

Perceiving Parkinson's

The First Victims In Parkinson's (Day 14)

We just saw that neuron loss that is the best pathological marker of Parkinson's; Lewy bodies are second-best. Nevertheless, many previous autopsy studies chose to analyze Lewy bodies as a marker of Parkinson's. Since some of these studies have important findings, their use of Lewy bodies is tolerable so long as we remember that the death and loss of neurons is the true pathology behind Parkinson's.

In 2003, the German-born neuroanatomist Heiko Braak and colleagues devised a **pathological staging scheme** for Parkinson's. Based on the distribution and severity of Lewy body formation within the brains of 168 people, 41 of whom had been diagnosed with Parkinson's in life, he classified his findings into mild, moderate, and severe cases of Parkinson's.



Heiko Braak, originator of a pathological staging scheme for Parkinson's within the brain.

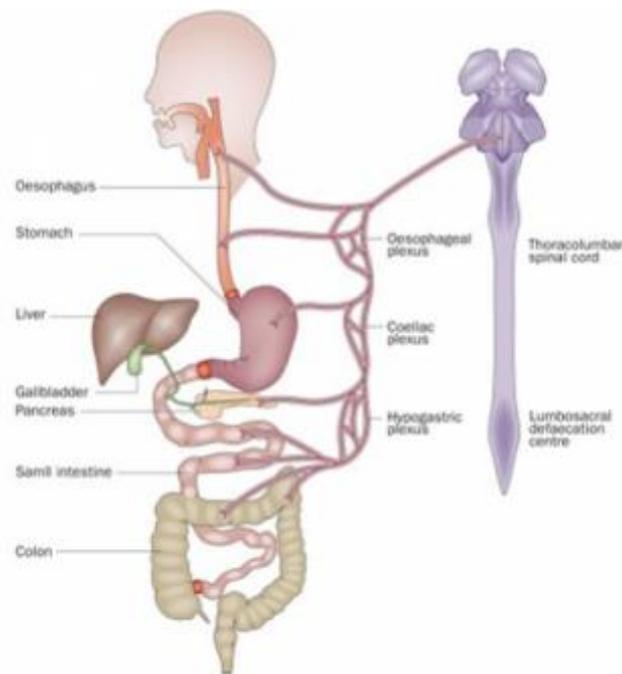
Braak categorized his findings as follows:

- (1) He classified **mild** cases as those that only had Lewy bodies in the **smell regions** (specific neurons in the brain responsible for smell) and **lower brainstem** (home to the neurons of the **vagus nerve**, a gigantic nerve that connects the brain to the gut's enteric nervous system).
- (2) He classified **moderate** cases as those that additionally had Lewy bodies in the **upper brainstem**, home to the **substantia nigra** which is essential for movement.
- (3) He classified **severe** cases as those that additionally had Lewy bodies in the **neocortex**, the thin outer layer of the brain that stores memories.

Based on these findings, Braak hypothesized that the neuron-killing process in Parkinson's occurs as follows - it starts in the **smell regions** or **lower brainstem**, then spreads to involve the substantia nigra, and lastly infiltrates the neocortex.

Braak did not examine the gut or its enteric nervous system in his autopsy series at the time. Had he done so, he would have also discovered something else that we have since learned - that Lewy bodies appear in the enteric nervous system **years** before a person is diagnosed with Parkinson's. In fact, Lewy bodies are present in the enteric nervous system of **nearly 100%** of people with Parkinson's and using the true pathological marker of neuron loss, **more than 90%** of the dopamine neurons in the enteric nervous system are lost in people with Parkinson's. Clearly, the enteric nervous system is affected very early in Parkinson's, and severely so.

These new facts spurred many researchers to modify Braak's initial scheme, some of whom now think that the neuron-killing process in Parkinson's starts in the **smell regions** or **enteric nervous system**, not the lower brainstem as Braak surmised. If the neuron-killing process starts in the smell regions then, at some point, it spreads to the rest of the brain. If the neuron-killing process starts in the enteric nervous system, it subsequently travels up the vagus nerve and creeps into the lower brainstem before spreading to involve the rest of the brain.



The vagus nerve connects the lower brainstem (top right) with the whole enteric nervous system.

This **modified** pathological staging scheme correlates rather well with the timeline of the clinical symptoms as they appear in Parkinson's:

(1) The **mild** pathological changes in Parkinson's, seen only in the smell regions and enteric nervous system, correlate with the initial symptoms of **loss of smell** or **constipation**. These symptoms usually occur years before a person is even diagnosed with Parkinson's such that by the time it is diagnosed, **up to 90%** of people already experience a degree of loss of smell and **up to 80%** of people already suffer from a degree of constipation.

(2) The **moderate** pathological changes in Parkinson's, seen additionally in the substantia nigra, correlate with the next symptoms that occur in Parkinson's - the cardinal motor symptoms of **tremor, bradykinesia, rigidity, and postural instability**. This is when the diagnosis of Parkinson's is made.

(3) The **severe** pathological changes in Parkinson's, seen additionally in the neocortex, correlate with the late symptom of **cognitive impairment** that occurs further down the road in Parkinson's.

Thus, based on both the pathological evidence and the clinical symptoms, the first victims in Parkinson's appear to be the **smell regions in the brain**, resulting in loss of smell years before the motor symptoms appear, and the **enteric nervous system in the gut**, resulting in constipation years before the motor symptoms appear. The neuron-killing process in Parkinson's preferentially attacks one or both these regions before it goes anywhere else, an observation we shall keep in mind as we go forward.

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References

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