Dopamine cell death in Parkinson's disease:
why do specific cells in the substantia nigra die first?

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•**Background:** The symptoms of Parkinson's disease develop as a result of the relatively selective death of dopamine-producing cells in an area of the brain called the substantia nigra. (***Figure A***). In the human brain the substantia nigra is more complex in structure than in other species in that it is made up four different groups of dopamine-producing cells. These four cell groups are called the dorsal, ventral, lateral and medial tiers (***Figure B***). In PD the ventral and lateral tiers of cells suffer extensive cell loss in the early stages of the disease, while the dorsal and medial tiers are relatively preserved. Currently it is unknown why specific dopamine cells within the substantia nigra appear to be more vulnerable to the disease process but we believe that this may be related to the way these cells make dopamine. Tyrosine hydroxylase (TH) is an enzyme involved in the production of dopamine, and humans have 4 different types of TH: TH1, TH2, TH3 and TH 4. Each type of TH regulates the production of dopamine via different biochemical events but the consequences of this for the cell are unknown. We are investigating the hypothesis that specific biochemical events will result in increased production of dopamine, and therefore increased production of dopamine metabolites and other substances associated with cell damage in Parkinson's disease.
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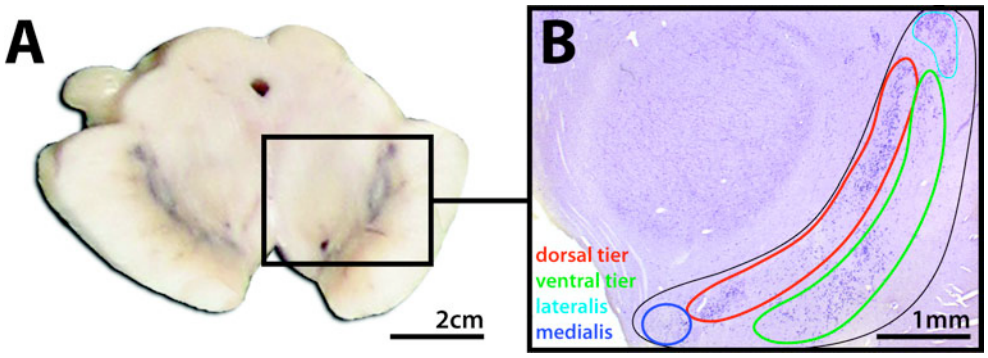

Figure legend: A Section through the human midbrain. The dark coloured substantia nigra is outlined in black.
B An enlarged image of the substantia nigra indicating the four tiers of cells.

Our research:.In this research project we are mapping the distribution of the different types of TH in each of the four tiers of the substantia nigra to investigate whether particular forms of TH are associated with cell death in Parkinson's disease. We are using biochemistry techniques to determine the different amounts of the four types of TH present and will also study the way in which each of the TH subtypes are controlled, and the consequences of this on the amount of dopamine produced. We hope this research will shed light on why particular dopamine-producing cells are more vulnerable in

Parkinson's disease and may lead to the development of new treatments or preventative approaches based on this knowledge. This project is partially supported by the National Health and Medical Research Council (NHMRC) of Australia but we are grateful for this Research Grant from Parkinson's NSW to support Ms Stefanie Reyes, a key researcher on this project, as Ms Reyes' position was not funded by the NHMRC.