Journée Scientifique – ED NSCo
11 Septembre 2017

Online transcranial direct current stimulation of the frontal cortex induces dopamine release in the striatum

A spatial and temporal analysis in healthy humans

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Equipe de recherche : Psychiatric disorders: from Resistance to Response (ΨR2)

Promotion : CH Le Vinatier / *Financement :* CSR F02

Centre hospitalier Le Vinatier

cermap imagerie du vivant

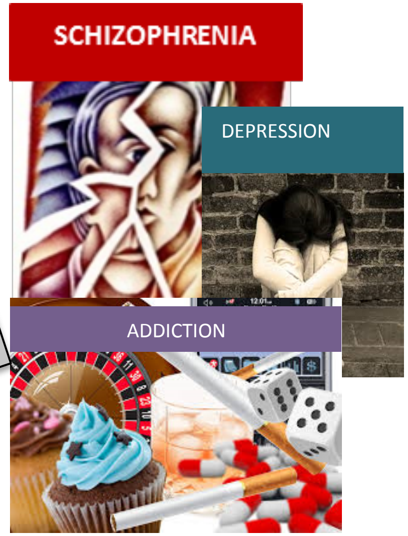
CRNL Lyon Neuroscience Research Center

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

cnrs

UCB

PSYCHIATRY



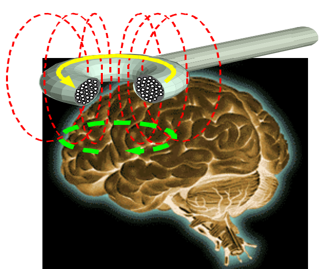
30-60 % symptoms stay resistant to available pharmacological approaches

American Psychiatric Association, Am J Psychiatry, 2004

NEW THERAPEUTIC APPROACHES

NEUROSTIMULATIONS

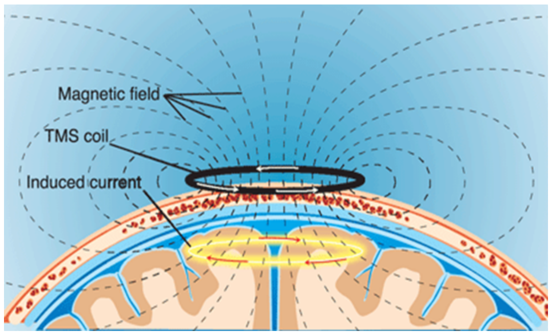
Transcranial Magnetic Stimulation
TMS

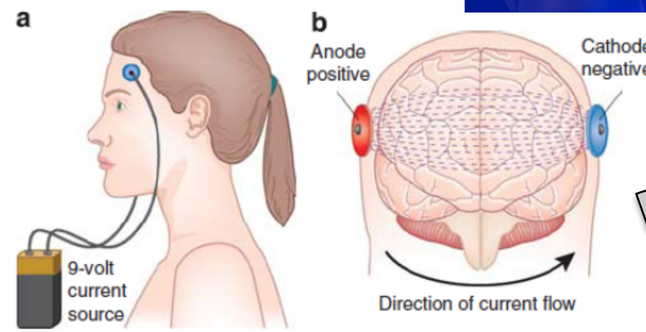


Transcranial Direct Current Stimulation
tDCS

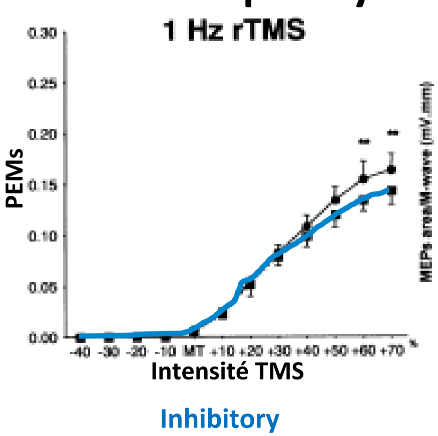
NEUROSTIMULATION

- TMS
- tDCS

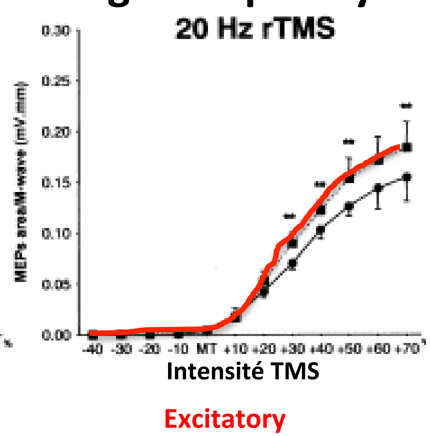




Low Frequency

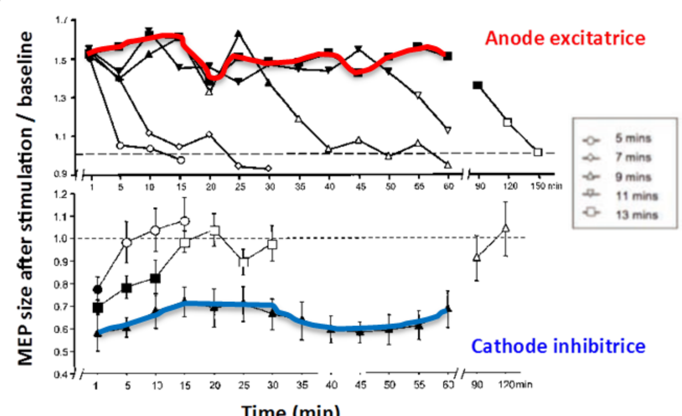


High Frequency



Gangitano et al., Clin Neurophysiol, 2002

Mesure du Potentiel Evoqué Moteur



Nitsche et al., Neurology, 2001
Nitsche et al., Clin Neurophysiol, 2003b

➢ **Cortical excitability** modulation

PSYCHIATRY

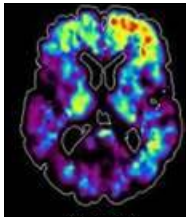
PREFRONTAL CORTEX ALTERATIONS

EXEMPLES

- DEPRESSION

  Left prefrontal cortex hypoactivity

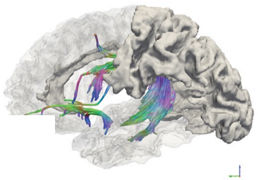
  Bunney&Bunney, Brain Res Rev, 2000
  George et al., Depression, 1994



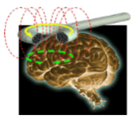
- ADDICTION

  Frontal network Dysconnectivity

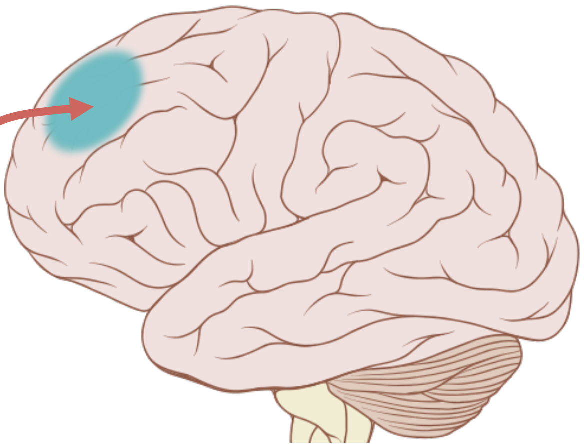
  Kravitz et al., Brain Research, 2015

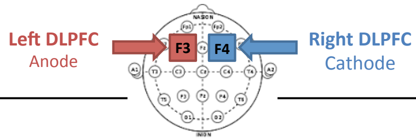


PREFRONTAL CORTEX



Neurostimulation

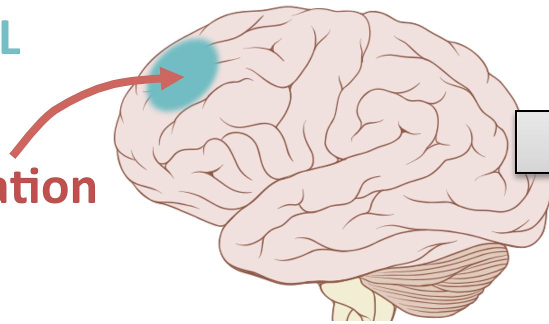




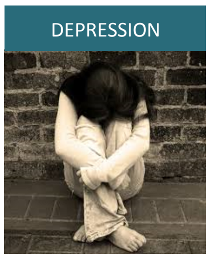
PSYCHIATRY

PREFRONTAL CORTEX

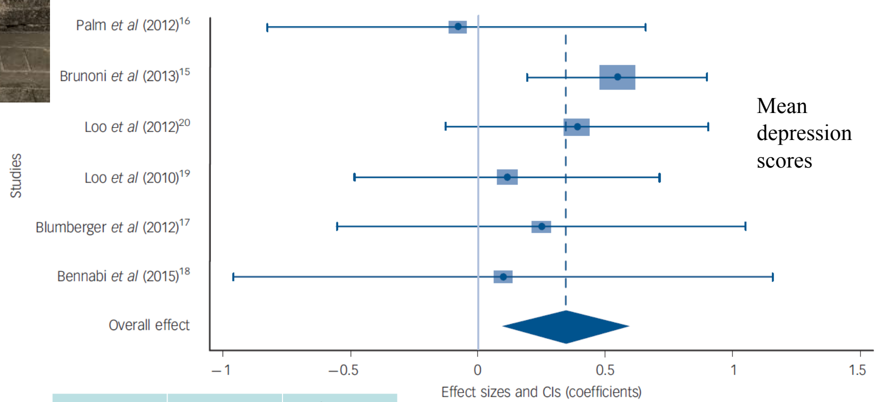
Neurostimulation



THERAPEUTIC EFFECT

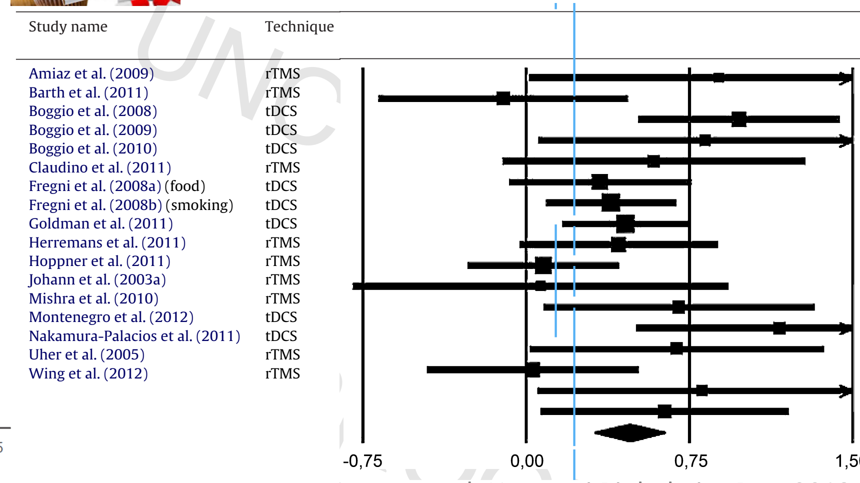


Brunoni……Loo, 2016. tDCS Efficacy in Depression Individual Patient Data Meta-Analysis



	Active	Sham
Response	34%	19%
Remission	23.1%	12.7%

Effects of DLPFC neurostimulation on craving (nicotine, food, alcohol, marijuana)



Jansen et al, Neurosci Biobehvior Rev, 2013

Associées à des altérations monoaminergiques, notamment dopaminergiques

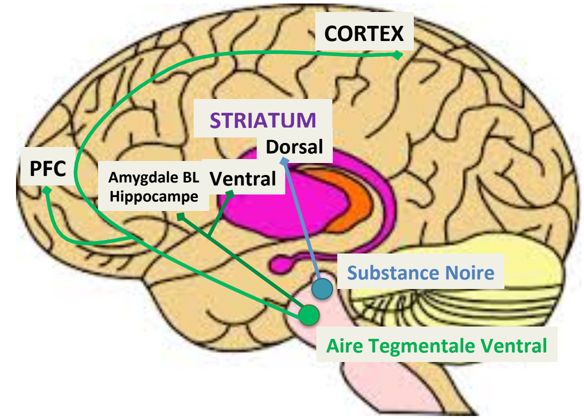
Brunelin et al., Am J Psychiat, 2012

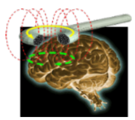
Effect of the stimulations on the dopaminergic transmission ?

DOPA-STIM

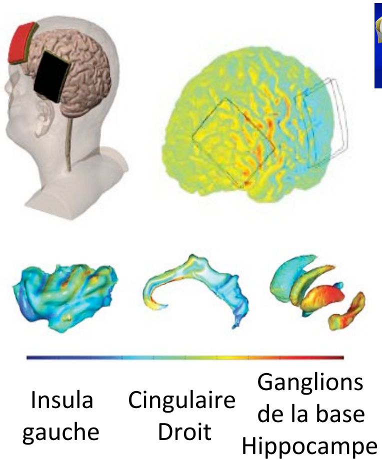
DLPFC 

Effect of bifrontal tDCS on the dopaminergic transmission ?





- **rTMS**
  rTMS on the DLPFC induces subcortical dopamine release
  Strafella et al., Brain, 2003
  Brunelin et al., Schizophr Res, 2011



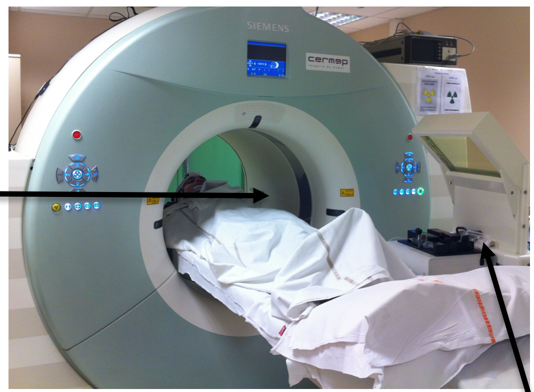
- **Etude chez l'animal**
  tDCS impacts the dopaminergic system in rat basal ganglia
  Tanaka et al., Front Syst Neurosci, 2013

- **Modélisation**
  tDCS seems to have an impact on subcortical areas such as basal ganglia
  Brunoni et al, Expert Rev. Med. Devices, 2014
  Bai et al, NeuroImage, 2014

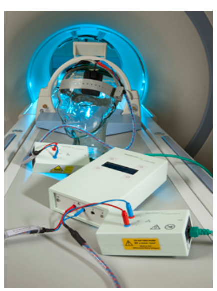
<u>HYPOTHESIS</u> : tDCS releases subcortical dopamine

Positron Emission Tomography (PET)

Intraveneous injection :
Radioactive tracer - [^{11} C]Raclopride

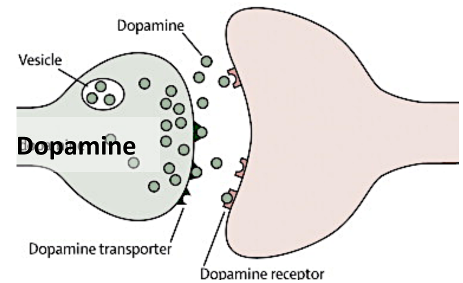


tDCS online

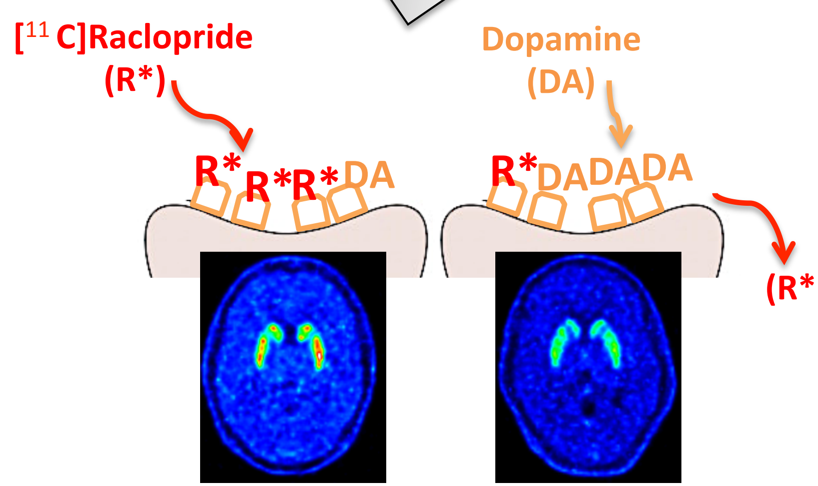


[^{11} C]Raclopride

Pre-synaptic Post-synaptic



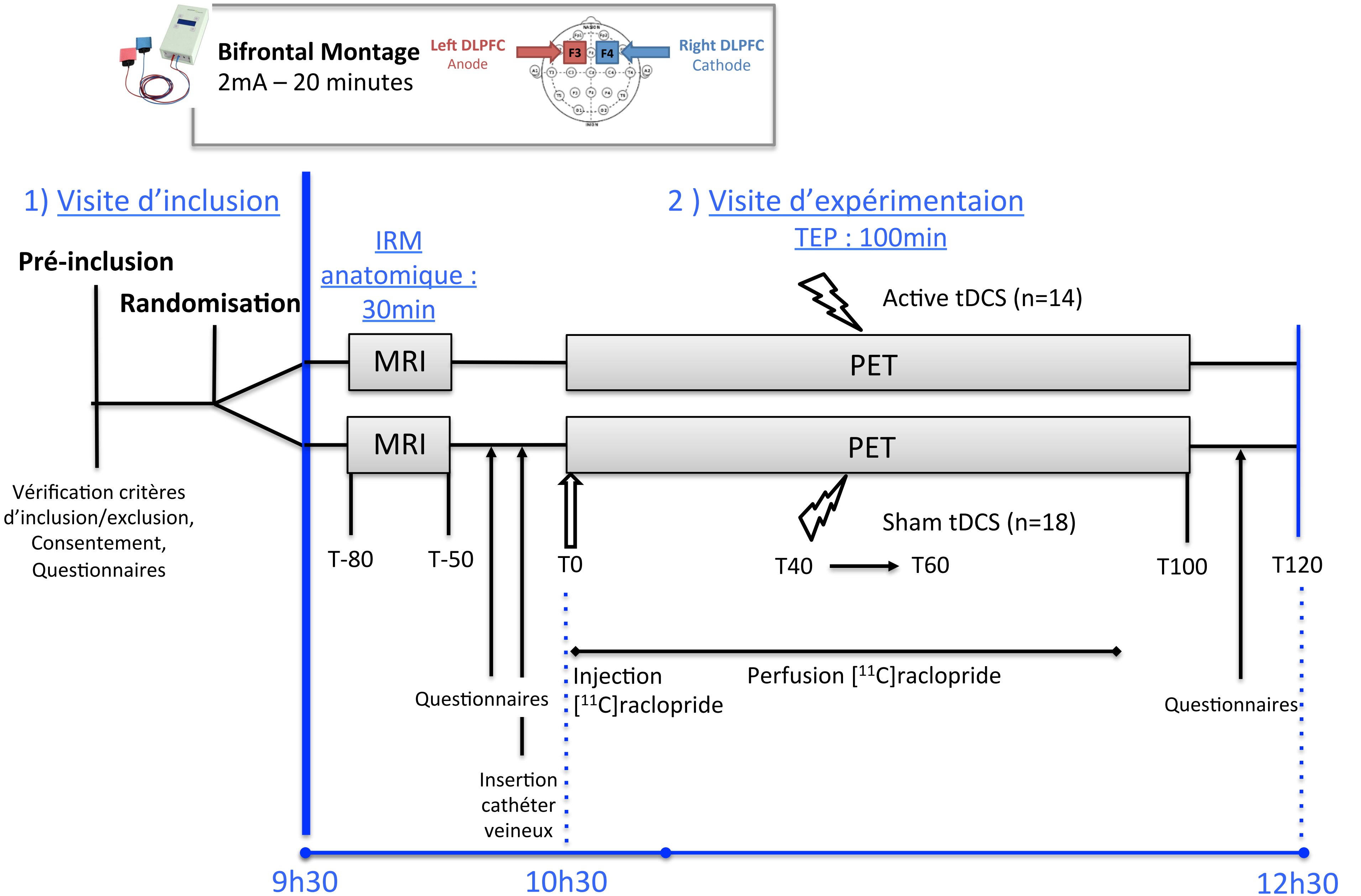
D2
Dopamine Receptors



Fixation radiotracer

Release of dopamine

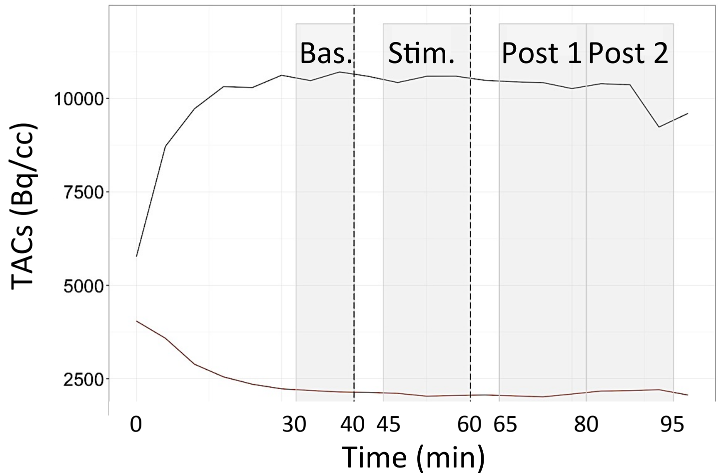
DOPA-STIM



Bifrontal Montage
2mA – 20 minutes
Left DLPFC
Anode
F3
F4
Right DLPFC
Cathode
1) Visite d'inclusion
Pré-inclusion
Randomisation
Vérification critères d'inclusion/exclusion, Consentement, Questionnaires
IRM anatomique : 30min
2) Visite d'expérimentaion
TEP : 100min
Active tDCS (n=14)
MRI
PET
MRI
PET
Sham tDCS (n=18)
T-80
T-50
T0
T40
T60
T100
T120
Questionnaires
Insertion cathéter veineux
Injection [11C]raclopride
Perfusion [11C]raclopride
Questionnaires
9h30
10h30
12h30

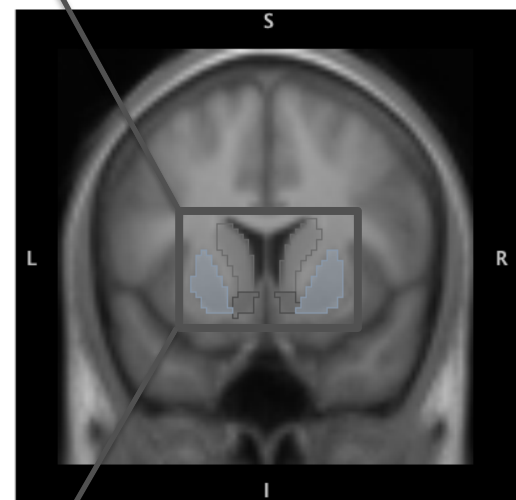
Methods - Kinetic Analysis (1 timepoint per 5 minutes) DOPA-STIM

- **Extraction of time activity curve (TACs)**
  In the region of interest (**striatum**) and reference region (**cerebellum**)



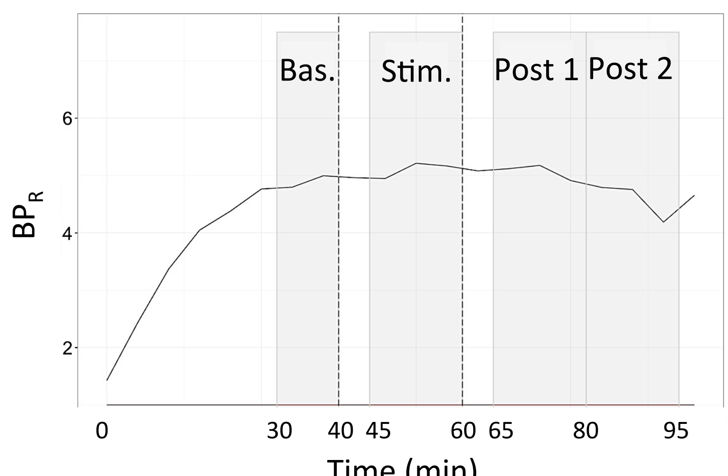
Striatum
(subcortical dopaminergic region)

Cerebellum
(reference region)



Regions of interest
Atlas on MRI

- **Binding potential (BP_R) → Extracellular Dopamine**
  Ratio of region of interest / cerebellum activities

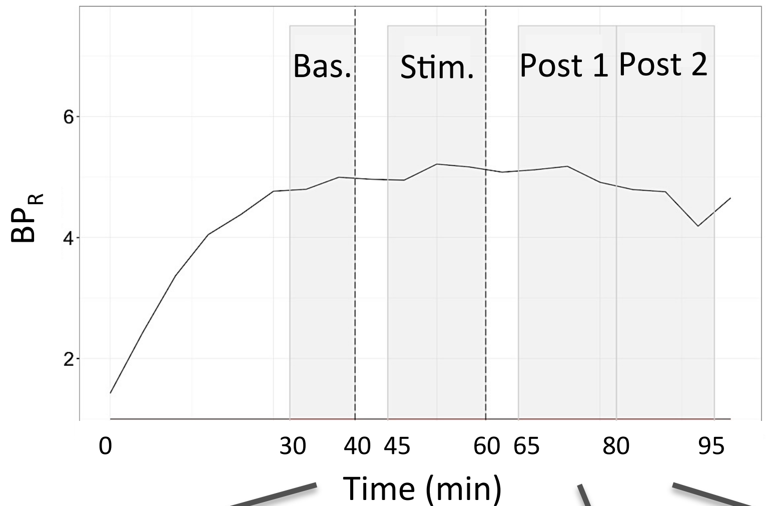


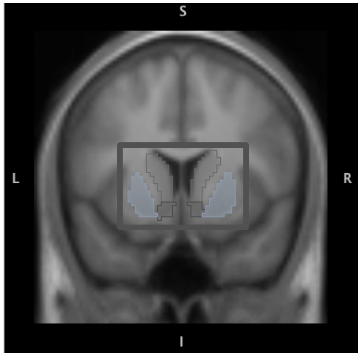
Striatum
(subcortical dopaminergic region)

Methods - Voxel-based analysis

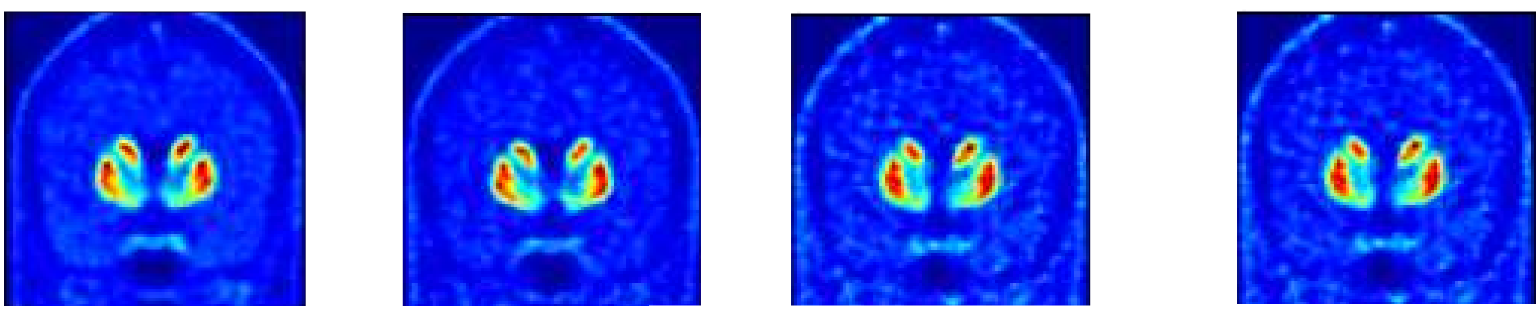
DOPA-STIM

- **Parametric Ratio Images for each time period**
  (baseline, stimulation, post 1, post 2)





Subregions of the striatum



Baseline **Stimulation** **Post 1** **Post 2**

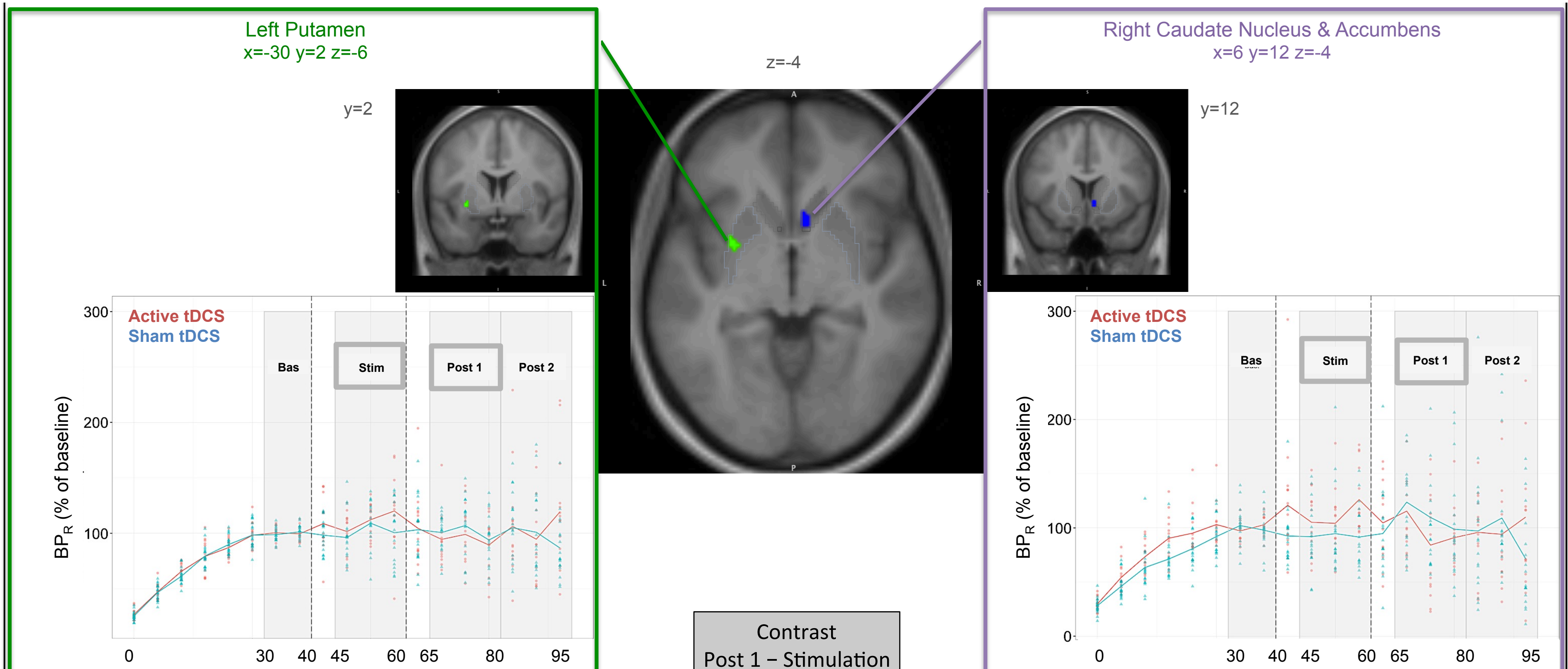
Flexible factorial design (Group * Timepoint)
($P_{uncorrected} < 0.001$, k>4)

Voxel-based analysis

DOPA-STIM

Acute effects

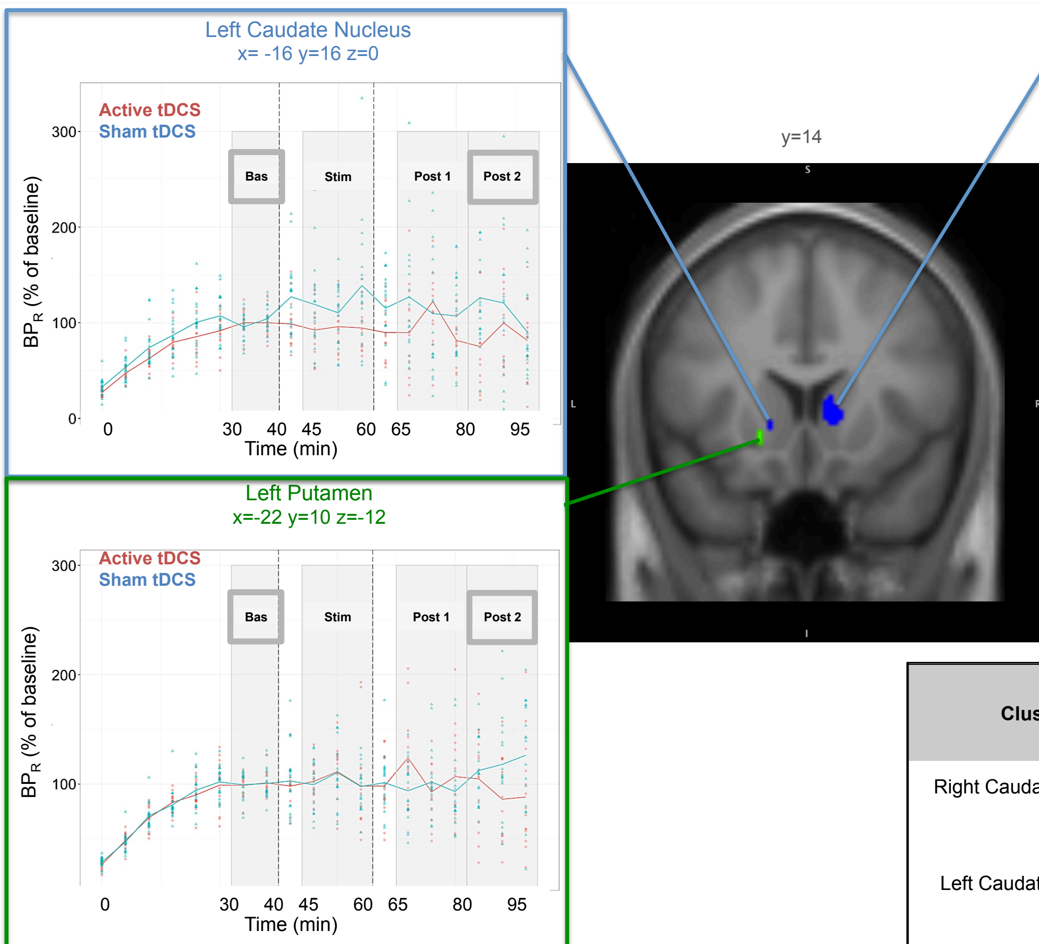
➢ BP_R decrease during the 20 minute period (**Post 1**) following the stimulation in the **striatum**, compared to the stimulation period

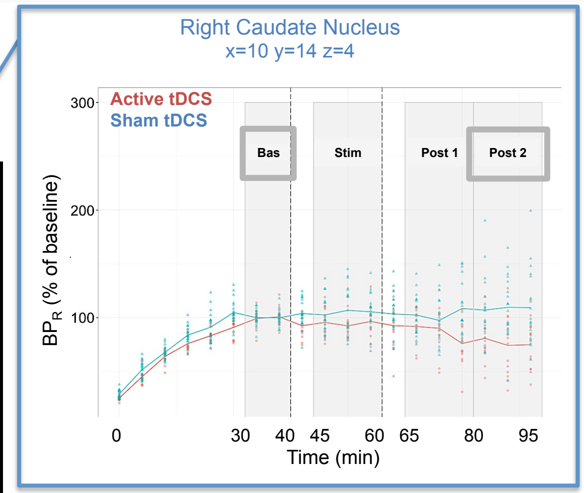


Cluster	Relative variation % (+/- sem)	Difference Active – Sham %	Parametric Analysis Z-score, $K_{cluster}$
Right Caudate and Accumbens Nuclei			z=4.17, k=18
Active tDCS	-13.34 (5.00)	-33.82	
Sham tDCS	20.48 (6.14)		
Left Putamen			
Active tDCS	-13.99 (5.82)	-13.989	z=3.53, k=24
Sham tDCS	-0.001 (4.25)		

Subsequent effects

- BP_R decrease during the 20 to 35 minutes period (**Post 2**) following the stimulation in the **striatum**, compared to the baseline and stimulation period





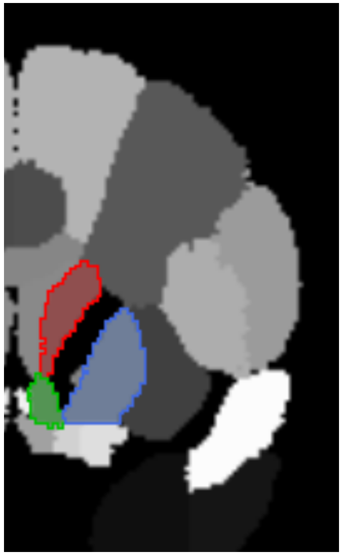
Contrast Post 2-Baseline

Cluster	Relative variation % (+/- sem)	Difference Active – Sham %	Parametric Analysis Z-score, $K_{cluster}$
Right Caudate Nucleus			
Active tDCS	-23.32 (3.22)	-31.97	z=4.40, k=45
Sham tDCS	8.65 (4.70)		
Left Caudate Nucleus			
Active tDCS	-14.60 (4.98)	-26.98	z=3.67, k=7
Sham tDCS	12.38 (9.59)		
Left Putamen			
Active tDCS	-6.95 (6.74)	-25.9	z=3.47, k=16
Sham tDCS	18.95 (5.59)		

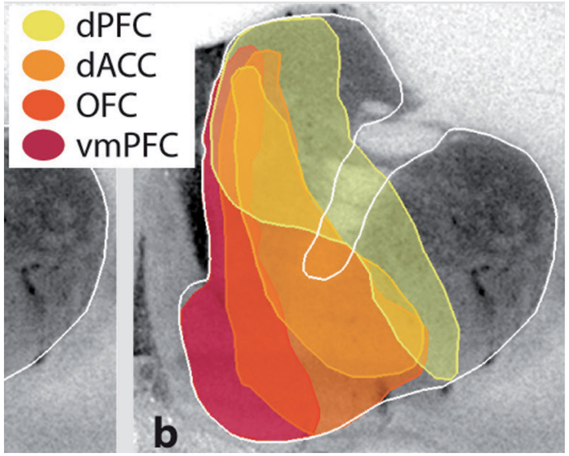
Voxel-based analysis

DOPA-STIM

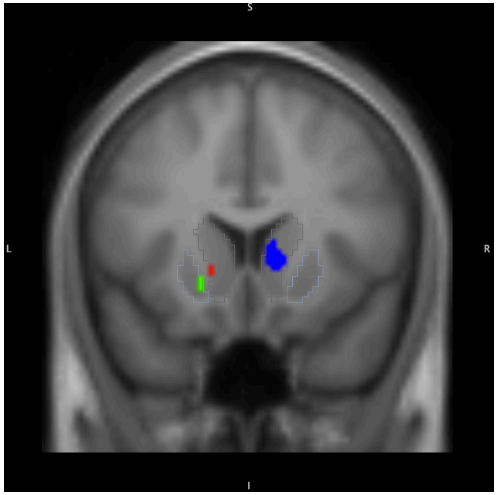
Anatomy (caudate, accumbens, putamen)	Cortical and functional connectivity (limbique, associatif, sensorimotor)	Significant clusters (dopamine release after tDCS)



Hammer Atlas



Haber, Dialogues Clin Neurosci, 2016
Martinez et al, 2003



Subsequent effects

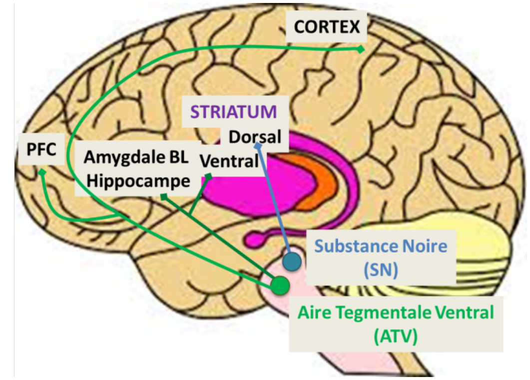
- Caudate Nucleus
- Nucleus Accumbens
- Putamen

- **Limbic** striatum : Ventral caudate and putamen and the nucleus accumbens)
- **Associative** striatum (cognition) : Rostral putamen + head of the caudate
- **Sensorimotor** striatum : Caudal and dorsolateral putamen and dorsolateral rim of the caudate

- **Limbic** and **associative** regions of the striatum

➢ These results suggest that bifrontal tDCS induces subcortical dopamine release specifically in the limbic and executive parts of the striatum, after the end of the stimulation.

Subcortical extracellular dopamine release in parts of the striatum involved in the **reward-motivation network**

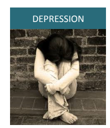


Pro-cognitive effects

Kuo & Nitsche, Neurosci Bull, 2015

Egerton et al, Neurosci Behav Rev, 2009

Therapeutic effects



Ex : Anhedonia

Cuthbert & Insel, BMC Med, 2013

Schlaepfer et al, NPP, 2014

Impact for further studies :

Condition where basal dopamine activity is altered

1. <u>Psychiatric – Biomarker</u>
   - Change in dopamine after the first tDCS session act as a biomarker for response to the cure ?
2. <u>Recreational use – auto-stimulation</u>
   - Interaction with medication or psycho-stimulant ?

DIY

Focus

Medication/drugs

ACKNOWLEDGMENTS

Equipe PsyR²

Marie-Françoise Suaud-Chagny
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cermap
imagerie du vivant

Nicolas Costes
Jérome Redoute
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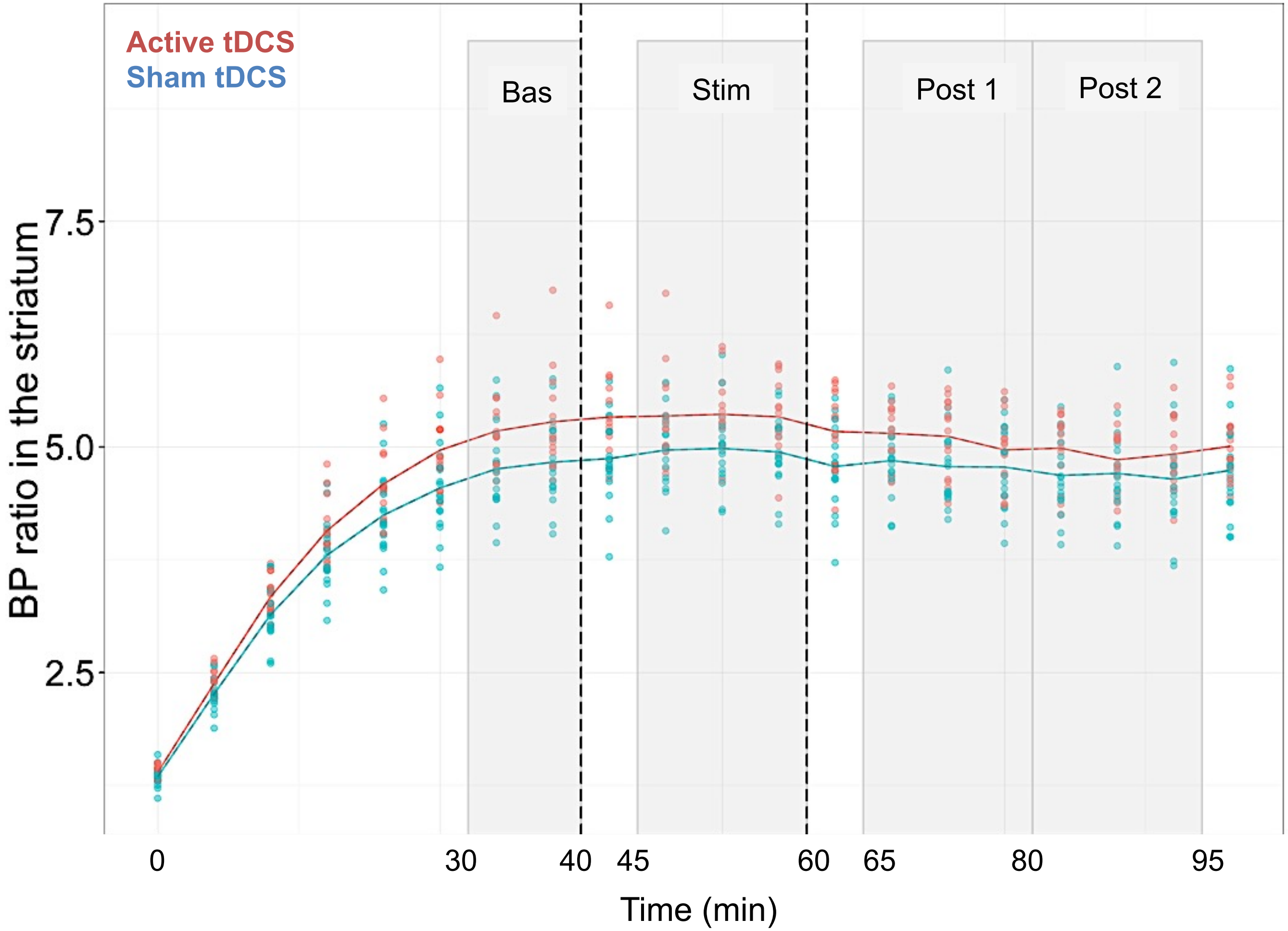
Frédéric Bonnefoi
Audrey Maurin
Inès Mérida

Centre hospitalier Le Vinatier

Promotion Vinatier
Lydie Sartelet
Véronique Vial

CSR du CH Le Vinatier

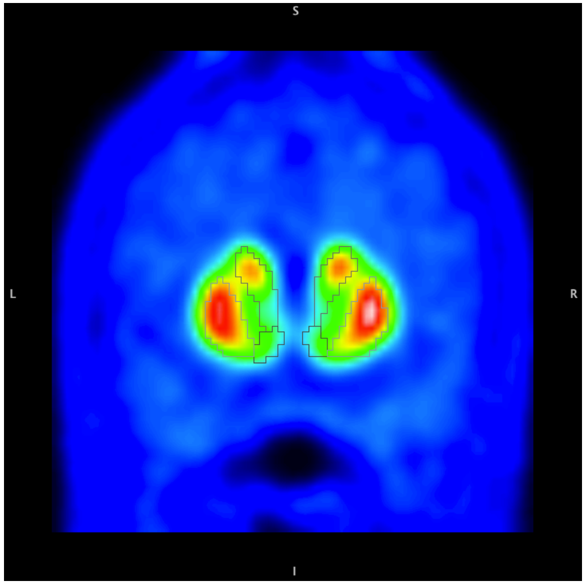


- 4 périodes :
  - Baseline : 30-40min
  - Stimulation : 45-60min
  - Post 1 : 65-80min
  - Post 2 : 80-95min

Methods - Voxel-based analysis

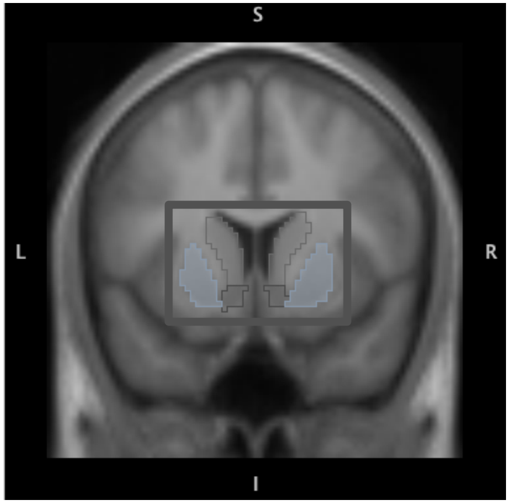
DOPA-STIM

- **Parametric Ratio Images for each time period**
  (baseline, stimulation, post 1, post 2)



Parametric PET image
Example: Baseline period

Striatum
(subcortical dopaminergic region)



Subregions of the striatum
Atlas on MRI

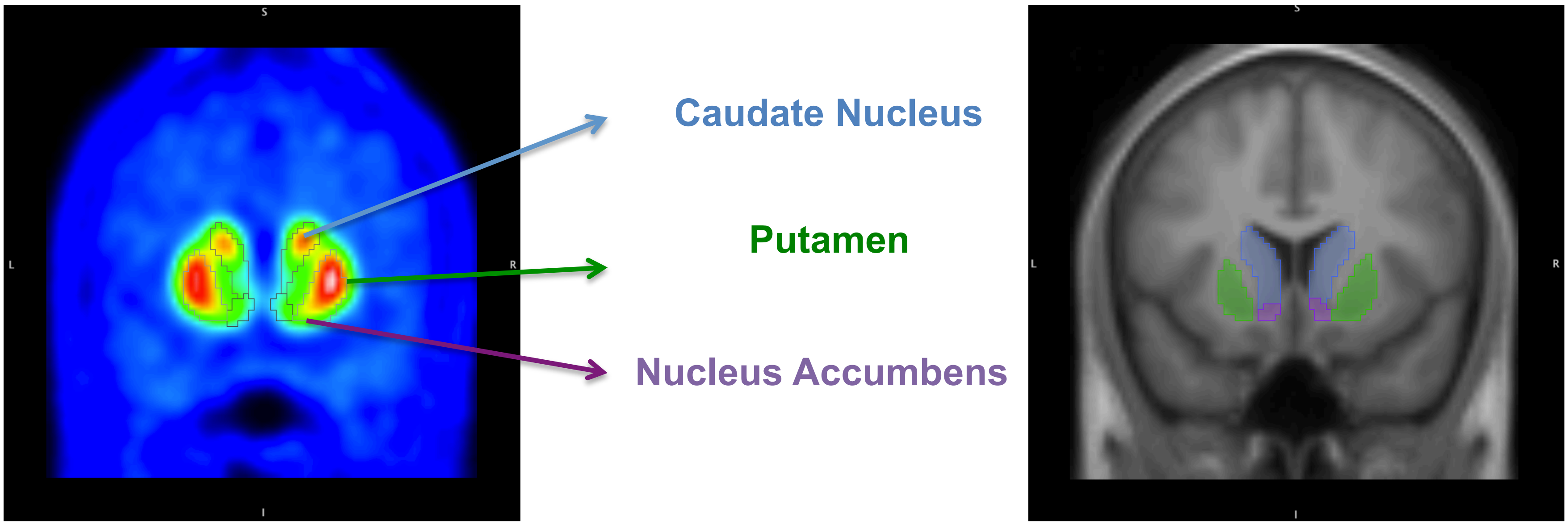
Regions were determined based on the adult brain atlas developed by A. Hammers et al. (2003)

Analysis were performed on SPM12 with a flexible factorial design (Group * Timepoint), in the striatum. Significant clusters from the parametric analysis ($P_{uncorrected} < 0.001$, $k>4$) were selected then a TAC extraction was done for each cluster. The BP_R relative variations were calculated for each contrast.

Methods - Voxel-based analysis

DOPA-STIM

- **Parametric Ratio Images for each time period**
  (baseline, stimulation, post 1, post 2)



Parametric PET image
Example: Baseline period

Subregions of the striatum
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