# The path to Parkinson's disease: All roads lead to the nigrosome

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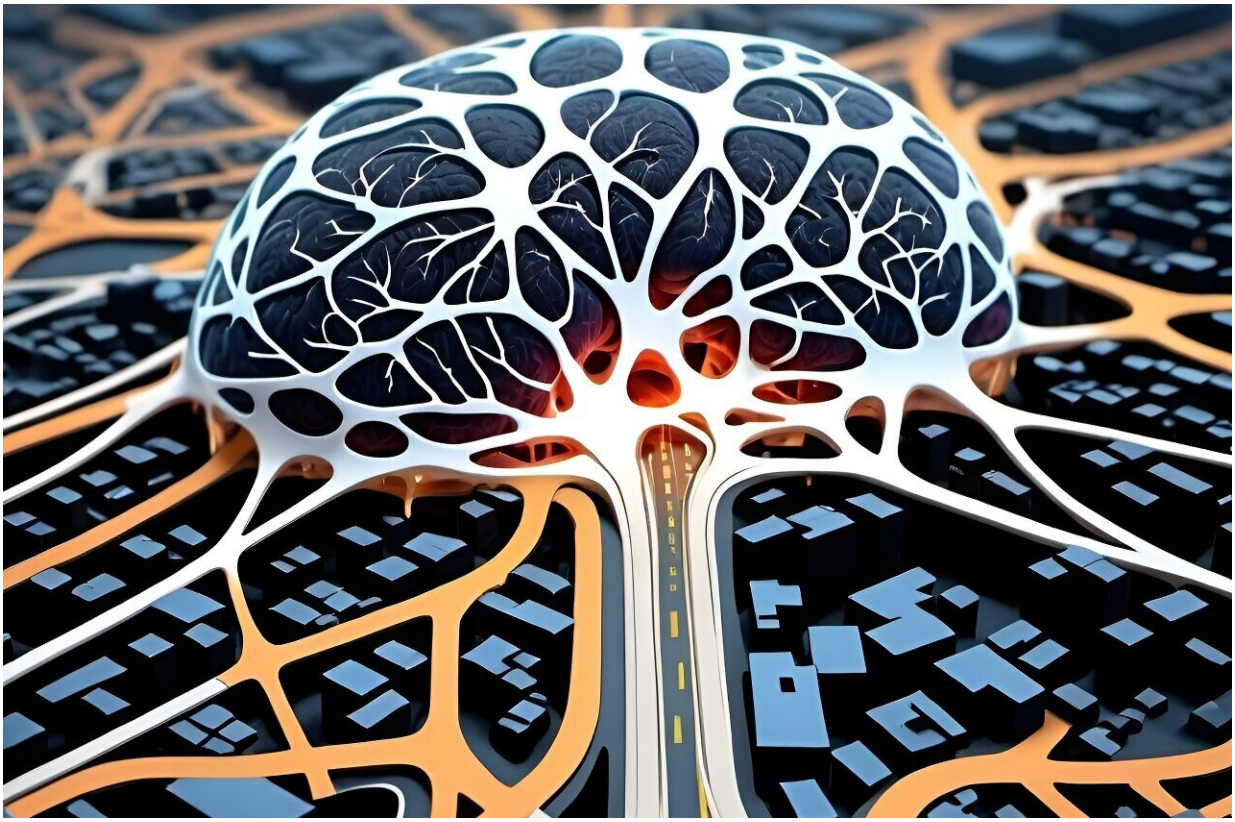

The nigrosome has an intricate and dense network of highways and streets, representing its rich vascularization. This dense network makes the nigrosome a major intersection, a key entry point for traffic, including not only necessary supplies but also potentially harmful elements. Credit: Image created by OpenArt AI tool

The main neuropathological feature of Parkinson's disease is the loss of dopaminergic neurons in the substantia nigra pars compacta. Specifically, dopaminergic neurons in the ventral tier of the substantia nigra pars compacta, also known as the nigrosome, are notably affected in Parkinson's disease, whereas those in the dorsal tier and ventral tegmental area demonstrate a much lower degree of degeneration.

## What is the nigrosome?

In 1999, Damier and colleagues identified two distinct sub-regions within the human substantia nigra using immunostaining against calbindin-D28K, a calcium-binding protein expressed in many neuronal populations. They found areas with low content of calbindin-D28K that they called nigrosome and others, highly stained with calbindin-D28K, that they called matrix.

Many studies have demonstrated that the nigrosome (also present in non-human primates) is the most vulnerable region of the substantia nigra. However, the specific reasons why these neurons are selectively vulnerable in Parkinson's disease, while others are more resilient, remain poorly understood.

Determinants of this selective vulnerability may include oxidative stress, dopamine toxicity, genetic factors, altered transport of molecules (including toxins) between blood and brain, and inflammatory and immune responses. Additionally, structural differences in the vasculature across various brain regions strongly influence where and how these factors manifest.

Therefore, our study aimed to investigate vascular structural changes in the nigrosome and other specific midbrain regions. Furthermore, we explored the differential impacts of inflammatory and immune cells on the vulnerability of dopaminergic neurons in these regions using a non-

human primate model of Parkinson's disease.

## A vulnerable highway in the midbrain's cityscape

Our study, recently published in *npj Parkinson's Disease*, uncovered a unique characteristic of the ventral tier of the substantia nigra pars compacta, known as the nigrosome.

Imagine the midbrain as a bustling city with various neighborhoods, each with its own network of roads and pathways. The nigrosome, in this cityscape, has an intricate and dense network of highways and streets, representing its rich vascularization.

This dense network makes the nigrosome a major intersection, a key entry point for traffic, including not only necessary supplies but also potentially harmful elements.

Under normal conditions, this busy hub ensures efficient delivery of nutrients and oxygen. However, in pathological circumstances, it becomes a double-edged sword. The very same highways that allow for efficient supply routes also make it an easy target for harmful invaders—toxins and immune cells, such as lymphocytes.

It's as if this area, because of its dense roadways, has become a favored route for these invaders, leading to traffic jams and blockages that exacerbate the vulnerability of the nigrosome.

Our observations in Parkinsonian animals confirmed this metaphor: Lymphocytes were seen preferentially flooding into this central hub, the nigrosome, while other neighborhoods in the midbrain remained relatively unaffected. This highlights the nigrosome's unique exposure and susceptibility, much like a critical crossroads in a city that, while essential, is also a vulnerable point for incoming threats.

Overall, our findings mark the first instance of proposing how specific mechanisms, such as neuroinflammation and immune cell infiltration, may exert a disproportionate influence on this region, likely attributable to its distinctive vascular cytoarchitecture.

Reducing the activation or entrance of T-cells with immunosuppressive drugs, or mitigating the deleterious effects of peripheral immune activity in this region, may one day enable clinicians to slow or delay the progression of the disease from the periphery to the CNS.

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**More information:** Tiziano Balzano et al, Neurovascular and immune factors of vulnerability of substantia nigra dopaminergic neurons in non-human primates, *npj Parkinson's Disease* (2024). DOI: 10.1038/s41531-024-00735-w

Tiziano Balzano is a postdoctoral researcher at HM CINAC (Centro Integral de Neurociencias Abarca Campal), Hospital Universitario HM Puerta del Sur, HM Hospitales, Madrid, Spain.