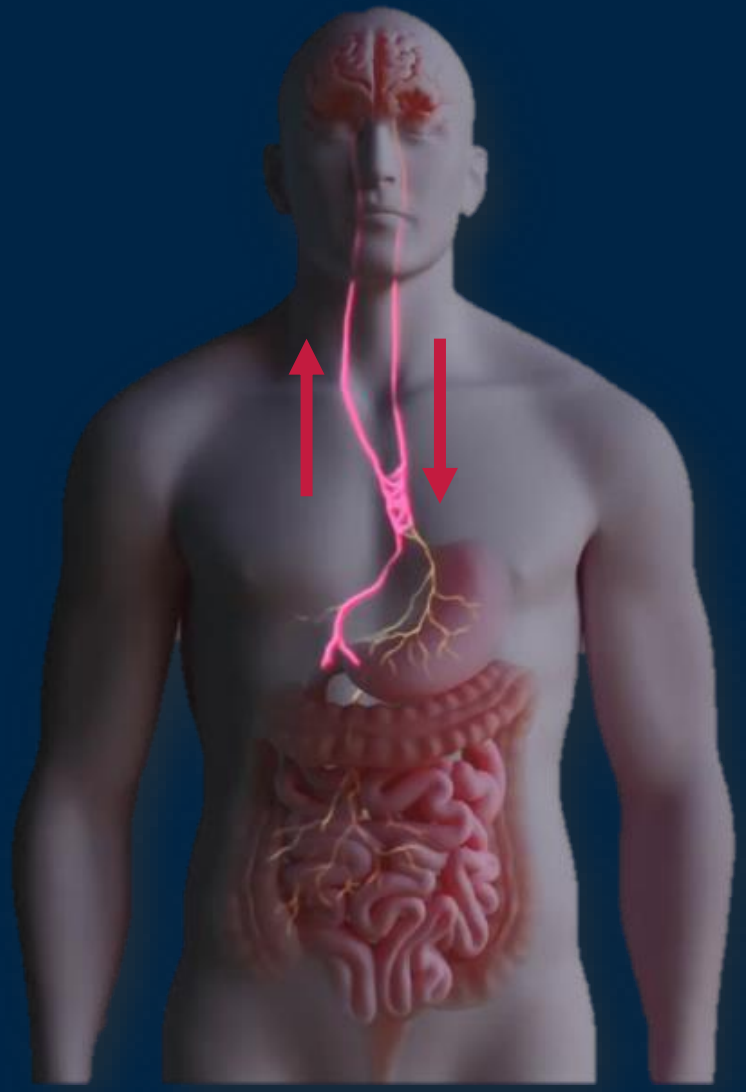


PRION-LIKE PHENOMENA IN LEWY BODY DISORDERS

CJD Conference 2024

Bethesda

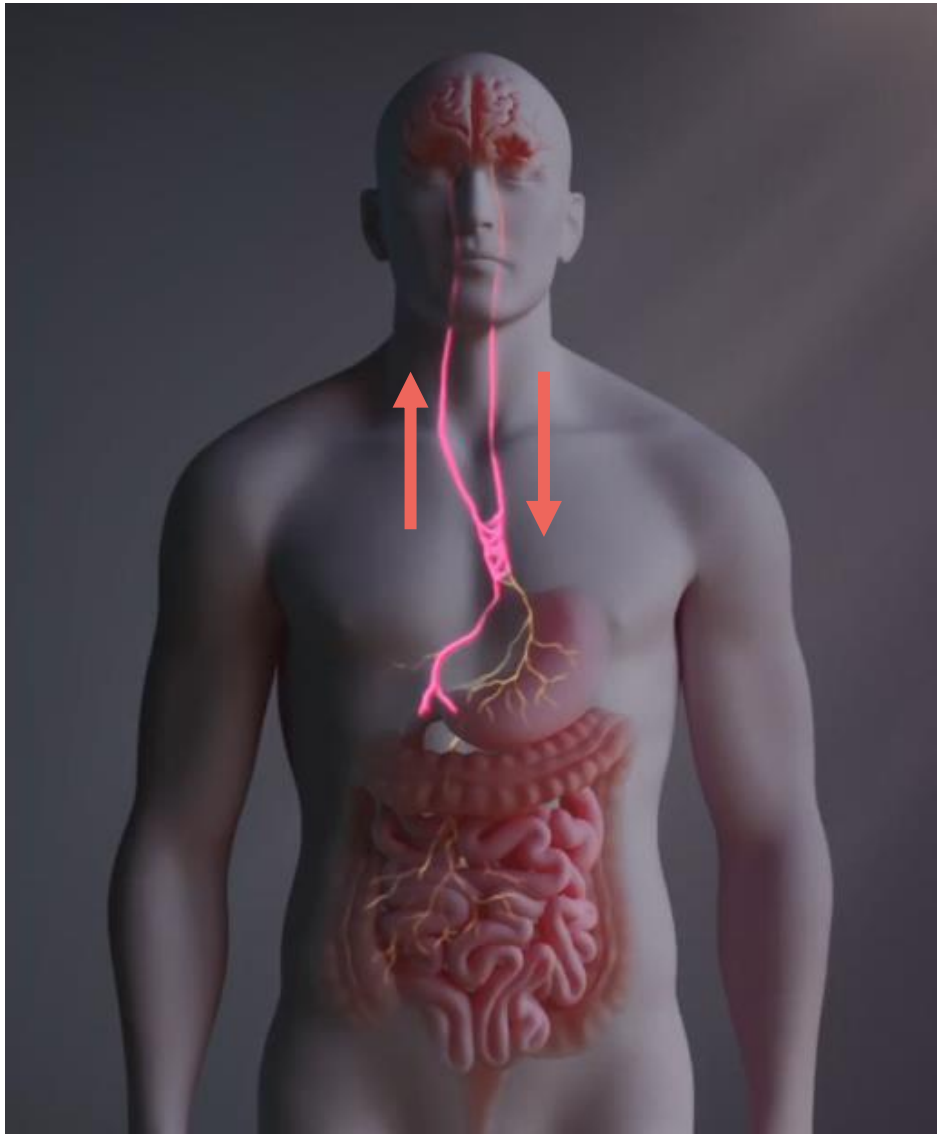
AARHUS UNIVERSITY
DEPARTMENT OF CLINICAL MEDICINE

13 NOV 2024

NATHALIE ARIANE E VAN DEN BERGE
ASSOCIATE PROFESSOR

THE GUT-BRAIN AXIS IN PD

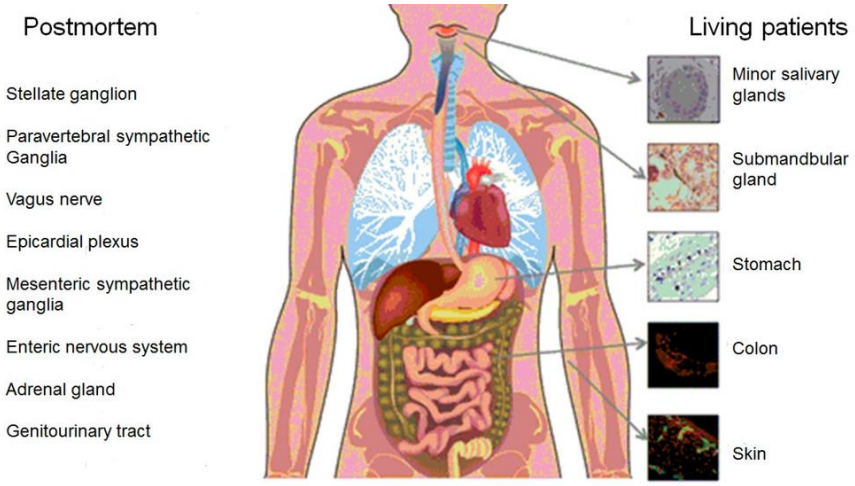
Transport of prion-like asyn strains in the peripheral and central nervous system



THE GUT-BRAIN AXIS IN PD

Non motor symptoms

Lewy pathology in multiple organs



Tolosa et al. Brain, 2015

Up to 20 years prior to diagnosis

Non-motor symptoms and peripheral pathology occur up to 20 years prior to motor symptoms (time of diagnosis)

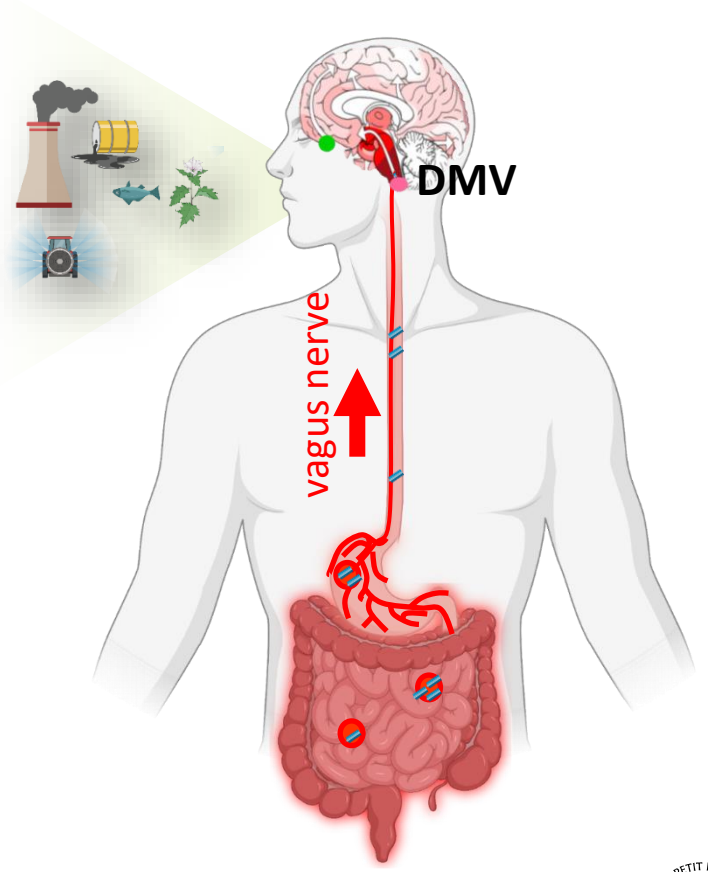
Large therapeutic window

→ Need for models that also mimic peripheral pathology and non-motor symptoms

THE GUT-FIRST HYPOTHESIS

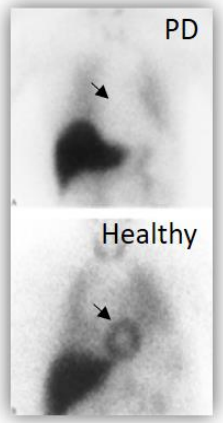
Alpha-synuclein pathology can propagate along the vagus nerve from the gut to the brain and back

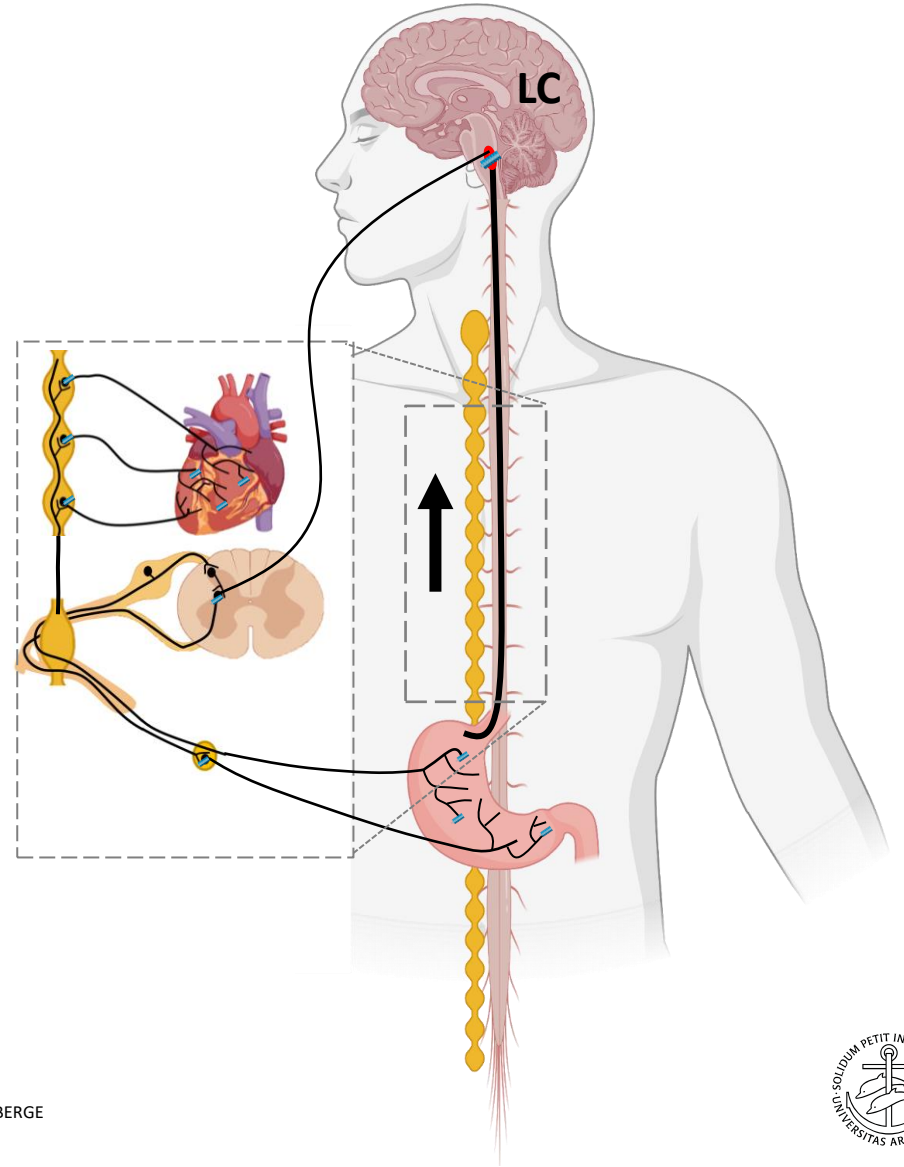
Parasympathetic gut-to-brain propagation (via vagus nerve)



SYMPATHETIC TRANSMISSION

What about the heart?





The gut-brain axis does not only constitute vagal propagation but also sympathetic gut-to-brain propagation

Gut > Autonomic ganglia > Heart

Gut > Autonomic ganglia > IML > LC

GUT-FIRST ANIMAL MODEL IN PD

Springer ACTA NEUROPATHOLOGICA
springer.com

Acta Neuropathol. 2019; 138(4): 535–550. PMCID: PMC6778265
Published online 2019 Jun 26. doi: 10.1007/s00401-019-02040-w PMID: 31254094

Evidence for bidirectional and *trans*-synaptic parasympathetic and sympathetic propagation of alpha-synuclein in rats

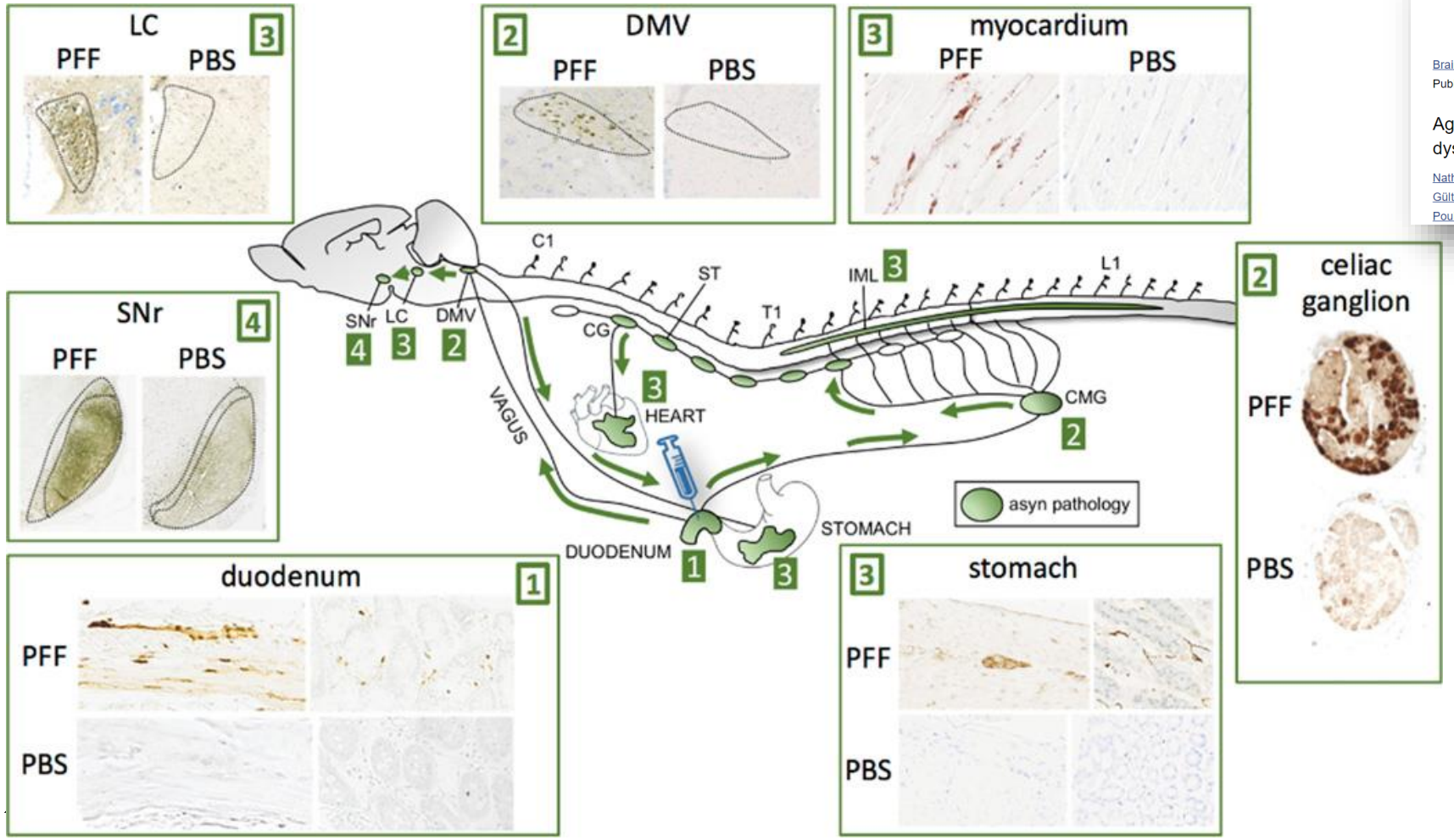
Nathalie Van Den Berge,[1,2] Nelson Ferreira,[3] Hjalte Gram,[3] Trine Werenberg Mikkelsen,[1] Aage Kristian Olsen Alstrup,[1,2] Nicolas Casadei,[4] Pai Tsung-Pin,[5] Olaf Riess,[4] Jens Randel Nyengaard,[6] Gültekin Tamgüney,[7,8] Poul Henning Jensen,[3] and Per Borghammer[1,2]

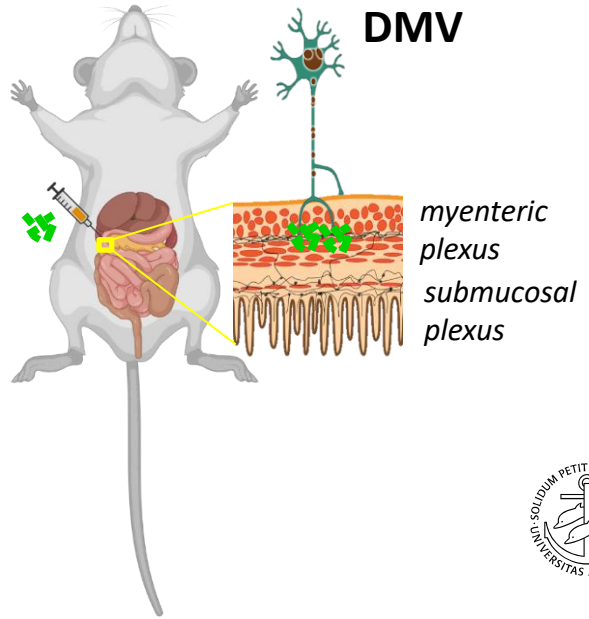
BRAIN

Brain. 2021 Jun; 144(6): 1853–1868. PMCID: PMC8320301
Published online 2021 Apr 20. doi: 10.1093/brain/awab061 PMID: 33880502

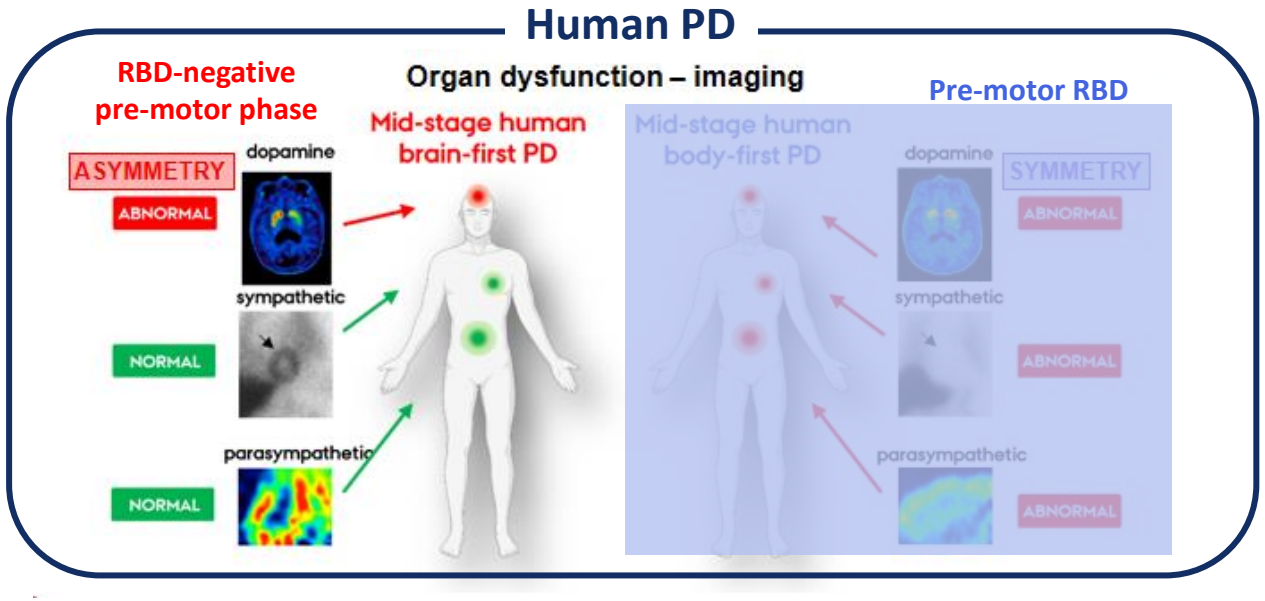
Ageing promotes pathological alpha-synuclein propagation and autonomic dysfunction in wild-type rats

Nathalie Van Den Berge,[1,2] Nelson Ferreira,[3,4] Trine Werenberg Mikkelsen,[1] Aage Kristian Olsen Alstrup,[1,2] Gültekin Tamgüney,[5,6] Páll Karlsson,[1,7,8] Astrid Juhl Terkelsen,[7,9] Jens Randel Nyengaard,[1,8,10] Poul Henning Jensen,[3,4] and Per Borghammer[1,2]

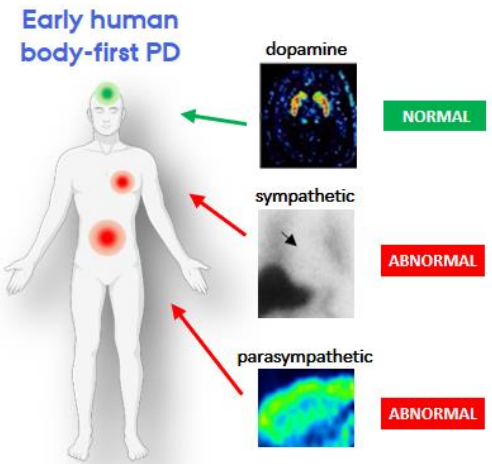




BODY-FIRST AND BRAIN-FIRST SUBTYPES IN PD



Early human body-first PD = iRBD without motor symptoms



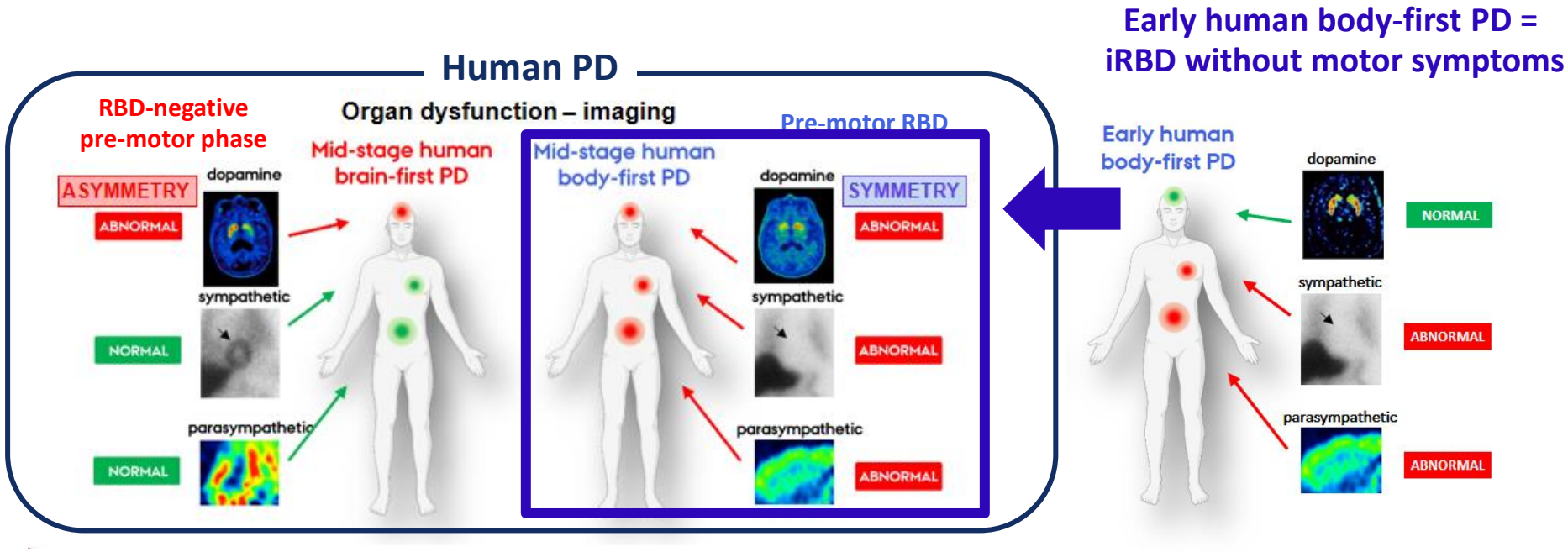
Borghammer & Van Den Berge, 2019, J. Parkinsons. Dis.

Horsager et al., 2020, Brain

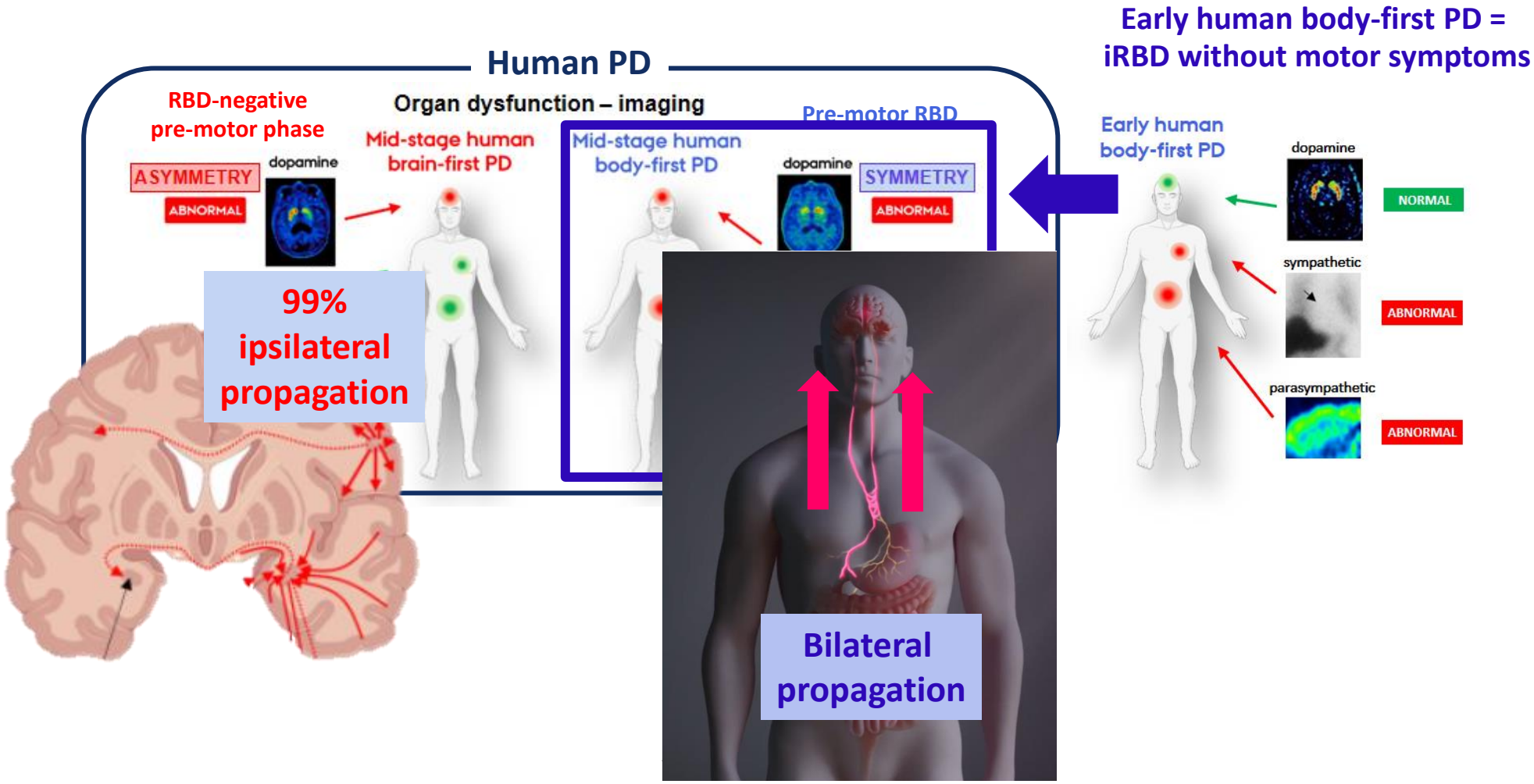
Borghammer et al., 2021, Neurobiol. Dis.

Horsager et al., 2022, Neurobiol. Dis.

BODY-FIRST AND BRAIN-FIRST SUBTYPES IN PD

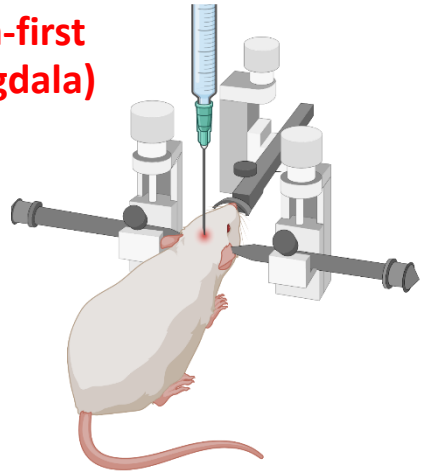


BODY-FIRST AND BRAIN-FIRST SUBTYPES IN PD

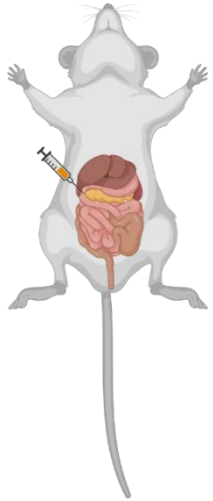


EVIDENCE FROM ANIMAL STUDIES

Brain-first (amygdala)



Body-first (gut)



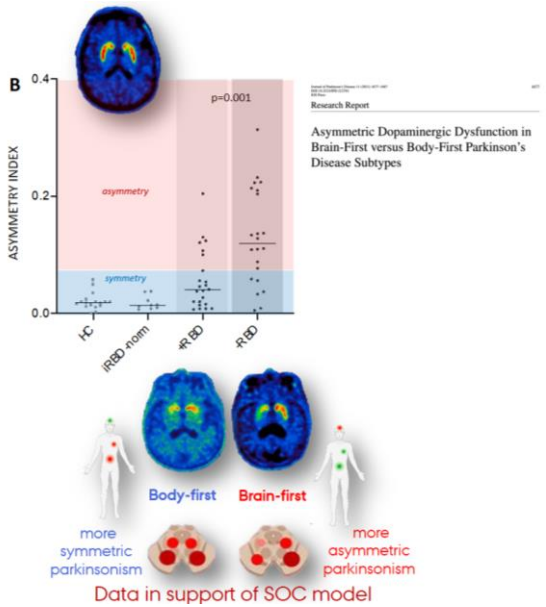
PE2I (DaT) PET

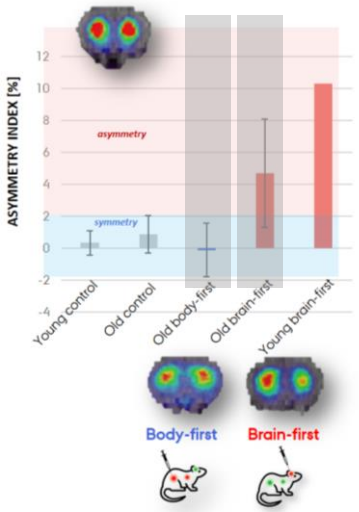
MIBG – Sympathetic innervation *(ex vivo)*

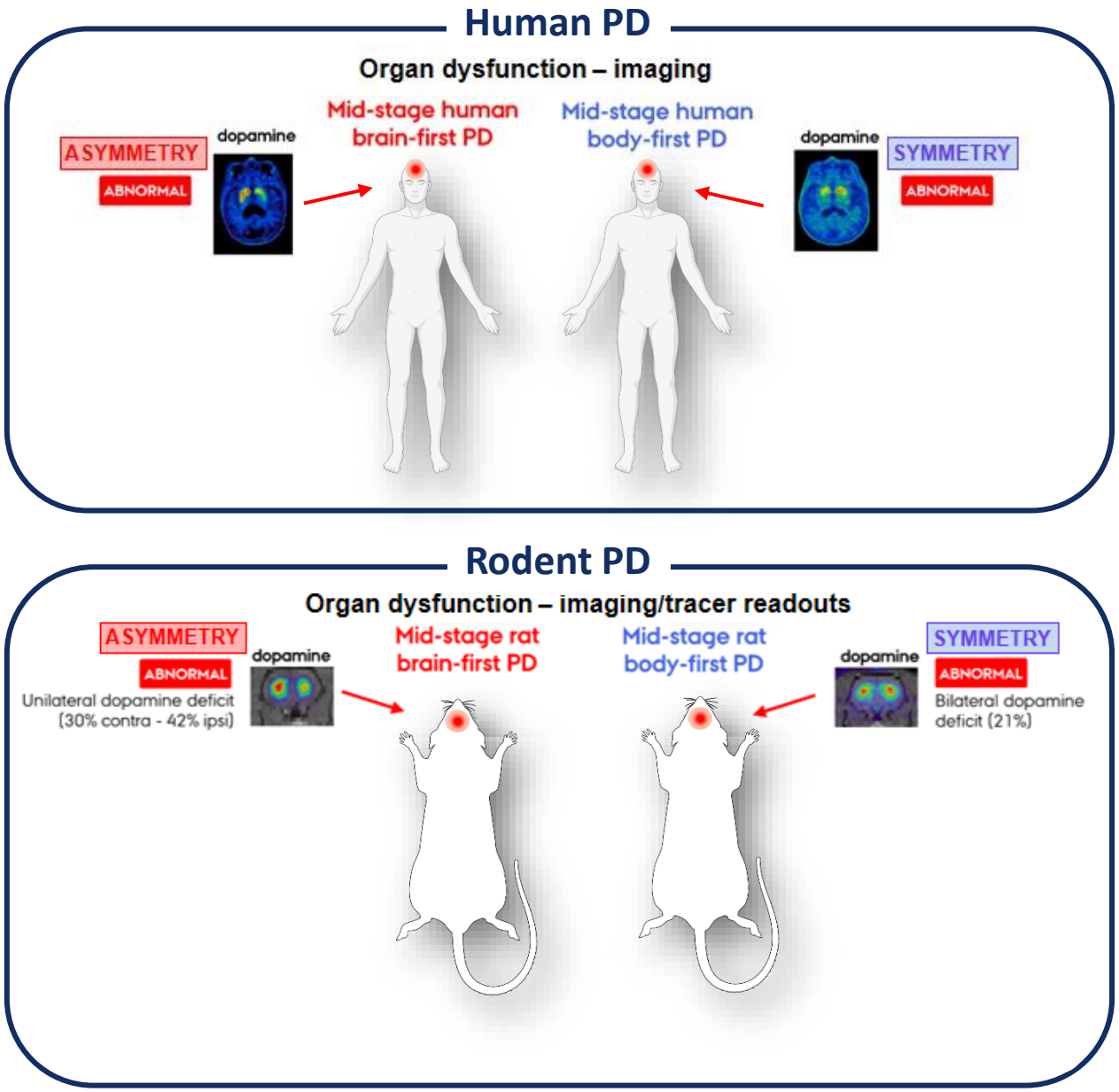
FEOBV – cholinergic innervation *(ex vivo)*

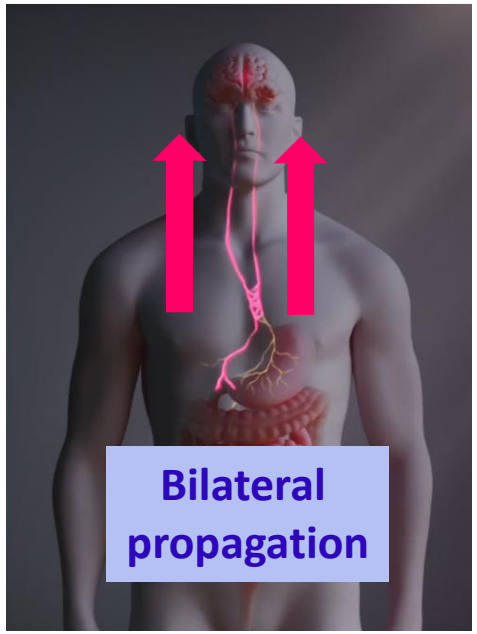
EVIDENCE FROM ANIMAL STUDIES

Van Den Berge et al., in preparation
Please do not copy









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Van Den Berge et al., in preparation
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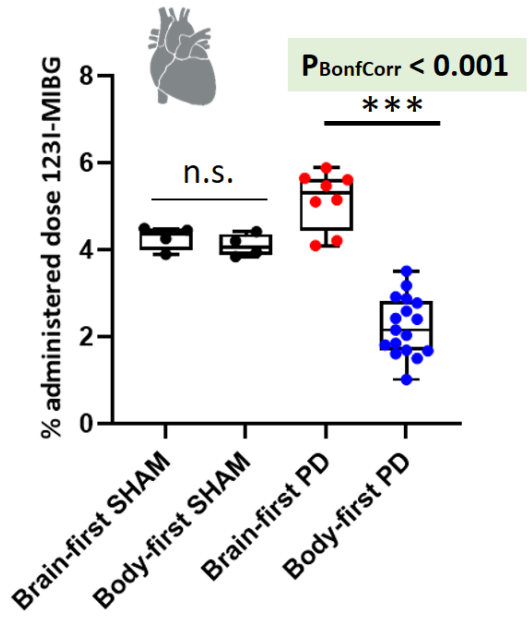

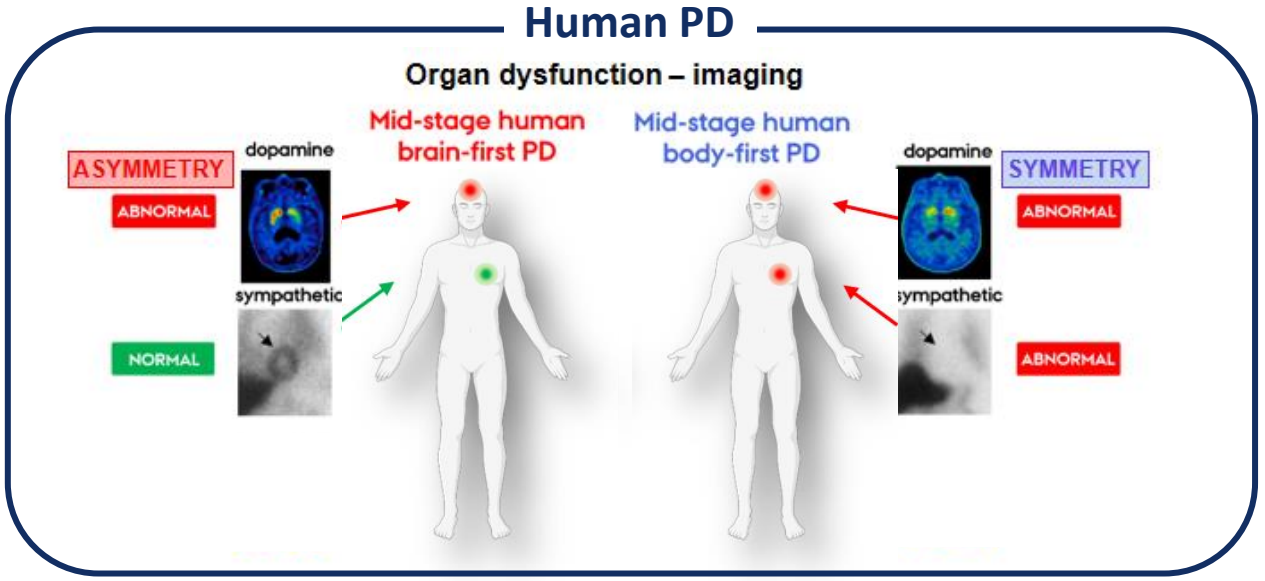

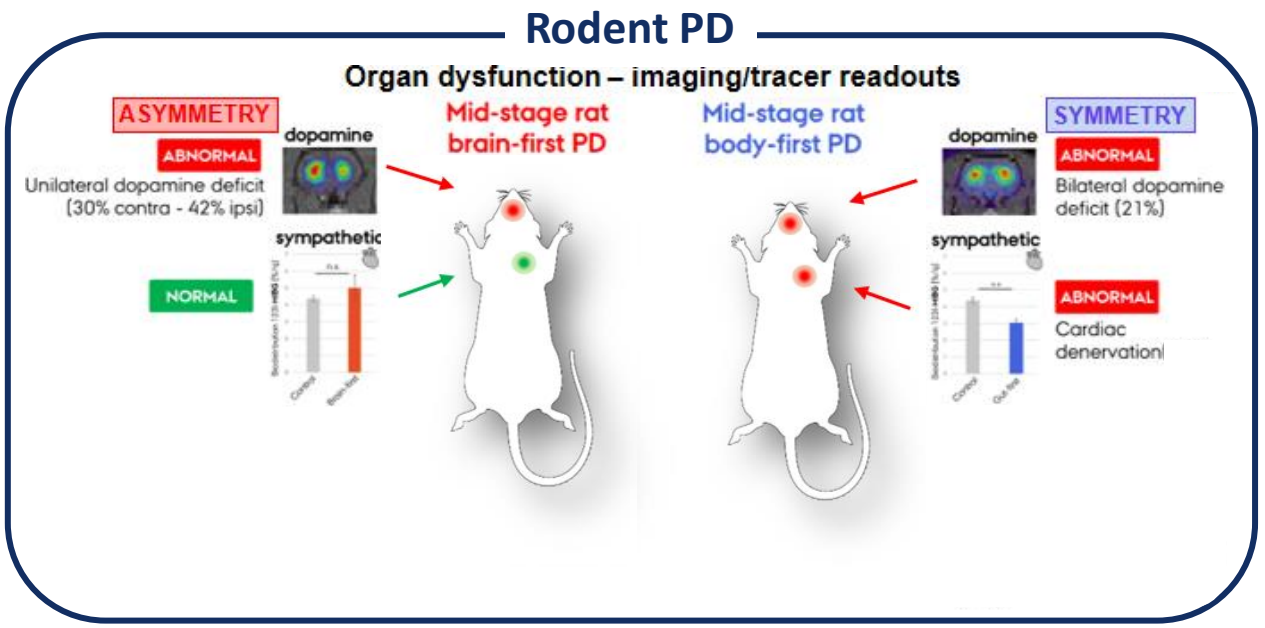

EVIDENCE FROM ANIMAL STUDIES

Van Den Berge et al.,
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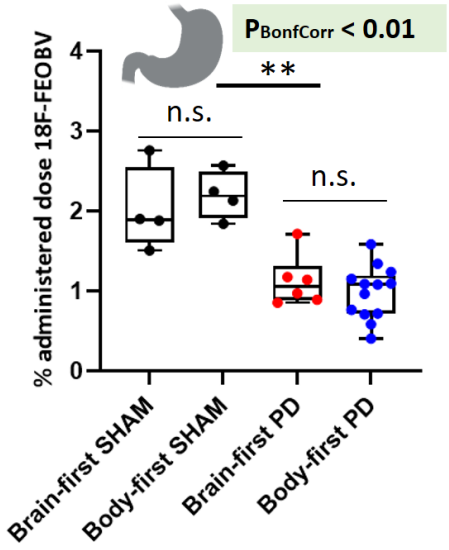
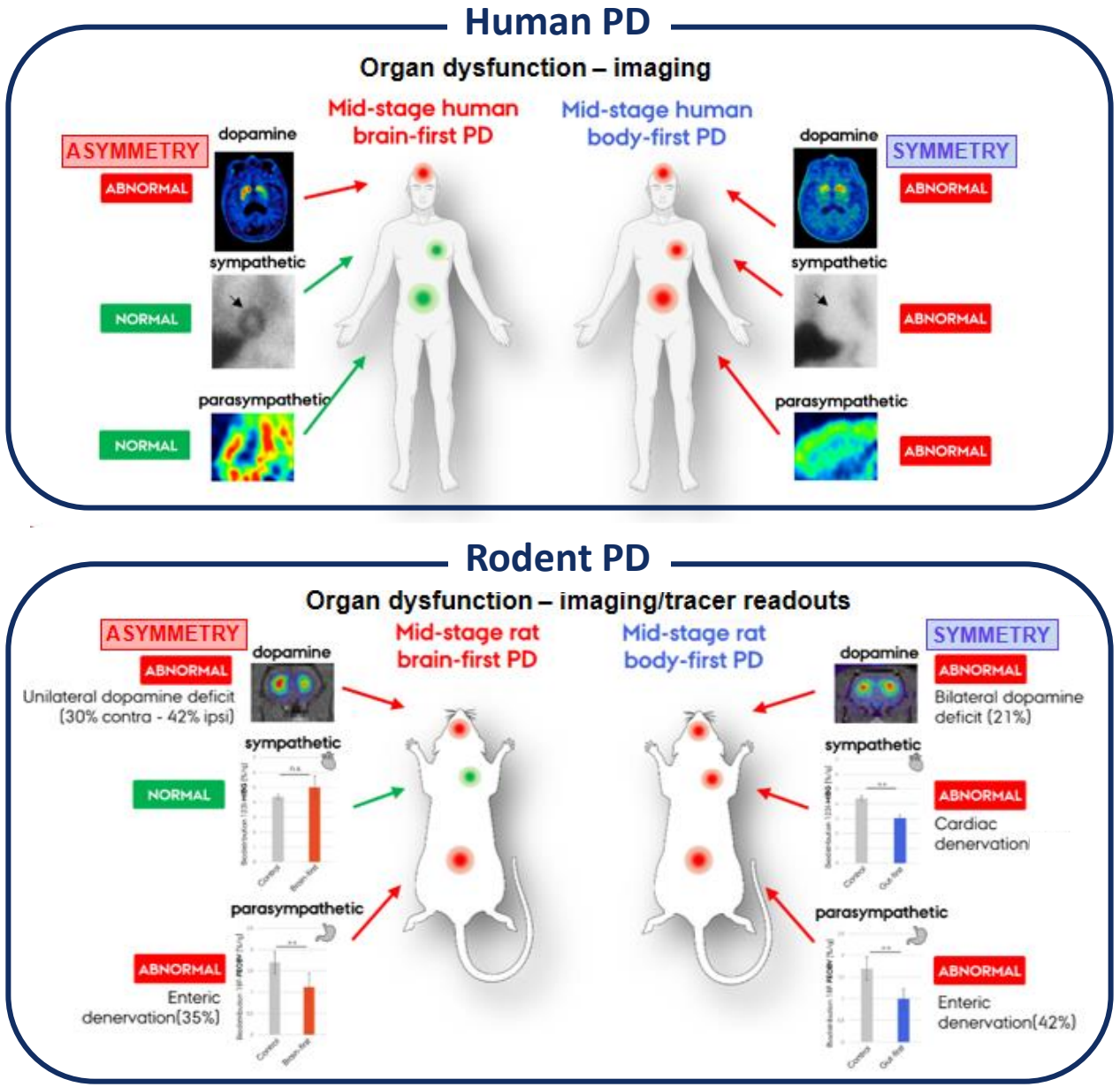


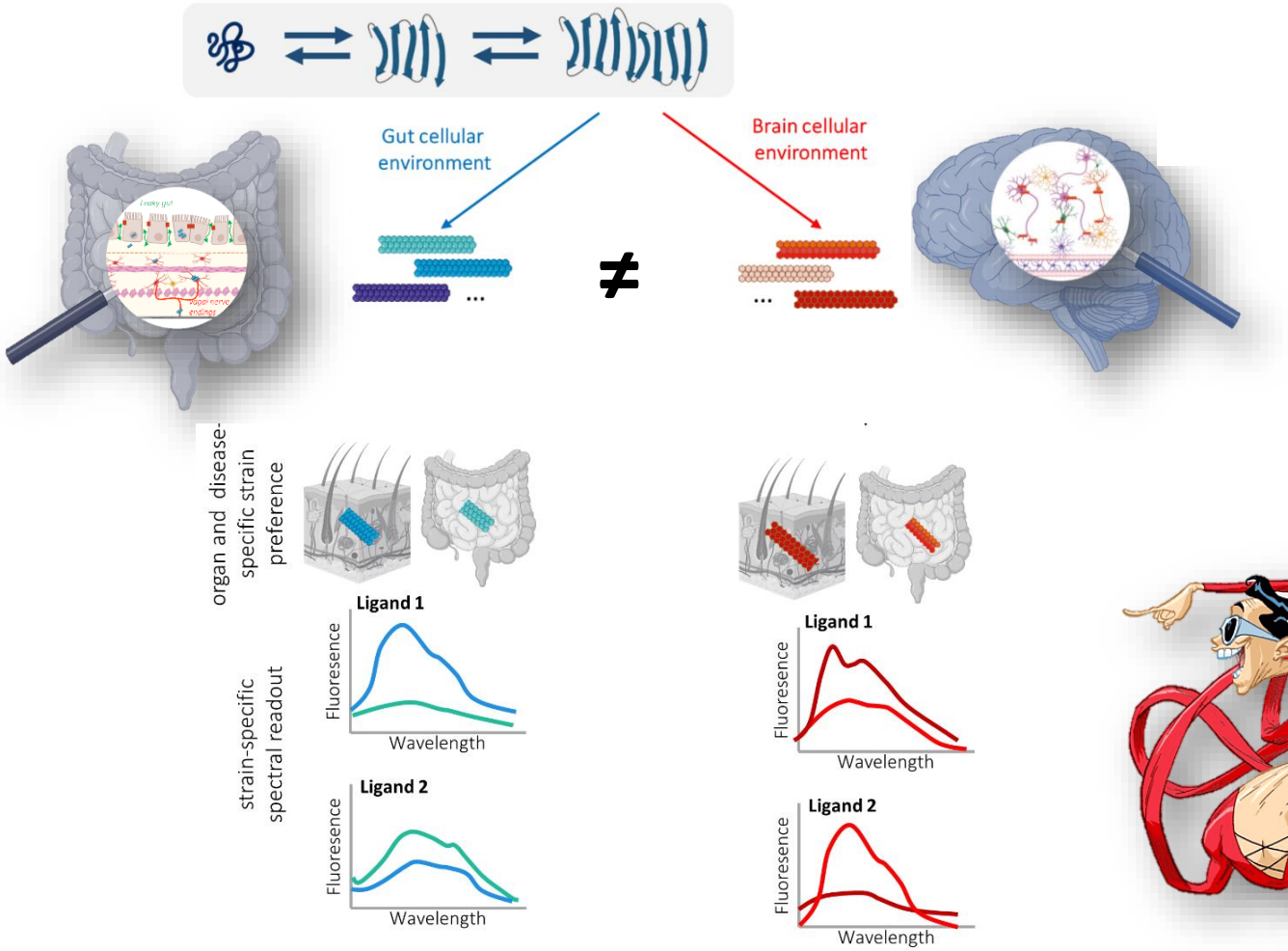


STRAIN VARIABILITY

frontiers | Frontiers in Aging Neuroscience
SYSTEMATIC REVIEW
published: 26 May 2022
doi: 10.3389/fnagi.2022.907293

Alpha-Synuclein Strain Variability in Body-First and Brain-First Synucleinopathies

Mie Kristine Just[1,2], Hjalte Gram[3], Vasileios Theologidis[3], Poul Henning Jensen[3], K. Peter R. Nilsson[4], Mikael Lindgren[5], Karoline Knudsen[1,2], Per Borghammer[1,2] and Nathalie Van Den Berge[1,2]

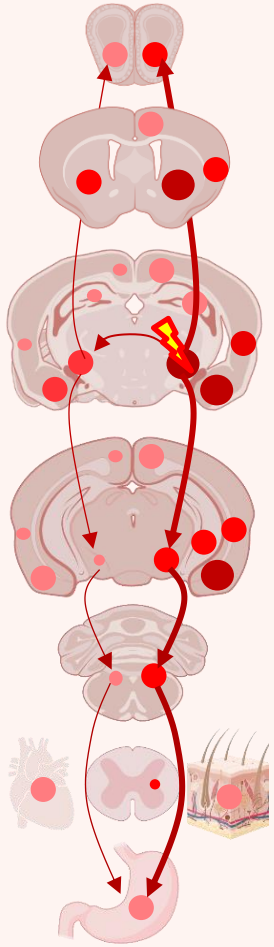


Impact: spectral characterization of subtype-specific strain differences in easy accessible tissue (gut and skin biopsies) may **enable early subtype-specific diagnosis**

STRAIN VARIABILITY

Van Den Berge et al.,
in preparation

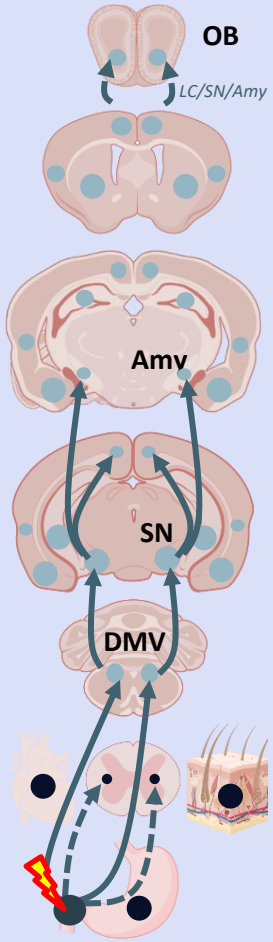
Advanced brain-first rat PD



asymmetric pathology

NO cardiac denervation

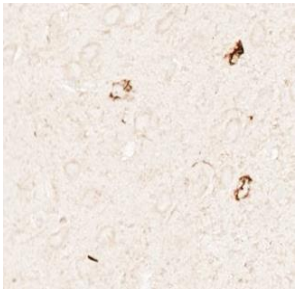
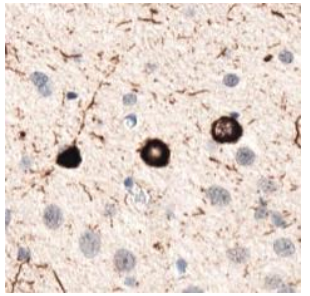
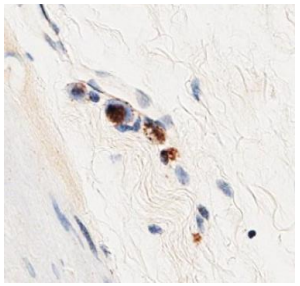
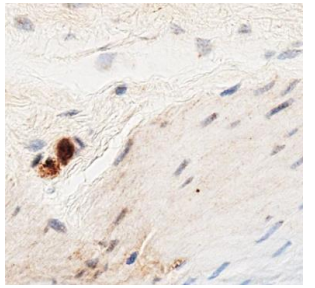
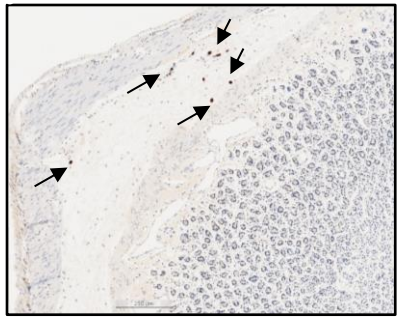
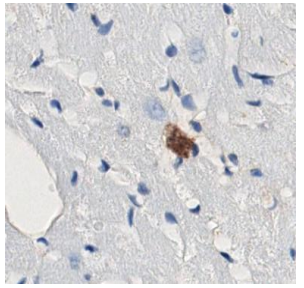
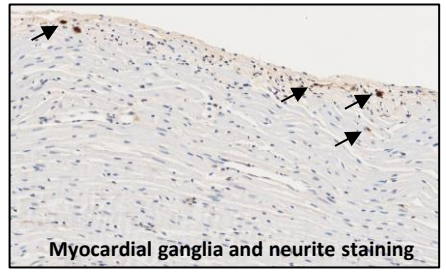
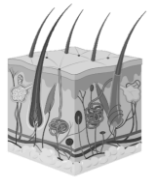
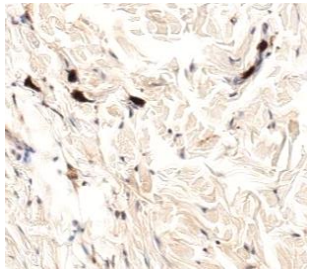
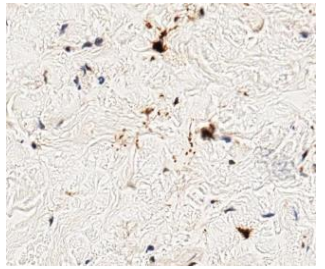
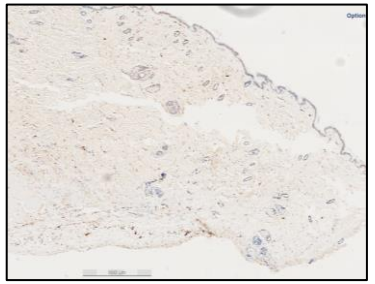
Advanced body-first rat PD



symmetric pathology

cardiac denervation

IHC – pSer129-asyn

	Body-first	Brain-first	
			
			
			 Myocardial ganglia and neurite staining
			

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Van Den Berge et al.,
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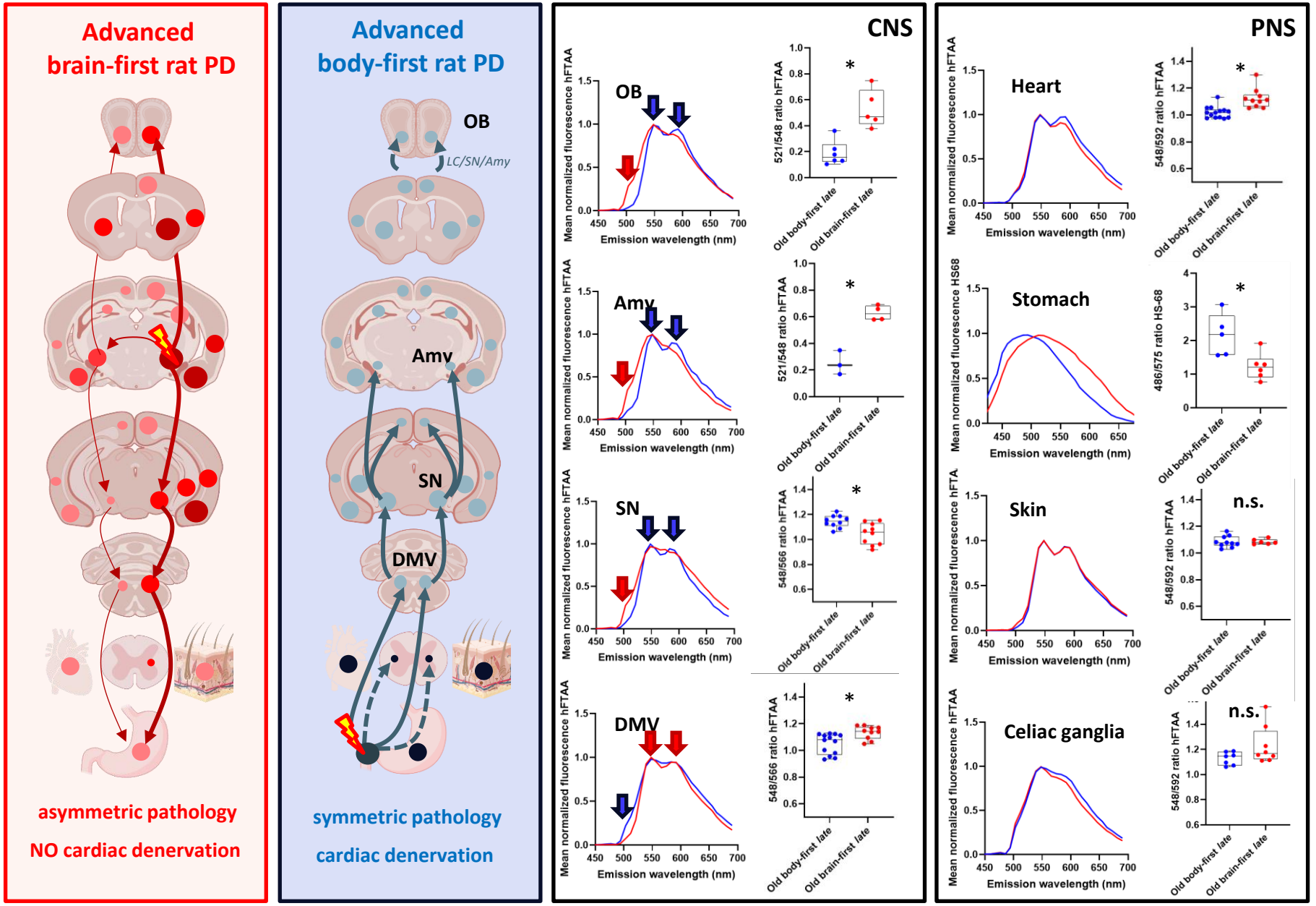

STRAIN VARIABILITY

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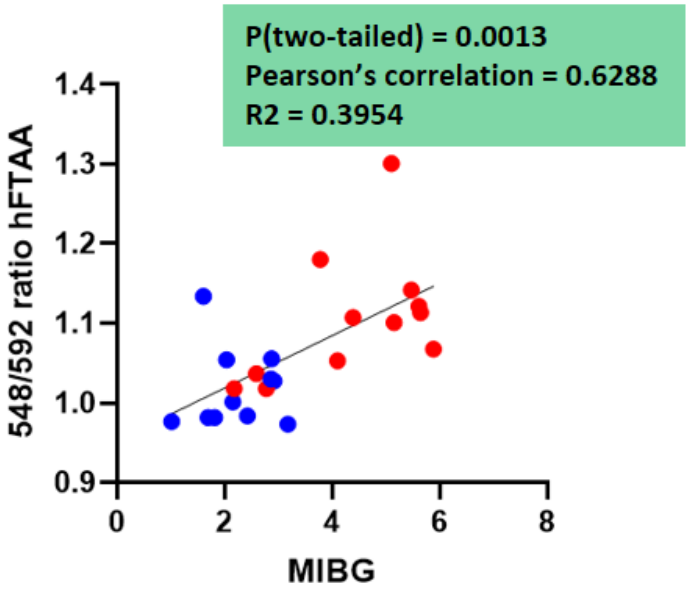
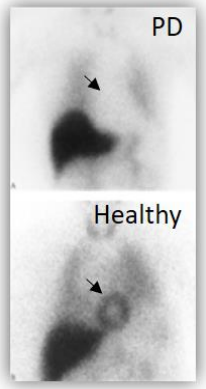
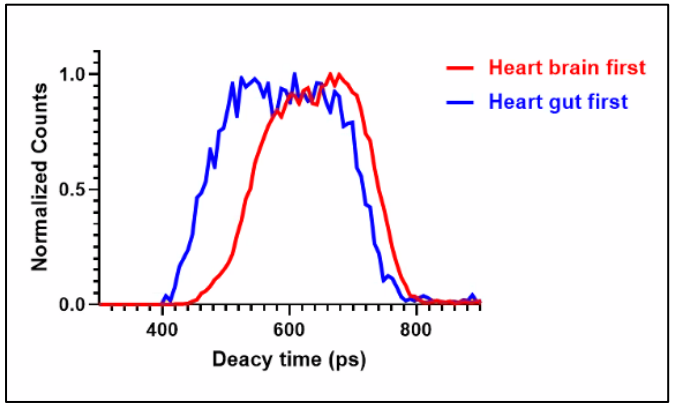
Asyn strain conformation in heart correlates to cardiac denervation



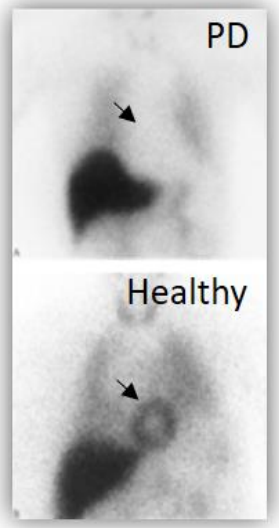


Fluorescence lifetime imaging hFTAA



SUMMARY

- Alpha-synuclein seeds display prion-like properties, including trans-synaptic transmission along vagal and sympathetic pathways
- The exact same seeds (recombinant asyn fibrils) are used for disease initiation in the gut or brain.
- The observed spectral differences between aggregates derived from brain and gut-seeded rats, indicate that pathology possesses different structural characteristics, depending on where the disease is initiated.
- Brain, heart and stomach.
- This difference is most obvious in the heart – which correlates to the disease phenotype.



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DEPARTMENT OF CLINICAL MEDICINE

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