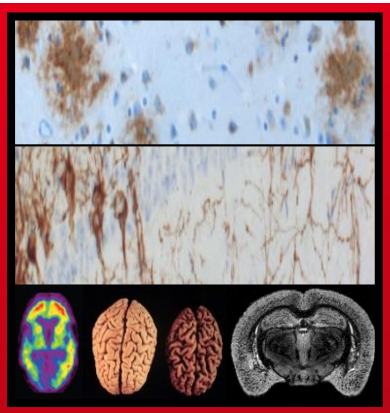
Iatrogenic transmission of β-amyloid and tau proteins
Importance for clinical and biomedical research on Alzheimer's disease



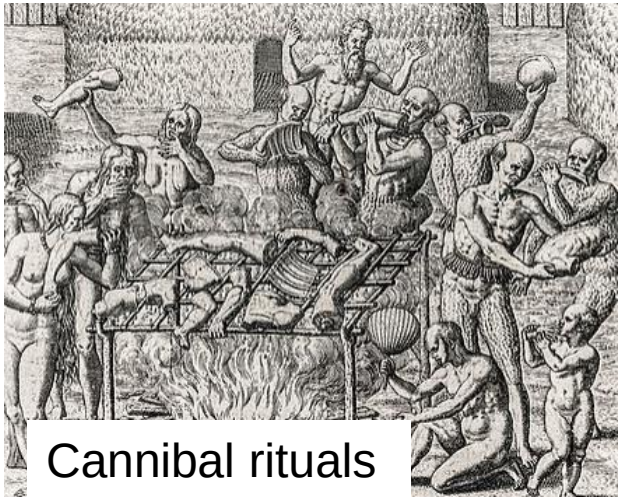
Marc Dhenain

Multimodal Imaging of
Neurodegenerative Diseases
and Therapies

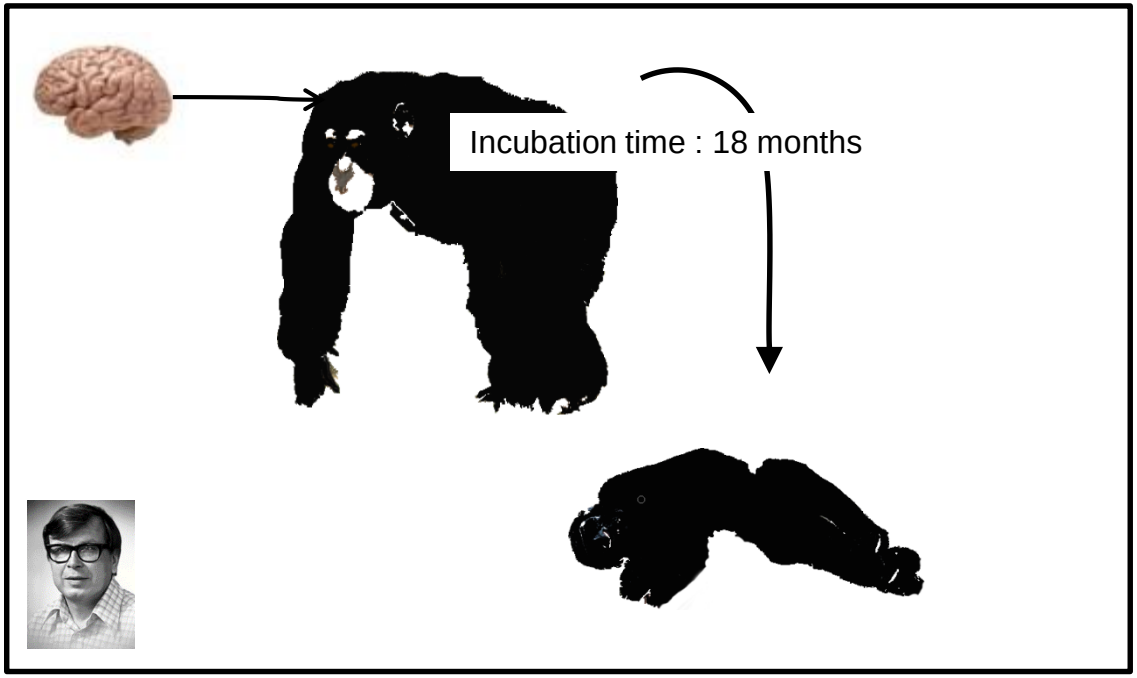
MIRCen, CEA-CNRS UMR 9199
Fontenay-aux-Roses

TRANSMISSIBILITY OF PRION DISEASES
Exemple of the kuru - Oral transmission

New guinea



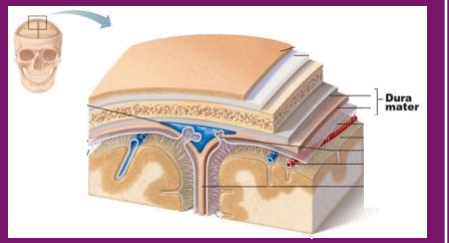
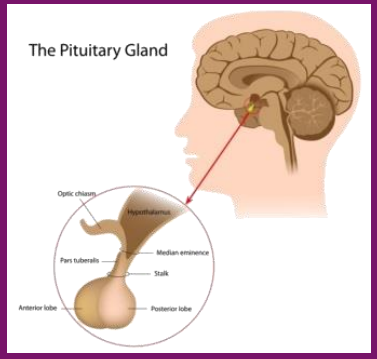
Cannibal rituals



Gajdusek Nature 1966 ; Science 1967 ; Nobel Prize 1976

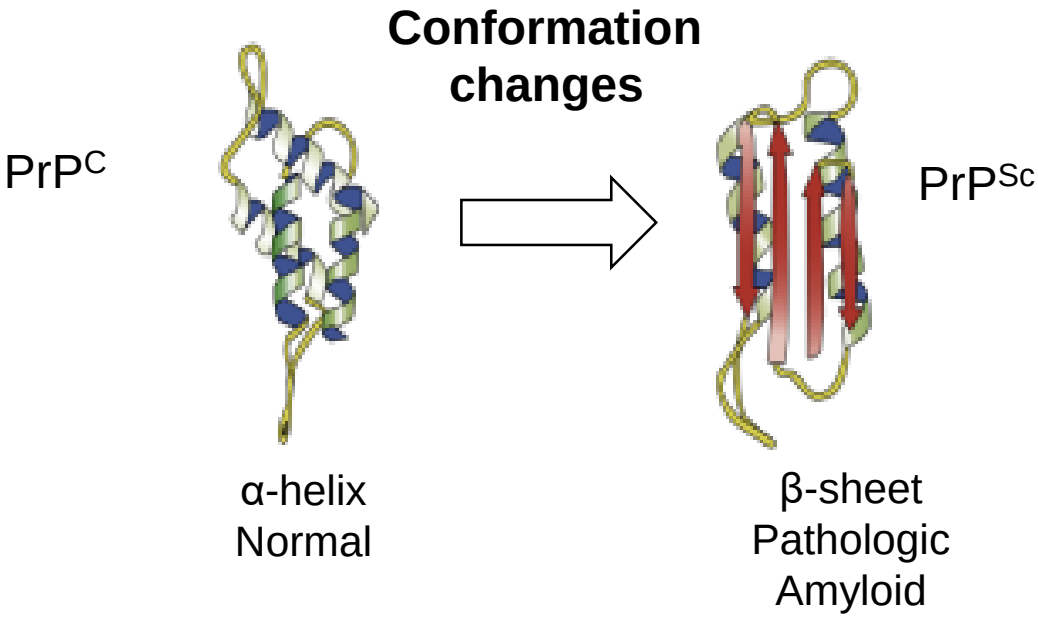
IATROGEN TRANSMISSION OF CREUTZFELDT-JAKOB DISEASES
470 cases reported following medico-surgical acts

Three main causes of contamination

	Surgical procedures		Medical procedures
	Dura matter grafts	Other Surgeries	Growth hormons
			
Total	228	4	226
Incubation (years)	1.3-30	1-2.3	5-42

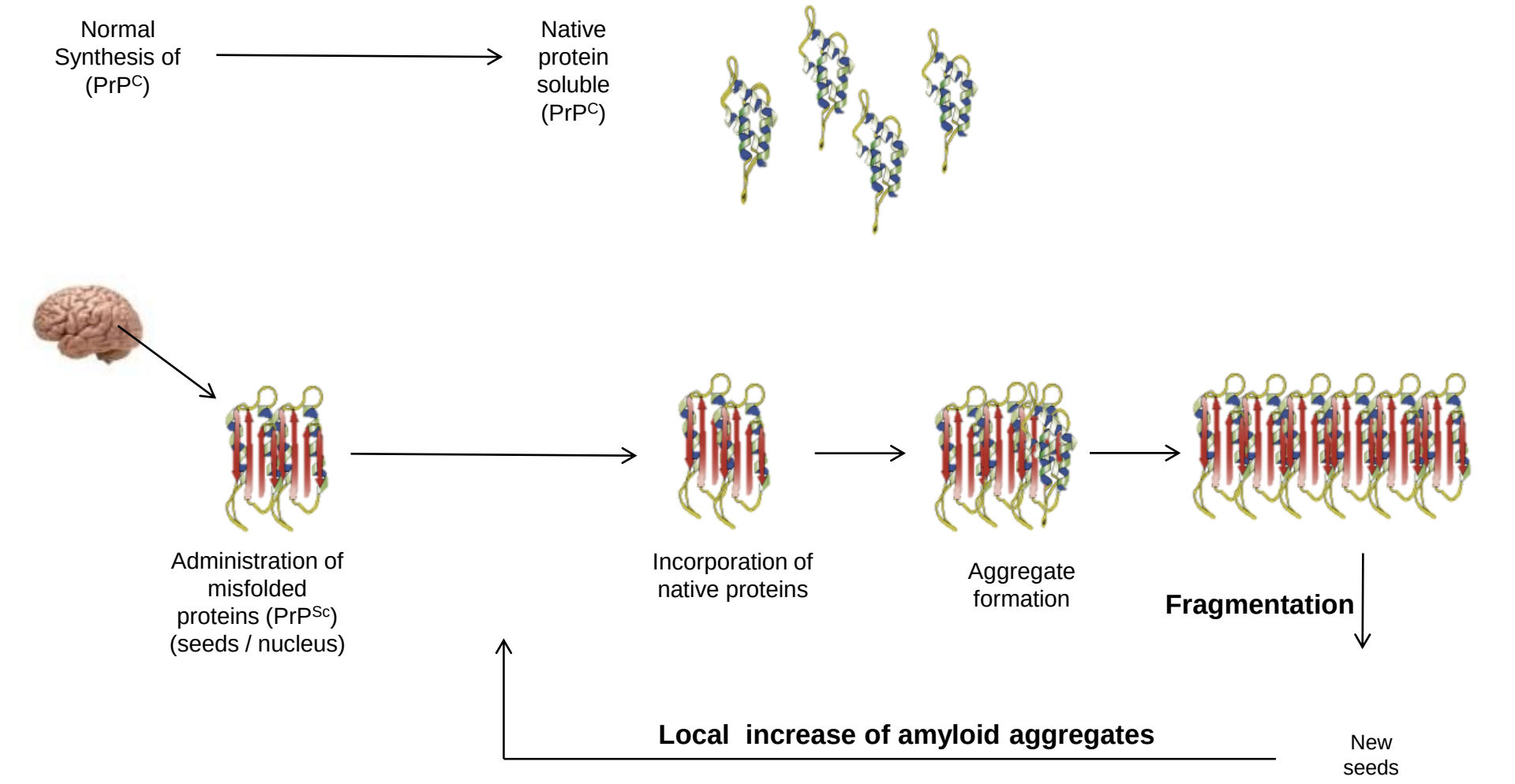
CONFORMATION CHANGES REQUIRED FOR TOXICITY OF PRIONS

Aguzzi

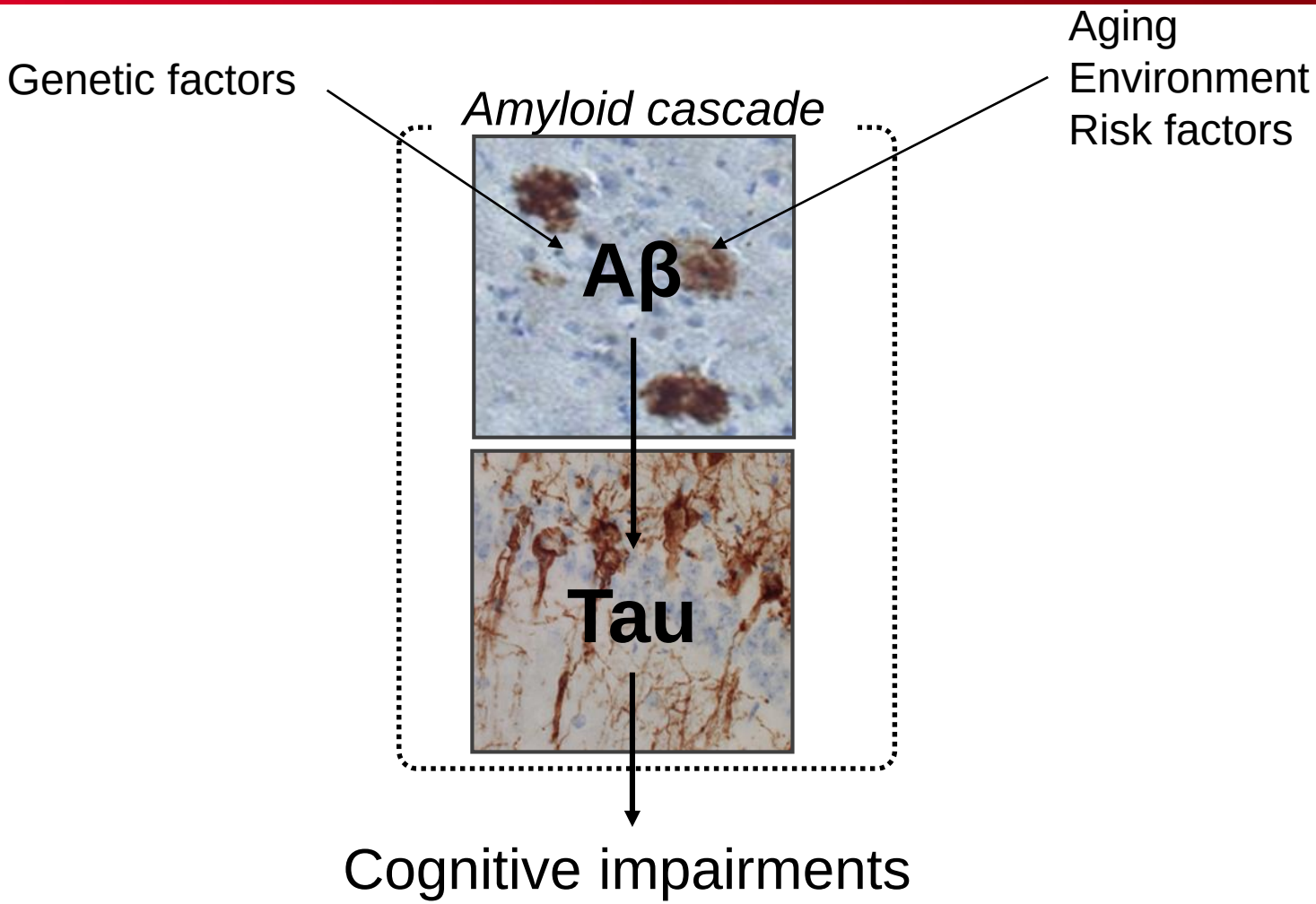


Bueler H, Aguzzi A, et al.. Cell 1993

MODEL FOR PROTEIN TRANSMISSION IN PRION DISEASES



ALZHEIMER'S DISEASE
Amyloid cascade hypothesis



Aβ and tau are misfolded proteins

→ Are Aβ and tau lesions transmissible ?

→ If so what can we learn on the disease after transmission ?

OBSERVATIONAL STUDIES IN HUMANS
Suspicion of Aβ transmission

(18 articles - 80 cases)

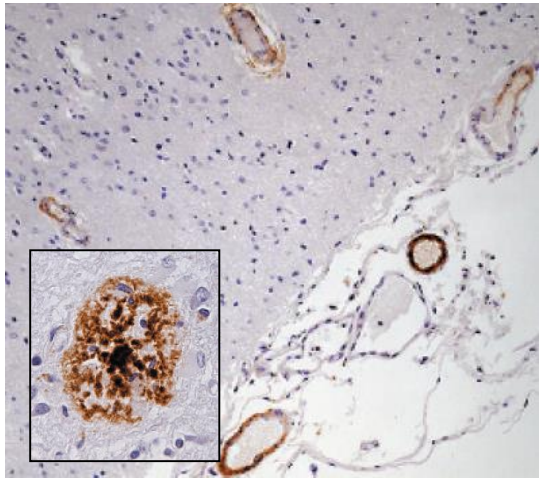
	Dura-matter grafts	Other surgeries	Growth hormons
Amyloid-β	37	12	31
80 cases	Preusser, 2006 (1) Frontzek, 2016 (5) Kovacs, 2016 (2) Hamaguchi, 2016 (11) Iwasaki (1) Herve, 2018 (1) Cali, 2018 (8) Banerjee, 2019 (3) Raposo, 2020 (1) Caropo, 2020 (1) Yoshiki, 2021 (1) Jaunmuktane, 2021 (2)	Jaunmuktane, 2018 (8) Hamaguchi, 2019 (2) Giaccone, 2019 (1) Jaunmuktane, 2021 (1)	Jaunmuktane, 2015 (4) Duyckaerts, 2018 (1) Ritchie, 2017 (23) Cali, 2018 (3)
21 Severe cases	Haemorrhages 9 cases	Haemorrhages 12 cases	

Very long delays between transmissions and pathology

Dhenain M. Bulletin de l'Academie nationale de medecine. 2021 Aug;205(7):792-9.

OBSERVATIONAL STUDIES IN HUMANS
Suspicion of Aβ transmission after dura matter graft (37 cases)

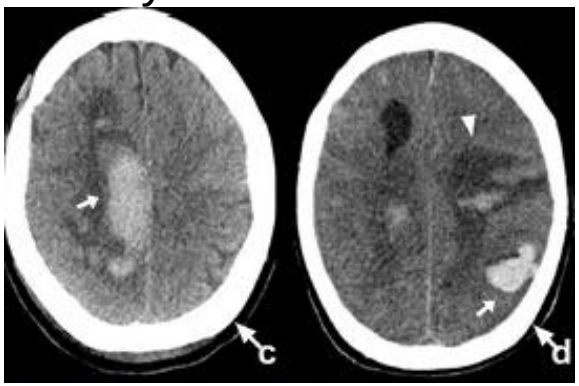
- 2006: Preusser. Journal of Neurology Neurosurgery and Psychiatry.

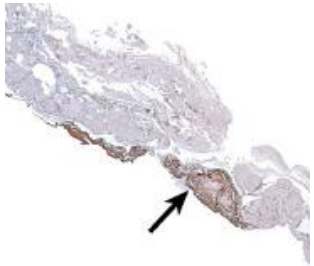


Brain trauma at 5 year → Dura matter graft
23 years after dura matter graft
→ Creutzfeldt-Jakob disease
→ Amyloid lesions (but possibly coincidental)

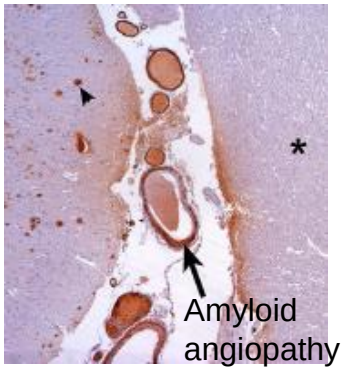
- 2018: Herve. Acta Neuropathol

Brain trauma at 2 years → Dura matter graft
44 years after dura matter graft





Amyloid-β
in dura-matter



Amyloid
angiopathy

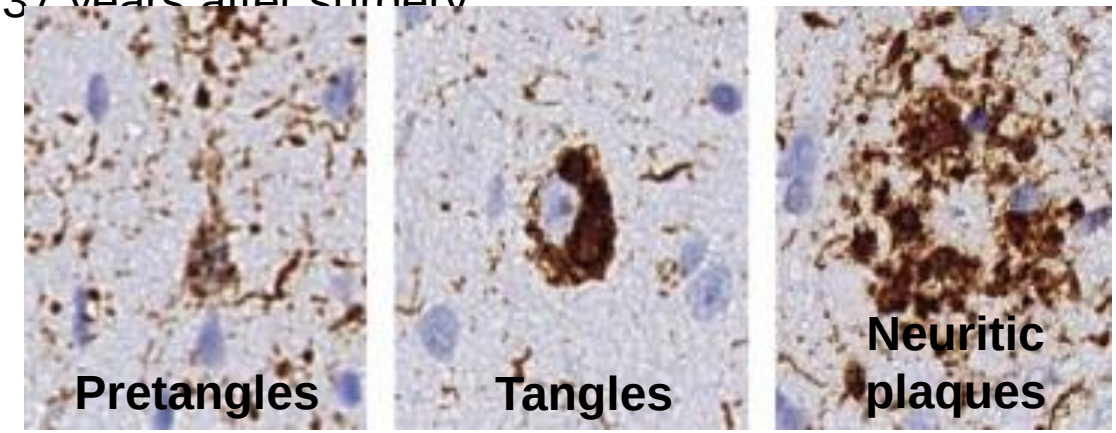
Cerebral haemorrhages, leading to clinical signs and fatalities

TRANSMISSIBILITY OF TAU IN HUMANS
(3 articles - 8 cases)

	Dure-matter graft	Other surgeries	Growth hormons
Tau	4	1	0
8 cases	Cali, 2018 (2) Jaunmuktane, 2021 (2)	Jaunmuktane, 2021 (1)	Duyckaerts, 2018 (Amyloid related – 24) Duyckaerts, 2018 (Amyloid related – 3) (but radiotherapy)

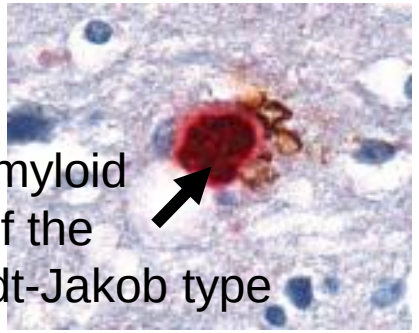
- 2021: Jaunmuktane. Acta Neuropathol.

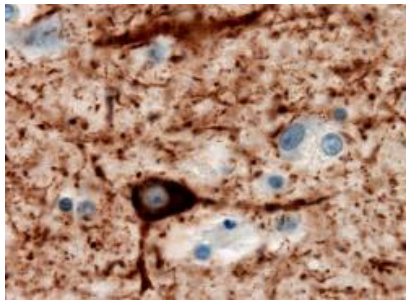
Brain surgery (medulloblastoma) at 4 years
(dura matter graft not reported)
37 years after surgery



- 2018: Duyckaerts. Acta Neuropathol.

Core of amyloid plaques of the Creutzfeldt-Jakob type





Radiotherapy related ?

QUESTIONS FOLLOWING OBSERVATIONAL DATA ON TRANSMISSIBILITY OF Aβ AND TAU IN HUMANS

- Are Aβ and tau pathologies really transmitted?
  - → Long incubation times
  - → Many confounding factors

- In the absence of severe cerebral hemorrhages
  - → Are there cognitive impairments?

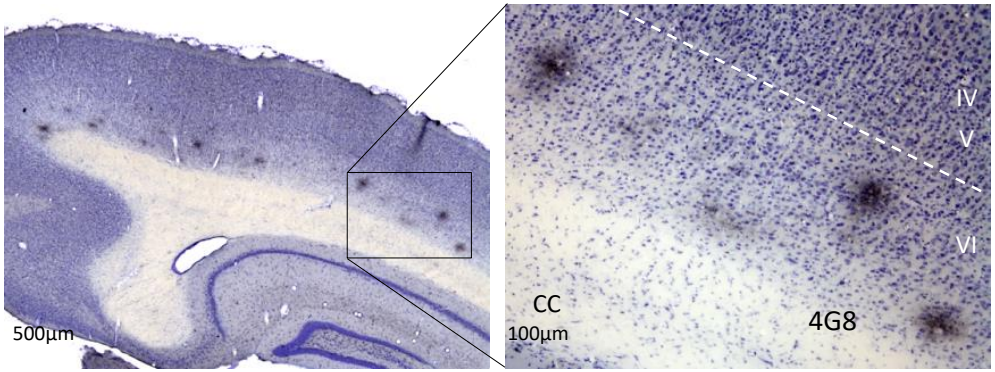
TRANSMISSION OF Aβ AND TAU PATHOLOGY IN PRIMATES ?
Evaluation in the mouse lemur primate

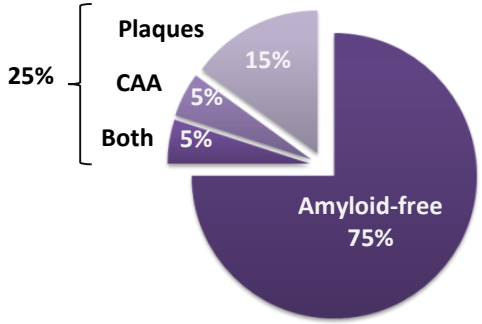
Mouse lemur

Maximal life span : 12 years, old at 5 years

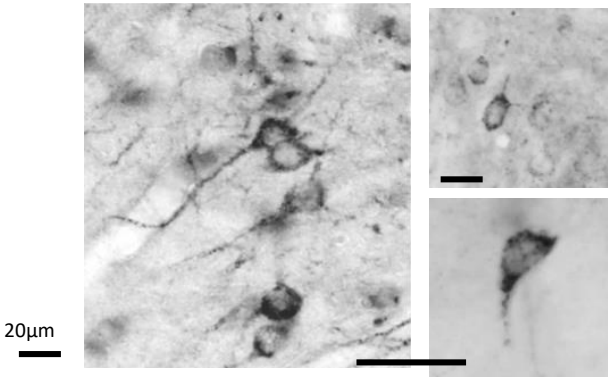
Aβ and tau occur spontaneously in **old** animals (n=20 animals aged from 6 to 11 years)

β-amyloidosis

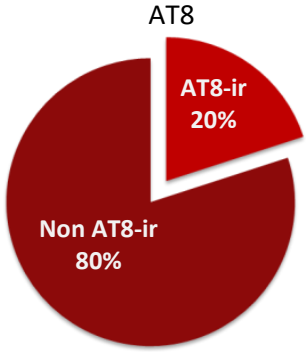




Tau pathology



AT8



See also Mestre-Frances. Neurobiol Dis. 2000; 7: 1-8.

PATHOLOGY TRANSMISSION IN PRIMATES
Experimental design: 2 studies

Human brains
Ctrl / AD

Homogenates

3.5 years
n=6/group

Parietal Ctx
+ Hippocampus
(4x6.25µl)

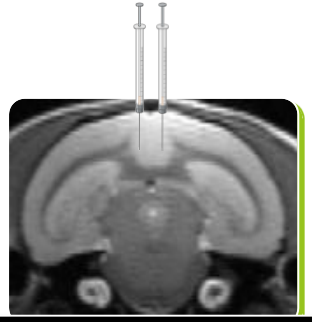
+18 months
Sacrifice

Gary C et al. Acta Neuropathologica Com 2019

Human brains
Ctrl / AD

Homogenates

1.5 years
n=6 Ctrl
N=12 AD



Posterior cingulate Ctx
+ corpus callosum
(4x6.25µl)

+21 months
Sacrifice

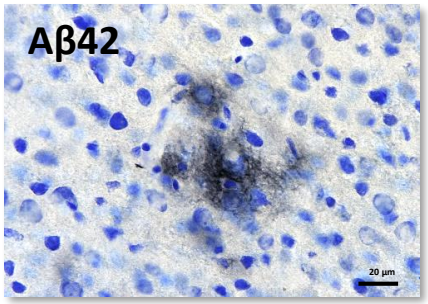
Lam S et al. Acta Neuropathologica Com 2021

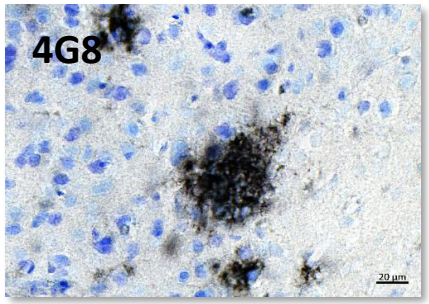
~4x1 pg $A\beta_{1\text{-}42}$
~4x0.1 µg phospho-tau181

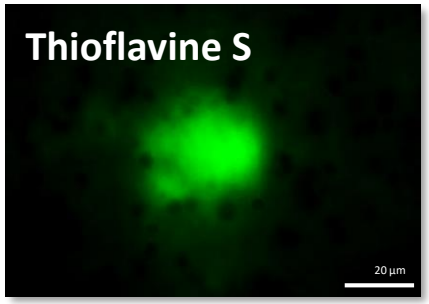
Aβ IS TRANSMIBLE IN PRIMATES

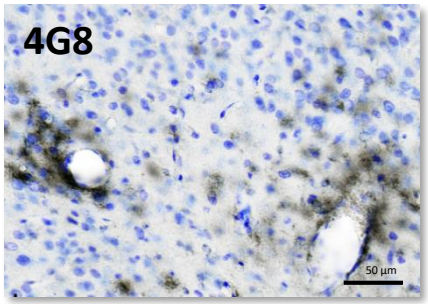
Aβ plaques

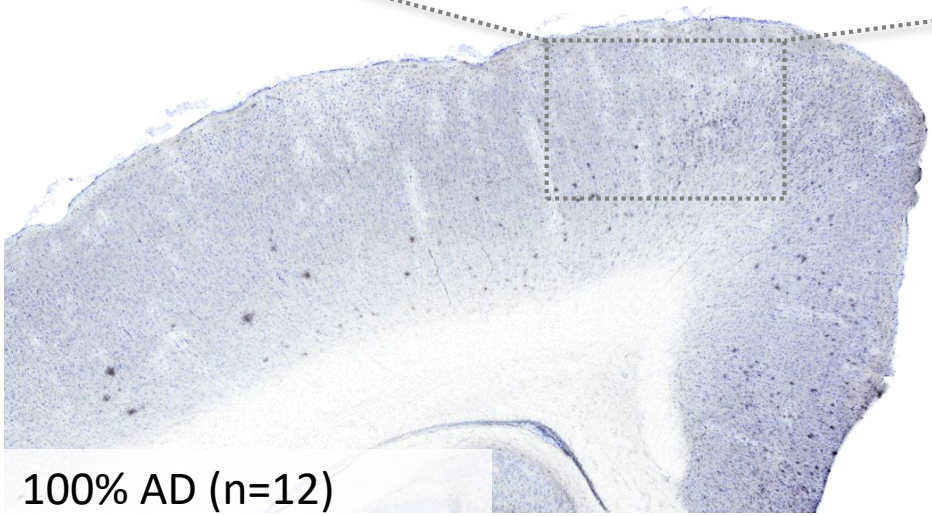
Vascular Aβ

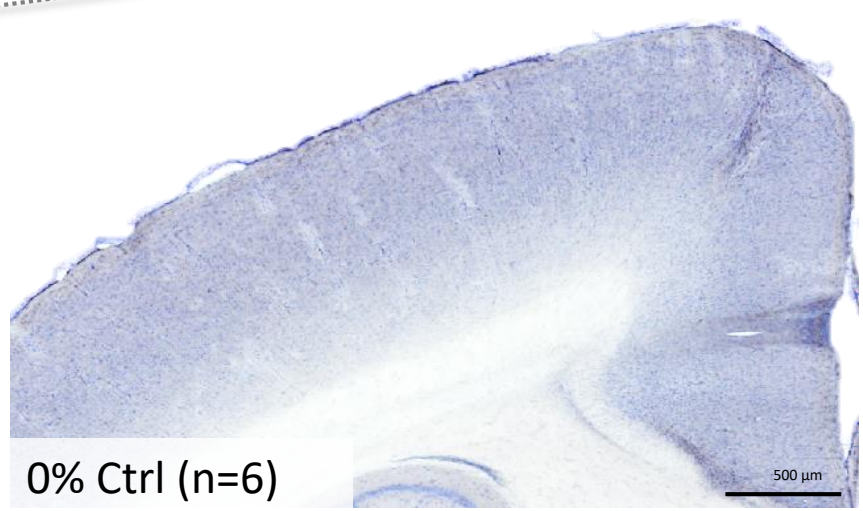








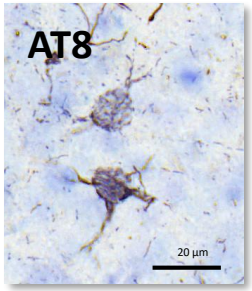


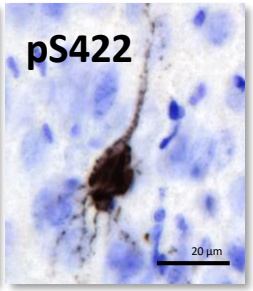


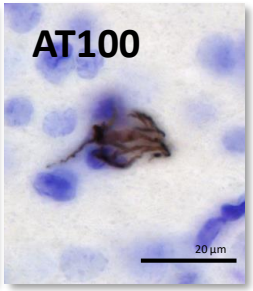
Lam S et al. Acta Neuropathologica Com 2021

TAU IS TRANSMISSIBLE IN PRIMATES

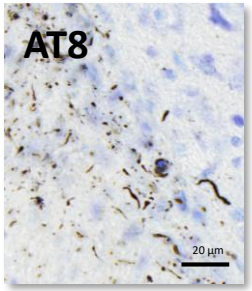
Neurofibrillary tangles

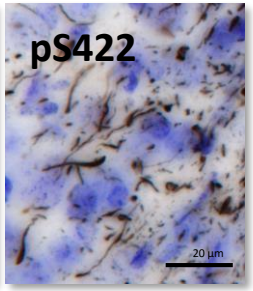


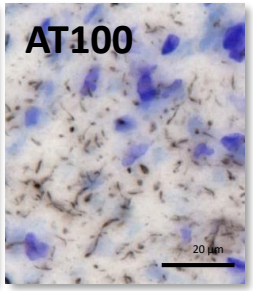


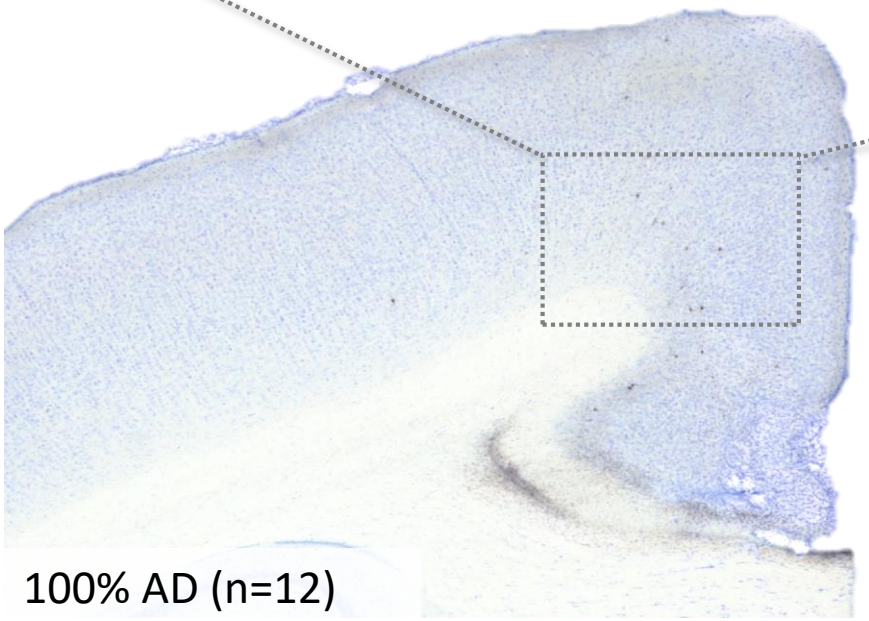


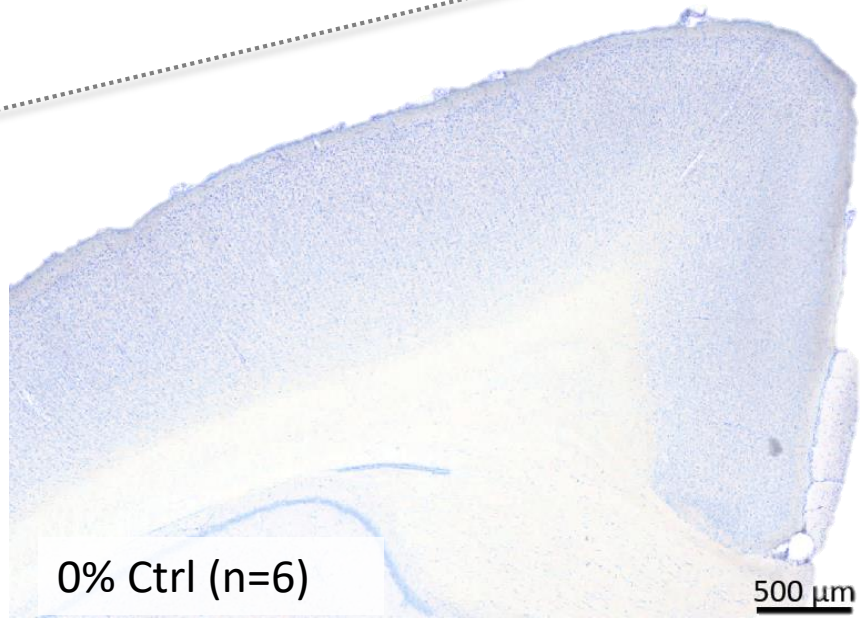
Neuropil threads







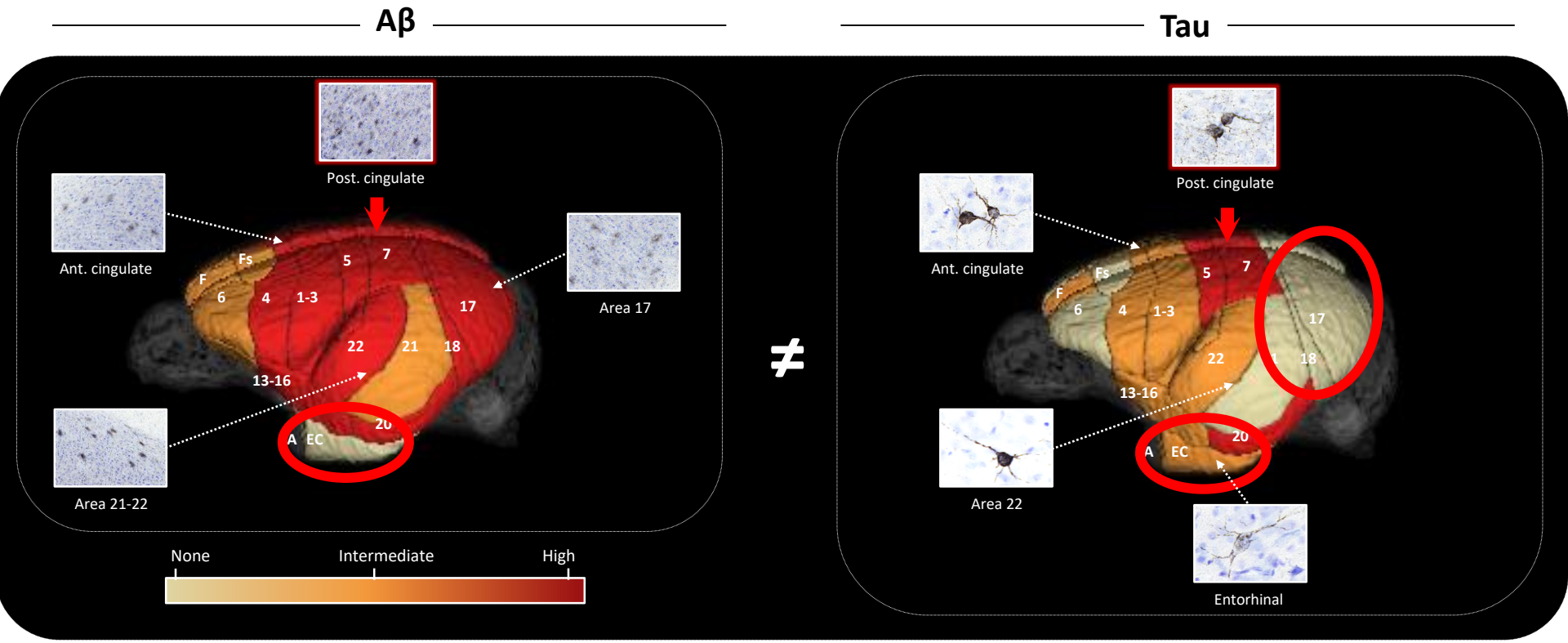




Lam S et al. Acta Neuropathologica Com 2021

Aβ AND TAU SPREAD IN THE BRAIN FROM A FOCAL POINT

Different locations of Aβ and tau pathology



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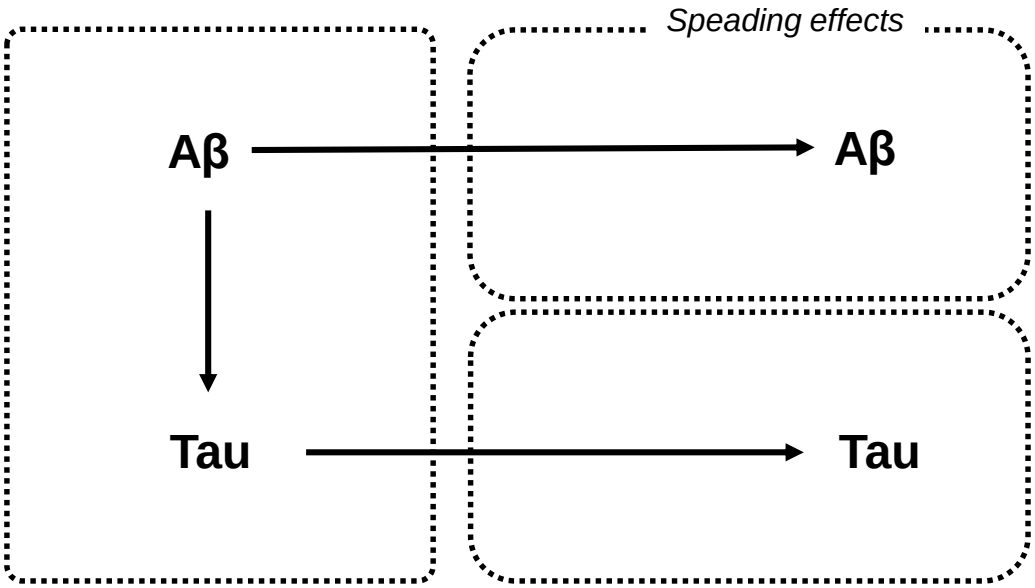
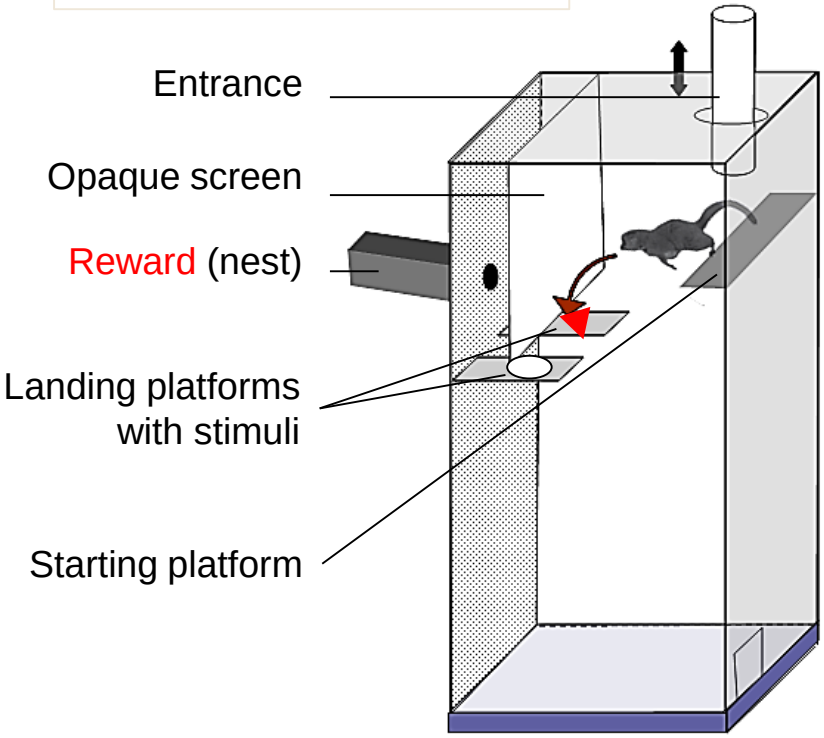
Critical roles of spreading mechanisms in AD

Region non-autonomous process

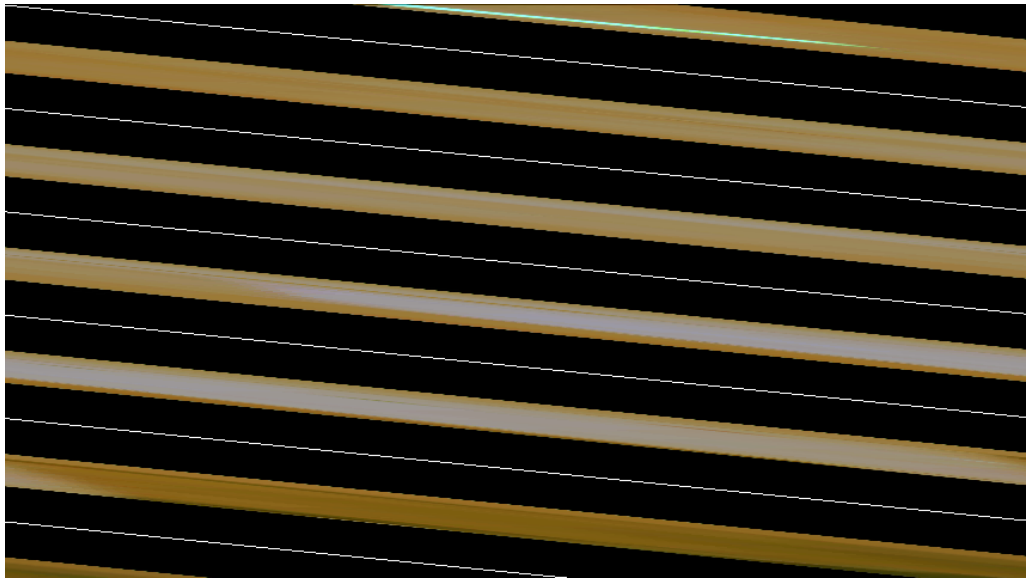


PATHOLOGY INDUCES COGNITIVE IMPAIRMENTS

Jumping stand apparatus

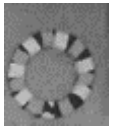


Try to think like a mouse lemur…
First trials based on
"win stay / lose shift strategy"

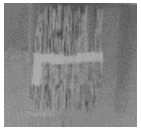


Success : 8 correct choices over 10 consecutive trials

Positive reinforcement



Negative reinforcement



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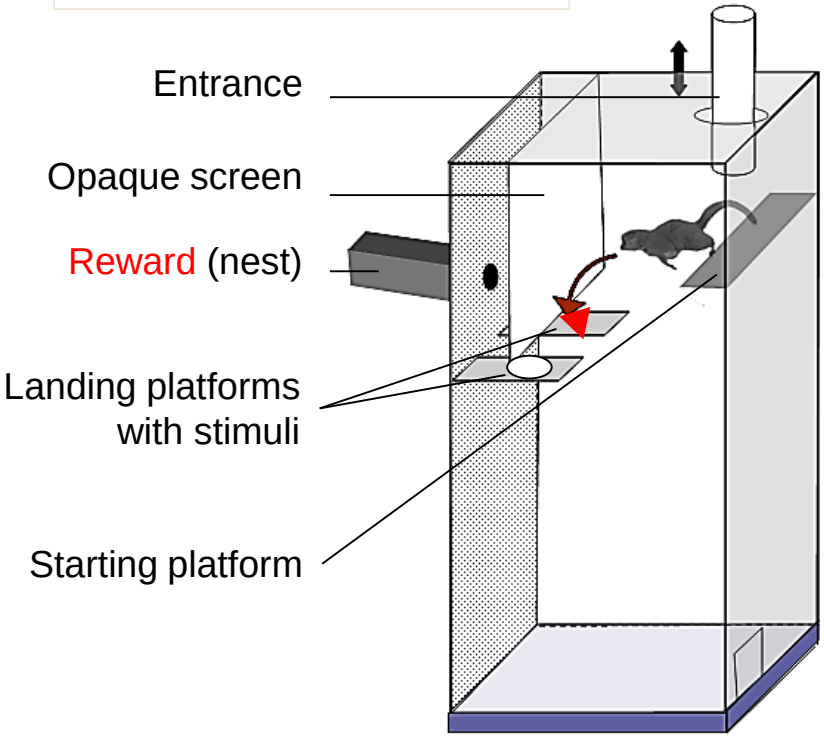
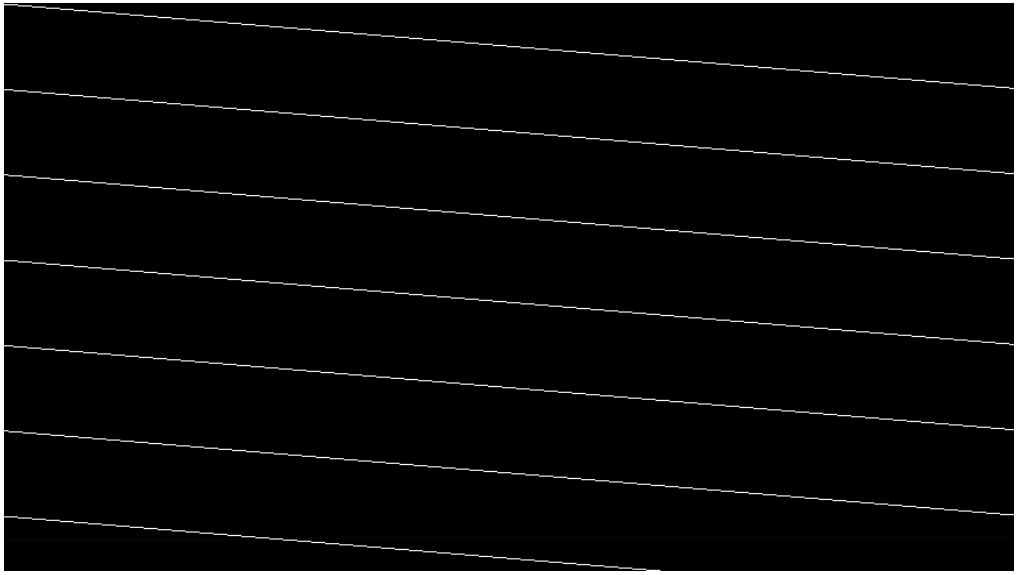
PATHOLOGY INDUCES COGNITIVE IMPAIRMENTS

Jumping stand apparatus

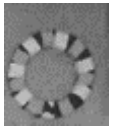


AD-inoculated mouse lemurs



Success : 8 correct choices over 10 consecutive trials

Positive reinforcement



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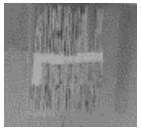

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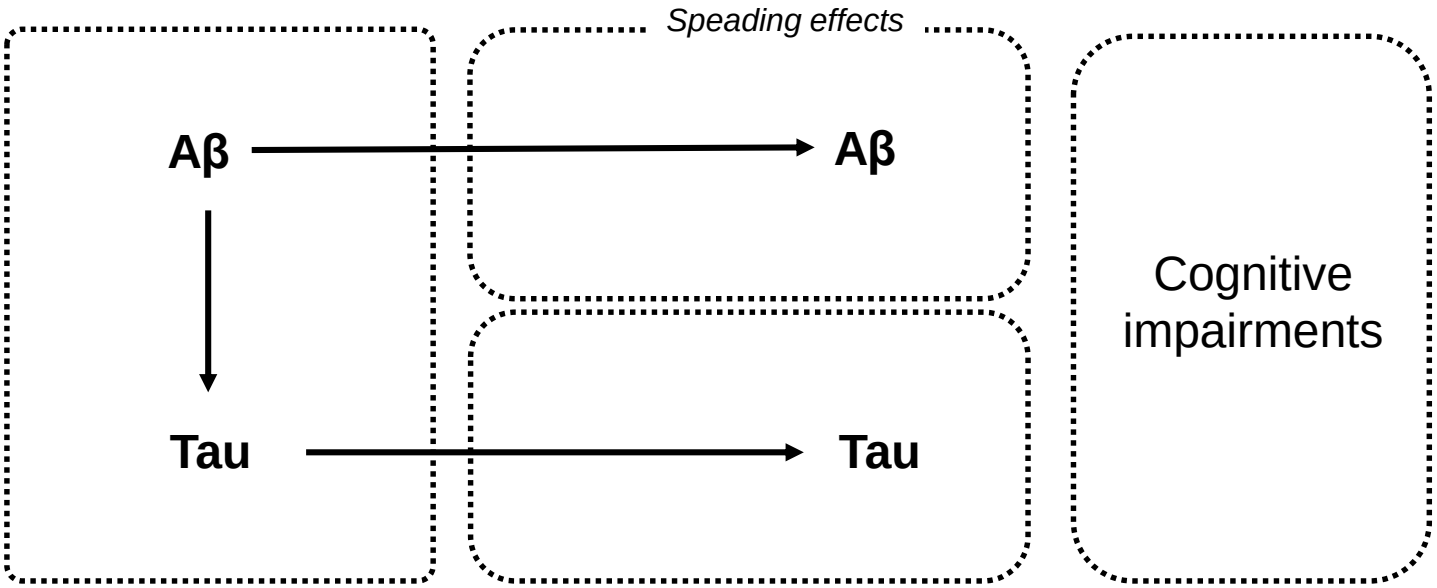
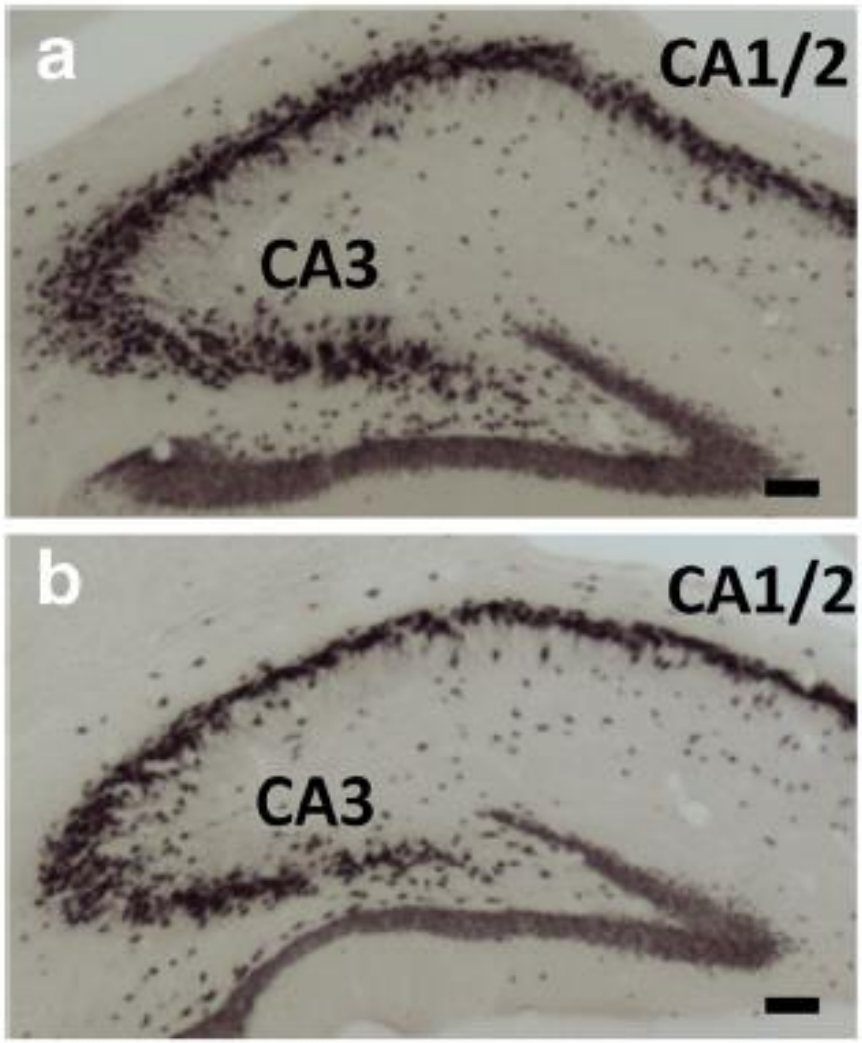
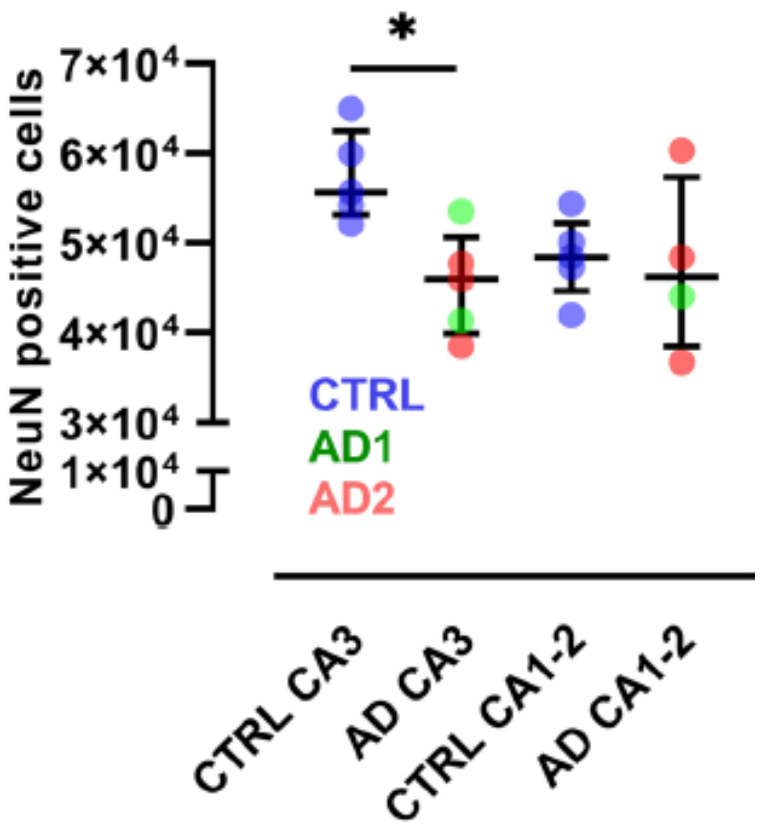
Aβ and/or tau transmissions can lead to cognitive impairments

Region non-autonomous process



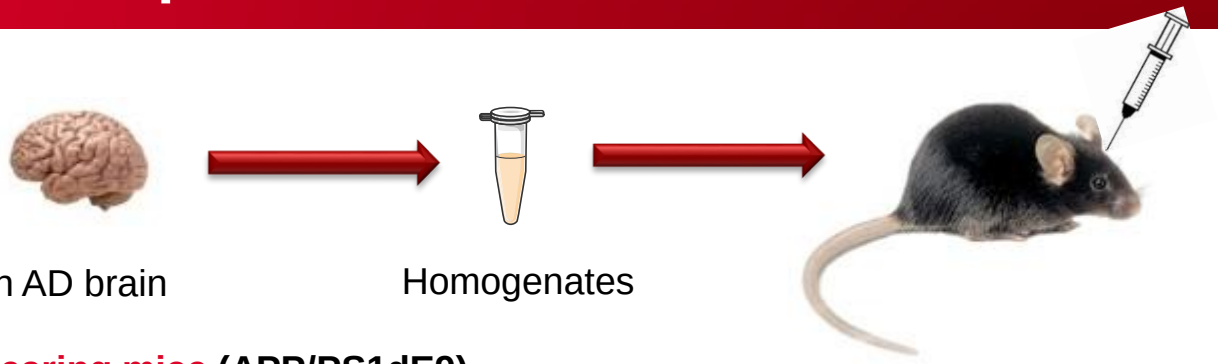
Aβ and/or tau transmissions can lead to neuronal loss





Gary. Acta Neuropathol Commun 2019. 7.

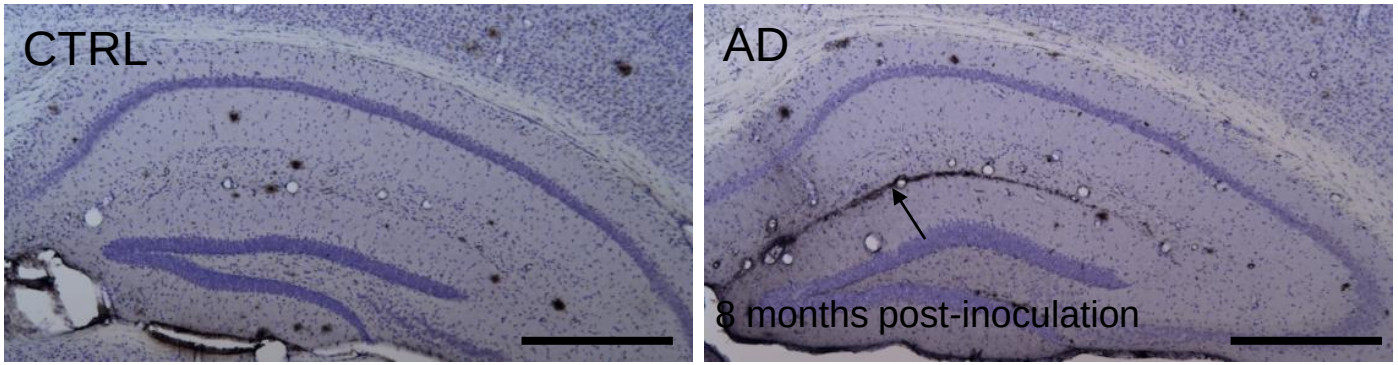
BACK TO MICE…
AMYLOID-β AND TAU TRANSMISSION IN RODENTS



Human AD brain

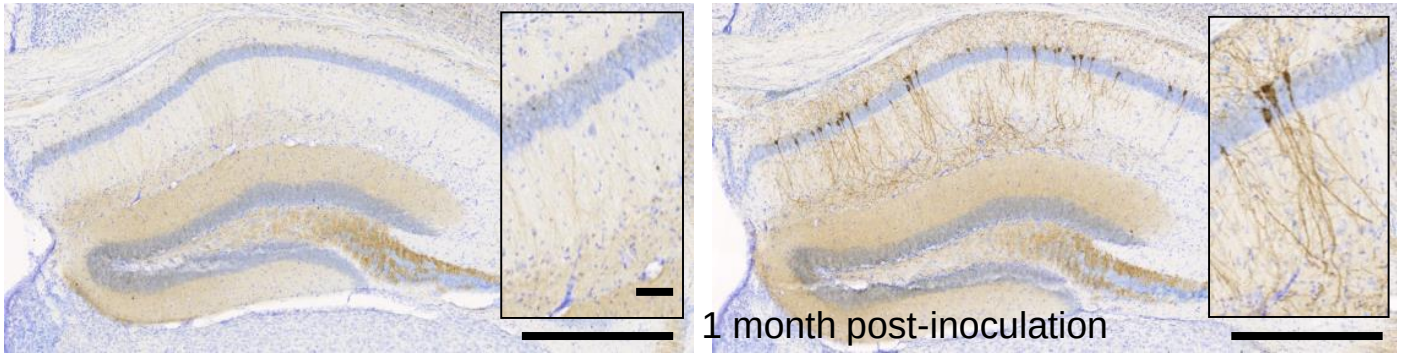
Homogenates

Transgenic amyloid-bearing mice (APP/PS1dE9)



Kane et al.,
J. Neurosc. 2000
Meyer-Luehman et al.
Science 2006

Transgenic mouse model of Tau (Tau30$^{+/+}$) based on overexpression of pathological Tau

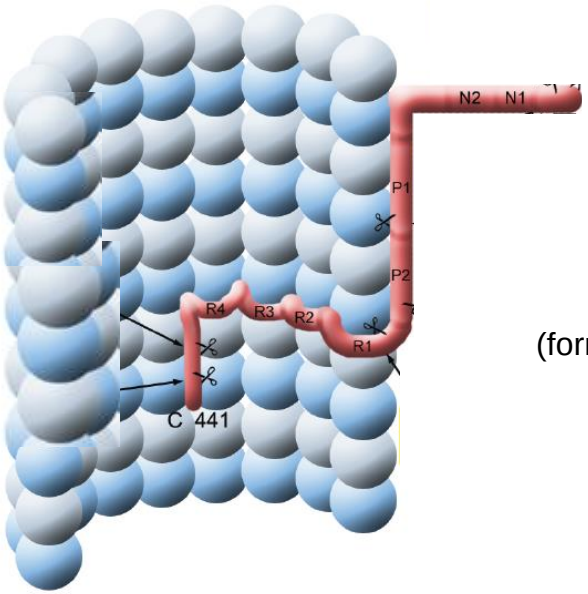


Clavaguera et al.,
Nature Cell Biology 2009

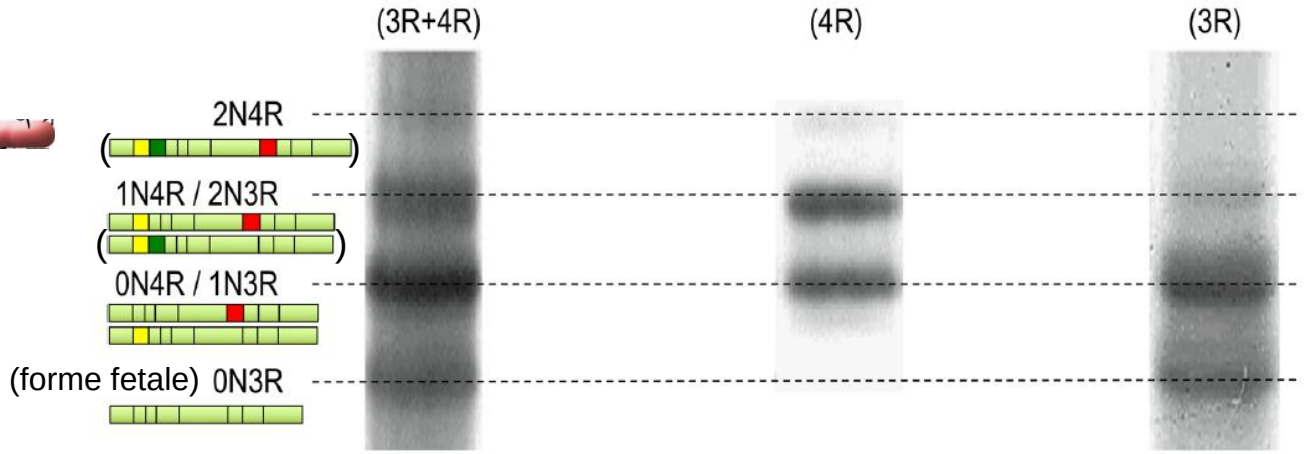
Gary. Acta Neuropathol Commun 2019. 7.

BACK TO MICE…
TAU TRANSMISSION IN RODENTS

Can we induce tau lesions in mice that do not overexpress human tau proteins ?



Alternative splicing



- Alzheimer's disease
- Amyotrophic lateral sclerosis / parkinsonism dementia complex of Guam
- British familial dementia
- Caribbean parkinsonism
- Chronic traumatic encephalopathy
- Down syndrome
- Fronto-temporal lobar degeneration with MAPT mutations
- Niemann-Pick disease type C

Mouse lemurs 3R/4R

- Argyrophilic grain disease
- Corticobasal degeneration
- Fronto-temporal lobar degeneration with MAPT mutations
- Progressive supranuclear palsy

Mice 4R

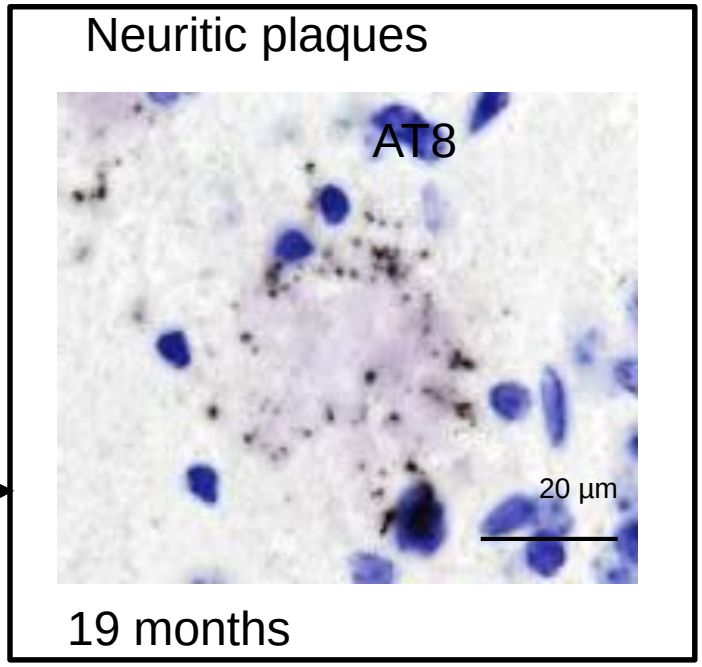
- Fronto-temporal lobar degeneration with MAPT mutations
- Pick's disease

[Buée, 2002]

AMYLOID-β INDUCES TAU PATHOLOGY
Example in amyloid-β bearing mice

APP/PS1dE9

Aβ overproduction



Amyloid cascade

Aβ

↓

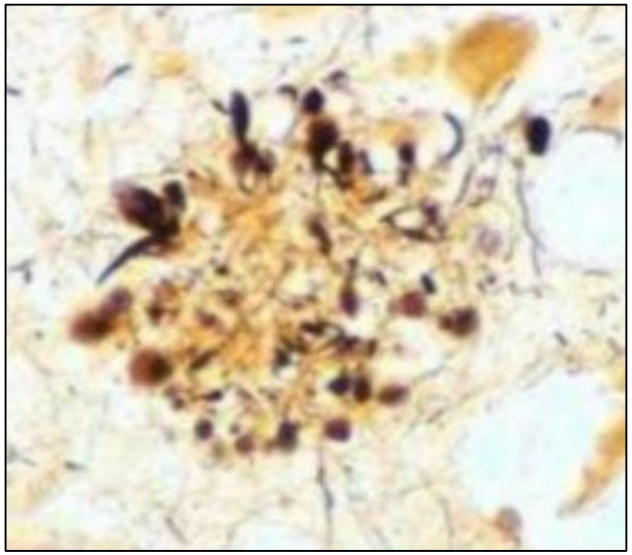
Tau

(neuritic plaques)

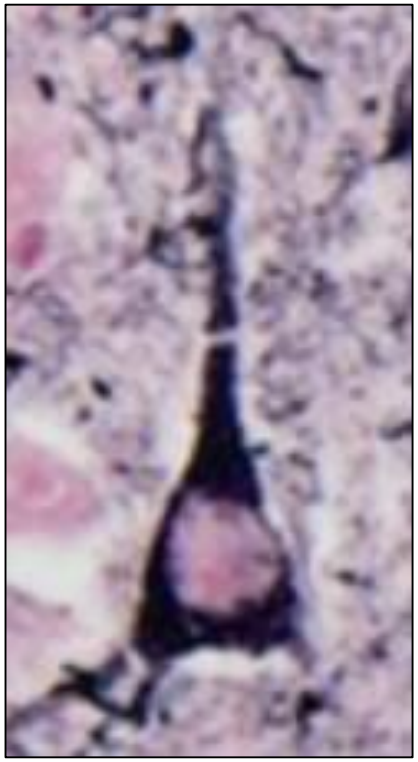
APP/PS1dE9: Lam, Acta Neuropathol Com, 2022
APP/PS1dE9: Metaxas, Scientific Reports,2019
APPPS1-21: Radde, Embo Reports, 2006;
Tg2576: Noda-Saita, 2004

Lack of neurofibrillary tangles or neuropil threads in mice without tau mutations

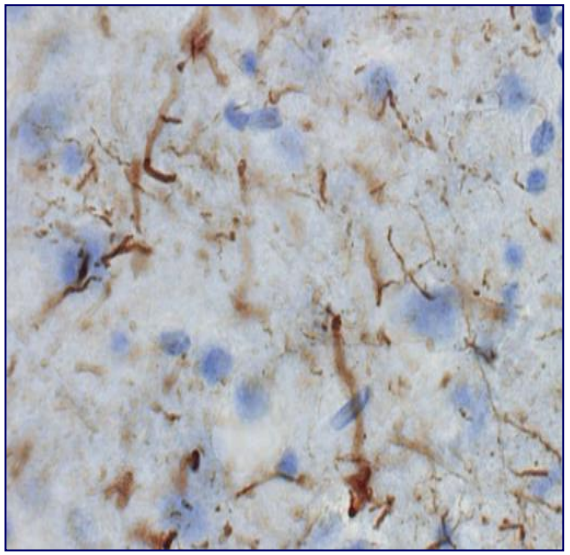
TAU PATHOLOGY IN ALZHEIMER'S DISEASE



Neuritic plaques**
(amyloid + tau)



Neurofibrillary tangles
(within cell soma)

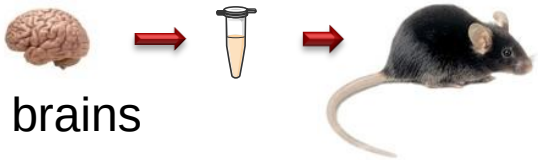


Neuropil threads*
(within neurites)

Found in Aβ mice

Not reproduced in Aβ mice

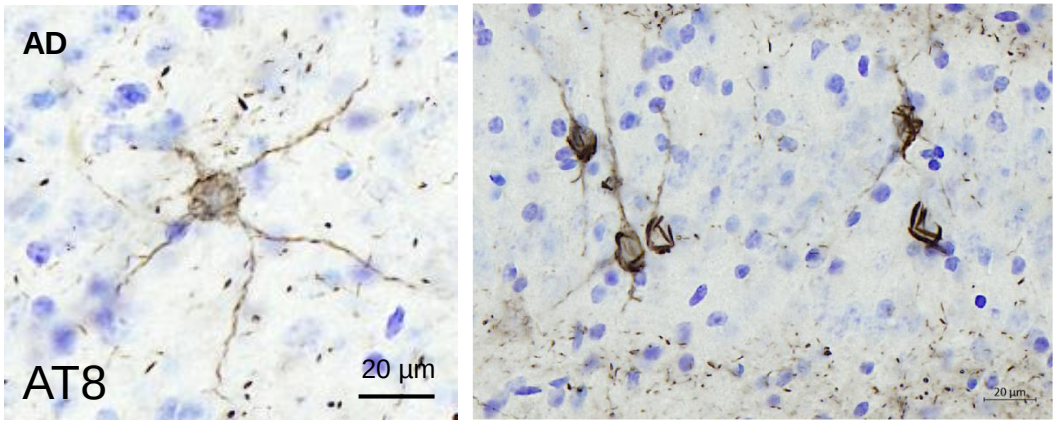
HETEROTYPIC TAU SEEDING
Neurofibrillary tangles, neuropil threads, neuritic plaques



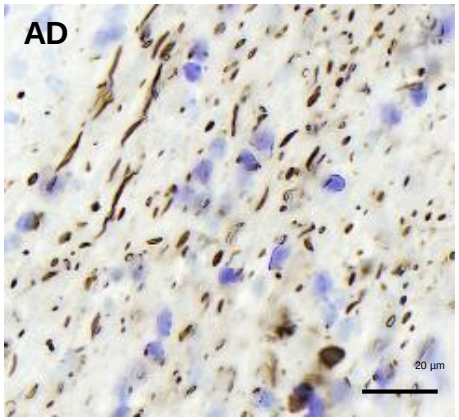
AD brains

Amyloid-bearing APP/PS1dE9

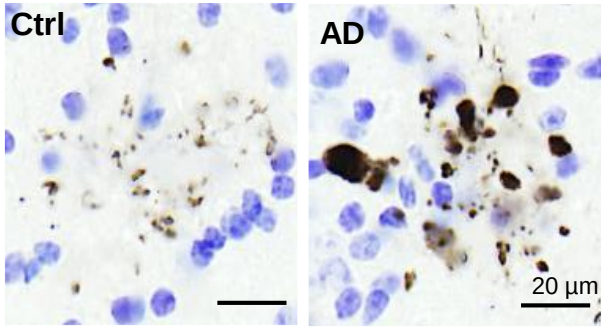
Neurofibrillary tangles



Neuropil threads



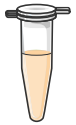
Neuritic plaques



Lam et al, Acta Neuropathol Com, 2022

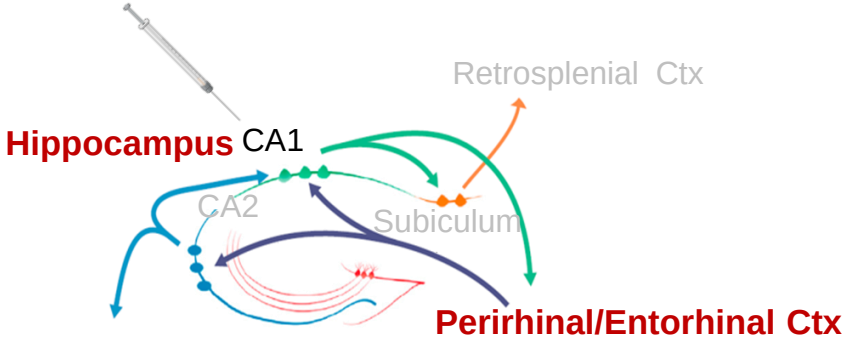
HETEROTYPIC TAU SEEDING
Spreading of tau pathology

Human brains
Ctrl / AD

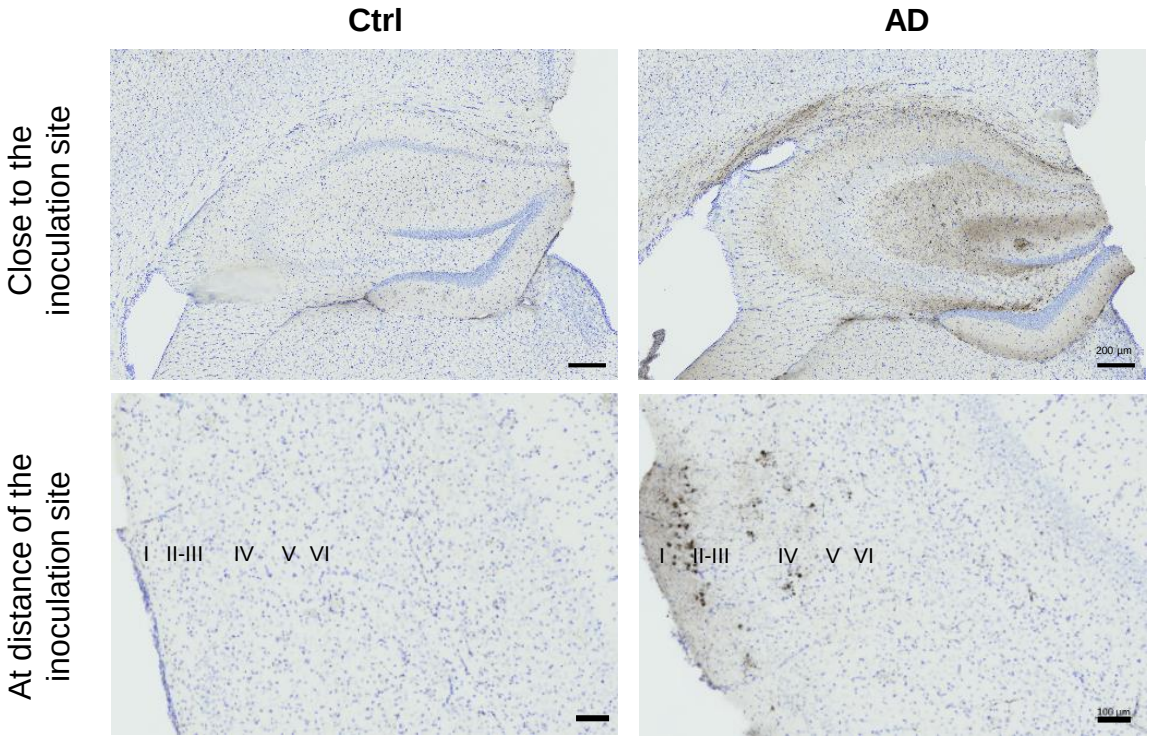


Homogenates

Amyloid-bearing
APP/PS1dE9



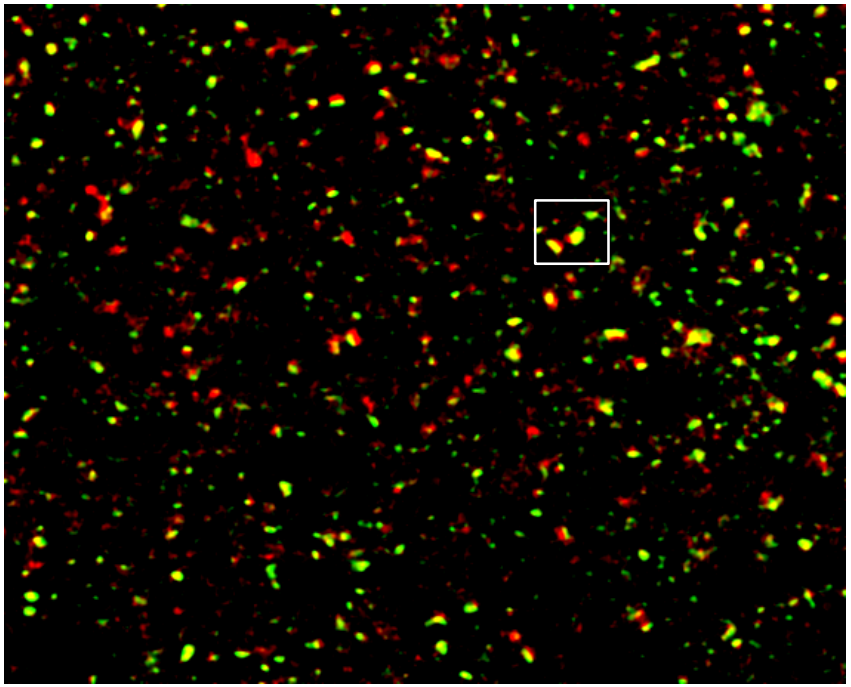
AT8
+ 8 months



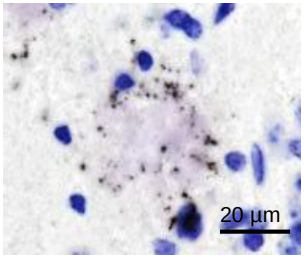
Lam et al, Acta Neuropathol Com, 2022

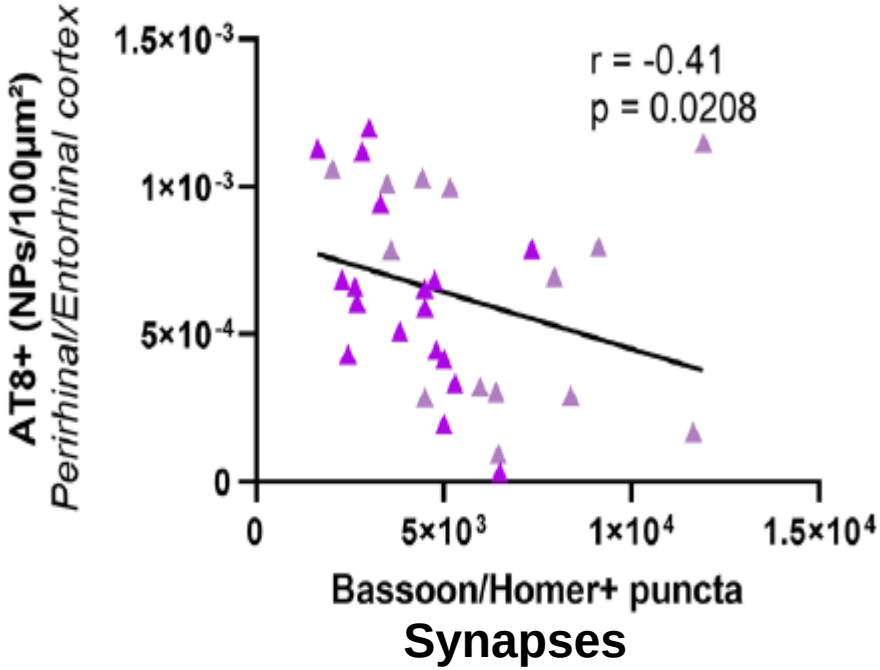
TAU PATHOLOGY IS THE MAIN CULPRIT FOR SYNAPSE IMPAIRMENTS

Synaptic quantification in peri/entorhinal cortex
Red : Bassoon
Green: Homer



Neuritic plaques





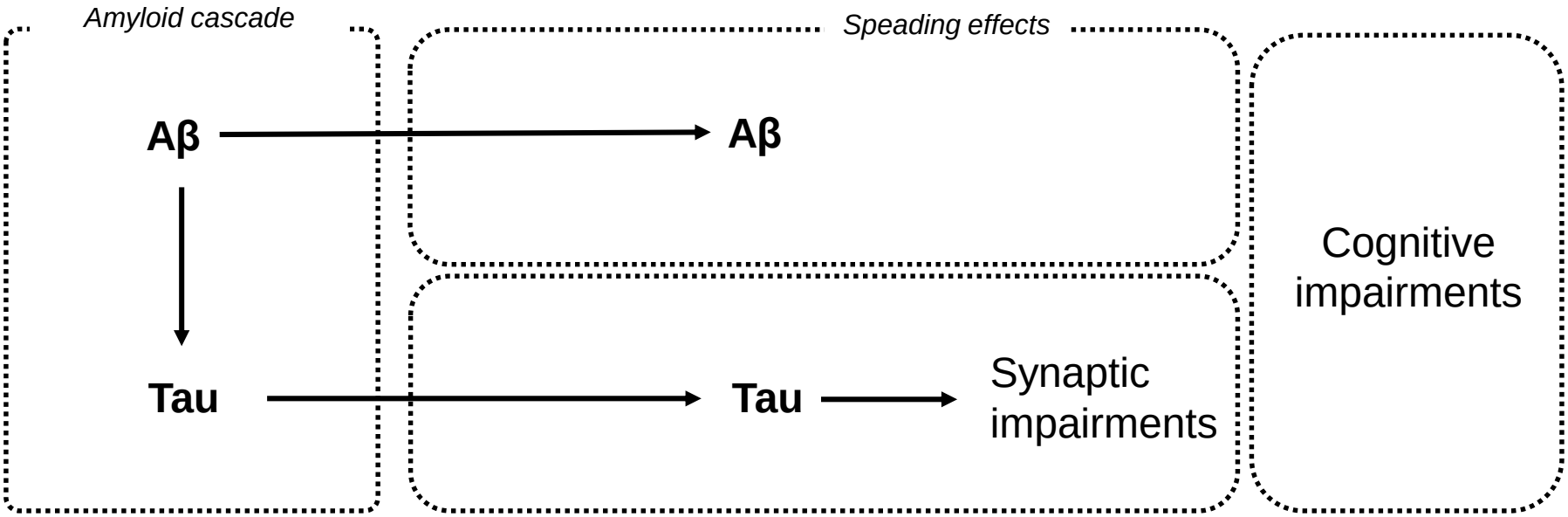
Synaptic impairment not associated with amyloid or astrocyte load

Lam et al, Acta Neuropathol Com, 2022

Aβ AND TAU PATHOLOGY

Region autonomous process

Region non-autonomous process



CONCLUSION

Aβ and tau are transmissible

- Tau pathology is transmissible in a primate
- Aβ and tau pathology are not specific to humans

Induction of Aβ and tau can induce clinical signs

- Recommendation to follow-up persons with iatrogen transmission risk

Opportunities for biomedical research and disease modelling

- Novel categories of non-transgenic animal models
- Heterotopic tau transmission in mice

Gary C et al. Acta Neuropathologica Com 2019
Lam S et al. Acta Neuropathologica Com 2021
Lam S et al. Acta Neuropathologica Com 2022

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