Exercises – *Origins of Parkinson's Disease beyond the brain*

1) Mechanism application

Compare the propagation of **α-synuclein** from the gut and from the olfactory bulb.

- What neuronal pathways have been proposed for each route?
- How do these pathways account for the sequence in which motor and non-motor symptoms appear?

2) Data critique

A recent *kidney-origin* study reported phosphorylated α-synuclein in patient kidney tissue and demonstrated kidney-to-brain propagation in mice.

- Why is the observation of aggregates in human kidney tissue not sufficient to establish causality?
- What additional experimental approaches would strengthen the kidney-origin hypothesis?

3) Experimental design

Design an experiment to test whether **gut dysbiosis** is a cause or a consequence of Parkinson's disease. Specify:

- Choice of human or animal model(s)
- Sampling strategy and time points
- Primary endpoints and appropriate controls
- One key statistical analysis you would apply

4) Integration of clinical and experimental evidence

- How do prodromal markers (e.g., constipation, hyposmia, REM sleep behaviour disorder) align with the "gut-first" and "nose-first" models of PD?
- Could kidney involvement suggest a different prodromal profile? Justify mechanistically.

5) Therapeutic implications

If Parkinson's can originate in multiple organs (gut, nose, kidney), why might a "one-size-fits-all" therapy fail?

- Propose one therapeutic strategy that could be effective across subtypes.

- Propose one strategy that would need to be tailored to the entry site, and explain how you would stratify patients.

6) Open discussion

If misfolded α-synuclein can originate in multiple organs, should Parkinson's disease be considered a **single disorder** or a **spectrum of related disorders**?
Discuss implications for:

- Diagnostic criteria
- Clinical trial design and endpoints
- Communication with patients and society