Autologous neural cell ecosystems (ANCE) transplantation as therapy for Parkinson's disease: a promising approach

Cognition day – the 5th of October 2016 – University of Fribourg

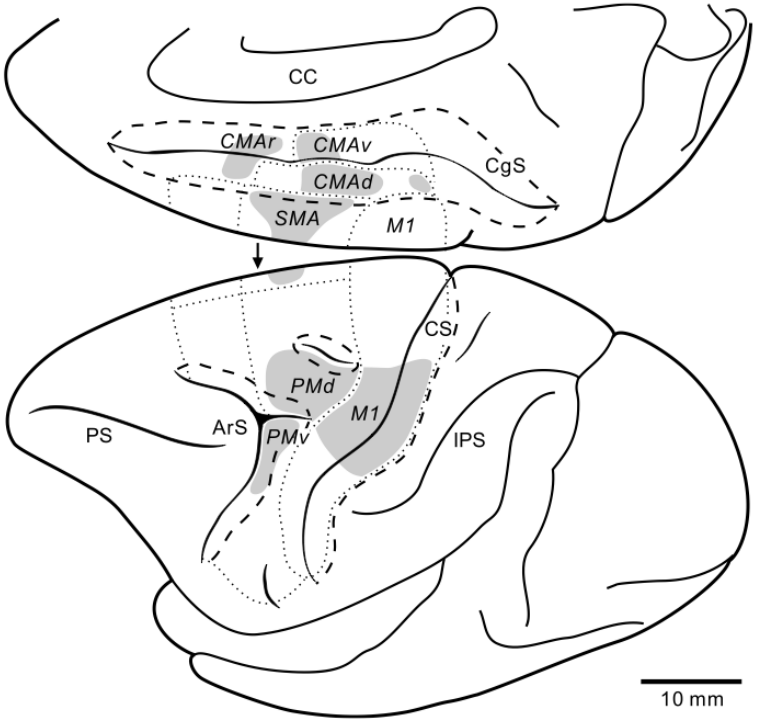
Simon Borgognon

Laboratory of Prof. Eric Rouiller (UNIFR)
In collaboration with Dr. Jocelyne Bloch & Dr. Jean-François Brunet (CHUV)

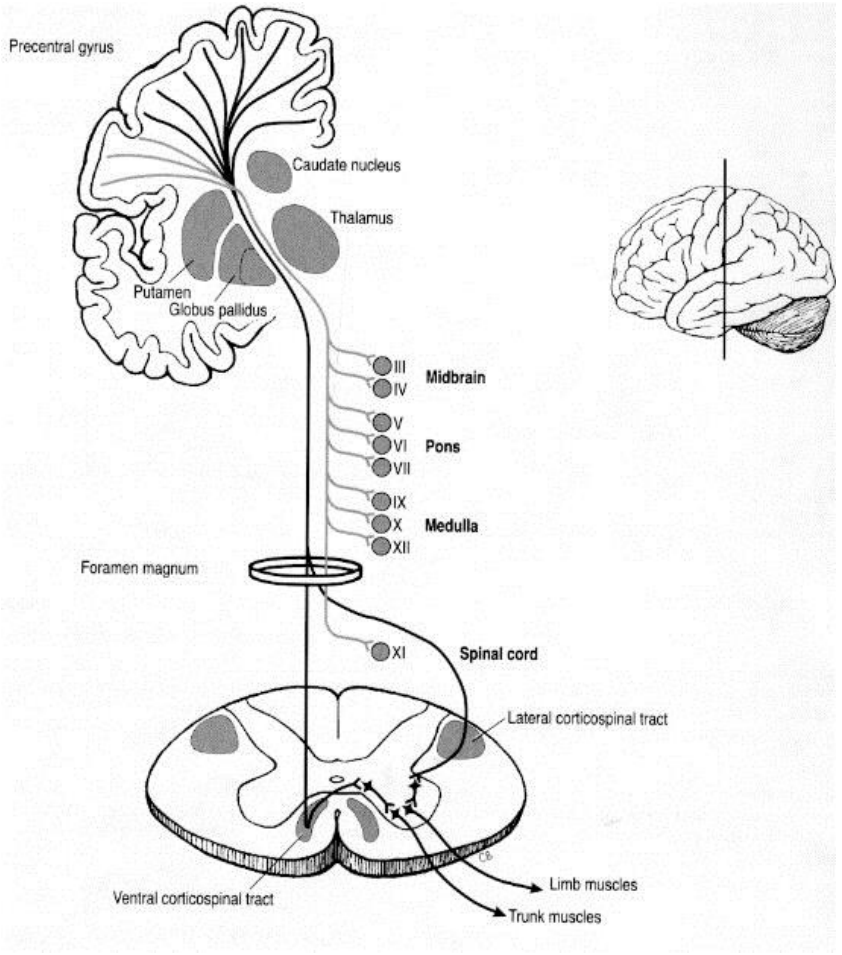
SPCCR

Basel declaration

Motor cortices & corticospinal tract (CST)

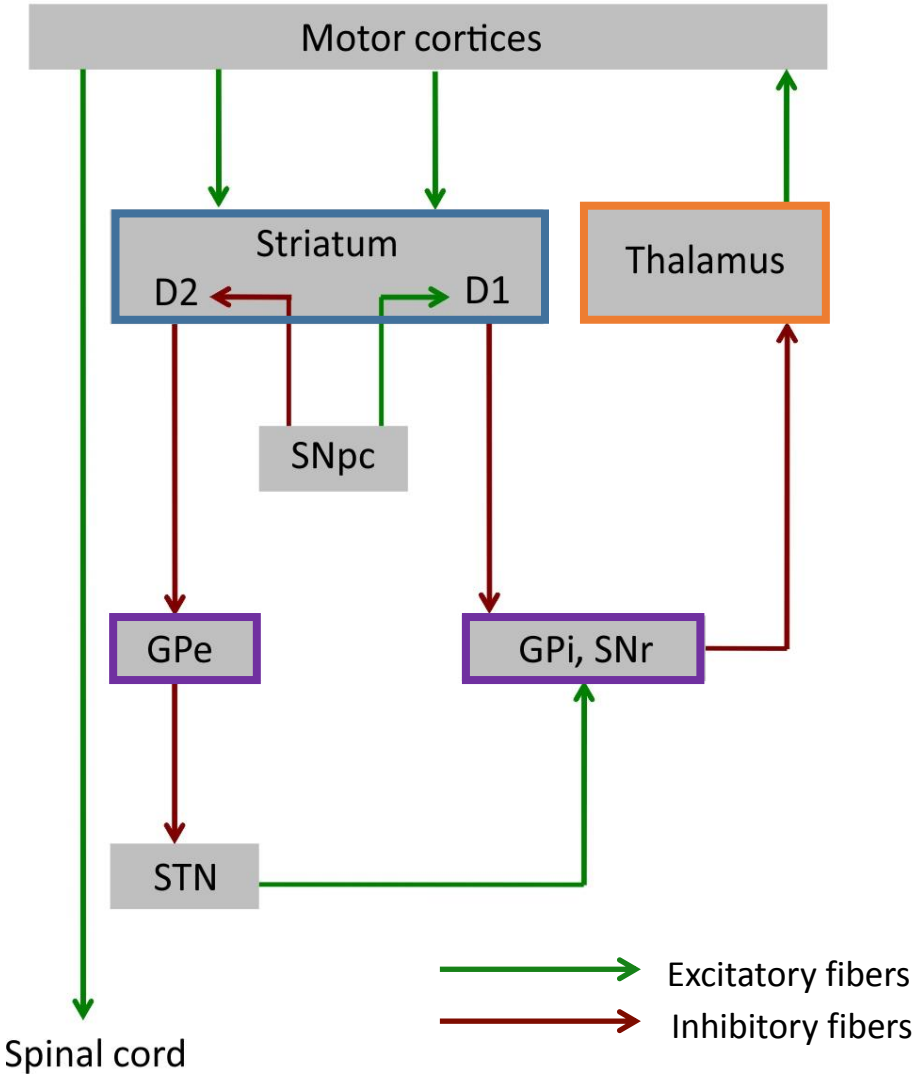


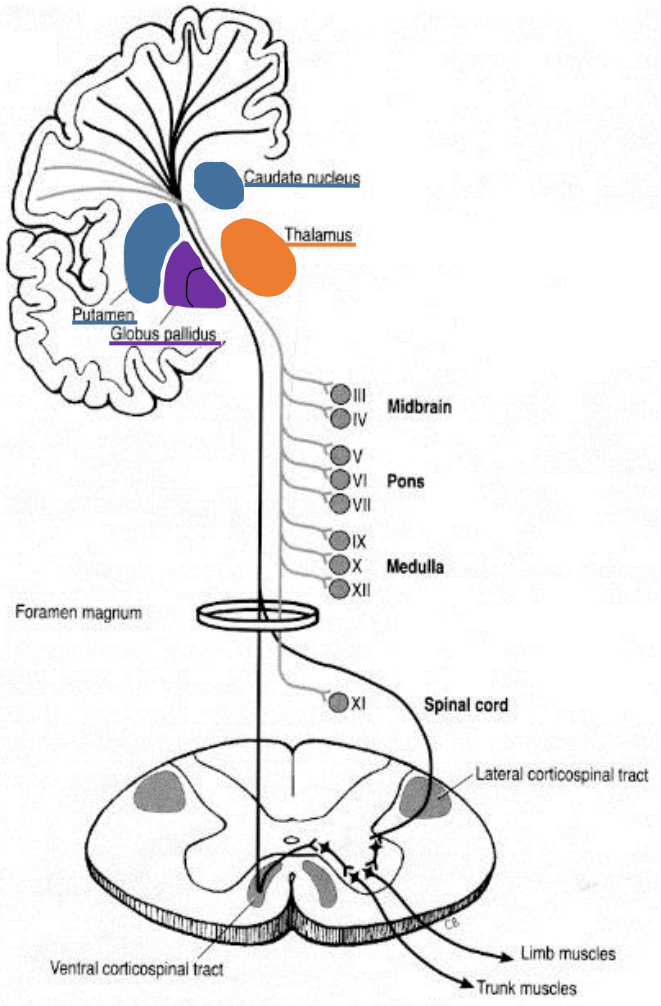
Dum & Strick (2002). *Physiology & Behavior*



http://www2.fiu.edu/~condon/pathway.htm

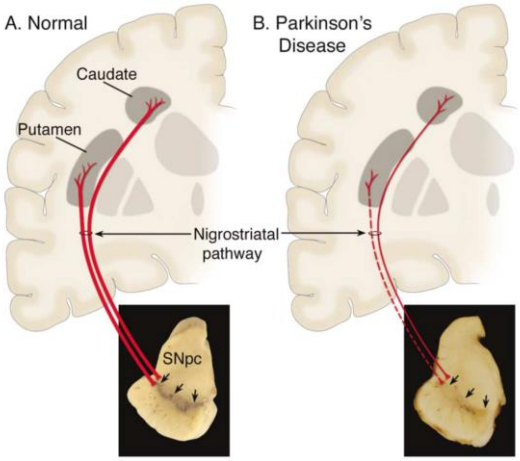
Simplified motor circuits: direct and indirect pathways



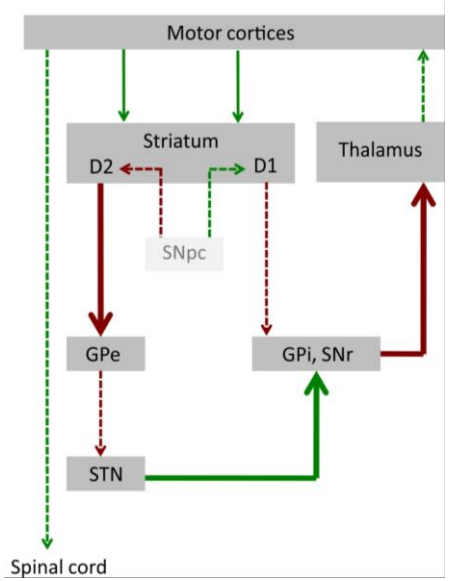


Adapted from DeLong & Wichmann (2007). *Arch. Neurol.*

Parkinson's disease (PD): 2nd most common neurodegenerative disease



Dauer & Przedborski (2003). *Neuron*



Gowers (1886). *A manual of disease of nervous system*

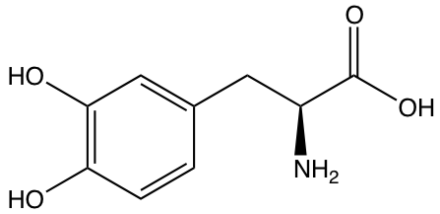
Wolter & Baumann (2014). *Parkinson Disease and Other Movement Disorders*

Parkinson's disease (PD): treatments

Pharmocological treatments:

Levodopa, dopa agonist, …

→ dyskinesia,...



Surgical approach:

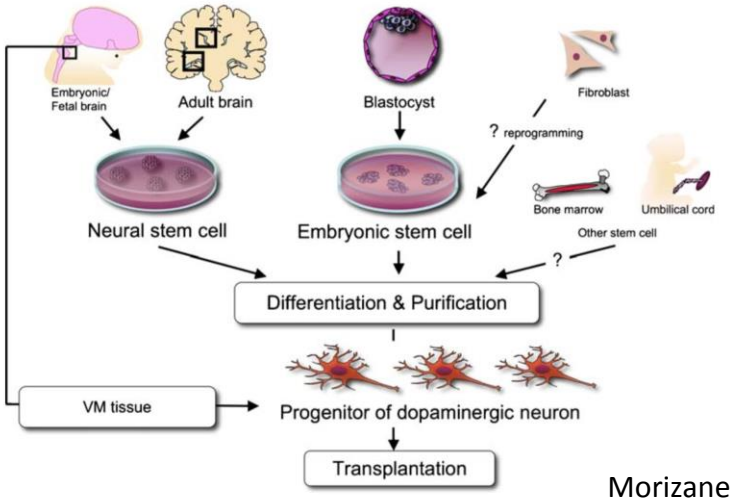
Deep brain stimulation (DBS)

→ symptomatic treatment

Cell therapies:

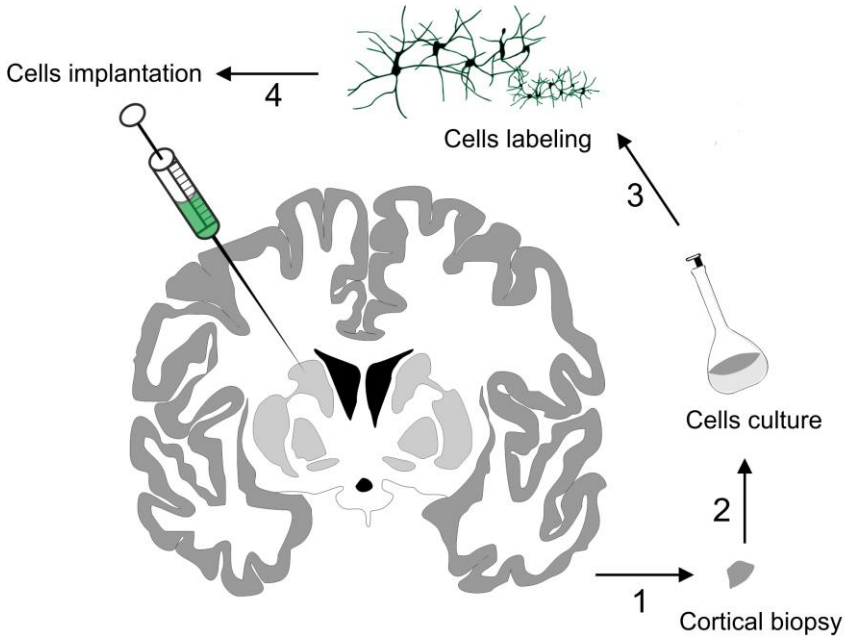
- Stem cells
- induced pluripotent stem cells (iPSCs)

→ Immune limitations, tumors, ...



Morizane et al. (2007). *Cell Tis. Res.*

Autologous neural cell ecosystems (ANCE) transplantation



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Brief Communication

Primate adult brain cell autotransplantation, a new tool for brain repair?

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Primate Adult Brain Cell Autotransplantation, a Pilot Study in Asymptomatic MPTP-Treated Monkeys

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Dr. Jocelyne Bloch & Dr. Jean-François Brunet

Primate Adult Brain Cell Autotransplantation Produces Behavioral and Biological Recovery in 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Induced Parkinsonian St. Kitts Monkeys

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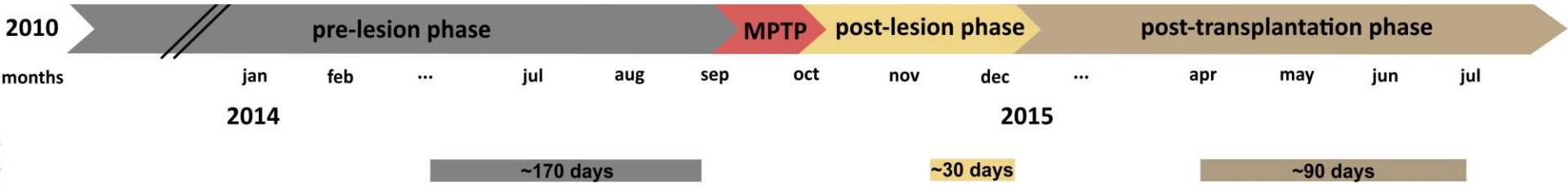
Experimental design

4 adult female macaque monkeys (*Macaca fascicularis*)
→ Parkinsonian (MPTP) lesion **AND** the cells transplantations

Bloch et al., 2014: efficiency of ANCE transplantation in parkinsonian monkeys

Present study: investigation of the ANCE impact assessing with brain imaging & with fine manual motor behavior



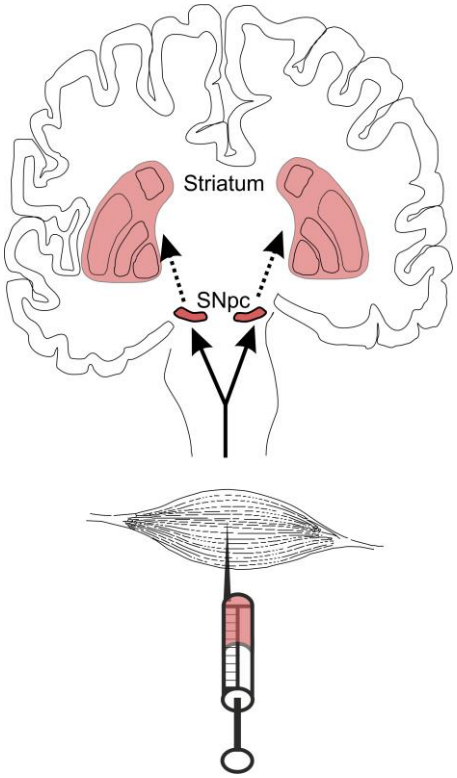
Comparison between PRE VS POST-LESION VS POST-TRANSPLANTATION for each monkey

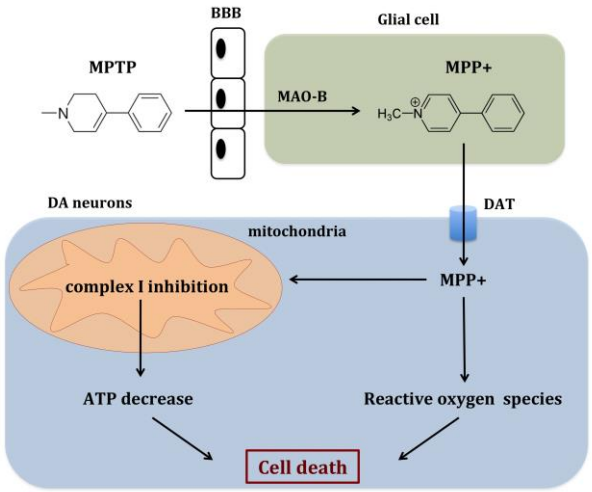
Pre-lesion phase: quantitative evaluation of the motor performance

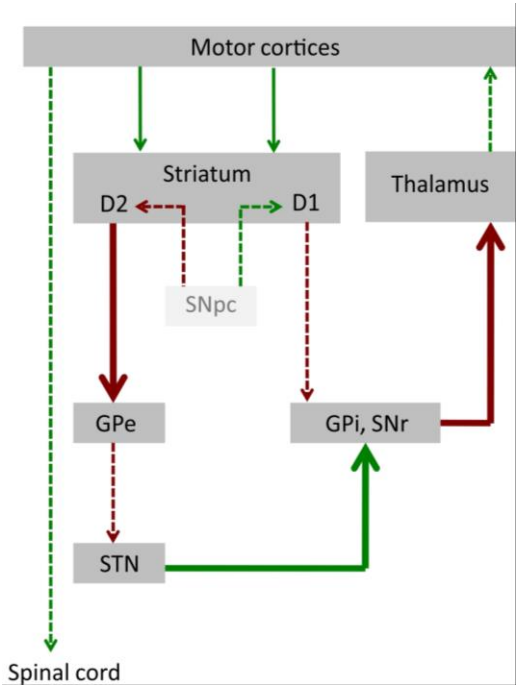
Modified-Brinkman board task

Reach and grasp drawer task

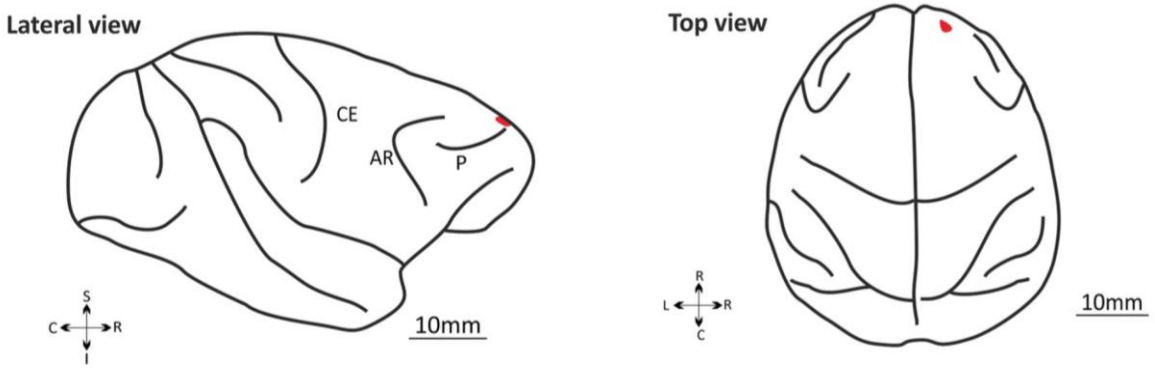
Parkinsonian lesion: the MPTP non-human primate model

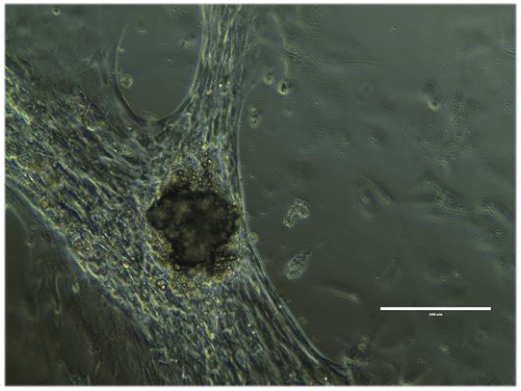






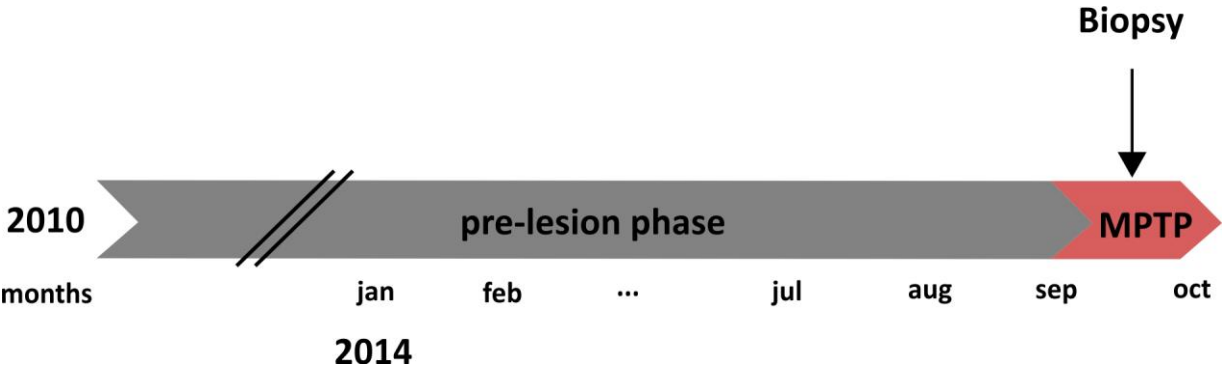
Cortical biopsies & cell cultures





~10mm^3 of cortical tissue from the dorsolateral prefrontal cortex (dlPFC)

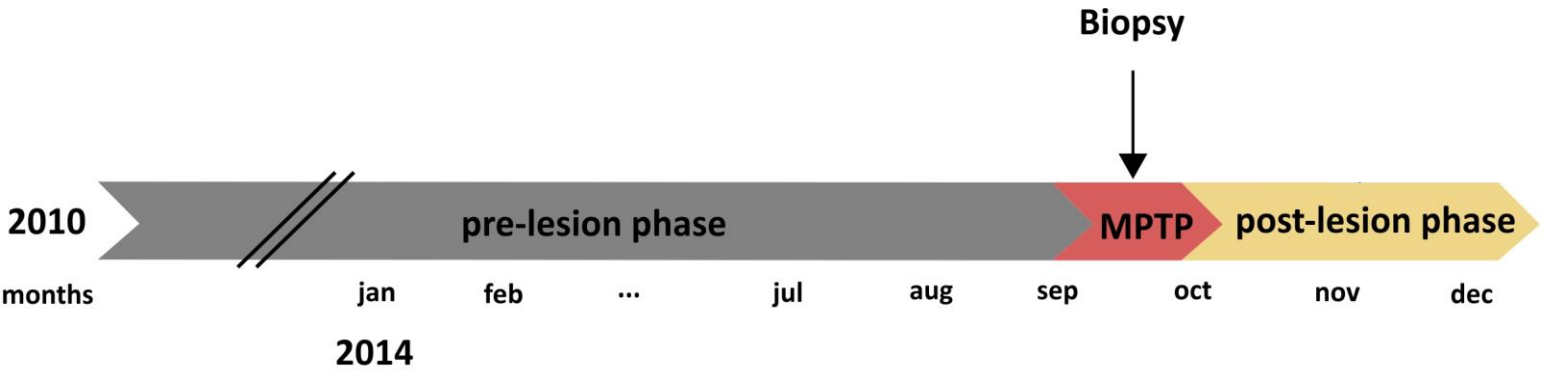
Ecosystem formation *in-vitro*



Post-lesion phase: quantitative evaluation of the motor deficits

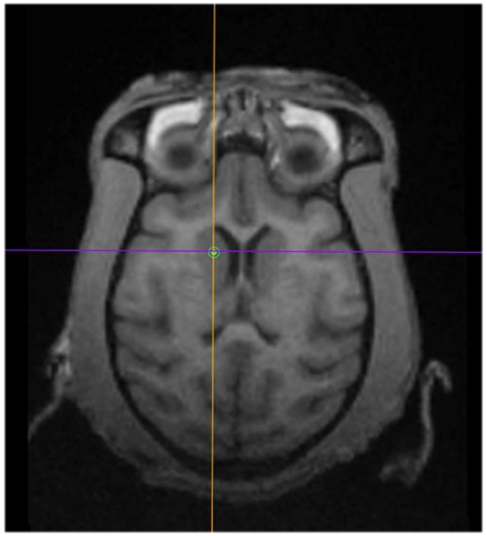
Monkey-MY – 7 days post-lesion

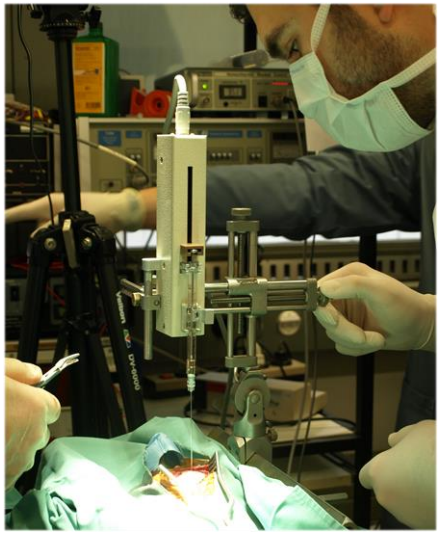
Monkey-MI – 14 days post-lesion



Cells transplantation: Stereotaxic implantations

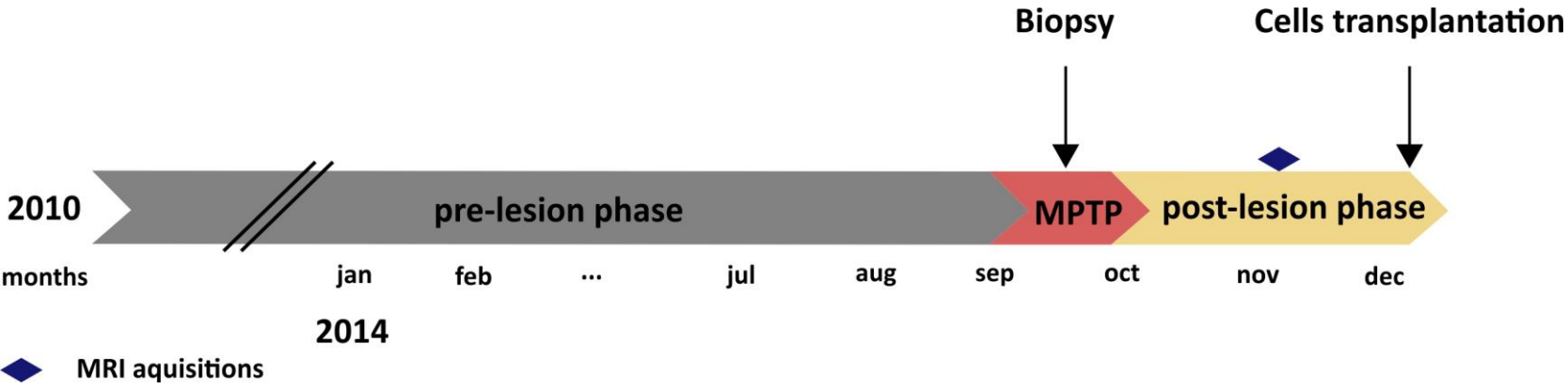
Coordinates in MRI scans → Transplantation





6 implantation sites within the Striatum

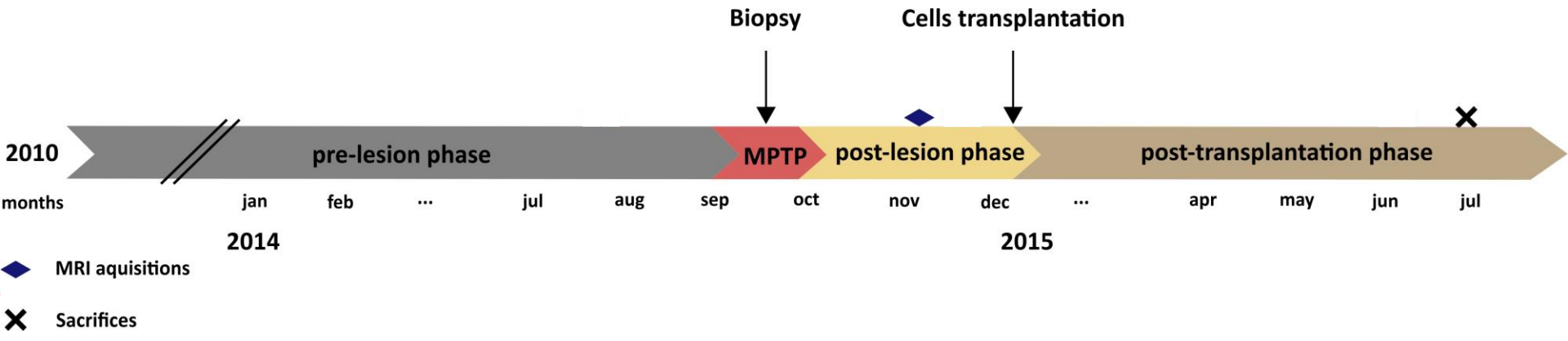
Left hemisphere	Right Hemisphere
Caudate nucleus	Caudate nucleus
Putamen anterior	Putamen anterior
Putamen posterior	Putamen posterior



Post-transplantation phase: quantitative evaluation of the motor improvement

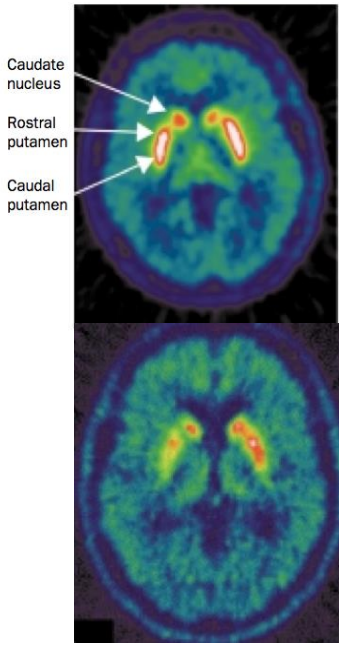
Monkey-MY – 6 months post-transpl.

Monkey-MI – 21 weeks post-transpl.



In-vivo imaging: state of the dopaminergic system with ^{18}F-Dopa PETscan

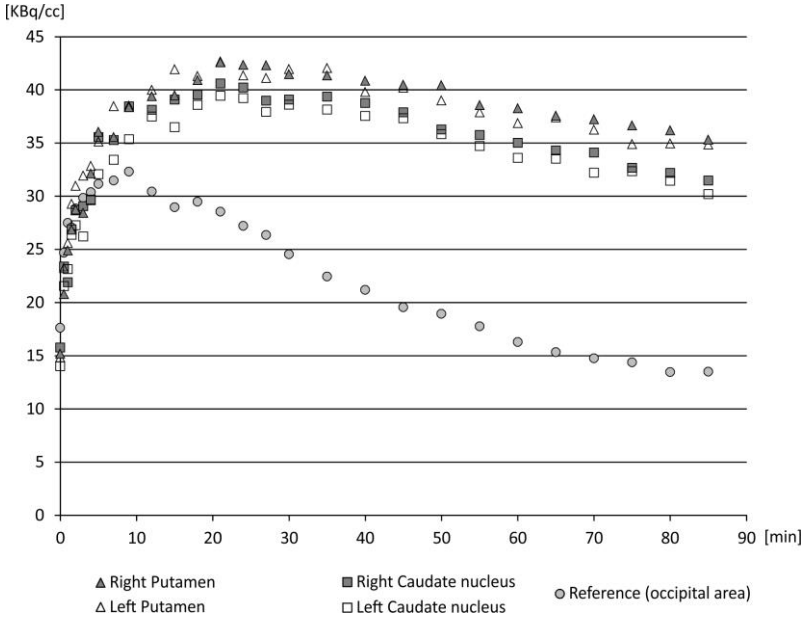
Example in human

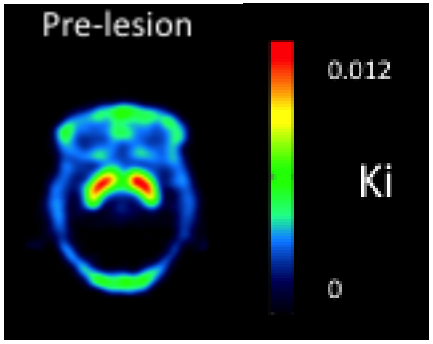


Healthy subject

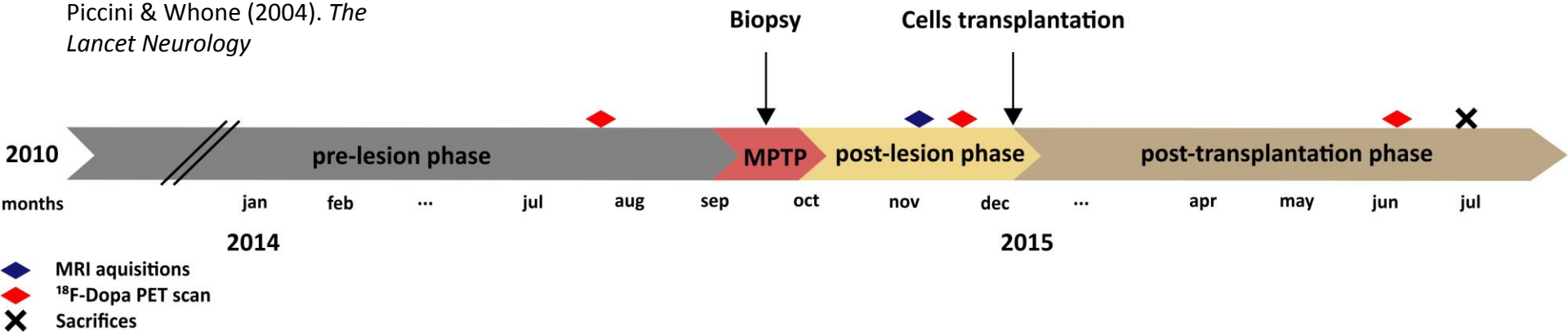
Subject with PD

Patlak algorithm → influx rate constant (Ki)

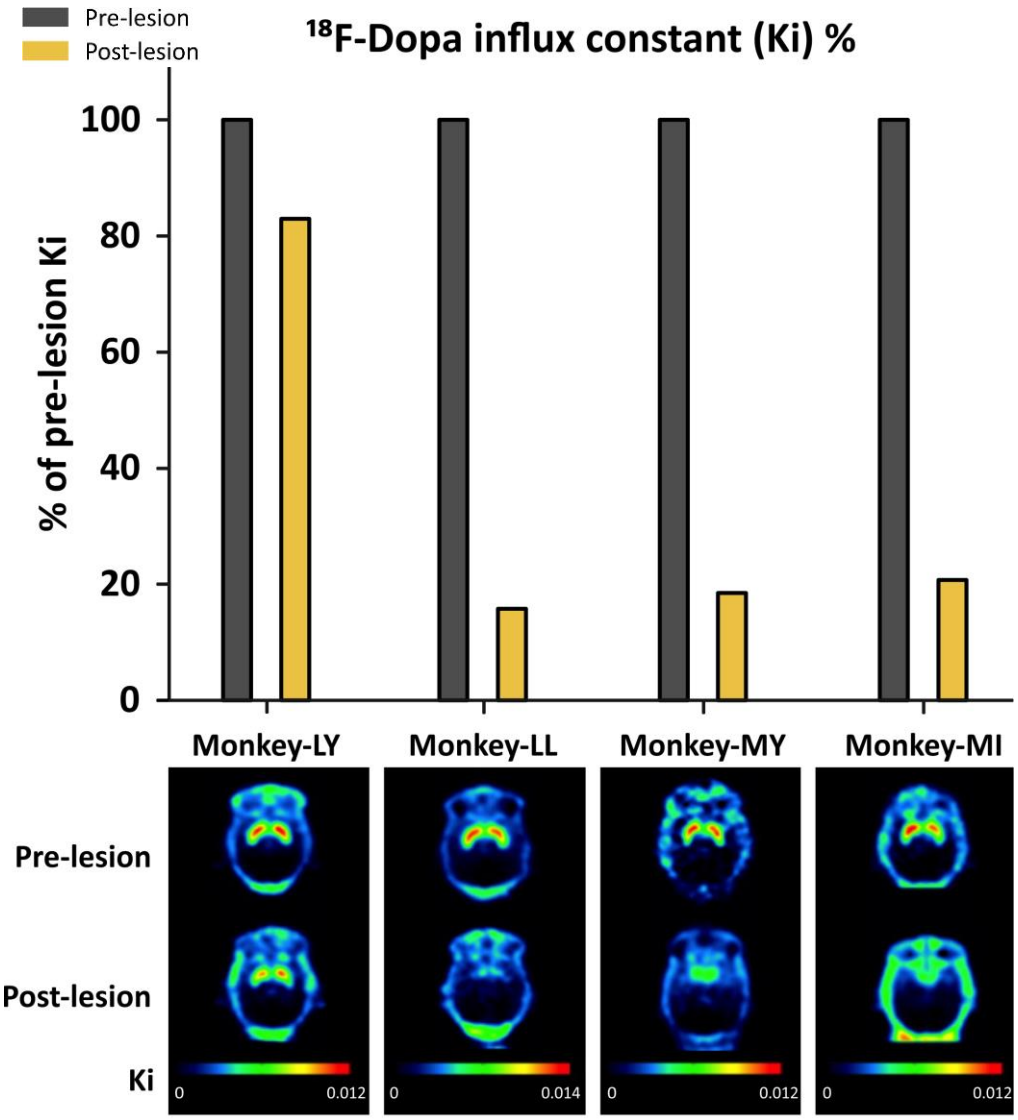




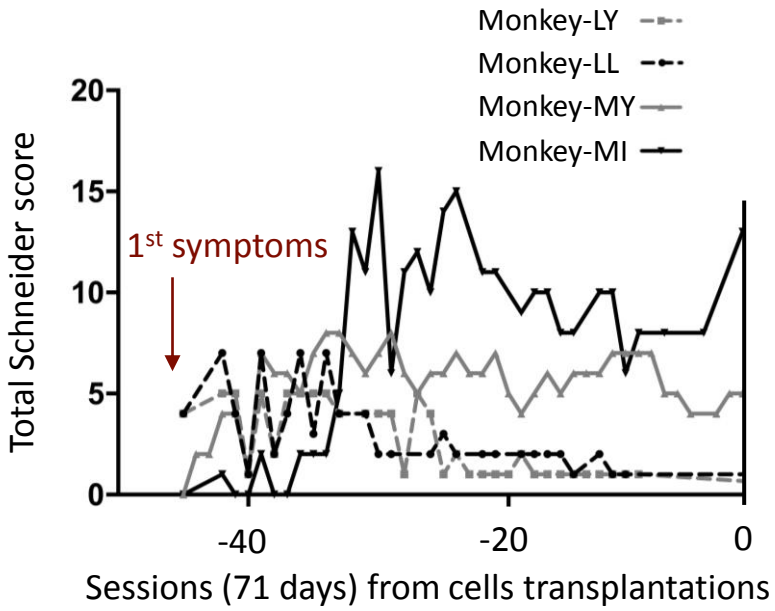
Piccini & Whone (2004). *The Lancet Neurology*



MPTP lesion and symptoms

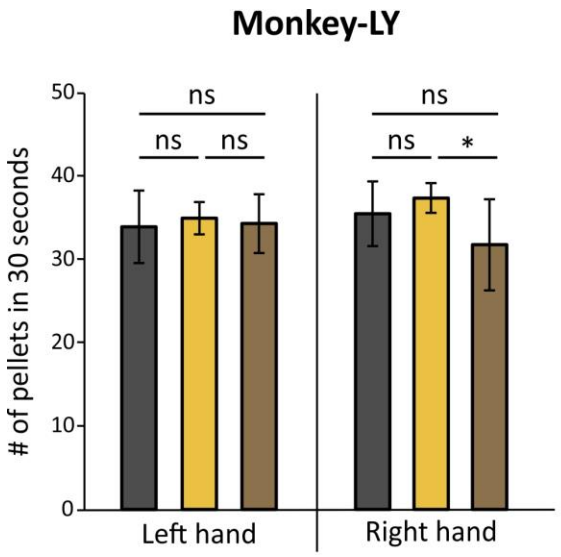


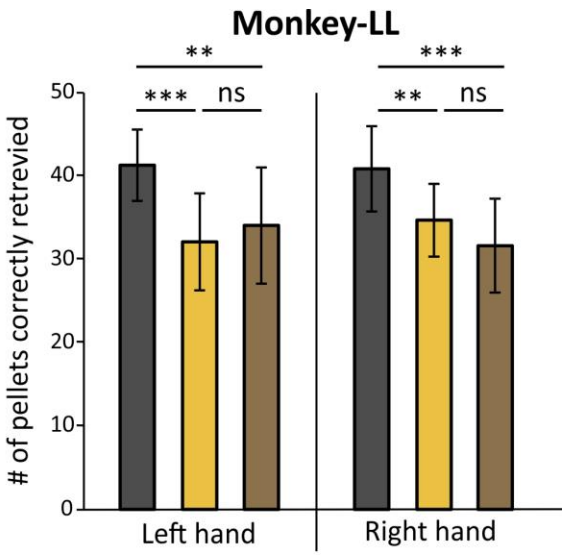
Parkinsonian symptoms evaluated with the Schneider scale

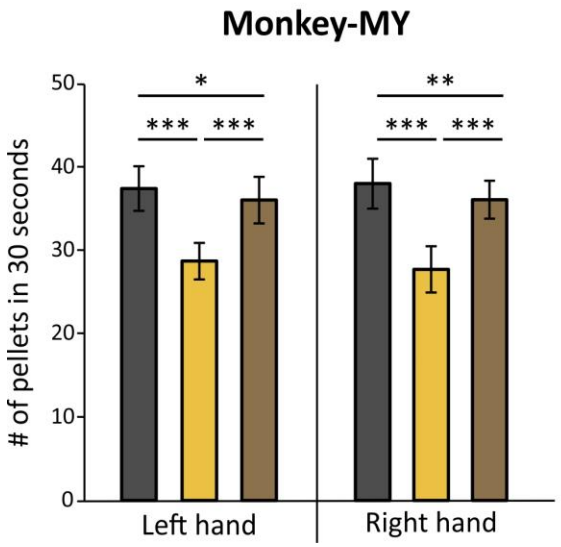


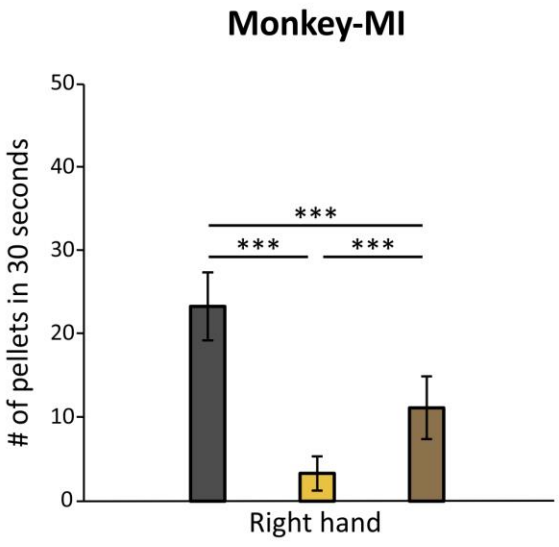
Monkey-LY → **resistant** to MPTP
Monkey-LL → **recovered** to MPTP
Monkey-MY → **moderate** PD symptoms
Monkey-MI → **severe** PD symptoms

Fine manual dexterity in the Modified-Brinkman board task

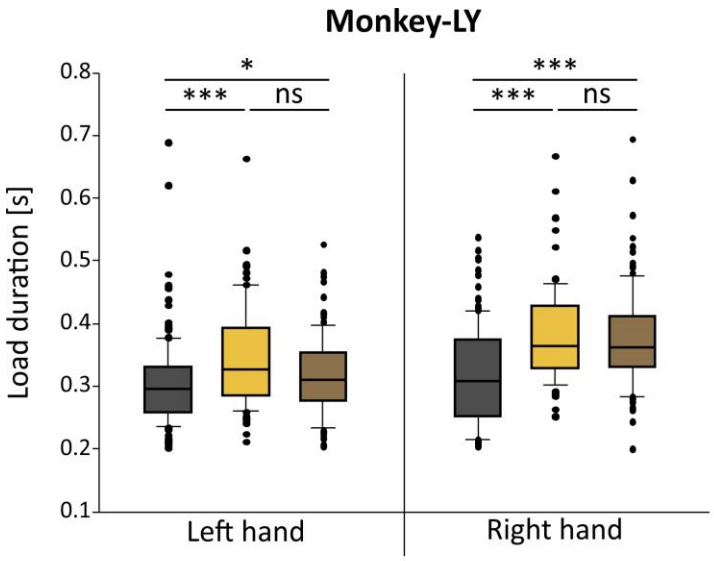


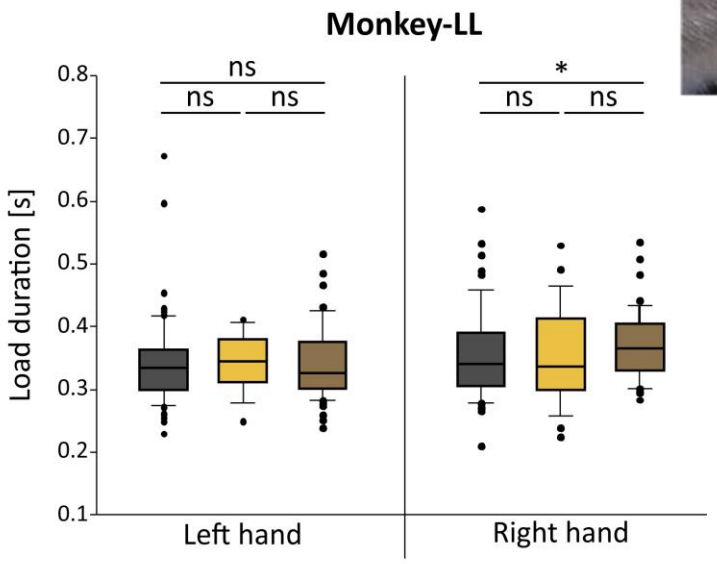


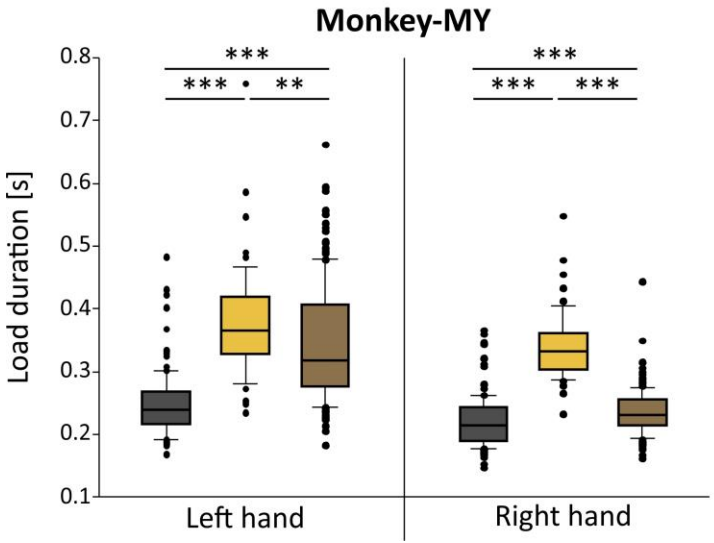


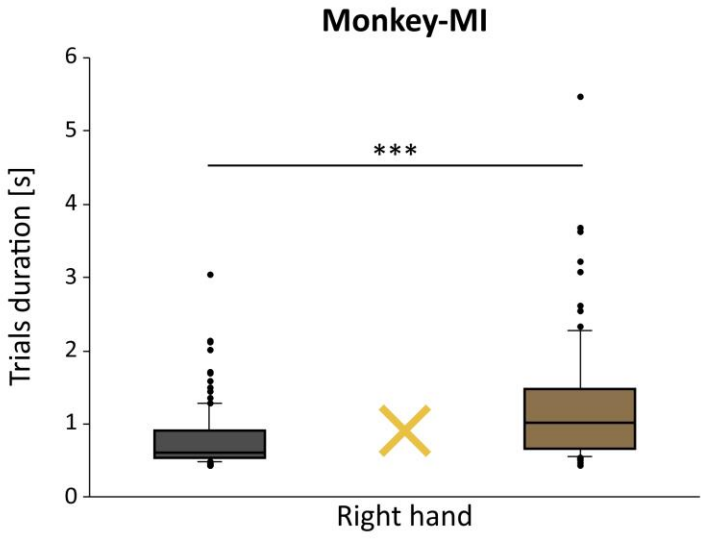


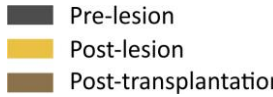
Time to execute movement in the drawer task



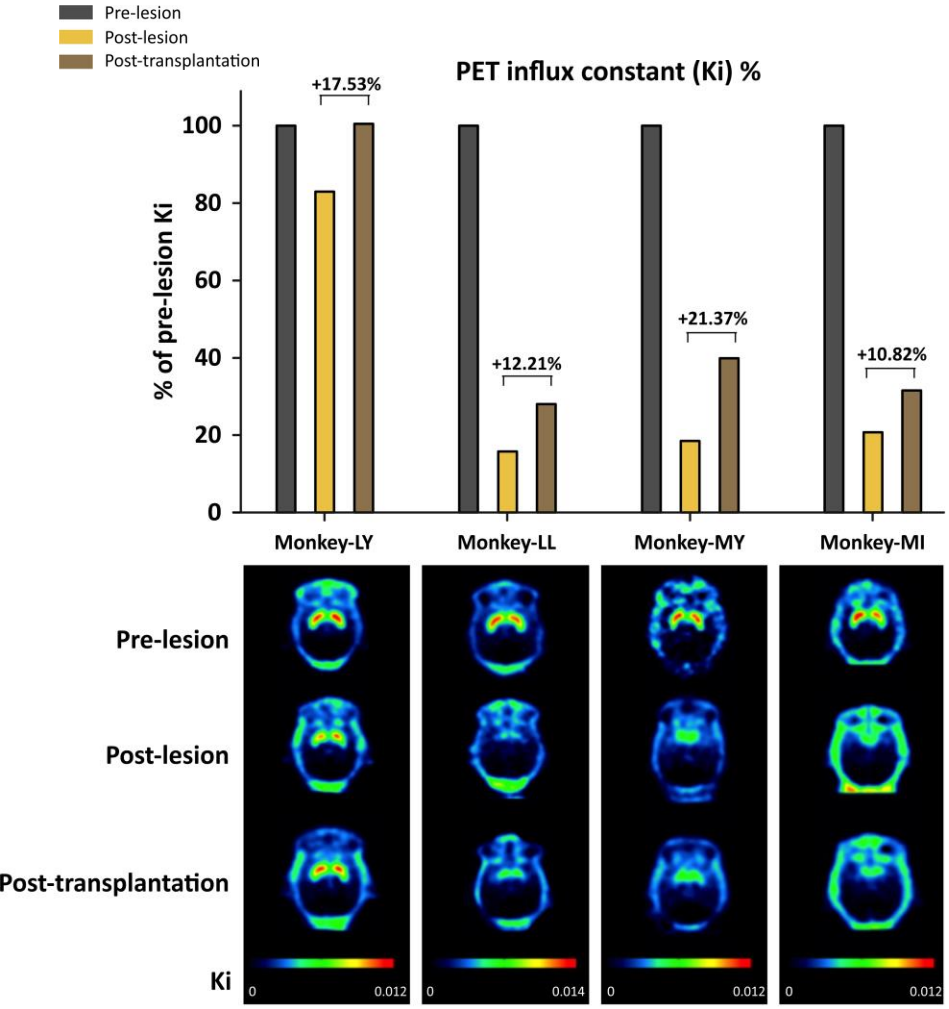








State of the dopaminergic system



- All the four animals were differentially affected by the MPTP lesion (**inter-individual variability**)

  - No correlation between lesion level and behavioral functions
  - Complexity of the MPTP model (Elsworth et al, (2000). *Neuroscience*)

- Cell transplantation promoted **recovery** in voluntary motor tasks and **increase of striatal activity**

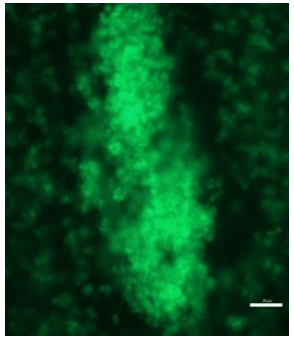
  - Consistent with previous studies: Brunet et al., (2009). *Cell transplant*. & Bloch et al., (2014). *J Comp. Neurol*.

- ANCE transplantation represents an **attractive approach** in order to treat brain dysfunction or brain lesion.

- This promising technique might add **new therapeutic strategies** leading to clinical applications.

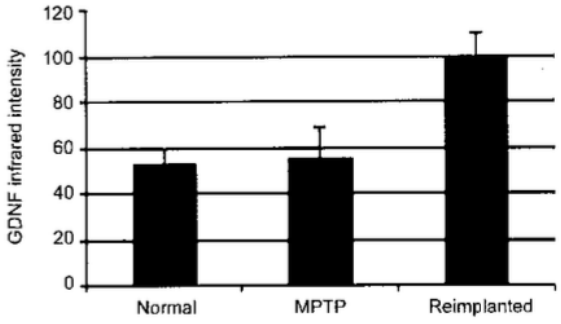
Next step: fate of the implanted cells

- **Histological readout**: cells survival, migration, astrocytes activation, 5-HT in resistant and/or recovered monkeys ?



Implanted cells in Monkey-MY, Caudate nucleus. Scale = 50um

- Hypothesis: release of neurotrophic factor (BDNF, GDNF,…) -> **Neuroprotection** effect ? **Sprouting** of the remaining dopamine fibers (already suggested by PETscan) ?



Brunet et al., (2009). *Cell transplant*.

Promising approach ?

Severe parkinsonian Monkey-MI
(4 days post-lesion)

Severe parkinsonian Monkey-MI
(10 weeks post-tranplantation)

Acknowledgments

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