IS PARKINSON'S DISEASE A PRION DISEASE?

I get my exercise by jumping on and off the bandwagon

Jeffrey H. Kordower, Ph.D.
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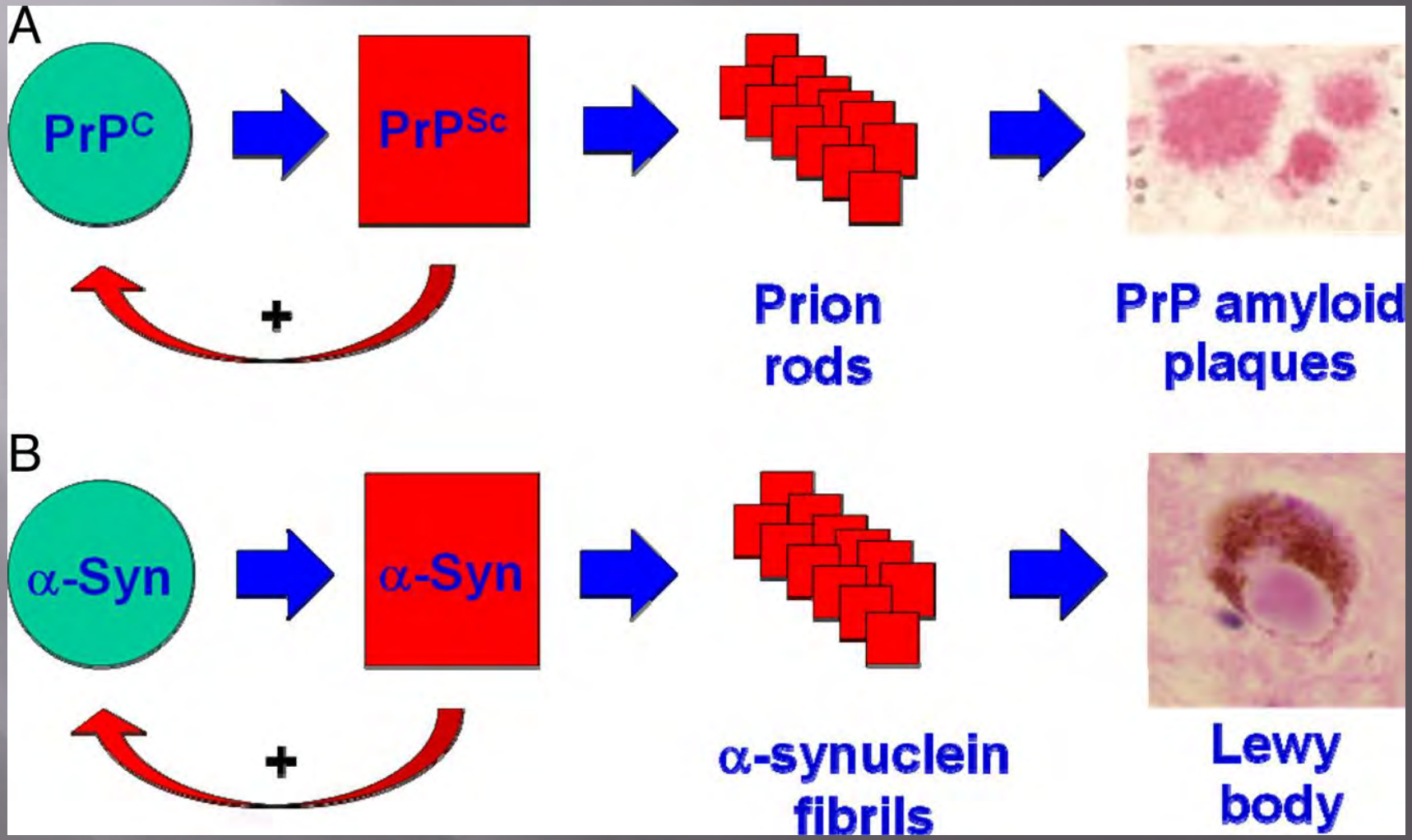
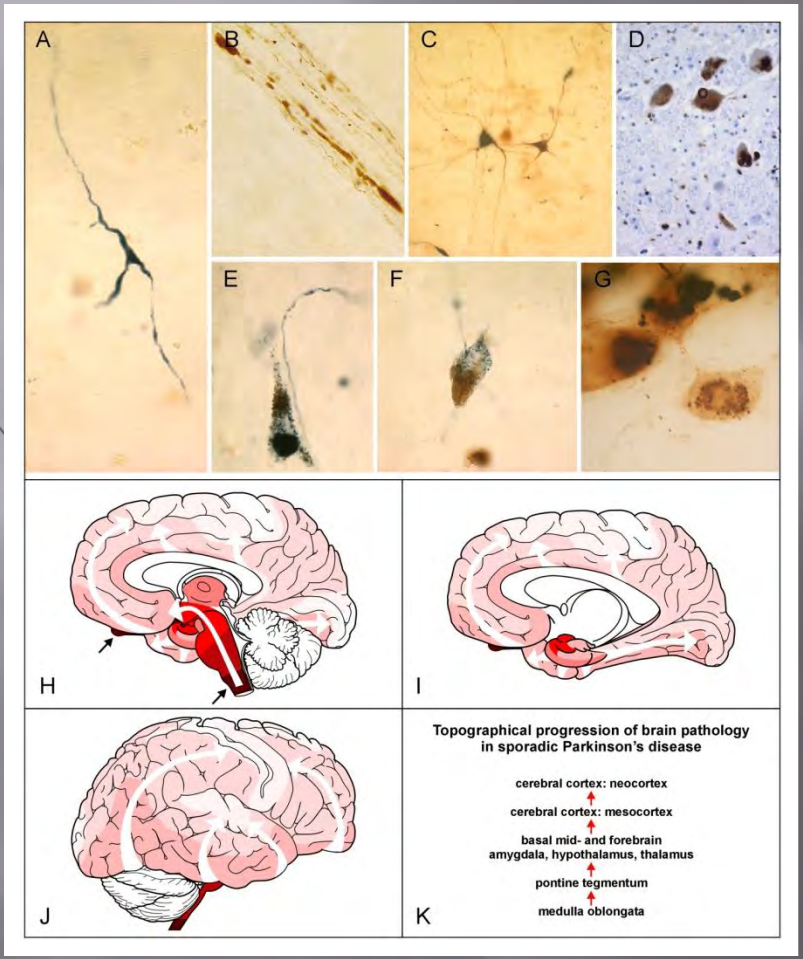
On Aging and Neurological Sciences
Rush University Medical Center

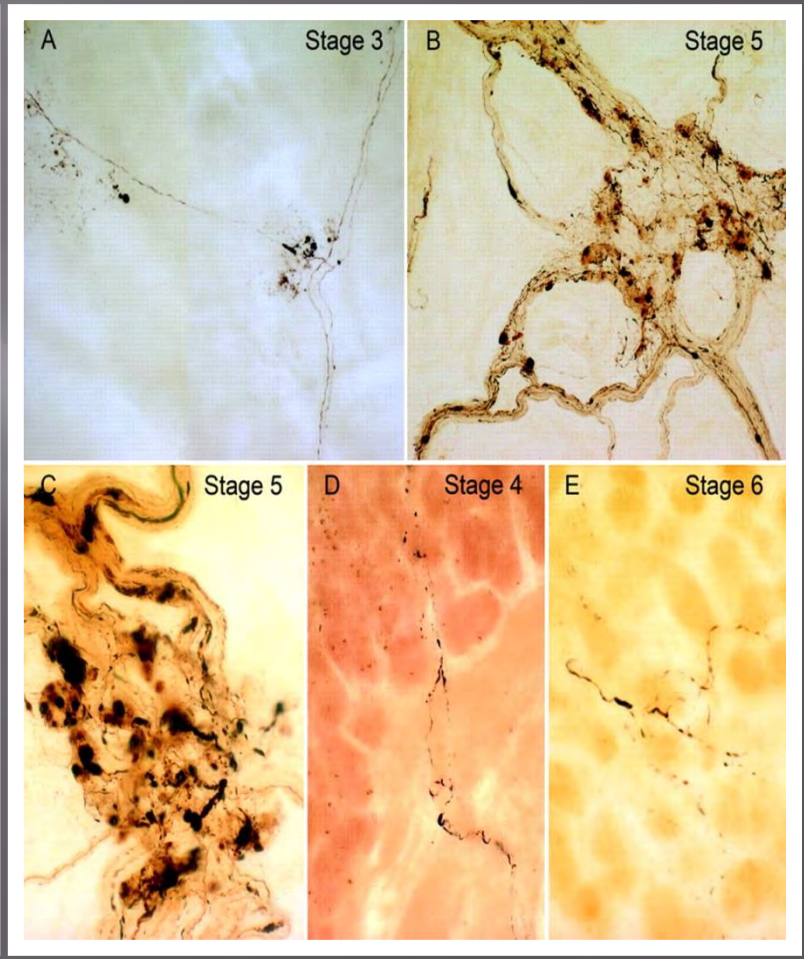
Is Parkinson's disease a prion disorder?

C. Warren Olanow[a,1] and Stanley B. Prusiner[b]

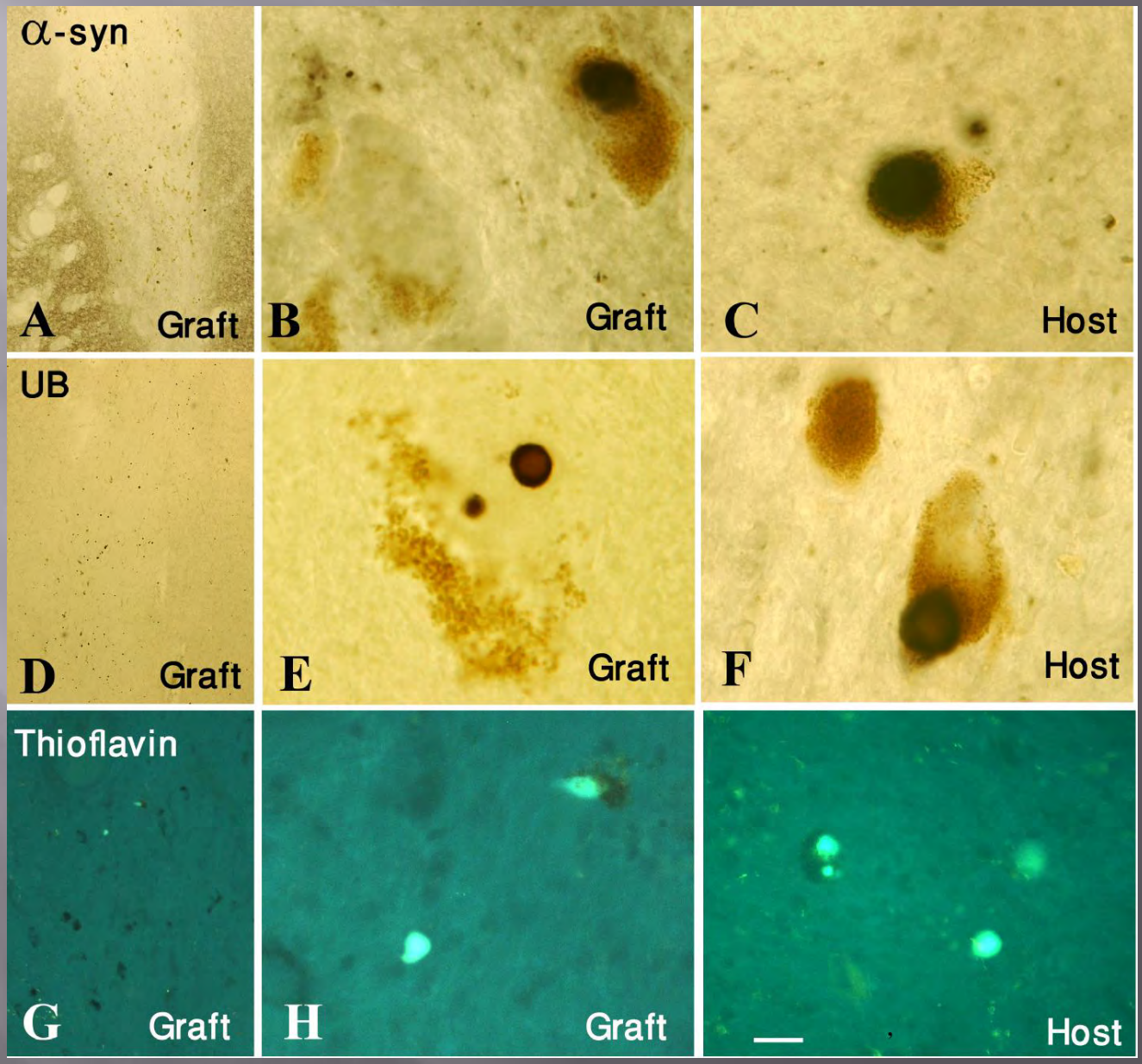


Autopsy Studies

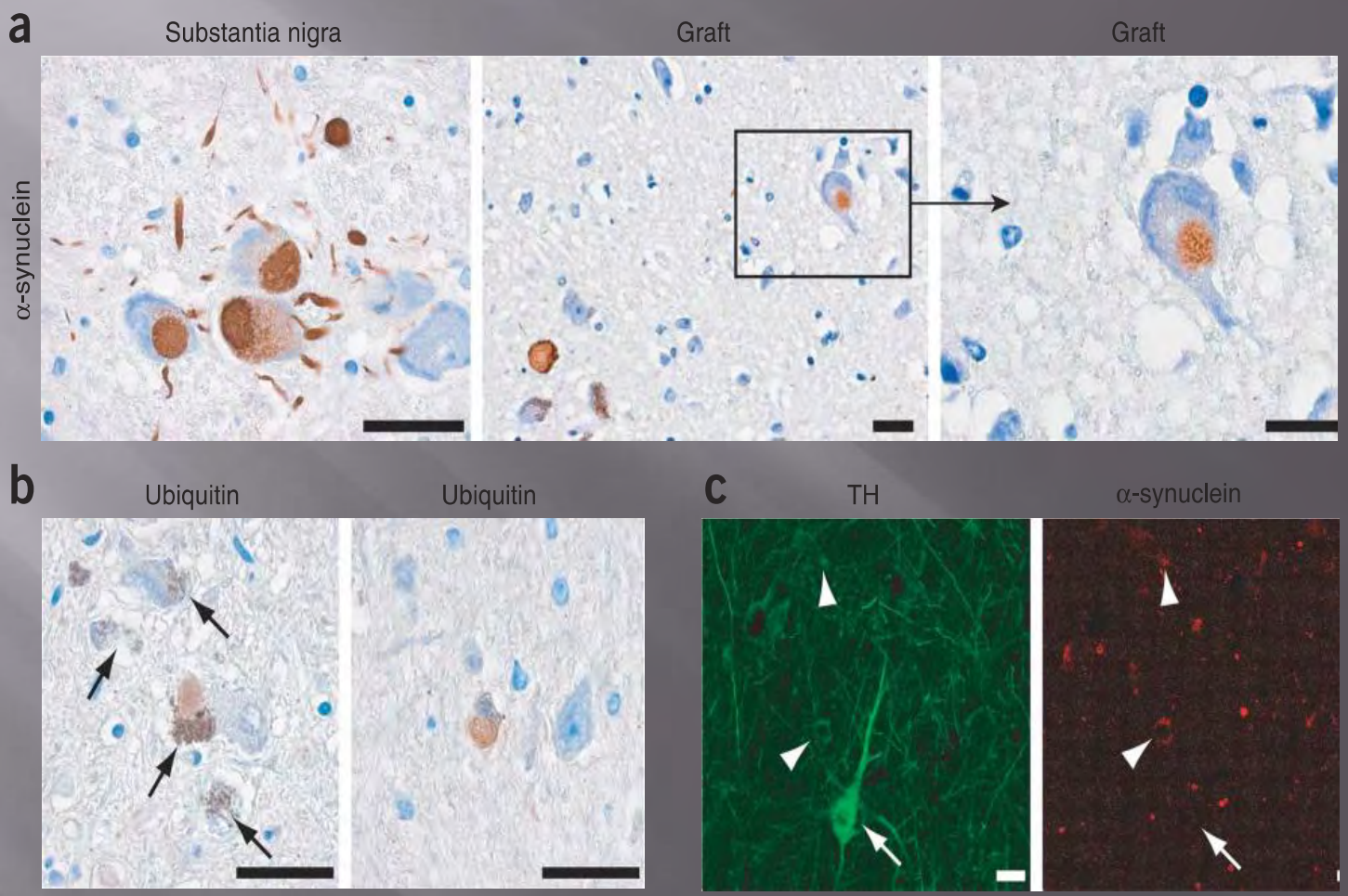




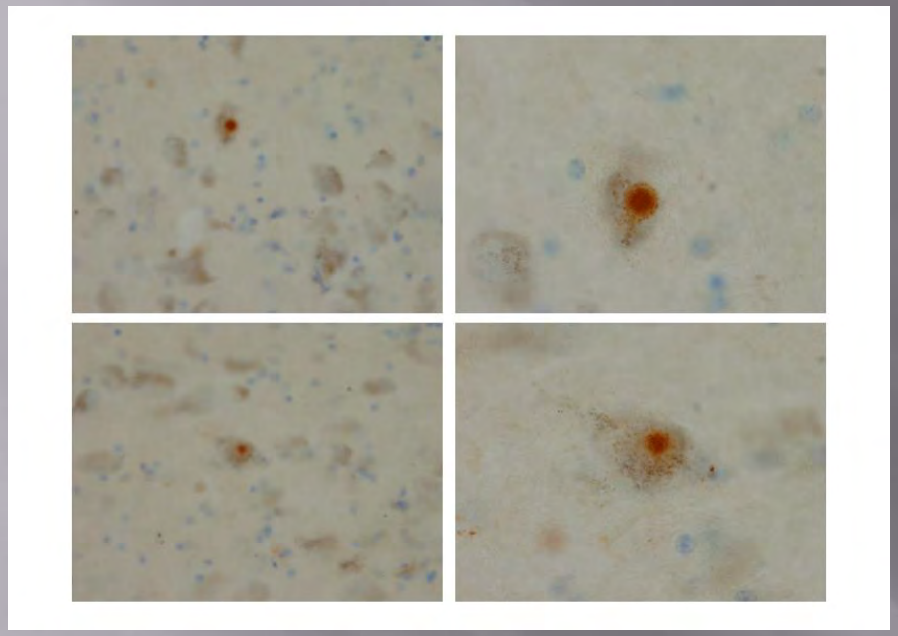
Braak & Del Tredici. Neurology 2008;70:1916

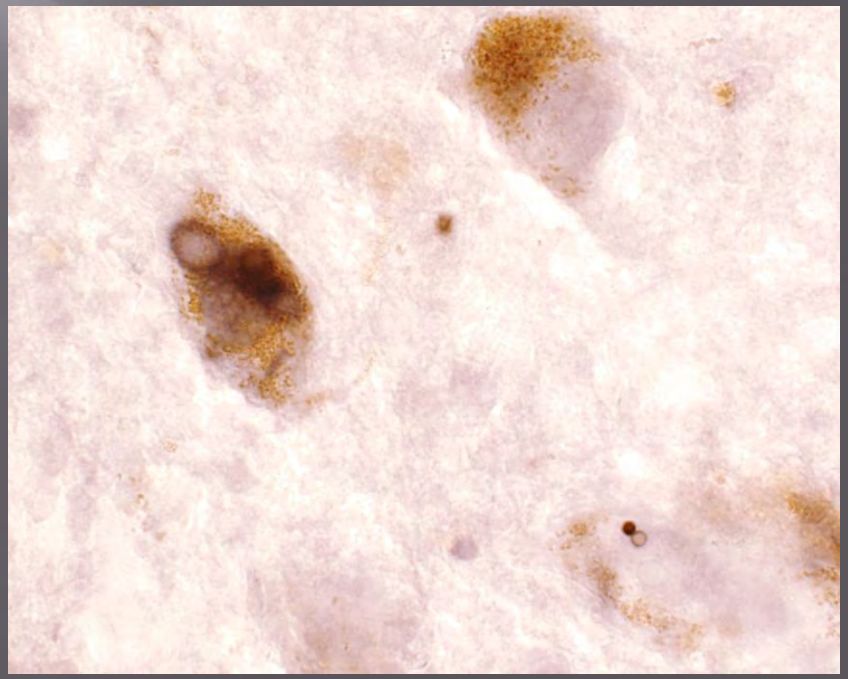

α-syn
A
Graft
B
Graft
C
Host
UB
D
Graft
E
Graft
F
Host
Thioflavin
G
Graft
H
Graft
Host

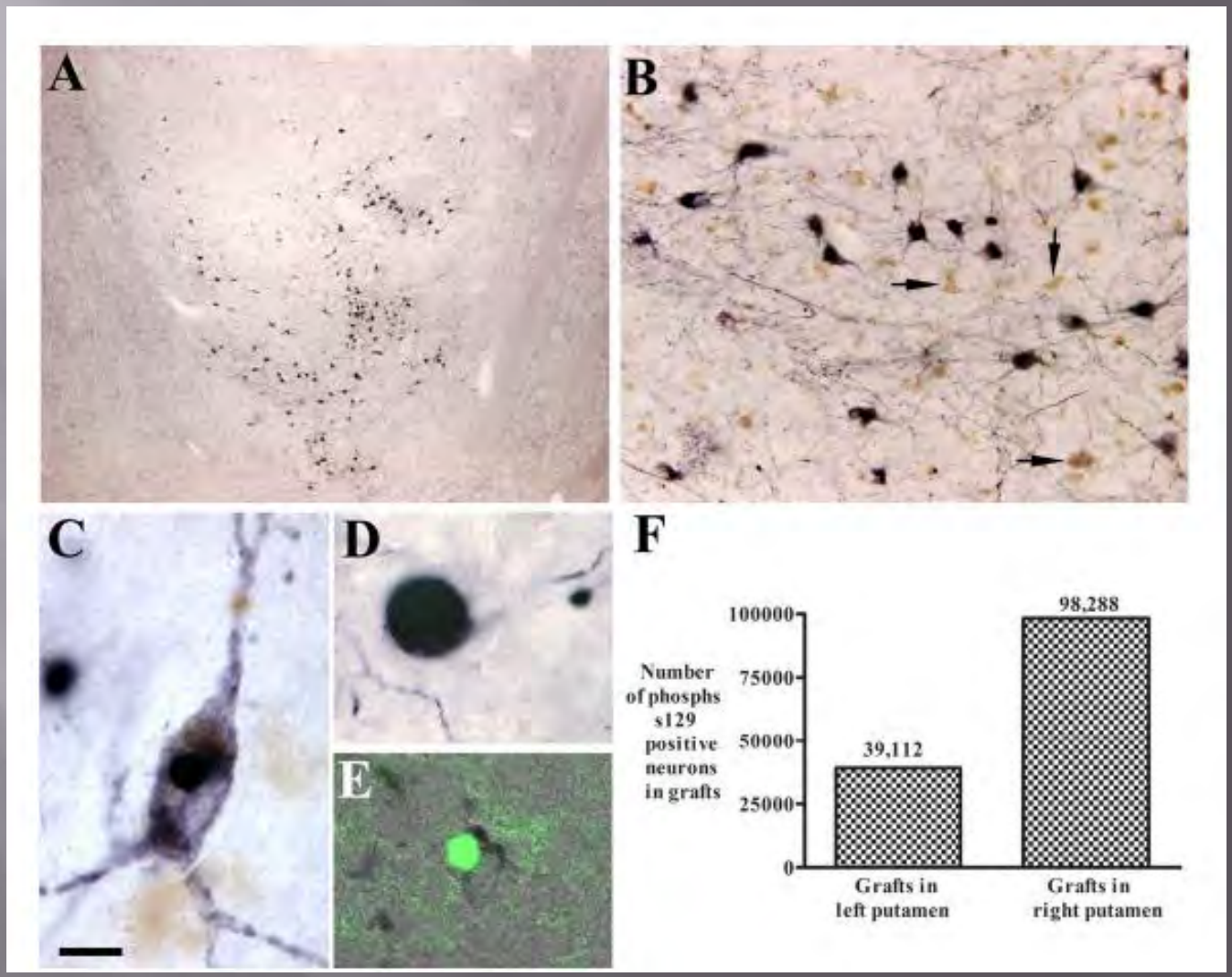
Who sees Lewy Bodies in Grafts?



Li et al., Nature Medicine, 2009

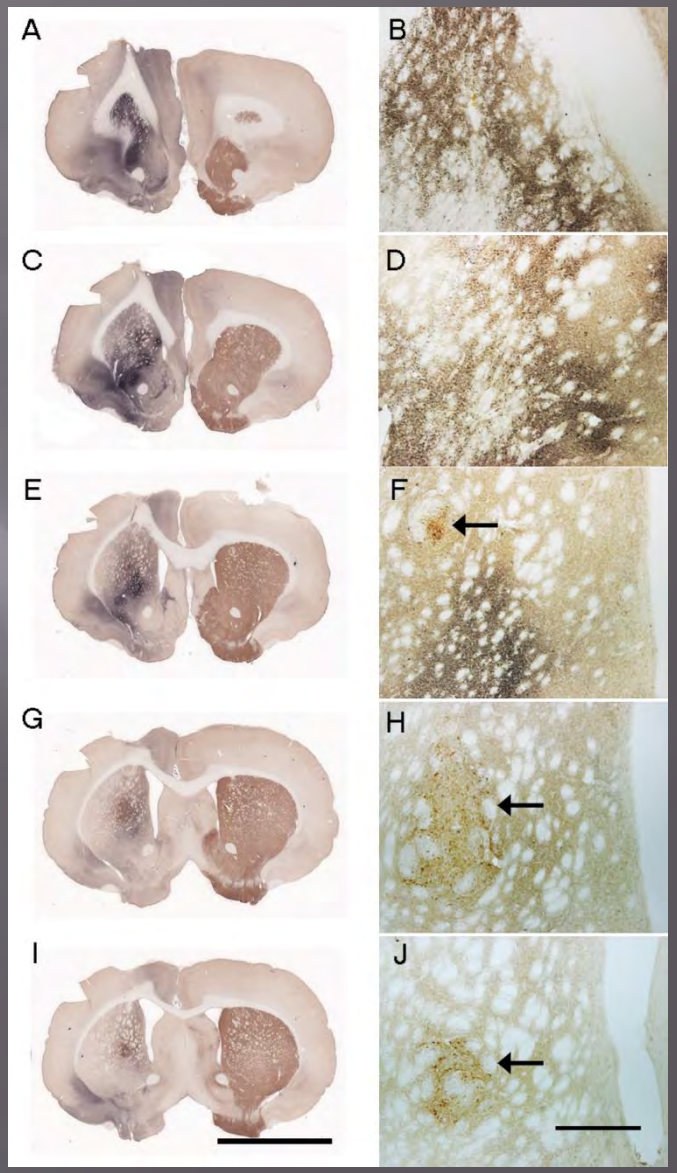




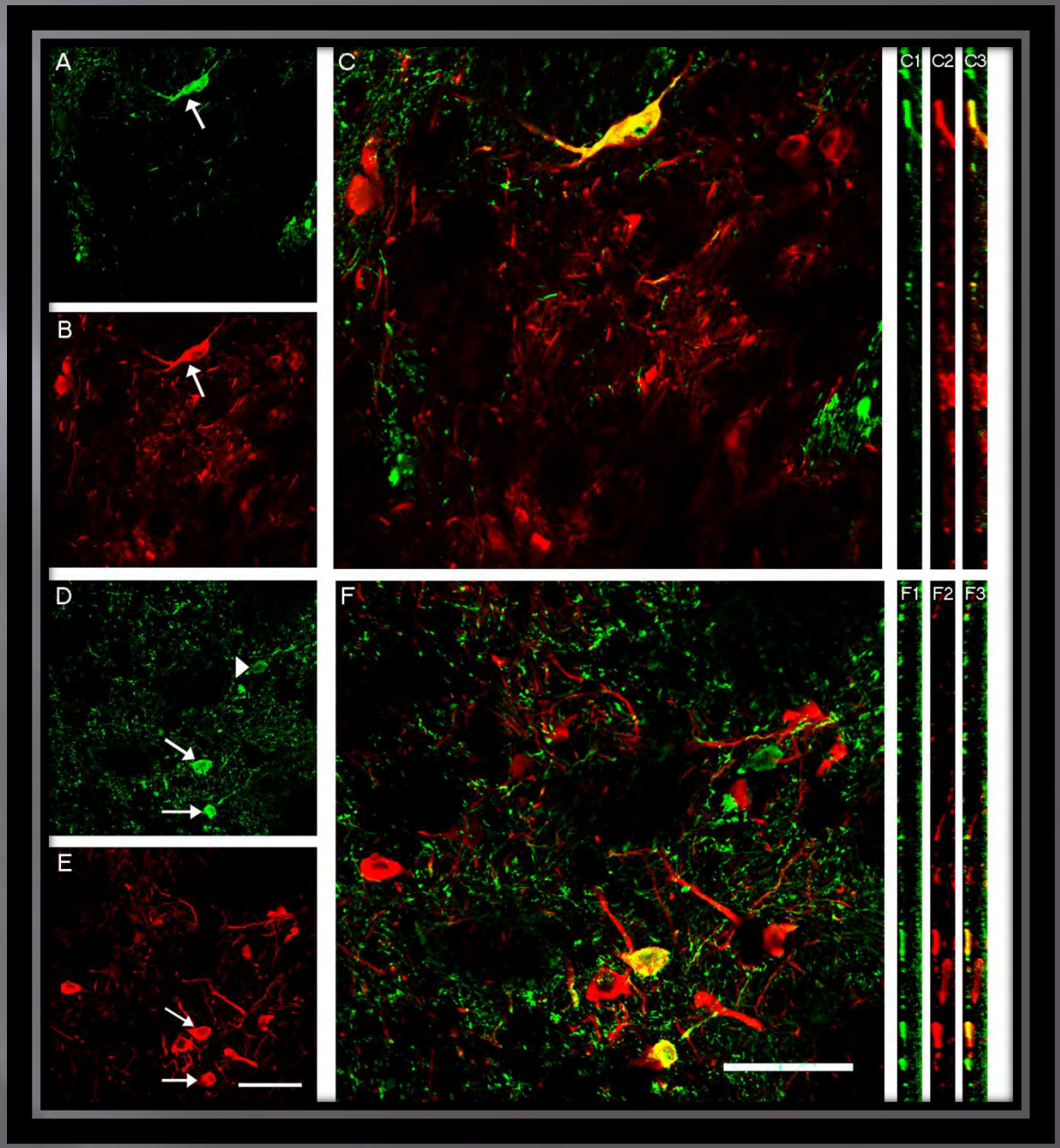

A
B
C
D
E
F
100000
75000
50000
25000
0
Number of phosphs s129 positive neurons in grafts
39,112
98,288
Grafts in left putamen
Grafts in right putamen

Grafts of dopamine cells placed into the striatum with viral over-expression of alpha synuclein

Note the physical segregation of the graft (brown) and gene delivery (black)



A small percentage (5%) of grafted neurons retrogradely transported host-derived alpha synuclein



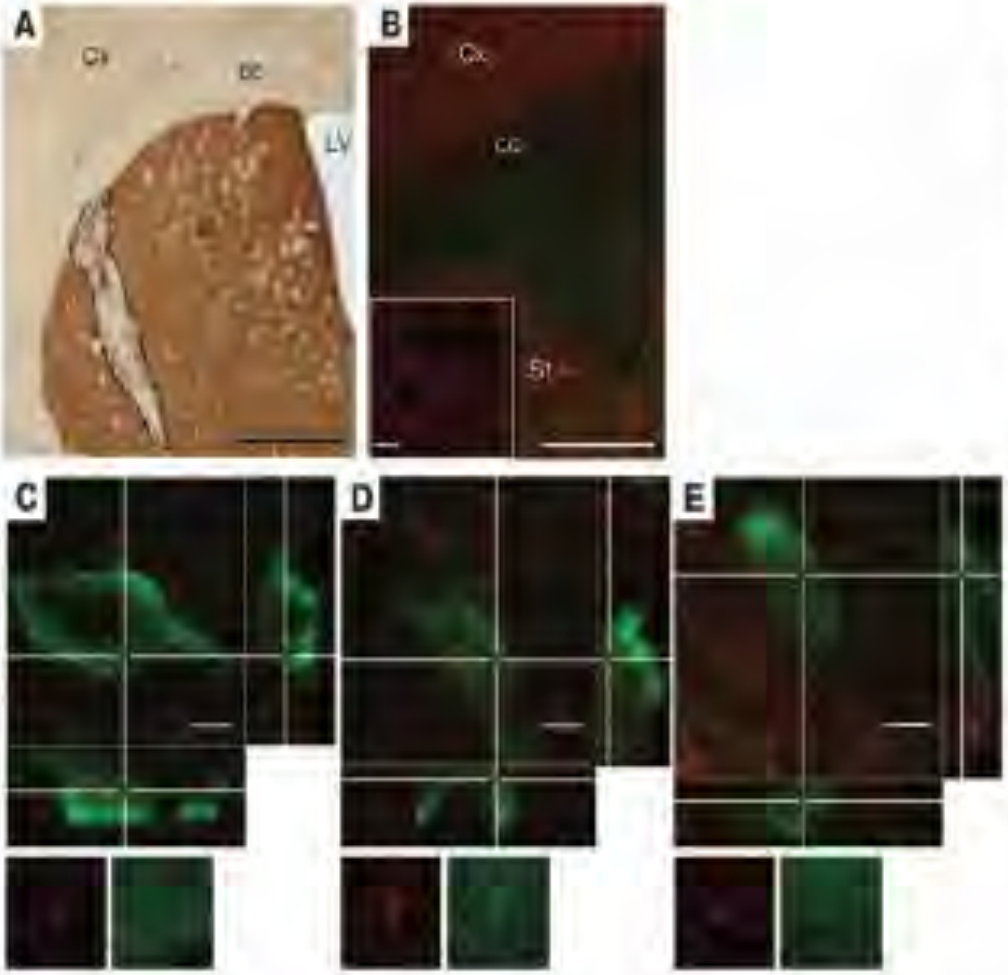


Figure 6

In vivo transmission of α-syn from mouse brain to a graft of dopaminergic neurons. (A) Representative coronal section from grafted human α-syn–overexpressing mouse stained with an antibody against TH. The dashed line delineates the transplant of TH-positive neurons in the host striatum. (B) Grafted neurons are identified by TH staining (green) within the human α-syn–positive (red) striatum of the host. The inset shows high magnification of human α-syn–positive accumulations in the host striatum. (C–E) Confocal 3D reconstruction of wild-type TH-positive cells (green) in transgenic mice overexpressing human α-syn. The cross points on human α-syn–positive dots (red) present within the transplanted cells. Reconstructed orthogonal projections are presented as viewed in the x-z (bottom) and y-z (right) planes. Cx, cortex; cc, corpus callosum; LV, lateral ventricle; St, striatum. Scale bars: 1,000 μm (A); 500 μm (B); 10 μm (B, Inset); 5 μm (C–E). Original magnification, ×1915 (C–E).

Hansen et al., 2011

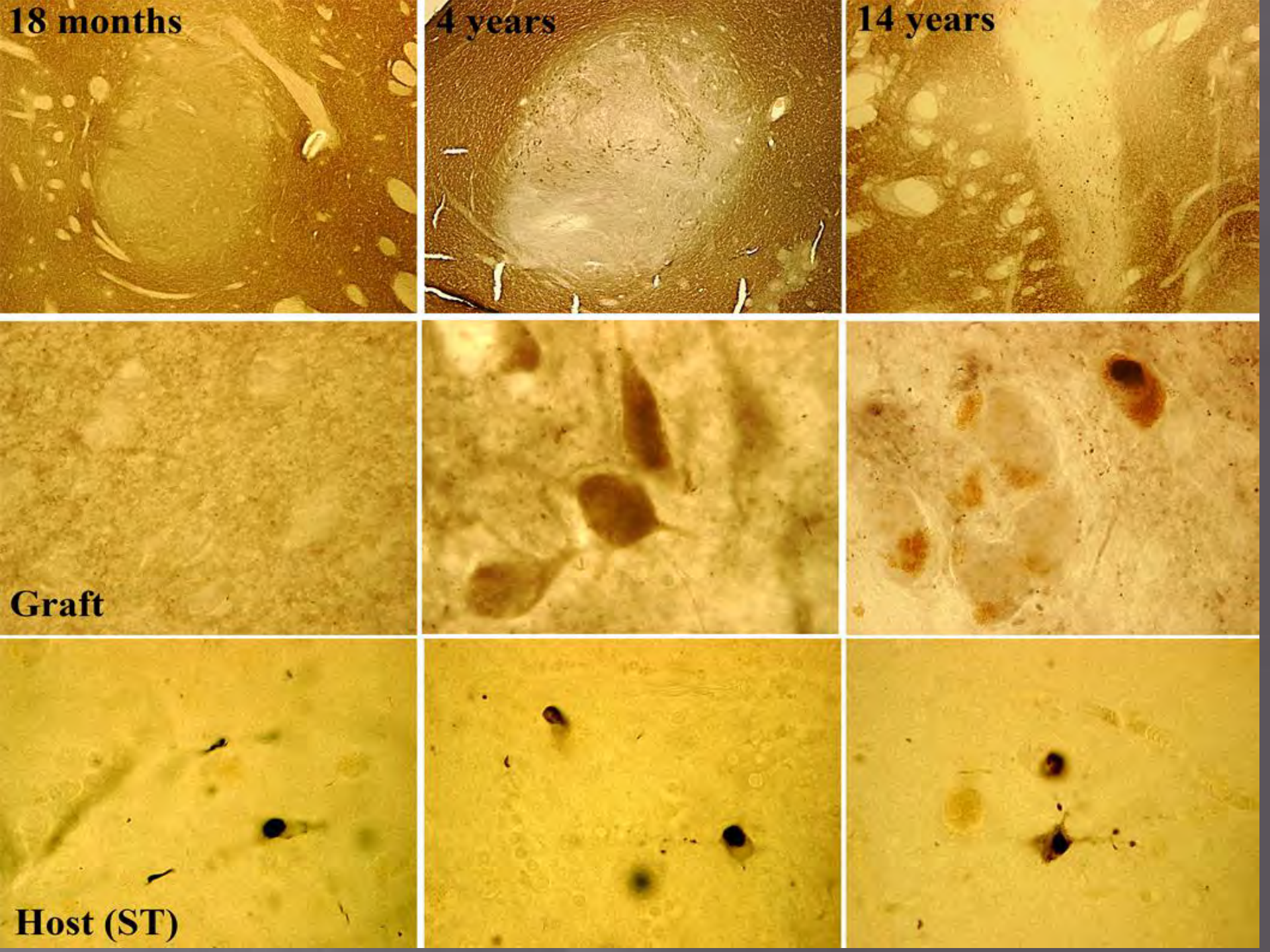
doi:10.1093/brain/awz104 BRAIN 2019: 0; 1–11 | 1

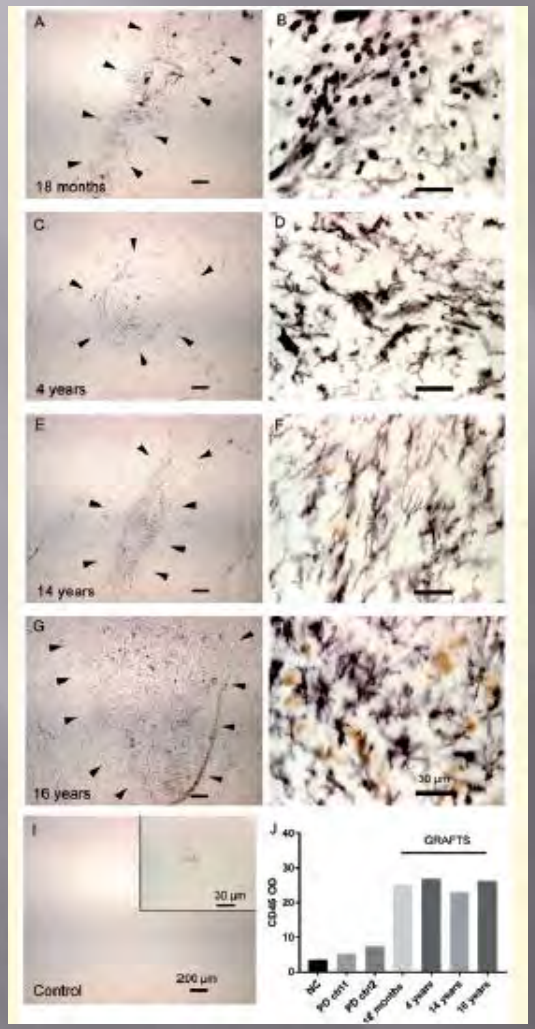
BRAIN
A JOURNAL OF NEUROLOGY

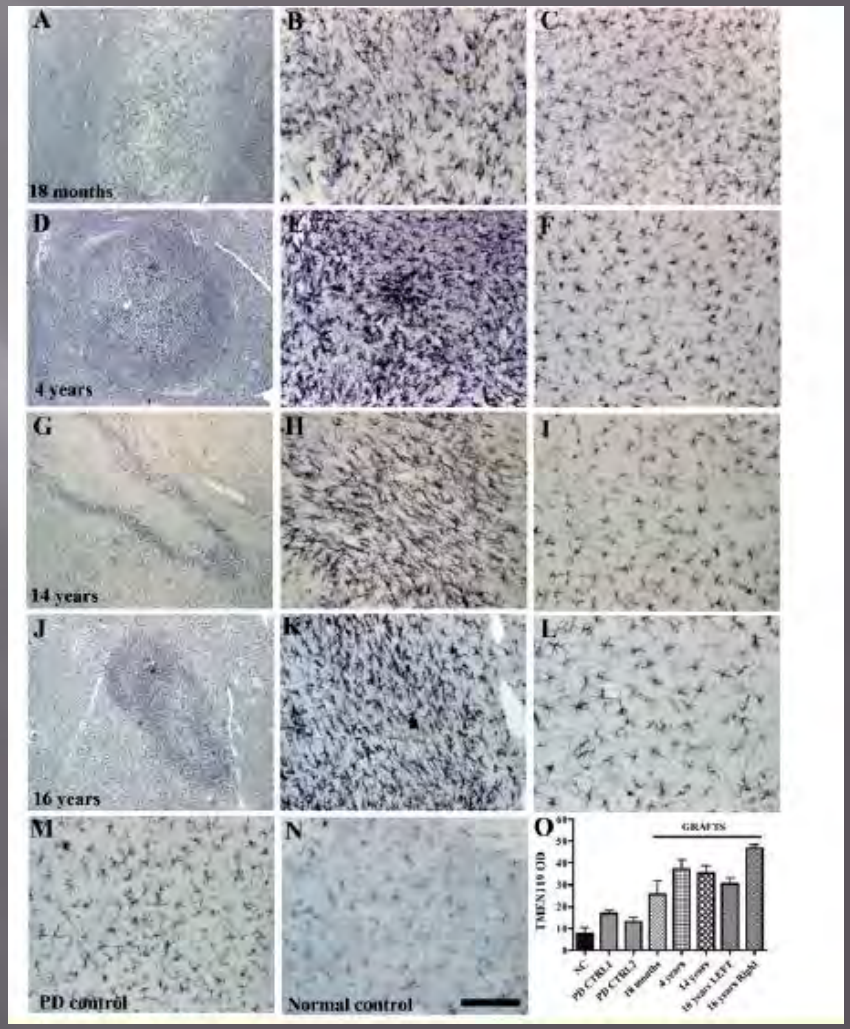
Temporal evolution of microglia and α-synuclein accumulation following foetal grafting in Parkinson's disease

C. Warren Olanow,[1,2] Mari Savolainen,[3] Yaping Chu,[3] Glenda M. Halliday[4] and Jeffrey H. Kordower[3]

We observed Lewy pathology in healthy embryonic dopamine neurons implanted into the striatum of patients with advanced Parkinson's disease. In the present study we examined the temporal relationship between the presence of inflammation with activated microglia and the emergence of α-synuclein pathology. Inflammation with activated microglia was observed in all grafts and at all time points examined between 18 months and 16 years as determined by both CD45 and TMEM119 staining. In contrast, α-synuclein was not detected at 18 months, only diffuse monomeric α-synuclein staining was observed at 4 years, and α-synuclein aggregates were not observed until 14–16 years after transplantation. Thus, there is evidence of inflammation and microglial activation in graft deposits long before the accumulation of α-synuclein pathology in implanted dopamine neurons. These observations raise the possibility that microglial activation contributes to the development of α-synuclein pathology, and supports the concept that microglia play an integral role in the propagation and spread of α-synuclein pathology.


18 months
4 years
14 years
Graft
Host (ST)


A
18 months
B
C
4 years
D
E
14 years
F
G
16 years
30 µm
I
30 µm
200 µm
Control
J
GRAFTS
CD68 OD
NC
PD ctrl
PD ctrl2
18 months
4 years
14 years
16 years

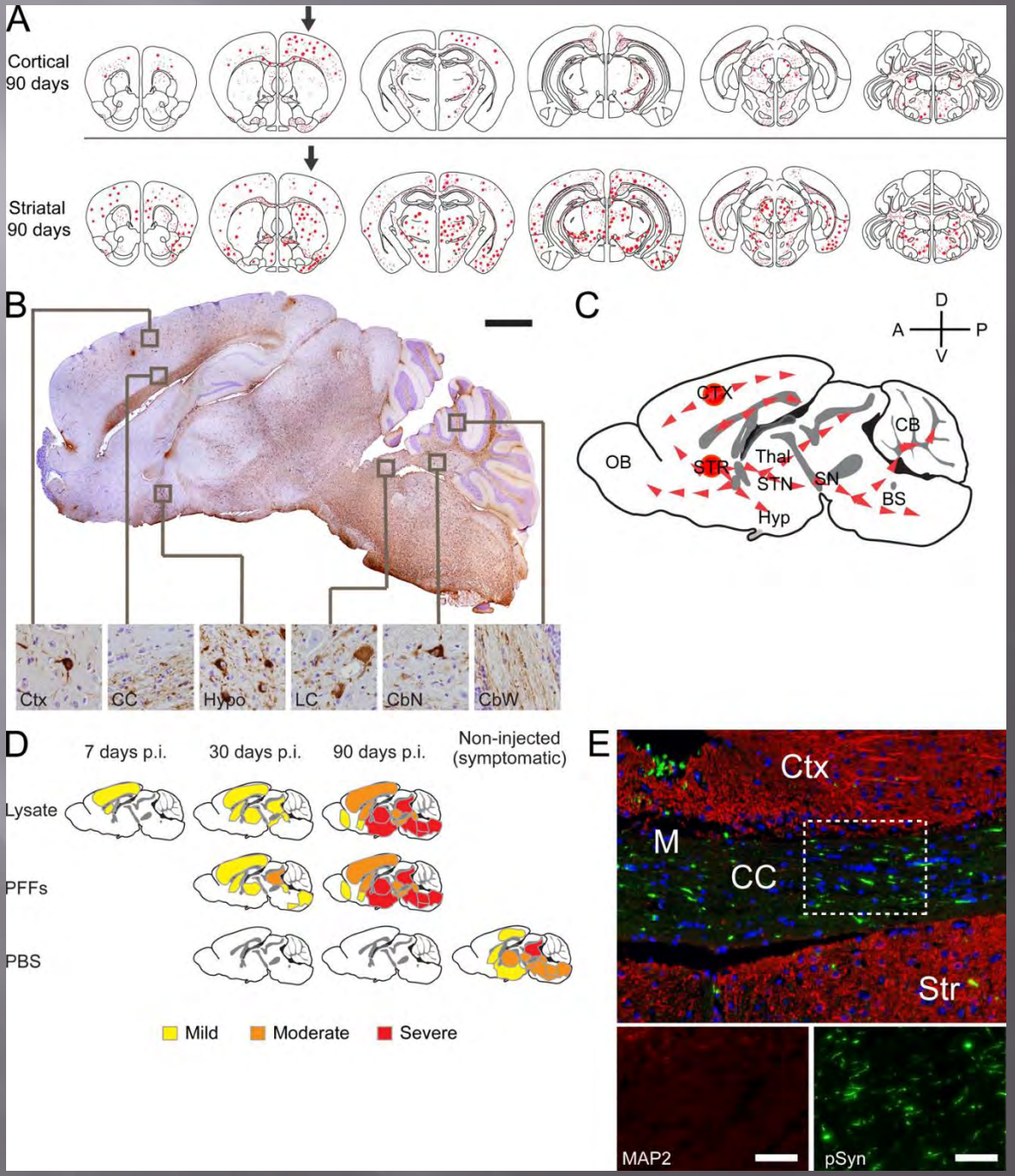

A
18 months
B
C
D
4 years
E
F
G
14 years
H
I
J
16 years
K
L
M
PD control
N
Normal control
O
GRAFTS
TMEN119 OD
NC
PD CTRL1
PD CTRL2
18 months
4 years
14 years
16 years LEFT
16 years Right

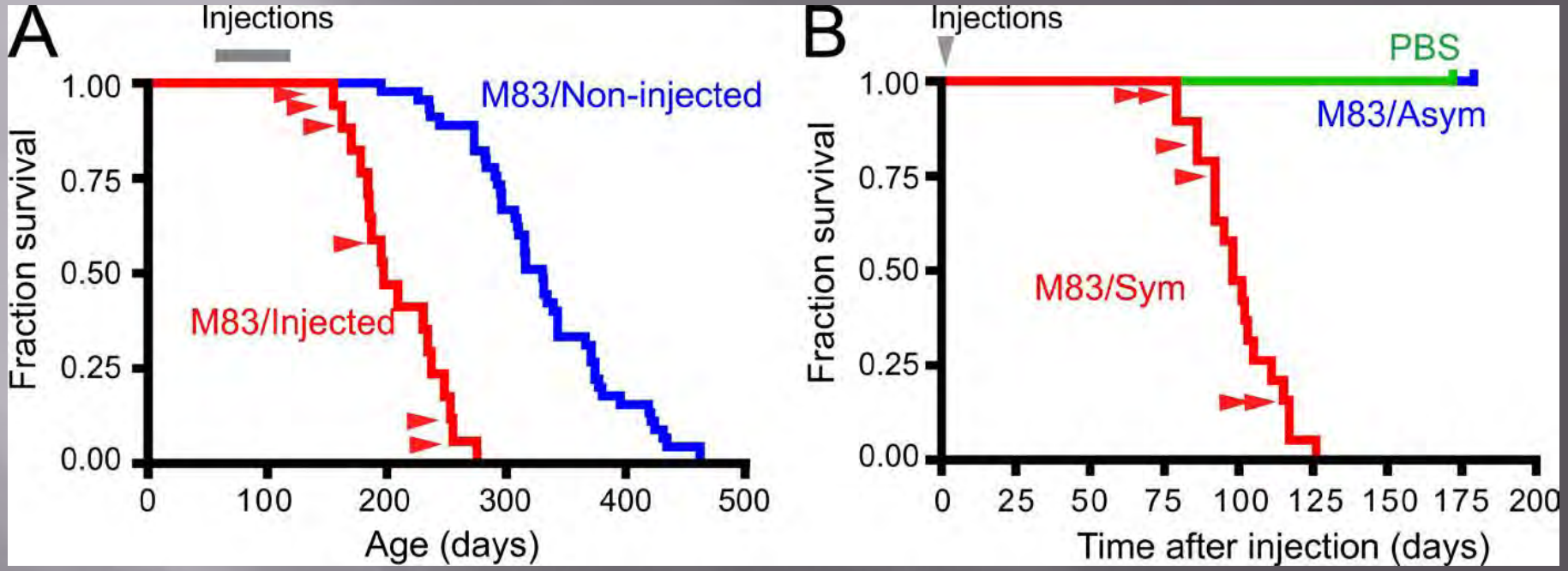
JEM Article

Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice

Kelvin C. Luk, Victoria M. Kehm, Bin Zhang, Patrick O'Brien, John Q. Trojanowski, and Virginia M.Y. Lee

The accumulation of misfolded proteins is a fundamental pathogenic process in neurodegenerative diseases. However, the factors that trigger aggregation of α-Synuclein (α-Syn), the principal component of the intraneuronal inclusions known as Lewy bodies (LBs), and Lewy neurites (LNs), which characterize Parkinson's disease (PD) and dementia with LBs (DLB), are poorly understood. We show here that in young asymptomatic α-Syn transgenic (Tg) mice, intracerebral injections of brain homogenates derived from older Tg mice exhibiting α-Syn pathology accelerate both the formation of intracellular LB/LN-like inclusions and the onset of neurological symptoms in recipient animals. Pathological α-Syn propagated along major central nervous system (CNS) pathways to regions far beyond injection sites and reduced survival with a highly reproducible interval from injection to death in inoculated animals. Importantly, inoculation with α-Syn amyloid fibrils assembled from recombinant human α-Syn induced identical consequences. Furthermore, we show for the first time that synthetic α-Syn fibrils are wholly sufficient to initiate PD-like LBs/LNs and to transmit disease in vivo. Thus, our data point to a prion-like cascade in synucleinopathies whereby cell–cell transmission and propagation of misfolded α-Syn underlie the CNS spread of LBs/LNs. These findings open up new avenues for understanding the progression of PD and for developing novel therapeutics.


A
Cortical
90 days
Striatal
90 days
B
Ctx
CC
Hypo
LC
CbN
CbW
C
D
A
P
V
CTX
CB
OB
Thal
STR
STN
SN
BS
Hyp
D
7 days p.i.
30 days p.i.
90 days p.i.
Non-injected
(symptomatic)
Lysate
PFFs
PBS
Mild
Moderate
Severe
E
Ctx
M
CC
Str
MAP2
pSyn

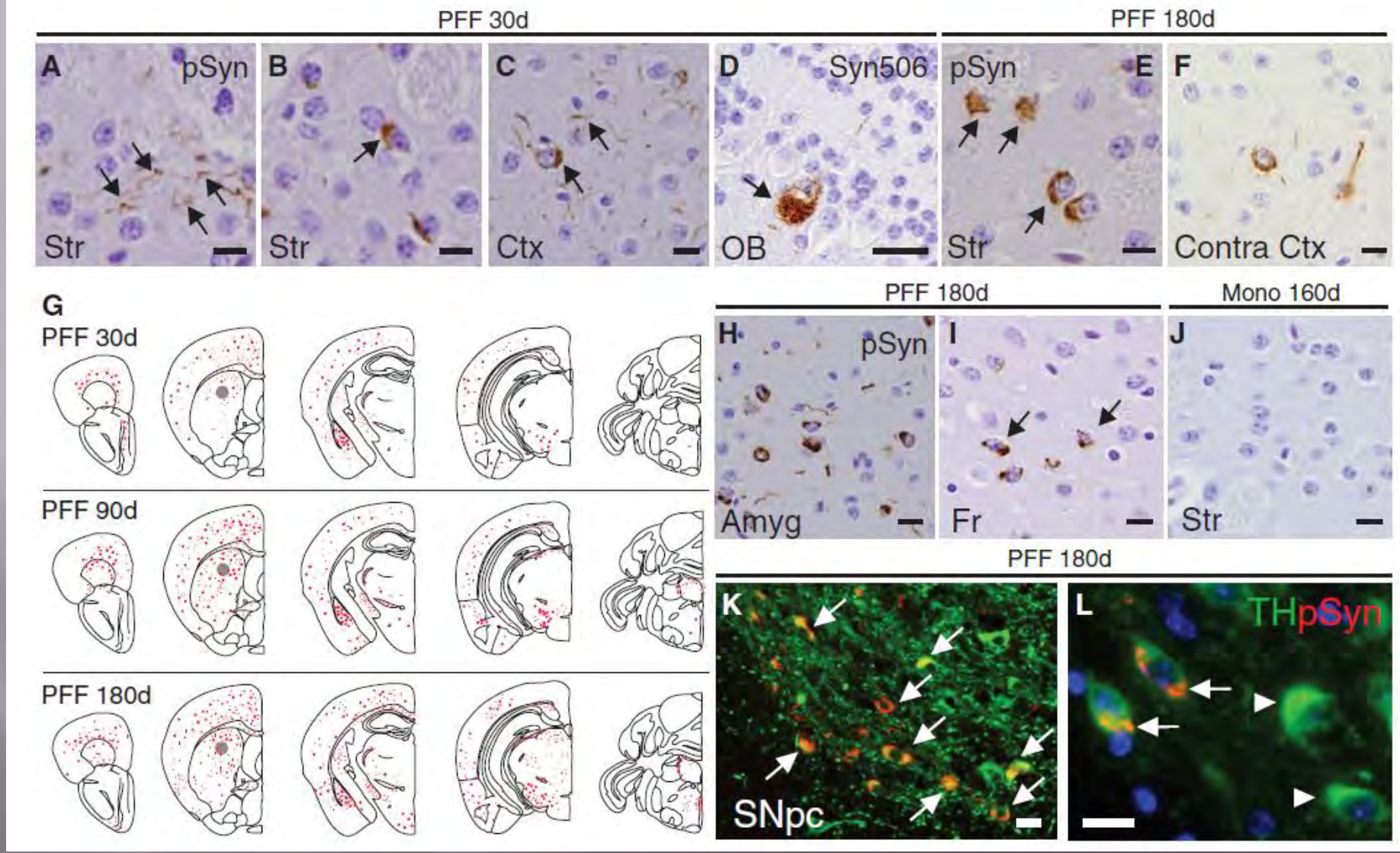

A
Injections
M83/Non-injected
M83/Injected
Fraction survival
1.00
0.75
0.50
0.25
0.00
0
100
200
300
400
500
Age (days)
B
Injections
PBS
M83/Asym
M83/Sym
Fraction survival
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
125
150
175
200
Time after injection (days)

Science

AAAS

Pathological α-Synuclein Transmission Initiates Parkinson-like Neurodegeneration in Nontransgenic Mice

Kelvin C. Luk, Victoria Kehm, Jenna Carroll, Bin Zhang, Patrick O'Brien, John Q. Trojanowski, Virginia M.-Y. Lee*


PFF 30d
PFF 180d
A
pSyn
Str
B
Str
C
Ctx
D
Syn506
OB
pSyn
E
Str
F
Contra Ctx
G
PFF 30d
PFF 90d
PFF 180d
PFF 180d
Mono 160d
H
pSyn
Amyg
I
Fr
J
Str
PFF 180d
K
SNpc
L
THpSyn

Acta Neuropathol (2014) 127:645–665
DOI 10.1007/s00401-014-1268-0

ORIGINAL PAPER

Amyloidogenic α-synuclein seeds do not invariably induce rapid, widespread pathology in mice

Amanda N. Sacino · Mieu Brooks · Michael A. Thomas · Alex B. McKinney · Nicholas H. McGarvey · Nicola J. Rutherford · Carolina Ceballos-Diaz · Janice Robertson · Todd E. Golde · Benoit I. Giasson

Table 1 Summary of intracerebral injections of mice

Strain	Number of mice	Injection site	Inoculum	Time post-injection (months)	Induced pSer129/81A staining	Authentic αS pathology[a]	
						Detection by multiple markers	Spread of αS pathology outside of injection site
M83 (A53T αS)	4	HC	2 μL 2 mg/mL 21–140 WT hfib αS	2	Yes	Yes	Yes
M83 (A53T αS)	4	HC	2 μL 2 mg/mL Δ71–82 αS	2	Yes, but limited[b]	No	No
M83 (A53T αS)	4	HC	2 μL PBS	2	No	No	No
M47 (E46K αS)	6	HC	2 μL 2 mg/mL 21–140 WT hfib αS	4	Yes	Yes	Minimal[b]
M47 (E46K αS)	6	HC	2 μL 2 mg/mL E46K FL hfib αS	4	Yes	Yes	Minimal[b]
M47 (E46K αS)	5	HC	2 μL 2 mg/mL A53T FL hfib αS	4	Yes	Yes	Minimal[b]
C57BL6/C3H	4	HC	2 μL 2 mg/mL 21–140 WT hfib αS	1	Yes	Yes	No
C57BL6/C3H	4	HC	2 μL 2 mg/mL 21–140 WT hfib αS	2	Yes	Yes	No
C57BL6/C3H	4	HC	2 μL 2 mg/mL 21–140 WT hfib αS	4	Yes	Yes	No
C57BL6/C3H	5	HC	2 μL 2 mg/mL FL WT mfib αS	2	Yes	Yes	No
C57BL6/C3H	4	CTX	2 μL 2 mg/mL 21–140 WT hfib αS	1	Yes	Yes, sparse	No
C57BL6/C3H	4	CTX	2 μL 2 mg/mL 21–140 WT hfib αS	2	Yes	Yes, sparse	No
C57BL6/C3H	4	CTX	2 μL 2 mg/mL 21–140 WT hfib αS	4	Yes	Yes, sparse	No
C57BL6/C3H	4	CTX	2 μL 2 mg/mL Δ71–82 αS	1	Yes	No	No
C57BL6/C3H	4	CTX	2 μL 2 mg/mL Δ71–82 αS	2	No	No	No
C57BL6/C3H	4	CTX	2 μL 2 mg/mL Δ71–82 αS	4	No	No	No
C57BL6/C3H	4	CTX	2 μL PBS	1	No	No	No
C57BL6/C3H	4	CTX	2 μL PBS	2	No	No	No
C57BL6/C3H	4	CTX	2 μL PBS	4	No	No	No

[a] αS pathology confirmed with multiple αS antibodies and aggregate markers

[b] See text for more specific details about induction and spread

Abstract

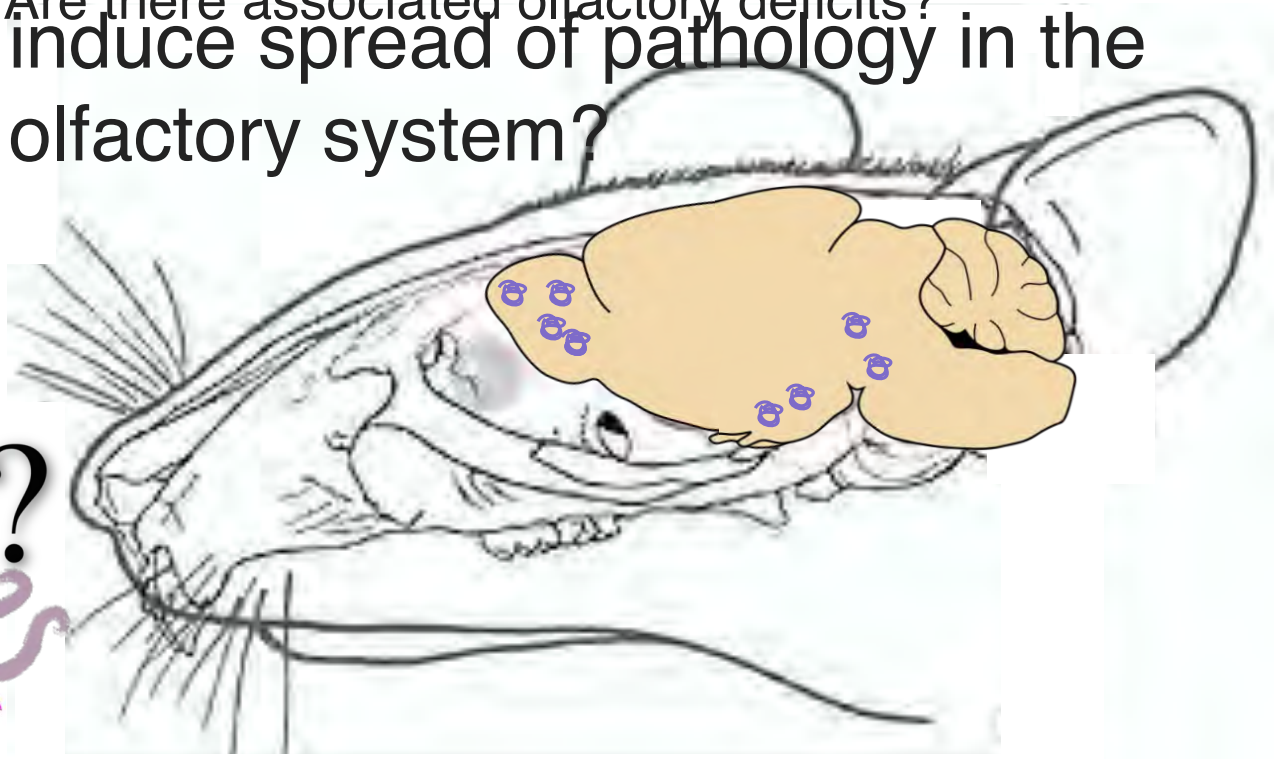
In order to further evaluate the parameters whereby intracerebral administration of recombinant α-synuclein (αS) induces pathological phenotypes in mice, we conducted a series of studies where αS fibrils were injected into the brains of M83 (A53T) and M47 (E46K) αS transgenic (Tg) mice, and non-transgenic (nTg) mice. Using multiple markers to assess αS inclusion formation, we find that injected fibrillar human αS induced widespread cerebral αS inclusion formation in the M83 Tg mice, but in both nTg and M47 Tg mice, induced αS inclusion pathology is largely restricted to the site of injection. Furthermore, mouse αS fibrils injected into nTg mice brains also resulted in inclusion pathology restricted to the site of injection with no evidence for spread. We find no compelling evidence for extensive spread of αS pathology within white matter tracts, and we attribute previous reports of white matter tract spreading to cross-reactivity of the αS pSer129/81A antibody with phosphorylated neurofilament subunit L. These studies suggest that, with the exception of the M83 Tg mice which appear to be uniquely susceptible to induction of inclusion pathology by exogenous forms of αS, there are significant barriers in mice to widespread induction of αS pathology following intracerebral administration of amyloidogenic αS.

Olfactory bulb pathology model

Create a model of progressive pathology of direct relevance to the "Braak model"

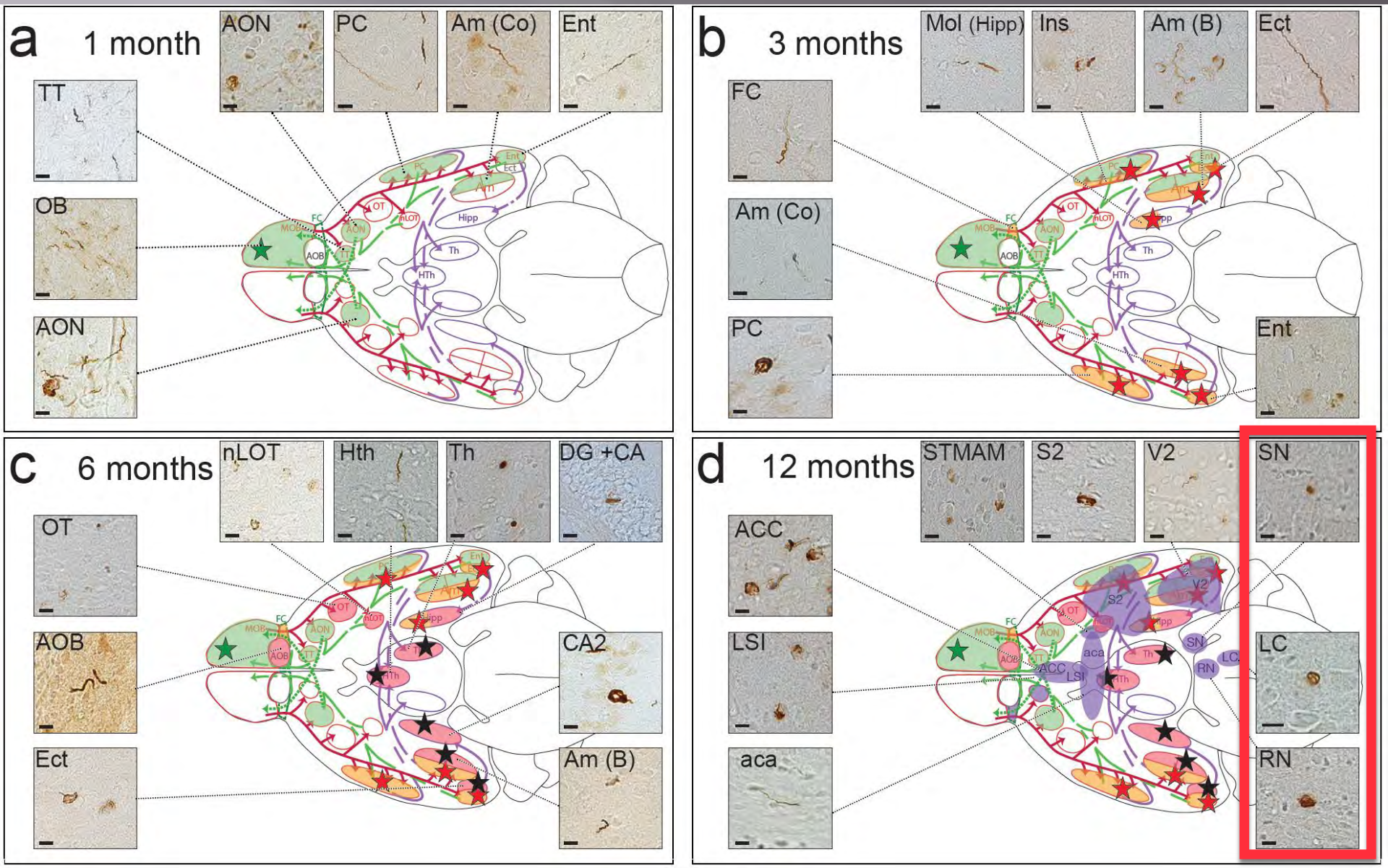
Can preformed α-synuclein fibrils induce spread of pathology in the olfactory system?

Are there associated olfactory deficits?



?

Spreading of Pser129 α-syn in brain



Preformed Fibril Injections into Cynomolgus Monkeys

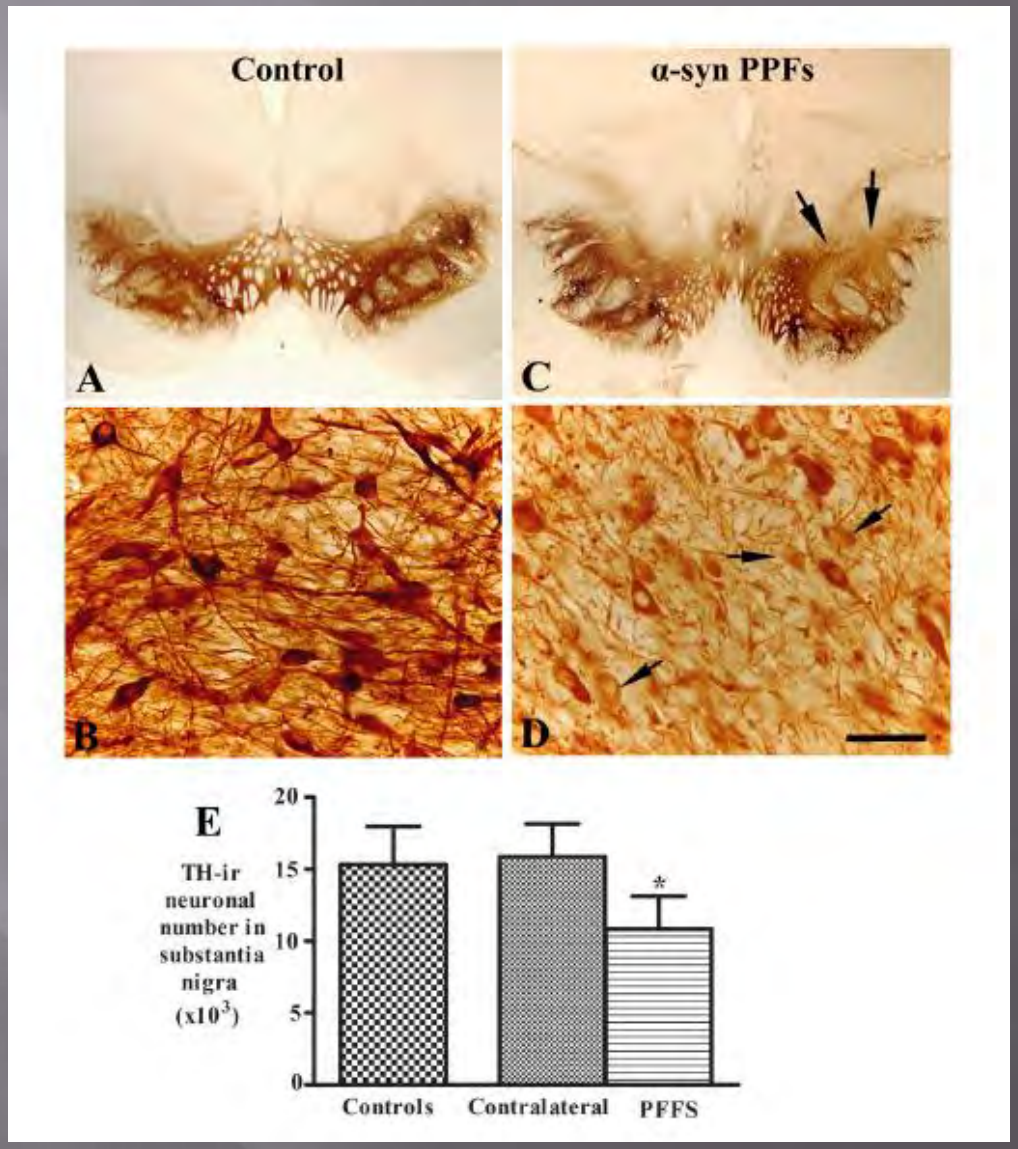
AAV-alpha synuclein: Nine young adult cynomolgus monkeys

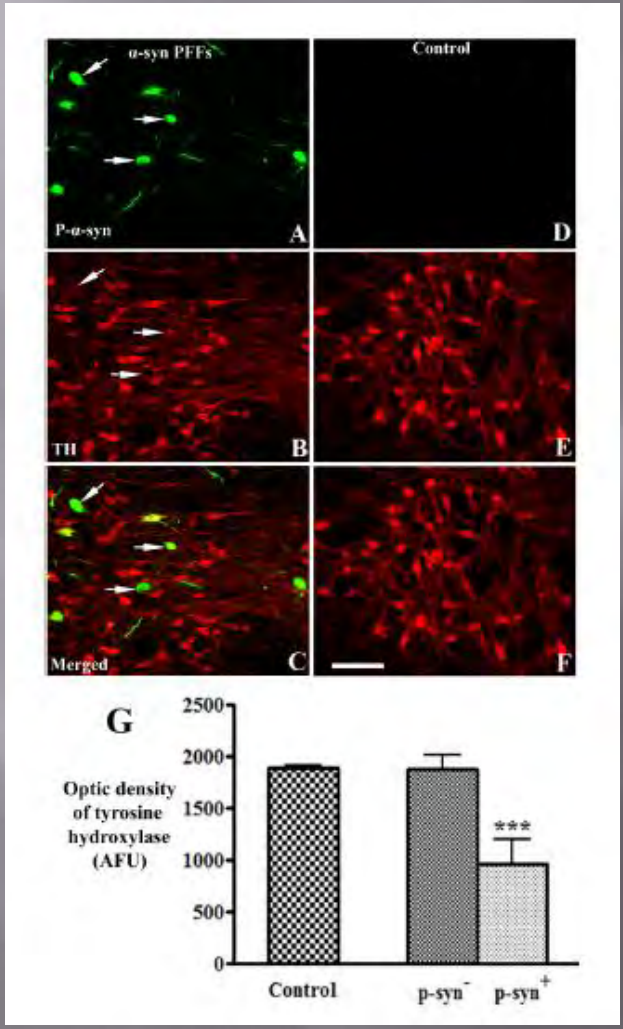
Monkeys operated on 2/20/13 (n=3), 2/21/13 (n=3), and 3/07/13 (n=3)

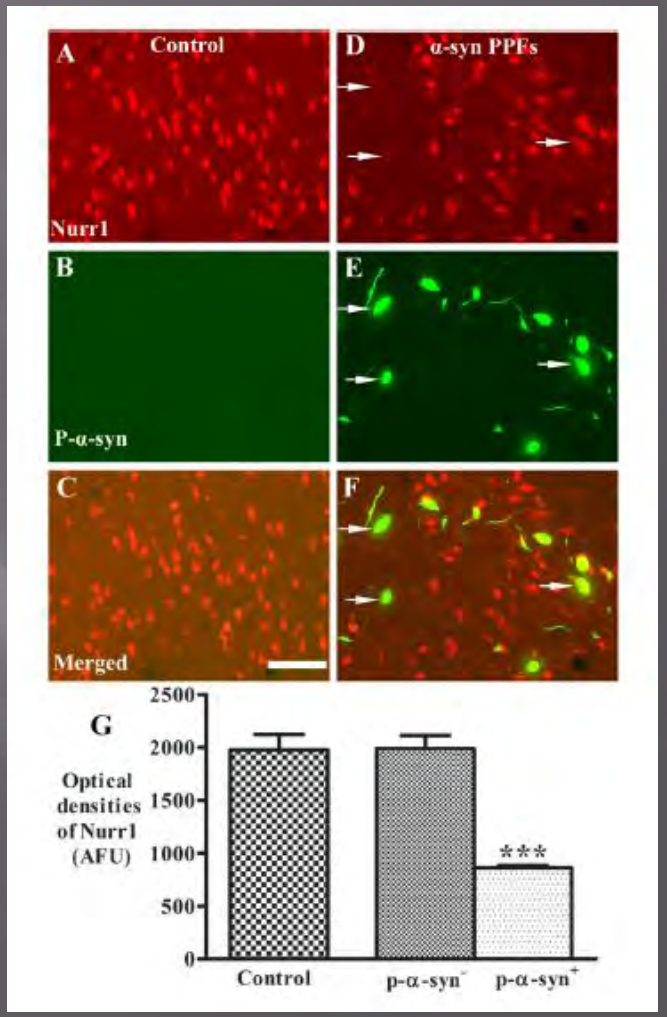
All received 3 injection right putamen (10ul, 10ul, 5ul) + 2 injections into the left medial prefrontal cortex (10ul each) + 2 injections tongue ipsilateral to medial prefrontal cortex injection side (left; 10ul each)

PE2I SPECT Scans at Baseline, 3,6,9,12, and 15 months

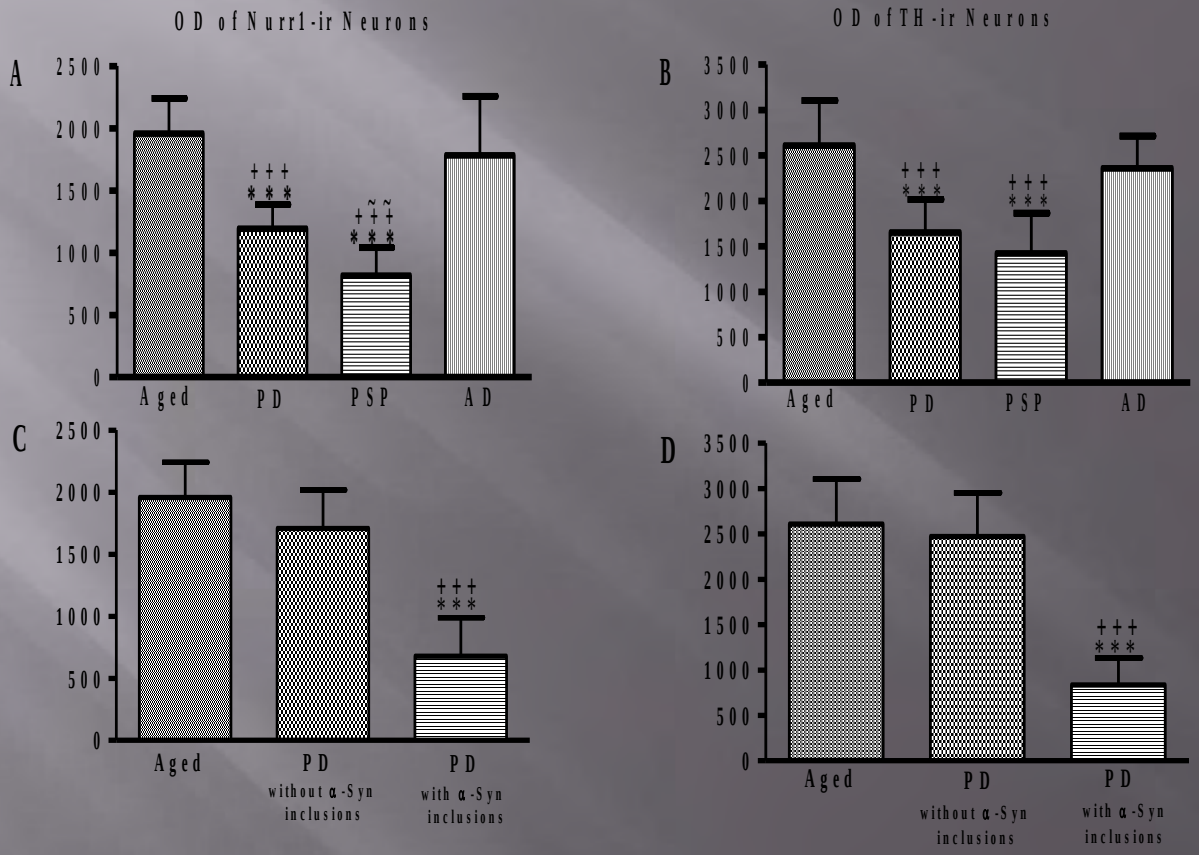
One animal died accidentally at 3 months.
Four monkey sacrificed at 12 months
Four monkeys have just been sacrificed at 18 months


Control
α-syn PPFs
A
C
B
D
E
TH-ir neuronal number in substantia nigra (x10^3)
20
15
10
5
0
*
Controls
Contralateral
PFFS

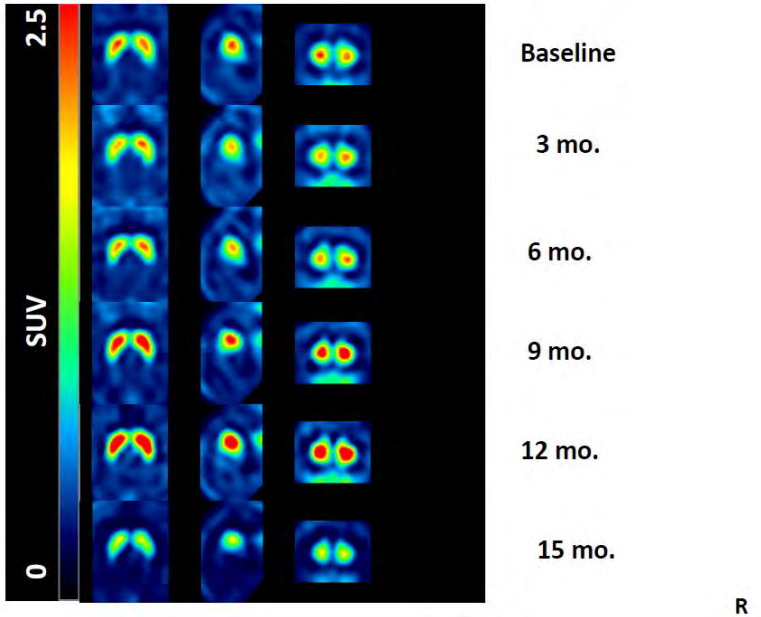

α-syn PFFs
Control
P-α-syn
A
D
TH
B
E
Merged
C
F
G
Optic density of tyrosine hydroxylase (AFU)
2500
2000
1500
1000
500
0
***
Control
p-syn⁻
p-syn⁺


A
Control
D
α-syn PPFs
Nurr1
B
E
P-α-syn
C
F
Merged
G
Optical densities of Nurr1 (AFU)
2500
2000
1500
1000
500
0
***
Control
p-α-syn⁻
p-α-syn⁺

Alpha-synuclein and PD



CN 8172 Baseline versus post-surgery 0-240 min SUM SUV image



Summary results 15 months – %Change from baseline

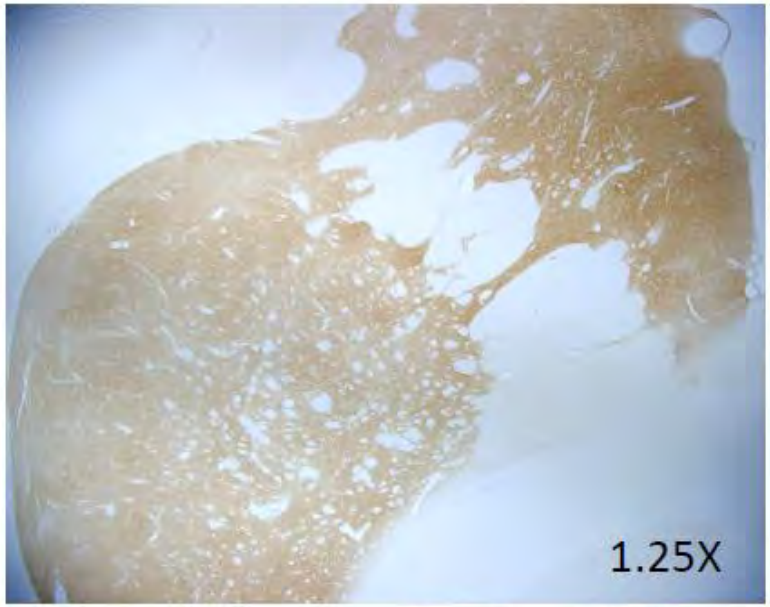
Occipital as reference region

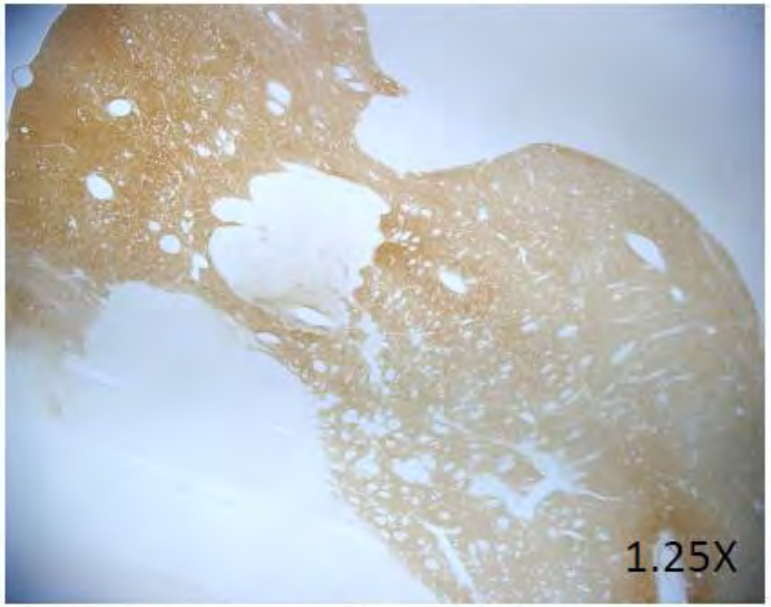
Animal ID	% Change 3 mo.		% Change 6 mo.		% Change 9 mo.		% Change 12 mo.		% Change 12 mo.	
	Left striatum	Right striatum	Left striatum	Right striatum	Left striatum	Right striatum	Left striatum	Right striatum	Left striatum	Right striatum
CN 8172	-13.4	-24.2	-21.7	-28.7	+37.63	+20.72	+30.47	+17.27	+1.61	-5.53
CN 8408	-1.4	-4.7	+98.4	+104.5	+59.69	+63.88	+50.76	+53.82	+31.09	+36.12
CN 8409	-5.4	-7.7	+66.6	+71.6	+62.82	+71.62	+120.37	+119.36	---	---
CN 8410	+6.6	+4.9	+51.8	+54.5	+83.93	+73.29	+68.92	+68.16	---	---
CN 8411	+40.7	+28.9	+43.0	+22.2	+116.96	+107.12	+106.24	+98.52	---	---
CN 8412	-23.0	-30.9	-29.9	-39.8	+29.82	+9.13	+57.00	+51.93	+22.82	+18.81
CN 8413	+19.4	+16.5	+80.4	+91.3	+55.90	+39.82	+105.30	+90.08	---	---
CN 8414	+14.6	+18.4	-17.9	-15.9	+17.14	+23.35	+51.10	+49.41	+39.31	+38.92
CN 8415	-25.0	-28.0	---	---	---	---	---	---	---	---

(-) = reduction; (+) = increase

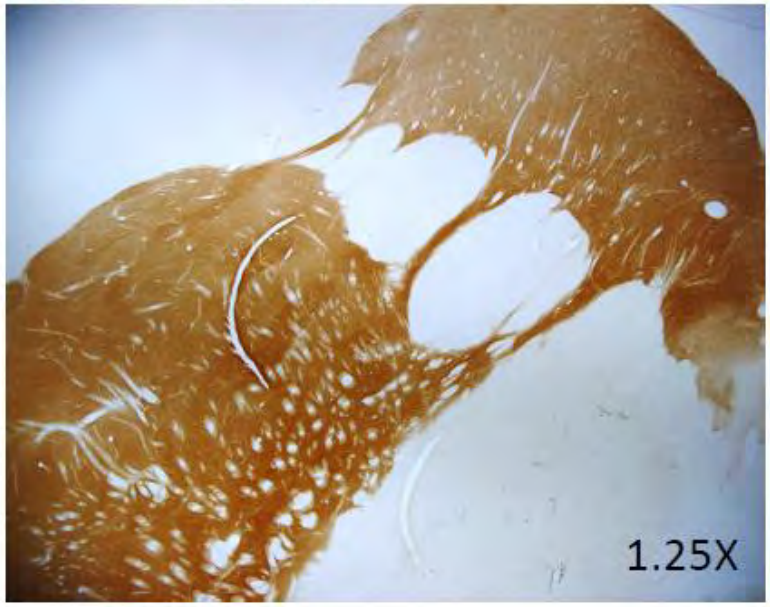
Control vs Fibril DAT 1:500

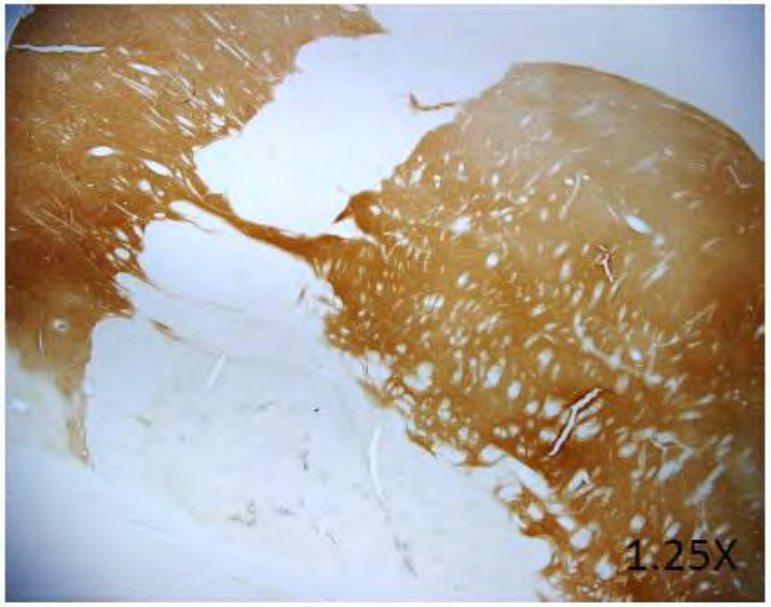
Control



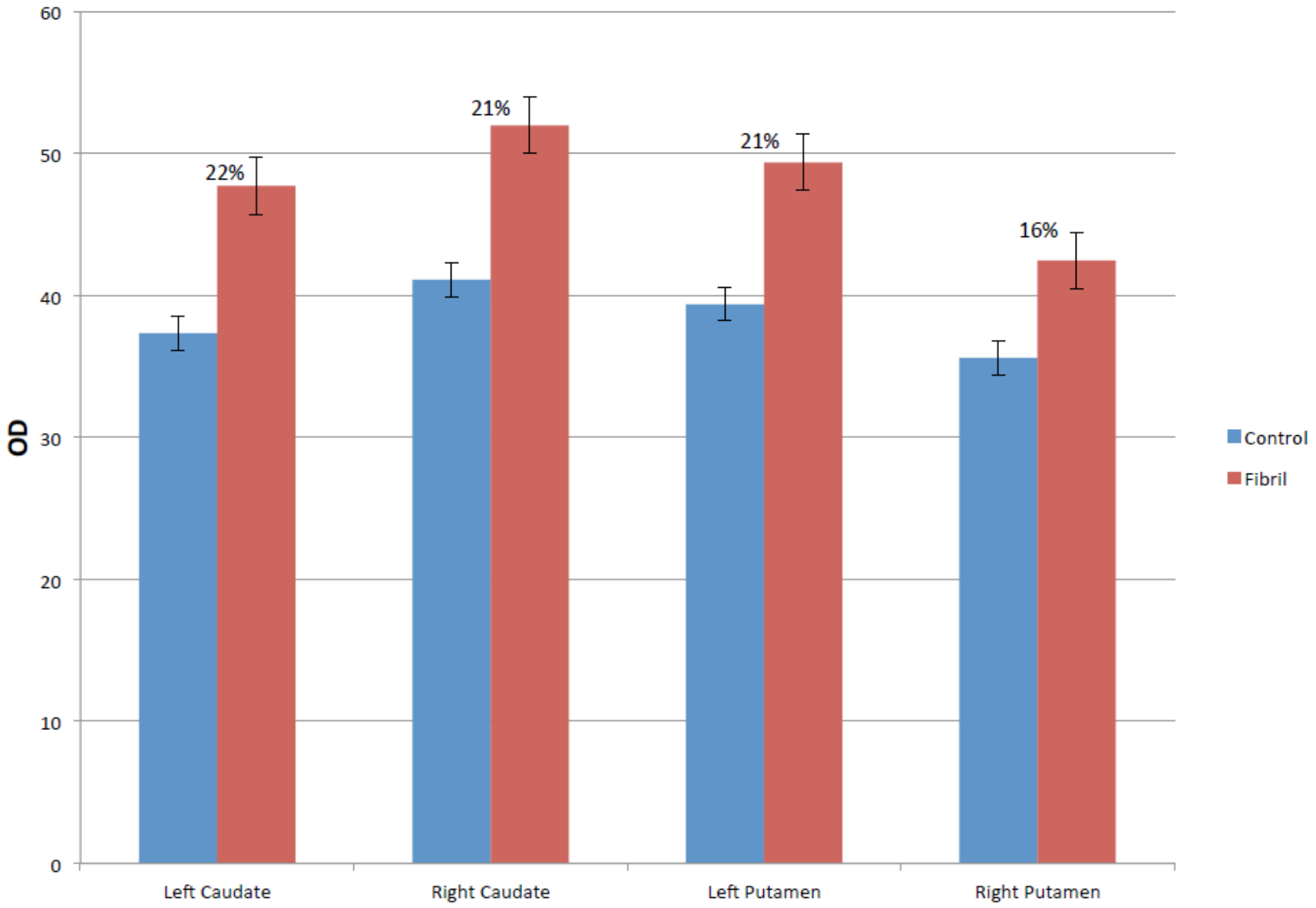


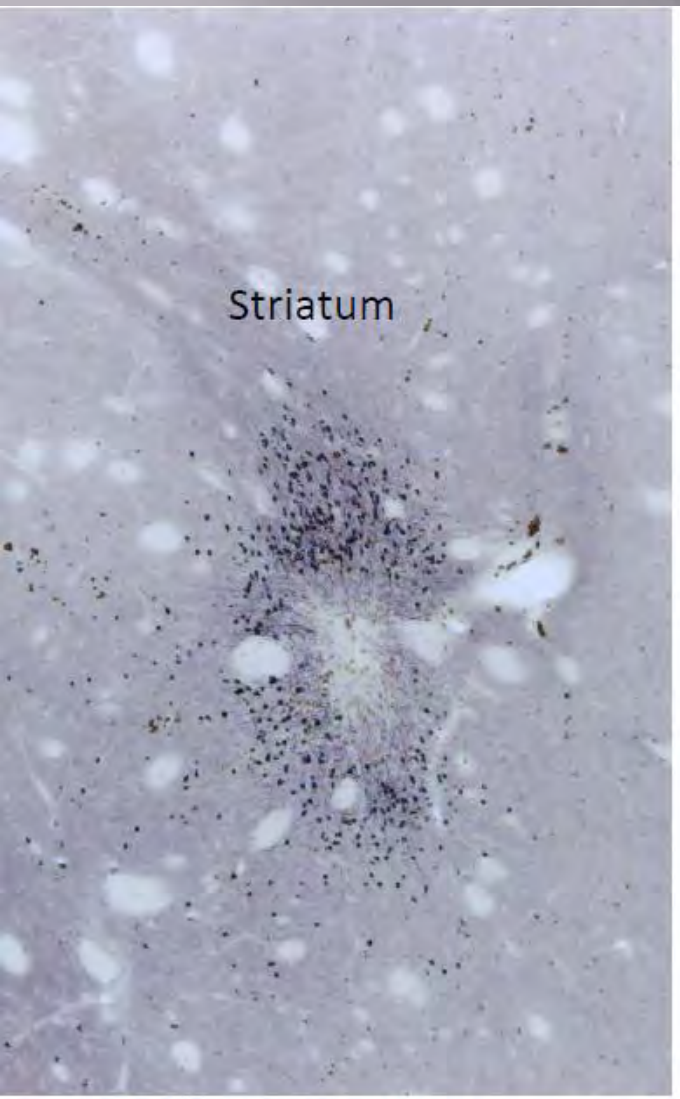
Fibril

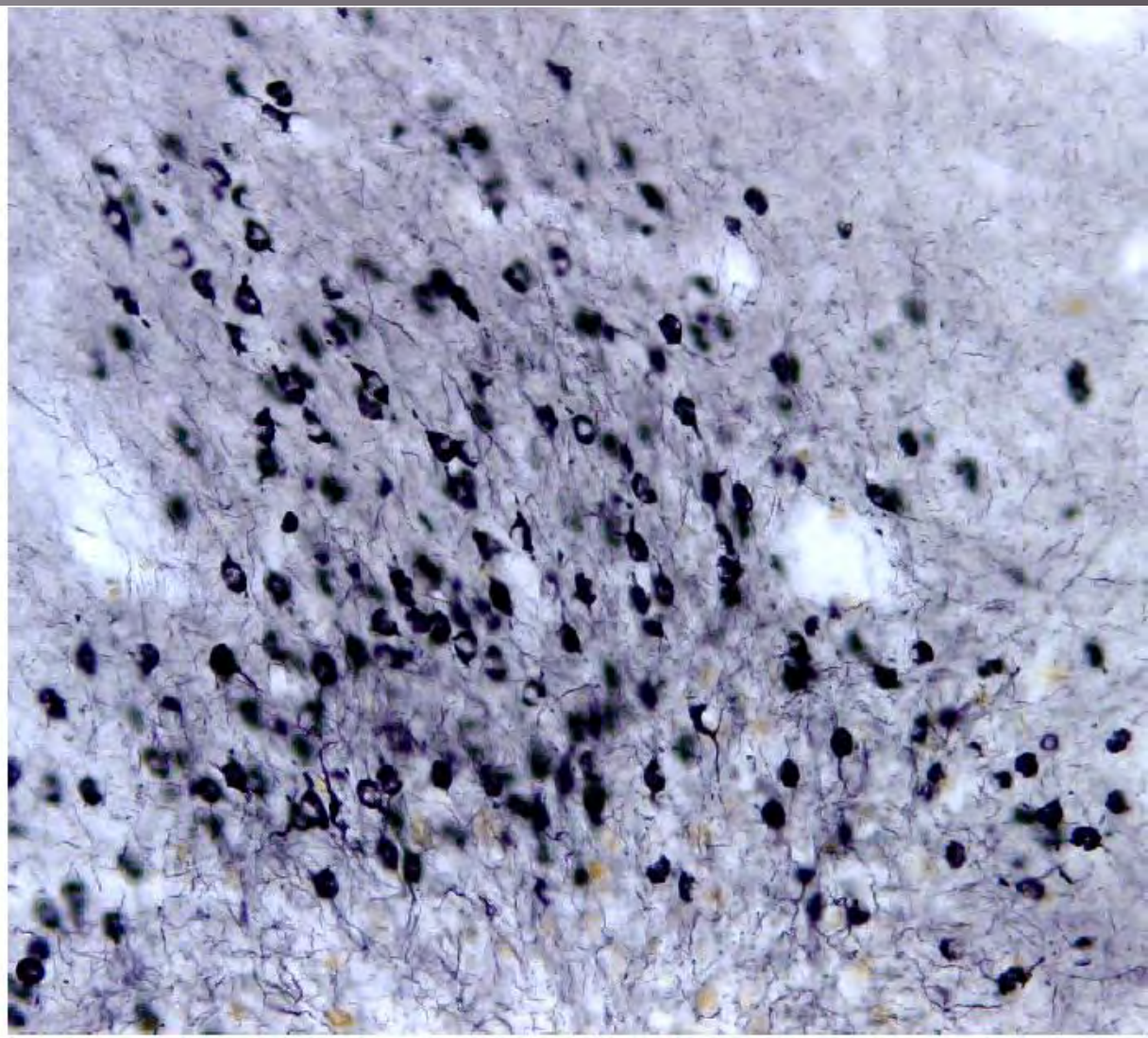


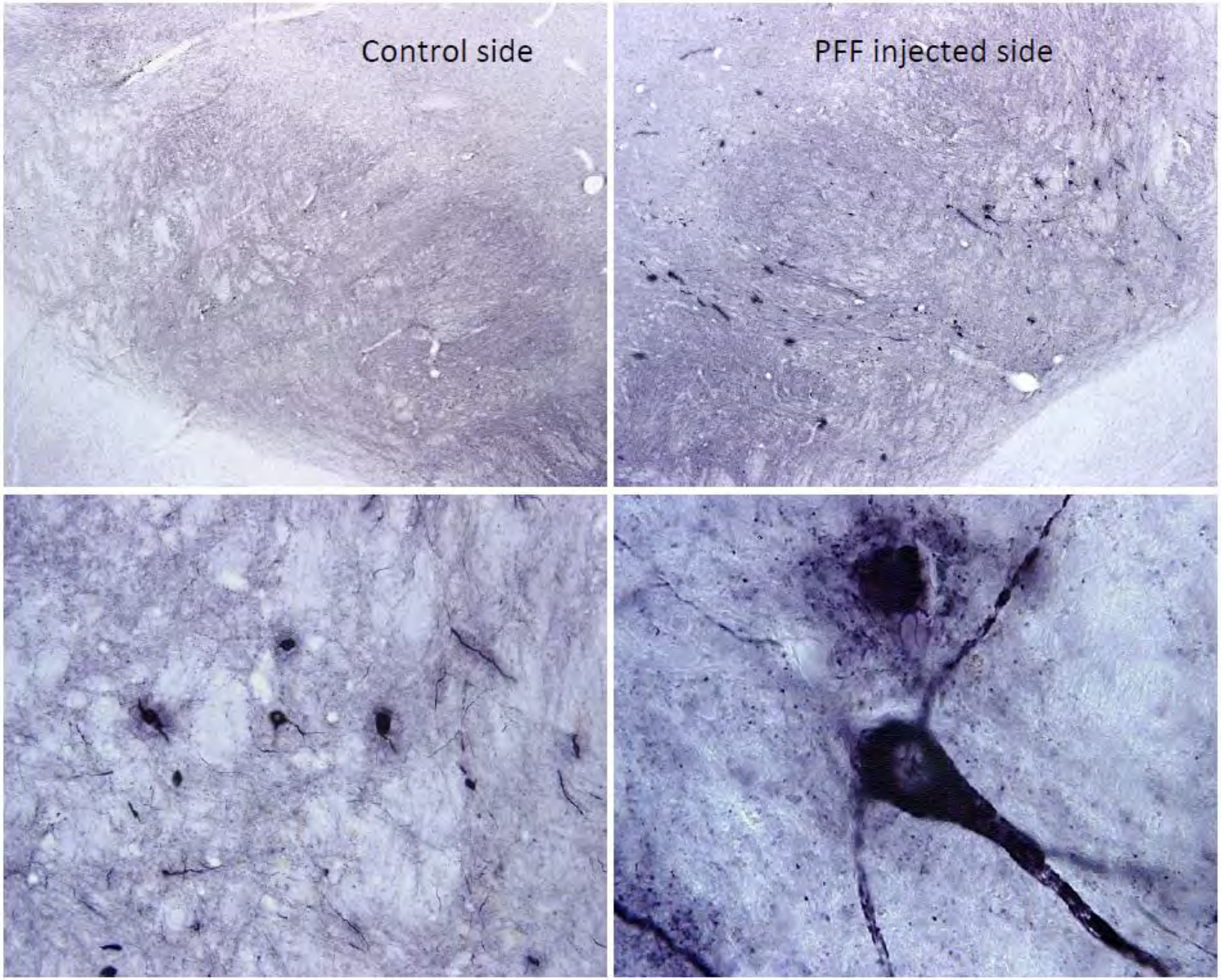


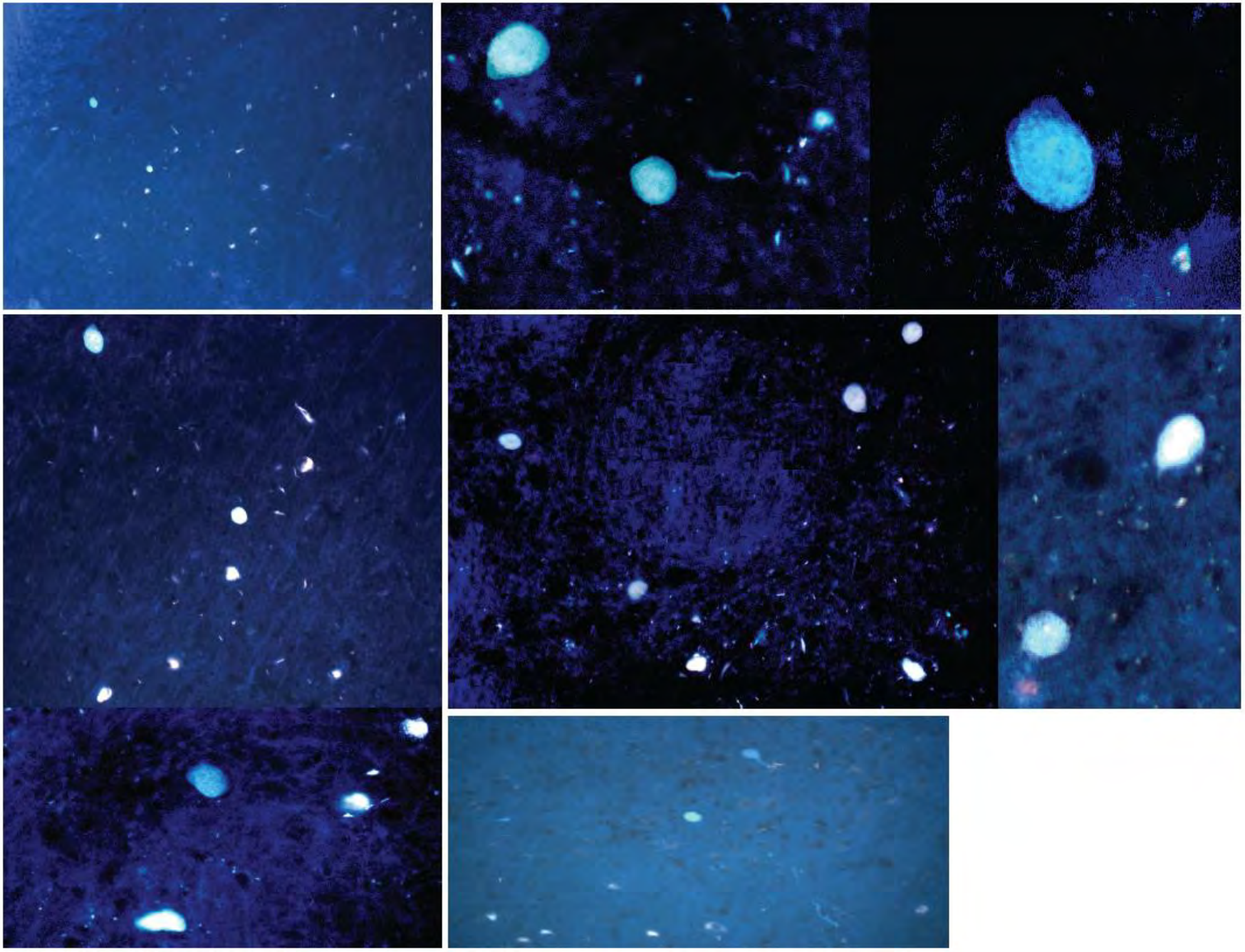
DAT Optical Density: Control vs Fibril




Striatum




Control side
PFF injected side



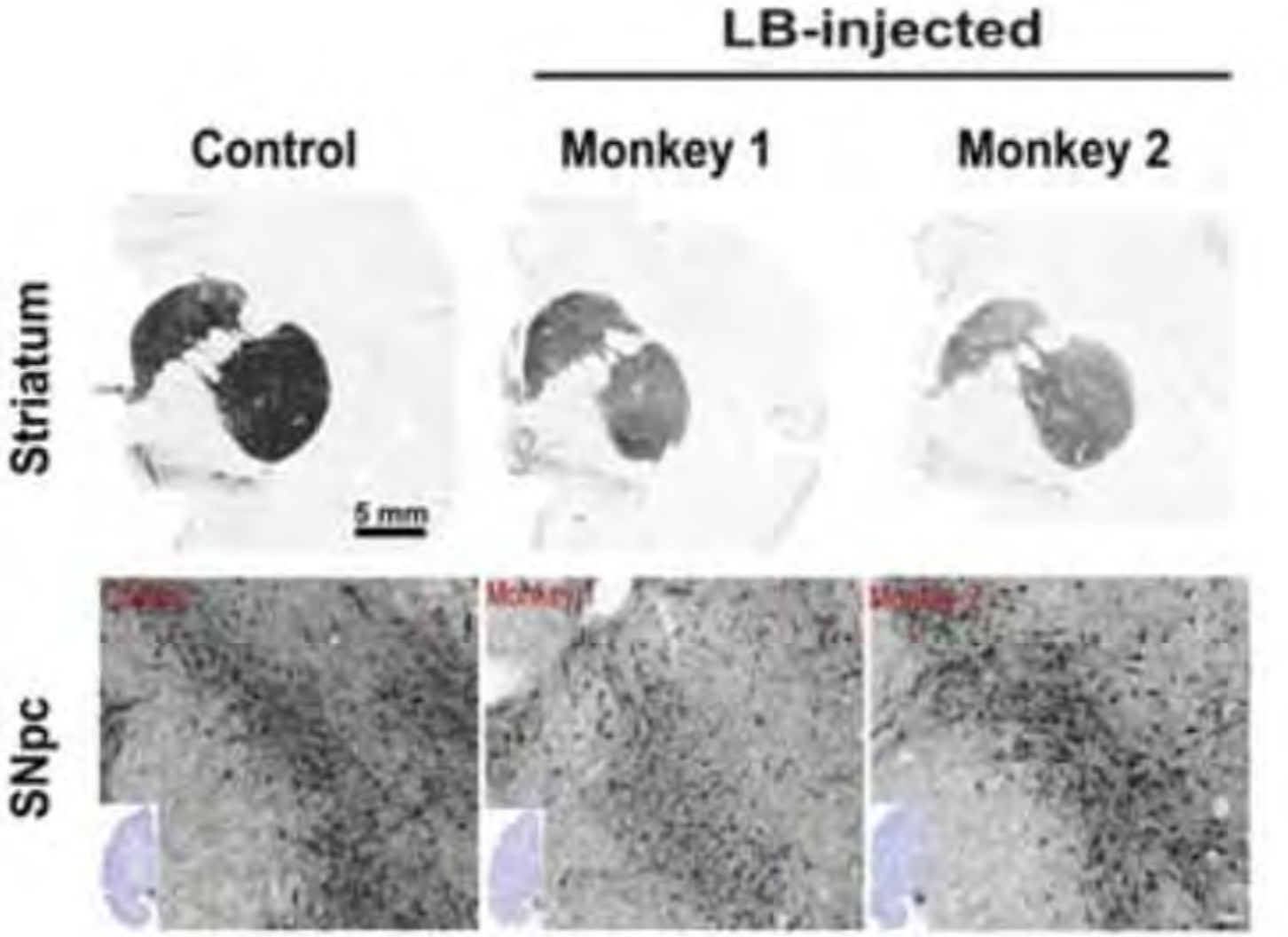
ANNALS *of Neurology*

RESEARCH ARTICLE

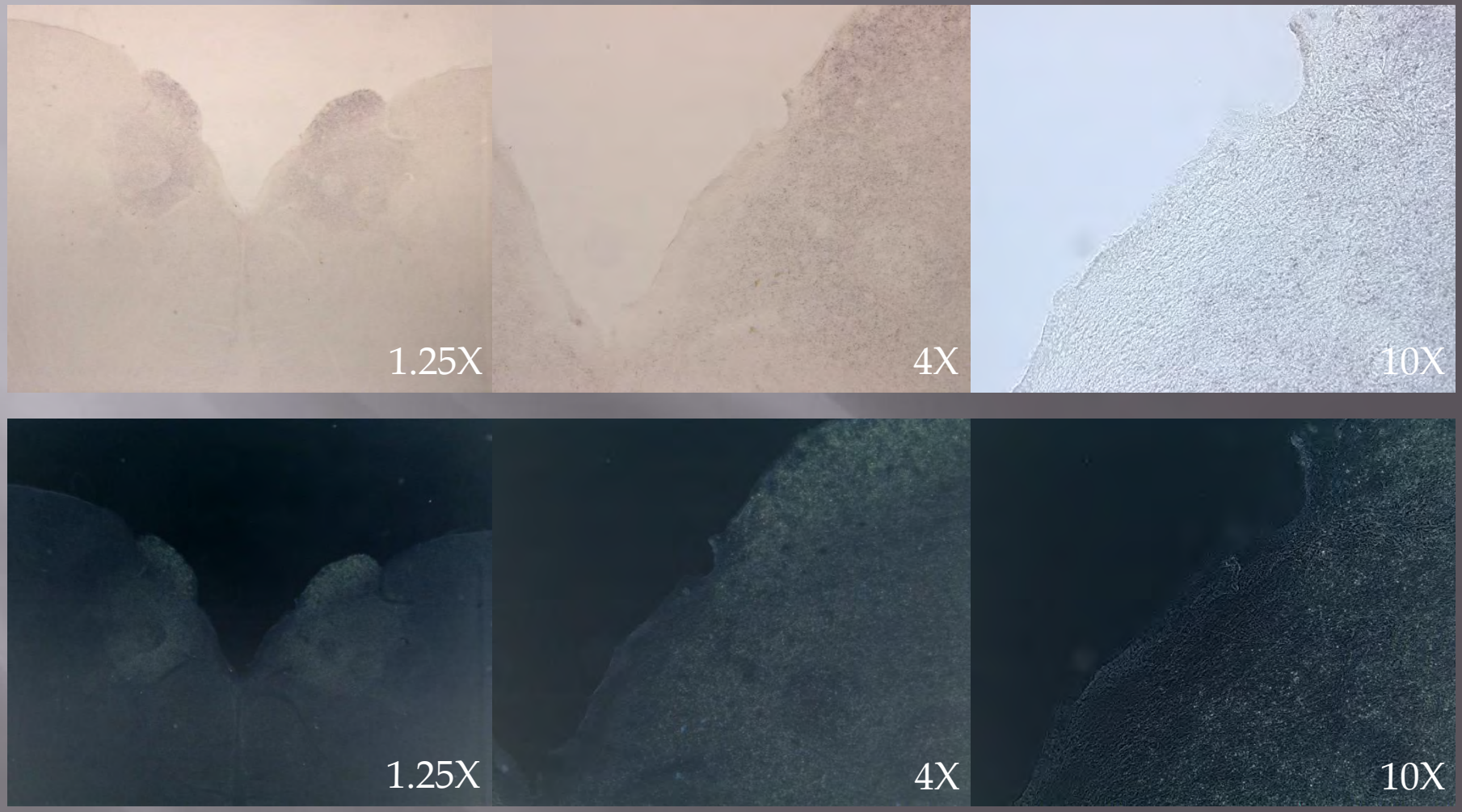
Lewy Body Extracts from Parkinson Disease Brains Trigger α-Synuclein Pathology and Neurodegeneration in Mice and Monkeys

Ariadna Recasens, PhD,[1] Benjamin Dehay, PhD,[2,3] Jordi Bové, PhD,[1] Iria Carballo-Carbajal, PhD,[1] Sandra Dovero,[2,3] Ana Pérez-Villalba, PhD,[4] Pierre-Olivier Fernagut, PhD,[2,3] Javier Blesa, PhD,[5] Annabelle Parent,[1] Celine Perier, PhD,[1] Isabel Fariñas, PhD,[4] José A. Obeso, MD, PhD,[5] Erwan Bezard, PhD,[2,3] and Miquel Vila, MD, PhD[1,6,7]

Lewy body extracts into monkeys (Recasens at al., Annals of Neurology, 2013)



LB509 1:500



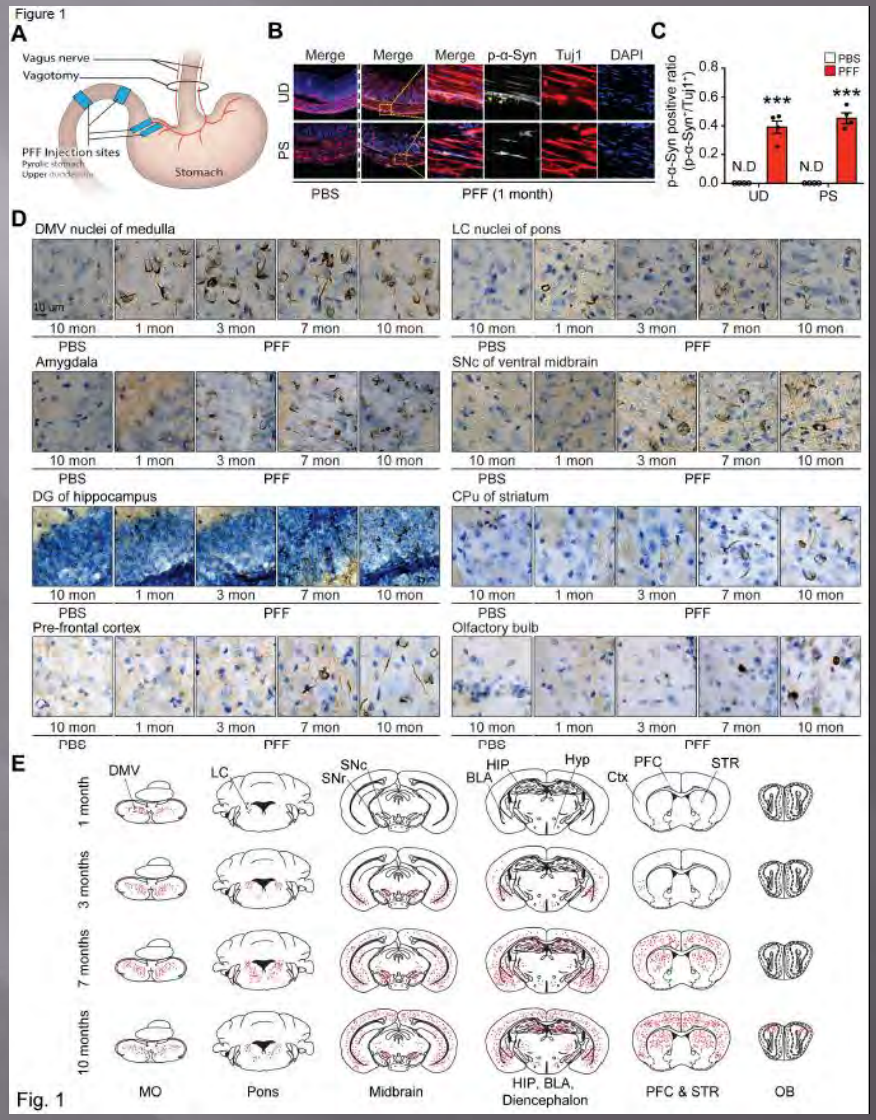


Figure 1
A
Vagus nerve
Vagotomy
PFF Injection sites
Stomach
B
Merge
Merge
Merge
p-α-Syn
Tuj1
DAPI
UD
PS
PBS
PFF (1 month)
C
PBS
PFF
p-α-Syn positive ratio (p-α-Syn+/Tuj1+)
0.8
0.6
0.4
0.2
0.0
***
***
N.D
N.D
UD
PS
D
DMV nuclei of medulla
10 um
LC nuclei of pons
Amygdala
SNc of ventral midbrain
DG of hippocampus
CPu of striatum
Pre-frontal cortex
Olfactory bulb
10 mon
1 mon
3 mon
7 mon
10 mon
PBS
PFF
E
DMV
LC
SNc
SNr
HIP
BLA
Hyp
PFC
Ctx
STR
1 month
3 months
7 months
10 months
MO
Pons
Midbrain
HIP, BLA, Diencephalon
PFC & STR
OB

Fig. 1

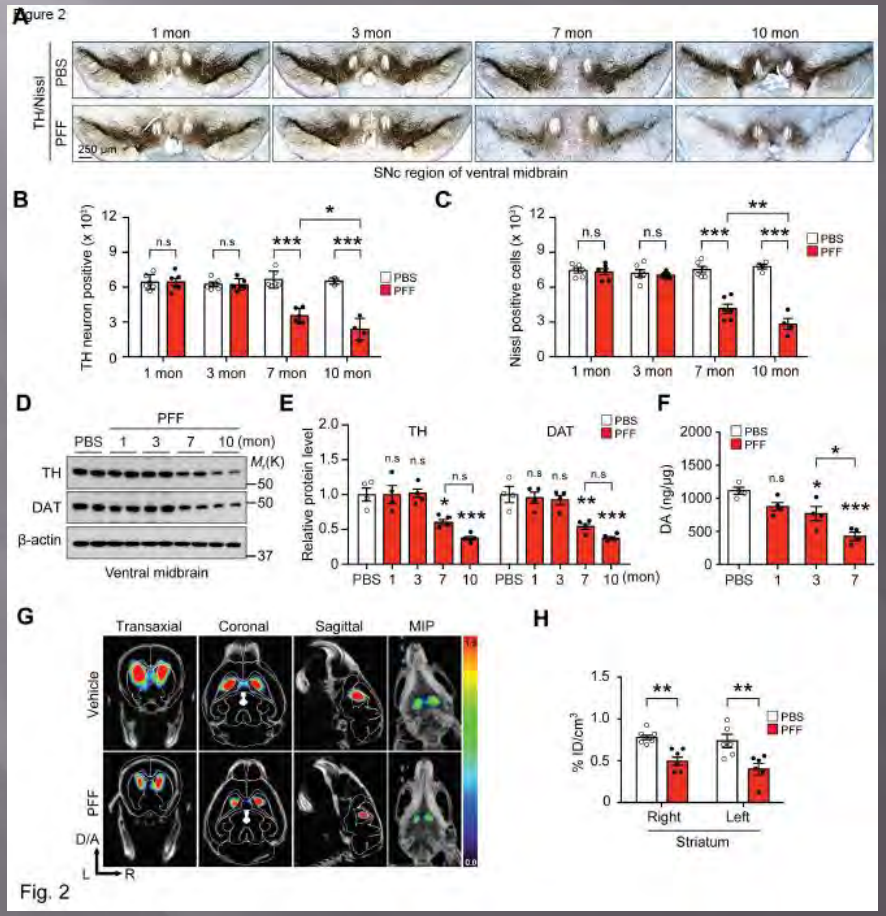


Figure 2
A
1 mon
3 mon
7 mon
10 mon
TH/Nissl
PBS
PFF
250 μm
SNc region of ventral midbrain
B
TH neuron positive (x 10³)
n.s
***
*
1 mon
3 mon
7 mon
10 mon
PBS
PFF
C
Nissl positive cells (x 10³)
**
D
PFF
PBS
1
3
7
10 (mon)
Mr(K)
TH
DAT
β-actin
50
50
37
Ventral midbrain
E
TH
DAT
Relative protein level
F
DA (ng/μg)
G
Transaxial
Coronal
Sagittal
MIP
Vehicle
PFF
D/A
L
R
H
% ID/cm³
Right
Left
Striatum

Fig. 2

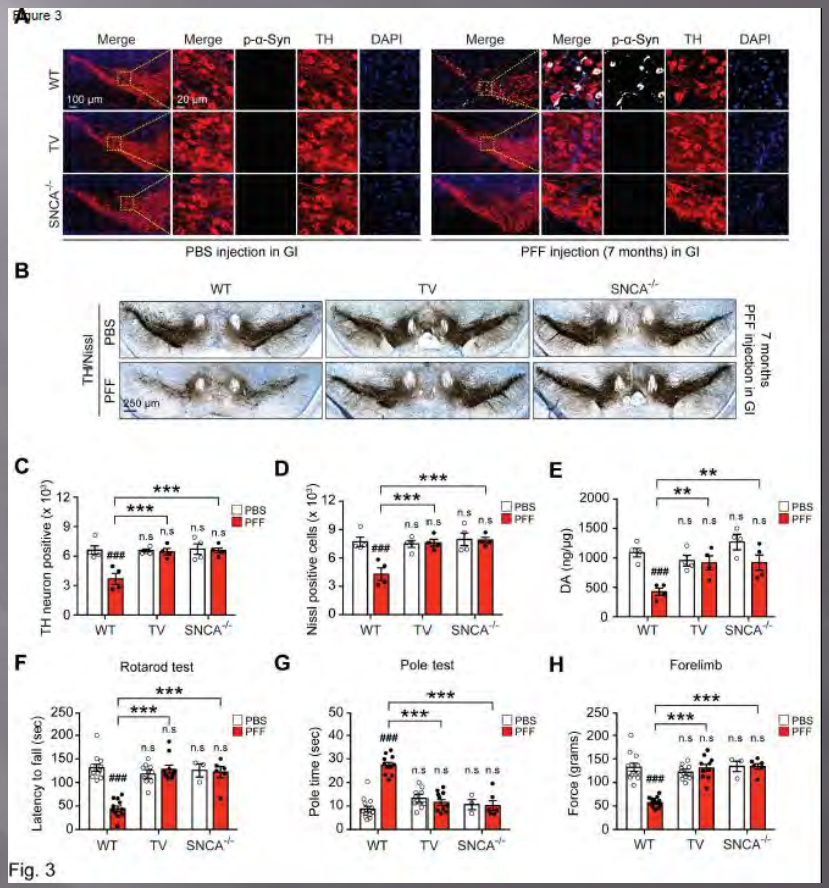


Figure 3
A
Merge
Merge
p-α-Syn
TH
DAPI
WT
TV
SNCA-/-
100 μm
20 μm
PBS injection in GI
PFF injection (7 months) in GI
B
WT
TV
SNCA-/-
TH/Nissl
PBS
PFF
250 μm
7 months
PFF injection in GI
C
TH neuron positive (x 10³)
D
Nissl positive cells (x 10³)
E
DA (ng/μg)
PBS
PFF
WT
TV
SNCA-/-
F
Rotarod test
Latency to fall (sec)
G
Pole test
Pole time (sec)
H
Forelimb
Force (grams)
n.s
###
***
**

Fig. 3

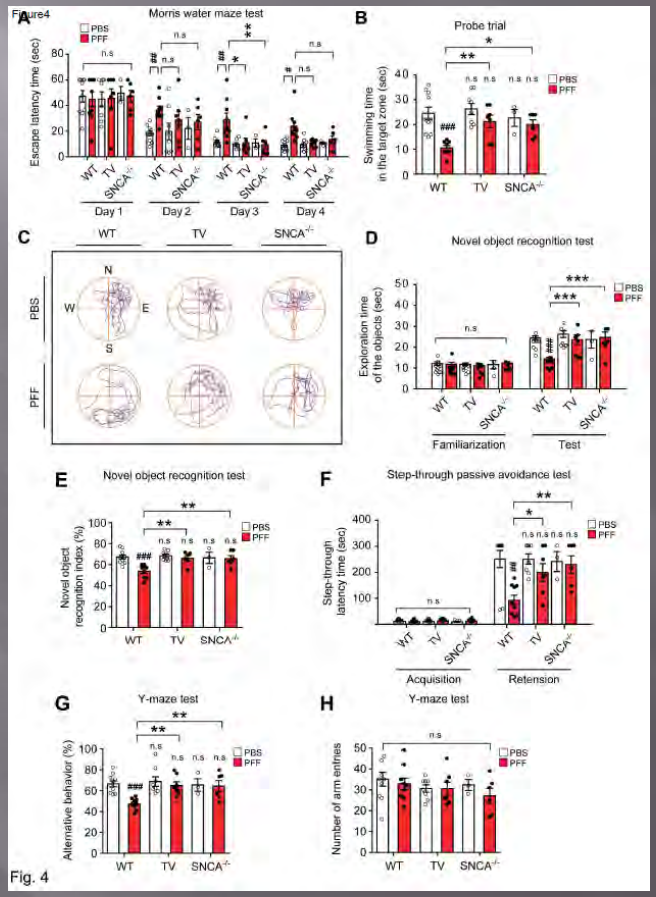


Figure4
A
Morris water maze test
PBS
PFF
Escape latency time (sec)
WT
TV
SNCA-/-
Day 1
Day 2
Day 3
Day 4
B
Probe trial
Swimming time in the target zone (sec)
C
N
W
E
S
PBS
PFF
D
Novel object recognition test
Exploration time of the objects (sec)
Familiarization
Test
E
Novel object recognition test
Novel object recognition index (%)
F
Step-through passive avoidance test
Step-through latency time (sec)
Acquisition
Retension
G
Y-maze test
Alternative behavior (%)
H
Y-maze test
Number of arm entries

Fig. 4

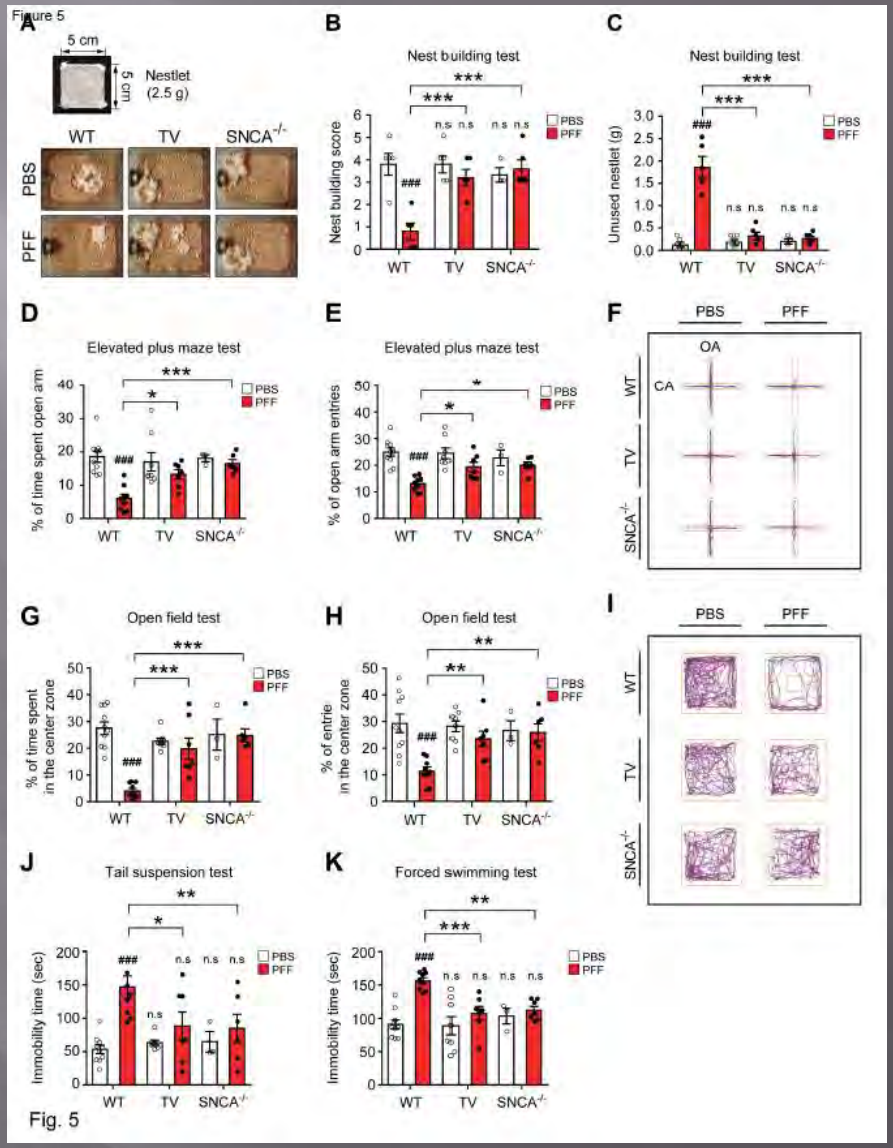


Figure 5
A
5 cm
5 cm
Nestlet
(2.5 g)
WT
TV
SNCA-/-
PBS
PFF
B
Nest building test
Nest building score
PBS
PFF
WT
TV
SNCA-/-
C
Nest building test
Unused nestlet (g)
D
Elevated plus maze test
% of time spent open arm
E
Elevated plus maze test
% of open arm entries
F
PBS
PFF
OA
CA
G
Open field test
% of time spent in the center zone
H
Open field test
% of entrie in the center zone
I
J
Tail suspension test
Immobility time (sec)
K
Forced swimming test
Immobility time (sec)

Fig. 5

Evidence for α-synuclein prions causing multiple system atrophy in humans with parkinsonism

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Contributed by Stanley B. Prusiner, July 22, 2015 (sent for review May 19, 2015)

Prions are proteins that adopt alternative conformations that become self-propagating; the PrP^{Sc} prion causes the rare human disorder Creutzfeldt–Jakob disease (CJD). We report here that multiple system atrophy (MSA) is caused by a different human prion composed of the α-synuclein protein. MSA is a slowly evolving disorder characterized by progressive loss of autonomic nervous system function and often signs of parkinsonism; the neuropathological hallmark of MSA is glial cytoplasmic inclusions consisting of filaments of α-synuclein. To determine whether human α-synuclein forms prions, we examined 14 human brain homogenates for transmission to cultured human embryonic kidney (HEK) cells expressing full-length, mutant human α-synuclein fused to yellow fluorescent protein (α-syn140*A53T–YFP) and $TgM83^{+/-}$ mice expressing α-synuclein (A53T). The $TgM83^{+/-}$ mice that were hemizygous for the mutant transgene did not develop spontaneous illness; in contrast, the $TgM83^{+/+}$ mice that were homozygous developed neurological dysfunction. Brain extracts from 14 MSA cases all transmitted neurodegeneration to $TgM83^{+/-}$ mice after incubation periods of ~120 d, which was accompanied by deposition of α-synuclein within neuronal cell bodies and axons. All of the MSA extracts also induced aggregation of α-syn*A53T–YFP in cultured cells, whereas none of six Parkinson's disease (PD) extracts or a control sample did so. Our findings argue that MSA is caused by a unique strain of α-synuclein prions, which is different from the putative prions causing PD and from those causing spontaneous neurodegeneration in $TgM83^{+/+}$ mice. Remarkably, α-synuclein is the first new human prion to be identified, to our knowledge, since the discovery a half century ago that CJD was transmissible.

Table 1. Demographic, clinical, and neuropathological characteristics of patient samples

Case	Country	Sex	Age at onset (y)	Duration (y)	Cause of death	Clinical diagnosis	Neuropathological diagnosis
C1	USA	M	77	NA	Cardiovascular disease	Nondiseased control brain	NA
PD1	UK	M	65	8.5		Tremulous hemiparkinsonism, REM sleep disorder, MSA questioned	Lewy body disease
PD2	UK	M	65	8	Myocardial infarction, acute renal failure, pneumonia	Hemiparkinsonism with autonomic features	Lewy body disease
PD3*	UK	M	66	9.5		Parkinsonism with drooling	Lewy body disease
PD5	Australia	M	63	9	Myocardial infarction	Parkinson's disease	Parkinson's disease
PD6	Australia	M	73	6	Myocardial infarction	Parkinson's disease	Diffuse Lewy bodies
PD7	Australia	M	74	8	Cerebrovascular accident	Parkinson's disease	Diffuse Lewy bodies
MSA1	UK	M	78	8		Atypical akinetic-rigid syndrome with prominent ataxia, PSP questioned	MSA
MSA2	UK	M	65	5.5		Akinetic-rigid syndrome with autonomic involvement	MSA
MSA3	UK	F	52	6	Bronchopneumonia	MSA-P	MSA
MSA4	UK	M	68	7	Pneumonia	MSA	MSA
MSA5	UK	M	52	8	Respiratory failure, pneumonia	Parkinsonism, MSA questioned	MSA
MSA6	UK	F	48	13	Pneumonia	Akinetic-rigid syndrome with antecolls and camptocormia: MSA vs. PD	MSA
MSA7	UK	M	52	12	Bronchopneumonia	MSA-C	MSA
MSA8	Australia	M	57	4	Aspiration pneumonia	MSA-P	MSA
MSA9	Australia	M	75	7	Cardiorespiratory failure	MSA-C	MSA
MSA10	Australia	M	56	8	Bronchopneumonia	MSA-P with early autonomic dysfunction	MSA
MSA11	Australia	M	59	2	Respiratory failure	MSA-P with early autonomic dysfunction	MSA
MSA12	USA	F	55	11	Acute bronchopneumonia	MSA	MSA
MSA13	USA	M	55	10	Chronic pneumonia	MSA	MSA
MSA14	USA	M	60	8		MSA-C	MSA

NA, not applicable.
*Clinical report for PD3 was incomplete.

Table 3. Effect of transgene and serial transmission on incubation period

Inoculum (brain region)	Mouse line	Primary transmission		Incubation time of mouse brain inoculated (d)	Secondary transmission in M83$^{+/-}$	
		Mean incubation time ± SEM (d)	n/n_0		Mean incubation time ± SEM (d)	n/n_0
No inoculum	TgM83$^{+/-}$	>412	0/6	259	>360	0/6
	Tg(*SNCA*) *Snca*$^{0/0}$	>580	0/9		ND	
	TgM83$^{+/-}$	143 ± 17*	7/8	105	113 ± 13†	5/5
MSA1 (basal ganglia)	WT	>360	0/7		ND	
	Tg(*SNCA*) *Snca*$^{0/0}$	>360	0/6		ND	
	TgM83$^{+/-}$	109 ± 12*	7/7	91	92 ± 5†	6/6
MSA2 (basal ganglia)	WT	>360	0/2		ND	
	Tg(*SNCA*) *Snca*$^{0/0}$	>360	0/5		ND	
9 m.o. spont. TgM83$^{+/+}$ (whole brain)	TgM83$^{+/-}$	222 ± 15*	6/6	205	193 ± 19	8/8
11 m.o. spont. TgM83$^{+/+}$ (whole brain)	TgM83$^{+/-}$	216 ± 18*	8/8	162	175 ± 8	8/8

n, number of ill mice; n_0, number of inoculated mice; ND, not determined.
*Data previously reported in ref. 13.
†Data previously reported in ref. 14.

Conclusions

- Multiple groups using multiple techniques can demonstrate transport (not necessarily transfer) of alpha syn across the neuraxis.
- Transmission, templating and transfer can readily occur in alpha synuclein over-expressors. Less so in wild type animals
- Olfactory bulb injections in wild-type works better than striatal injections
- This spread can be blocked with antibodies
- Transmission from the periphery to the brain has now been demonstrated

Collaborators

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  - Ben hiller
  - Rachel Harker
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  - Virginia Lee
  - John Q. Trojanowski
  - Kelvin Luk
- Institute for Neurodegenerative Disease
  - Ken Marek
  - John Seibyl
  - Gilles Tamagnan