

Co-Pathology in Parkinson's Disease – How Does it Affect the Outcome?

Shigeo Murayama¹⁻³, Tomoyasu Matsubara¹, & Yuko Saito^{1,4}

1. Brain Bank for Aging Research, Tokyo Metropolitan Institute for Geriatrics and Gerontology
2. Brain Bank for Neurodevelopmental, Neurological and Psychiatric Disorders, United Graduate School of Child Development, Osaka University (cross appointment)
3. Department of Neuroetiology and Diagnostic Science, Graduate School of Medicine, Osaka Metropolitan University
4. Department of Radiology, National Center of Neurology and Psychiatry Hospital

COI

No COI for Profit Organization

This presentation is supported by **the Committee on Promoting Collaboration in Life Sciences** through its Domestic and International Cooperation Program. which is funded by Japan's Ministry of Education, Culture, Sports, Science and Technology.

Honorable Member and Chairperson of the Brain Bank Committee:
the Japanese Society of Neuropathology

Honorable Member, the Japanese Society of Neurology and
the Japanese Society of Dementia Research

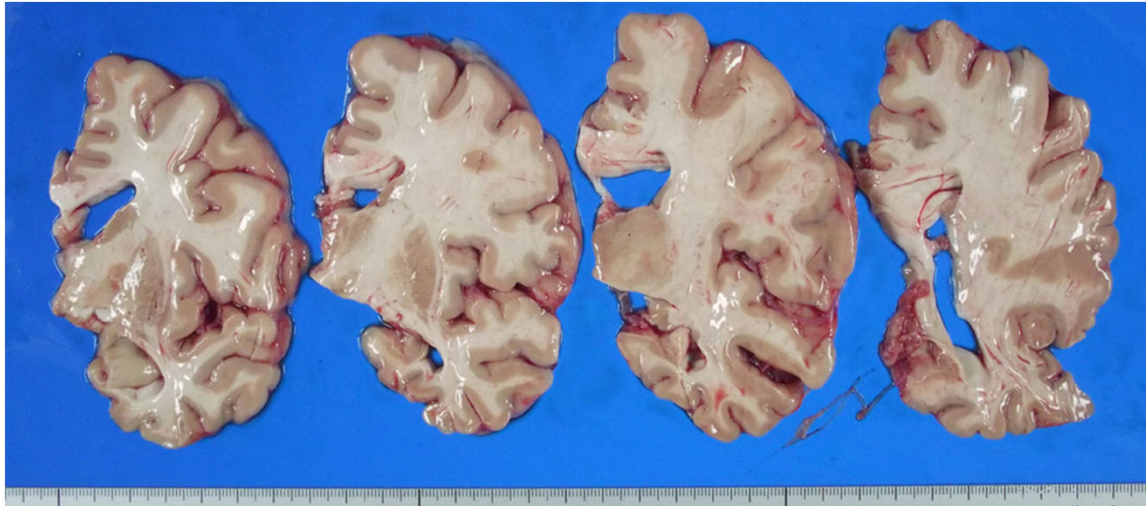
Senior Editorial Board, Journal of Neuropathology and Experimental Neurology
30- year membership of **American Association of Neuropathologists**

Senior Lecturer: Doshisha University & Division of Health Sciences, Graduate School of Medicine, Osaka University

Neuropathology Consultant: Kitasato Medical School
National Hospital Organization Shizuoka Epilepsy and Neurology, Sagamihara Hospital
Kameda, Yokohama Rosai and Toranomon Hospitals

My Profile

- I am a Zen priest in Soto School (曹洞宗).
- I was taught that those who receive food offered to Buddha (仏飯) should devote their lives to all living beings (衆生).
- Establishing a nationwide brain bank network in Japan is my life's work, which I regard as the path of a Bodhisattva (菩薩行).
- I will go wherever needed to honor brain bank donors' wishes and support physicians who want to contribute to brain banking. I have participated in around 4,000 brain-cutting procedures.



The first autopsy of a JADNI participant was performed at Tohoku University shortly after the Great East Japan Earthquake. The journey from Tokyo to Sendai took six hours.

To promote Neurology and Neuropathology

- Establishment of **the JSNP Board of Neuropathology** (2020-)
- Establishment of the first **brain bank** in Japan (1999-)
- One of the founders and Chairperson (1987-2020) and Honorable Member of **Neuromuscular Conference**, nationwide clinical and pathological conference of neuromuscular disorders
- Secretary General of **Kanto Clinical and Neuropathological Conference** (2001-) with Pathologists, Neurologists, Psychiatrists and Neuroradiologists
- Co- Vice President of International Society of Neuroathology (2017-2023) with Professor Sun-Hye Park, Seoul University

Activity in Osaka University:

To educate symptomatology for medical students, residents and staffs

To educate residents of pathology and neurology for all neuropathological diagnosis, including biopsy of neuromuscular disorders, brain biopsy of neurosurgical material and autopsy.



From Google Scholar



Japanese Brain Bank Network for Neuroscience Research (JBBNNR)

University of Tokyo, Kagawa, Tokyo Medical, Kitasato and Teikyo Universitis;
NCGM, NHO Tokyo, Shimoshizu, Shizuoka Epi. Neuro., Okayama West and Okinawa Hosp.
Toranomon, Yokohama Rosai, Kameda, Chikamori and Tokyo Teishin Hosp.

**Brain Bank for Neurodevelopmental,
Neurological and Psychiatric Disorders**

Osaka University

Brain Bank for Aging Research

TMIG

**Brain Donation &
Autopsy Consent**

Tokyo Metr. Inst. for Geriatr. & Gerontol.

Clinical, Radiological & Pathological Database

CoBiA (Platform for Supporting Cohort Studies and
Biospecimen Analysis),

**Open Resource for
Education and Research**

Choice of Resource

Researcher

**Fukushimura
Hosp.**

**National Institute for Neurology
and Psychiatry: NCNP**

National Sagamihara Hosp

Mihara Mem. Hosp

Brain Bank Committee, Jap. Soc. Neuropath.

Late Em. Prof.
Yasuo Ihara
the Univ. of Tokyo
registered to BBAR 2023



Backbone of Brain Bank for Aging Research

- **Symptomatology** is neurology neuropathology including psychopathology.
- **Dynamic Neuropathology**, originally for PET in Cambridge, is correlation of neuroimage and background pathology for treatment and care of living patients.
- **Molecular Neuropathology**, including biomarker and molecular studies of postmortem brain and body resource forms counterpart of morphological neuropathology.
- **Statistical Neuropathology** is based on a large data set of reliable neuropathological diagnosis.

Today's Topics

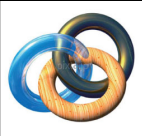
1. Lewy body pathology in an aging cohort
2. Comorbidities and Outcomes in Parkinson disease, focusing on Alzheimer pathology

Today's Topics

1. **Lewy body pathology in an aging cohort**
2. Comorbidities and Outcomes in Parkinson disease, focusing on Alzheimer pathology



Brain Bank for Aging Research (BBAR)



Tokyo Metropolitan Institute for Geriatrics and Gerontology

Resources of consecutive autopsy cases (with informed consent of brain banking) from a general geriatric hospital (<https://www.tmig.or.jp/brainbank/>)

In House Aging Cohort Resource

1. Paraffin blocks, glass slides and frozen liver, heart and kidney (1972.5-) for Clinical, Radiological and Pathological Research **2,574**
2. 1+ frozen pieces of brain (mainly 1985.1.1-) **2,504**
1 + Genome Expression Research
3. 2+ frozen half brains (2001.7-) **1,478**
Basic Neuroscience Research

All Japan Depository of Neurological and Psychiatric Disorders **240**

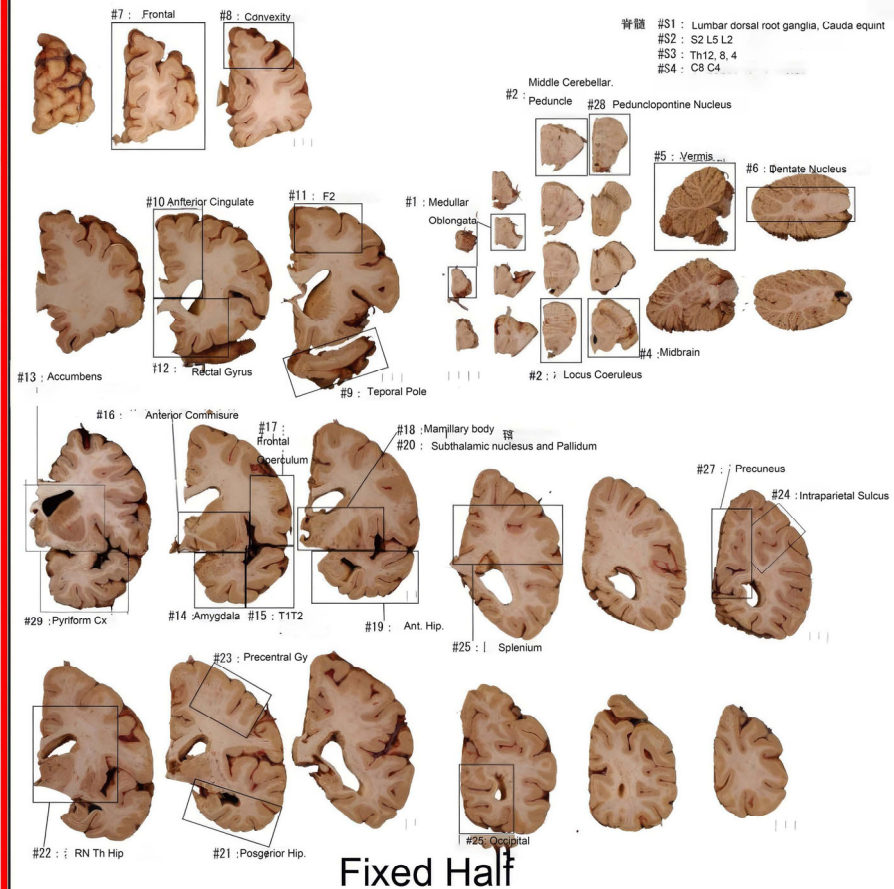
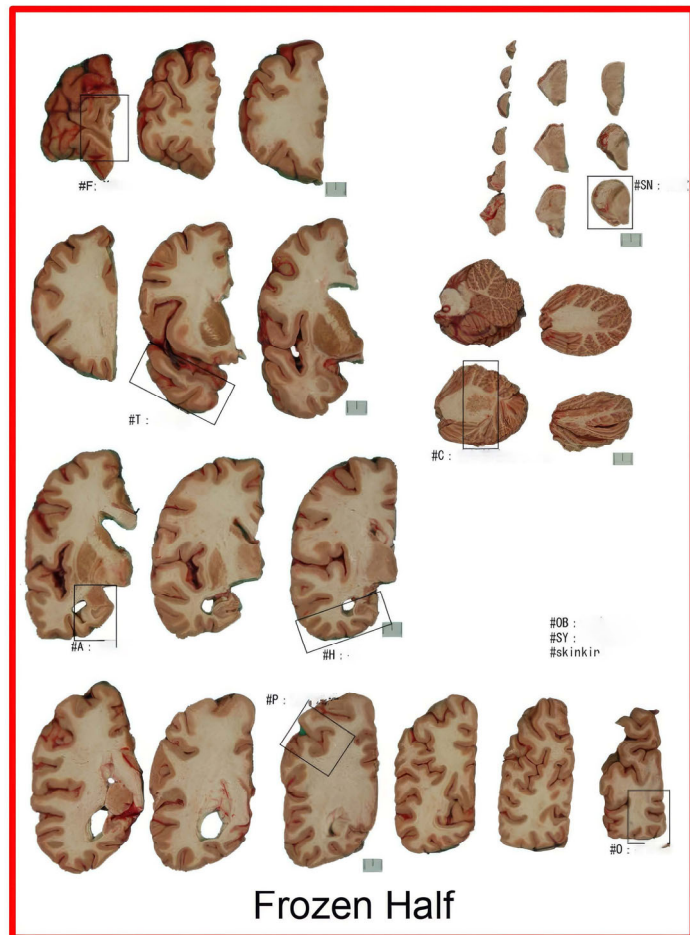


Full Autopsy including Brains

- An attending brain bank doctor (specially qualified neuropathologist), a resident and a technician (specially trained)
- An attending board- certified general pathologist, an autopsy technician and two pathology technicians.
- Frozen brains, spinal cords, peripheral nervous system, heart, liver and kidney
- The technician freezes tissues immediately.

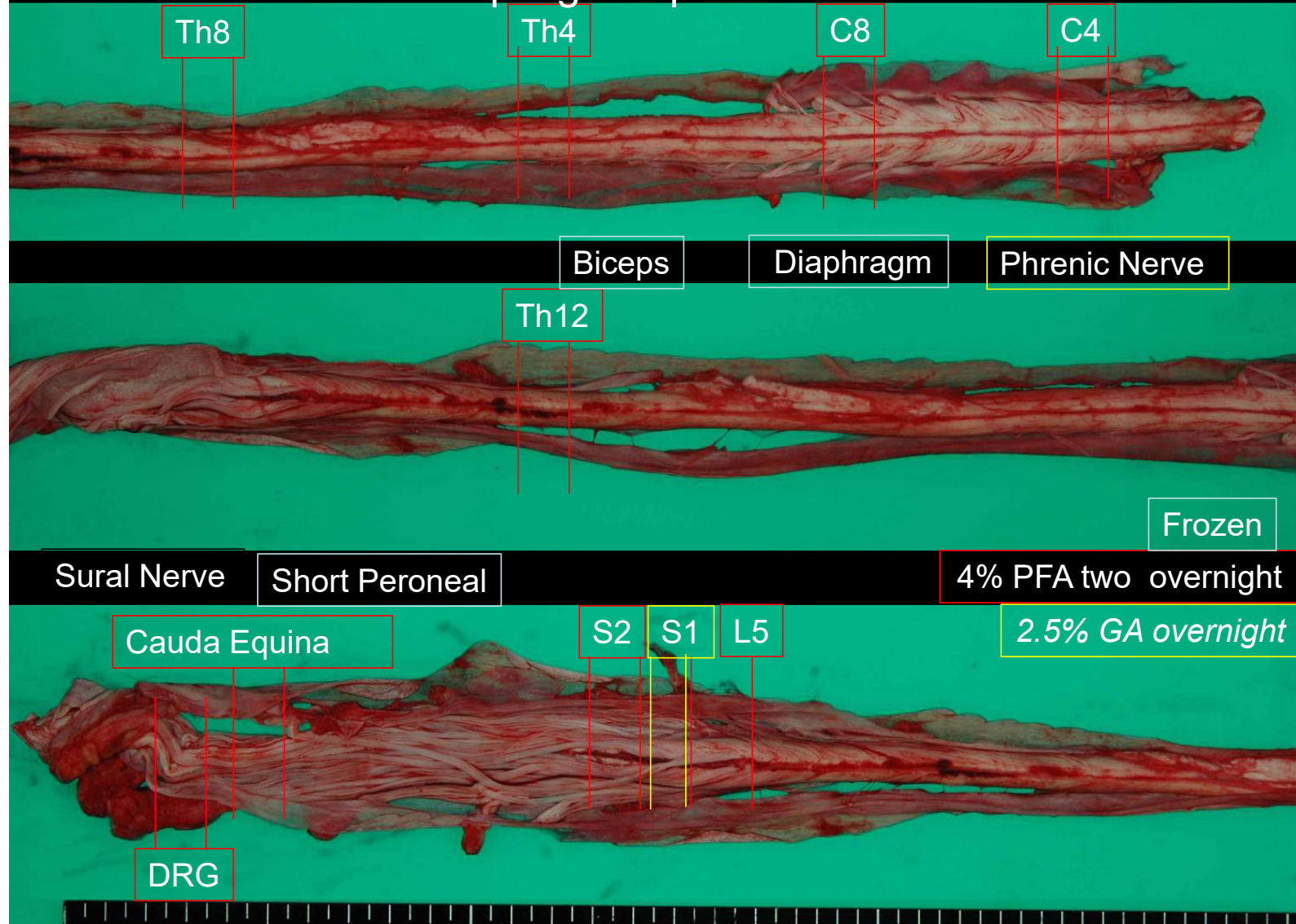


BBAR Protocol (<https://www.tmig.or.jp/brainbank/>)



8 areas: 4% paraformaldehyde over 2 nights
(McGeer's method @ British Columbia, suitable for Xenuim)

Sampling of Spinal Cord



BBAR Degenerative Pathology Database

BBAR	Y96XX									
A/G	CDR	PMI	NFT	AT8	SP	CERAD	Thal	LB	LB score	DLB 3rd
93M	3	11:22	4/3	3/3	2	2	5	4	4	Limbic (amygdala predominant)
Grain	AA	AT	UD	TDP	ApoE	RIN				NPD
0.5/ 0.5	1C	1	3	T1M1S0	3/3	8.1				AD, LBD, CVDE

A/G age/ gender

CDR (clinical dementia rating):

0-3

PMI: postmortem interval

NFT (tangle: Braak Stage):

0-6

AT8 (tangle: AT8 Stage)

0-6

SP (senile plaque: Braak Stage):

0-3

CERAD

0-3 (0- C)

Thal (amyloid Thal Stage)

0-5

Lewy (Lewy body, BBAR Stage):

0-5

DLB score (DLB 1st Consensus Guideline)

DLB 3rd (DLB 3rd Consensus Guideline)

Grain (argyrophilic grain, Saito Stage):

0-3

AA (amyloid angiopathy, BBAR Stage):

0-3

AT (astrocytic tangle):

0-3

UD (ubiquitinated dots):

0-3

TDP (TDP-43 proteinopathy, temporal, medulla and spinal)

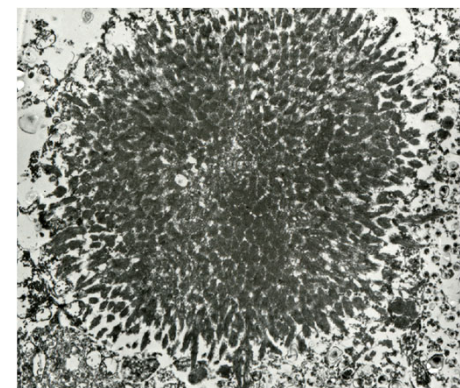
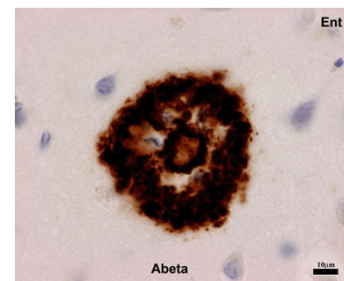
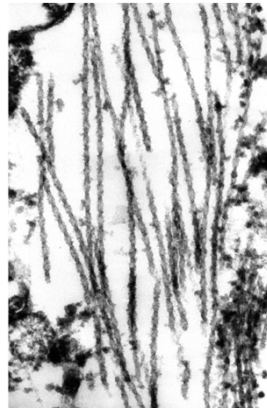
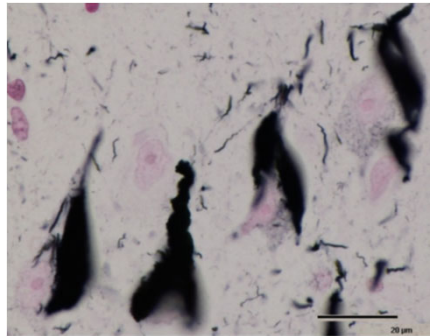
0-3

ApoE (apoE genotyping)

RIN (RNA integrity number)

NPD: neuropathologic diagnosis (AD: Alzheimer disease; LBD: Lewy body disease; CVDE: embolic infarct)

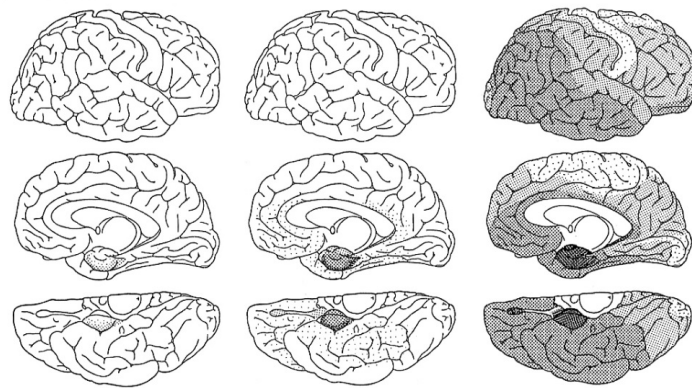
Braak's Staging of Alzheimer Pathology



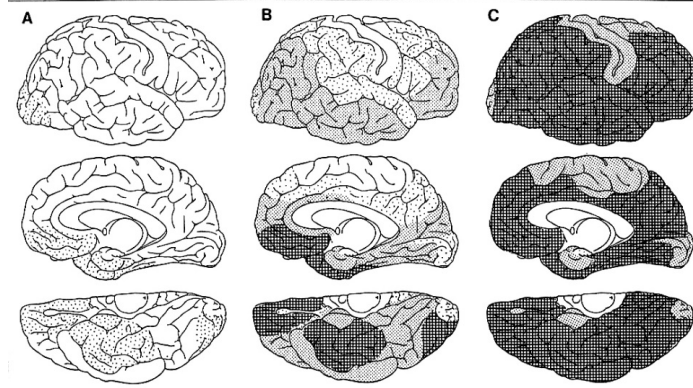
transentorhinal
I - II

limbic
III - IV

isocortical
V - VI



NFT stage Neurofibrillary changes

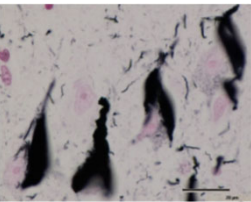


SP stage

Amyloid

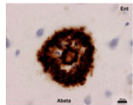
BBAR Frozen Brain Resource (N = 2560)

Braak Senile Plaque (SP) Stage and Braak NFT Stage



Braak
NFT

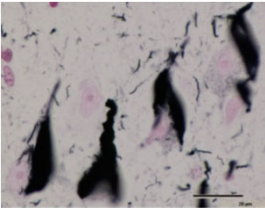
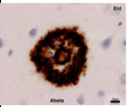
Braak SP



	Braak NFT	0	I	II	III	IV	V	VI	Total
Braak SP 0		59 (58.9)	364 (75.7)	140 (81.6)	46 (85.7)	13 (85.7)	1 (81.0)	0	623 (76.4)
A		33 (67.0)	458 (77.5)	358 (83.3)	101 (87.1)	21 (92.2)	2 (95.5)	0	973 (80.6)
B		9 (74.7)	176 (79.4)	123 (82.7)	86 (86.3)	31 (92.3)	3 (82.7)	1 (94.0)	429 (82.6)
C		2 (72.5)	52 (79.8)	88 (82.4)	105 (85.8)	113 (86.3)	125 (86.1)	50 (83.7)	535 (84.6)
Total		103 (63.1)	1050 (77.3)	709 (82.7)	338 (86.3)	178 (88.0)	131 (86.1)	51 (83.9)	2560 (80.7)

CERAD represents neuritic (containing PHF) plaque and Thal staging correlates with Braak NFT Staging

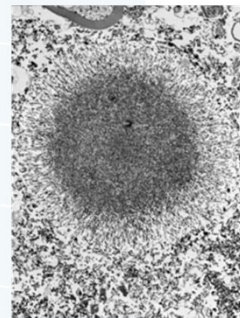
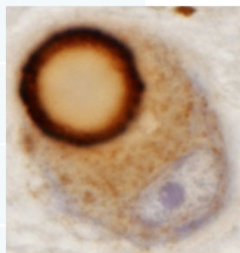
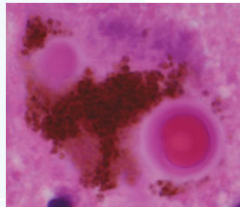
Categorization based on Braak's Staging

		NFT STAGE 						
		0	I	II	III	IV	V	VI
S P 	0	MSC (55.2%)			NFTC (7.2%)			
	A							
	B	PSC (17.6%)			ADC (20.0%)			
	C							

MSC: minimal senile change; NFTC: NFT dominant change
 PSC: plaque- dominant change; ADC: Alzheimer disease change

BBAR Stage of Lewy Body Pathology (Lewy- related alpha- synucleinopathy: LBAS)

Stage	LBAS	Lewy Body			LB score	SN loss of pigment		PA	Dem.	
		ANS	SN/ Stri	Limb/ NC						
0	-	-	-	-	0	-				
0.5	+	+/-	-	-	0	-				
1	+	+/-	+/-	+/-	0	0				Preclinical
2	+	+/-	+/-	+/-	0-10	+	-	-		Prodromal
3	+	+	+	+	0-2 (10)	+	+	-		PD w/o D
4	+	+	+	+	3-6 (10)	+/-	+/-	+		PDD/ DLBL
5	+	+	+	+	7-10	+/-	+/-	+		PDD/ DLBN

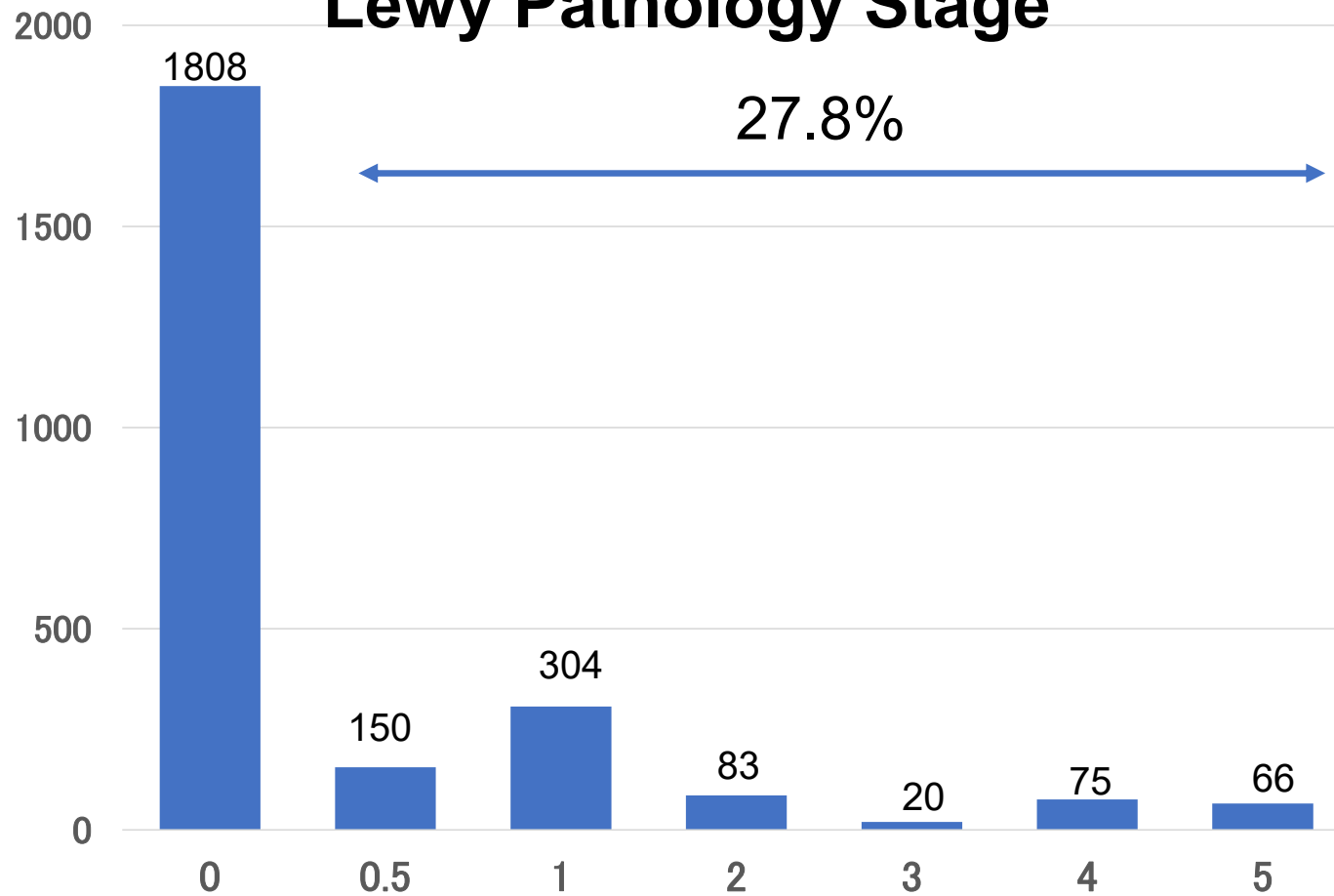


LBAS: positive α -synuclein immunocytochemistry and negative Gallyas staining: **LB:** identified with H&E staining

Saito Y, et al: J Neuropath Exp Neurol. (2004)

BBAR Frozen Brain Resource (N = 2560)

Lewy Pathology Stage

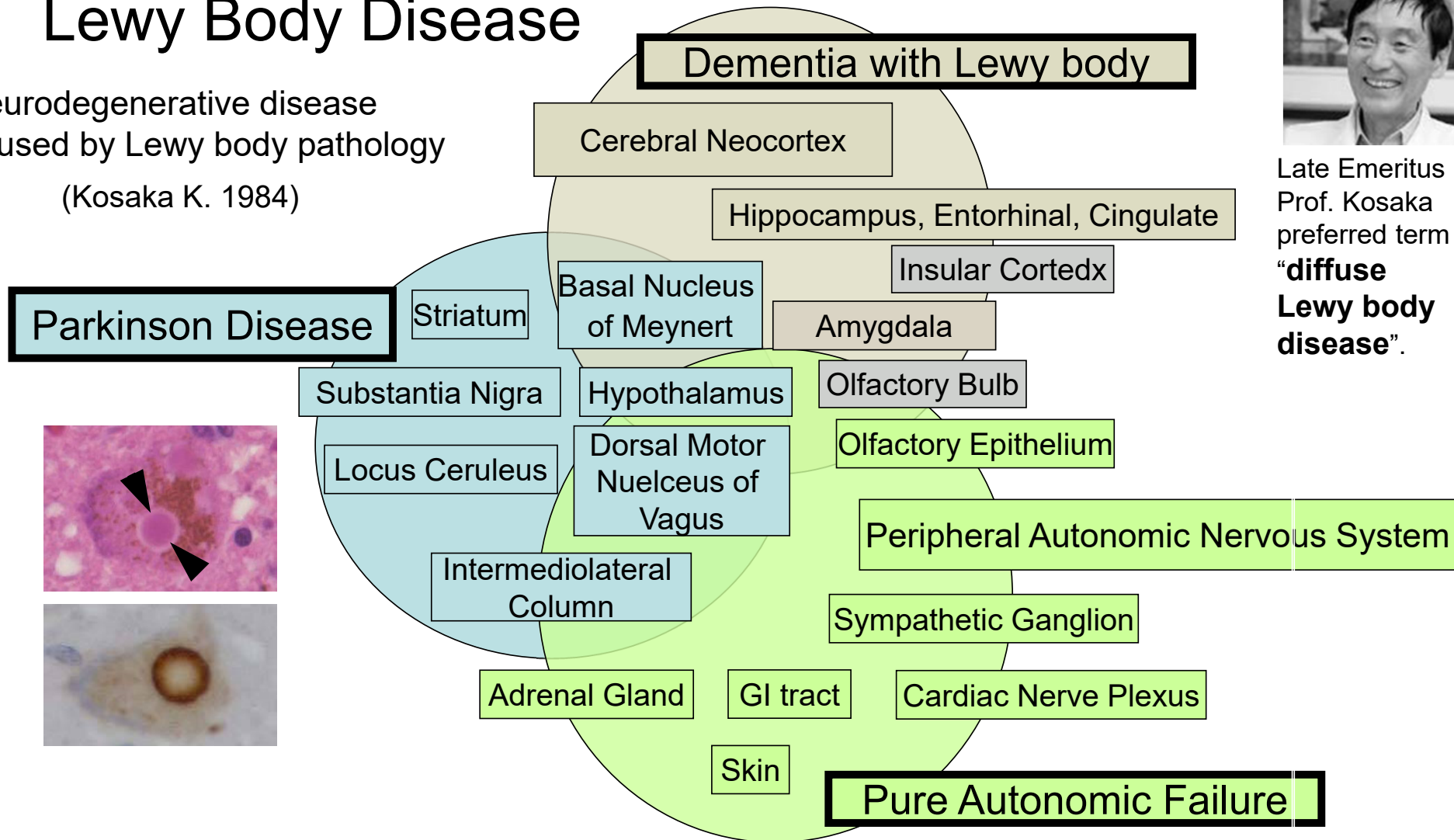


Lewy Body Disease

Neurodegenerative disease
caused by Lewy body pathology
(Kosaka K. 1984)



Late Emeritus
Prof. Kosaka
preferred term
**“diffuse
Lewy body
disease”**.



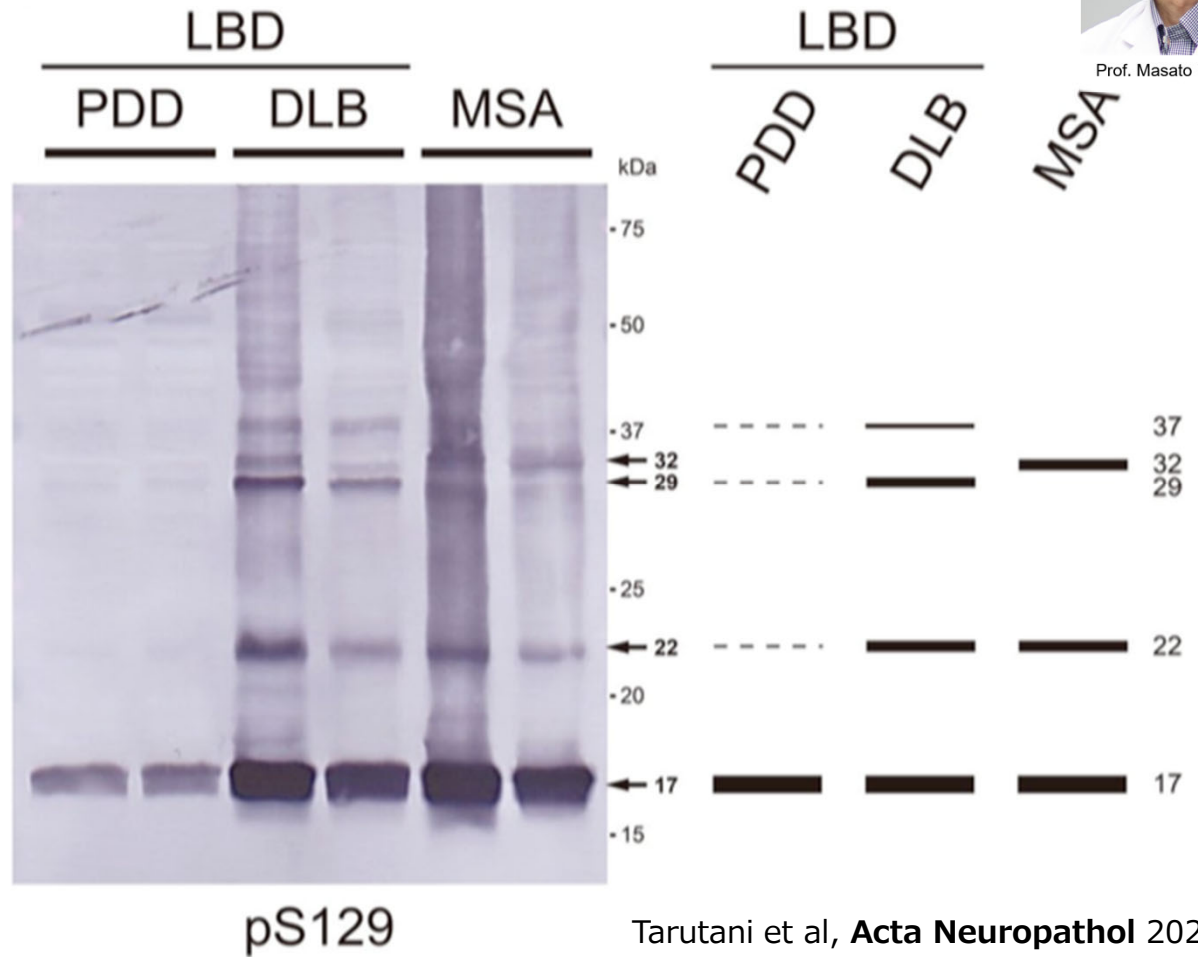
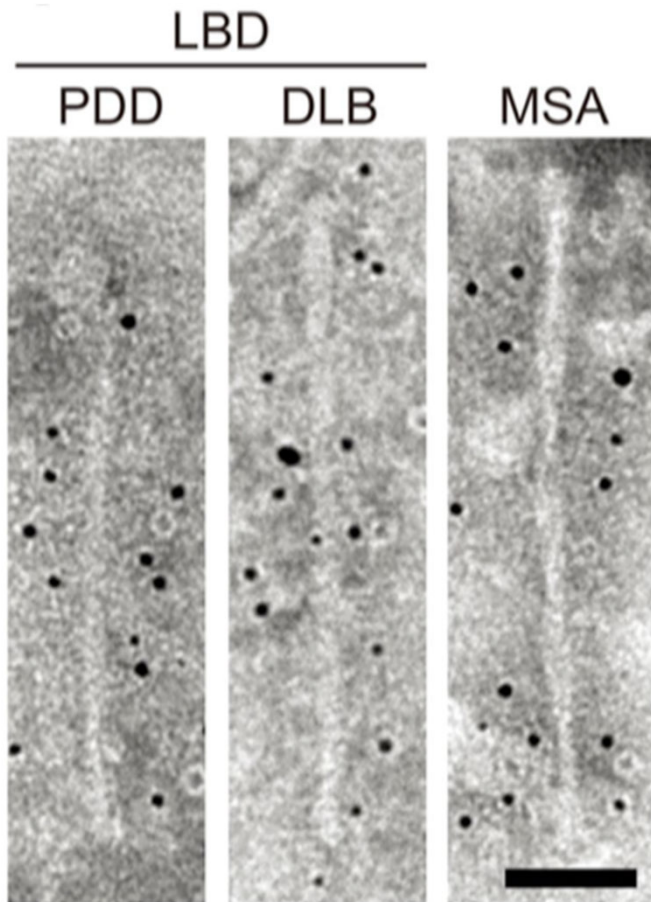
Whole Body Screening $\longleftrightarrow$ tau $\longleftrightarrow$ Lewy TDP $\longleftrightarrow$ A β $\longleftrightarrow$

[illegible]

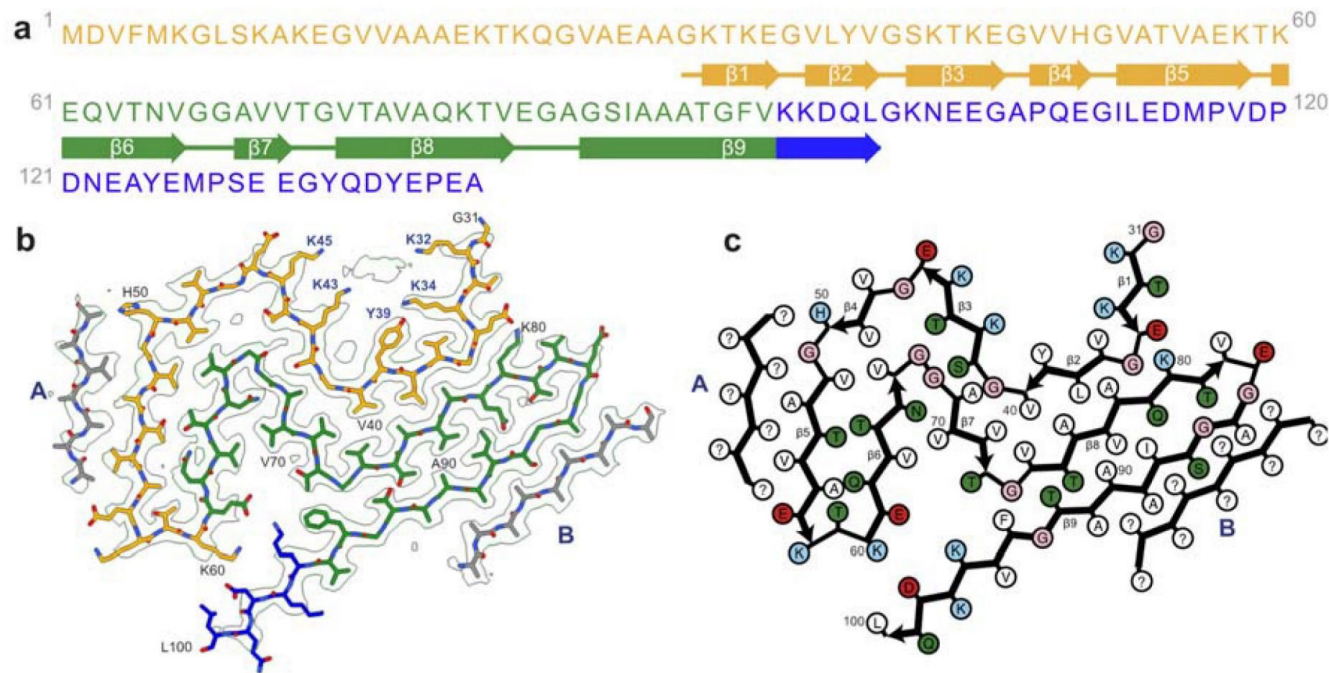
Negative EM and Western blotting demonstrate the same structure of α synuclein fibrils PDD and DLB cases but different from MSA.



Prof. Masato Hasegawa



Tarutani et al, **Acta Neuropathol** 2022.



Prof. Michael Goedert

Lewy body fold
Nature
2022

Figure 2. Cryo-EM structure of α -synuclein filaments from Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies (Lewy fold). (a). Amino acid sequence of human α -synuclein. N-terminal region (residues 1-60) in orange, NAC region (residues 61-95) in green and C-terminal region (residues 96-140) in blue. Thick connecting lines with arrowheads indicate β -strands. (b). Cryo-EM density map and atomic model of the Lewy fold. The filament core extends from G31-L100. Islands A and B are indicated in grey. (c). Schematic of the Lewy filament fold of α -synuclein. Negatively charged residues are in red, positively charged residues in blue, polar residues in green, apolar residues in white, sulfur-containing residues in yellow and glycines in pink. Thick connecting lines with arrowheads indicate β -strands. Unknown residues are indicated by question marks.

Systemic Lewy Body Pathology: Reports from BBAR

Saito, 2003, 2004

JNEN

Senile Brain

Sakashita, 2021

Neuropathology

Submandibular Gland
(*JSNP Award*)

Ito, 2014

Int. J. C.E.P

GI tract

Ikemura, 2008

JNEN

Shishido 2010

Neurology

Skin

Sumikura, 2015

Acta Neuropath Com

DRG, Spinal cord

Sengoku, 2008

JNEN (Cover)

(*Moore Award*)

Olfactory bulb

Funabe, 2013

Neuropathology

(*Jsnp Award*)

Saito 2016

Movement Disorders (Cover)

Olfactory Epithelium

Mitsui, 2006

JNS

Matsubara 2021

Neurology

Heart

Tanei, 2021

Acta Neuropath

Esophagus

Fumimura, 2007

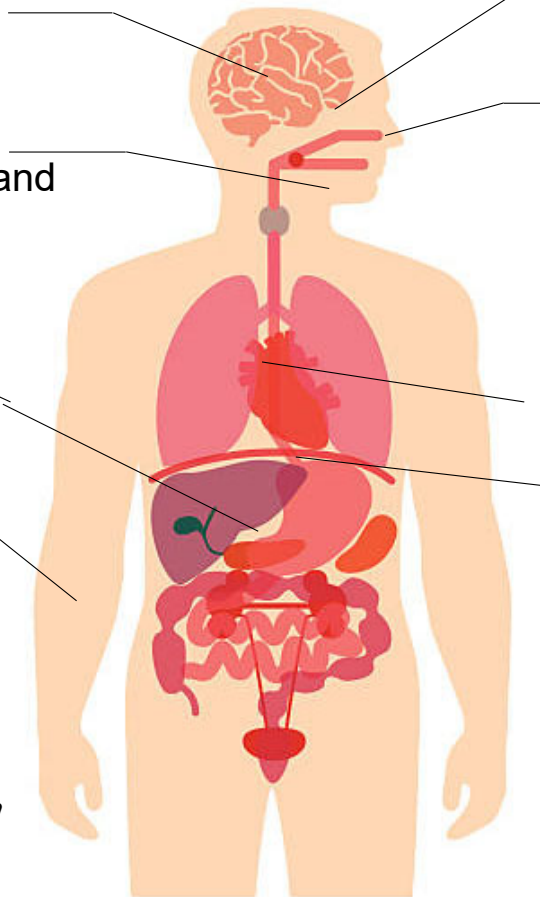
JNEN

Adrenal gland

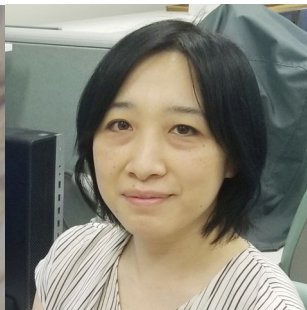
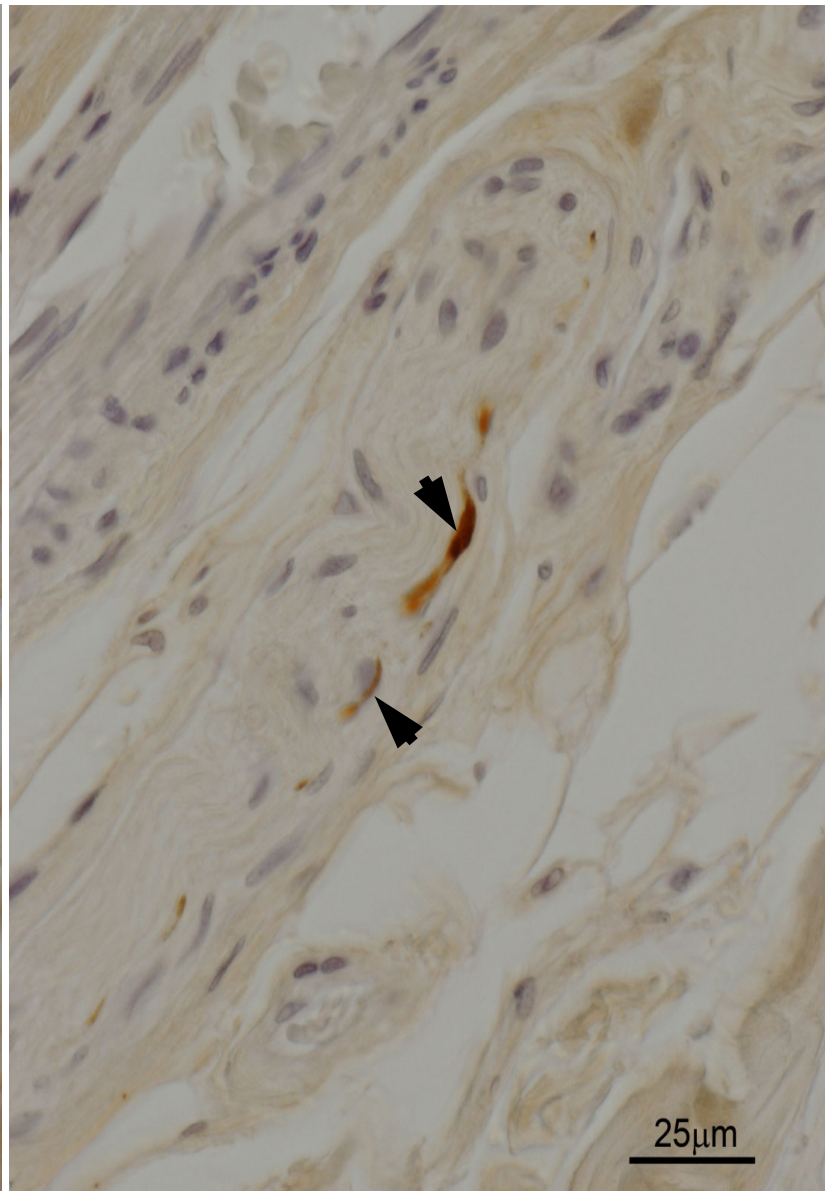
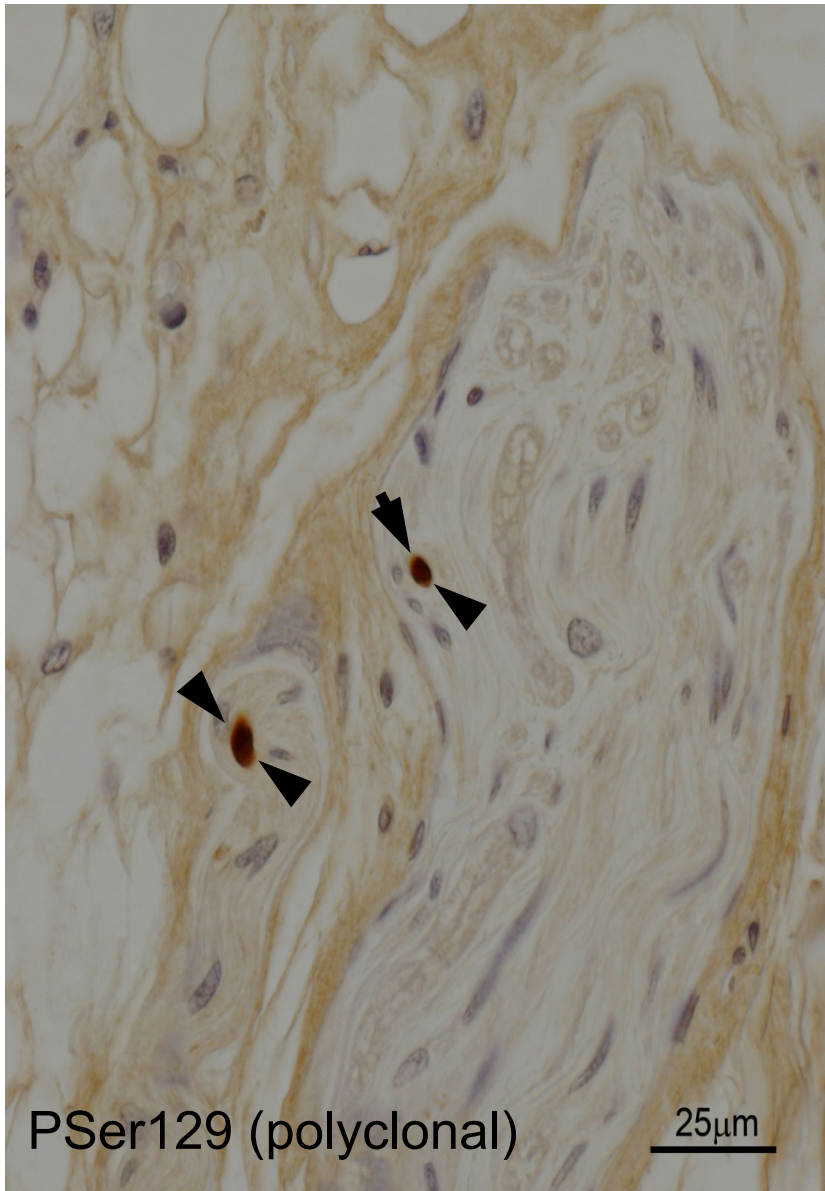
Hatsuta, 2016

J Park Dis

Spinal ventral roots



Skin



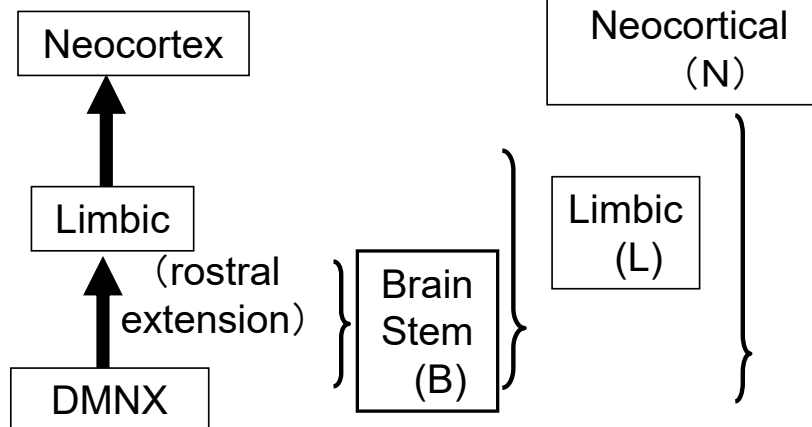
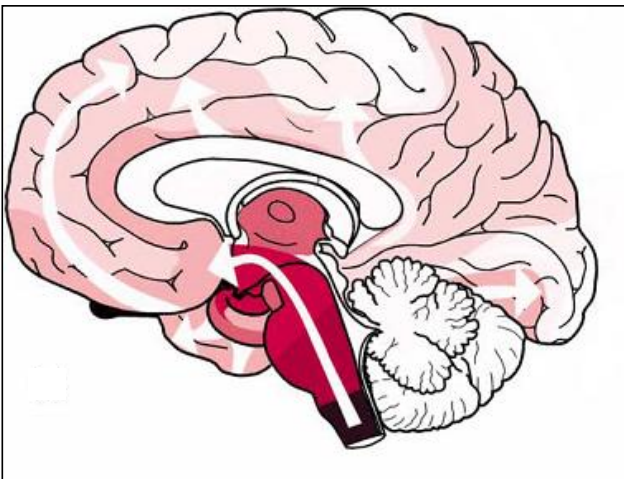
Dr. Masako Ikemura
JNEN 2008

Tokyo University Thesis
Department of Pathology

The first
report of skin
involvement
in LBD

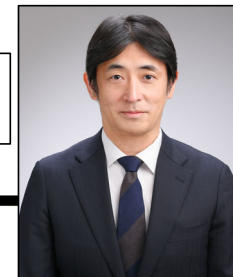
Clinical Test
for PD
commercially
available in
USA 2023.

Braak's Rostral Extension Pradigm of Lewy body pathology

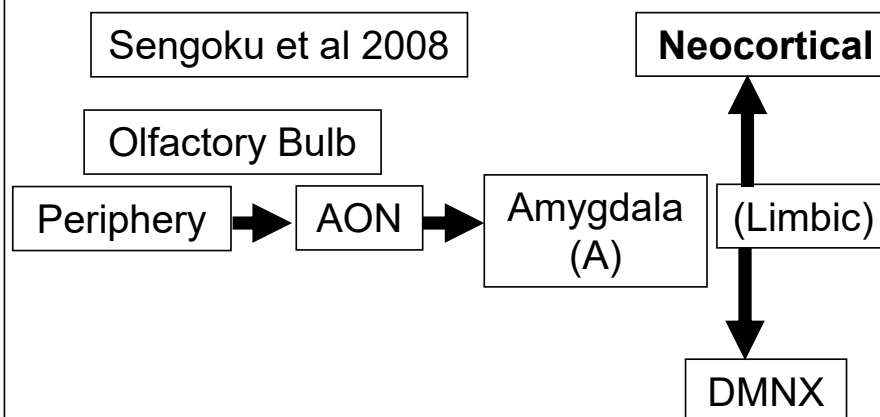
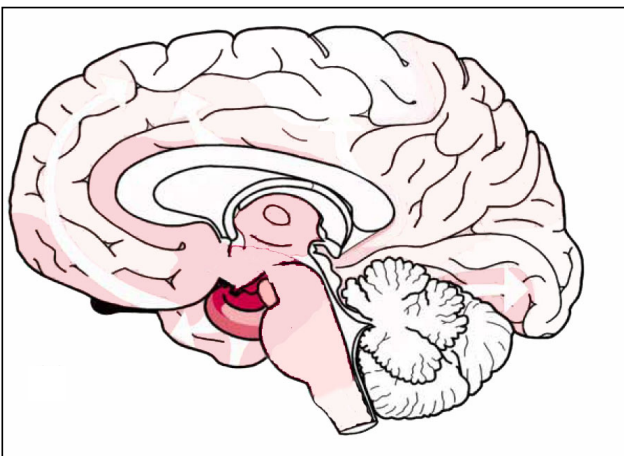


Body First

Renpei Sengoku
JNEN 2008



Olfactory- Amygdala Extension of Lewy body pathology



Brain First



**American Association of Neuropathologists
Moore Award**

Presented to
R. Sengoku, Y. Saito, M. Ikemura, H. Hatsuta, Y. Sakiyama, M. Sawabe,
K. Inoue, H. Mochizuki and S. Murayama

For the Best Paper on Clinico-Pathological Correlation
Incidence and Extent of Lewy Body-Related α -synucleinopathy in
Human Aging Olfactory Bulb

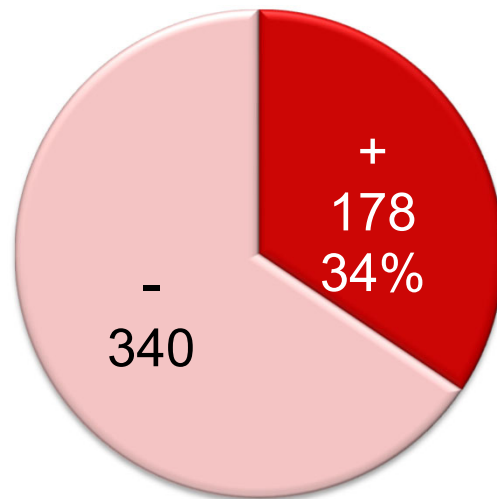
San Diego, California
7 April 2008

Raymond A. Sobel
Awards Committee Chair
Jeffrey A. Goldman
President
George Perry
Secretary-Treasurer

Lewy body disease body resource

One third of geriatric cohort contained Lewy pathology in the body.

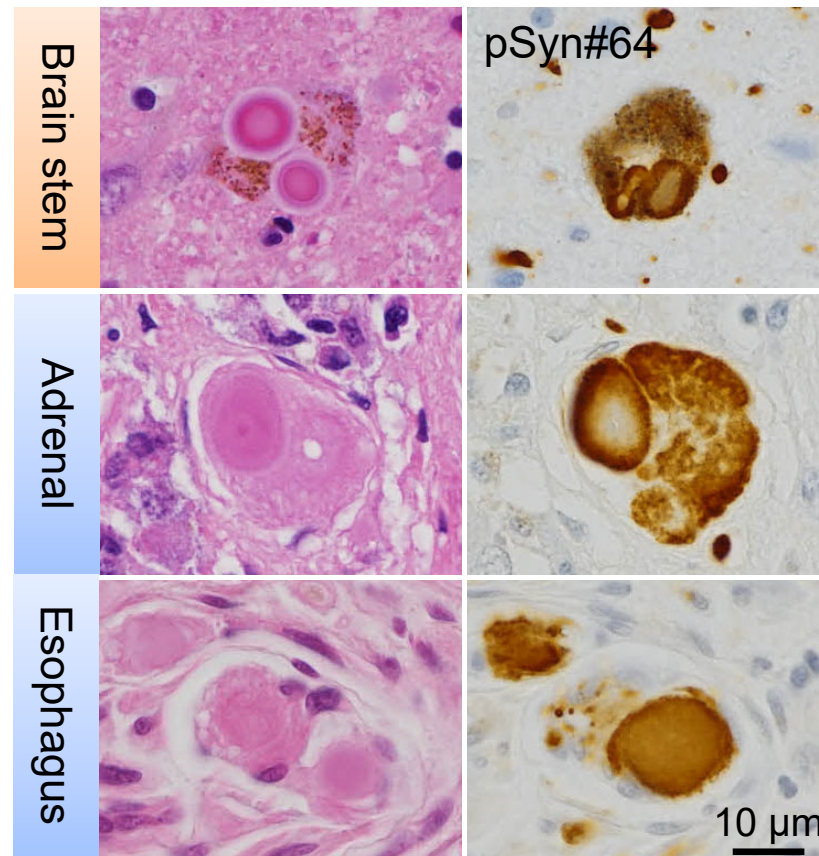
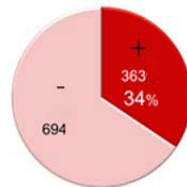
TMIGG consecutive autopsy cases 1,057 (2003~2018)



518

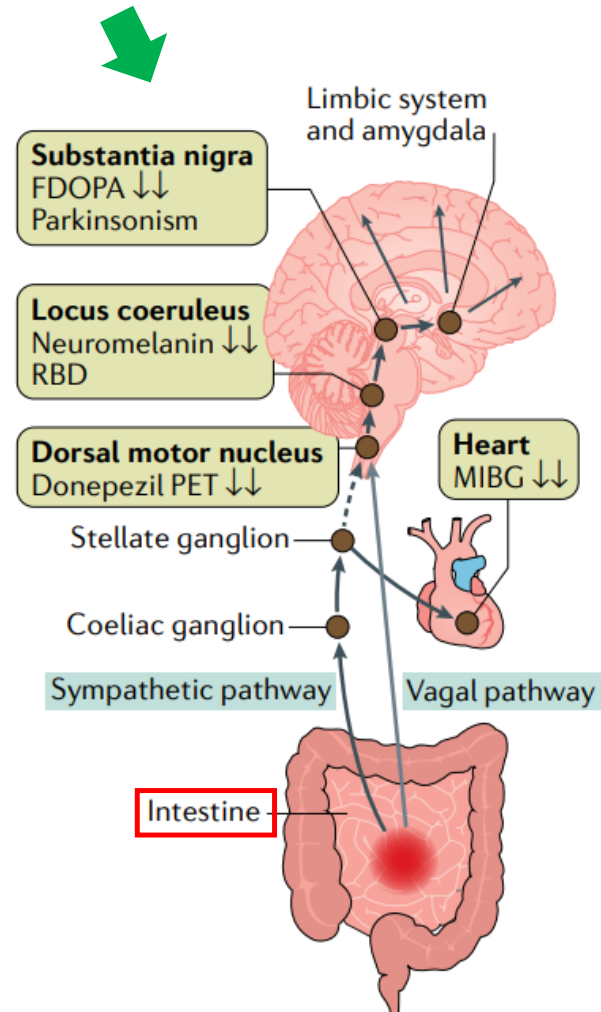
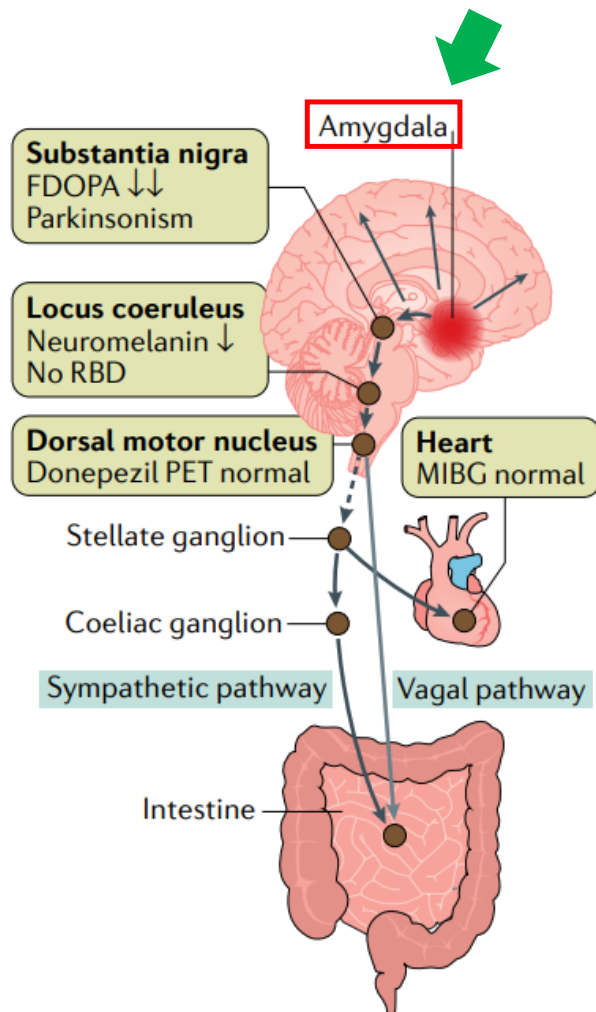
(2008- 2018)

To examine GI tracts carefully



Dr. Zenichi Tanei
Dpt. Pathology
Tokyo University

BRAIN-FIRST VS. BODY-FIRST



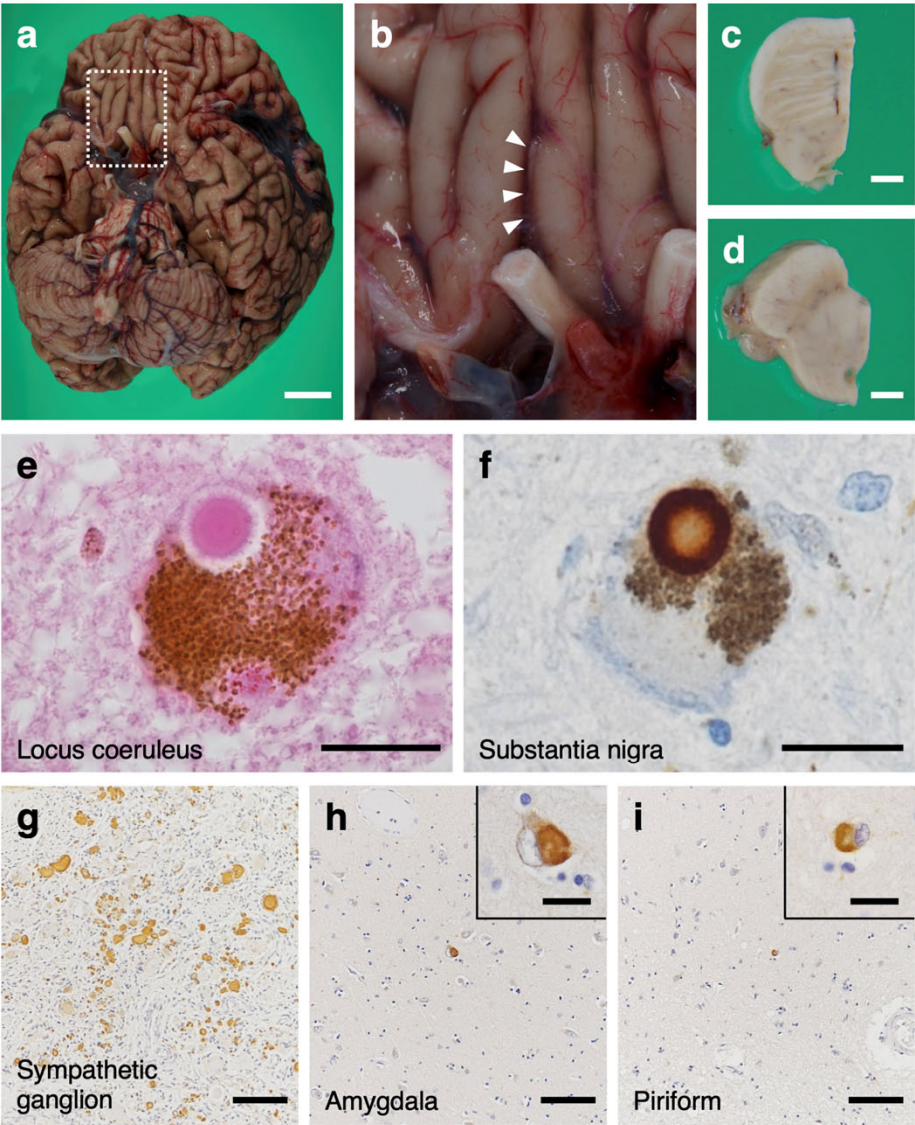
Prof. Borghammer

PD with olfactory hypoplasia

Matsubara T, et al
J Neurol. 2024
A case from NCNP



LBAS abundant in PANS, brainstem and Meynert, but sparse in limbic system and neocortex.
= Body First Case



j

	HE Lewy body	p-α-syn LBAS
Cerebral cortex		
Precentral gyrus	-	-
Supramarginal gyrus	-	±
Middle frontal gyrus	-	±
Middle temporal gyrus	-	+
Limbic system		
Anterior cingulate	+	+
Insular	-	+
Trans Enthrinal	-	+
Cornu ammonis (CA2-plexus)	-	±
Amygdala	+	+
Piriform	+	+
Olfactory tract remnant	-	±
Basal Ganglia		
Putamen	-	±
Globus pallidus	-	±
Nucleus basalis of Meynert	++	+++
Thalamus	-	+
Cerebellum		
Cerebellar cortex	-	-
Dentate nucleus	-	-
Brainstem		
Edinger-Westphal Nucleus	+	++
Substantia nigra	++*	++*
Locus coeruleus	+	++*
Dorsal vagal nucleus	+	++*
Spinal cord		
Anterior horn	-	±
Intermediate lateral nucleus	-	+
Onuf's nucleus	-	±
Peripheral nervous system		
Adrenal grand	+	+++
Sympathetic ganglion	+	+++
Heart	-	±*
Esophagus	-	±
Skin	-	±

0: None
1+: <5/region
2+: >5/region

0: None
±: only neurites
1+: 1 NCI/field
2+: 2-3 NCIs/field
3+: ≥4 NCIs/field

* accompanied with severe neuronal loss/denervation

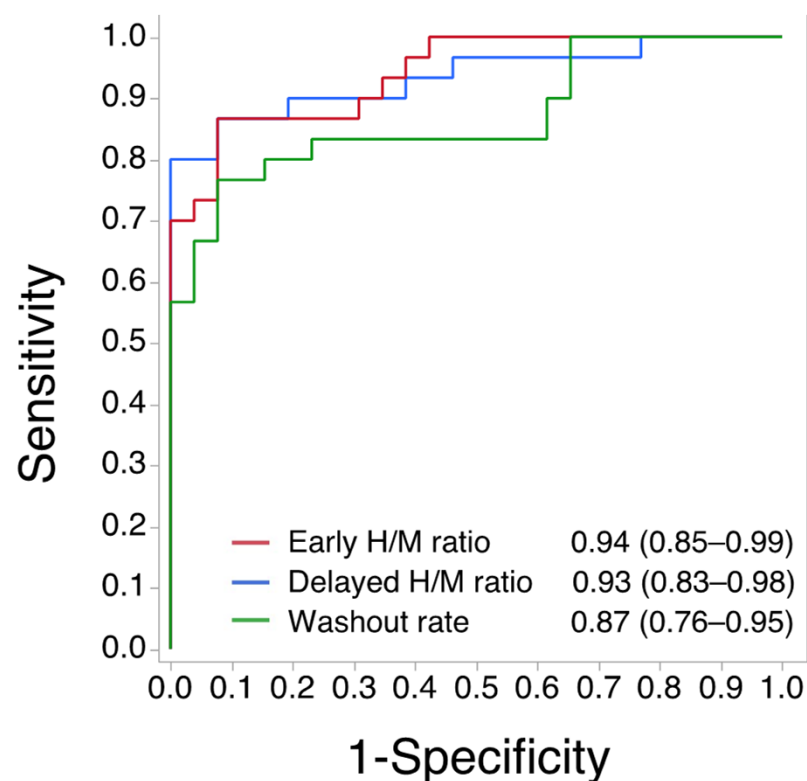
Autopsy Validation of MIBG Cardiac Scintigraphy

Matsubara T et al
Neurology 2022

Patient Background (n = 56) (1995- 2020)

	Total (n=56)	LBD (n=30)	Non-LBD (n=26)
M:F	29:27	17:13	12:14
Age of Death (year), mean $\pm$ SD (range)	82.2 $\pm$ 9.3 (41–99)	84.9 $\pm$ 7.5 (68–99)	79.0 $\pm$ 10.2 (41–91)
Onset to Autopsy (year), mean $\pm$ SD (range)	5.0 $\pm$ 4.2 (0.1–16.2)	5.0 $\pm$ 4.7 (0.2–16.2)	5.0 $\pm$ 3.6 (0.1–12.3)
Last test to Autopsy (year), mean $\pm$ SD (range)	3.9 $\pm$ 3.0 (0.1–12.8)	4.1 $\pm$ 3.2 (0.1–12.8)	3.8 $\pm$ 2.8 (0.3–8.6)
Total Clinical Course (year), mean $\pm$ SD (range)	8.9 $\pm$ 4.8 (0.5–19.0)	9.1 $\pm$ 5.0 (2.4–19.0)	8.8 $\pm$ 4.6 (0.5–18.5)
Initial Symptom			
Motor, n (%)	37 (66.1)	18 (60.0)	19 (73.1)
Cognition, n (%)	17 (30.4)	10 (33.3)	7 (26.9)
ANS, n (%)	2 (3.6)	2 (6.7)	0 (0)
Past History			
DM, n (%)	10 (17.9)	4 (13.3)	6 (23.1)
HT, n (%)	23 (41.1)	13 (43.3)	10 (38.5)
Coronary disease before scintigraphy, n (%)	1 (1.8)	0 (0)	1 (3.9)
Severe renal failure, n (%)	1 (1.8)	0 (0)	1 (3.9)

Specificity of MIBG cardiac scintigraphy is high enough for pathological diagnosis



¹²³ I-MIBG Cardiac Scinti	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)
Early H/M ratio (cut off: 2.20)	21	9	1	25	70.0 (50.6–85.3)	96.2 (80.4–99.9)
Delayed H/M ratio (cut off: 2.20)	24	6	2	24	80.0 (61.4–92.3)	92.3 (74.9–99.1)
Delayed H/M ratio (cut off: 1.81)	24	6	0	26	80.0 (61.4–92.3)	100.0 (86.8–100.0)
Washout rate (cut off: 34%)	24	6	4	22	80.0 (61.4–92.3)	84.6 (65.1–95.6)

Matsubara T et al *Neurology* 2022

Today's Topics

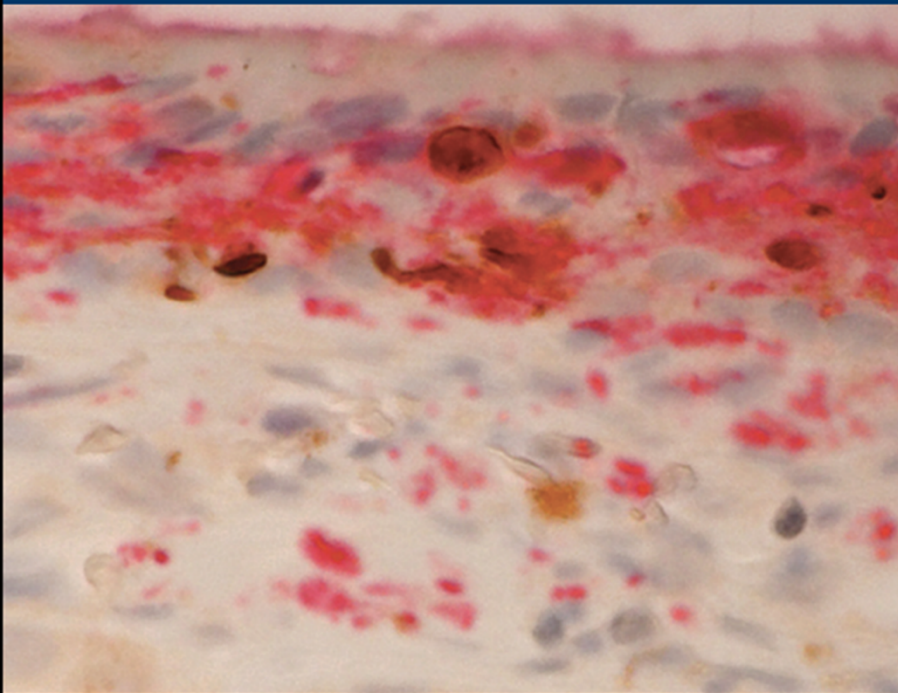
1. Lewy body pathology in an aging cohort
2. Comorbidities and Outcomes in Parkinson disease, focusing on Alzheimer pathology



Official Journal of the International Parkinson and Movement Disorder Society

Movement Disorders

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WILEY

red: PGP 9.5, brown: psyn#64

Lewy Body Pathology Involves the Olfactory Cells in Parkinson's Disease and Related Disorders

Yuko Saito, MD, PhD,^{1*} Ayako Shioya, MD, PhD,^{1,2}
Terunori Sano, MD,¹ Hiroyuki Sumikura, MD, PhD,^{3,4}
Miho Murata, MD, PhD⁵ and Shigeo Murayama, MD, PhD^{3,4}



Prof. Yuko Saito
Movement Disorders
2016

The Director of
NCNP Brain Bank
(2000- 2009)

The first report of LBD in olfactory epithelium

- ✓ Consecutive 47 adult autopsy cases of National Center of Neurology and Psychiatry (NCNP)
- ✓ 7 out of 8 PD contained Lewy body pathology
- ✓ One preclinical case presented with the pathology.

NCNP (Parkinson Disease Center) Autopsy Cases of Lewy Body Disease (2010- 2019)

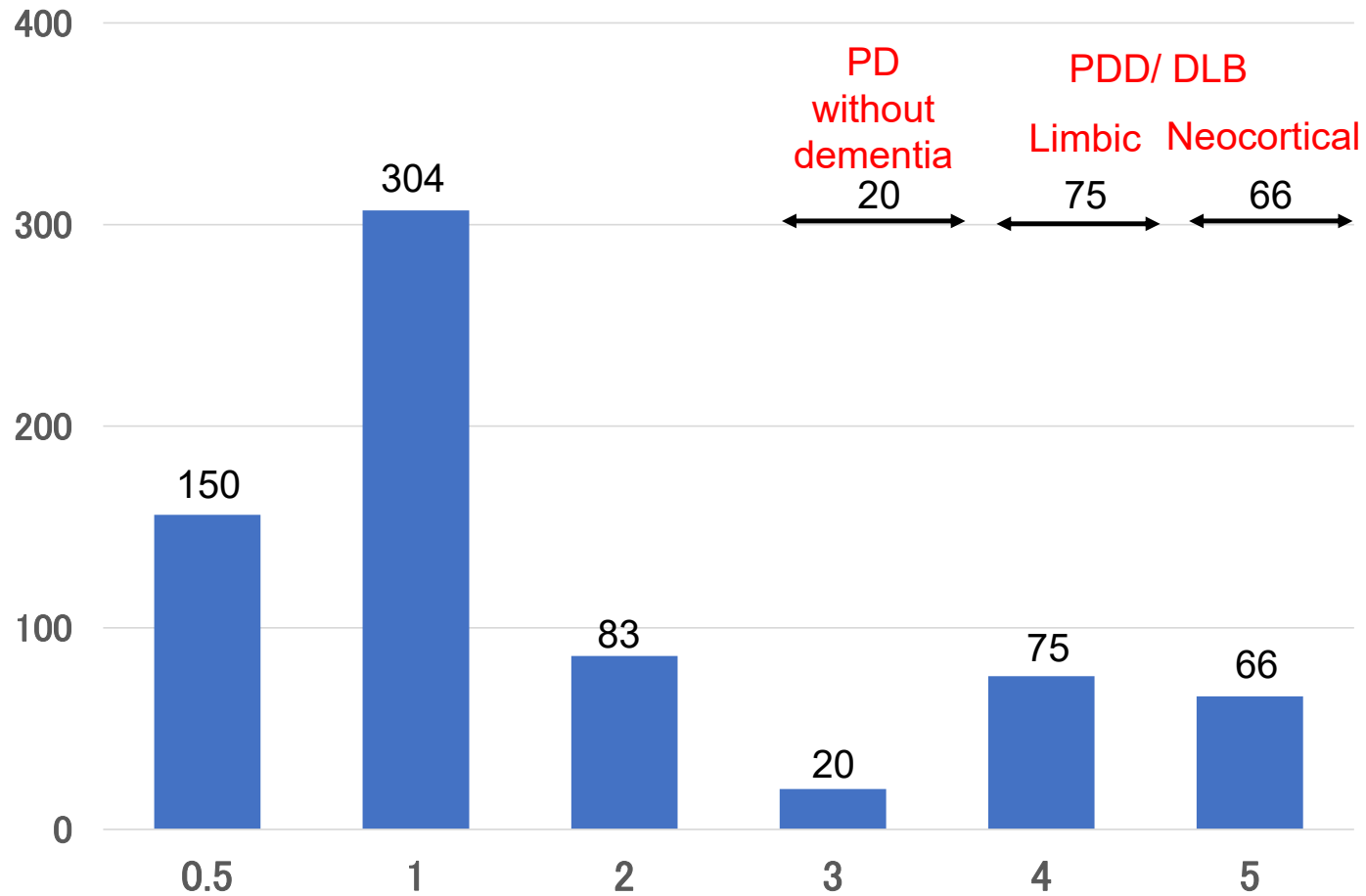
#	age	gender	DX	BBARS	DLBCG	NFT	SP	ADNC	AGD	TDP43	Others
1	60	M	PD	3	N	1	1	MSC	1	0	Psy OH
2	61	F	PD	3	L	2	0	MSC	0	N/E	
3	71	F	PD	3	L	2	0	MSC	3	1	
4	73	M	PD	3	L	2	1	MSC	1	0	RBD Psy
5	78	M	PD	3	L	1	0	MSC	2	1	post DBS
6	80	M	PD	3	N	1	2	MSC	2	0	post Vim
7	81	F	PD	3	N	2	0	MSC	0.5	1	
8	81	M	PD	3	N	1	0	MSC	0.5	0	
9	85	M	PD	3	N	1	1	MSC	0.5	0	
10	80	F	PDD	4	L	2	3	PSC	0	1	
11	80	M	PDD	5	N	2	3	PSC	1	N/E	
12	81	F	PDD	5	N	2	3	PSC	0	1	
13	87	F	PDD	5	N	2	3	PSC	0	2	
14	74	F	DLB	5	N	2	3	PSC	1	0	
15	87	M	DLB	5	N	1	3	PSC	N/E	1	
16	89	M	DLB	5	N	2	3	PSC	3	2	
17	86	M	DLB AD form	5	N	4	3	ADC	1	1	pMSA
18	88	F	DLB AD form	5	N	5	3	ADC	2	0	

Predominantly members of the Japan PD Association with brain bank donation

Psy: psychiatric symptoms
OH: orthostatic hypotension
Vim: Vim pallidotomy
pMSA: preclinical MSA

BBAR Frozen Brain Resource (N = 711/ 2560)
Lewy Pathology Stage ≥ 0.5

from an aging
cohort in a Tokyo
suburb with
roughly one
million residents

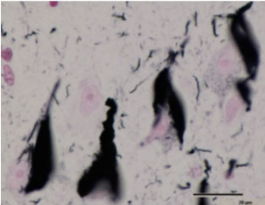
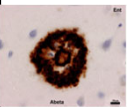


BBAR Frozen Brain Resource (N = 2560)
Braak SP Stage and Braak NFT Stage
BBAR LBD Stage = 3 (N = 20, PD without dementia)

Braak SP	Braak NFT	0	I	II	III	IV	V	VI	Total
0		0	4 (78.8)	1 (86.0)	0	0	0	0	5 (80.2)
A		2 (69.0)	3 (79.3)	6 (84.0)	1 (77.0)	0	0	0	12 (79.8)
B		0	2 (72.5)	0	0	0	0	0	2 (72.5)
C		0	0	1 (81.0)	0	0	0	0	1 (81.0)
Total		2 (69.0)	9 (77.6)	8 (83.9)	1 (77.0)	0	0	0	20 (79.2)

Parkinson disease without dementia

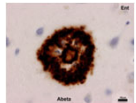
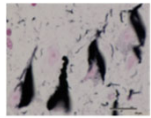
Categorization based on Braak's Staging

		NFT STAGE 						
		0	I	II	III	IV	V	VI
S P 	0	MSC (55.2%) 16			NFTC (7.2%) 1			
	A							
	B	PSC (17.6%) 3			ADC (20.0%) 0			
	C							

MSC: minimal senile change; NFTC: NFT dominant change

PSC: plaque- dominant change; ADC: Alzheimer disease change

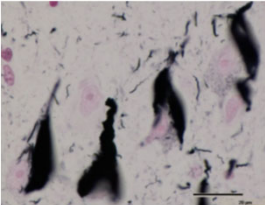
BBAR Frozen Brain Resource (N = 2560)
Braak SP Stage and Braak NFT Stage
BBAR LBD Stage = 4 (N = 34, PDD)



		Braak NFT							Total
		0	I	II	III	IV	V	VI	
Braak SP	0	0	3 (81.0)	3 (83.3)	0	0	0	0	6 (82.2)
	A	0	6 (76.3)	14 (85.1)	1 (90.0)	0	0	0	21 (82.8)
	B	0	1 (81.0)	3 (74.3)	0	0	0	0	4 (76.0)
	C	0	1 (73.0)	0	2 (88.0)	0	0	0	3 (83.0)
	Total	0	11 (77.7)	20 (83.2)	3 (88.7)	0	0	0	34 (81.9)

Parkinson disease without dementia

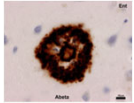
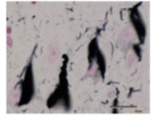
Categorization based on Braak's Staging

		NFT STAGE 						
		0	I	II	III	IV	V	VI
S P	0	MSC (55.2%) 26			NFTC (7.2%) 1			
	A							
	B	PSC (17.6%) 5			ADC (20.0%) 2			
	C							

MSC: minimal senile change; NFTC: NFT dominant change

PSC: plaque- dominant change; ADC: Alzheimer disease change

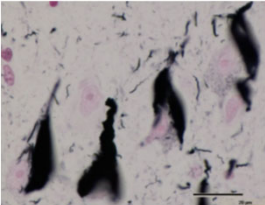
BBAR Frozen Brain Resource (N = 2560)
Braak SP Stage and Braak NFT Stage
BBAR LBD Stage = 5 (N = 16, PDD)



		Braak NFT							Total
Braak SP		0	I	II	III	IV	V	VI	
	0	0	0	0	1 (83.0)	0	0	0	1 (83.0)
	A	0	0	4 (86.2)	1 (86.0)	0	0	0	5 (86.2)
	B	0	1 (88.0)	1 (76.0)	0	0	0	0	2 (82.0)
	C	0	1 (74.0)	4 (81.8)	0	2 (71.0)	1 (82.0)	0	8 (78.1)
Total		0	2 (81.0)	9 (83.1)	2 (84.5)	2 (71.0)	1 (82.0)	0	16 (81.4)

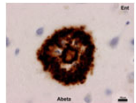
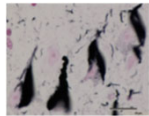
Parkinson disease without dementia

Categorization based on Braak's Staging

		NFT STAGE 						
		0	I	II	III	IV	V	VI
S P	0	MSC (55.2%) 4			NFTC (7.2%) 2			
	A							
	B	PSC (17.6%) 7			ADC (20.0%) 3			
	C							

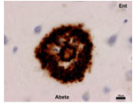
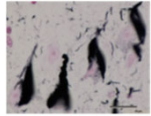
MSC: minimal senile change; NFTC: NFT dominant change
PSC: plaque- dominant change; ADC: Alzheimer disease change

BBAR Frozen Brain Resource (N = 2560)
Braak SP Stage and Braak NFT Stage
BBAR LBD Stage = 4 (N = 42, DLB limbic form)



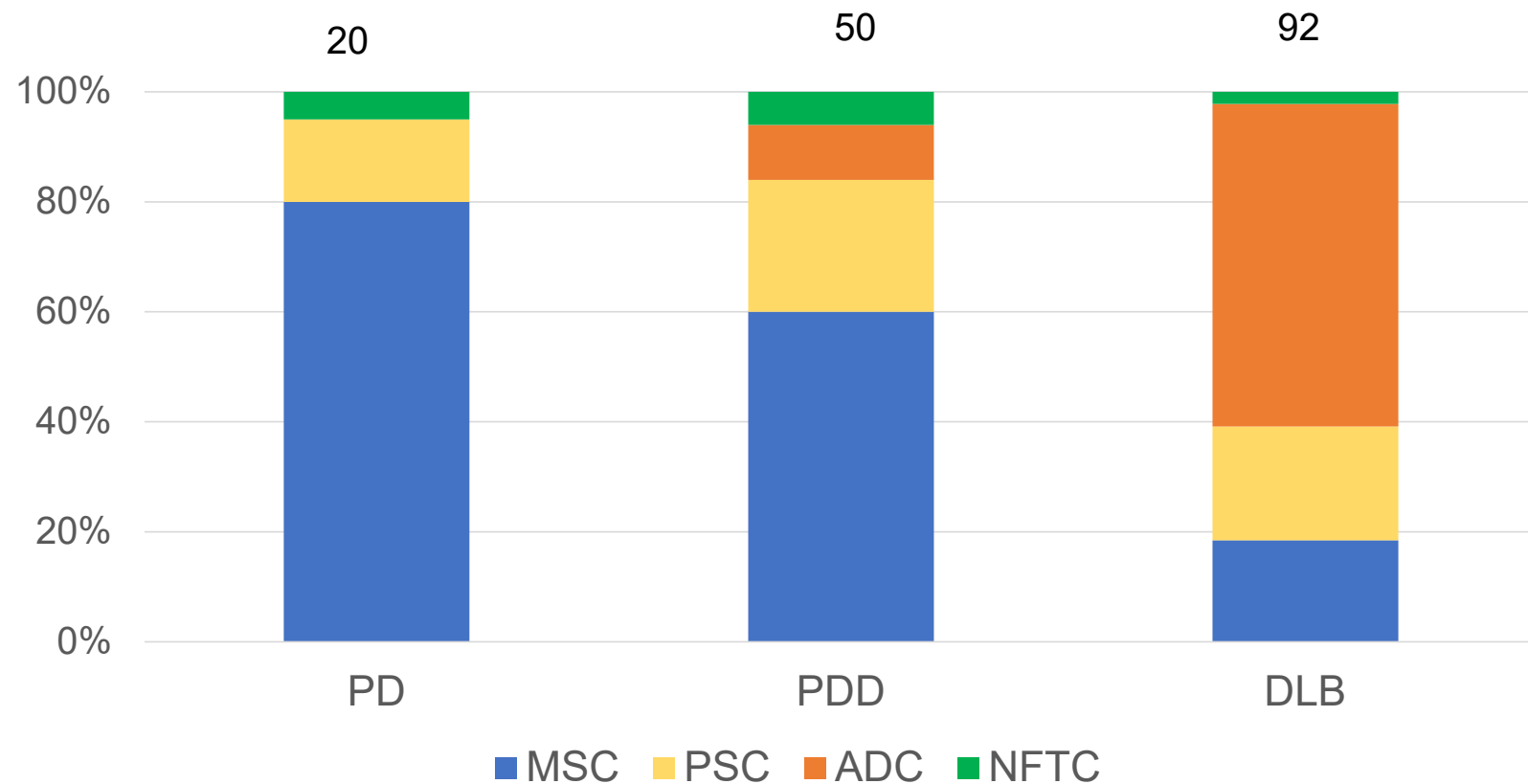
		Braak NFT							Total
		0	I	II	III	IV	V	VI	
Braak SP	0	0	3 (83.0)	2 (89.0)	0	0	0	0	5 (85.4)
	A	0	2 (90.0)	6 (93.2)	1 (88.0)	0	0	0	9 (91.9)
	B	0	4 (84.0)	0	3 (88.0)	1 (93.0)	0	0	8 (86.6)
	C	0	0	2 (86.0)	3 (83.3)	5 (84.8)	5 (84.8)	5 (78.2)	20 (83.1)
	Total	0	9 (85.0)	10 (90.9)	7 (86.0)	6 (86.2)	5 (84.8)	5 (78.2)	42 (85.9)

BBAR Frozen Brain Resource (N = 2560)
Braak SP Stage and Braak NFT Stage
BBAR LBD Stage = 5 (N = 50, DLB)



		Braak NFT							Total
		0	I	II	III	IV	V	VI	
Braak SP	0	0	0	0	0	1 (81.0)	0	0	1 (81.0)
	A	0	3 (84.0)	1 (80.0)	0	0	0	0	4 (83.0)
	B	0	2 (80.0)	5 (89.6)	1 (86.0)	1 (99.0)	0	0	9 (88.1)
	C	0	0	6 (84.7)	4 (85.3)	14 (90.1)	9 (84.6)	3 (89.7)	36 (87.2)
Total		0	5 (82.4)	12 (86.3)	5 (85.4)	16 (90.1)	9 (84.6)	3 (89.7)	50 (86.9)

BBAR- Registered Cases with Frozen Brain Tissue (n = 162/ 2560)

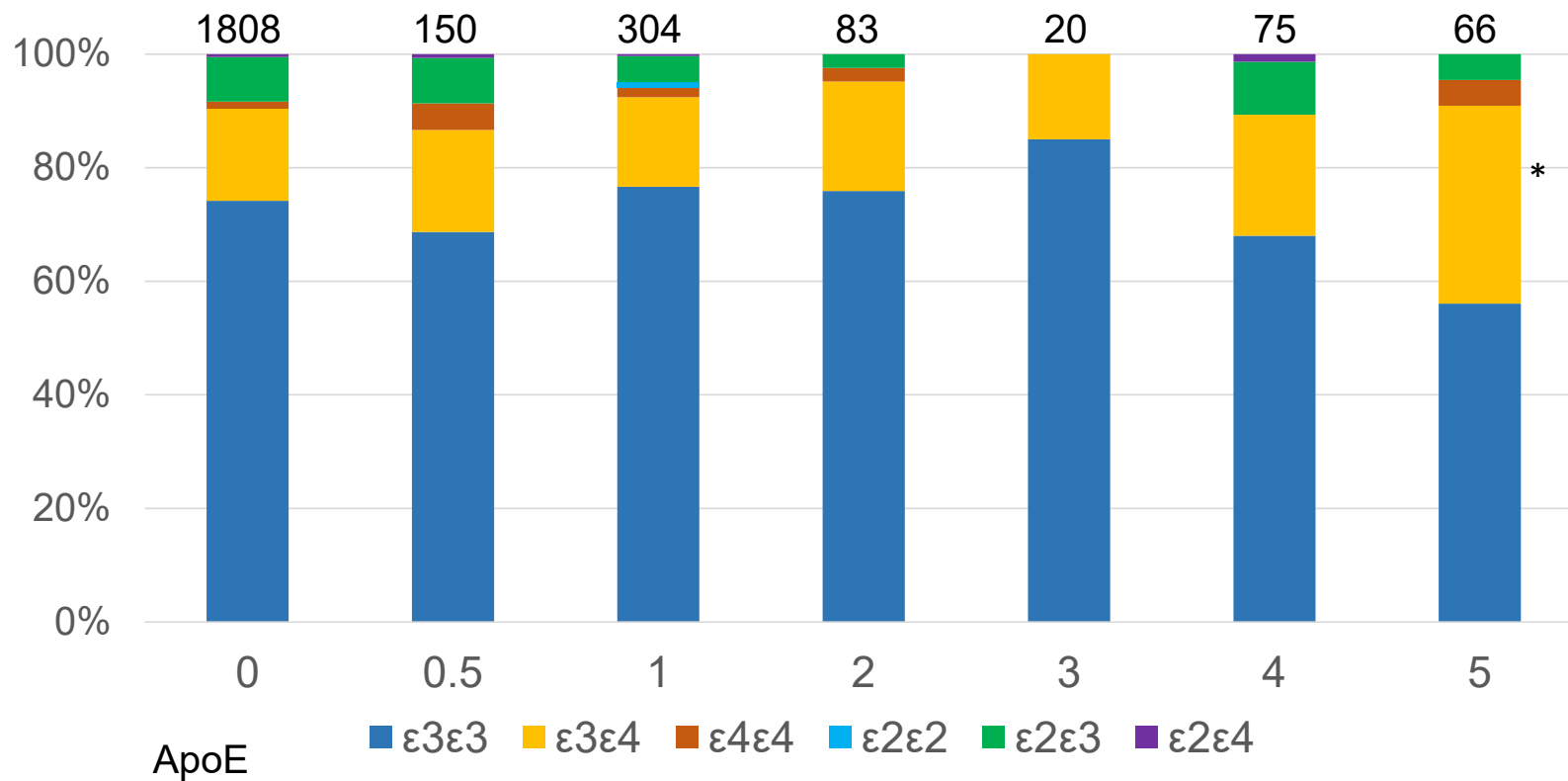


BBAR- Registered Cases with Frozen Brain Tissue and ApoE genotyping (n = 161/ 2560)

	PD (n = 20)	PDD (n = 50)	DLB (n = 92)
Mean Age at death (years)	79.2	81.8	84.4
Sex (F:M)	10:10	23:26	49:43

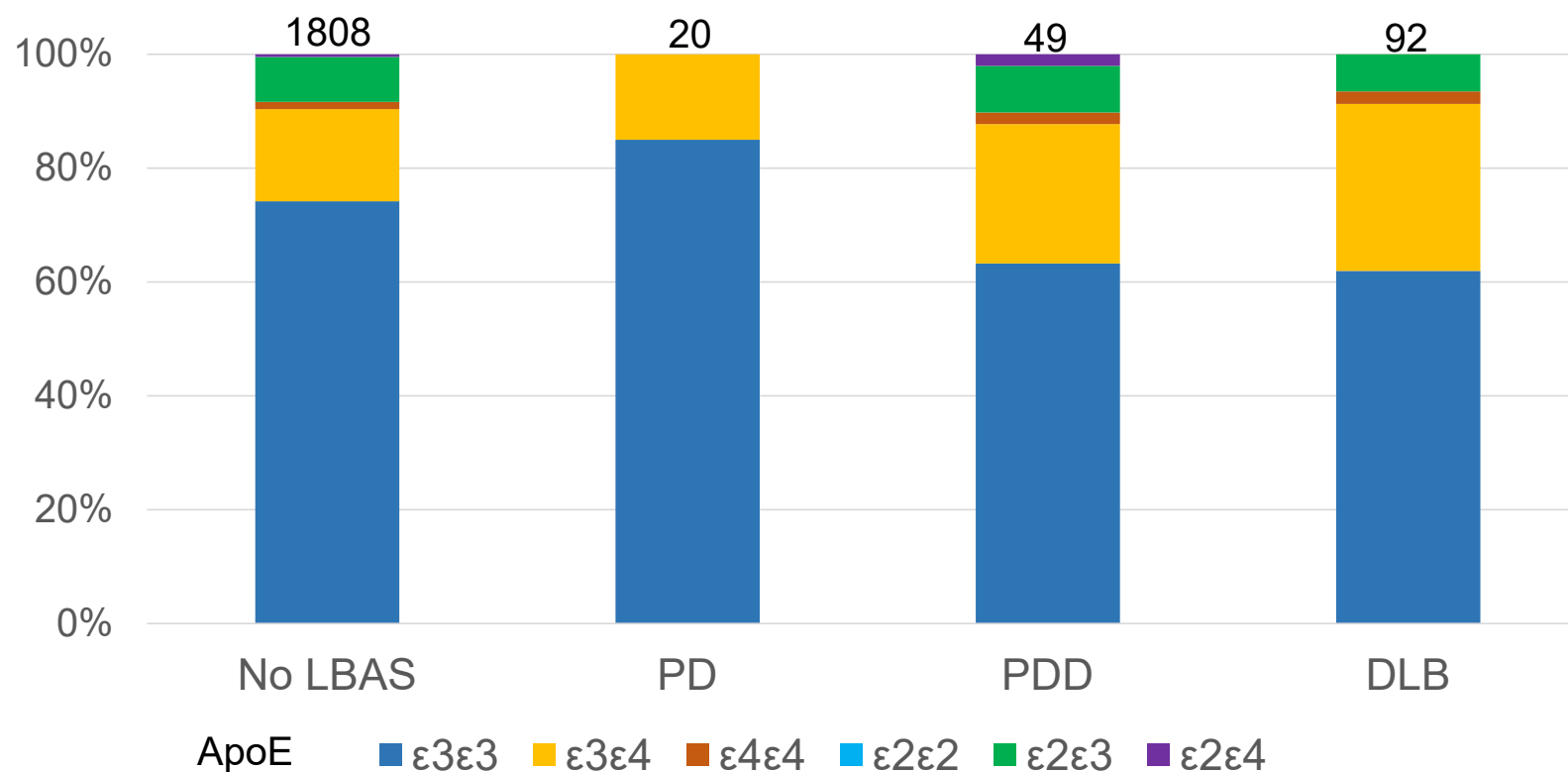
	Mean Age at death (years)	Sex (F:M)	Phenotype (PD:PDD:DLB)
$\epsilon 3/\epsilon 3$ (n = 105)	85.2	56:49	17:31:57
$\epsilon 3/\epsilon 4$ (n = 42)	81.3	20:22	3:12:27
$\epsilon 4/\epsilon 4$ (n = 3)	85.0	1:2	0:1:2
$\epsilon 2/\epsilon 2$ (n = 0)	-	-	-
$\epsilon 2/\epsilon 3$ (n = 10)	84.3	4:6	0:4:6
$\epsilon 2/\epsilon 4$ (n = 1)	90.0	1:0	0:1:0

BBAR- Registered Cases with Frozen Brain Tissue and ApoE genotyping (n = 2506/ 2560)

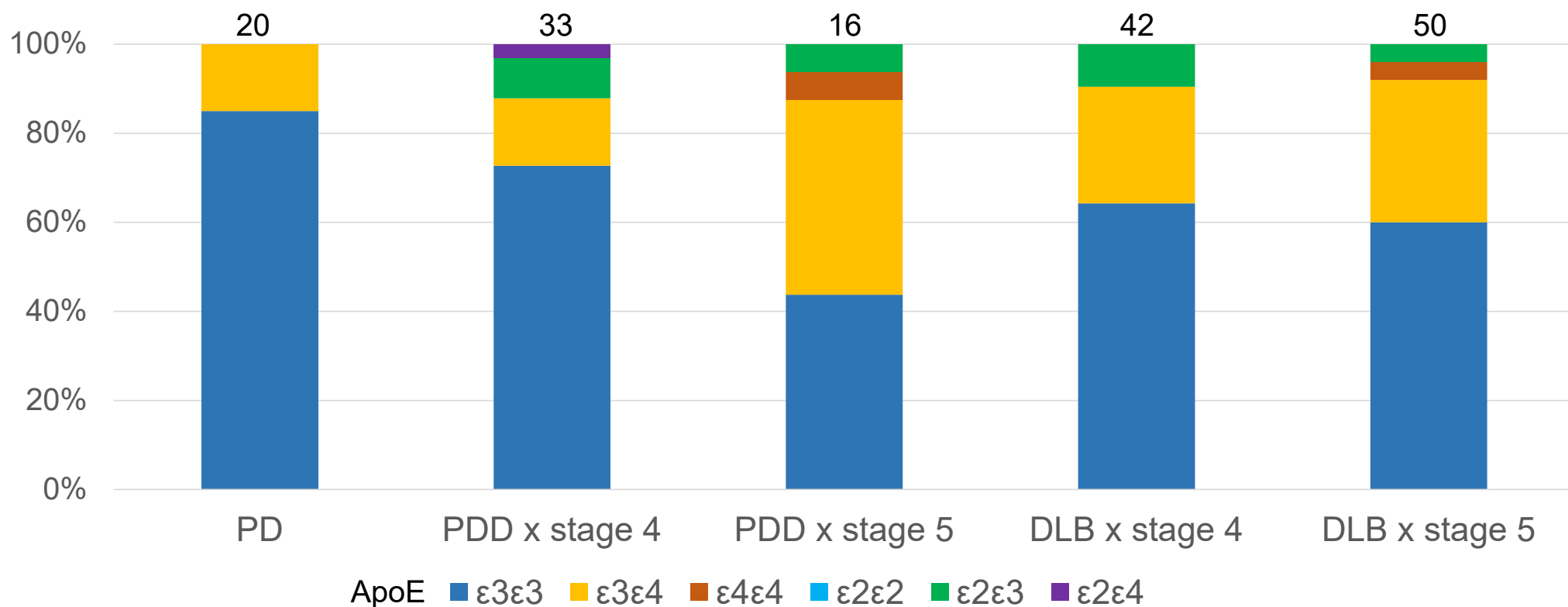


The ε3/ε4 genotype is more frequent in Stage 5, confirming Dr. Saito's JNEN 2004 report: Lewy body pathology in aging.

BBAR- Registered Cases with Frozen Brain Tissue and ApoE genotyping (n = 161/ 2560)



BBAR- Registered Cases with Frozen Brain Tissue and ApoE genotyping (n = 161/ 2560)



LB stage	APOE						Sum	APOE		Sum
	e33	e34	e44	e22	e23	e24		e4(+)	e4(-)	
LB-0	1341	293	23	0	142	9	1808	325	1483	1808
LB-0.5	103	27	7	0	12	1	150	35	115	150
LB-1	233	48	5	3	14	1	304	54	250	304
LB-2	63	16	2	0	2	0	83	18	65	83
LB-3	17	3	0	0	0	0	20	3	17	20
LB-4	51	16	0	0	7	1	75	17	58	75
LB-5	37	23	3	0	3	0	66	26	40	66
Sum	1845	426	40	3	180	12	2506	478	2028	2506

Apolipoprotein E Genotyping and Lewy Body Stage

	Lewy Body Stage					
	0	I	II	III	IV	V
Genotyping						
23	72	12	1	0	2	1
33	673	103	28	7	18	8
34	133	15	13	1	2	10*
44	13	2	0	0	0	1
Allelic Frequency						
2	72	12	1	0	2	1
3	1,551	233	70	15	40	27
4	159	19	13	1	2	12**

* p < 0.0001, compared with LB stage 0.

** p < 0.001, compared with LB stage 0.

Genotype Distributions of the Paraoxonase 1 (PON1) Polymorphisms							
Genotypes	n	Frequency	Men		Women		p*
			LB stage 0-I (n = 237)	LB stage II: (n = 24)	LB stage 0-I (n = 230)	LB stage II: (n = 20)	
G(-907)C							
GG	122	0.24	56	8	57	1	0.1056
GC	763	0.51	175	13	114	14	
CC	126	0.25	61	3	57	5	
G (-824)A							
GG	272	0.53	129	7	123	13	0.372
GA	198	0.39	89	12	90	7	
AA	41	0.08	19	5	17	0	
G (-161)A							
GG	416	0.81	192	18	188	18	0.5805
GA	70	0.14	31	4	33	2	
AA	25	0.05	12	5	8	0	
G (-125)C							
GG	41	0.81	195	18	188	18	0.5512
GC	67	0.14	29	3	33	2	
CC	25	0.05	14	2	9	0	
T (-107)C							
TT	21	0.42	102	9	92	11	0.1171
TC	17	0.34	80	7	78	8	
CC	12	0.24	54	11	58	1	
55pol							
TT (LL)	43	0.84	201	18	195	18	0.8557
TA (LM)	76	0.15	37	6	50	3	
AA (MM)	3	0.01	0	0	3	0	
192pol							
GG	17	0.35	71	8	94	6	0.492
AG	9	0.57	152	13	114	11	
AA	42	0.08	16	3	20	3	

* Fisher exact probability test, LB stages 0-4 versus LB stages II-V.

In our 2004 report, the apoE ε4 allele was significantly more frequent in LB Stage 5 than in LB Stage 0.

In the current report, the apoE ε4 allele was significantly more frequent in LB Stage 4 or 5 than in LB Stage 0.

In our 2004 report, among male cases, the paraoxonase 1 (PON1) G(2824)A polymorphism differed significantly between those at LB stage II or higher and those below stage II.

In this report apoE e4 allele is significantly more frequent in LB Stage 2 or higher than those below Stage 2. No gender difference in this cohort.

The APOE-e4 effects for LB stages

1) LB stages 4/5 vs. 0_{Ref}

LB stage	APOE		Sum
	e4(+)	e4(-) _{Ref}	
LB-4/5	43	98	141
LB-0 _{Ref}	325	1483	1808
Sum	368	1581	1949

OR = 2.00 (95% CI, 1.37 - 2.90)

P_{Fisher} = 0.0005

2) LB stages 2/3/4/5 vs. 0/0.5/1_{Ref}

LB stage	APOE		Sum
	e4(+)	e4(-) _{Ref}	
LB-2/3/4/5	64	180	244
LB-0/0.5/1 _{Ref}	414	1848	2262
Sum	478	2028	2506

OR = 1.59 (95% CI, 1.16 - 2.14)

P_{Fisher} = 0.0045

Saito Y, et al : Lewy related alpha- synucleinopathy in Aging. JNEN. 2004.

Discussion and Conclusion

1. Parkinson disease without dementia lacked Alzheimer disease neuropathological changes (ADNC) in two different cohorts:

NCNP Brain Bank mainly of the members of the Japan PD Association

Brain Bank for Aging Research representing an aging cohort

2. Parkinson disease with dementia is categorized to plaque dominant senile change like DLB in NCNP BB, but in BBAR cohort, many cases are classified into minimal senile change, partly because of difficulty in determining motor or cognitive impairment for terminal stage of aged Parkinson disease with extensive care.

3. The apoE ϵ 4 allele was significantly more common in Lewy Body Stages 4–5 than in Stage 0 and in Stage 2 or higher than in Stages below 2. These findings suggest that ϵ 4 allele influences Lewy body pathology severity through a primary or secondary pathway.

Take Home Message

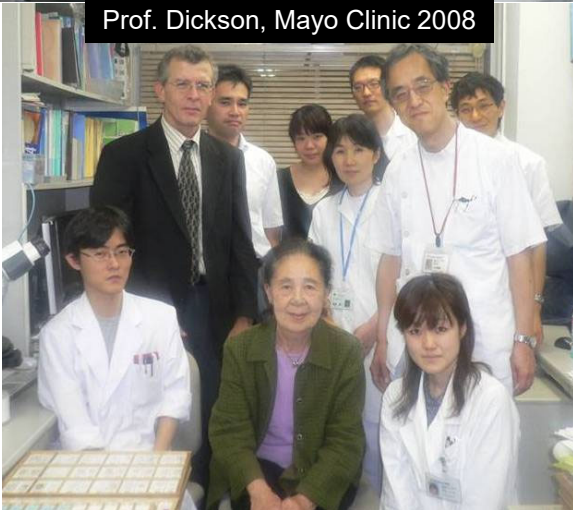
- Neuropathology of Parkinson disease is influenced by Alzheimer pathology in aging.
- Parkinson disease without Alzheimer pathology may escape from dementia.
- ApoE ϵ 4 genotype affect extension of Lewy body pathology, through primary path or secondary path possibly by senile plaque pathology.
- A therapeutic trial for amyloid-positive Lewy body dementia is underway. This presentation may provide a rationale for such a trial.

International Standardization of Brain Bank for Aging Research

Prof. Graeber, Imperial College of London, 2007



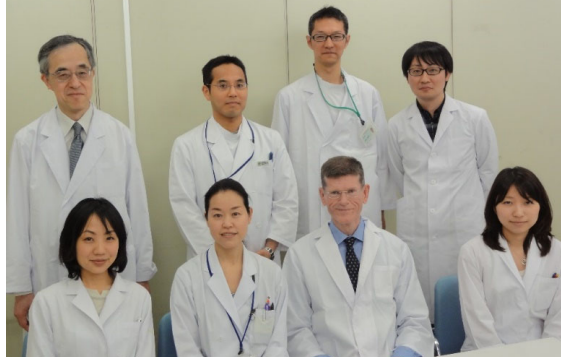
Prof. Dickson, Mayo Clinic 2008



Prof. Hedley- Whyte, MGH 2010



Prof. Cairns, Washington University 2013



2018

DATE September 28 (Fri.), 2018 13:00-16:30 VENUE Tokyo Metropolitan Geriatric Hospital & Institute of Gerontology (Japan)

Julie A. Schneider (Rush University Medical Center, USA)
Bradley T. Hyman (Mass. General Hospital, Harvard Medical School, USA)
Bernardino Ghetti (Indiana University, USA)
Colin L. Masters (The University of Melbourne, Australia)
Ingeborg Huitinga (Netherlands Institute for Neuroscience, The Netherlands)
Shigeo Murayama (Tokyo Met. Geriatric Hosp. & Inst. of Gerontology, Japan)



Prof. Kovach 2022



Brain Bank for Aging Research (BBAR) Member (2026)

BBAR (Neuropathology and Bioresource Center)

Director	Yuko Saito
Secretary General	Shigeo Murayama
Researcher	Hana Aoki
	Akira Arakawa
	Manato Hara
	Kayoko Ukai
Visiting Researcher	Tomoyasu Matsubara
	Akiko Uchino
Research Manager	Maho Morishima
Technician	Hiroshi Koga
	Jin Hasegawa
Coordinator	Fumino Kobayashi

PET Center (Clinical Neuroimages)

Director	Kenji Ishii
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Radiology

Chair	Toshiaki Akashi
-------	-----------------

Neurology

Chair	Atsushi Iwata
Vice chair	Hiroshi Nishina
Senior	Ryoko Ihara
	Taro Bannai
	Masanori Kurihara
Staff	Keiko Hatano
	Asuka Kitamura
Research fellow	Satoru Morimoto

Rehabilitation

Tadayuki Kato

Psychiatry

Ko Furuta

Neurosurgery

Shigehiko Takanashi

Pathology

Chair	Tomio Arai
Vice Chair	Hirofumi Rokutan