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Challenging selective vulnerability in Parkinson's disease: a systematic review and meta-analysis

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Abstract

Selective vulnerability is widely assumed in Parkinson's disease (PD), but whether dopaminergic neurons of the substantia nigra are uniquely vulnerable has not been established. Explanations of neuronal degeneration in Parkinson's disease often centre on the distinctive properties of substantia nigra dopaminergic neurons. Whether these properties are necessary for substantial neuronal loss remains unclear. We reviewed 164 post-mortem studies and synthesised neuronal counts and densities from 149 studies using multilevel meta-analysis. Only 18% of brain regions of the Allen Brain Atlas had been examined. Substantial neuronal loss extended beyond dopaminergic and pigmented populations, challenging explanations centred on dopamine or neuromelanin. Evidence for other cell-autonomous hypotheses was mixed, with some findings contradicting their predictions. Sparse data limit these comparisons and leave the timing of loss unresolved. Our analysis identifies where further sampling could improve precision and where comparisons of affected and potentially spared populations could clarify selective vulnerability.

Introduction

The identification of nigral neuronal loss, the discovery of striatal dopamine depletion and the success of levodopa established the nigrostriatal system at the centre of Parkinson's disease (PD) research (Parent and Parent 2010; Przedborski 2017). Degeneration of dopaminergic neurons in the substantia nigra pars compacta is a characteristic pathological finding (Hughes et al. 1993). The clinical picture also extends beyond nigrostriatal dysfunction, including olfactory impairment that can precede a diagnosis of PD (Ross et al. 2008). Understanding PD therefore requires a broader account of which neuronal populations degenerate and what makes them susceptible.

Post-mortem studies have documented loss of noradrenergic (neurons in the locus coeruleus (Chan-Palay and Asan 1989; Huynh et al. 2021), cholinergic neurons in the basal nucleus of Meynert in PD with dementia (Whitehouse et al. 1983), and serotonergic neurons in the median raphe nucleus (Halliday, Blumbergs, et al. 1990). Loss also occurs in other parts of the dopamine system, including the ventral tegmental area (VTA) (Uhl et al. 1985). Within the substantia nigra pars compacta, ventrolateral populations are particularly affected (Fearnley and Lees 1991). This uneven loss is commonly described as selective vulnerability (Surmeier et al. 2017). Explaining the pattern requires reliable estimates of loss across populations and direct comparisons between them.

Proposed mechanisms of PD include interacting defects in mitochondrial function, protein handling and the cellular environment. Identifying these processes, however, does not explain why their effects differ across neuronal populations. Dopamine metabolism and neuromelanin have both been implicated in vulnerability (Masato et al. 2019; Filimontseva et al. 2025; Surmeier et al. 2017). Quantitative comparisons within and across neuronal classes can test how far these explanations extend, including whether substantial loss occurs in populations without the proposed feature. Such comparisons require estimates from both affected and potentially spared populations.

Neuronal counts have accumulated over decades but remain dispersed across studies. Giguère et al. (2018) compiled reported losses in a narrative review, while Zarow et al. (2003) compared several nuclei within one cohort using matched methods. Neither pooled estimates across the wider literature. Low statistical power can obscure true effects and inflate effect estimates among statistically significant findings, complicating comparisons of neuronal loss across populations (Button et al. 2013). Quantitative synthesis can estimate the extent of loss across populations while accounting for uncertainty and differences between studies (Higgins et al. 2009).

We preregistered a systematic review and used Bayesian multilevel meta-analysis to estimate neuronal loss across eligible populations defined by region and neuron type. We examined the distribution of loss and the limits it places on proposed explanations of selective vulnerability. We also identified gaps in anatomical coverage and populations with substantial estimated loss that require independent replication or more precise measurement.

Results

Evidence remains concentrated in a few regions

We identified 164 post-mortem studies of Parkinson's disease published between 1963 and 2025. Of these, 149 contributed to the meta-analysis, representing 144 neuronal populations in 84 brain regions. Fifteen studies did not contribute eligible quantitative PD–control comparisons (Supplementary Table S1). Less precise estimates were associated with greater neuronal loss in the study–population model (standard-error slope -0.80 on the log-ratio scale; 95% credible interval, -1.30 to -0.31; Supplementary Figure 2).

Research focused on the substantia nigra (SN) (65 studies), locus coeruleus (LC) (20), basal nucleus (BN) (14) and ventral tegmental area (VTA) (10). Among broader anatomical groups, the midbrain appeared in 78 studies, compared with 22 for the pons, 16 for the medulla, ten for the cortex and three for the cerebellum (Fig. 1a). Together, the studies covered only 18% of countable brain atlas labels (109 of 597). Four studies examined enteric populations.

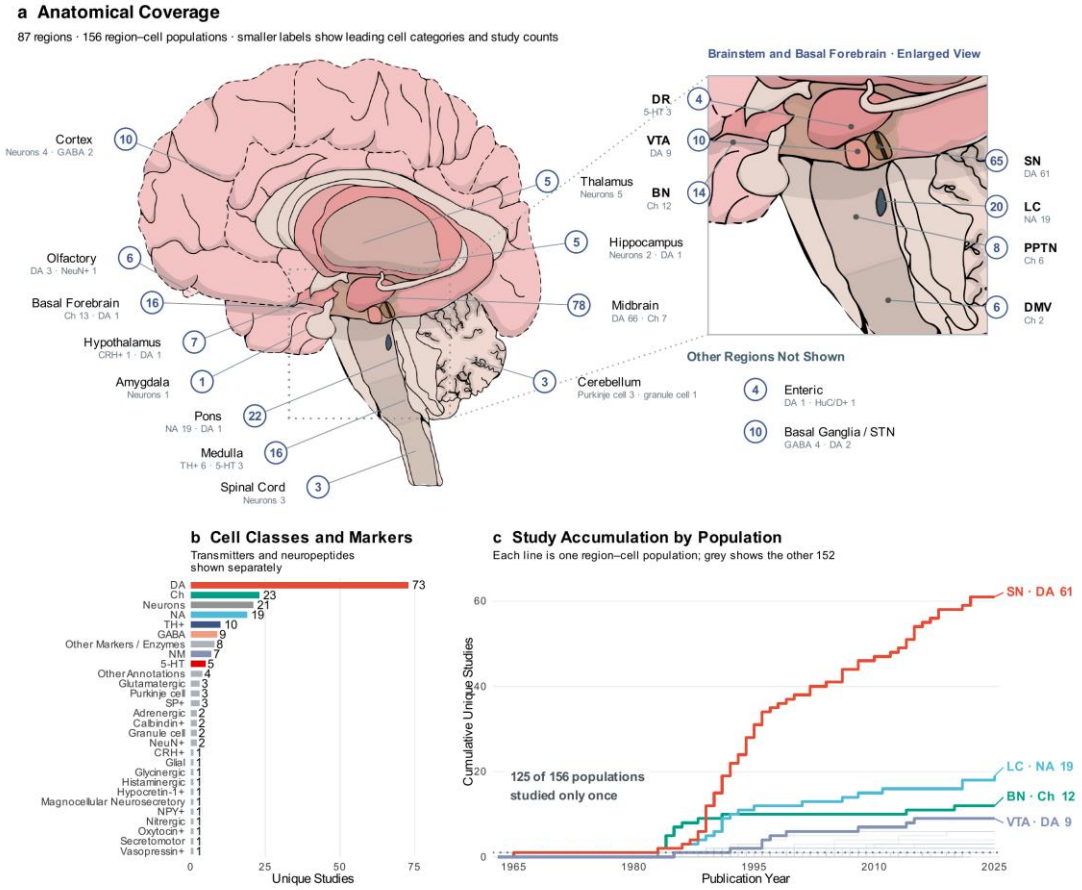


Figure 1: Anatomical and cellular concentration of the PD neuropathology evidence base. (a) Distinct studies by broad anatomical group (left) and selected nucleus (right), displayed in numbered badges. The dotted outline and grey connectors identify the brainstem and basal-forebrain region enlarged at right. Smaller labels show study counts for up to two leading cell categories per broad group and one per selected nucleus, with ties resolved alphabetically. Positions are schematic, including projected lateral structures. Groups summarise 87 curated regions; a study can contribute to several groups. (b) Distinct studies by recorded cell class or marker category, in descending order. Transmitter and neuropeptide categories are shown individually. Remaining single-study marker/enzyme, glial and other annotations are grouped, with each study counted once per bar. Categories can overlap within a publication. (c) Cumulative distinct studies for all 156 region–cell populations, highlighting SN DA, LC NA, BN Ch and VTA DA. Each publication contributes at most once per population. The dotted line marks one study, the final count for 125 populations. Separate publications need not represent independent donor cohorts. SN, substantia nigra; LC, locus coeruleus; BN, basal nucleus of Meynert; VTA, ventral tegmental area; DR, dorsal raphe nucleus; PPTN, pedunculopontine tegmental nucleus; DMV, dorsal motor nucleus of the vagus; STN, subthalamic nucleus; DA, dopaminergic; Ch, cholinergic; NA, noradrenergic; GABA, gamma-aminobutyric acid; TH+, tyrosine hydroxylase-positive; NM, neuromelanin-pigmented; 5-HT, serotonergic; SP+, substance P-positive; NeuN+, neuronal nuclear antigen-positive; CRH+, corticotropin-releasing hormone-positive; NPY+, neuropeptide Y-positive; HuC/D+, HuC/HuD-positive. Full population terminology is provided in the repository population label key.

Evidence was also concentrated in a few neuronal classes. Dopaminergic (DA) neurons were examined in 73 studies, cholinergic (Ch) neurons in 23 and noradrenergic (NA) neurons in 19. GABAergic (GABA) and serotonergic (5-HT) neurons appeared in nine and five studies, respectively, while glutamatergic neurons and Purkinje cells each appeared in three (Fig. 1b). A further ten studies reported tyrosine hydroxylase-positive (TH+) counts and seven reported neuromelanin-pigmented (NM) counts without assignment to a transmitter class. Twenty-one studies reported neurons without a specified type, predominantly using general histological stains such as cresyl violet, Nissl, and haematoxylin and eosin (H&E) (Fig. 1b). Glycinergic, histaminergic and nitrergic populations were each examined in one study.

This concentration persisted across the publication record. By 2025, SN DA neurons had been examined in 61 studies, compared with 19 for LC NA, 12 for BN Ch and nine for VTA DA neurons (Fig. 1c). Of the 156 region–cell populations recorded in the review, 125 (80%) appeared in only one study and 31 in two or more. Six decades of counting therefore provided repeated observations for a few populations while leaving most without replication.

Substantial estimated loss extends beyond the best-studied populations

Estimates across all 144 modelled populations show a wide range of neuronal deficits (Fig. 2a,b). Among populations studied more than once, SN DA and LC NA neurons had the largest estimated losses: 67% (95% credible interval, 63–70%) and 63% (58–68%), respectively. Several populations represented by one study also had large estimated losses, including substance P-positive (SP+) neurons in the medullary reticular formation (Med RF) (58%, 38–73%) and median raphe (MnR) (58%, 42–70%). Two studies supported an estimated 46% loss in parafascicular nucleus of thalamus (Pf) neurons (30–58%; Fig. 2a).

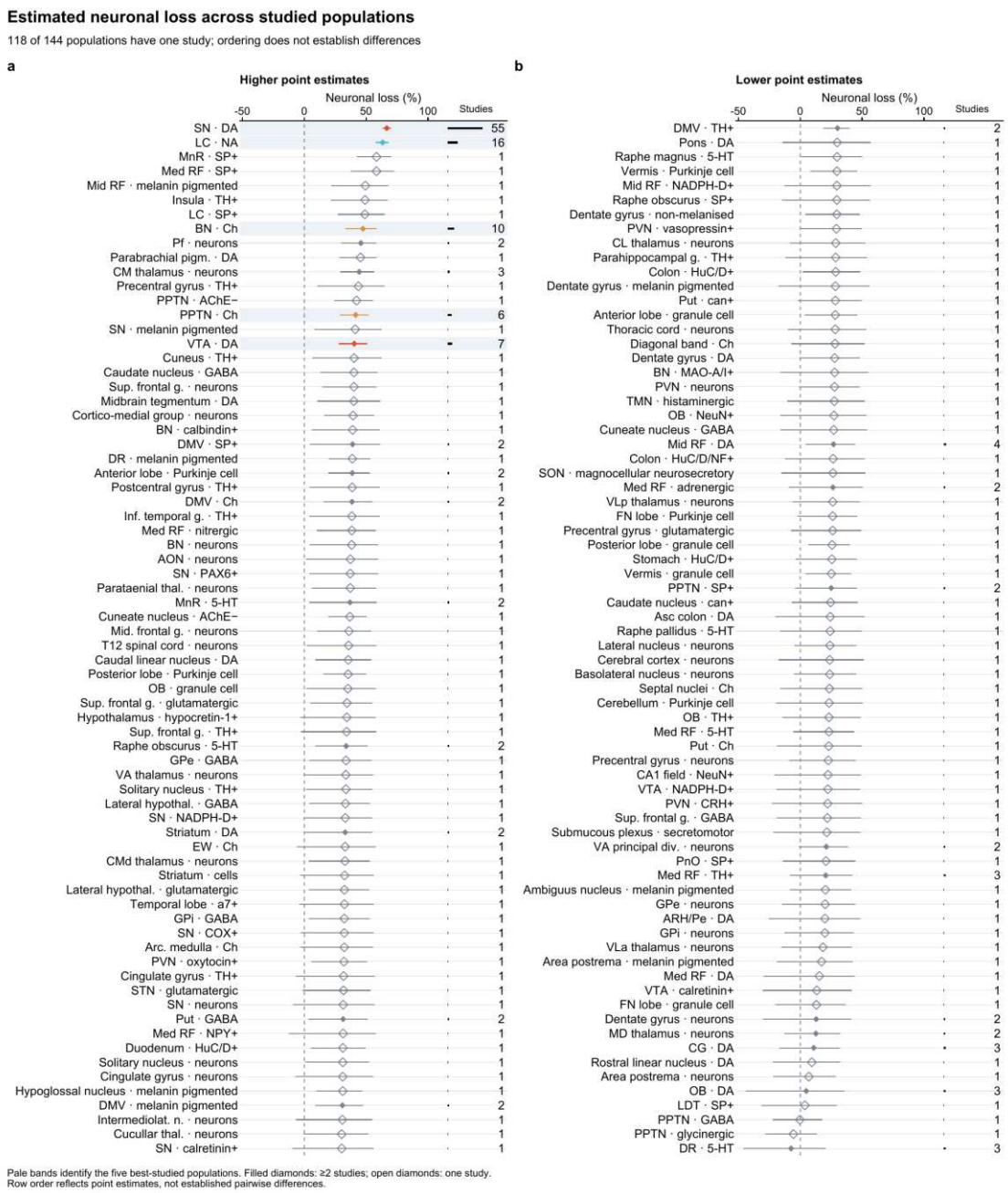


Figure 2: Estimated neuronal loss and 95% credible intervals across all 144 fitted neuronal populations. Pale bands highlight the five most-studied populations, coloured by transmitter class. Filled diamonds denote two or more studies; open diamonds denote one. Bars and numbers at the right show the number of contributing studies. Populations are ordered by point estimate, without implying established pairwise differences. Cell labels retain source-study marker definitions. The repository population label key provides the complete label key and abbreviations.

Some population estimates combined opposing observations. The two studies of intrinsic striatal TH+ neurons reported approximately 56% higher and 78% lower counts in PD than in controls (Porritt et al. 2006; Huot et al. 2007). Partial pooling drew the combined estimate towards the shared distribution, so it should be interpreted alongside the disagreement between studies.

The olfactory bulb (OB) DA estimate was imprecise: 5% loss, with an interval spanning both higher and lower counts in PD (-44 to 36%; Fig. 2b). The extracted group means from all three contributing studies were 13–108% higher in PD than in controls (Huisman et al. 2004, 2008; Mundiñano et al. 2011), but partial pooling shifted the population estimate towards loss.

Population comparisons constrain proposed explanations of vulnerability

Substantial loss extended beyond the pigmented midbrain populations that shaped early accounts of selective vulnerability (Hirsch et al. 1988). LC NA and BN Ch neurons showed substantial loss outside the DA class, while estimates within the DA class varied: 40% (28–51%) in VTA, 11% (-17 to 32%) in central grey substance of midbrain (CG), and 5% (-44 to 36%) in OB neurons (Fig. 3a). Dopaminergic identity is therefore not necessary for substantial loss, limiting explanations that require this identity in every affected population. This does not exclude a contribution from dopamine and its reactive metabolites within DA neurons (Masato et al. 2019). Similarly, BN Ch neurons showed 47% (33–58%) loss outside the classical pigmented catecholaminergic populations (Fig. 3b). Together with affected pigmented SN DA and LC NA populations, this extends the observed deficits beyond the populations emphasised in neuromelanin-based accounts, without excluding a contribution of neuromelanin within pigmented populations (Whitehouse et al. 1983; Filimontseva et al. 2025).

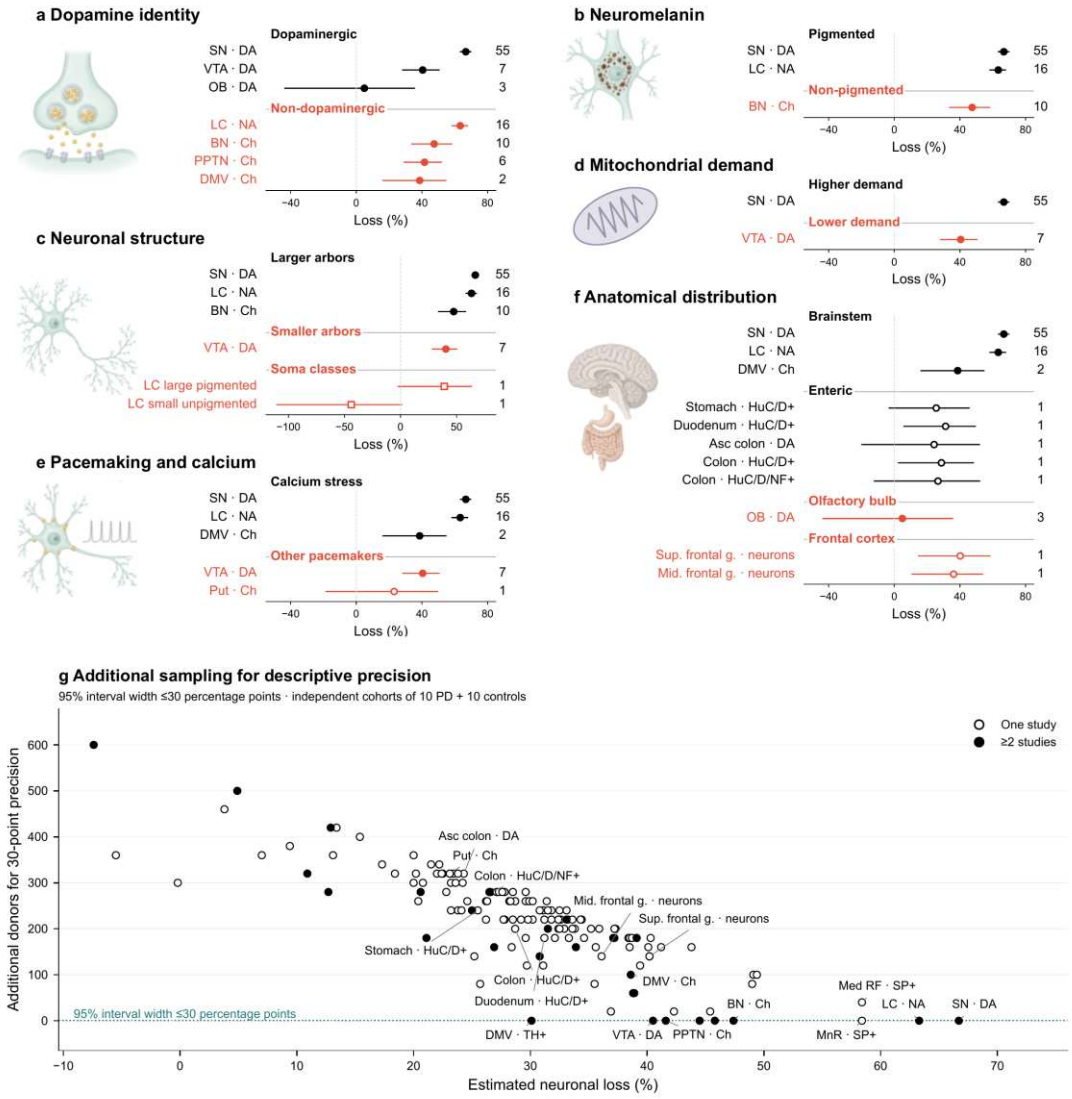


Figure 3: Neuronal loss and additional sampling across populations. (a–f) Populations grouped by dopamine identity, neuromelanin, neuronal structure, mitochondrial demand, pacemaking and calcium stress, and anatomical location. Circles and bars show pooled loss and 95% credible intervals; negative values indicate higher counts or densities in PD. Numbers give contributing studies. Open points denote one study; filled points denote at least two. Black and red distinguish reference and comparison groups, without testing rejection of a hypothesis. VTA labels describe relative arbor size and demand compared with SN. Other pacemakers does not imply absence of calcium signalling. Annotations draw on separate human and non-human literature (Methods: Biological annotations and morphology). Panel c also shows large pigmented and small unpigmented LC neurons from Hoogendijk et al. (1995), table 3 in that publication. Open squares show reductions from group means for five PD and five control donors, with approximate 95% confidence intervals. These classes share donors and overlap the pooled LC evidence; they are illustrative comparisons. Panel c uses a wider horizontal range. (g) Estimated loss against additional donors needed for a conditional 95% interval width of at most 30 percentage points. All fitted populations are shown. Open points denote one study; filled points denote multiple studies. Points on the zero line already meet the target. Planning assumes independent cohorts of 10 PD and 10 control donors, a fixed log-ratio posterior centre and fixed cohort variance. New observations may change both estimated loss and heterogeneity. These calculations describe conditional precision, not assurance or detection power. Illustrations are schematic. The repository population label key defines population labels; Supplementary Table S2 provides planning results and 20- and 40-point sensitivity targets.

Human and chimpanzee cortical axon-density measurements and basal-forebrain neuron counts suggest extensive axonal arbours in Ch neurons (Raghanti et al. 2008; Raghanti et al. 2011; Wu et al. 2014). These population-derived estimates, considered alongside substantial BN Ch loss, are consistent with the proposed link between axonal extent and vulnerability (Fig. 3c). Several included studies also measured soma size or described dendritic shortening and loss. However, the axonal-arbour estimates used here came from separate anatomical studies and were not linked to donor-level loss in this synthesis. The comparison therefore does not establish that axonal maintenance demands caused the observed loss.

Mouse experiments link calcium entry during autonomous activity to mitochondrial oxidant stress in SN DA, LC NA and DMV Ch neurons Guzman et al. (2015). Our human synthesis identifies loss in these populations and in VTA DA neurons. Mouse VTA DA pacemaking can persist after replacement of extracellular calcium with magnesium (Khaliq and Bean 2010), but this does not establish absence of calcium-associated stress under normal conditions. Figure 3e places human loss estimates alongside experimental physiological evidence; it does not directly test whether calcium-associated stress explains differences in vulnerability.

The anatomical comparison identified affected brainstem and enteric populations. Ascending-colon DA neurons had an estimated 24% loss (95% credible interval, -20 to 52%; Fig. 3f), based on one study, with the interval spanning no loss. The OB provides a rostral comparison: its DA loss estimate remained uncertain, while the partially pooled estimates indicated lower counts in the superior and middle frontal gyri. These estimates incorporate information across populations; they should not be read as independent confirmation of loss in both regions by the original cortical counting study (Halliday et al. 2005). These findings concern regions relevant to Braak staging and brain-first/gut-first accounts (Braak et al. 2003; Borghammer and Van Den Berge 2019), but anatomical proximity and cross-sectional deficits cannot establish the direction or sequence of degeneration. Clinical information was available in 105 of 164 studies (64%), but inconsistent reporting prevented adjustment to a common level of clinical severity.

Precision of population estimates

We assessed precision using a target 95% interval width of no more than 30 percentage points, approximately ±15 percentage points around the estimated loss (Methods: Precision planning). This was a practical target for narrowing uncertainty about the magnitude of loss; it did not define categories of low, moderate or high loss. Only 9 of 144 populations met the target. Eight of these were represented by multiple studies, including SN DA, LC NA, BN Ch, VTA DA and PPTN Ch; one was represented by a single study. Because partial pooling draws information from other populations, a narrow model interval can arise even when direct evidence is limited to one study. Meeting the precision target therefore does not, by itself, establish independent replication.

For the 135 populations falling short of the target, the median conditional requirement was 220 additional donors (range 20–600). Medullary reticular formation SP+ neurons, reported by Halliday, Li, et al. (1990), required an estimated 40 additional donors (Fig. 3g). These estimates describe the sampling needed to narrow uncertainty around the magnitude of loss under the assumptions specified in Methods: Precision planning. Two populations met the narrower 20-point target and 24 met the broader 40-point target (Supplementary Table S2).

Robustness to study methods and annotation

Adjustment for counting method changed the overall loss estimate from 31.0% to 30.4%. Model-adjusted loss was 35.5% (26.4–43.8%) under manual counting, 25.6% (13.9–36.3%) under computer-assisted counting and 29.3% (18.2–39.5%) under stereology (95% credible intervals; Supplementary Table S3). The 95% credible intervals for all pairwise method contrasts included

zero, leaving differences between methods unresolved rather than establishing equivalence. Counting method also varied with publication era, study quality and the populations studied, so these comparisons cannot isolate a causal effect of counting technique.

Excluding inferred neuron-type labels gave 33.7% loss, compared with 30.9% in the corresponding all-data analysis (Supplementary Table S4). The association between risk-of-bias checklist scores and estimated loss remained uncertain (log-ratio slope 0.043 per point; 95% credible interval, -0.009–0.094; Supplementary Table S5). These associations cannot isolate the contribution of individual methodological features.

Discussion

Selective vulnerability needs explicit comparisons: which populations are disproportionately affected, relative to which others, and at what stage of disease? The concept has expanded from regional selectivity to anatomical, chemical and molecular explanations, yet most evidence still comes from a few familiar populations. Our synthesis brings these observations together and shows substantial neuronal deficits beyond SN DA neurons. These findings constrain explanations that require dopaminergic identity or neuromelanin in every affected population, while leaving the broader distribution of selectivity unresolved.

Across 149 studies and 144 neuronal populations, estimated neuronal loss averaged 31%. This estimate describes the populations studied, rather than the fraction of all neurons lost in PD. Substantial LC NA and BN Ch loss shows that dopaminergic identity is not necessary for marked degeneration. BN Ch loss also extends beyond classically neuromelanin-containing populations. Both features may contribute to vulnerability, but neither is required for substantial loss. Co-pathology may also contribute, although basal nucleus loss has been reported in PD without concomitant Alzheimer's disease (Nakano and Hirano 1984). Inconsistent reporting prevents us from quantifying its contribution to the pooled LC and BN estimates.

These findings do not establish that degeneration is non-selective. Loss across several systems can coexist with selective loss within each region. The missing evidence is the comparison with neighbouring or related populations that may be spared. Six decades of counting have covered only 18% of countable brain atlas labels, and most populations have been studied once. Repeated studies confirm degeneration in familiar targets without establishing how exceptional those targets are. The resulting map reflects both vulnerability and the choice of populations to study.

Less-studied populations provide further evidence that substantial deficits are not confined to the usual targets. Estimated loss was 58% in medullary reticular formation SP+ neurons (95% credible interval, 38–73%; Halliday, Li, et al. 1990) and 58% in median raphe SP+ neurons (42–70%; Gai et al. 1991). These estimates need independent replication. Under our planning assumptions, 40 additional donors would narrow the medullary reticular formation estimate to a 95% credible interval no wider than 30 percentage points. Replication could establish whether these deficits recur; comparisons with potentially spared populations would test their selectivity.

Adjusting for whether studies used manual counting, computer-assisted counting or stereology changed estimated neuronal loss from 31.0% to 30.4%. Model-adjusted neuronal loss remained substantial under stereology: 66% in SN DA (64–69% with other counting methods), 63% in LC NA (61–66%), 44% in BN Ch (41–49%) and 39% in VTA DA neurons (36–45%). Differences between counting methods remained uncertain. Neuronal loss did not clearly differ between studies with higher and lower risk-of-bias checklist scores. Inconsistent reporting of co-pathology and donor exclusion criteria limited our ability to assess how cohort composition contributed to differences in neuronal loss. Less precise studies also reported greater loss, so funnel asymmetry remains a concern when interpreting the pooled estimates.

An explanation of vulnerability must account for timing as well as distribution. Our exploratory Fearnley–Lees analysis did not establish different cross-sectional age slopes between PD and controls (Fearnley and Lees 1991; Methods: Robustness checks). Deficits could therefore predate the sampled ages. These counts cannot distinguish earlier degeneration, developmental differences or age-related failure of compensation (Schwamborn 2018). Inconsistent donor-level clinical reporting further limited comparisons across disease stages. Future studies should link neuronal counts to each donor's age at symptom onset, diagnosis and death, with disease duration clearly defined. Reporting dementia status and assessed co-pathology would also help separate differences in cohort composition from differences between neuronal populations.

The evidence therefore supports substantial neuronal deficits across several systems, while leaving their regional and cellular selectivity incompletely tested. Progress requires replicated comparisons of affected and potentially spared populations, preferably measured in the same donors. Studies should prioritise under-sampled populations with substantial estimated loss and include neighbouring or related populations as explicit comparators. Shared anatomical definitions, counting protocols and donor-level data would make these comparisons easier to combine across studies. Together, these steps would allow proposed mechanisms of vulnerability to be tested against defined population differences rather than inferred from familiar examples.

Methods

Review design and eligibility

We preregistered the review with PROSPERO on 13 July 2021 (CRD42021265515). The protocol comparison documents subsequent changes, including narrower disease eligibility and revised statistical analysis (Supplementary Table S6, supplied in the Supplementary Information). Reporting uses PRISMA 2020 guidance (Page et al. 2021), with outstanding reporting items identified in the PRISMA checklist.

We included human post-mortem case-control studies reporting neuronal counts or densities in idiopathic Parkinson's disease, with or without dementia, and controls without known neurodegenerative disease. We excluded separately classified dementia with Lewy bodies, atypical or secondary parkinsonism, primary Alzheimer's disease, familial cases, single-case reports, animal studies, reviews and conference abstracts. Coexisting pathology within otherwise eligible PD cohorts was not uniformly excluded. Meta-analysis required comparable quantitative PD and control measurements.

We reassessed eligibility during extraction, excluding young-onset PD cohorts and the short-duration striatal group in Porritt et al. (2006). Supplementary Tables S1, S7 and S8 document study and subgroup exclusions and diagnostic classifications. We recorded age matching, blinding and neuropathological confirmation where reported.

Search and study selection

We searched MEDLINE, EMBASE, BIOSIS and Web of Science without publication-year restrictions and updated the searches in 2025 (Supplementary Table S9, supplied in the Supplementary Information). During search development, we checked whether the searches retrieved studies identified by Giguère et al. (2018). We prioritised English-language publications, but translated and included a Japanese-language study (Ohno et al. 1991). We did not search preprints, grey literature or theses.

After deduplication across databases, four reviewers (WL, MS, JC and JAM) screened titles and abstracts. At least two reviewers assessed each record independently. Disagreements were

resolved by discussion, with SB consulted where needed. Five reviewers (WL, MS, JC, JAM and SB) participated in full-text assessment. The PRISMA flow diagram and Supplementary Tables S1, S7 and S8 document study selection and exclusions.

Exact executed search histories remain unverified, and 26 retrieval records have unresolved dispositions (the PRISMA checklist and Supplementary Table S9).

Data extraction and risk of bias

Five reviewers (WL, MS, JC, JS and JAM) extracted study characteristics, diagnostic groups, brain regions, neuron types, markers, counting methods, group means, sample sizes and measures of variability into a shared database. We also recorded age, disease characteristics, age matching and blinding where available. We digitised values reported only in figures and calculated group summaries from individual observations where available. Disagreements were resolved by checking the source and discussing the extraction. Supplementary Table S10 describes the modelled study-population comparisons; Supplementary Table S11 summarises counting methods, blinding and age matching across included studies.

We assessed risk of bias using an adapted eight-item Joanna Briggs Institute checklist (Joanna Briggs Institute 2017; Supplementary Table S12). Scores counted affirmative responses, with higher scores indicating more criteria met. JAM checked and corrected selected ratings against source records. Records do not establish independent duplicate assessment of every full text or risk-of-bias rating.

Data preparation and population definitions

We standardised region, neuron-type and marker labels using curated mappings (Supplementary Table S8 and the repository atlas mappings). We inferred broader neuron classes from region and marker where possible and recorded these inferences. We combined SNc and unspecified SN DA measurements, and paranigral and VTA DA measurements (McRitchie et al. 1997). We excluded whole-midbrain DA counts combining A8–A10 populations, nigral m-calpain measurements and two non-neuronal CA1 populations. Marker-defined subsets were retained separately, and unresolved whole-striatum labels were not assigned to caudate or putamen.

We selected one measurement per study–population combination, prioritising stereology, then computer-assisted and manual counting; preferred markers; then larger combined sample sizes. Selection was independent of estimated loss. The repository marker-priority list gives marker priorities; TH, DBH and neuromelanin had equal priority for noradrenergic neurons. This reduced 282 eligible measurements to 261 estimates, removing 21 duplicates from 20 study–population combinations.

We derived standard deviations from reported variability where possible and treated values exceeding ten times the absolute mean as missing. Missing values were imputed using the median coefficient of variation from the same paper, then the same population, then the dataset-wide 75th percentile. Eighteen effects from eight studies included an imputed standard deviation.

For 19 effects from 17 studies, we combined repeated summaries using average means, rounded average sample sizes and root-mean-square standard deviations (Supplementary Table S13). This approximation does not reconstruct the variance of averaged measurements. Independent PD faller and nonfaller groups were pooled by sample size, including between-group variation, with their shared control group retained once (Karachi et al. 2010).

We mapped anatomical labels to the Allen Brain Atlas ontology (Hawrylycz et al. 2012). Deduplication and exclusion of ventricular, sulcal, subarachnoid and white-matter labels left 597

entries in the coverage denominator. Because parent and child labels can overlap anatomically, coverage refers to atlas labels rather than brain volume. The repository atlas mappings report the mappings from source labels to atlas entries.

A shared dictionary standardises region, neuron-class and marker names across the text, figures and analytical tables (the repository population label key). The anatomical mapping table retains source labels and atlas identifiers verbatim.

Statistical analysis

We used R 4.6.1 (R Core Team 2026), metafor 5.0.1 for effect-size calculations (Viechtbauer 2010), and brms 2.23.0 with Stan for Bayesian meta-analysis (Bürkner 2017).

For each study and population, we calculated the log ratio of mean neuronal count or density in PD to that in controls. We used metafor::escalc with measure = "ROM", correct = TRUE and vtype = "LS" for small-sample bias correction and large-sample sampling variances (Hedges et al. 1999; Lajeunesse 2015). Results are expressed as percentage loss:

$$R = \frac{\overline{x}_{\mathrm{PD}}}{\overline{x}_{\mathrm{control}}}, \qquad L = 100(1 - R).$$

Here, $\overline{x}$ is the group mean count or density, R the ratio of means and L the percentage loss. Positive loss indicates lower counts or densities in PD; negative loss indicates higher values. These are cross-sectional differences relative to controls. Marker-defined counts can also change with marker expression (McRitchie et al. 1997; Huot et al. 2007).

We fitted a Bayesian multilevel model with random intercepts for study and population (region–cell type). The study intercept captures shared variation within papers; the population intercept represents average loss in each population. Partial pooling draws uncertain estimates towards the overall distribution. Sampling variances were fixed, and sampling errors were independent conditional on the model effects.

The intercept prior was Student-t(3, −0.5, 2.5); random-effect standard deviations had half-Student-t(3, 0, 2.5) priors. Four chains each used 4,000 iterations, including 2,000 warmup iterations (adapt_delta = 0.95; max_treedepth = 12; seed = 42). Diagnostics and software versions are archived with the code.

We transformed posterior mean log ratios to percentage loss and posterior quantiles to 95% credible intervals. The overall mean describes the sampled populations, not the fraction of all neurons lost.

Biological annotations and morphology

Figure 3 uses qualitative annotations from separate anatomical and physiological literature. Pigmentation follows conventional classifications. Arbor and metabolic comparisons draw on rodent reconstructions, culture experiments and primate anatomical estimates (Matsuda et al. 2009; Wu et al. 2014; Pacelli et al. 2015; Giguère et al. 2019; Su et al. 2026). No common quantitative threshold was applied. Pacemaking was distinguished from calcium-linked stress (Guzman et al. 2010; Sánchez-Padilla et al. 2014; Goldberg et al. 2012; Khaliq and Bean 2010). Comparator labels do not imply absence of calcium signalling or oxidative stress. Annotations were not measured in the reviewed donors.

We screened abstracts and extraction labels for morphology measures and checked selected full texts; this was not an exhaustive full-text review (Supplementary Table S14). Soma size, dendrites and fibre density were considered separately, without pooling. Figure 3c compares large

pigmented and small unpigmented LC neurons from the same five PD and five control donors (Hoogendijk et al. 1995). Reductions use group means, with approximate confidence intervals from the log-ratio delta method and Welch–Satterthwaite degrees of freedom. These classes differ in size and pigmentation and overlap the pooled LC evidence.

Robustness checks

We added counting method as a three-level factor, with manual counting as the reference, and the eight-item risk-of-bias score as a continuous predictor in separate Bayesian models (Supplementary Tables S3 and S5). Random effects and sampler settings were unchanged. We tested sensitivity to inferred neuron-type labels using the same frequentist REML population model for all labels and reported labels only; these estimates use confidence intervals (Supplementary Table S4). We assessed small-study effects by adding effect-size standard error to the Bayesian model (Egger et al. 1997). A negative slope indicates greater loss in less precise studies, but does not identify the cause of funnel asymmetry (Supplementary Figure 2).

For the exploratory Fearnley–Lees analysis, we regressed counts from 36 control and 20 PD donors on age at death, PD/control group and their interaction, then repeated the analysis at ages ≥50 years (Fearnley and Lees 1991). The PD-minus-control slope differences were −1.6 neurons/year (95% confidence interval, −7.9 to 4.6) and −1.2 (−8.2 to 5.9), respectively. These are cross-sectional associations.

Precision planning

We used SampleSizeMeans 1.2.3 to estimate additional independent cohorts of 10 PD and 10 control donors needed for a conditional 95% interval width of at most 30 percentage points (Joseph and Bélisle 2023). This is a working precision target, not a threshold for biological importance. We included all 144 fitted populations and tested widths of 20 and 40 points (Supplementary Table S2). We approximated each log-ratio posterior by a normal distribution and fixed its mean. Future cohort variance was fixed at the posterior mean between-study variance plus one tenth of the sum of squared median group coefficients of variation. We converted the percentage-point target to log-ratio width, used mu.varknown, and rounded requirements up to whole cohorts before checking the target. These scenarios estimate conditional precision, not detection power or the probability of reaching the target. We report replication separately because partial pooling can produce narrow intervals with limited direct evidence. Donor requirements cannot be summed across populations.

Reproducibility

Data preparation and analysis use R. The repository contains curated extractions, mapping rules, analysis scripts, recorded package versions and the edited manuscript. Access details are given in the Data and Code Availability statement. OpenAI Codex assisted with code development, source checking and manuscript editing. The authors are responsible for the analyses and final content.

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Author Contributions

Will Lunt and Jay A. Moore contributed equally and are joint first authors.

WL, MS, JC and JAM screened records. WL, MS, JC, JAM and SB assessed full-text eligibility and risk of bias. WL, MS, JC, JS and JAM extracted and curated data. JAM performed the formal analysis, verified extractions and corrected risk-of-bias assessments against source records. SB resolved screening disagreements. NGS supervised the study and secured funding. All authors reviewed and edited the manuscript.

Competing Interests

The authors declare no competing interests.

Data Availability

Curated study extractions, analysis datasets and mapping rules are available at https://github.com/neurogenomics/pd-systematic-review-and-meta-analysis, release v1.0.0 (https://github.com/neurogenomics/pd-systematic-review-and-meta-analysis/releases/tag/v1.0.0). Supporting records include atlas mappings, population labels and marker priorities.

Code availability

Analysis code and the reproduction guide are available at https://github.com/neurogenomics/pd-systematic-review-and-meta-analysis, release v1.0.0. The guide describes how to inspect the supplied results and refit the models from curated data, including dependencies and model settings.

Ethics Statement

This study is a systematic review and meta-analysis of previously published data from post-mortem studies. No new human tissue was collected or analysed. Ethics approval was not required.

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