 (2)	NA	
Any oxidative stressor	35 (40)	93 (28)	2.0 (1.2–3.6)	0.012
Mitochondrial complex I inhibitors				
Benomyl	7 (7)	15 (4)	1.9 (0.70–5.0)	0.207
Carbendazim	1 (1)	2 (1)	2.2 (0.19–25)	0.529
Cyhalothrin	1 (1)	1 (0)	3.8 (0.22–64)	0.359
Permethrin	16 (16)	41 (12)	1.5 (0.77–2.9)	0.244
Pyridaben	0 (0)	1 (0)	NA	
Rotenone	19 (19)	32 (9)	2.5 (1.3–4.7)	0.005
Thiabendazole	3 (3)	12 (3)	0.8 (0.23–3.1)	0.778
Any complex I inhibitor	36 (38)	92 (27)	1.7 (1.0–2.8)	0.041

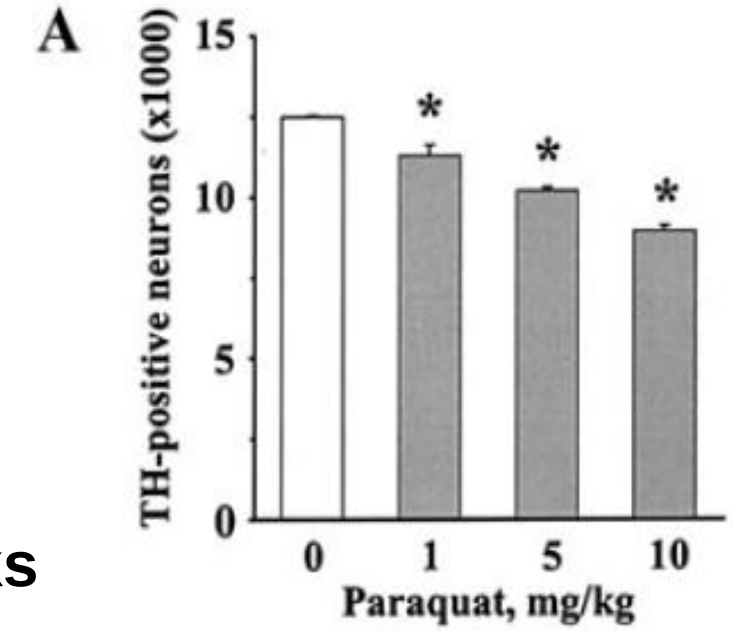
NA, not available. Analyses used logistic regression adjusted for reference age tertile, sex, state, and cigarette smoking.

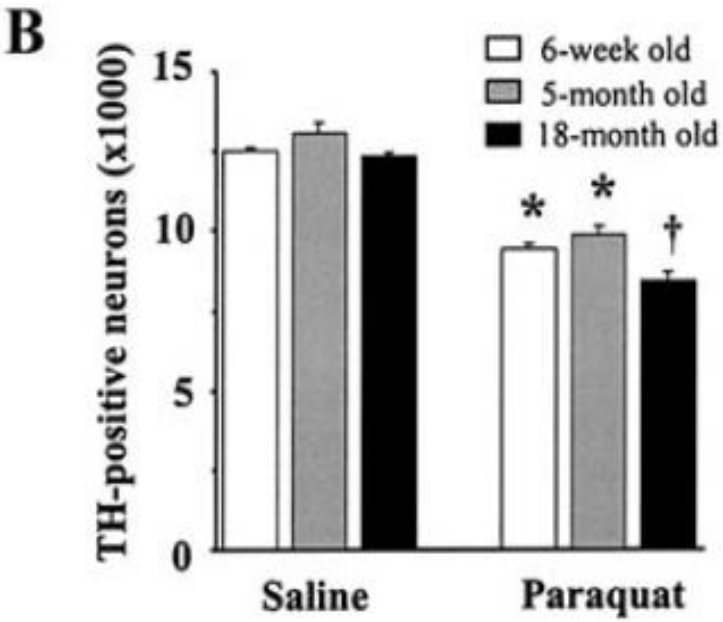
Tanner et al. (2011) *Env. Health Persp.*

Paraquat reduces dopamine neurons in the substantia nigra of mice

1x/week for 3 weeks

Measure neurons 7 days after last injection





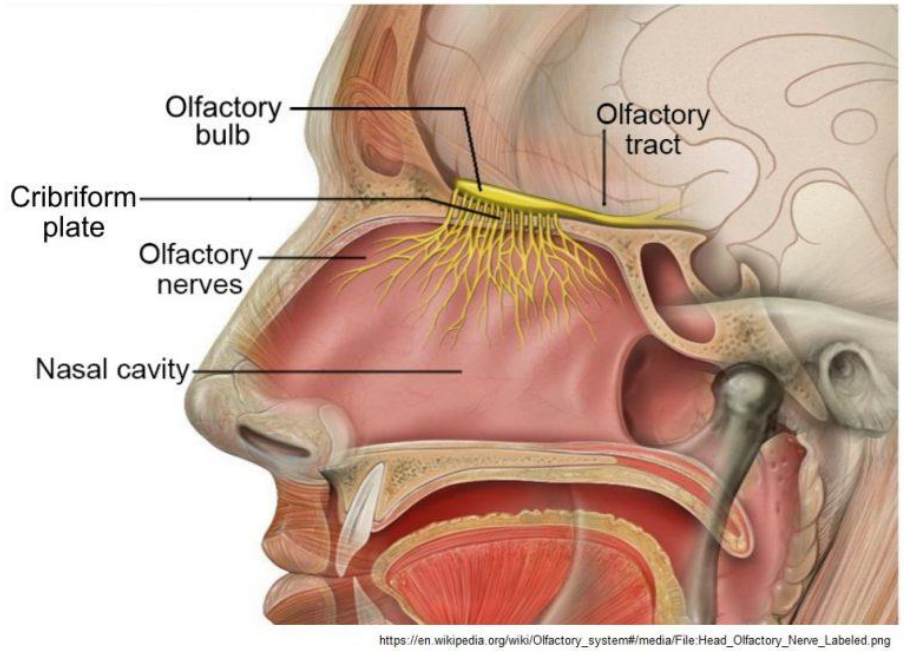
McCormack et al. (2002) *Neurobiology of Disease*

Pesticides can be inhaled

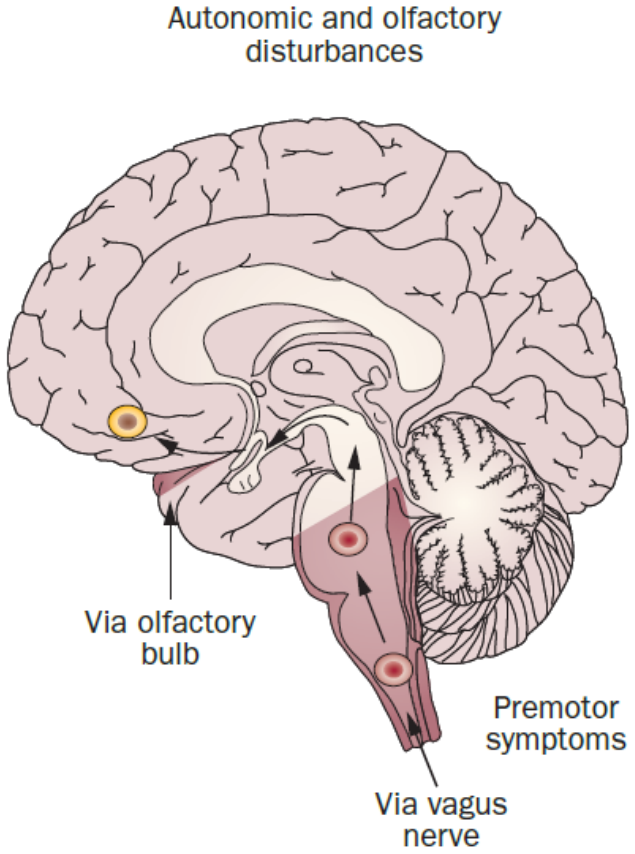
USDA; Associated Press

Olfactory pathway in PD

- The olfactory bulb is a highway to the brain



https://en.wikipedia.org/wiki/Olfactory_system#/media/File:Head_Olfactory_Nerve_Labeled.png



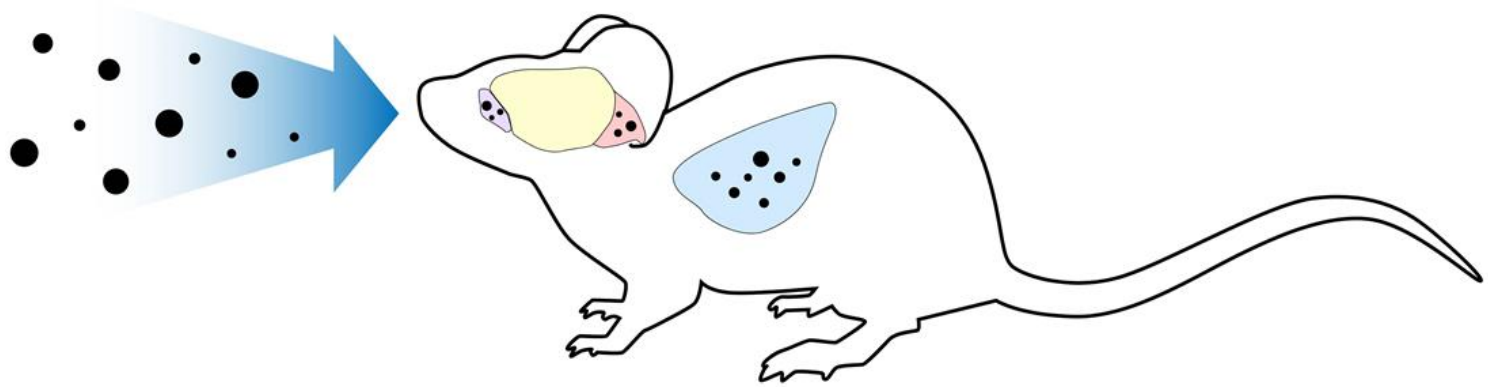
Braak Hypothesis

Doty (2012) *Nature Reviews Neurology*

Does paraquat *inhalation* lead to PD-like symptoms in laboratory settings?

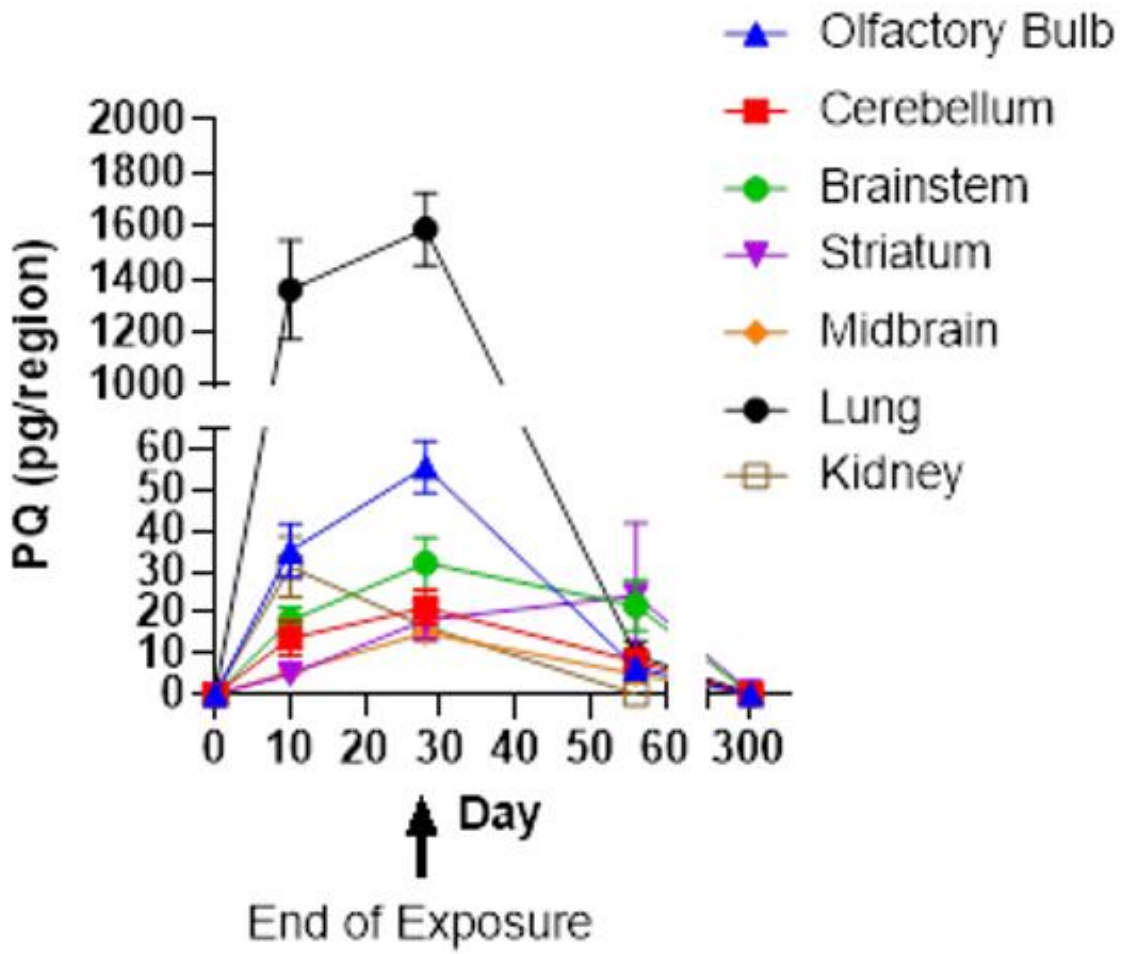
Are there lasting effects in the brain long after exposure?

Paraquat Exposure
4 hr/day, 5 days/week
Age: Day 120-150



Outcome measures
Paraquat accumulation in brain
Behavioral changes *(140 days after exposure)*
Dopamine changes *(270 days after exposure)*

Paraquat accumulates in the brain



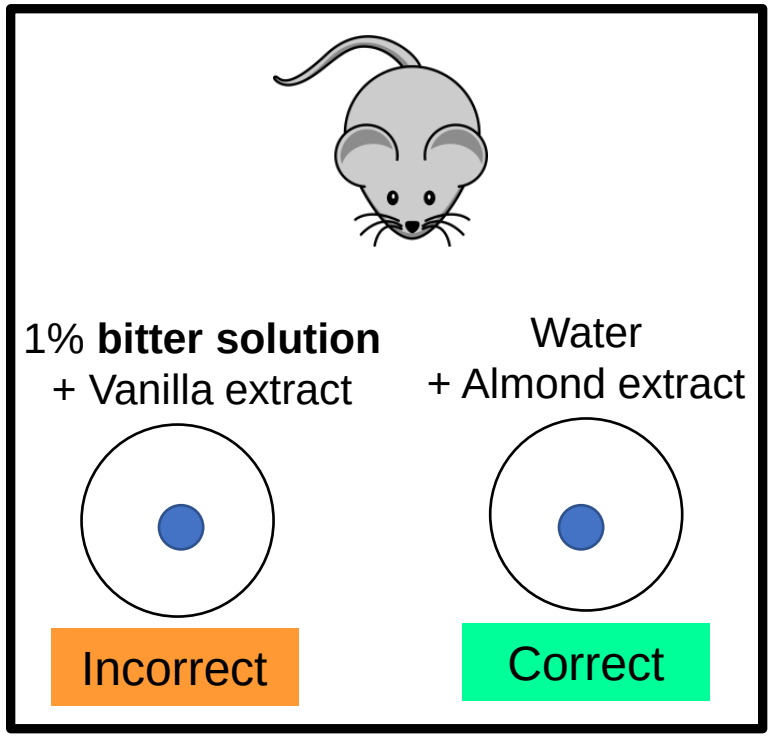
n = 5 per time point

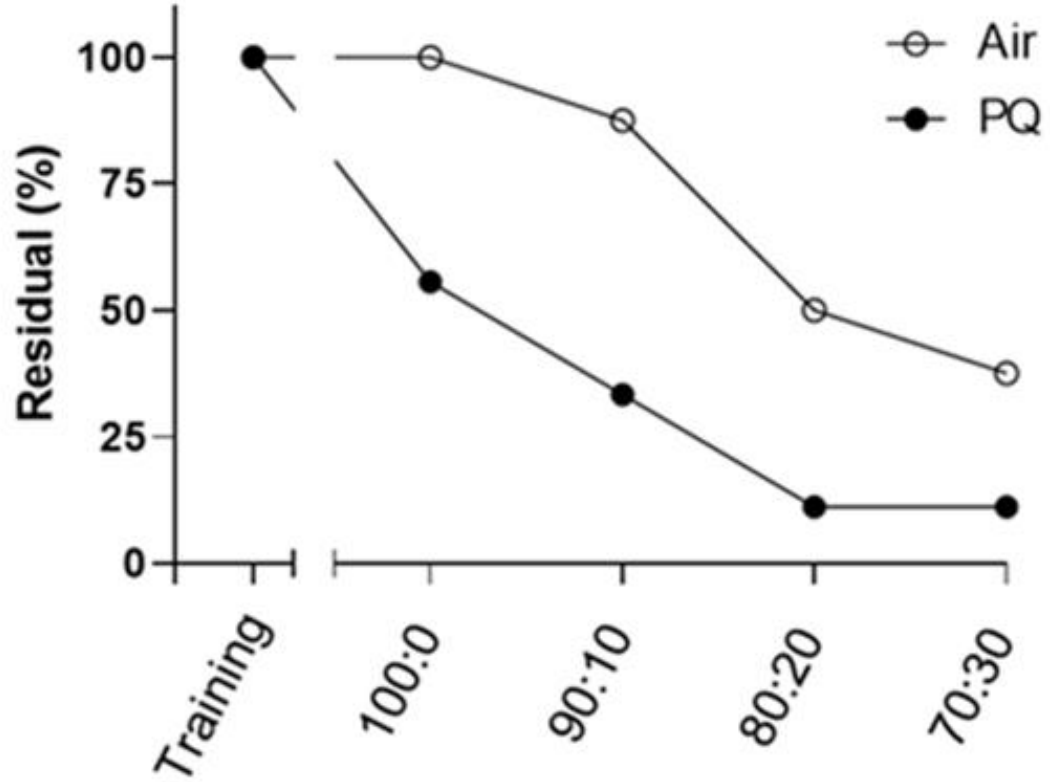
Anderson et al. (2021) *Tox. Sci.*

Hyposmia Present in ~90% of PD Patients

Richard Doty, University of Pennsylvania Smell Identification test

Paraquat impairs ability to smell in mice



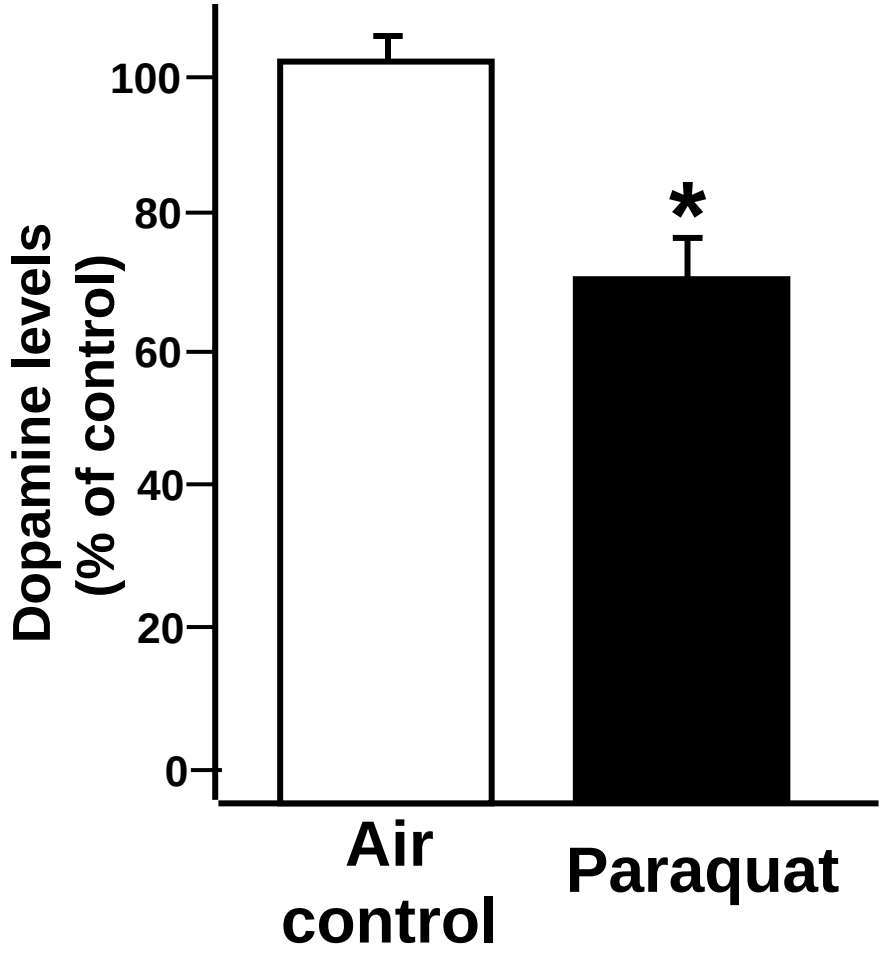


n = 8-9 per treatment

Anderson et al. (2021) *Tox. Sci.*

Paraquat decreases midbrain dopamine

~25% reduction in dopamine levels



n = 8-9 per treatment; data represents % control ± SE; Student's t test, asterisks indicate $p < 0.05$

Anderson et al. (2021) *Tox. Sci.*

OXFORD
SOT | Society of Toxicology
academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 180(1), 2021, 175–185

doi: 10.1093/toxsci/kfaa183
Advance Access Publication Date: 29 December 2020
Research Article

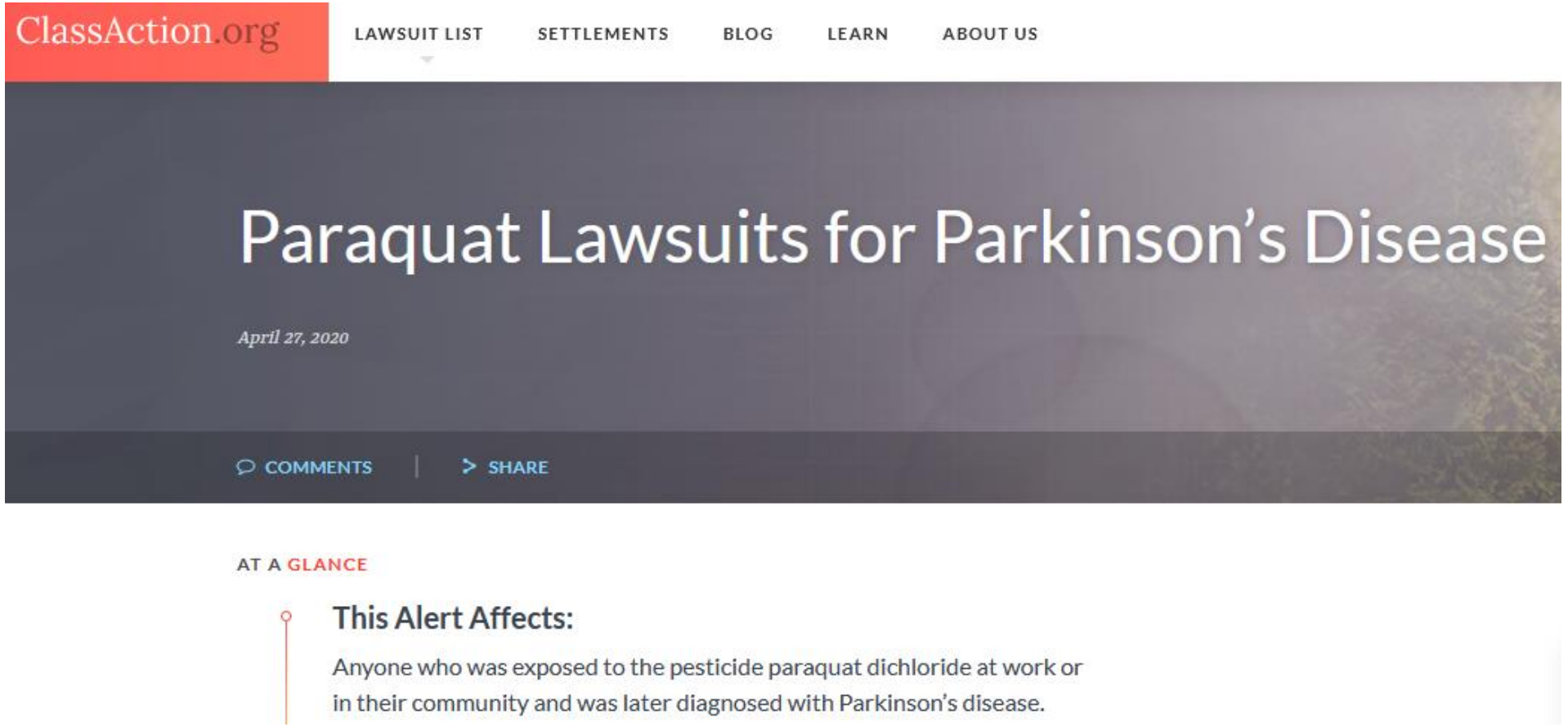
Inhaled paraquat enters brain, impairs sense of smell in male mice

Previous Article | Next Article

In a novel mouse inhalation study, paraquat entered the brain and other tissues and affected sense of smell in males only.

BY ASHLEY PEPPRIELL

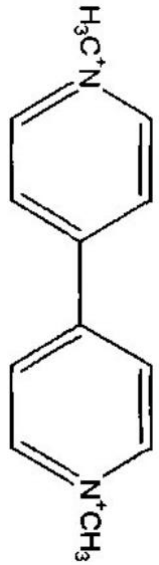
https://factor.niehs.nih.gov/2021/2/papers/paraquat/index.htm

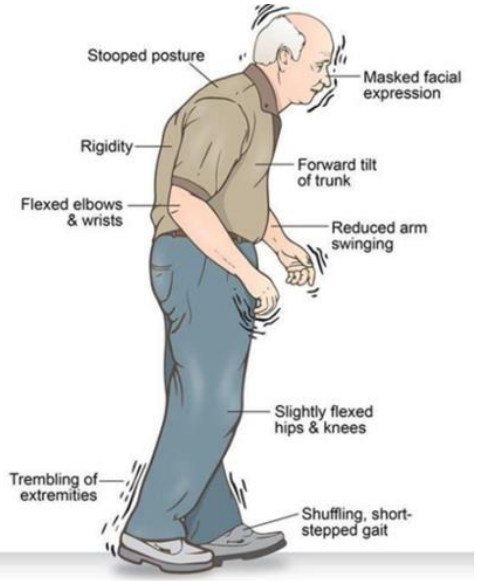


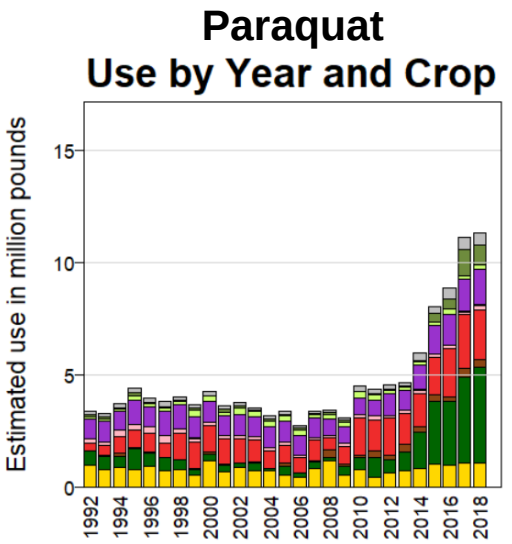
https://www.classaction.org/paraquat-pesticide-parkinsons-toxicity-lawsuits

Summary and Conclusion

- Herbicides, like paraquat, can cause PD-like symptoms in humans and animals
- Understanding the early non-motor symptoms can help in early diagnosis and treatment
- Reducing exposure to harmful chemicals and pollutants can help lower risk for PD







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Thank You for Joining Us Today!

Our team will compile answers for any questions not addressed during the session. Find those answers on our Brain Awareness webpage in the following days.

Join our Upcoming Sessions:

- Wednesday 6pm – Brain and Mental Health Discussion Panel
- Thursday 3pm, 4pm, 6pm – Autism, Diverse Brains, Drug Abuse and the Brain

- For questions about the Brain Awareness Week at SUNY Empire, email brainawareness@esc.edu.