

“What if our understanding of Parkinson’s disease is also impeding our ability to find cures?

Could it be that generating hypotheses based on what we think we know, along with our rigid funding models, is making it nearly impossible to find what we really need to know?”

[link](#)

Cell loss in Parkinson's disease?

A meta-analysis re-evaluating the evidence for selective vulnerability

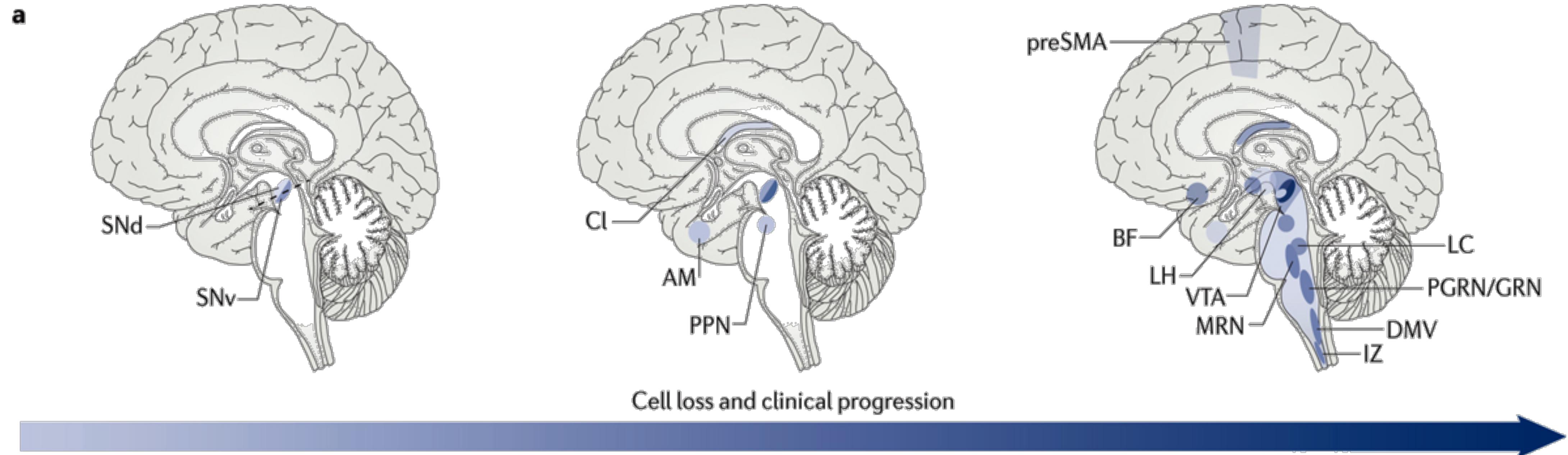
Samuel Burke

PhD Neuroscience, Université de Montréal

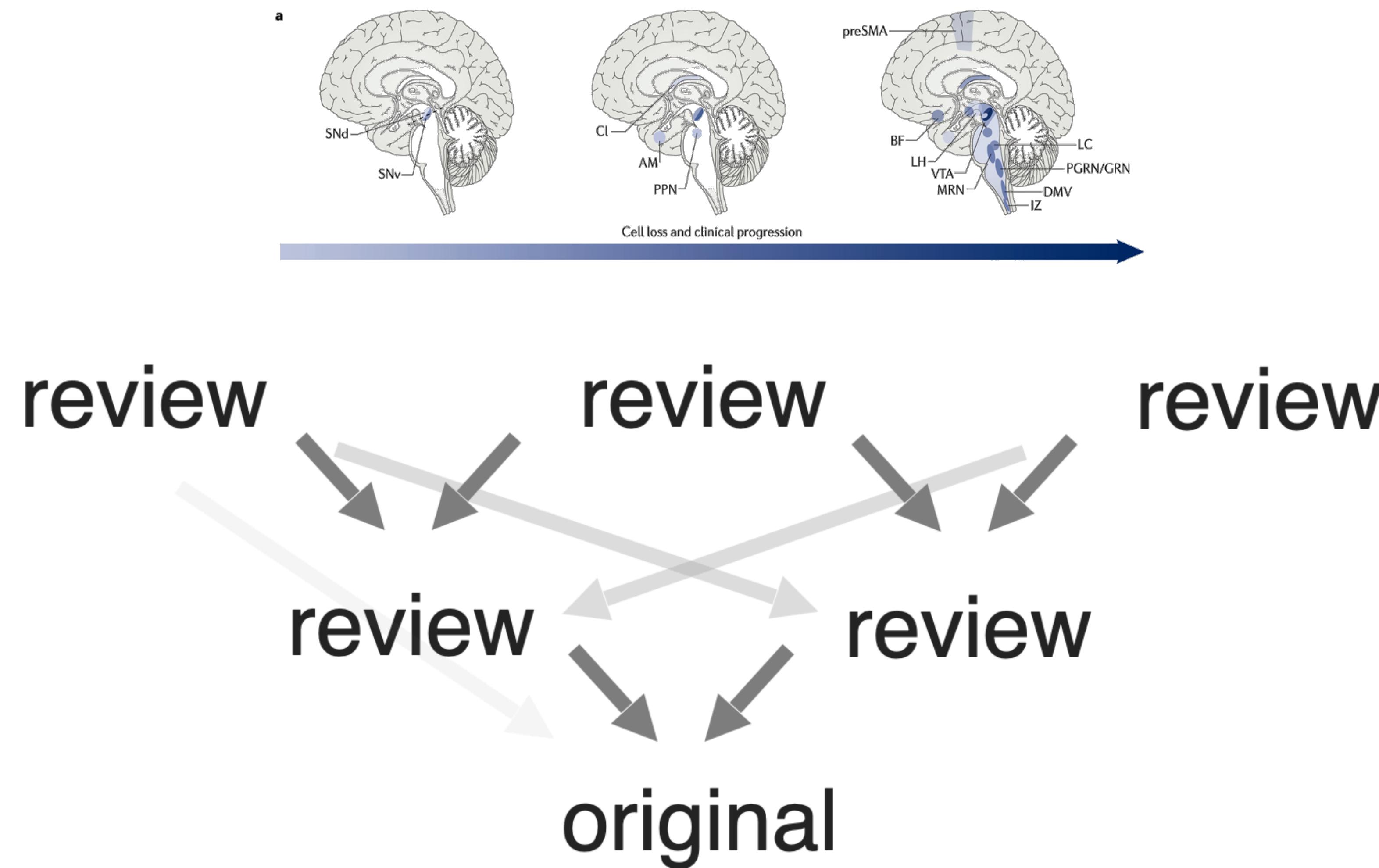
Project: William Lunt, Samuel Burke, Émilie Cottard, Alan Murphy, Maitri Shah, Ji Sang, Jethro Choi, Sarah Dawson, Julian Higgins and, Nathan Skene

This is very much a work in progress

Selective vulnerability



Selective vulnerability



Our claim and hope

- We don't know* which neurons/cells *die* in the context of *PD*, nor in which order
- Open questions:
 - PD vs PDs
 - Correlates of loss
- We need to know, **urgently**
- We know that other imaging modalities give support to the order of degeneration

* with enough certainty

This is a work in progress



On Cell Loss and Selective Vulnerability of Neuronal Populations in Parkinson's Disease

Nicolas Giguère[†], Samuel Burke Nanni[†] and Louis-Eric Trudeau^{*}

CNS Research Group, Department of Pharmacology and Physiology, Department of Neurosciences, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada

Region	Number of studies	Technique					Statement of comparison to controls	Other regions analyzed			Correlation of loss to disease progression
		Observational	Manual	Computer assisted	Stereology	N (controls)		Stated that was blinded and age matched	1 or more	3 or more	
SNC	38	10	8	8	12	612 (452)	8/38	7/38	17/38	6/38	11/38
LC	18	5	4	9	0	221 (113)	5/18	3/18	10/18	7/18	2/18
NBM	13	1	12	0	0	162 (137)	5/13	3/13	6/13	2/13	0/13
PPN	11	0	3	4	4	108 (89)	3/11	3/11	5/11	2/11	2/11
Hypothalamus	9	1	6	1	1	74 (63)	6/9	2/9	1/9	1/9	1/9
DMV	7	2	2	2	1	49 (37)	0/7	0/7	6/7	2/7	1/7
Raphe nuclei	7	0	3	3	1	97 (49)	0/7	2/7	5/7	3/7	0/7
VTA	8	0	3	4	1	43 (39)	0/8	1/8	6/8	2/8	1/7

The narrative of selective vulnerability — why *it is* important

The filter through which research (QRPs?) get squeezed

- individuals
- groups
- journal
- funders

Why *it is* important

How Lazy Reading and Semantic Sloppiness May Harm Progress in Synucleinopathy Research

> While confronted with the increasing complexity of the neurobiology of Parkinson's disease (PD), we face the ever-increasing sloppiness of the conceptual definitions associated with poor methodological characterizations and the use of unacknowledged proxies, all of which are harmful contributors to the overall slow progress of PD research

Canonization of false facts

> Publication bias in favor of positive findings influences the distribution of published results. We find that unless a sufficient fraction of negative results are published, false claims frequently can become canonized as fact. Data-dredging, p-hacking, and similar behaviors exacerbate the problem.

> A final saving grace is that even after false claims are established as facts, science can still self-correct. In this paper, we have assumed for simplicity that claims are independent propositions, but in practice claims are entangled in a web of logical interrelations. When a false claim is canonized as fact, inconsistencies between it and other facts soon begin to accumulate until the field is forced to reevaluate the conflicting facts. Results that resolve these conflicts by disproving accepted facts then take on a special significance and suffer little of the stigma placed upon negative results. Until the scientific community finds more ways to deal with publication bias, this may be an essential corrective to a process that sometimes loses its way.

The natural selection of bad science

> We term this process the natural selection of bad science to indicate that it requires no conscious strategizing nor cheating on the part of researchers. Instead, it arises from the positive selection of methods and habits that lead to publication.

How do we count cells in brain tissue?

- What has been done
- The many challenges
- The variables that matter
 - The quantification method
 - The anatomy
 - The stain
 - The diagnosis
 - The clinical variables
- What should be done (we've known about this for a long time)
 - Standards

Neuroscience



Zoe Williams

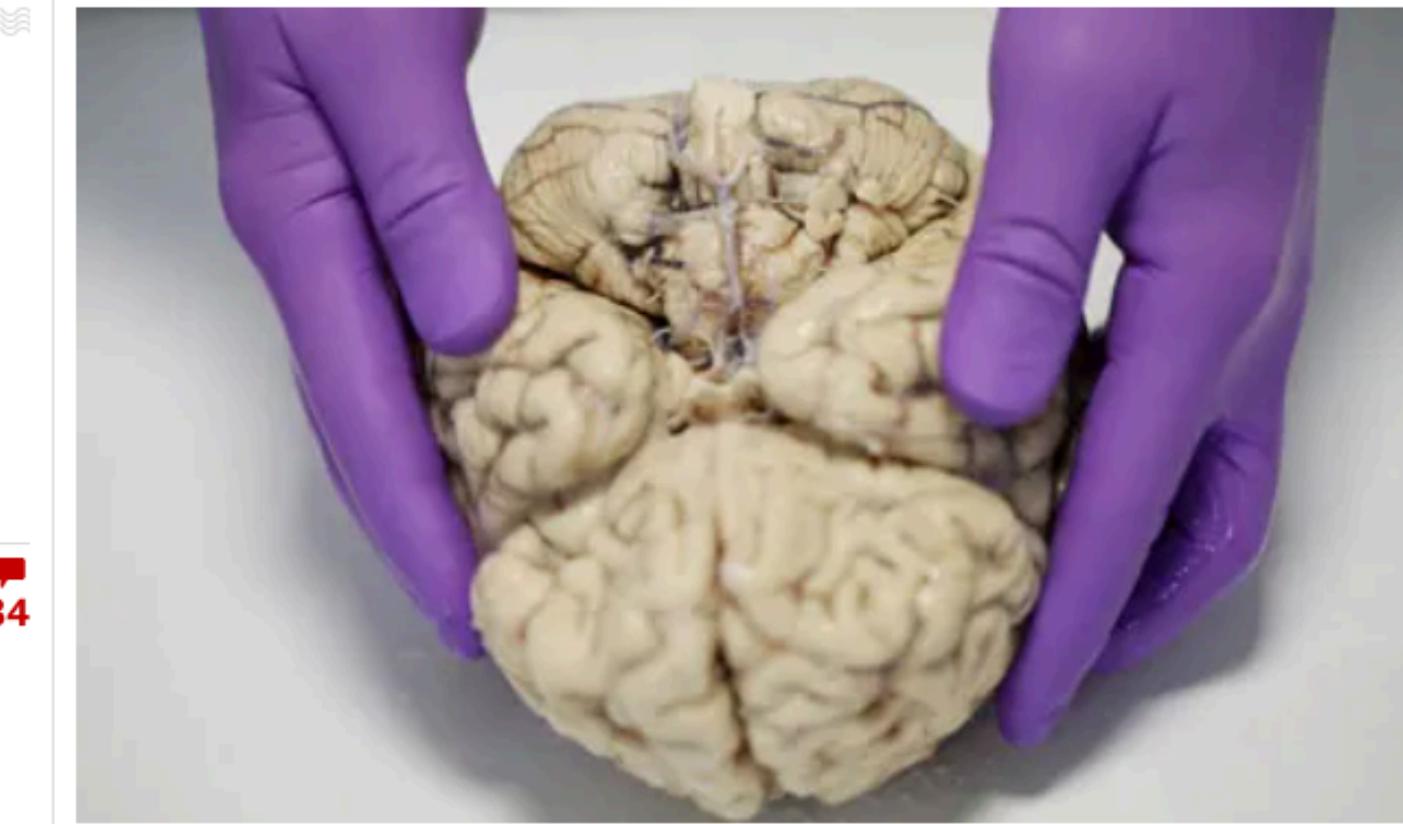
@zoesqwilliams

Wed 28 Mar 2012 20.00 BST



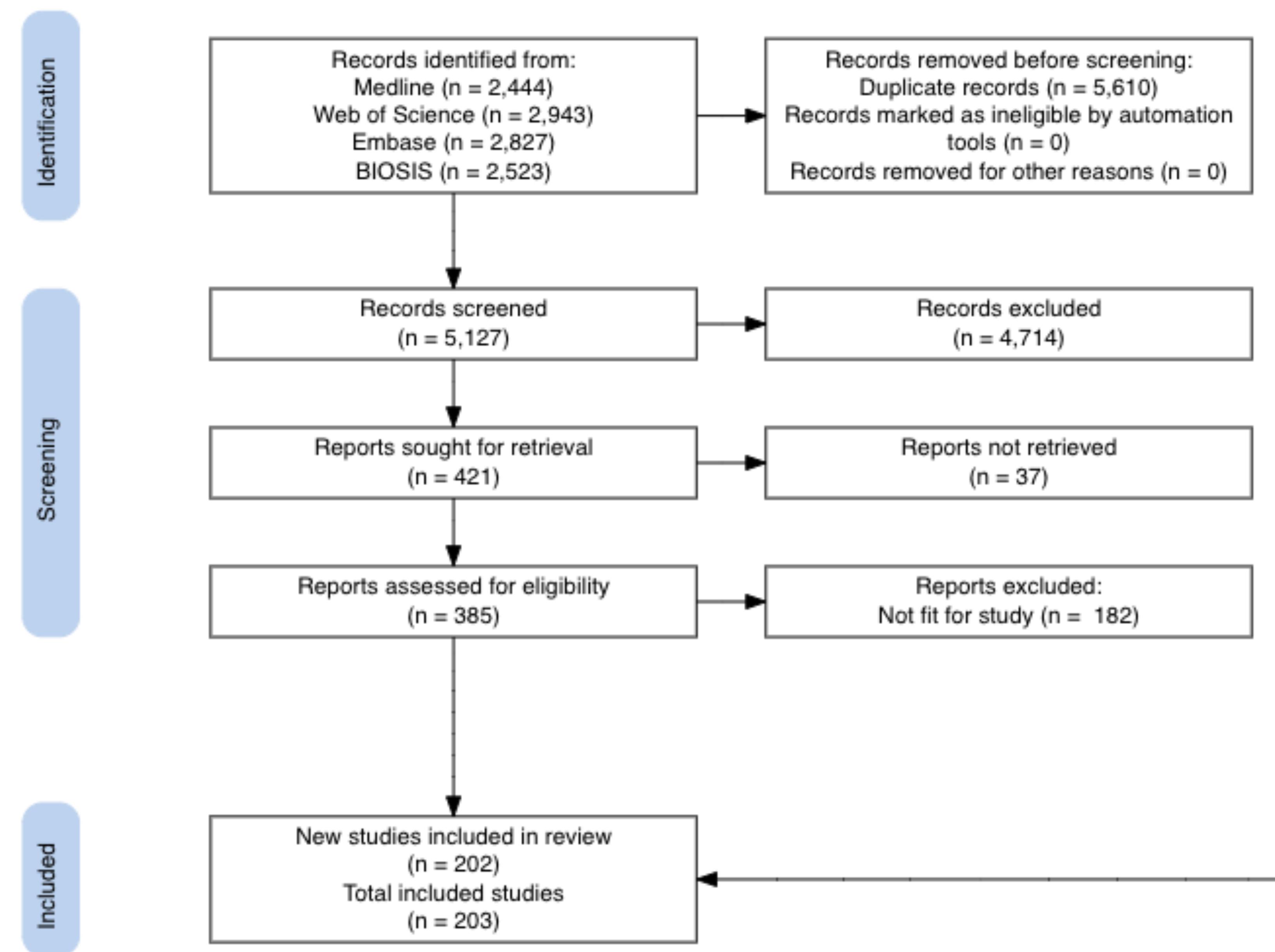
'Dissecting brains is pretty intense'

What's it like to spend your career cutting up people's grey matter? A neuropathologist at the UK's Brain Bank reveals all



Steve Gentleman prepares to dissect a human brain. Photograph: Graeme Robertson for the Guardian

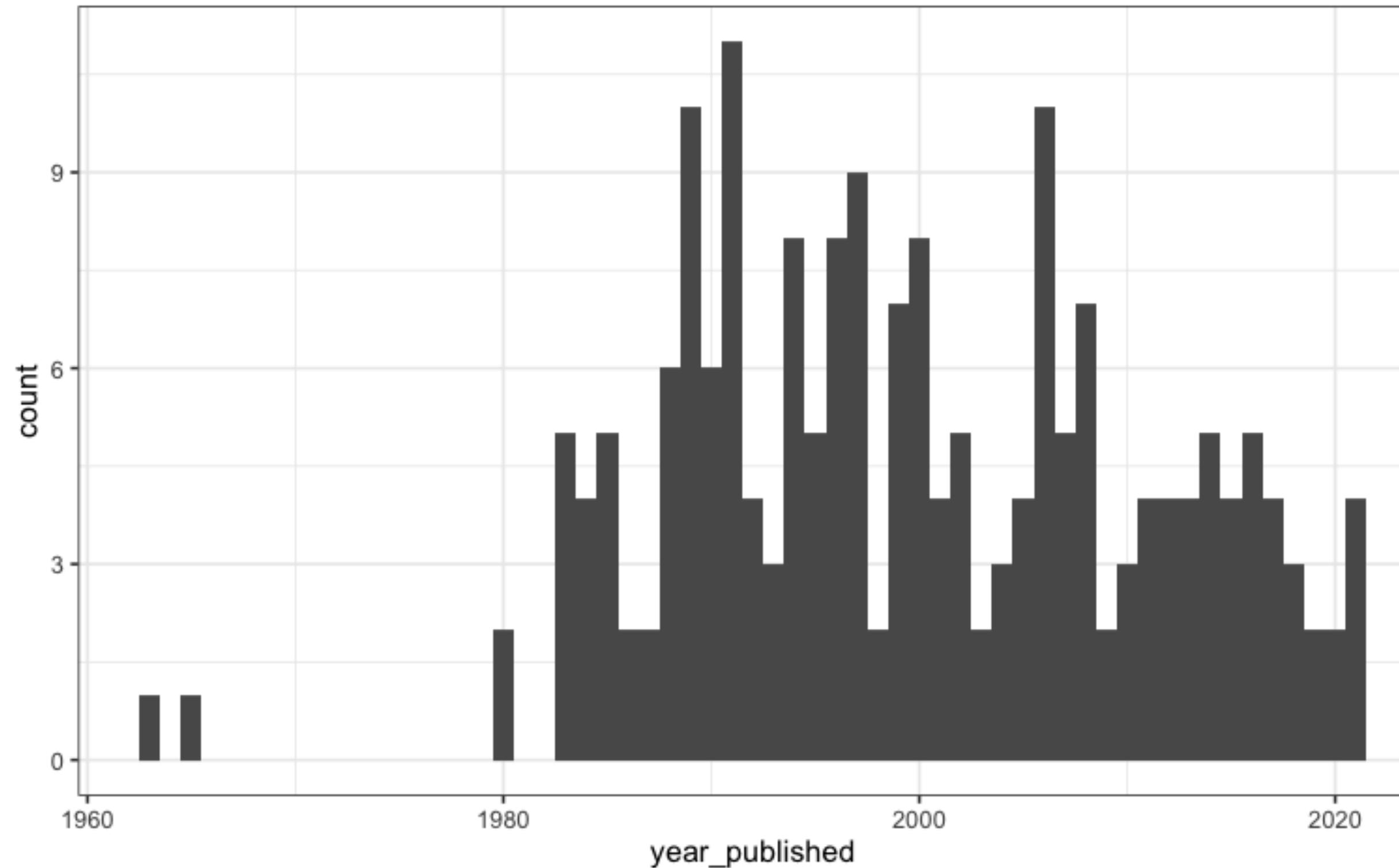
Identification of new studies via databases and registers



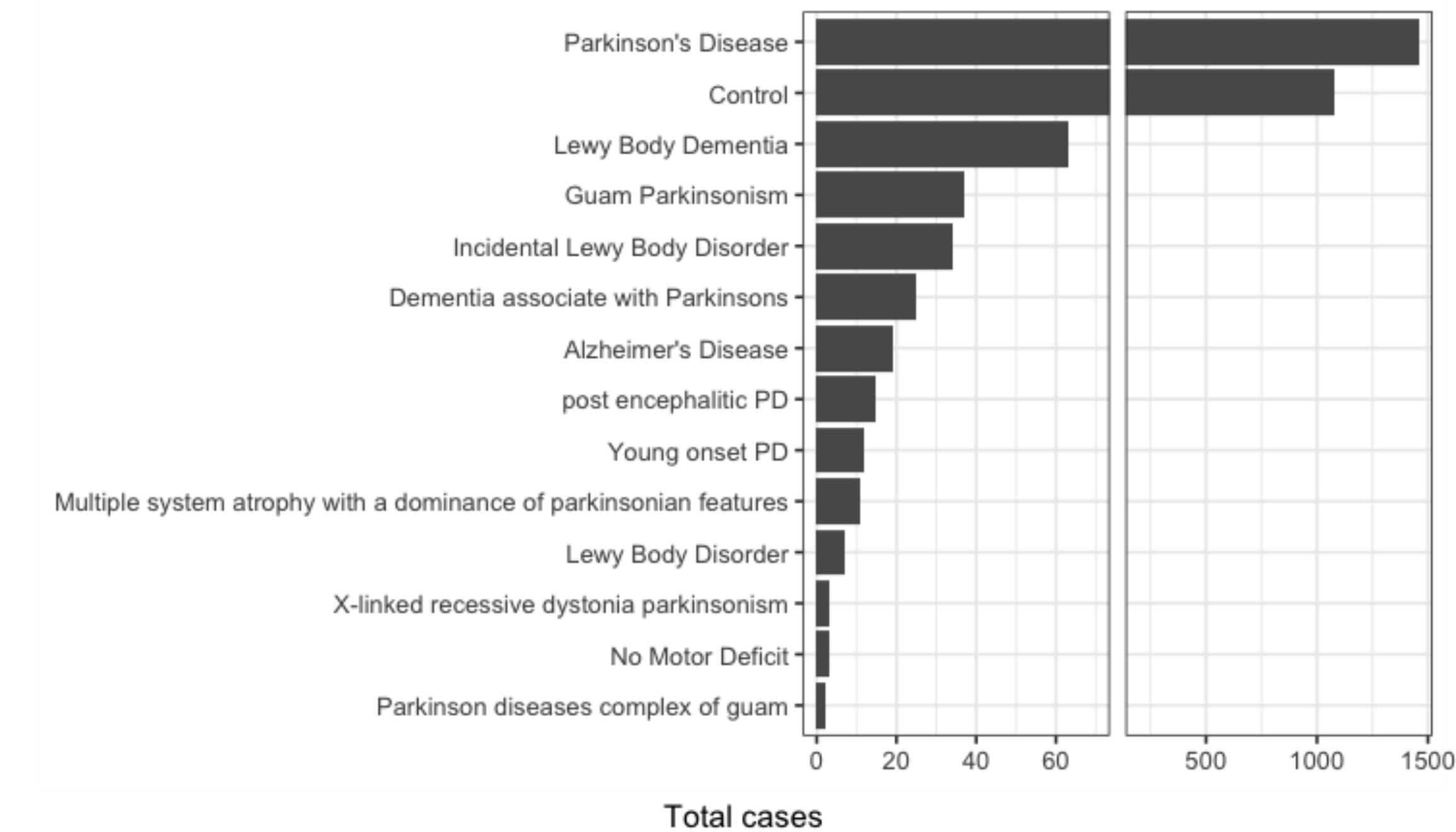
Summary of data

- Number of papers
- Number of cases
- Number using computer assisted / stereology
- Number looking at multiple regions
- What the data looks like-ish
- Number of studies with clinical variables etc

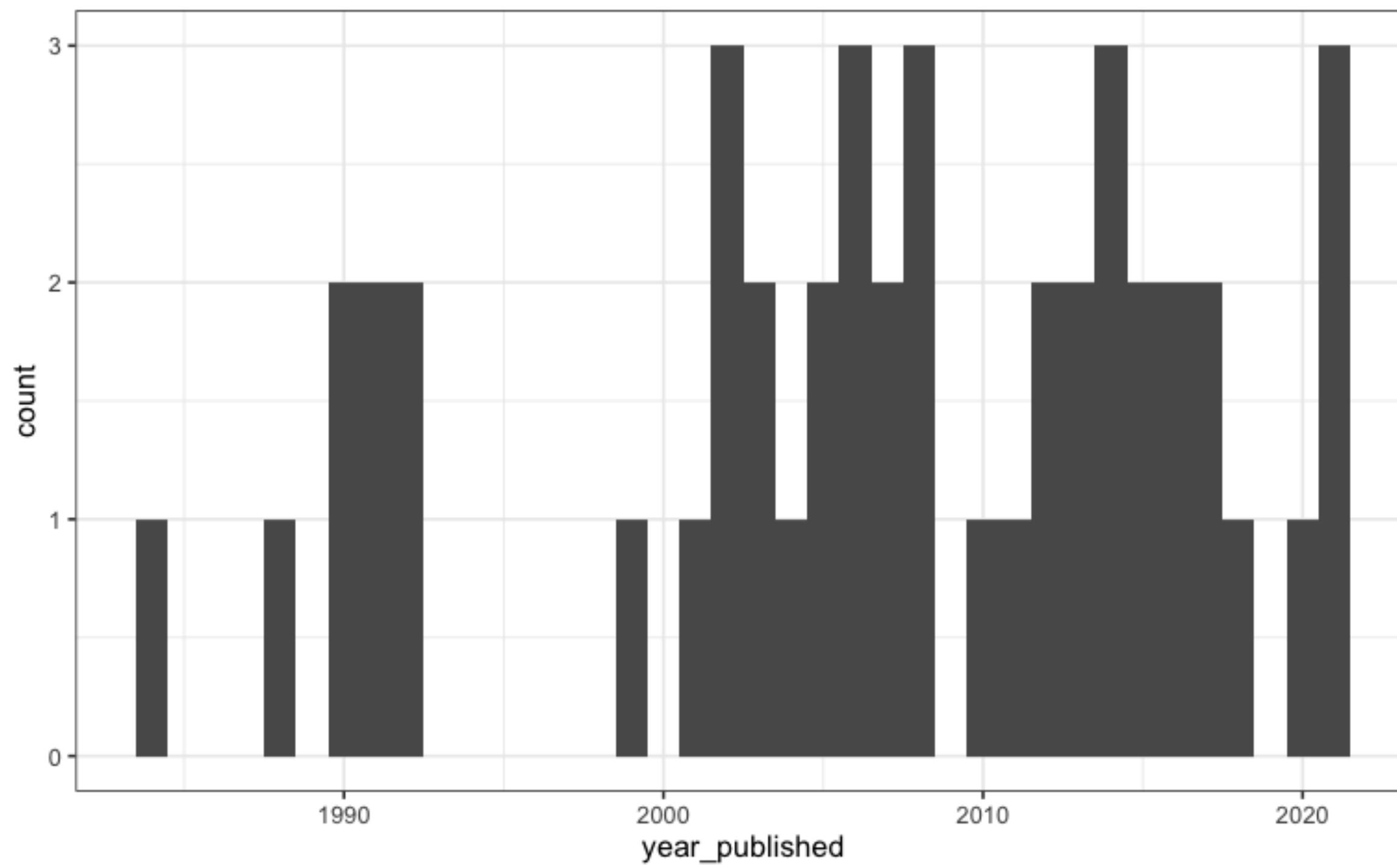
Summary



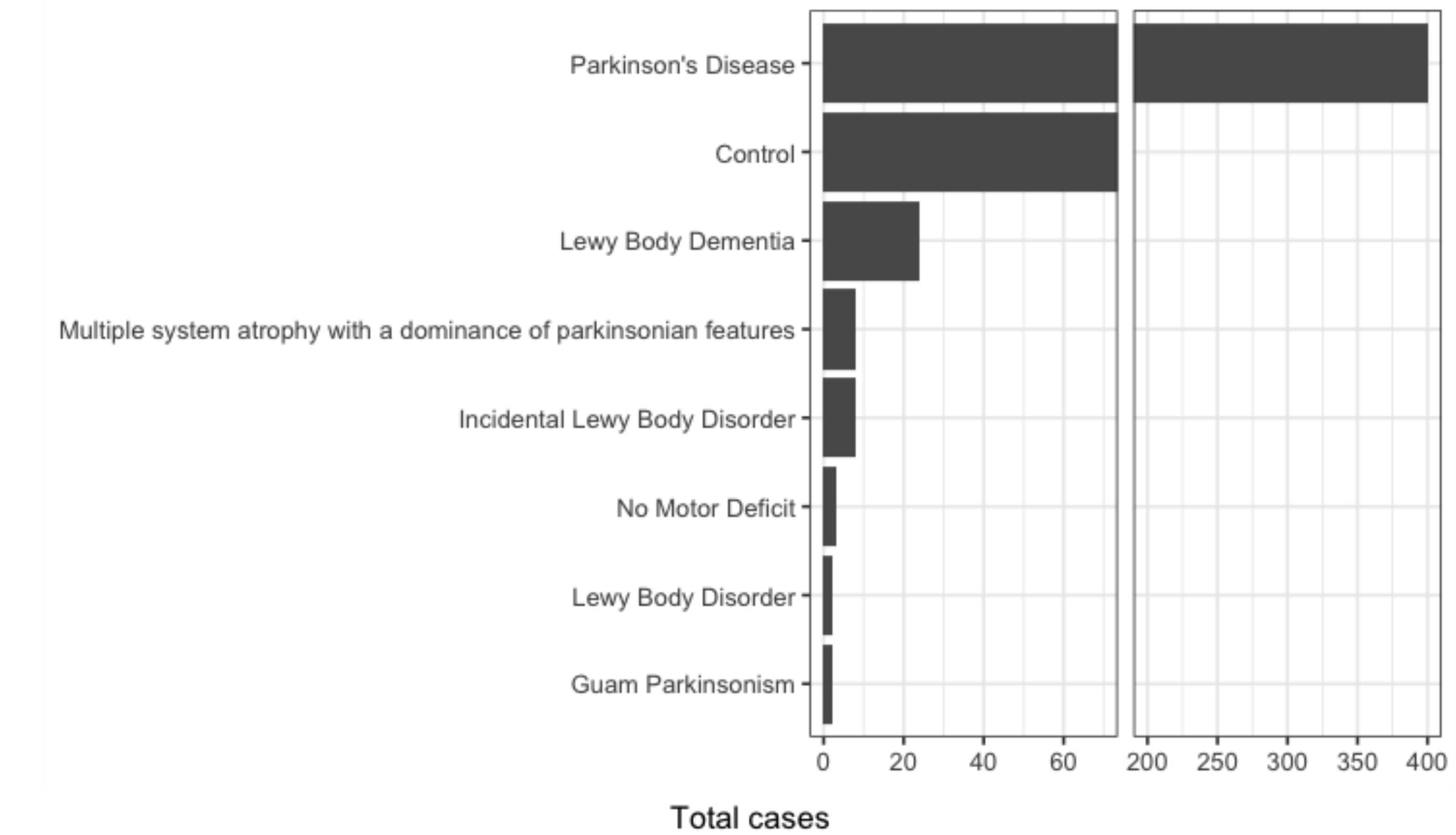
Observations by group - diagnosis/groups



Summary - stereology



Observations by group - diagnosis/groups



Variables collected

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[1] "PMID"          "age_of_onset"      "age_of_onset_sd"    "disease_duration"  "hoehn_yahr_score"  
[6] "hoehn_yahr_score_sd" "braak_stage"     "braak_stage_sd"    "age_of_onset_sd_1"   "UPDRS_score"  
[11] "UPDRS_score_sd"   "disease_duration_sd" "MMSE"           "MMSE_sd"          "percen_l-dopa_response"  
[16] "year_published"   "rob_score"        "data_type"        "n"                 "case_no"  
[21] "group"          "sub-group"       "region"          "sub-region"       "stain_marker"  
[26] "cell_type"        "quantification_method" "age_range_lower_bound" "age_range_upper_bound" "age_mean_years"  
[31] "age_mean_years-sd" "age_years"        "percent_of_control" "percent_of_total"    "mean_number"  
[36] "number"          "number_x10^3"      "number_x10^6"       "number_x10^9"       "density"  
[41] "number_per_mm^2"   "number_per_cm^2"    "number_per_mm^3"    "percentage_loss"   "AU"  
[46] "magnification"    "per_ganglion"     "SEM"             "SD"                "CV"  
[51] "p_value"         "CI"
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The data

Correlates of dementia in Parkinson's disease

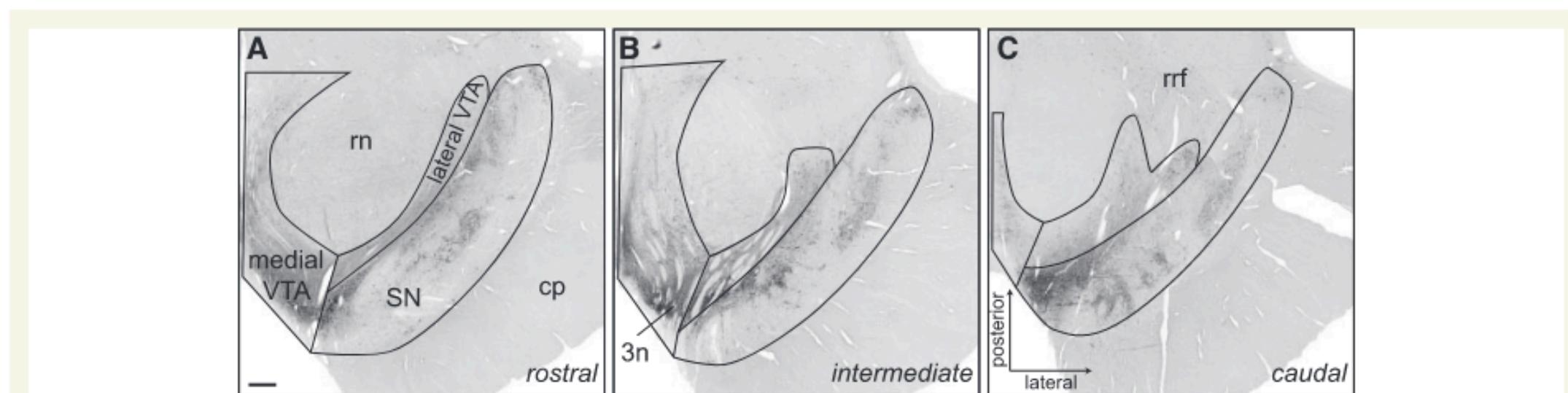
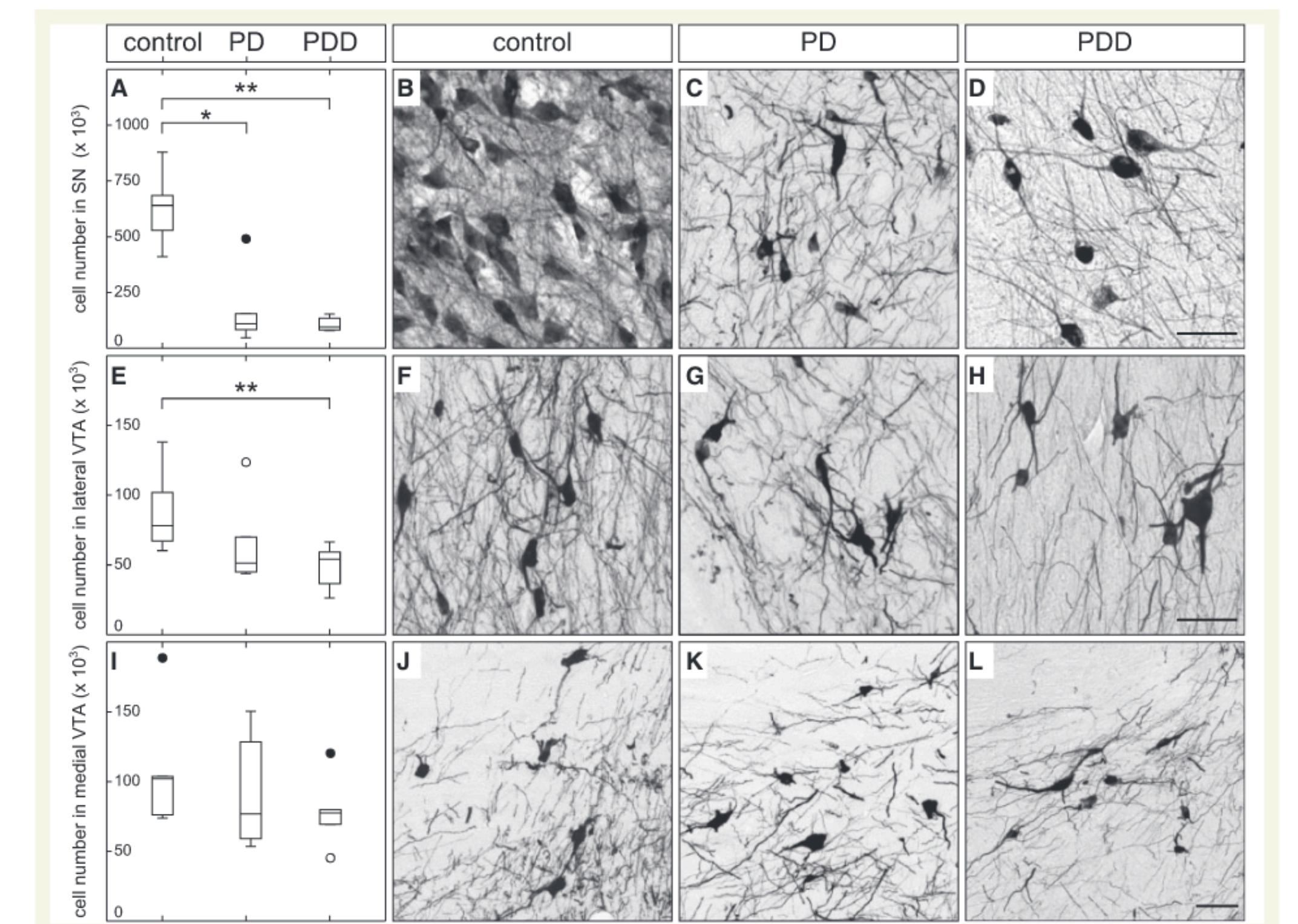
Brain 2014; 137; 2493–2508 | 2495

Table 1 Clinical and demographic characteristics of cases included in the histological analyses

Case number	Age	Onset of PD	Duration of PD	Duration of dementia	HY stage (/5)	CDR (/3)	Plaque (/3)	NFT (/6)	Cause of death	PMI (h)	Fixed brain weight (g)
Ctrl1	85	-	-	-	0	0	0	0	Multiple myeloma	4	943
Ctrl2	89	-	-	-	0	0	1	3	Renal failure	7	1079
Ctrl3	87	-	-	-	0	0	1	3	Sepsis	39.5	1099
Ctrl4	84	-	-	-	0	0	1	3	Acute myocardial infarction	21	991
Ctrl5	89	-	-	-	0	0	0	0	Septicaemia	78	1211
Median (IQR)	87 (4)				0	0	1 (1)	3 (3)		21 (33)	1079 (108)
PD1	76	48	28	-	5	0	0	0	Parkinson's disease 28 years	18	1102
PD2	72	56	16	-	5	0	1	1	Adenocarcinoma of lung with metastasis	4	1200
PD3	84	74	10	-	5	0	0	2	Ruptured aortic aneurysm	5	1228
PD4	91	79	12	-	5	0	1	5	Parkinson's disease	20	1092
PD5	74	45	29	-	5	0	1	3	Cardiopulmonary arrest	18	1066
Median (IQR)	76 (10)	56 (26)	16 (16)		5 (0)	0	1 (1)	2 (2)		18 (13)	1102 (108)
PDD1	88	76	12	7	5	2	2	0	Parkinson's disease dementia	22	1253
PDD2	76	47	29	5	5	3	0	0	Hypostatic chest infection	29	1370
PDD3	83	70	13	8	5	3	1	2	Aspiration pneumonia	10	1208
PDD4	80	63	17	2	4	2	1	0	Cerebrovascular accident (24 h); hypertension 12 months	9.5	1140
PDD5	87	54	33	3	5	1	0	3	Cerebrovascular accident	20	1127
PDD5	61	51	10	3	5	3	0	0	Hypostatic pneumonia	39	1795
Median (IQR)	82 (9)	59 (16.5)	15 (14)	5 (0)	5 (0)	3 (1)	1 (1)	0 (1.5)		21 (15)	1231 (183)

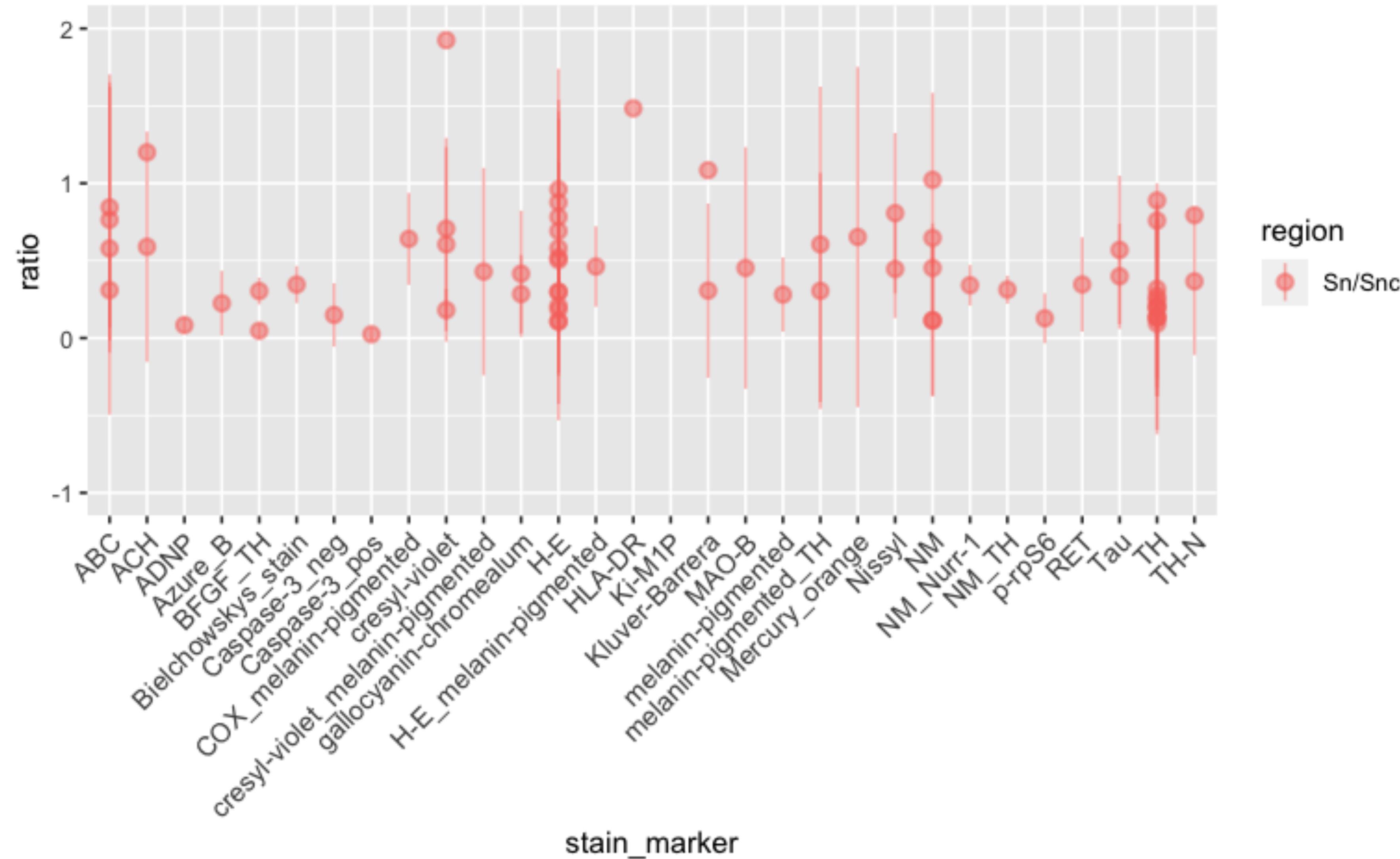
Age and duration of Parkinson's disease and dementia are indicated in years. Medians are presented with (interquartile range, IQR).

CDR = clinical dementia rating; ctrl = control; HY = Hoehn and Yahr; NFT = neurofibrillary tangle; PD = Parkinson's disease; PDD = Parkinson's disease with dementia; PMI = post-mortem interval.

**Figure 2** Photomicrographs of three representative transverse tyrosine hydroxylase-stained sections through the midbrain showing inclusion boundaries for substantia nigra (SN) and lateral and medial VTA at rostral (A), intermediate (B) and caudal (C) levels. Scale bar = 1 mm. cp = cerebral peduncle; rn = red nucleus; rrf = retrorubral field; 3n = exiting third nerve.

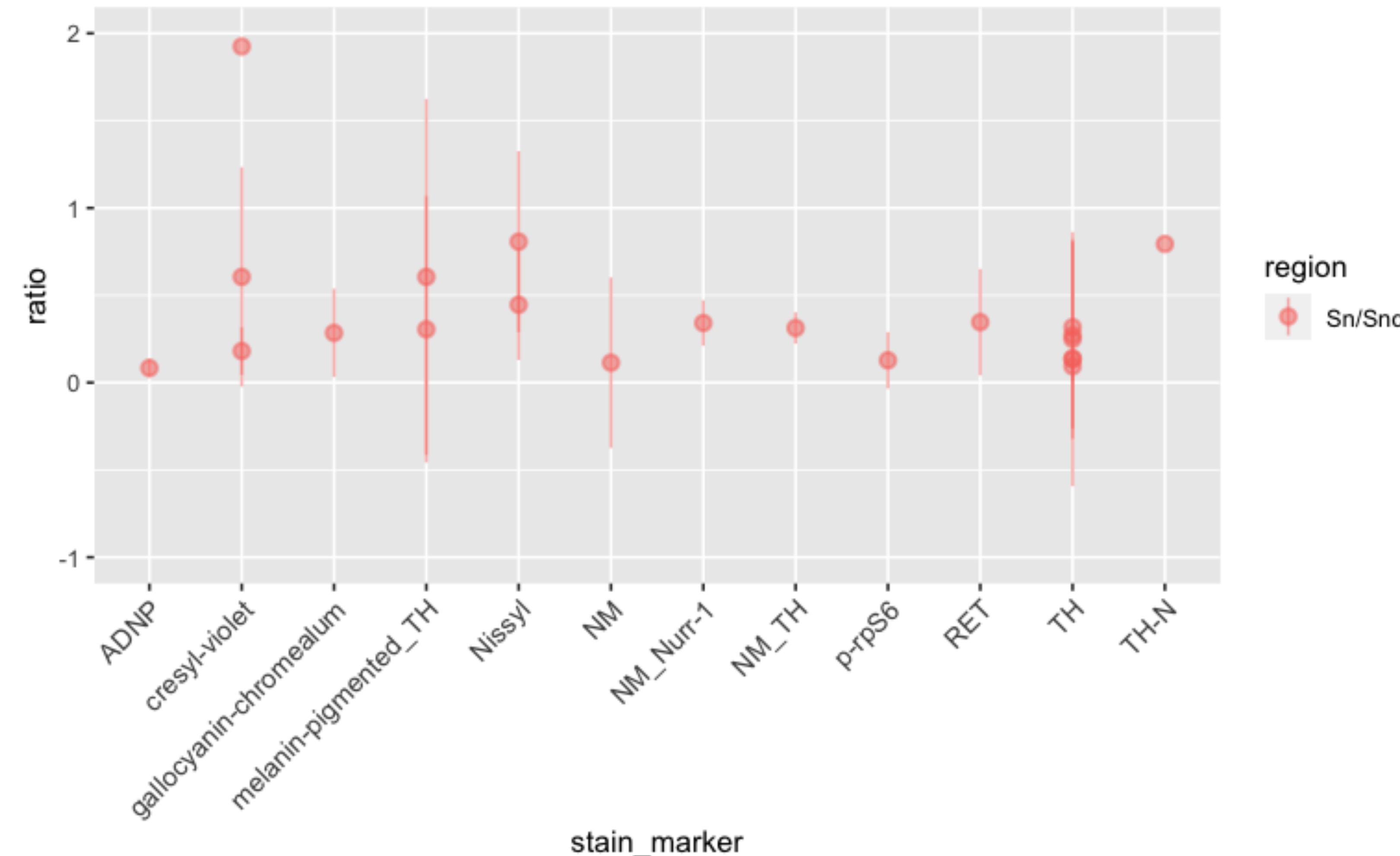
Meta-analysis *in progress*

Do not conclude things from these data yet as the analysis pipeline is very much a work in progress



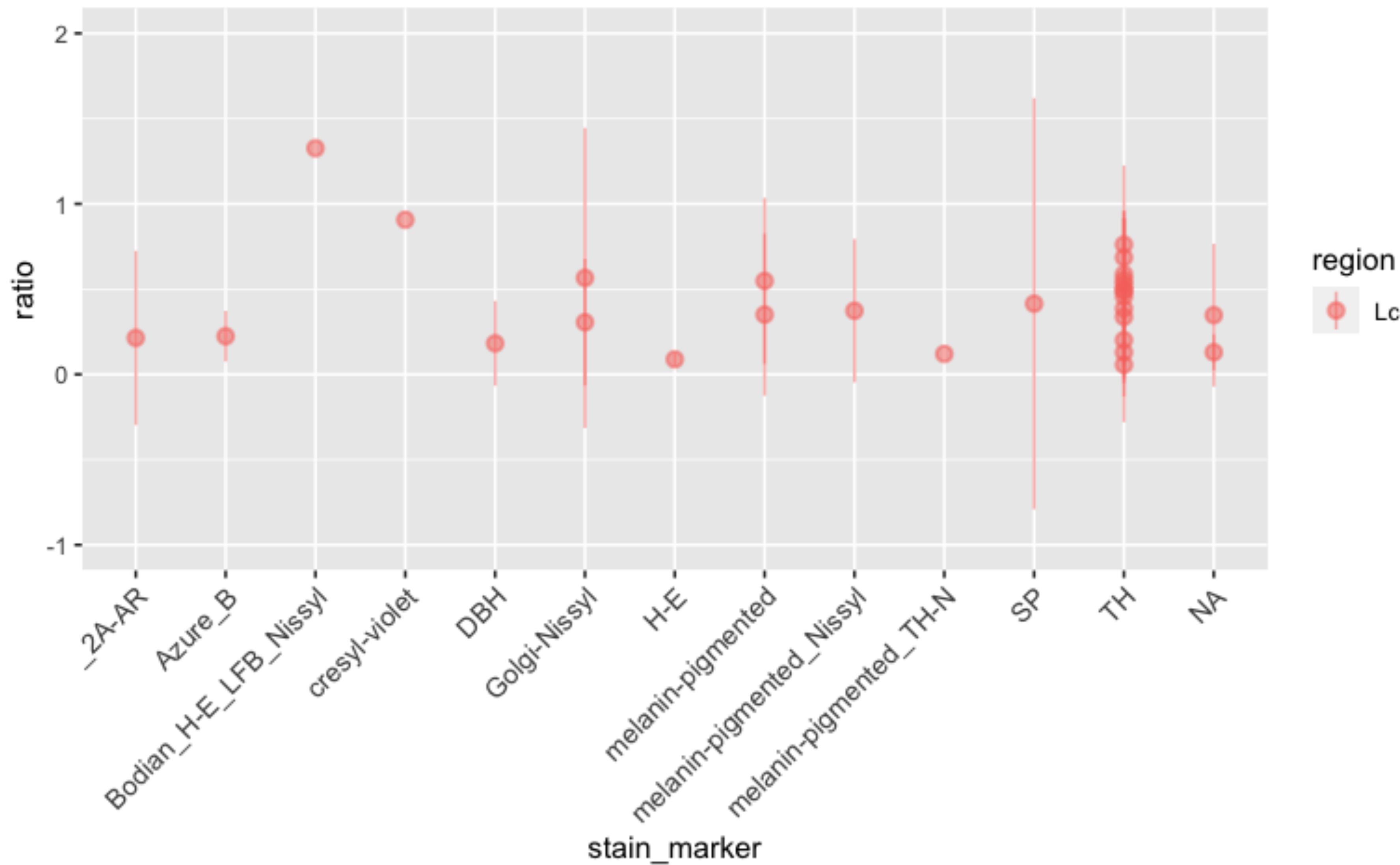
Meta-analysis *in progress*

Do not conclude things from these data yet as the analysis pipeline is very much a work in progress
Stereology only



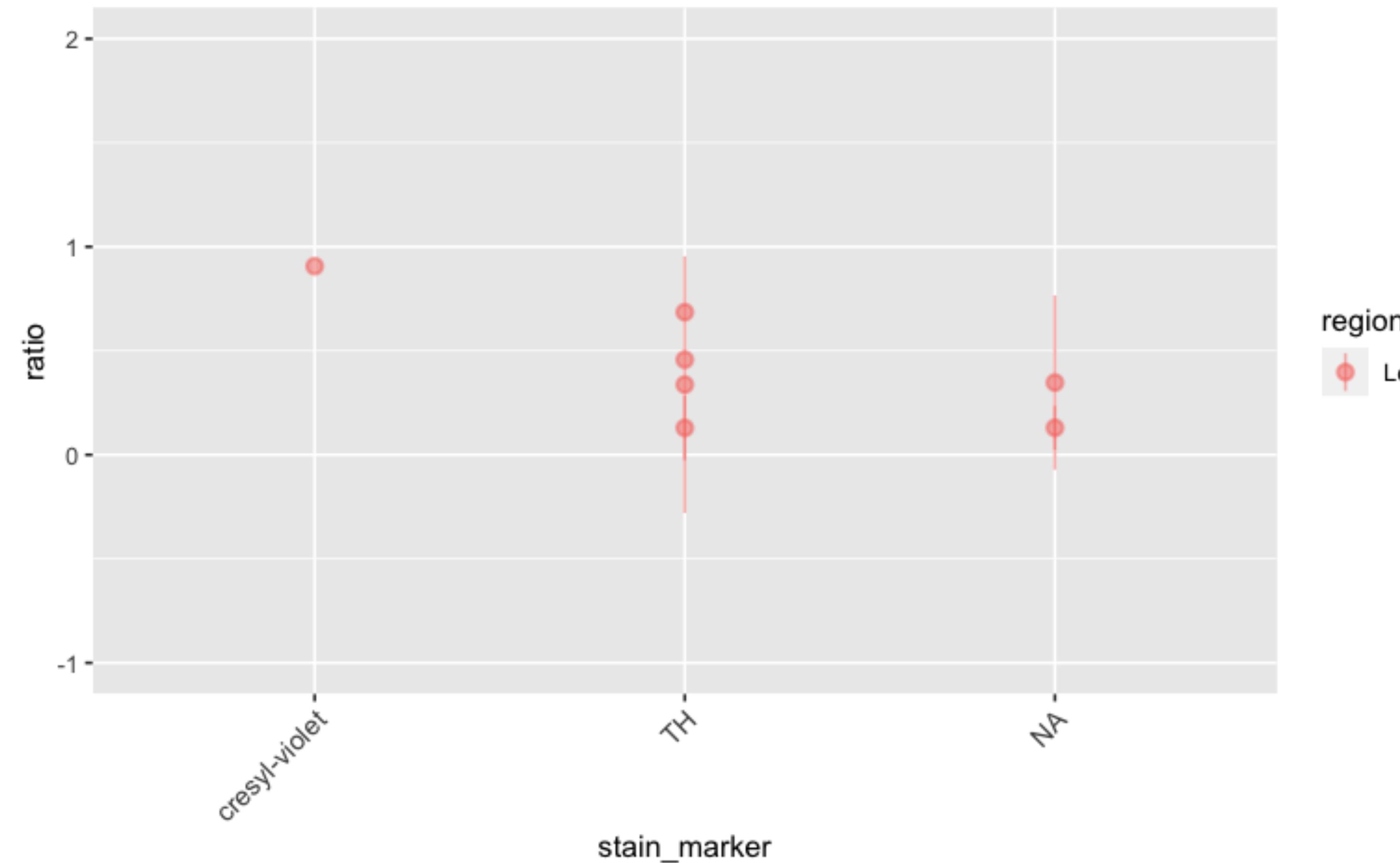
Meta-analysis *in progress*

Do not conclude things from these data yet as the analysis pipeline is very much a work in progress



Meta-analysis *in progress*

Do not conclude things from these data yet as the analysis pipeline is very much a work in progress
Stereology only



<原 著>

黒質の色素神経細胞と非色素神経細胞の比率 —正常加齢と錐体外路系疾患における検討—

大野 大二¹⁾³⁾ 水谷 俊雄¹⁾ 嶋田 裕之²⁾ 勝沼 英宇³⁾

<要 約> 黒質の色素神経細胞（以下 PN と略す）数と非色素神経細胞（以下 NN と略す）数の比率（PN/NN 比）と加齢の関係を明らかにするために、32歳から106歳までの正常加齢群45例を計測学的に調べた。その結果、PN、NN の絶対数は加齢に伴に減少していたが、PN/NN 比はほぼ一定（4.8）で、加齢との相関は認められなかった。一方、パーキンソン病（以下 iPD と略す）15例、孤発性OPCA（以下 MSA と同義に扱う）10例、進行性核上性麻痺（以下 PSP と略す）5例について調べた結果、iPD と MSA における PN/NN 比はほぼ同じであったが、iPD では PN のみ減少し、MSA では NN に比べて PN の減少が大きかった。一方、PSP では PN、NN がとも減少するために PN/NN 比の低下は僅かであった。正常加齢群における PN/NN 比が加齢による影響をほとんど受けないことは、絶対数の減少があってもバランスが保たれることを示唆するもので、加齢に伴う錐体外路症状を考える上で重要な所見であると考えられた。また、NN の出力系は脳幹被蓋や視床に向うので、PSP に代表される、NN の減少を伴う橋被蓋の萎縮は精神症状の出現との関係で注目された。

Key words: 黒質、色素神経細胞、非色素神経細胞、加齢、錐体外路系疾患

緒 言

較検討した。

著 >

Ratio of substantia nigra pigmented neurons to non-pigmented neurons

1) Examination of normal aging and extrapyramidal disorders 1

Daiji Ohno 1) Toshio Mizutani 1) Hiroyuki Shimada 2) Katsunuma English words³⁾

Summary: To clarify the relationship between the ratio of the number of substantia nigra pigmented neurons (hereinafter abbreviated as PN) and the number of non-pigmented neurons (hereinafter abbreviated as NN) (PN / NN) and aging, from the age of 32 Forty-five patients in the normal aging group up to 106 years were examined by measurement. As a result, the absolute numbers of PN and NN decreased with aging, but the PN / NN ratio was almost constant (4.8), and no correlation with aging was observed. On the other hand, Parkinson's disease (hereinafter referred to as Parkinson's disease). PN / NN ratio in iPD and MSA as a result of examining 15 cases (abbreviated as PD), 10 cases of sporadic OPCA (hereinafter referred to as MSA), and 5 cases of progressive supranuclear palsy (hereinafter abbreviated as PSP). Was almost the same, but only PN decreased in iPD, and PN decreased more in MSA than in NN. On the other hand, in PSP, the decrease in PN / NN ratio was slight because both PN and NN decreased. The fact that the PN / NN ratio in the normal aging group is hardly affected by aging suggests that the balance is maintained even if the absolute number decreases, and the extrapyramidal symptoms associated with aging are observed. It was considered to be an important finding for consideration. Also, since the output system of NN is directed to the brain stem cover and the thorax, atrophy of the bridge cover accompanied by a decrease in NN, represented by PSP, is a psychological symptom. It was noticed in relation to its appearance. Key words: Substantia nigra, pigmented neurons, non-pigmented neurons, aging, extrapyramidal disorders.

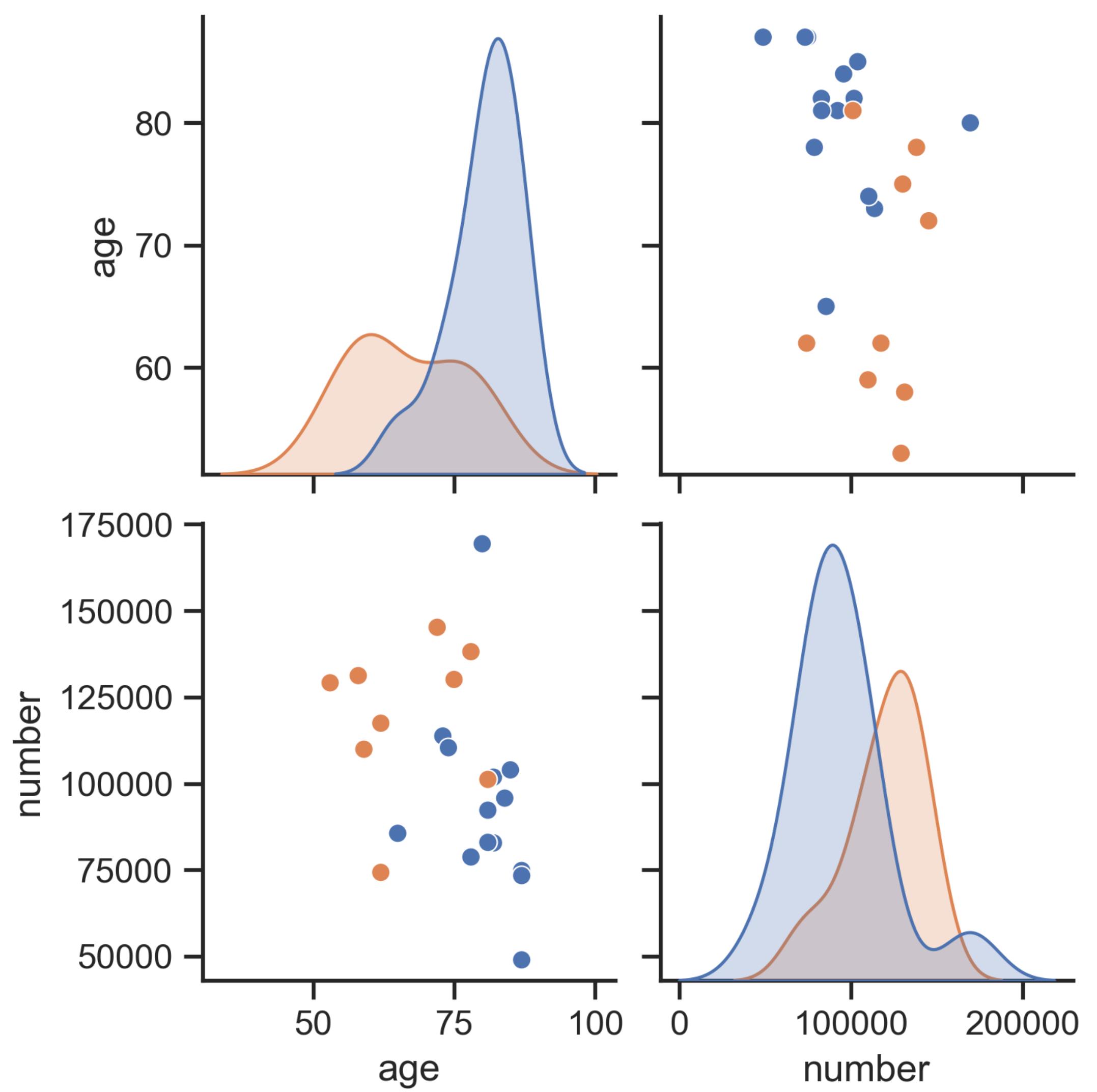
We compared and examined.

Google Lens

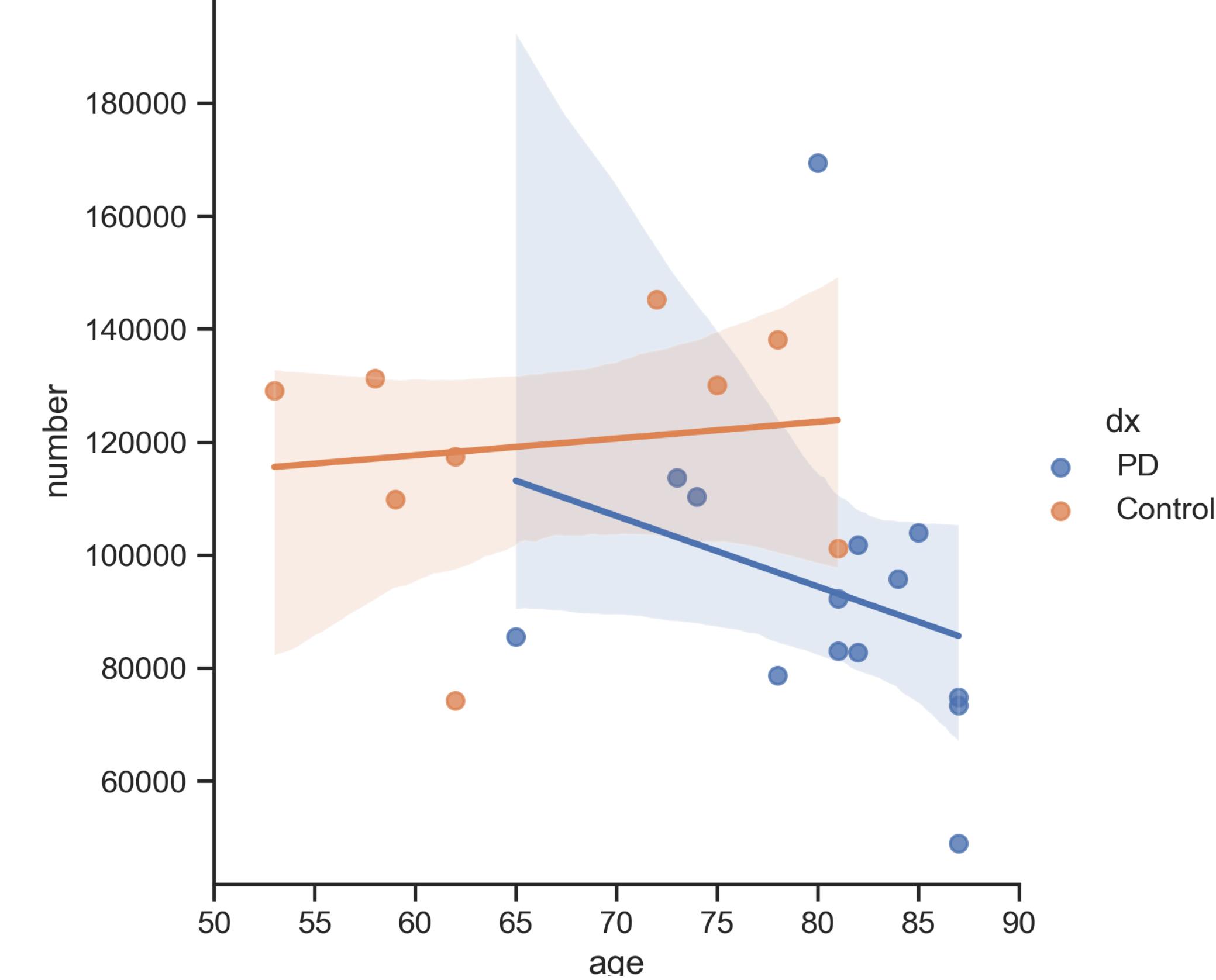
Auto-detect

English

Original



dx
PD
Control



Questions to you

- Does it matter?
- What outcome would we need to find, for people to change?
- What are we missing in the telling of the story that misses the crux