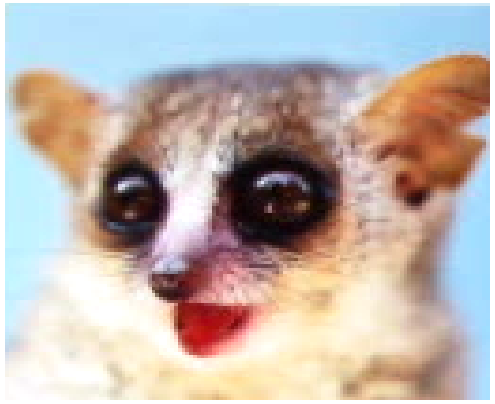
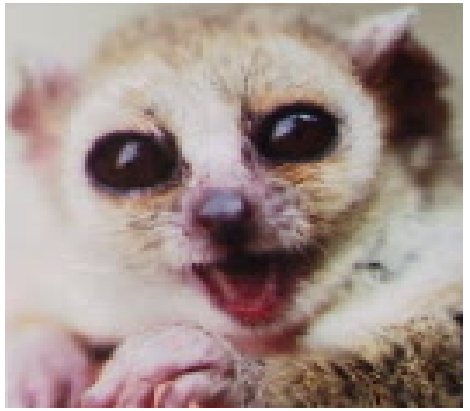
Le microcèbe, modèle émergeant du vieillissement cérébral






Fabien Pifferi, Jérémy Terrien, Fabienne Aujard

Adaptive Mechanisms and Evolution Unit, UMR CNRS MNHN 7179

Integrative Biology of Adaptation Team

08 Novembre 2022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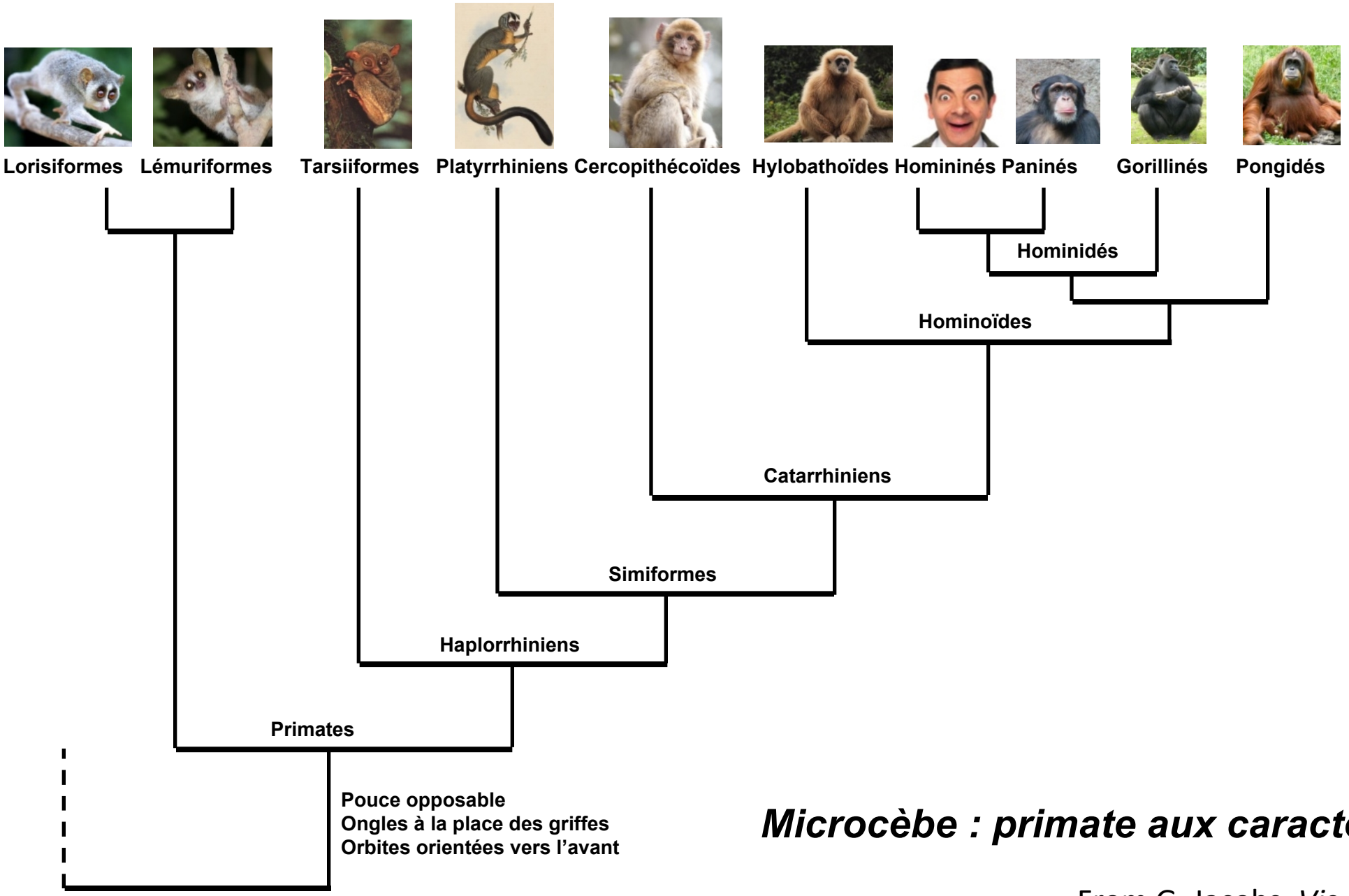
Phylogénie des primates



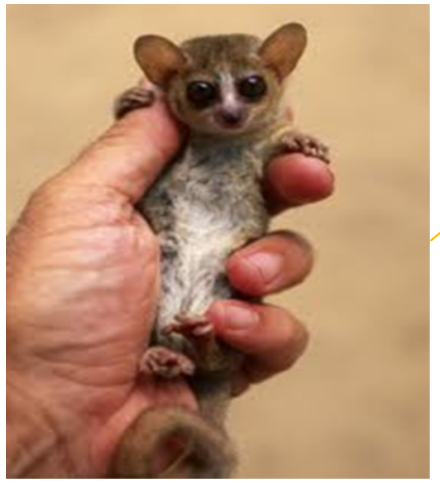
Microcèbe : primate aux caractères ancestraux

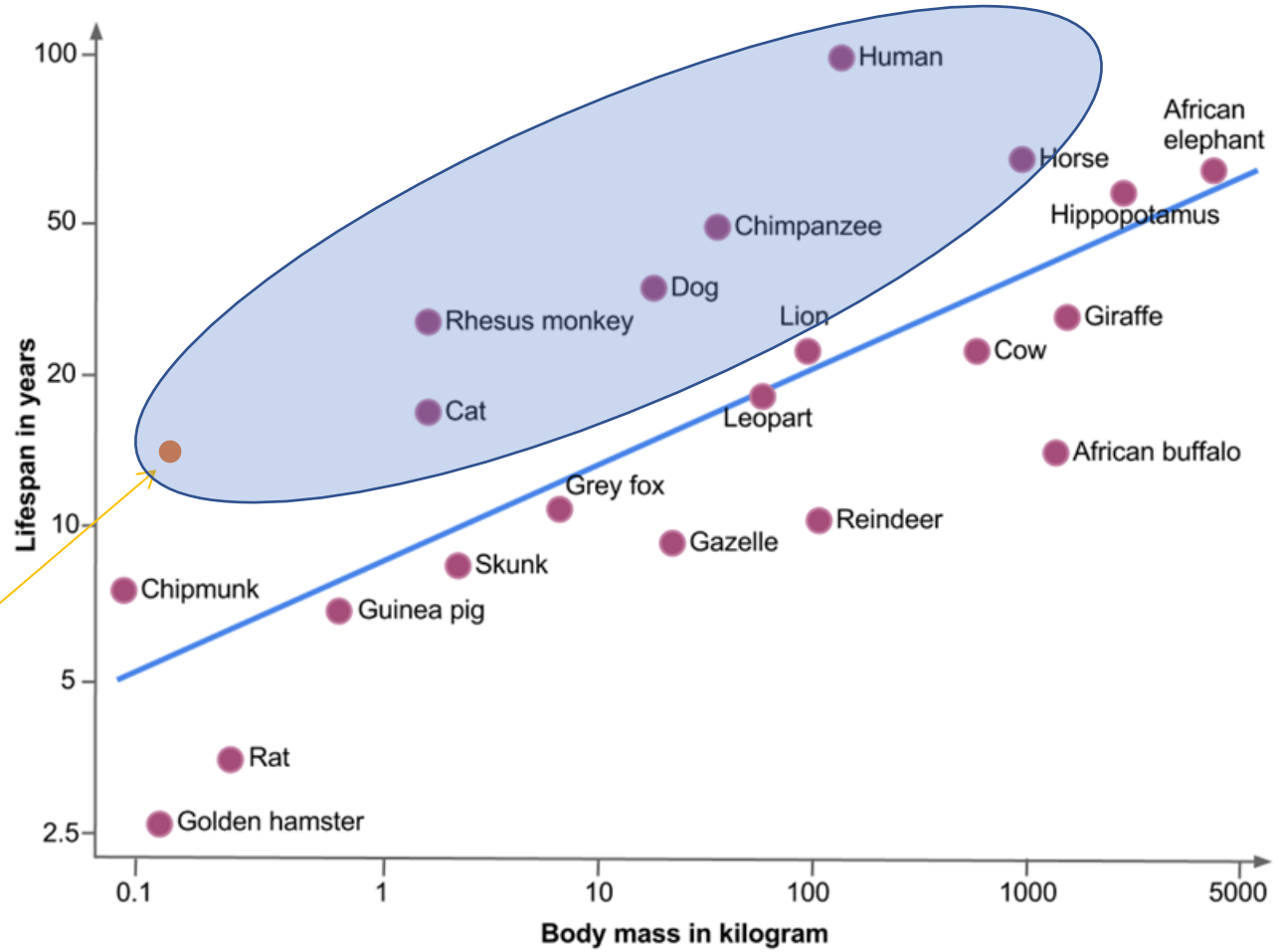
From G. Jacobs. *Vis. Neuroscience*, 2008

The grey mouse lemur (*Microcebus murinus*)

Small prosimian primate, originating from Madagascar

- Nocturnal
- Long lifespan for a small sized species

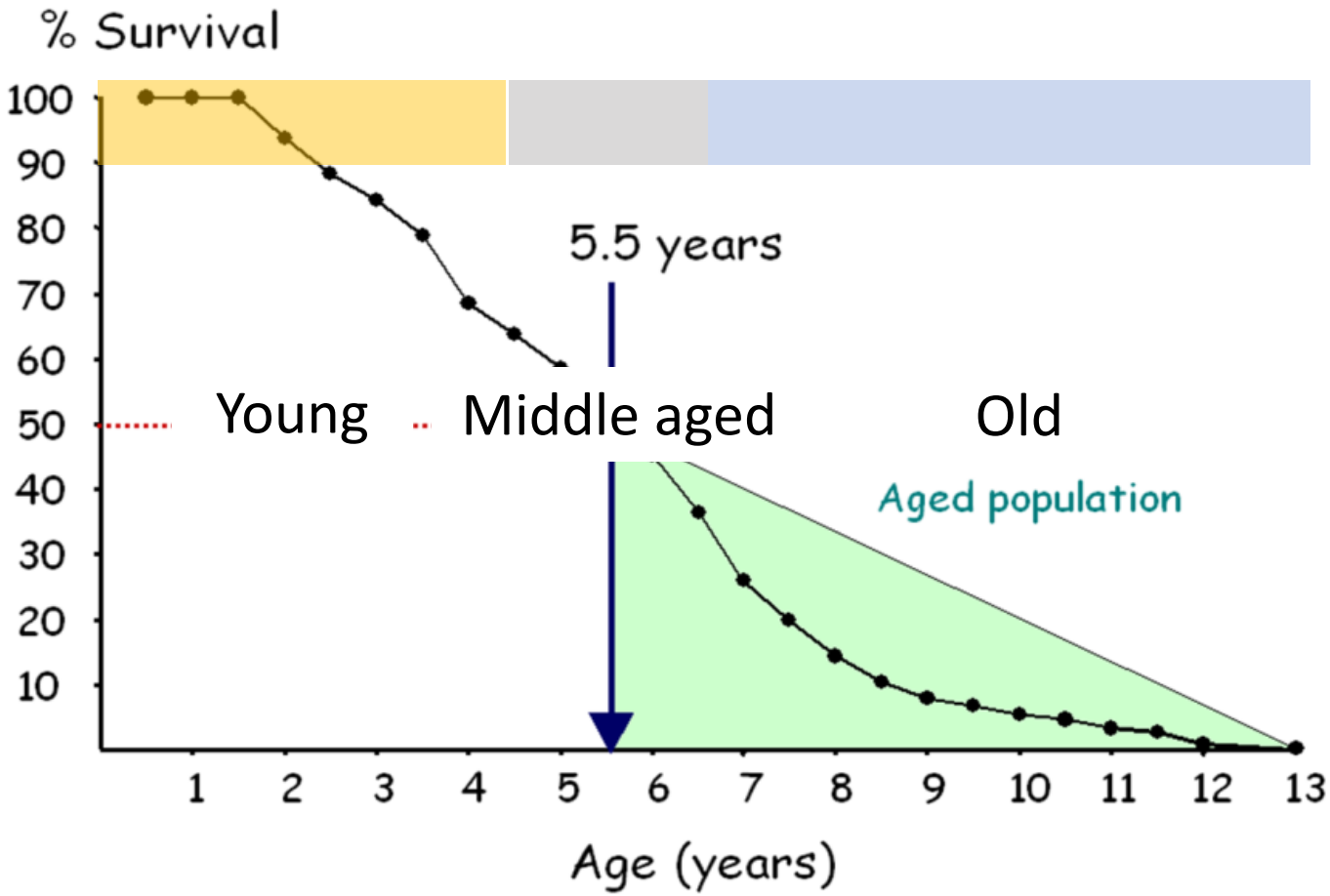




Max. lifespan = 13.8 y. in captivity, <100g, easy breeding

Psychomotor aging in M. murinus

Survival and aging of captive mouse lemur



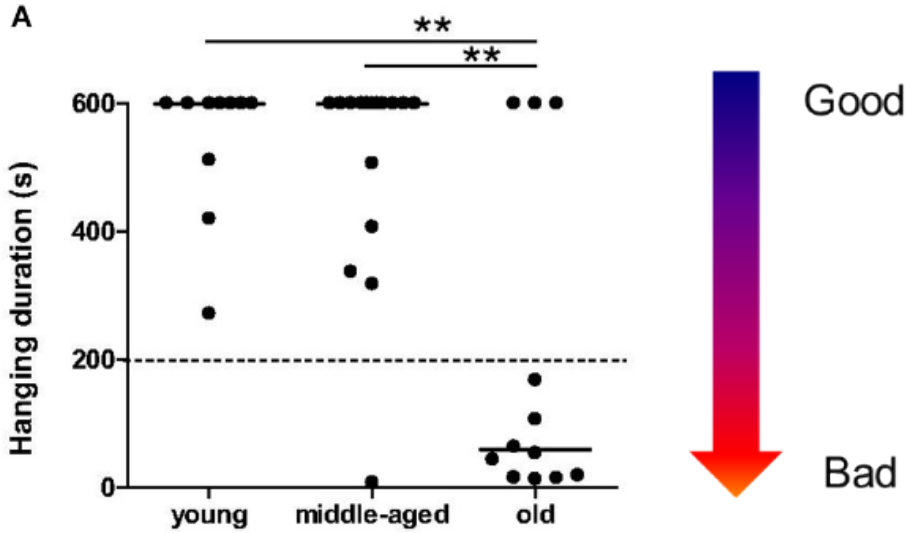
Survival curve of MM in the colony (n=288)

3 sub-populations can be defined: young (<4.5), middle aged (4.5-6.5) and old (>6.5)

Djelti et al. 2017

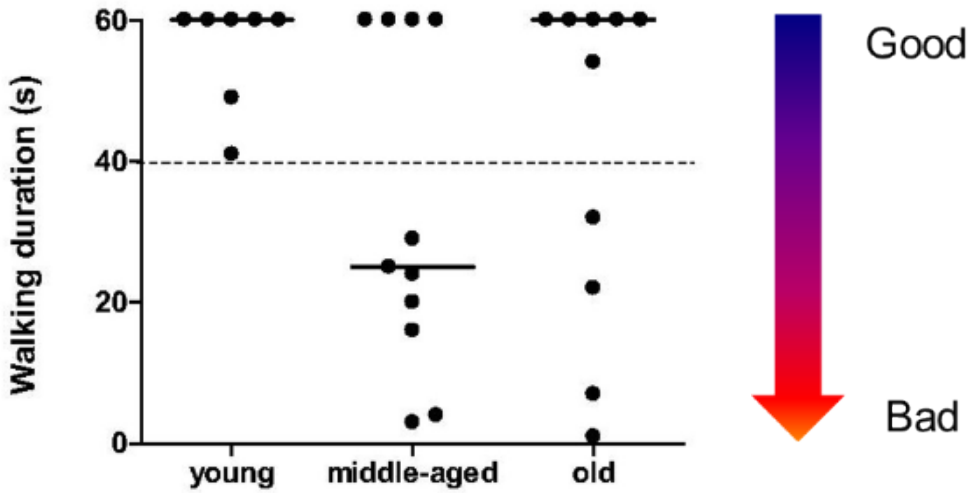
Aging of sensory-motor functions

Muscle strength (hanging task)



Muscle strength significantly decreases in old animals

Motor coordination (rotating rod task)

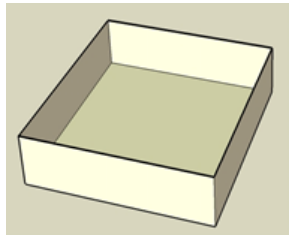


No significant changes in motor coordination task
2 sub-populations

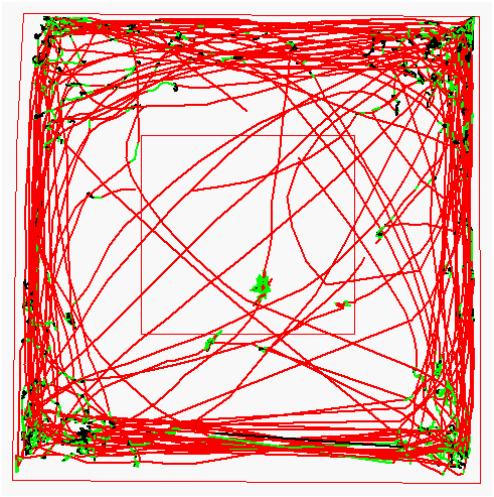
Languille et al. Frontiers in Neuroscience 2015

Aging of cognitive functions

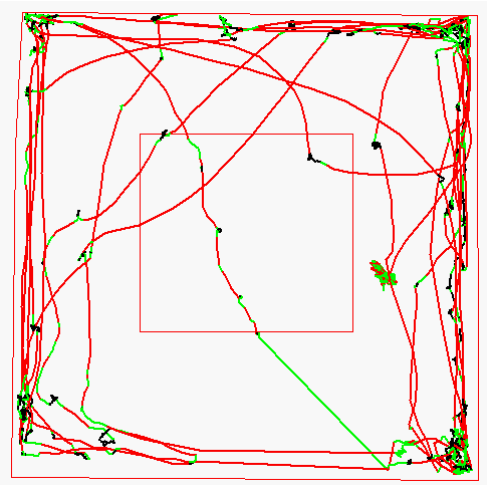
Numerous tests adapted to captive mouse lemurs (spatial, visual, working and emotion memory, anxiety, aggressiveness, visual discrimination, executive functions…and more!)



Anxiety in an open-field task



- High exploratory behavior
- Numerous center crossings
- Short latency of 1st movment

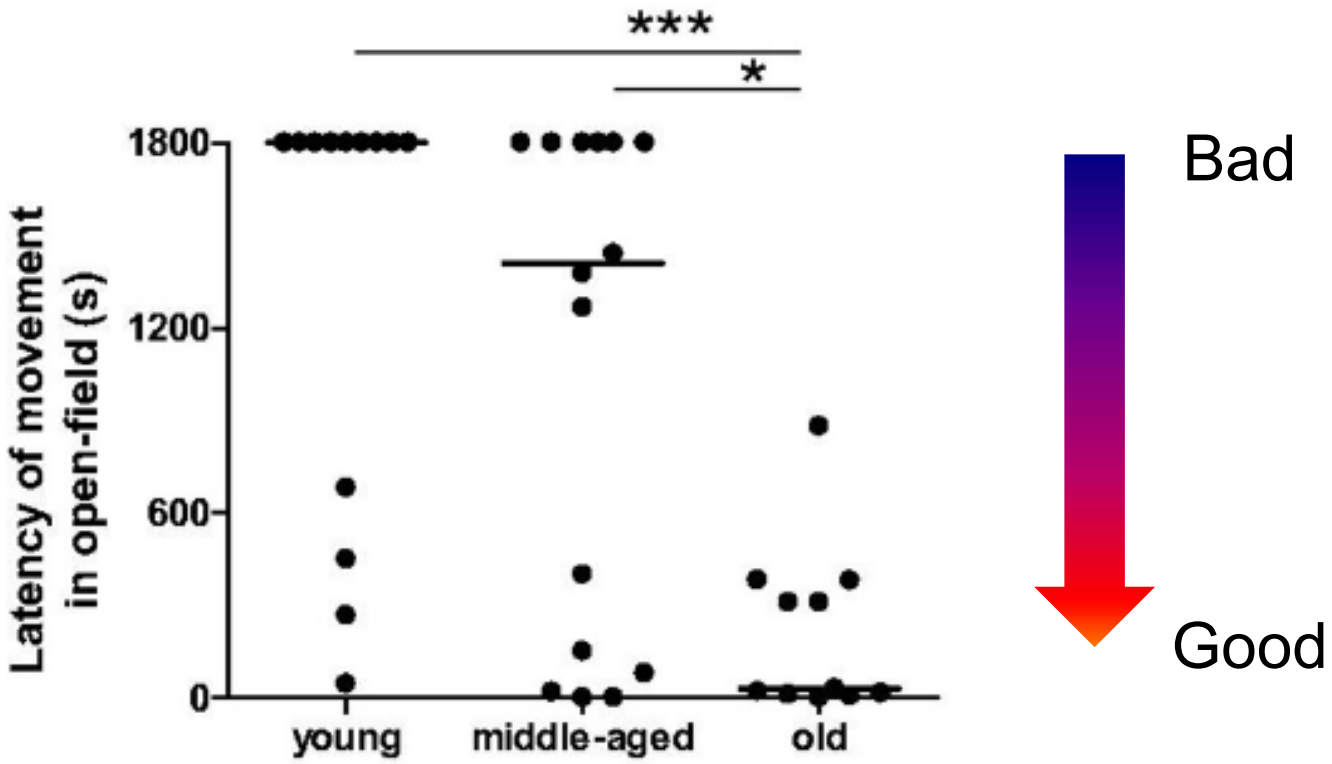


- Low exploratory behavior
- Few center crossings
- Long latency

(*Picq 1993-1995-1998-2007-2015; Languille 2015*)

Cognitive functions

Anxiety in an open-field task

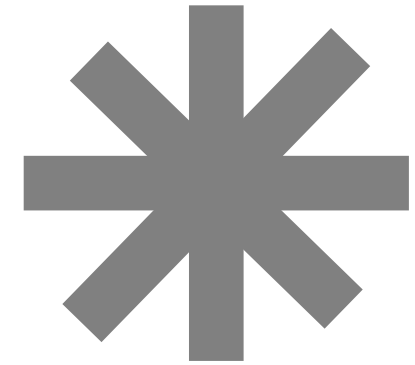


Anxiety decreases with age. Validated in other emotion related tasks.

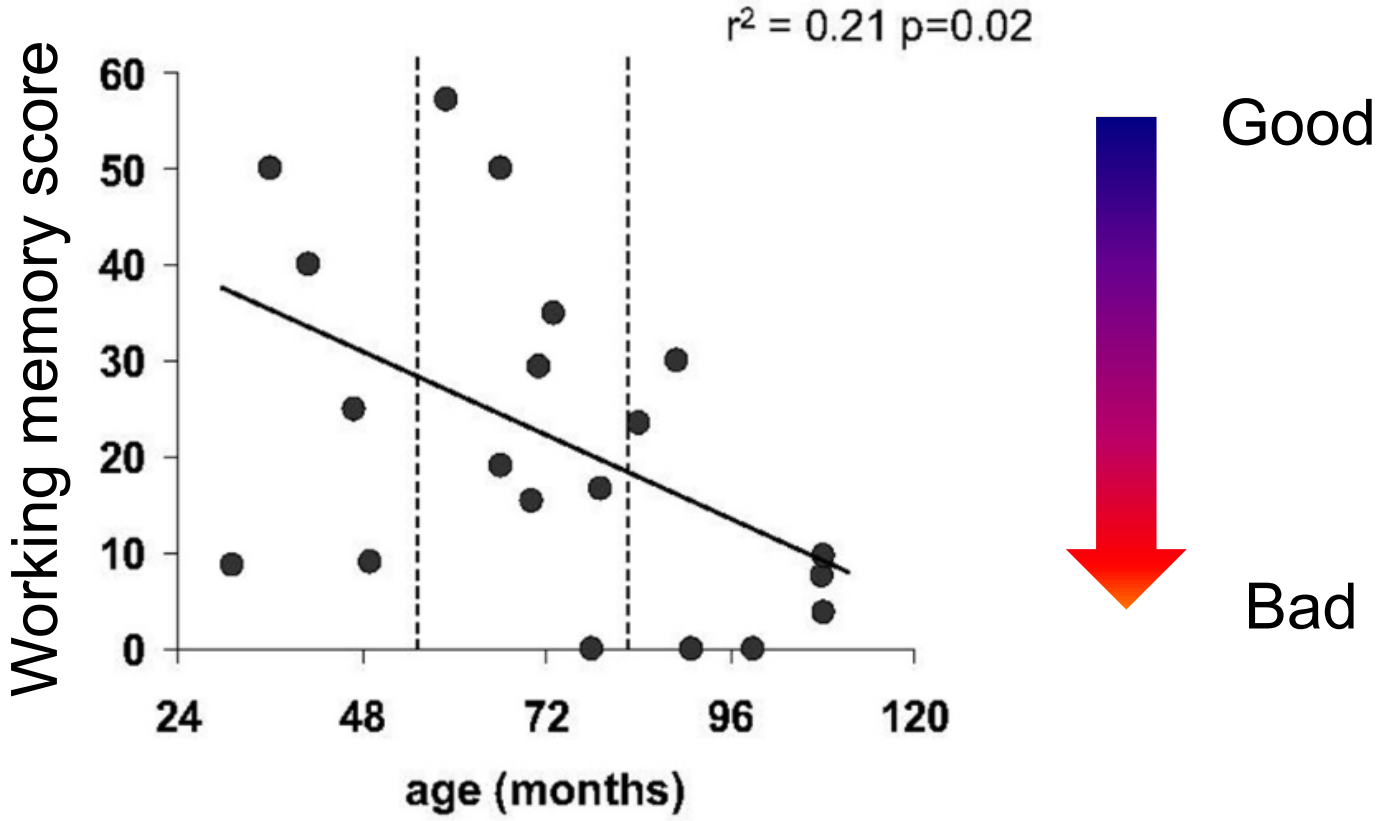
(*Languille 2015*)

Cognitive functions

Working memory (spontaneous alternation task, executive function)
Animals have to explore the maze, without visiting already visited arms



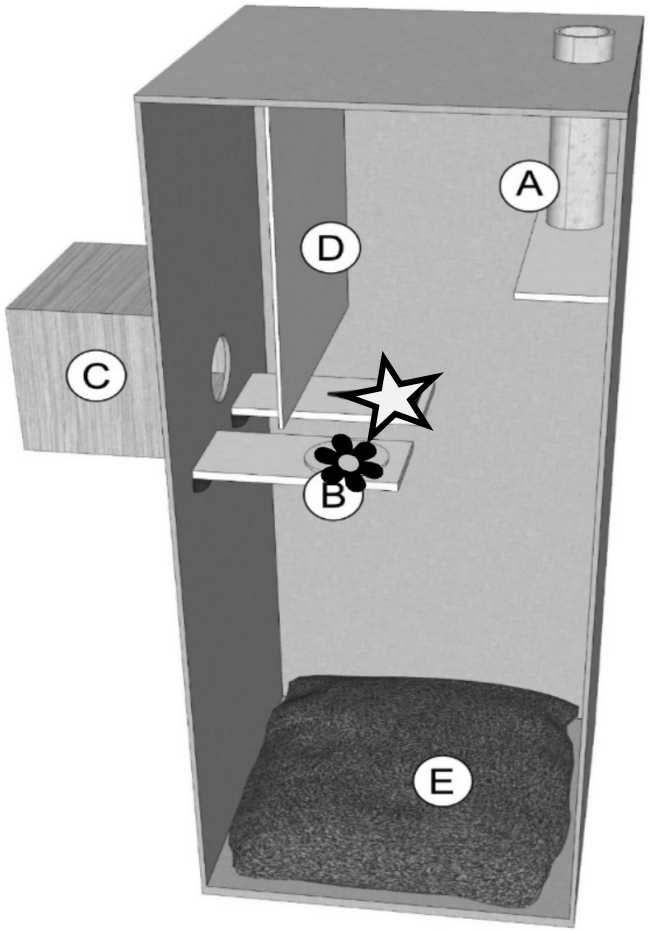
radial arm maze

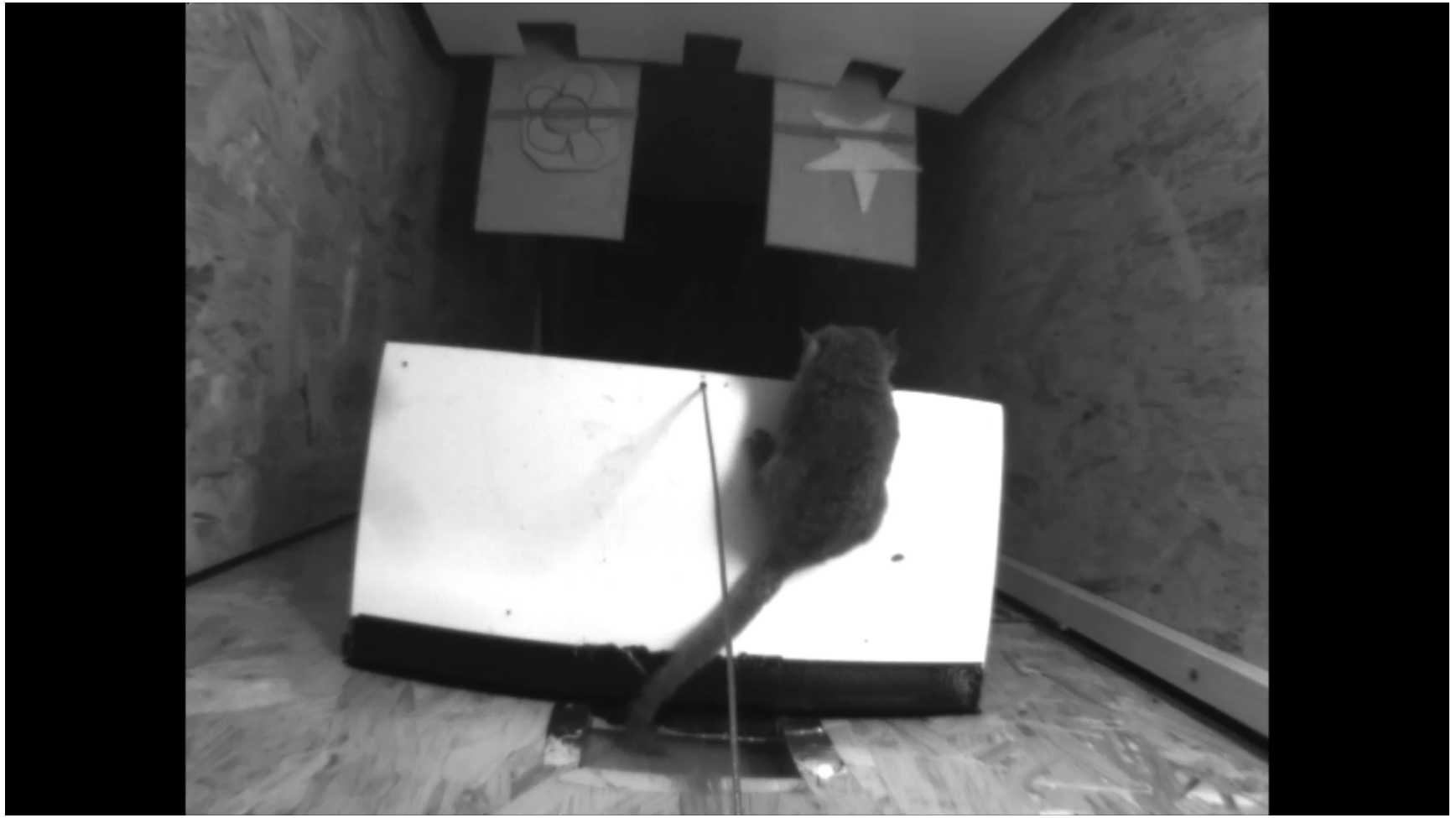


Working memory significantly decreases with age

(Languille et al. 2015)

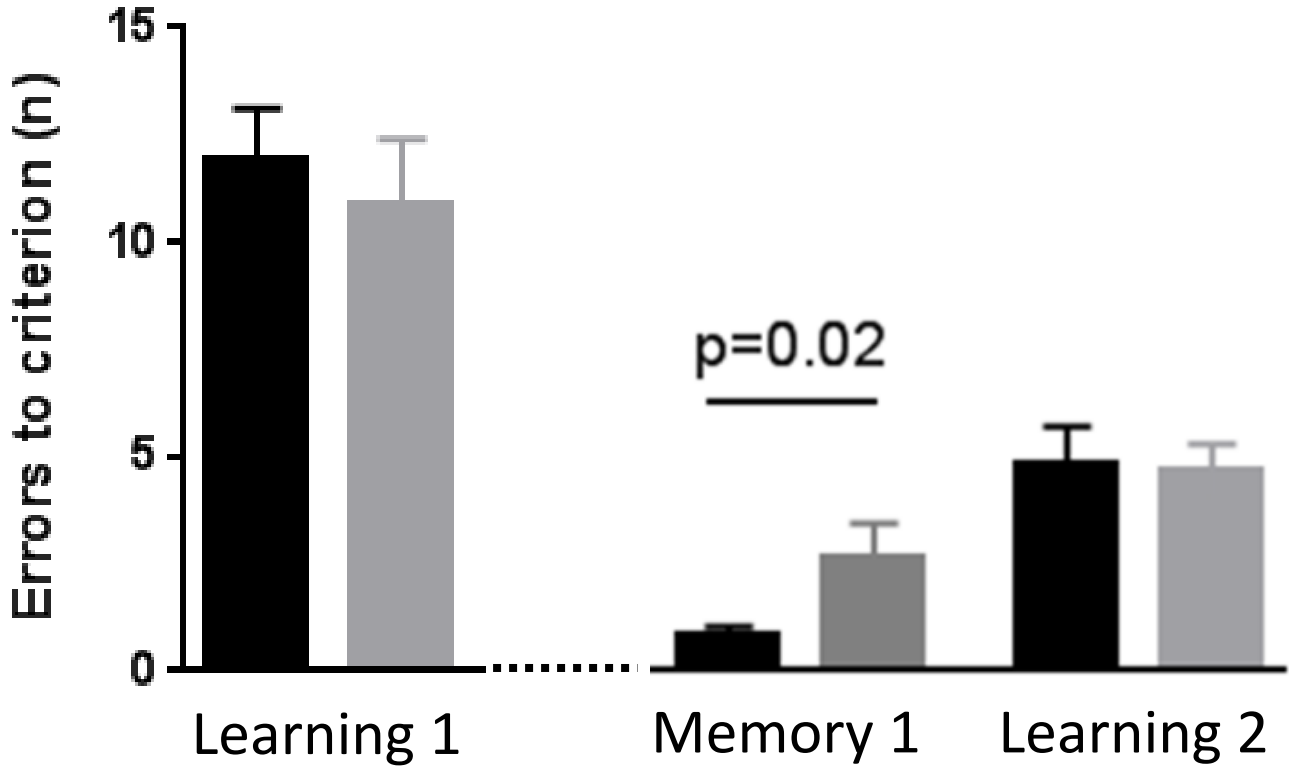
Visual discrimination task





Learning criterion: 8 successful trials/10 (80% success)

Visual discrimination task



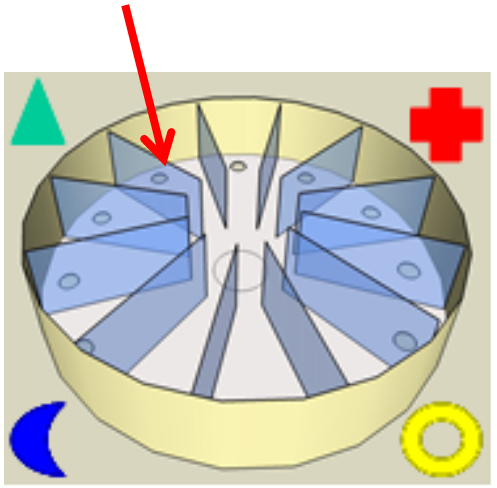
Age affects memory but not learning in the early stages of aging

Picq et al., PLoS ONE 2015

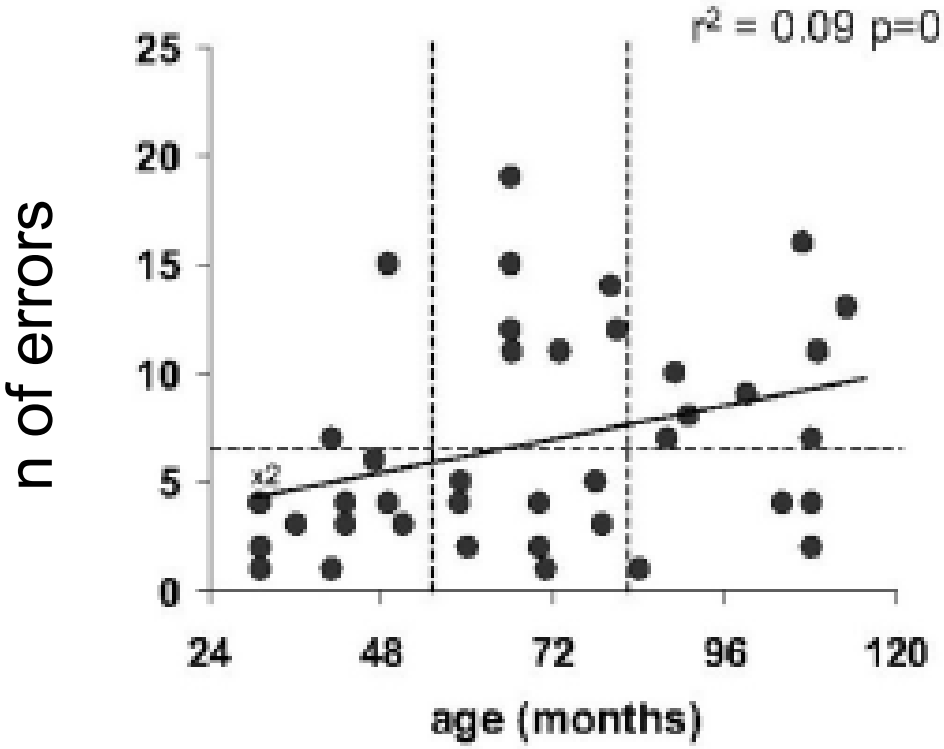
Cognitive functions

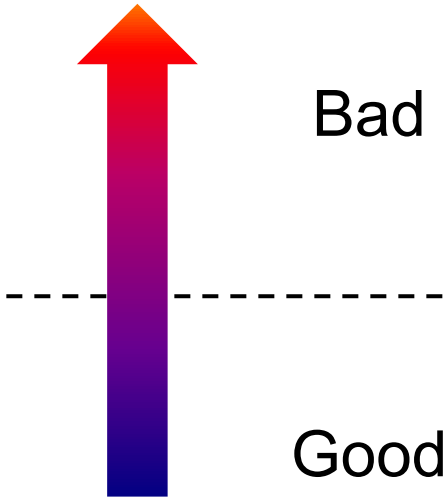
Reference spatial memory

Animals have to locate a previously learned exit



Barnes maze

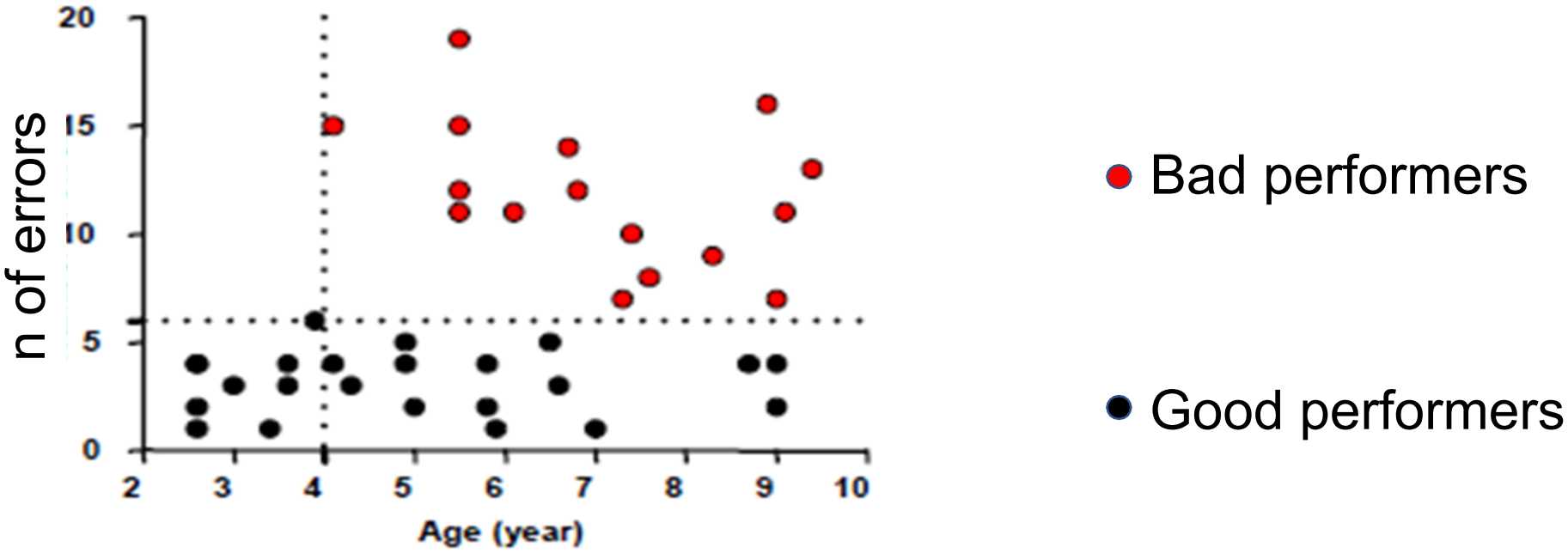




Number of errors increases with age, but a subset of middle aged and old animals does not seem to be affected

Exploring differences between good and bad performers

Biomarkers of cognitive decline?

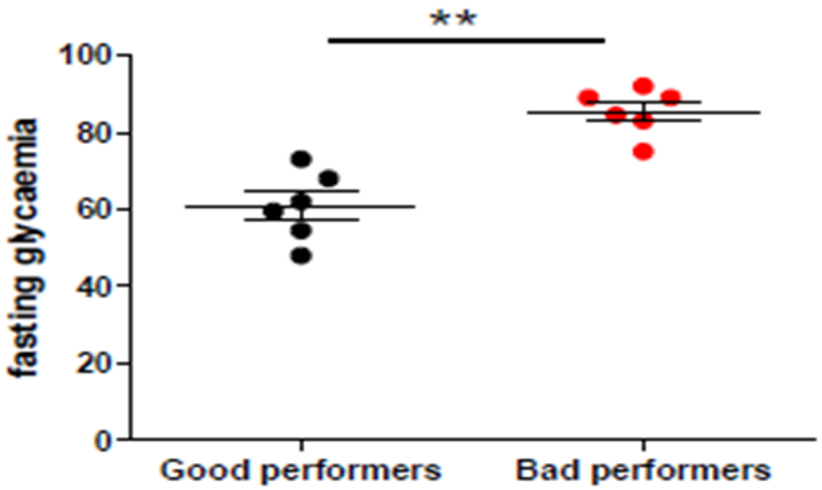


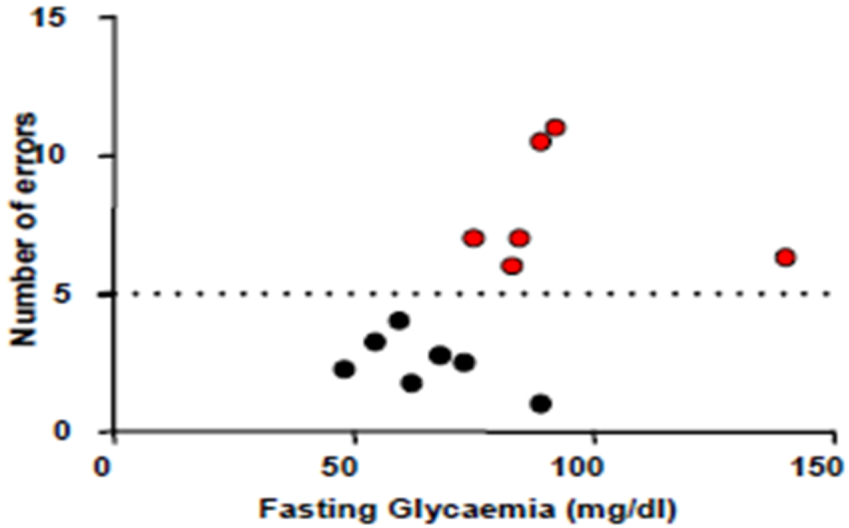
Target biomarker: glucose intolerance

Glucose intolerance and diabetes are strong risk factors of developing dementia in human, these parameters were assessed within groups of good and bad performers

(Djelti et al. *2017)*

p<0,01

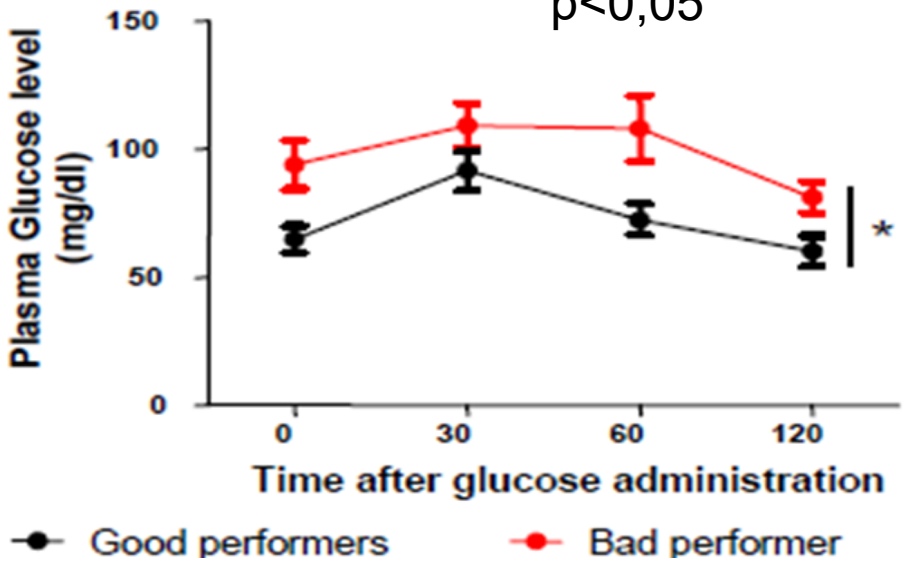




p<0,05

Oral glucose tolerance test

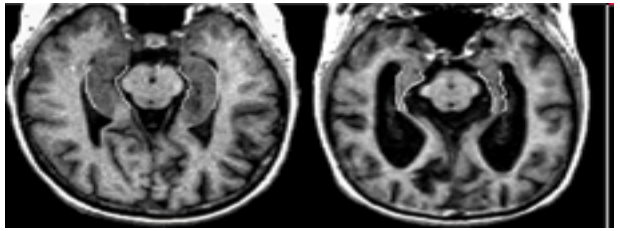
p<0,05



Animals with bad performances in reference memory tests have impaired glucose tolerance and higher fasting glycaemia. Could be good biomarker of neurodegeneration

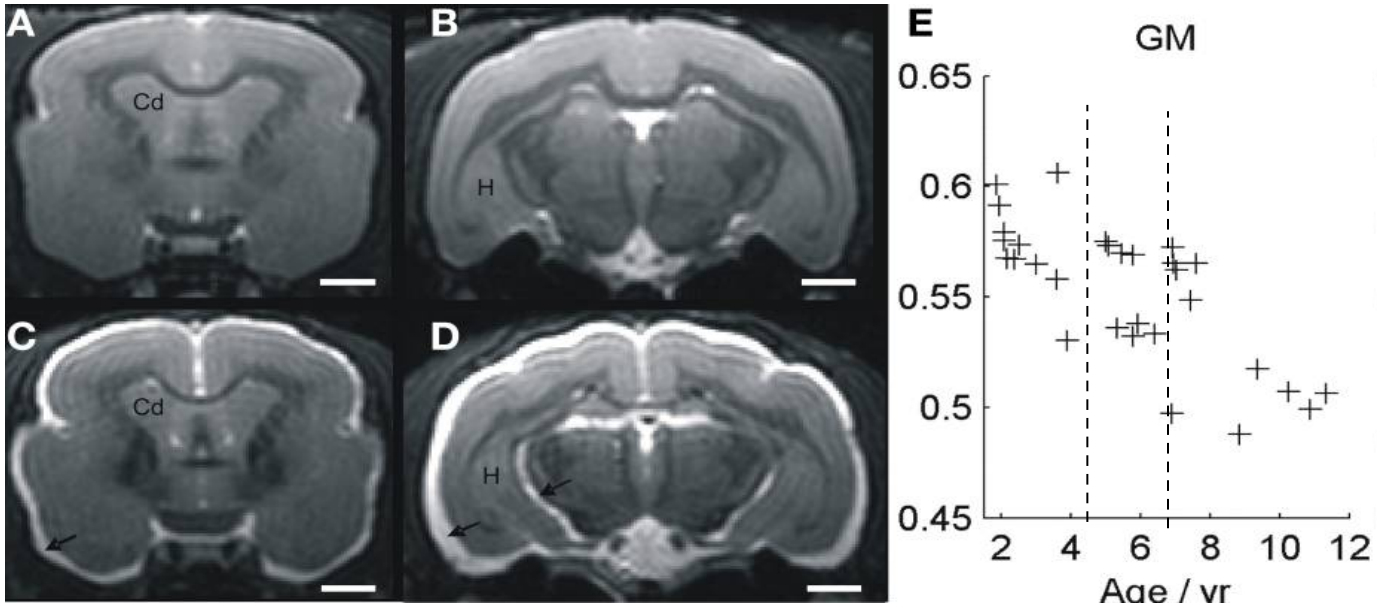
Brain atrophy

In Human, brain atrophy appears during healthy aging and strongly increases with neurodegeneration



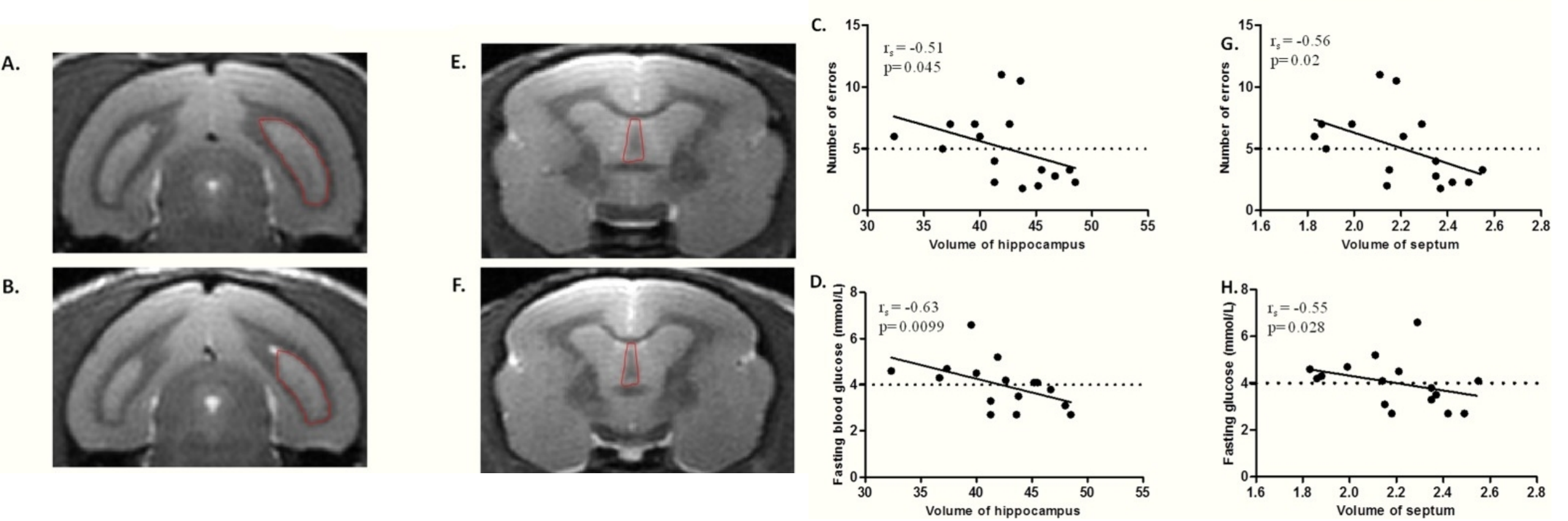
Young

Aged



Picq 2012 Neurobiol. aging

Relation between cognition, brain atrophy and glycaemia

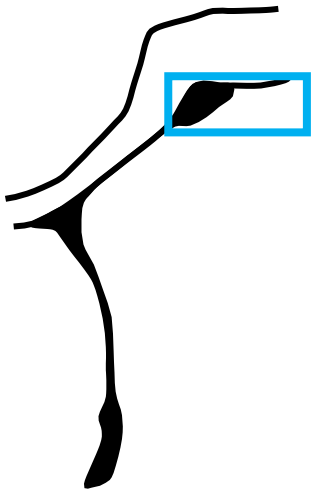


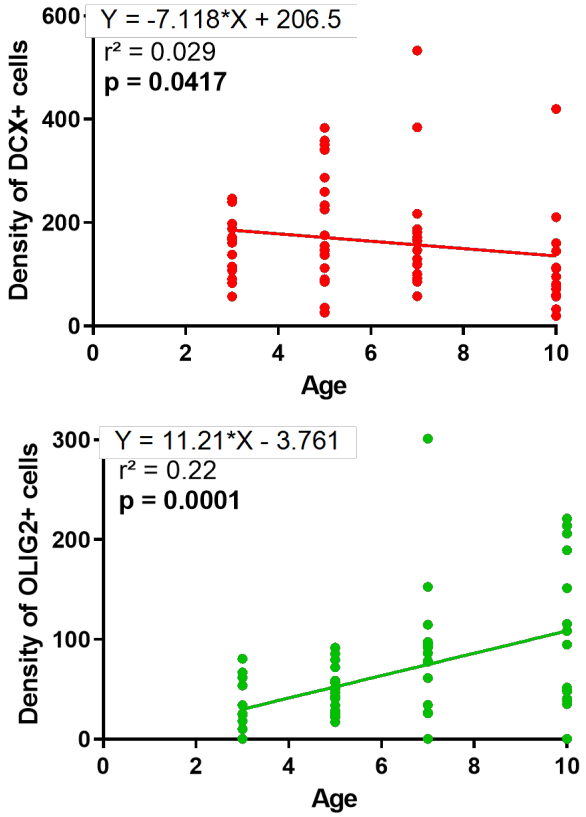
Significant correlation between reference memory (n errors), brain regions volume (atrophy), and fasting blood glucose

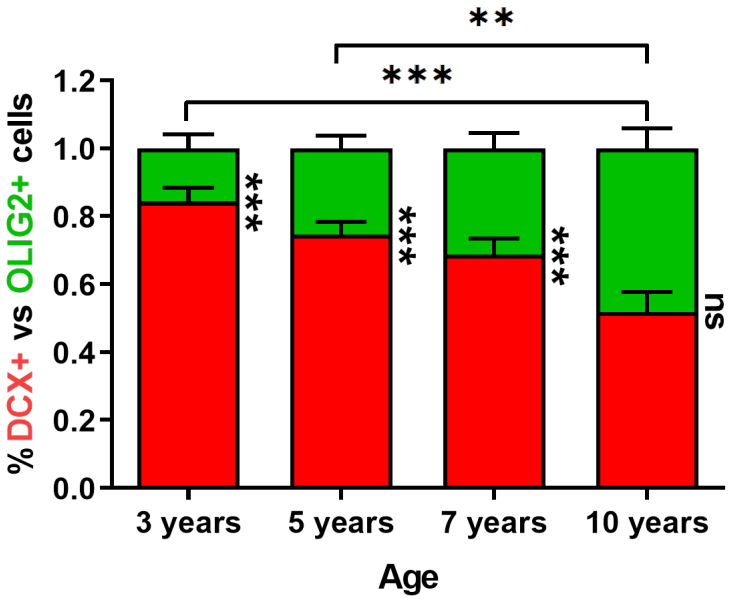
Djelti et al. Aging 2017 ; Nadkarni et al. Neuroimage 2019

Neurogenesis

The neuron/glia balance in hippocampus (distal SVZ)





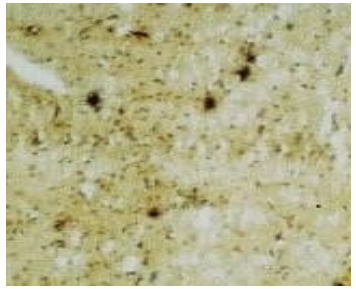


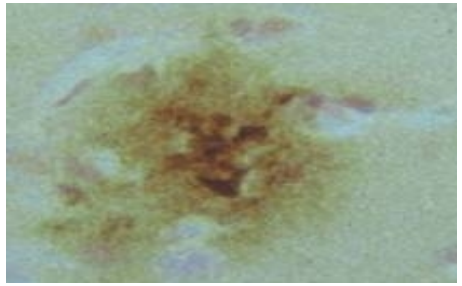
In young animals, in 85% of cases stem cells will generate neural cells, while in aged animals it becomes 50/50 neural/glial cells.
Cell fate is less favorable to neurons during aging

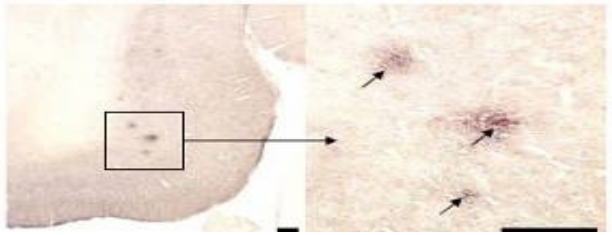
Butruille et al. *in prep.*

Neurodegeneration

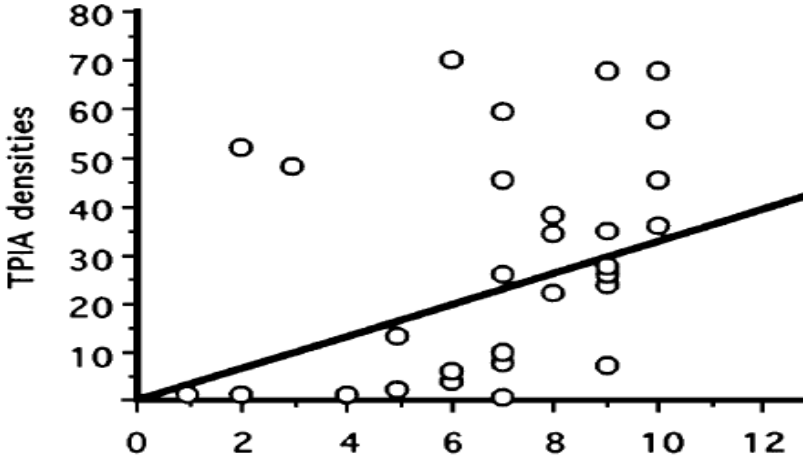
Presence of β-amyloid
-Intracellular (cortex, hippocampus)
-Extracellular : Aβ-42 plaques (cortex)

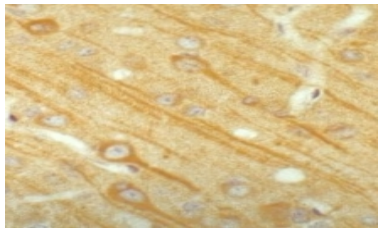


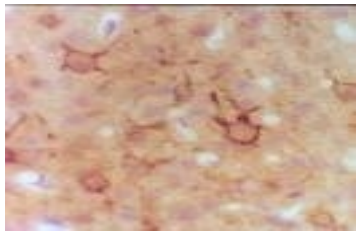




Presence of agregated Tau protein
(frontal cortex)







Normal *Agregated*

TPIA = Tau protein immunoreactive - accumulations

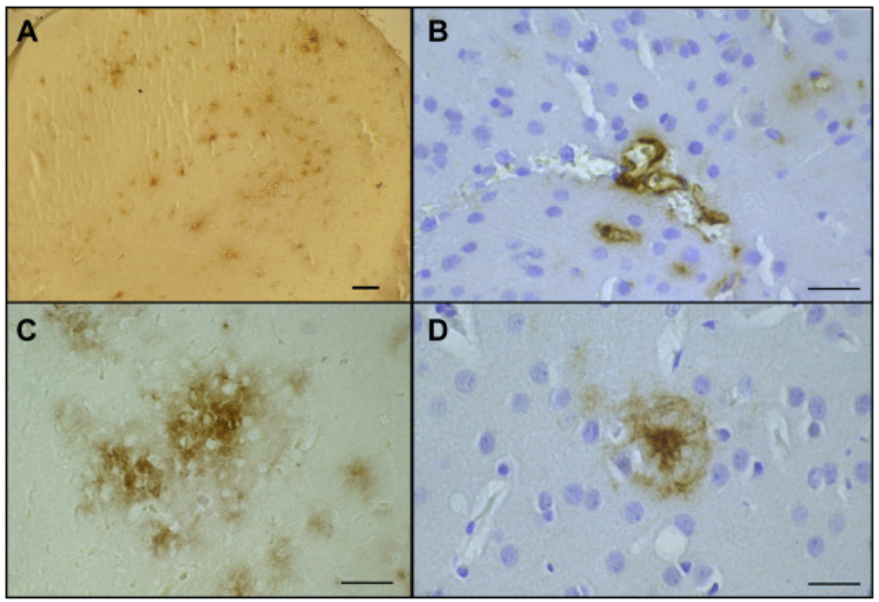
Mestres-Frances et al. 1996-2000, Dhenain et al. 2000, Kraska et al. 2009

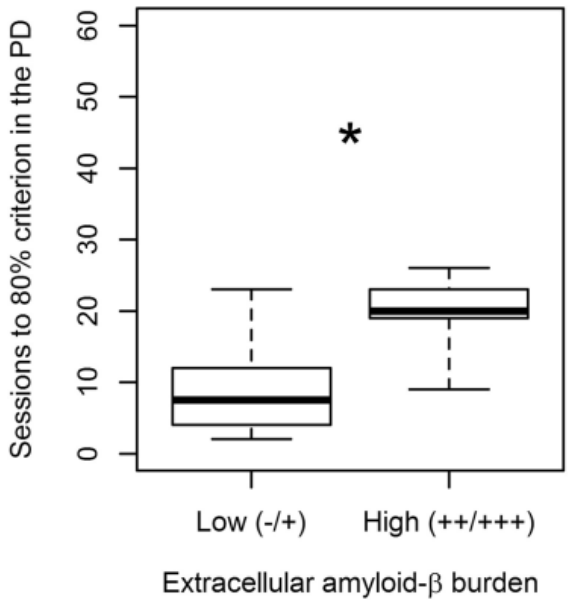
Neurobiology of Aging
Volume 94, October 2020, Pages 207-216

Regular article

Linking cognition to age and amyloid-β burden in the brain of a nonhuman primate (*Microcebus murinus*)

Daniel Schmidtke [a, b], Elke Zimmermann [a, b], Stéphanie G. Trouche [c], Pascaline Fontès [c], Jean-Michel Verdier [c], Nadine Mestre-Francés [c]

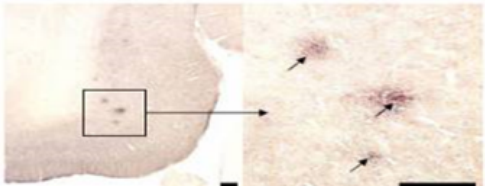




Neurodegeneration

a subpopulation of mouse lemurs (~10%) does not fit the description of normal brain aging:

Severe changes in behavior, and severe impairment in specific memory and cognitive functions.
Correlates very well with brain atrophy but also neuron death, presence of amyloid plaques, and altered glycemic parameters.



Microcebus age-associated neurodegeneration **(MAAN)** syndrome (Bons et al. *Genes Brain and Behav*. 2006)

Does not perfectly mimics AD, but shows very interesting similarities, and can be considered as one of the rare non-genetic, spontaneous AD model.

Induction of AD-like pathology in mouse lemur

(coll. Dr. M, Dhenain, MIRCEN, CEA Fontenay-aux-Roses)

Gary *et al. Acta Neuropathologica Communications* (2019) 7:126
https://doi.org/10.1186/s40478-019-0771-x

Acta Neuropathologica Communications

RESEARCH Open Access

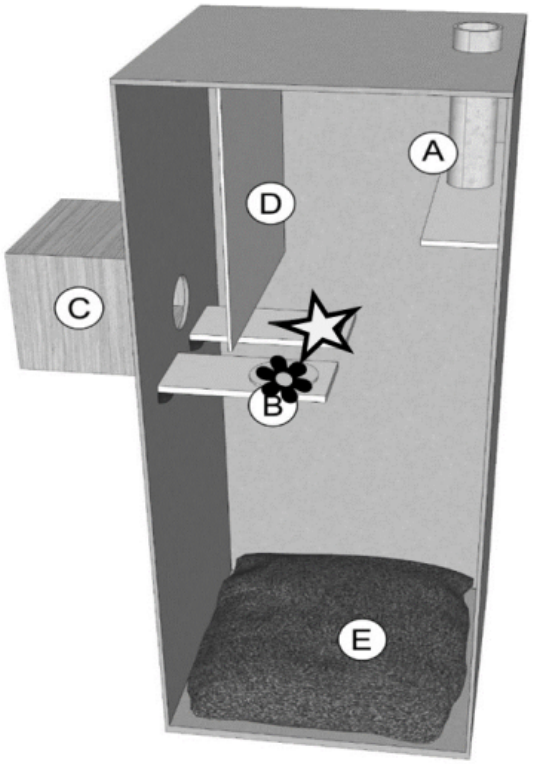
Encephalopathy induced by Alzheimer brain inoculation in a non-human primate

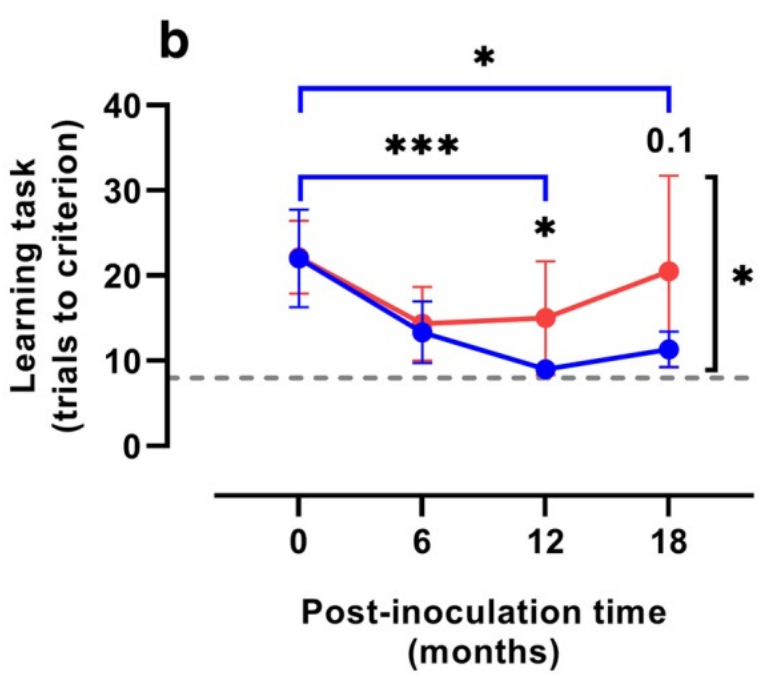
Charlotte Gary[1,2], Suzanne Lam[1,2†], Anne-Sophie Hérard[1,2†], James E. Koch[1,2,3], Fanny Petit[1,2], Pauline Gipchtein[1,2], Stephen J. Sawiak[4,5], Raphaëlle Caillierez[6], Sabiha Eddarkaoui[6], Morvane Colin[6], Fabienne Aujard[7], Jean-Philippe Deslys[8], French Neuropathology Network[9], Emmanuel Brouillet[1,2], Luc Buée[6], Emmanuel E. Comoy[8], Fabien Pifferi[7†], Jean-Luc Picq[1,2,10†] and Marc Dhenain[1,2*]

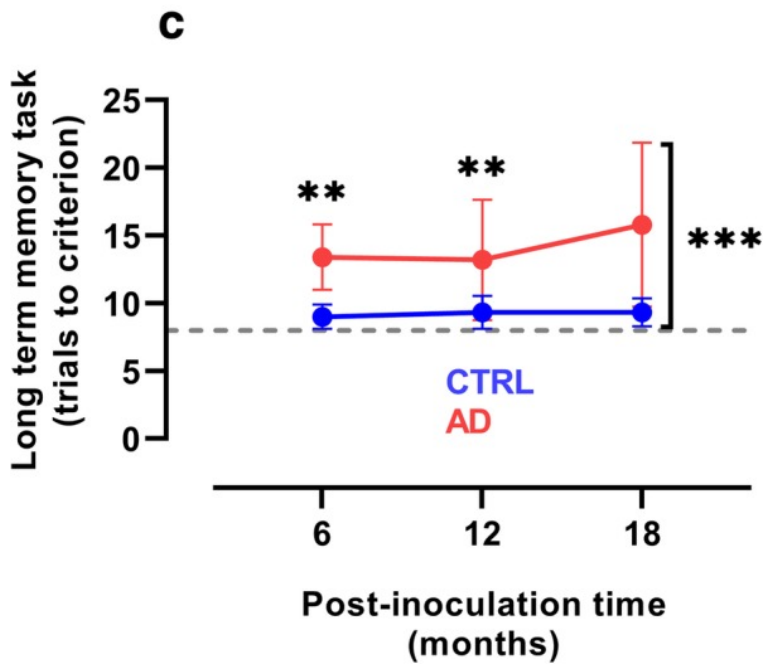
Based on the prion hypothesis of AD: experimental transmission of amyloidosis and Tau pathology by brain inoculation of AD human brain homogenates

(AD *vs* CTL, n=12 young adults, 18 months of follow-up)

Induction of AD-like pathology in mouse lemur







Reliable and fast mimicking of an AD-like pathology (protein aggregates, brain atrophy, cognitive decline)

Gary et al. Acta Neuropathol Commun. 2019

GENETICS

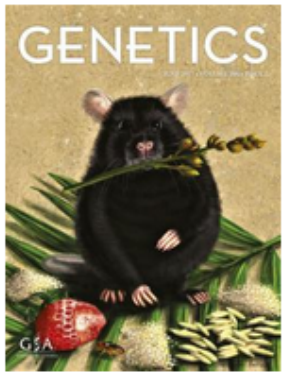
The Mouse Lemur, a Genetic Model Organism for Primate Biology, Behavior, and Health

Camille Ezran, Caitlin J. Karanewsky, Jozeph L. Pendleton, Alex Sholtz, Maya R. Krasnow, Jason Willick, Andriamahery Razafindrakoto, Sarah Zohdy, Megan A. Albertelli and Mark A. Krasnow

GENETICS *June 1, 2017 vol. 206 no. 2 651-664; https://doi.org/10.1534/genetics.116.199448*

PUBLICATION INFORMATION

Volume 206 Issue 2, June 2017



Collaboration M. Krasnow, U. Stanford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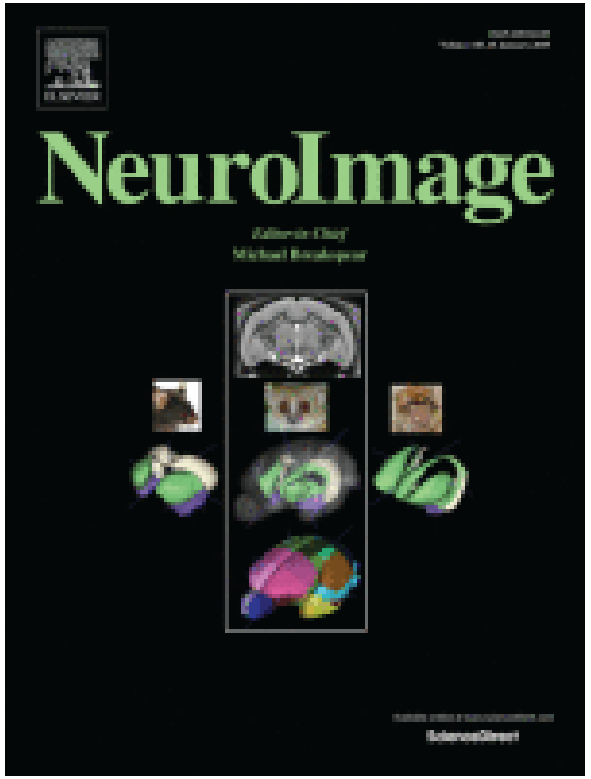
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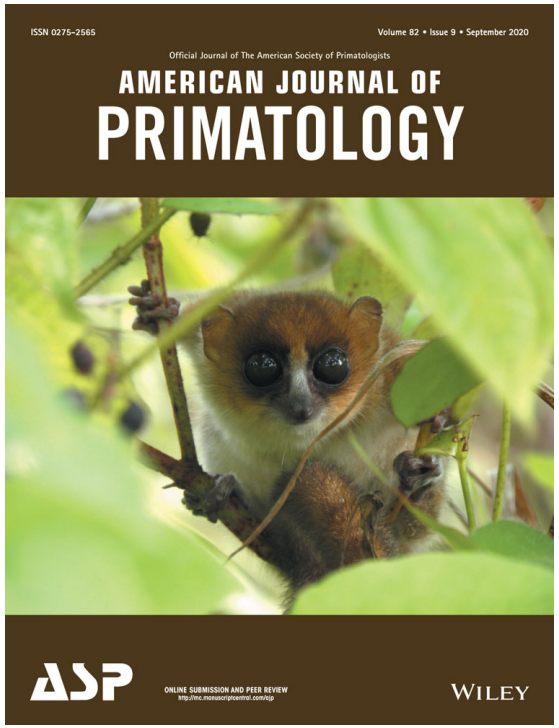
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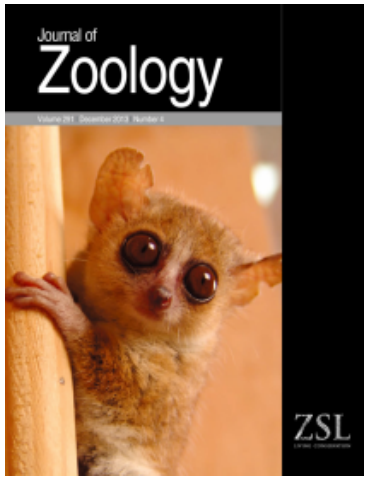
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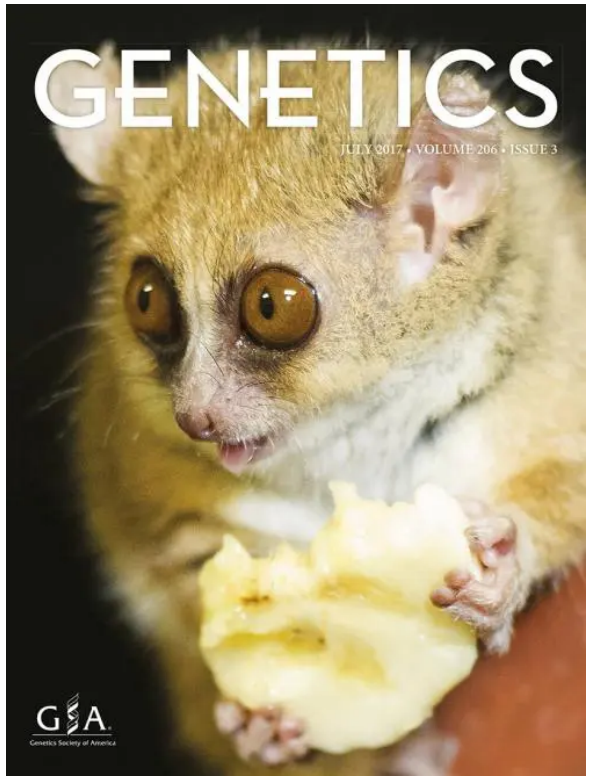
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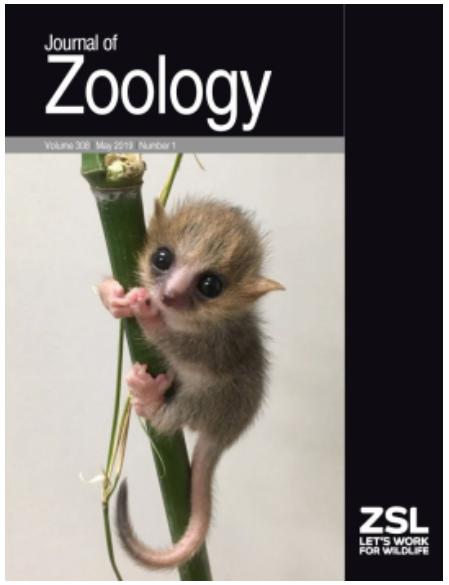
MAKE WAY FOR
THE MOUSE LEMUR
If a US biochemist has his way, the world's tiniest primate could become a top research animal for genetics.
BY LESLIE ROBERTS


Journal of
Zoology
ZSL
LET'S WORK FOR WILDLIFE

Merci de votre attention

Le site CNRS-MNHN de Brunoy (91)

Remerciements :
Marc Dhenain (CEA), Fabienne Aujard, Martine Perret

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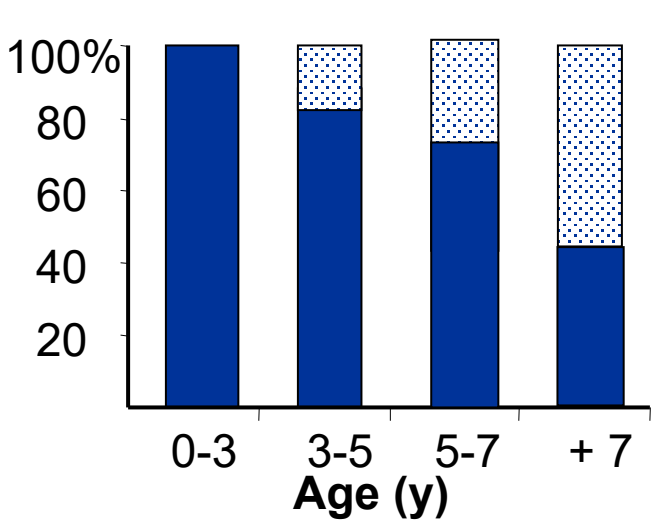
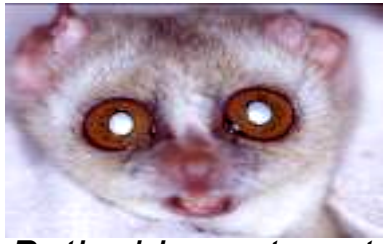
Aging of sensory-motor functions

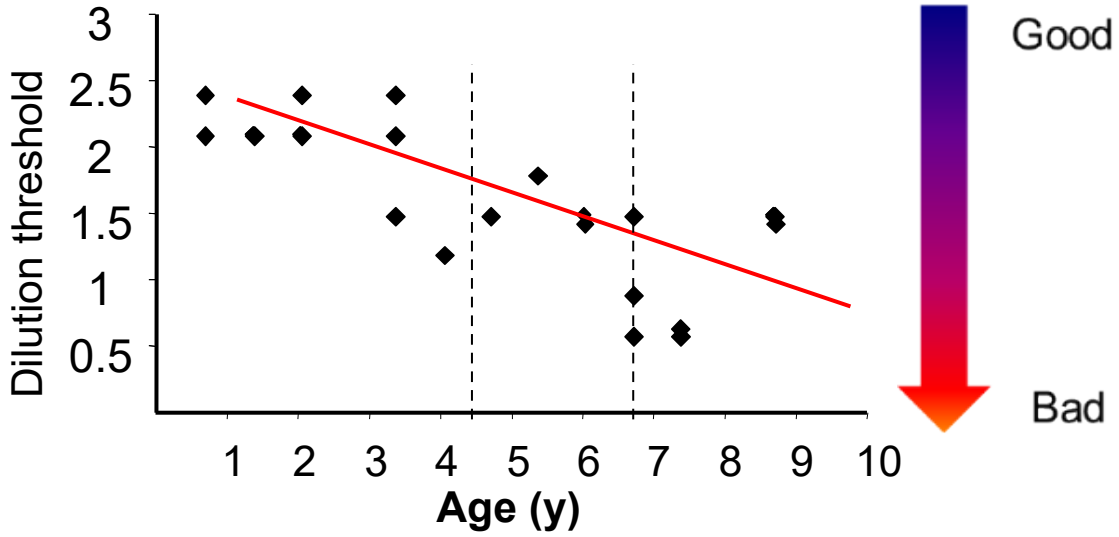
Vision





Both sides cataract
(9 y.o.)

Olfaction



Vision slowly declines with age. Close to 60% of the more than 7 y.o. animals, exhibit at least an eye pathology

Olfaction is also declining significantly with age
+ declining auditory functions (Schopf, 2014)

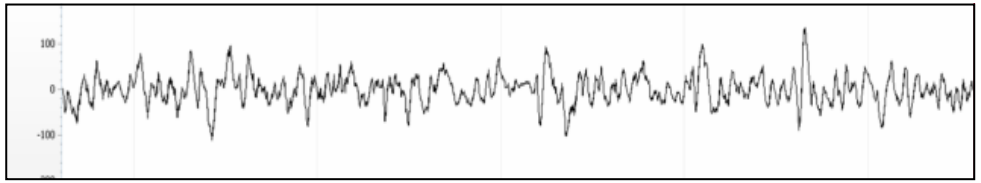
➔Very similar to humans…what about brain functions?

Cayetanot et al Neuroreport 2005 ; Beltran et al Vet Ophthalmology 2007

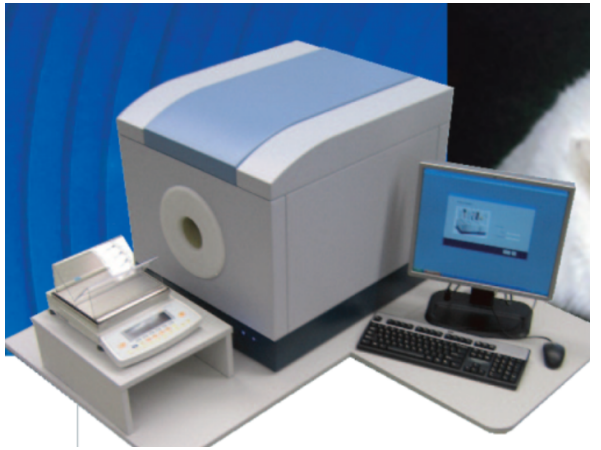
2. Exemple de stratégie nutritionnelle anti-vieillissement : la restriction calorique

Tools to study aging in mouse lemur

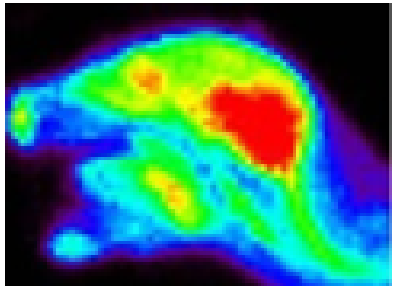
Electrophysiology (EEG/ECG/EMG, sleep-wake cycles)

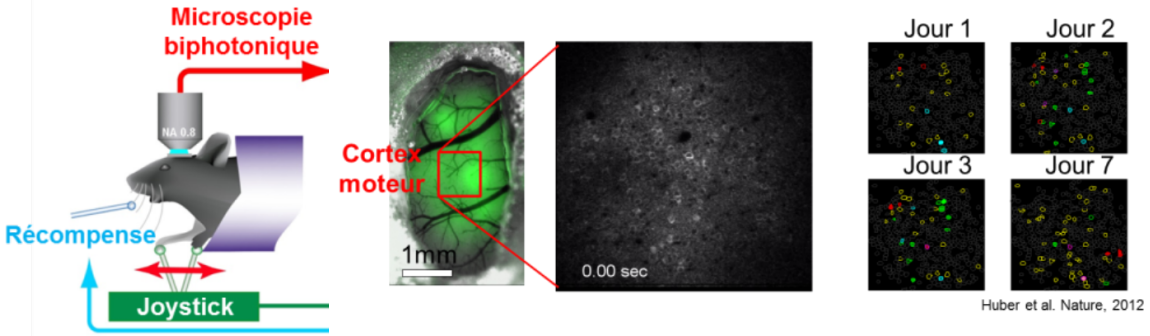


Metabolism studies: respirometry, indirect calorimetry, MRI (body composition)



Imaging (PET, MRI) collaborative work





In vivo 2-photons imaging (collaboration D. Huber, U. Geneva)

NeuroImage 185 (2019) 85–95

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

A 3D population-based brain atlas of the mouse lemur primate with examples of applications in aging studies and comparative anatomy

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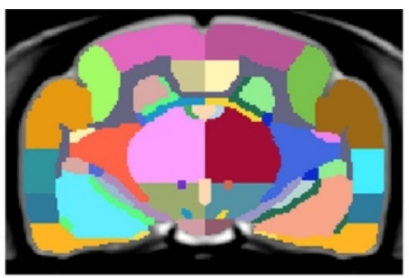
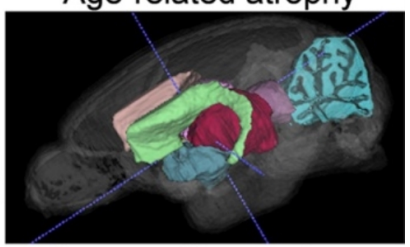
NITRC
NeuroImaging Tools & Resources Collaboratory

34 mouse lemurs → template

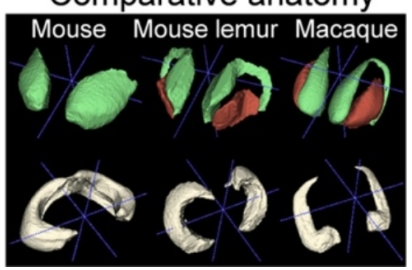


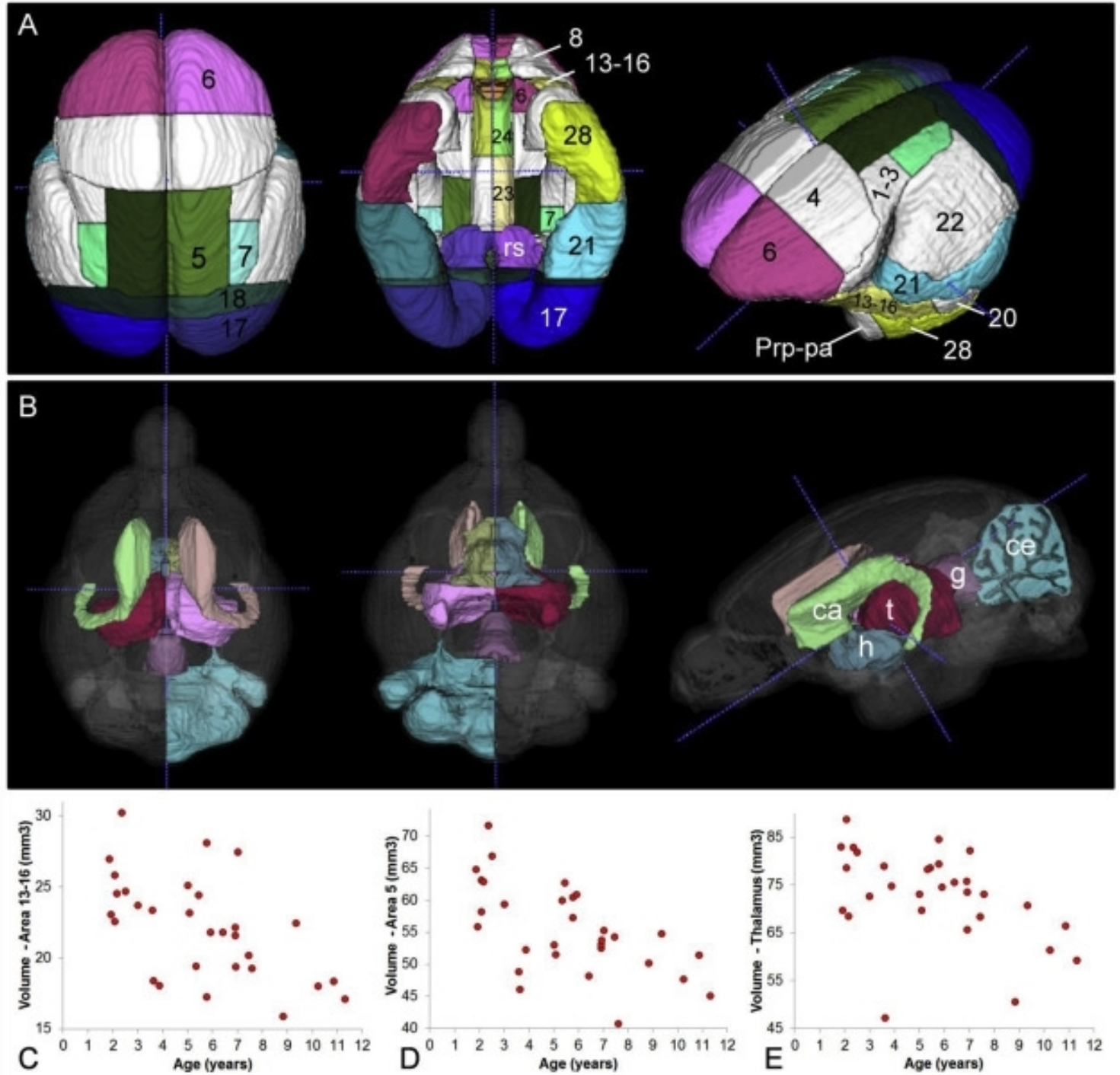
120 structures delineated
Whole brain 3D atlas

Examples of applications:
Age-related atrophy



Comparative anatomy

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Prp-pa
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t
h
Volume - Area 13-16 (mm3)
Age (years)
C
Volume - Area 5 (mm3)
Age (years)
D
Volume - Thalamus (mm3)
Age (years)
E

Methodology article | Open Access

Hybrid de novo genome assembly and centromere characterization of the gray mouse lemur (*Microcebus murinus*)

Peter A. Larsen †, R. Alan Harris †, Yue Liu, Shwetha C. Murali, C. Ryan Campbell, Adam D. Brown, Beth A. Sullivan, Jennifer Shelton, Susan J. Brown, Muthuswamy Raveendran, Olga Dudchenko, Ido Machol, Neva C. Durand, Muhammad S. Shamim, Erez Lieberman Aiden, Donna M. Muzny, Richard A. Gibbs, Anne D. Yoder, Jeffrey Rogers and Kim C. Worley

†Contributed equally

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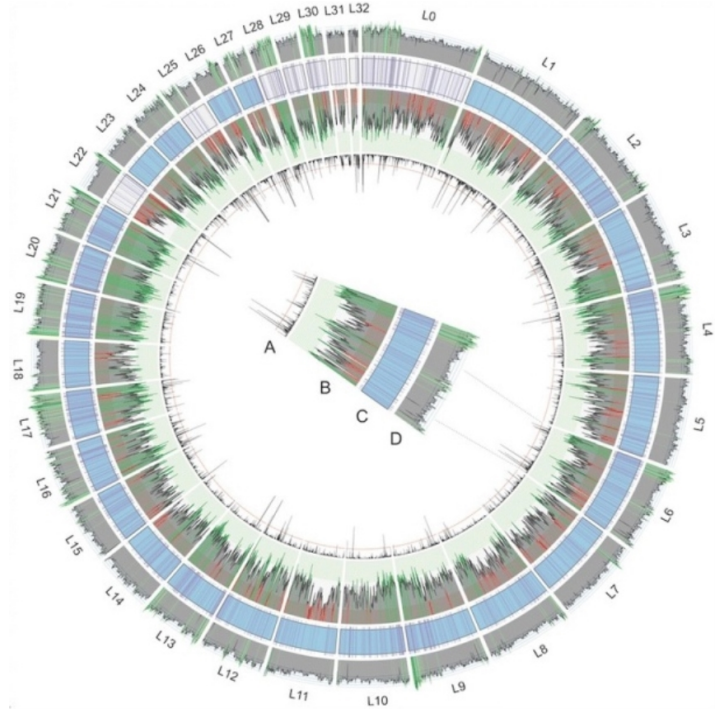
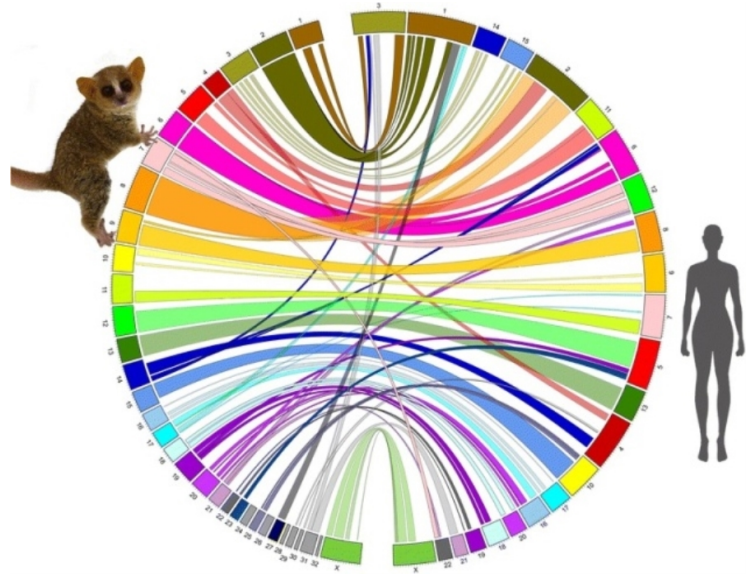
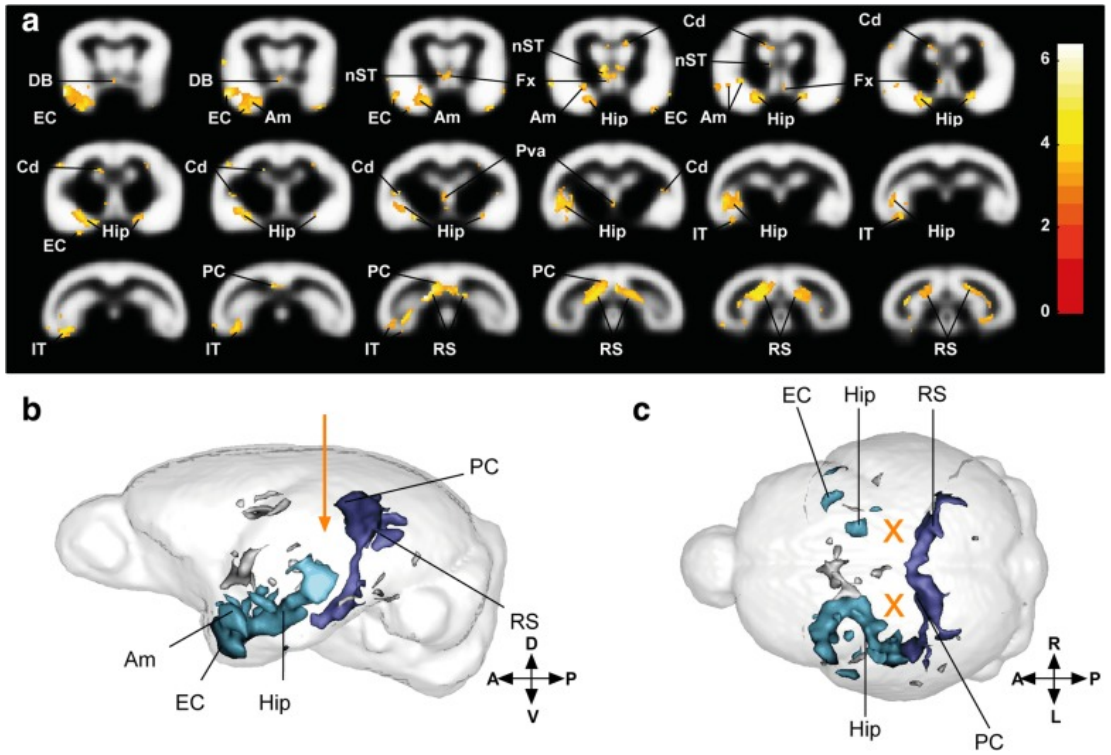
https://doi.org/10.1186/s12915-017-0439-6
Received: 20 June 2017 | **Accepted:** 10 October 2017 | **Published:** 16 November 2017



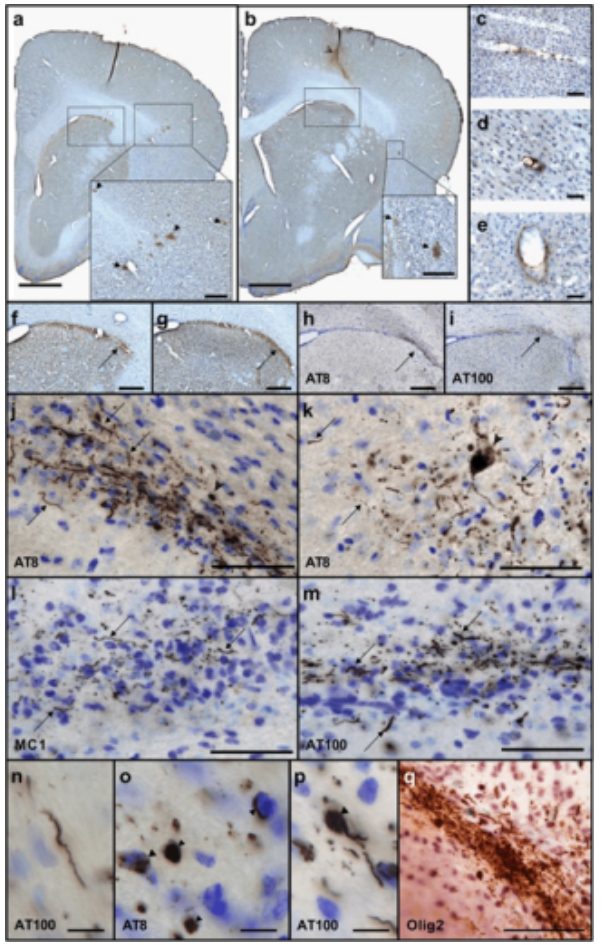


Induction of AD-like pathology in mouse lemur

Apparition of cerebral atrophy (first signs of atrophy 6 months post-inoculation)

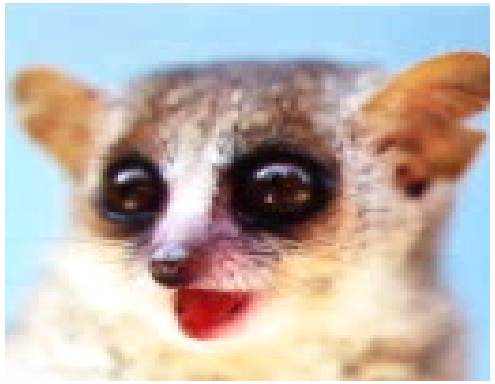
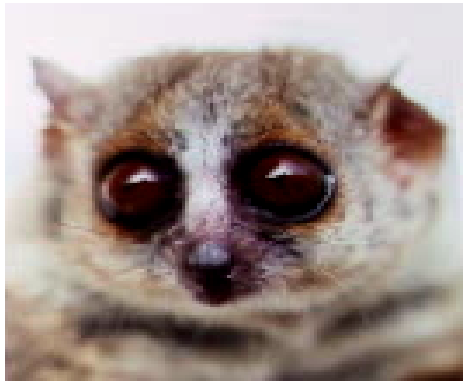
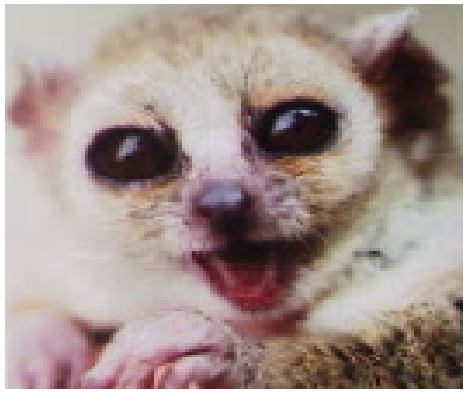
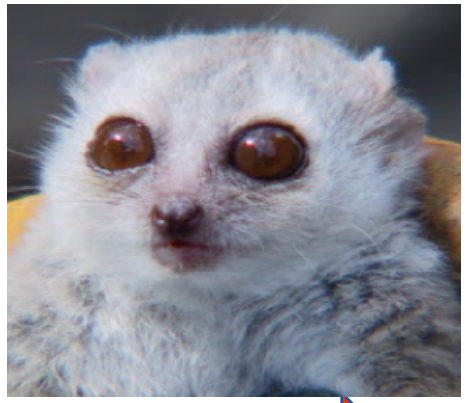


Spreading of Ab and Tau proteins aggregates in the whole brain after 18 mo.



Gary et al. Acta Neuropathol Commun. 2019

Nutritional anti-aging strategies

Optimal cognitive functions → **Altered cognitive functions**

Metabolic alterations

Risk factors

Polyphenols

Calorie Restriction

Omega-3 fatty acids

Physical activity

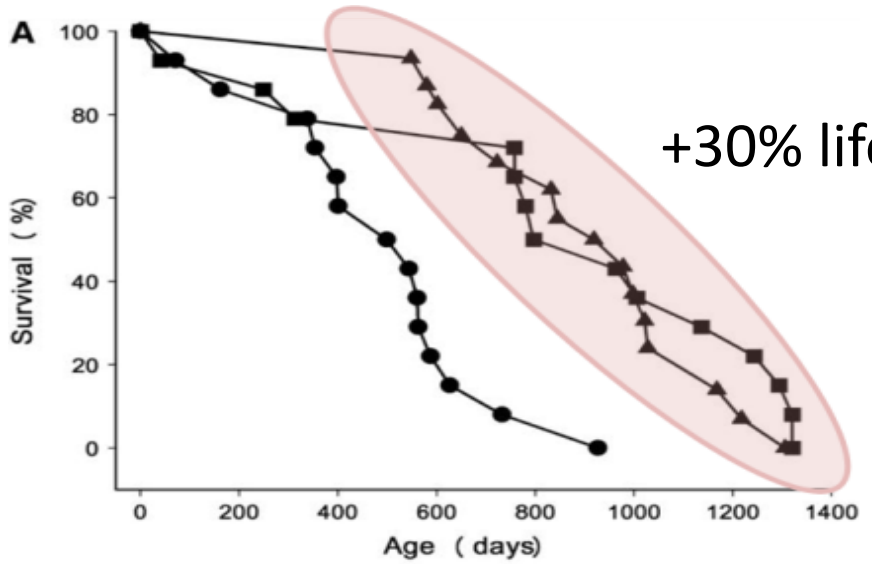
First experimental demonstration of the impact caloric restriction in rats: McCay, J. Nutr. 1935

THE EFFECT OF RETARDED GROWTH UPON THE LENGTH OF LIFE SPAN AND UPON THE ULTIMATE BODY SIZE [1]

C. M. McCAY, MARY F. CROWELL AND L. A. MAYNARD
Animal Nutrition Laboratory, Cornell University, Ithaca

ONE FIGURE

(Received for publication January 18, 1935)



+30% lifespan

Calorie restriction increases longevity in several species, from yeast to rodents

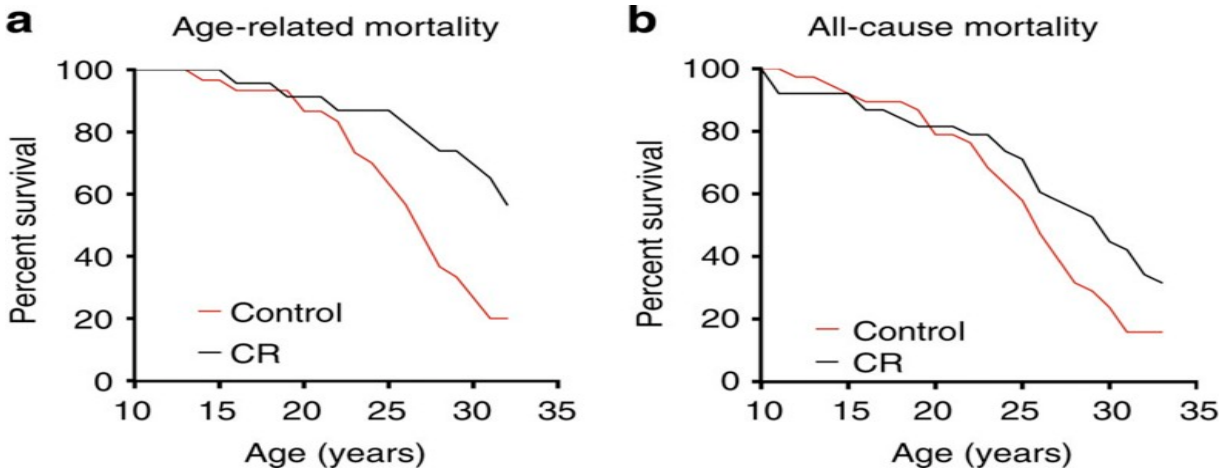
CR in primates? No consensus…

In Humans

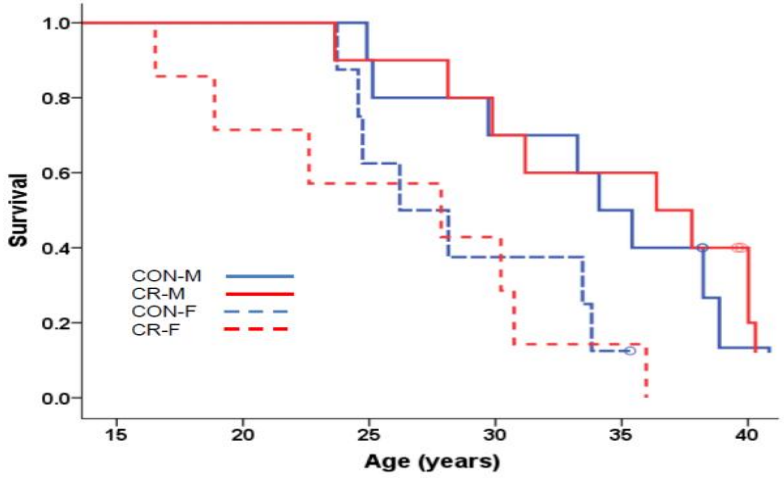
The Okinawa « restricted » diet could be the reason of prolonged longevity, but could also be the cause of low birth weight and malnutrition
(Le Bourg E. Gerontology. 2012)

In macaques, two contradictory studies…

Wisconsin National Primate Research Center Study



National Institute on Aging Study



Validation in primates still missing and suspected to impair cognition

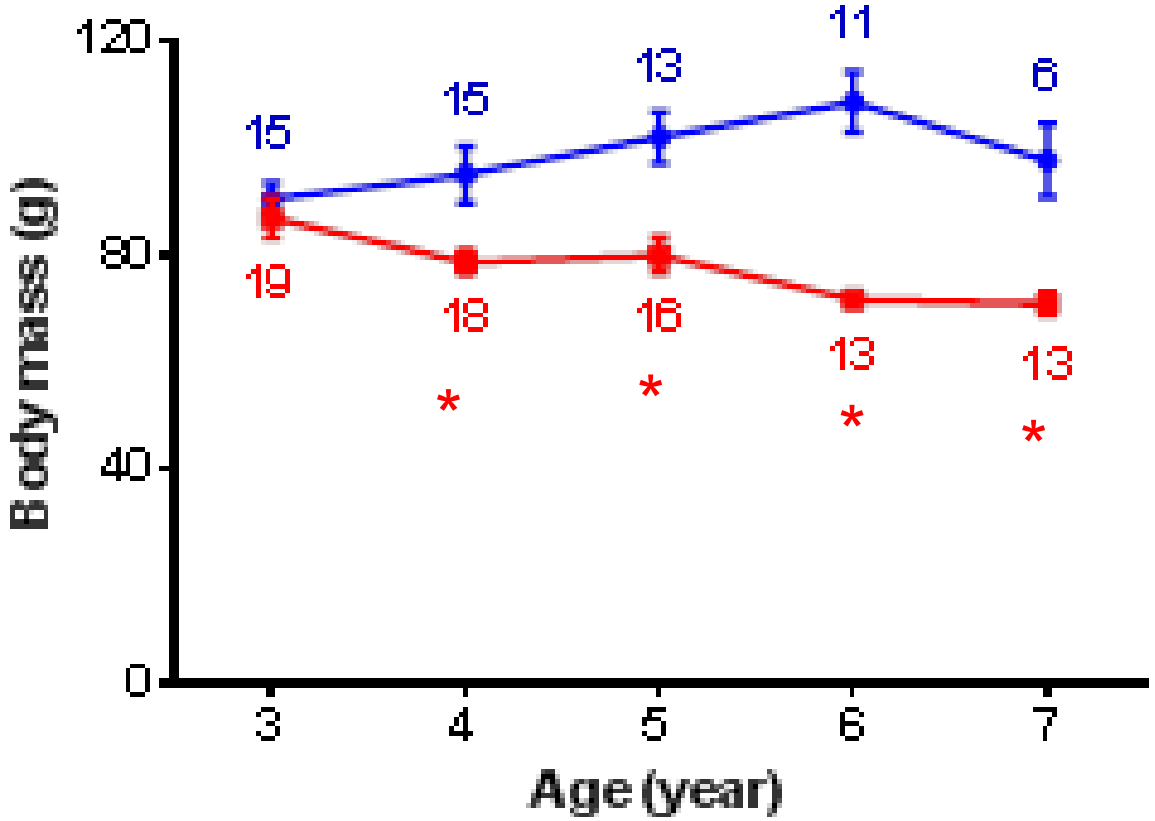
The RESTRIKAL project

24 males at the begining of the study (inclusion around 3 y.o.)

Longitudinal follow-up of age-related markers and lifespan

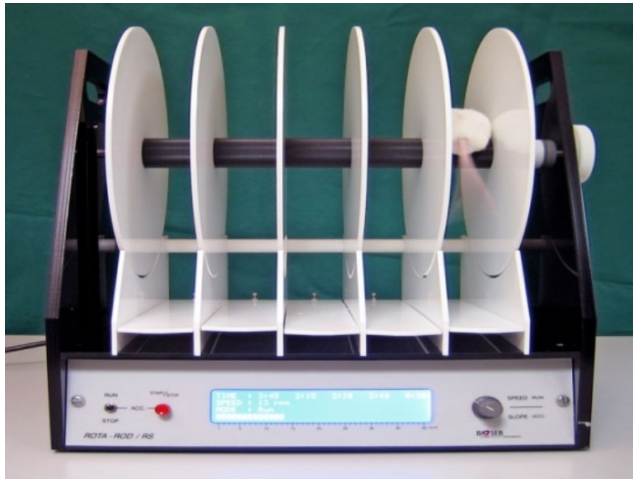
Apparition of age-related pathologies

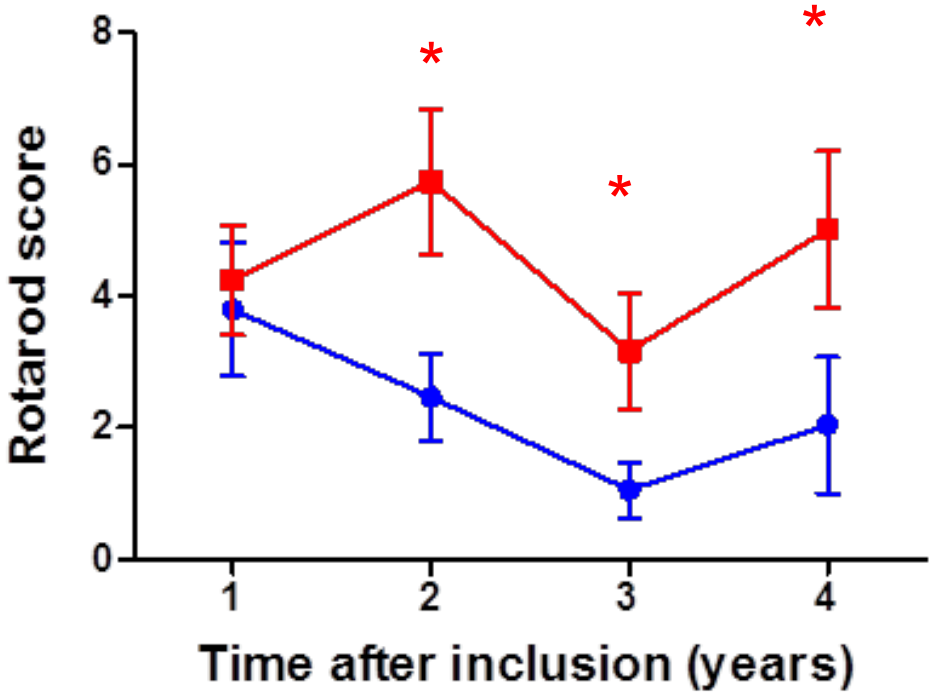
Impact of CR on body weight



Impact of CR on sensory-motor functions

Motor coordination (Rotarod)



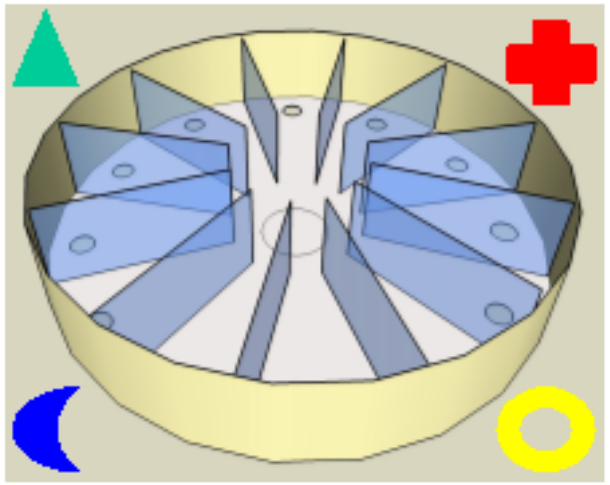


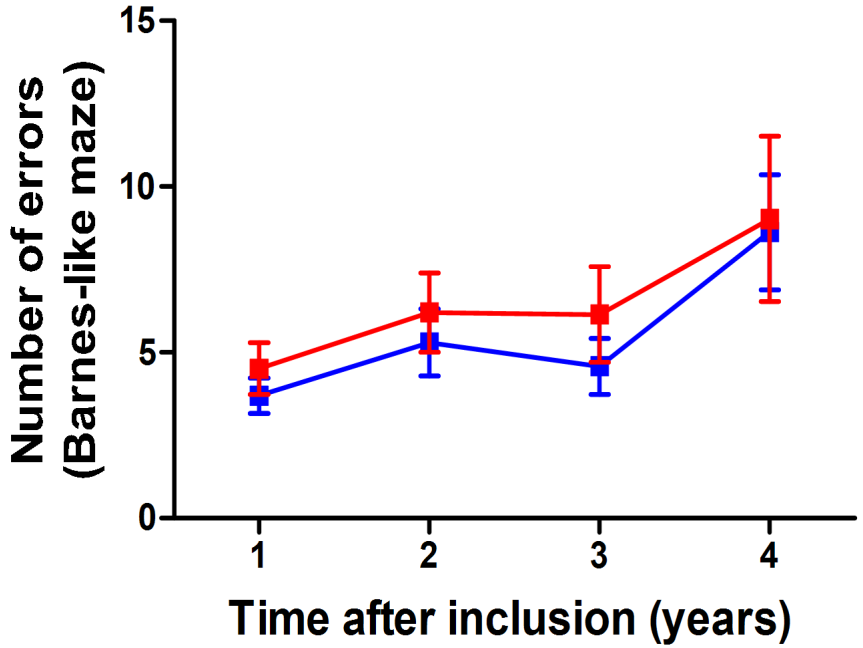
Amelioration of motor coordination (rotarod)
Maintained force (measured in a high jump task)

Dal-Pan/Pifferi et al. Plos One 2011; Dal-Pan et al. Age 2010

Impact of CR on cognitive functions

Reference memory task





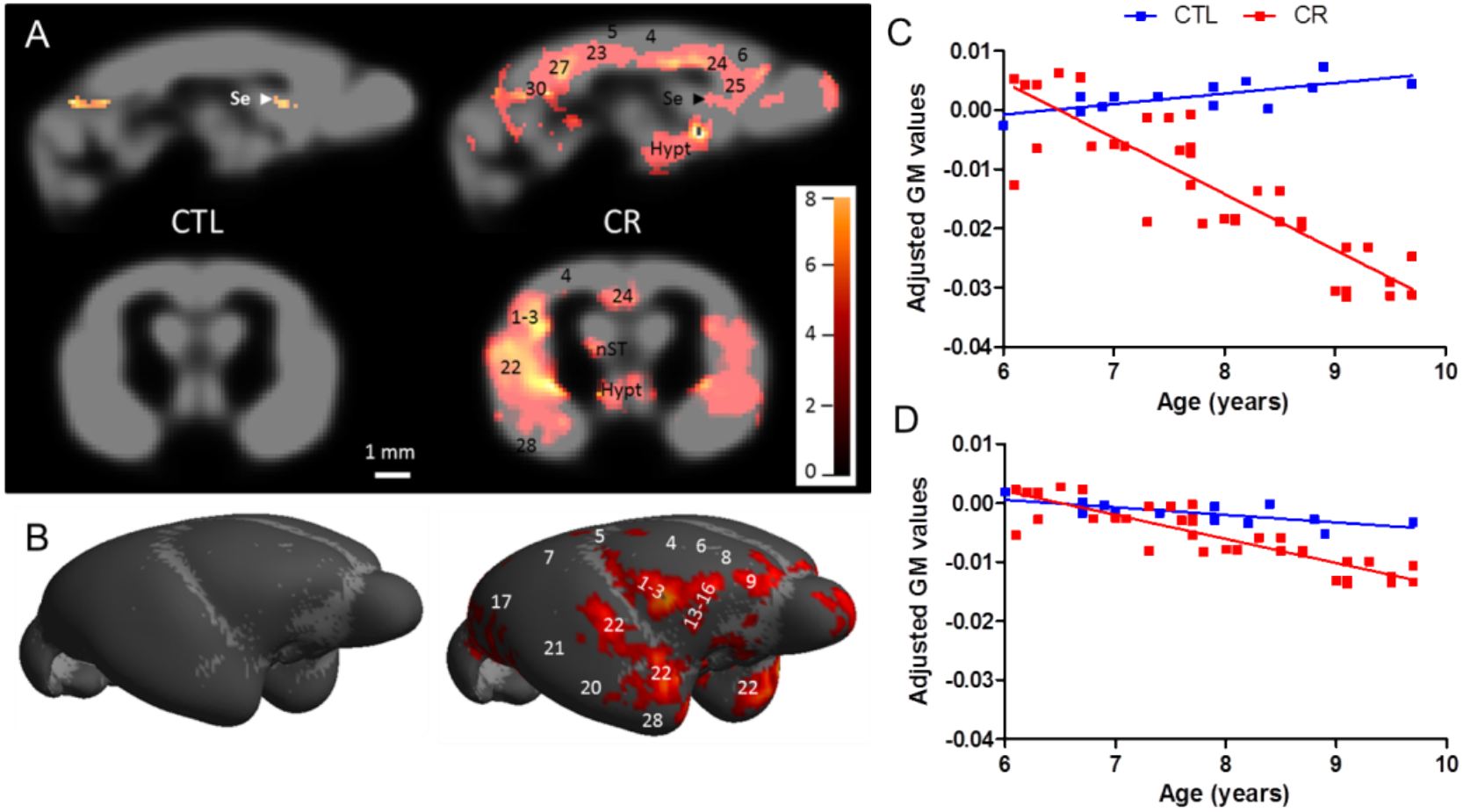
NS

- No alteration of cognitive performances (spatial, working and emotion memory) between CTL and CR animals

- Better glucose tolerance and Insulin response

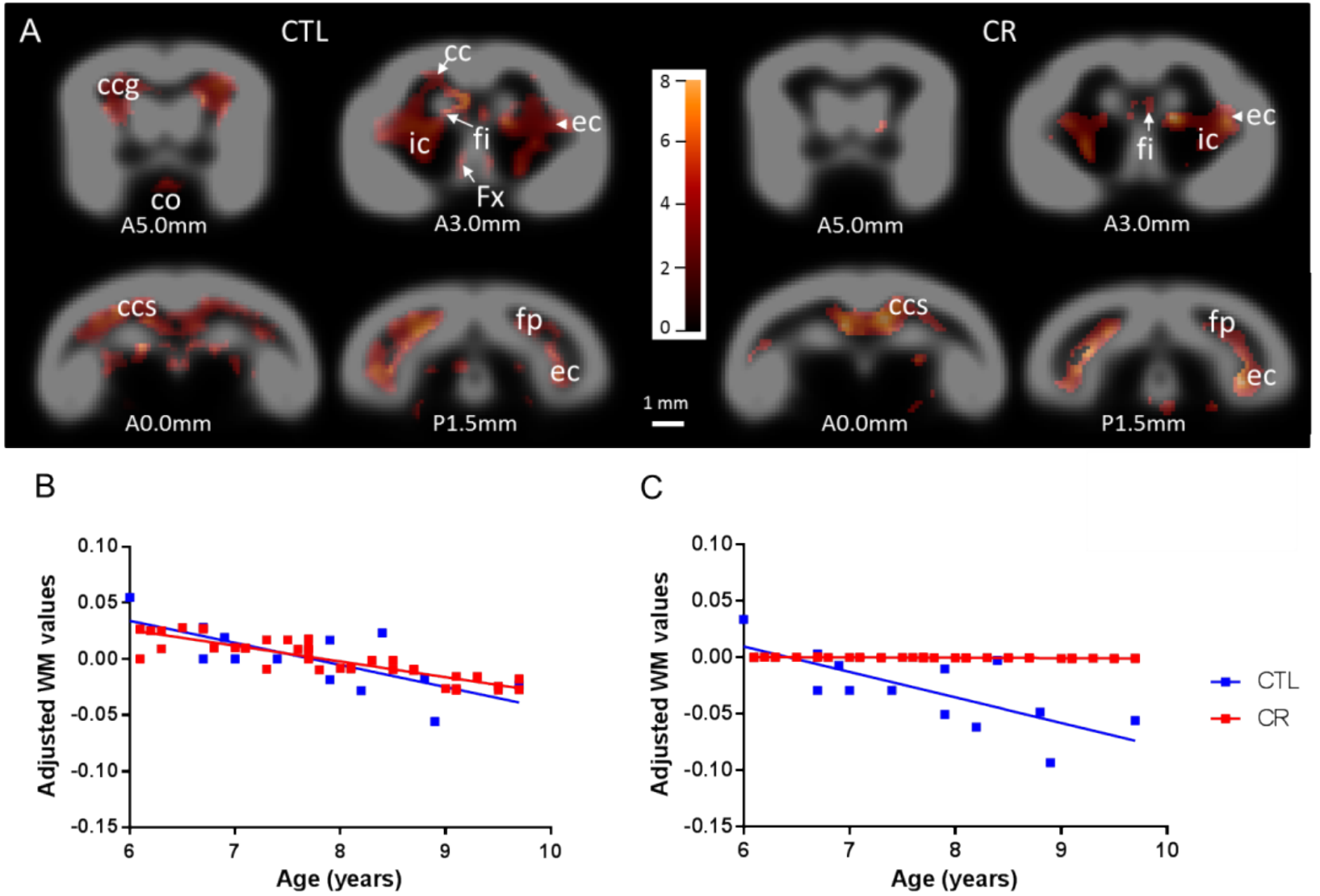
Dal-Pan/Pifferi et al. Plos One 2011; Dal-Pan et al. Age 2010

Impact of CR on age-related brain atrophy



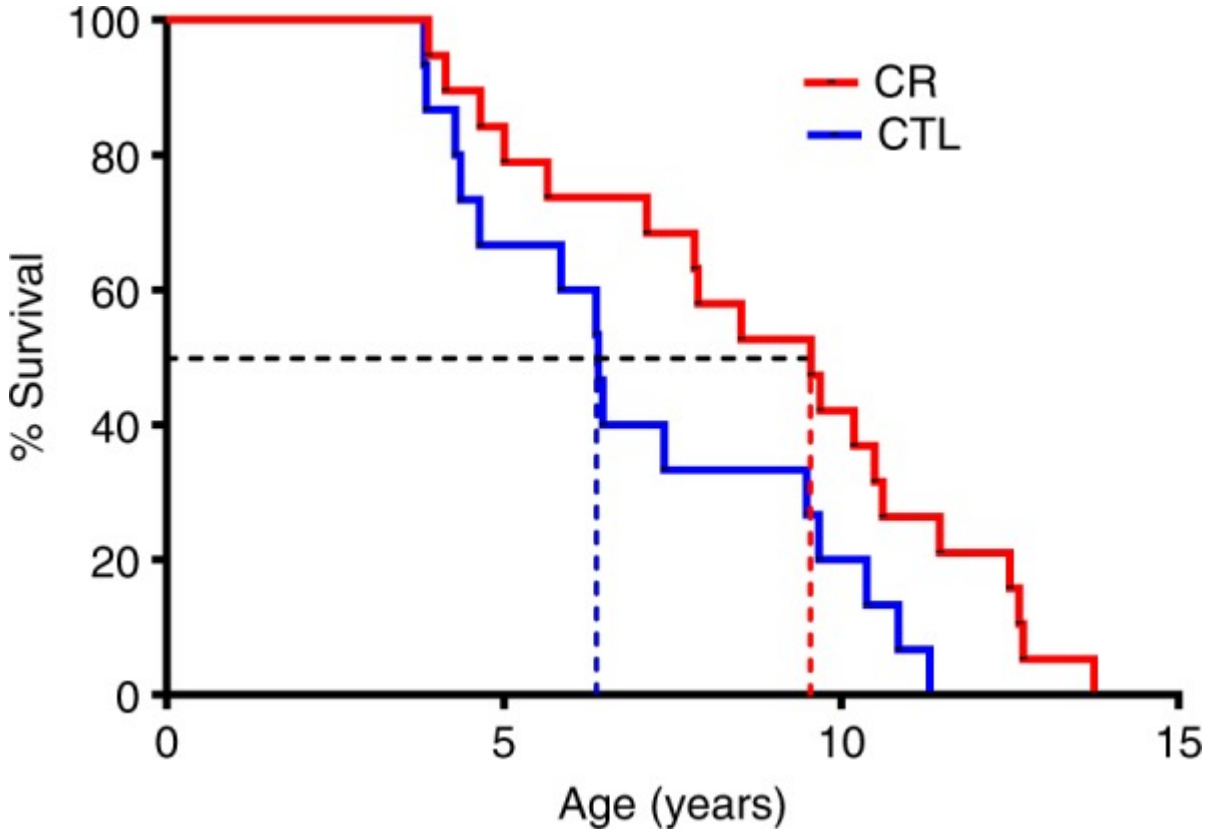
Significant but probably marginal GM atrophy in CR fed animals (no effect on cognition)

Impact of CR on age-related brain atrophy



CR is protecting against white matter atrophy!

Impact of CR on all cause mortality



Median lifespan:
CTL = 6.4 y.
CR = 9.6 y.

CR increases lifespan and maximal observed longevity

Pifferi, Terrien et al. 2018 Commun. Biol.

The breeding colony of Brunoy

UMR CNRS-MNHN 7179: Laboratory dedicated to Ecology and Physiology

History of Brunoy's breeding colony

Funded in 1967 by Dr. Petter in a laboratory of the National Museum of Natural History (Brunoy)

Animal importation from 1967 to 1972 (before the establishment of Washington's Convention)

April/October 1967: 7 males -13 females
September/December 1968: 17 - 56 females
October 1970: 7 males - 35 females
Mars 1972: 18 males - 38 females

After March 1972 no more animals have been imported.

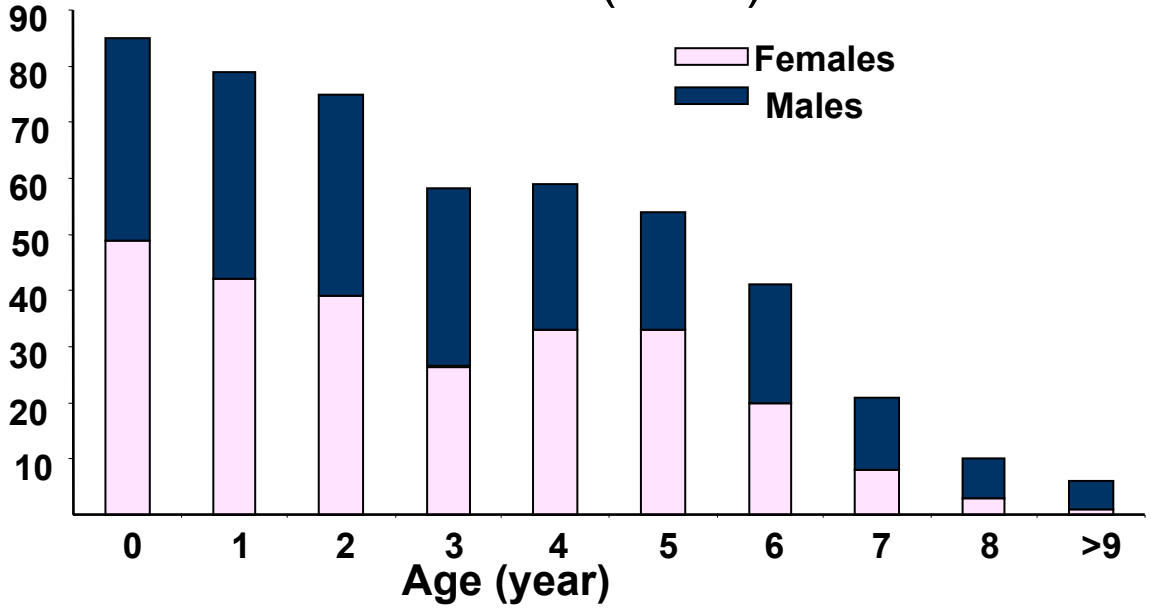
Brunoy's breeding colony

>330 m^2 of building dedicated to more than 500 animals living in rooms ($3m^3$) and cages ($2m^3$ and $1m^{3)}$ and $0.5m^3$ when animals need to be isolated

All cages contain lots of branches, supports and a least two wooden nests

Brunoy's breeding colony

Mouse lemurs alive (~450)



Production: 80 to 100 young individuals per year

Fully dedicated to research (government fundings)

2 days

10 years