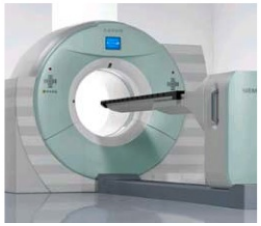
Neurophysiological impact of transcranial direct current stimulation (tDCS) in healthy subjects

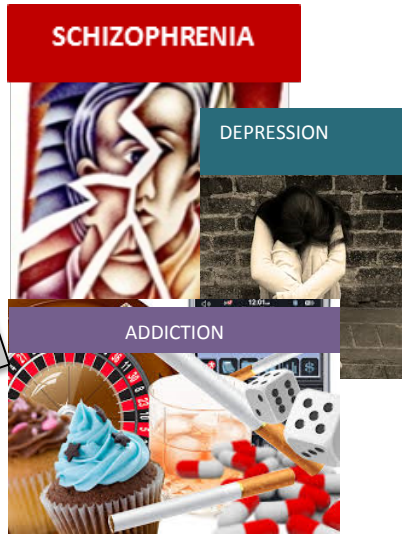


PhD student: Clara Fonteneau

Thesis supervisor: Marie-Françoise Suaud-Chagny

Team: Psychiatric disorders: from Resistance to Response (ΨR2)
Lyon Neuroscience Research Center (CRNL)

PSYCHIATRY



30-60 % symptoms are resistant to pharmacological approaches

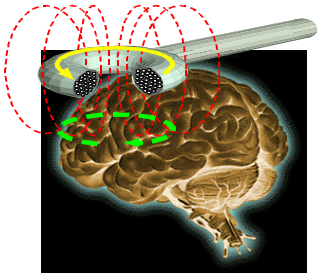
American Psychiatric Association, Am J Psychiatry, 2004

DEVELOPMENT OF NEW THERAPEUTIC APPROACHES

NEUROSTIMULATIONS

Transcranial Magnetic Stimulation

TMS

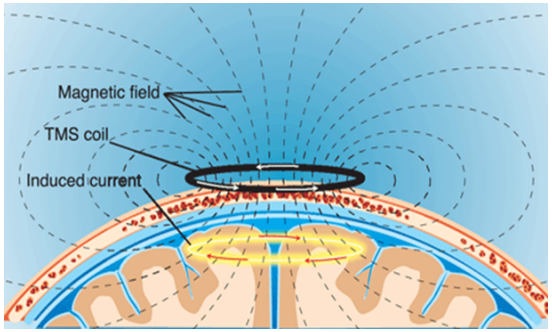


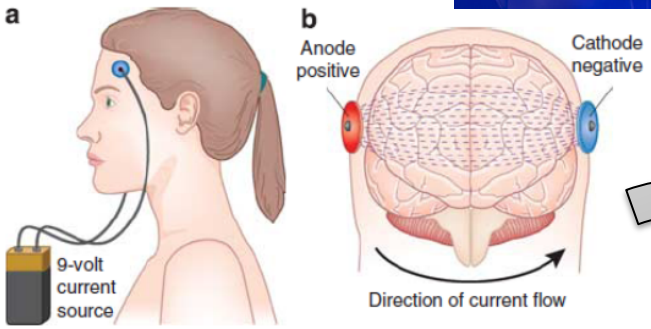
transcranial Direct Current Stimulation

tDCS

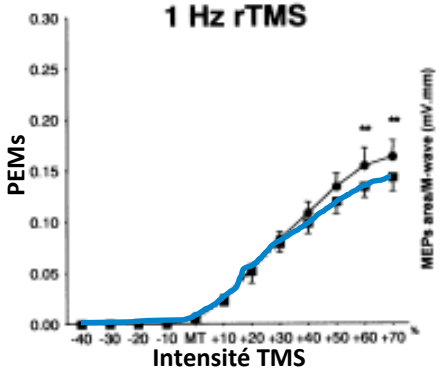
NEUROSTIMULATION

- TMS
- tDCS



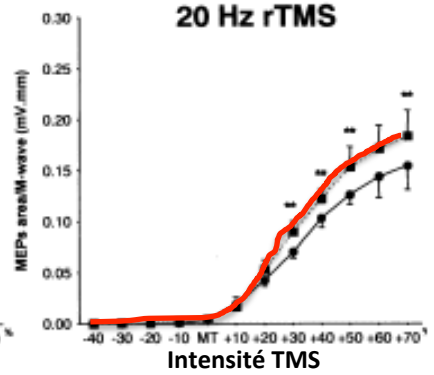


Low Frequency



Inhibitory

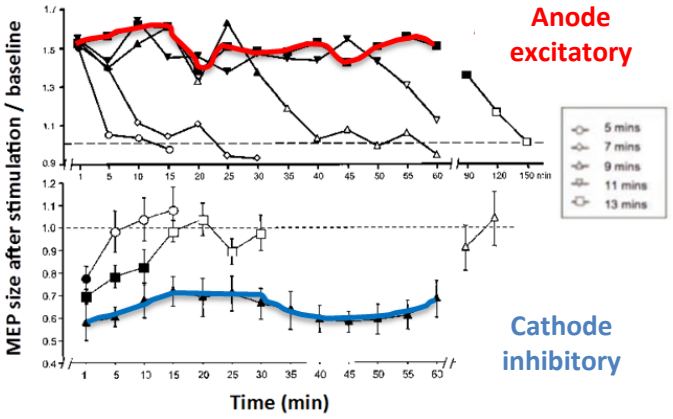
High Frequency



Excitatory

Gangitano et al., Clin Neurophysiol, 2002

Primary Motor Cortex Stimulation



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

➢ Modulation of **cortical excitability**

PSYCHIATRY

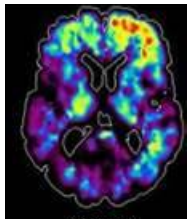
PREFRONTAL CORTEX ALTERATIONS

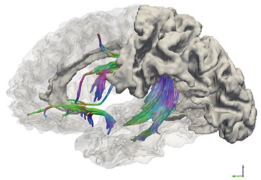
Associated with monoaminergic alterations, such as dopaminergic

Brunelin et al., Am J Psychiat, 2012

EXAMPLES

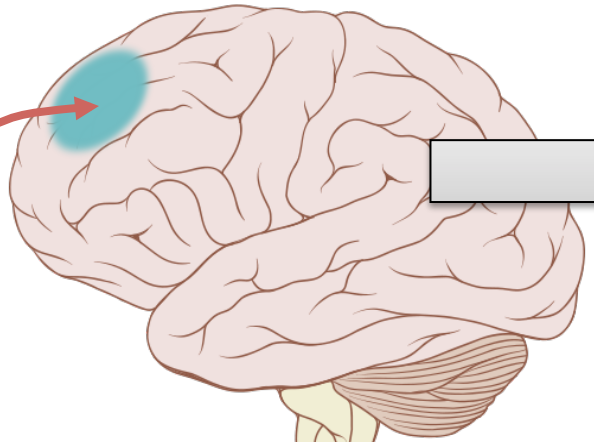
- DEPRESSION
  Left prefrontal cortex hypoactivity
  Bunney&Bunney, Brain Res Rev, 2000
  George et al., Depression, 1994
- SCHIZOPHRENIA
  Fronto-temporal regions dysconnectivity
  Ottet et al. , PLoS One, 2013
  Lawrie et al. , Biol Psychiat, 2002
- ADDICTION
  Frontal regions dysconnectivity
  Kravitz et al., Brain Research, 2015





PREFRONTAL CORTEX

Neurostimulation



THERAPEUTIC EFFECTS

Neurophysiological correlates

Prefrontal Neurostimulations

Prefrontal Neurostimulations → An effect in **local** and in **connected regions**

1- Brain activity (ASL)
Antal et al., Human Brain Mapping, 2014
Stagg et al., J Neurosci, 2013

2- Functional connectivity in and between networks, like resting state networks (fMRI)
Keeser et al, Journal of Neuroscience, 2011
Saoite et al, Front Hum Neurosci, 2013
Mondino et al, Schiz Bull, 2015

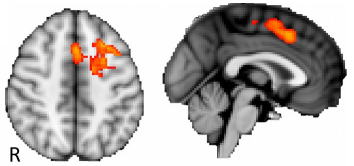
3- Structural connectivity (DTI)
Peng et al., J Affective Disorders, 2012

4- Subcortical dopaminergic transmission (PET)
Strafella et al., Brain, 2003; Pogarell, J Psy Res, 2006
Cho&Strafella, PLoS One, 2009; Brunelin et al., Schizophr Res, 2011

EXAMPLES

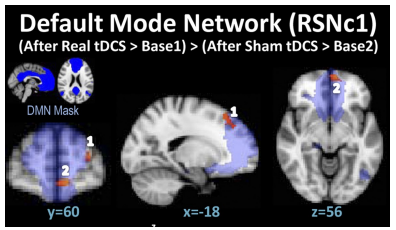
Healthy sujects

Anode vs Cathode



Stagg et al., J Neurosci, 2013

Healthy sujects



Keeser et al, J Neurosci, 2011

Patients with depression

Modification of anisotropic fraction after rTMS

Healthy sujects

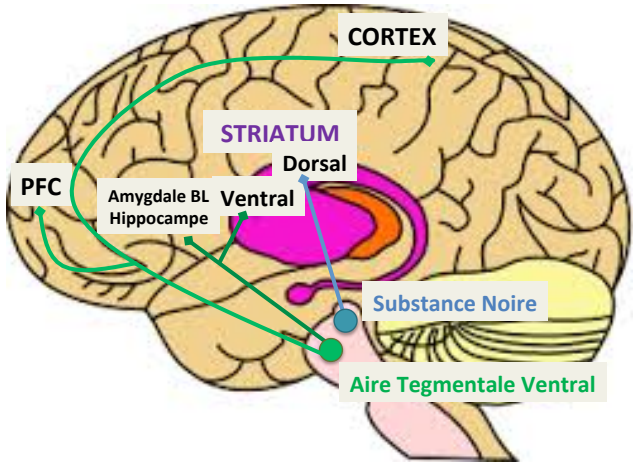
Subcortical Dopamine ↗

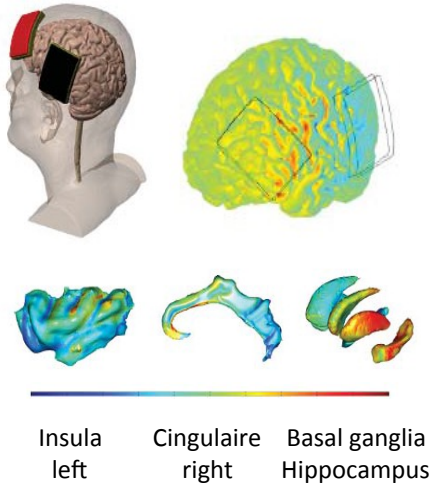
tDCS effects on dopaminergic transmission ?

Temporal and functional organisation ?

Prefrontal tDCS

tDCS effects on dopaminergic transmission ?





- **Animal study**

  tDCS impacts the dopaminergic system in basal ganglia of rats.

  Tanaka et al., Front Syst Neurosci, 2013

- **Modelling**

  Fronto-temporal tDCS impacts subcortical regions, such as basal ganglia.

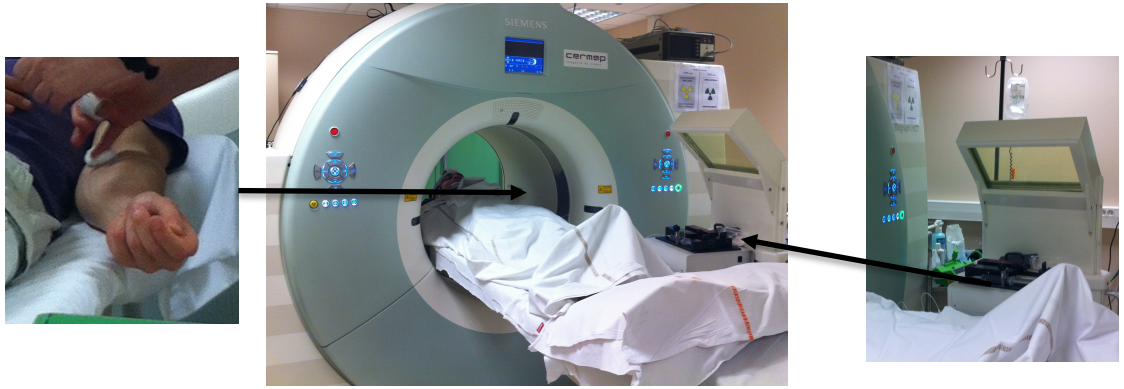
  Brunoni et al, Expert Rev. Med. Devices, 2014

⇒ HYPOTHESIS : tDCS impact subcortical dopamine transmission

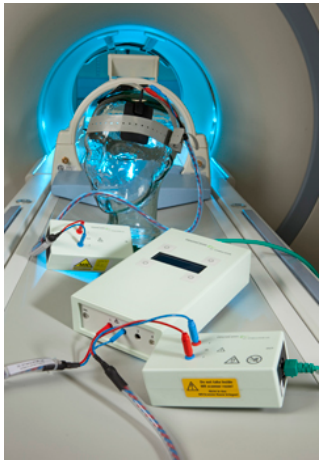
Positron Emission tomography (PET)

Intravenous injection :
Bolus + Perfusion of a radioactive tracer

Brunelin et al., Schizophrenia Res, 2011

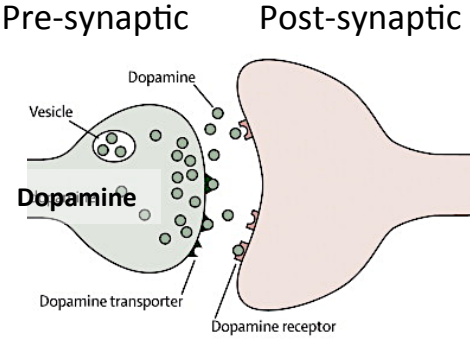


tDCS online

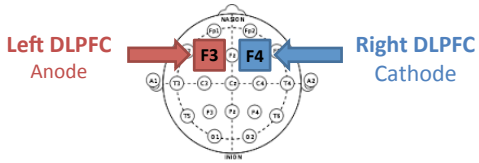


[^{11}C]Raclopride

Dopaminergic Receptor
D2

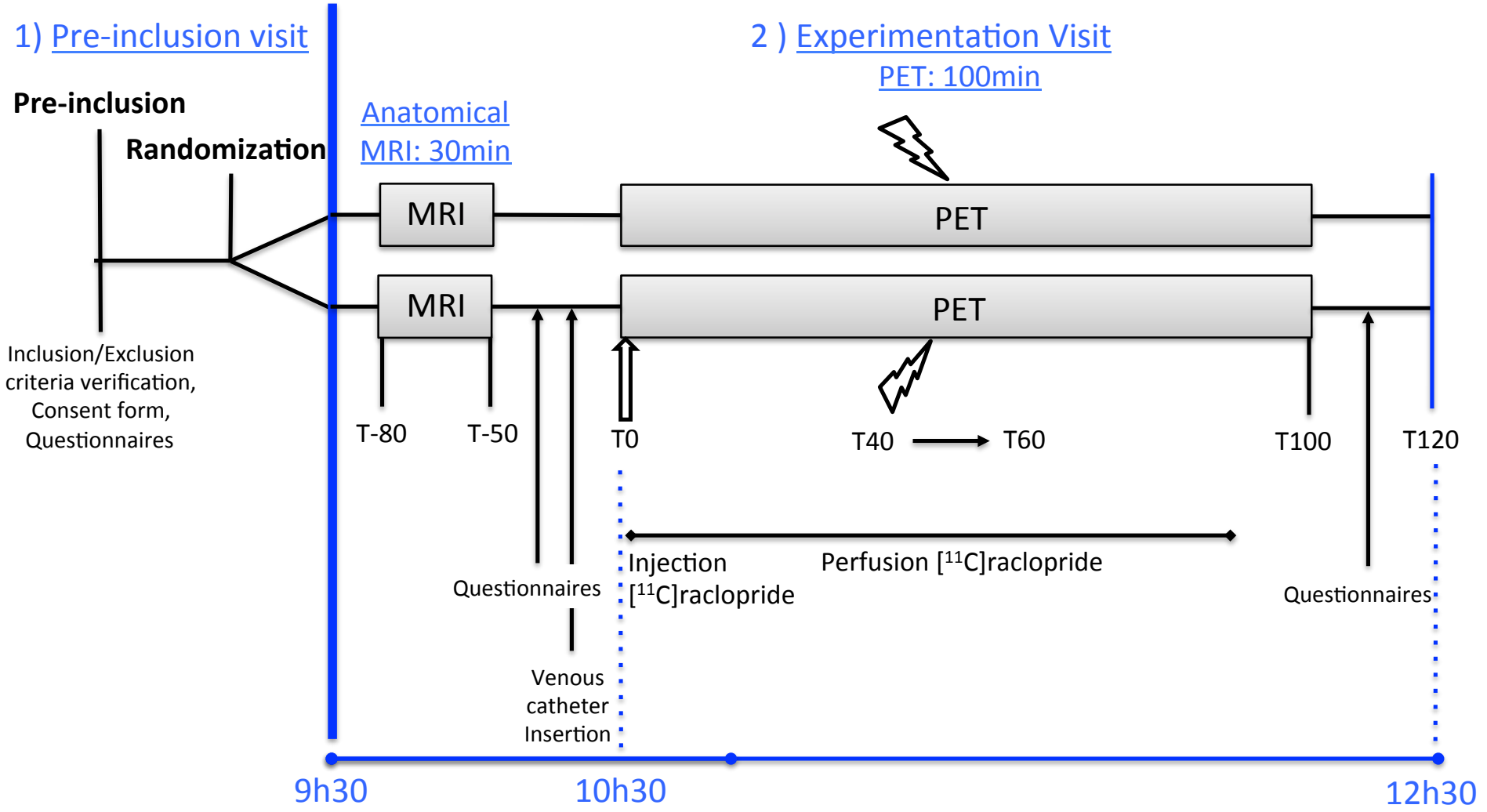


Bifrontal montage
2mA – 20 minutes

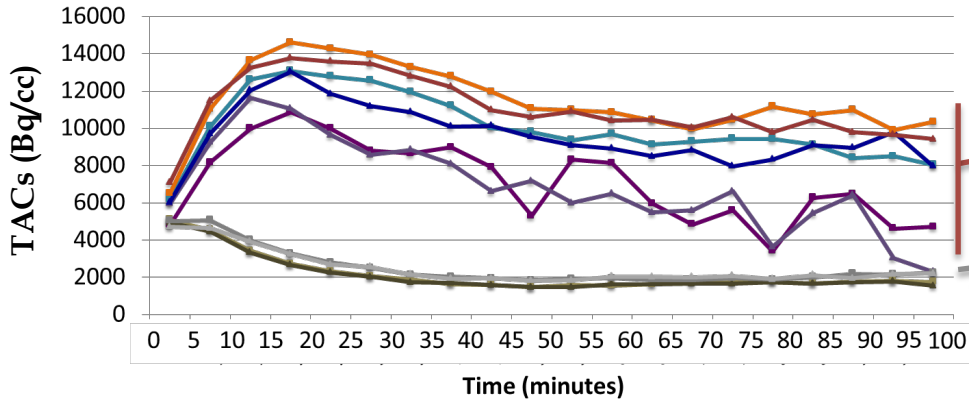


DOPA-STIM

Healthy subjects	ACTIVE	PLACEBO
n	15	15



1) Extraction of time activity curve (TACs) in each region of interest in the right and left hemispheres



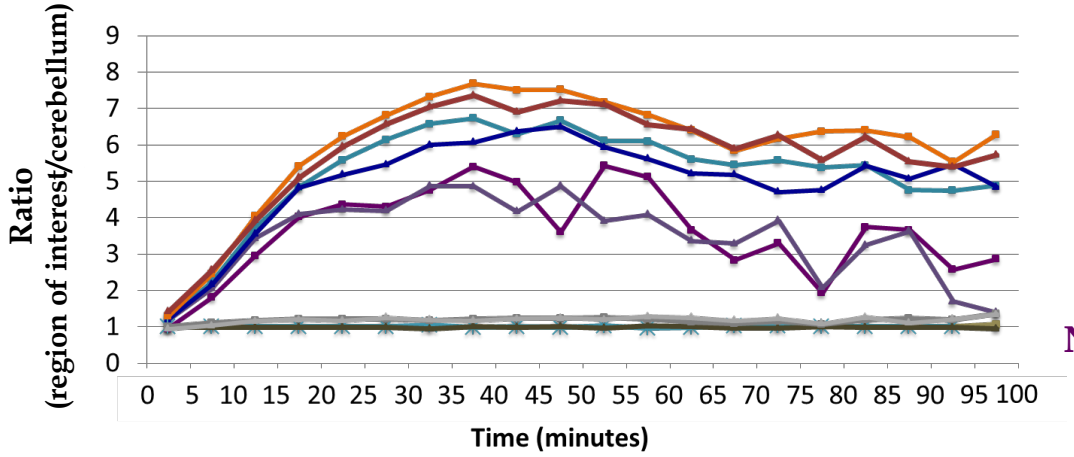
3 subcortical dopaminergic regions (**nucleus accumbens**, **caudate nucleus**, **putamen**)

1 control region (precentral gyrus)

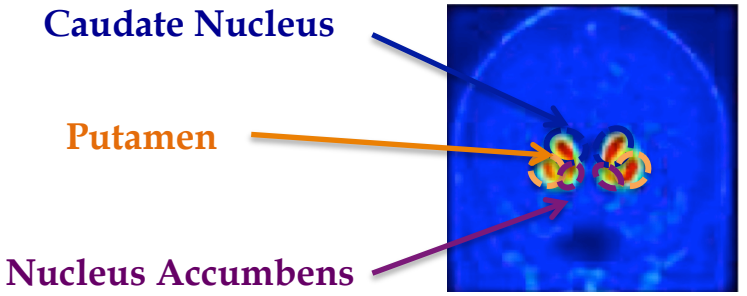
1 reference region (cerebellum)

2) Binding potential (BP_R) = ratio of region of interest/mean left and right cerebellum activities

→ Extracellular Dopamine



PET image
Regions of interest



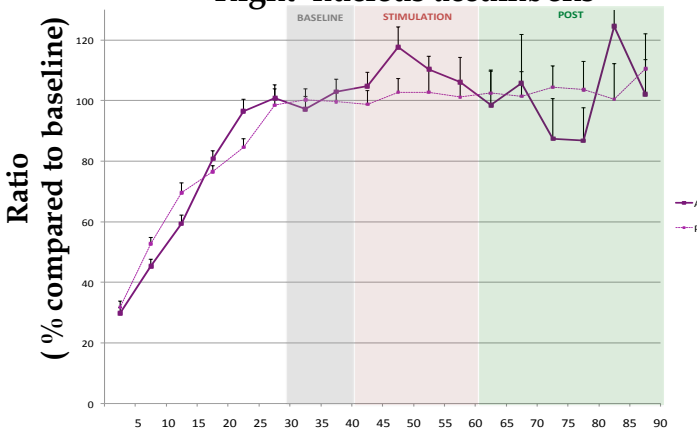
Regions were determined based on the adult brain atlas developed by A. Hammers et al (2003, King's College)

Preliminary data
n=7 active group / n=10 placebo group

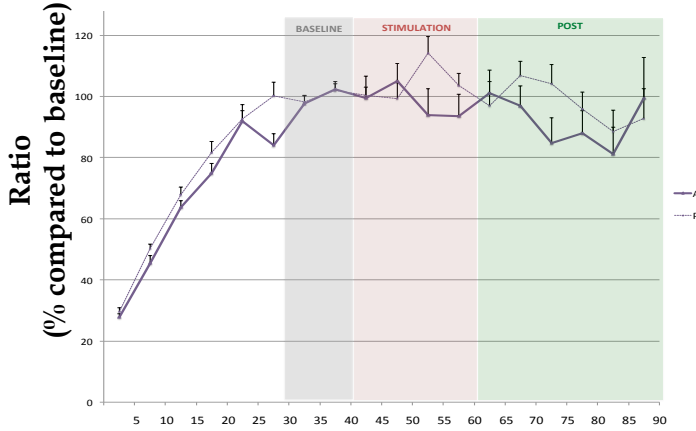
DOPA-STIM

Nucleus Accumbens

Right nucleus accumbens

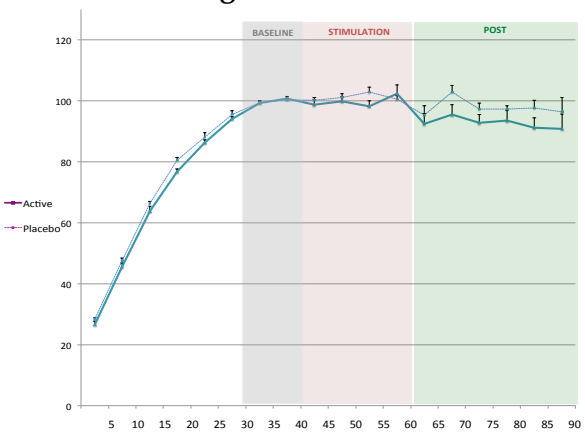


Left nucleus accumbens

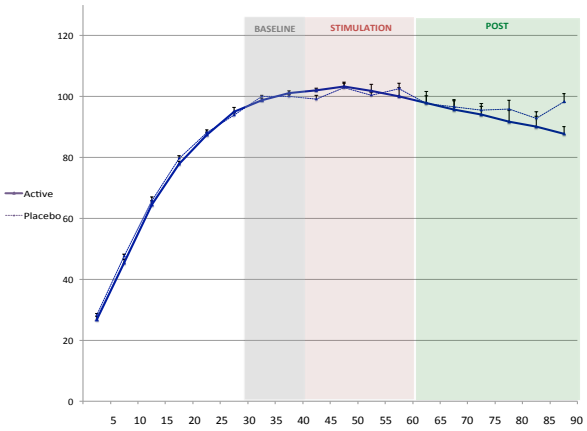


Caudate Nucleus

Right caudate nucleus

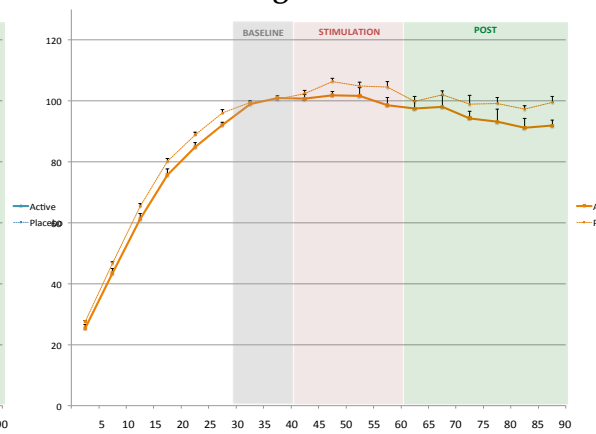


Left caudate nucleus

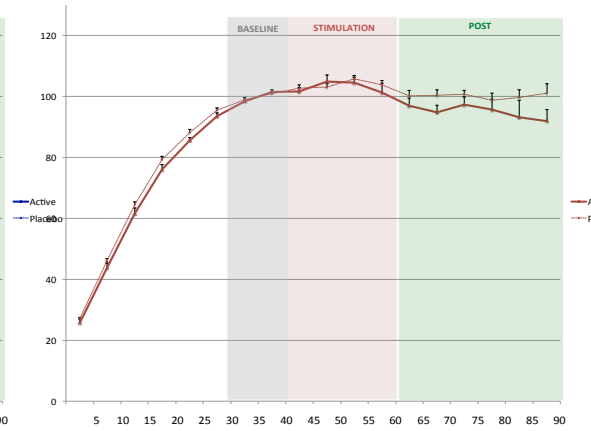


Putamen

Right Putamen



Left Putamen



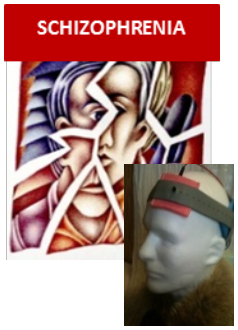
Data are expressed as mean±sem

⇨ tDCS impacts subcortical dopaminergic transmission.

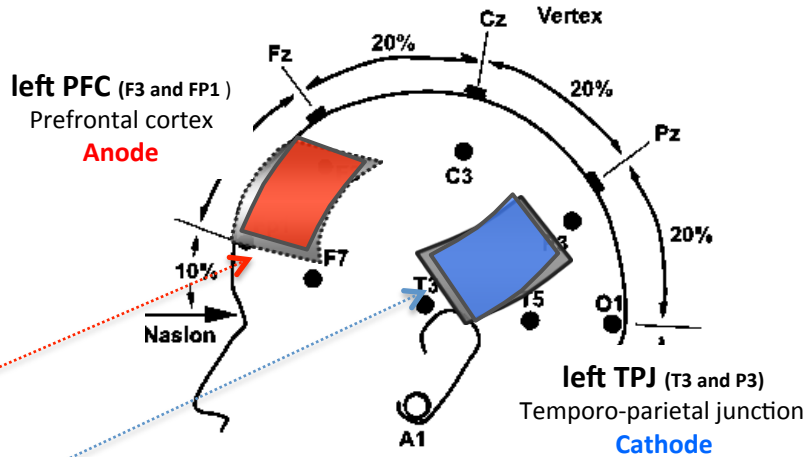
<u>Acute effects of tDCS</u>: Specifically in the nucleus accumbens.

<u>Subsequent effects of tDCS</u>: Seem to be generalized

COMBI-STIM



SCHIZOPHRENIA



Pathophysiology

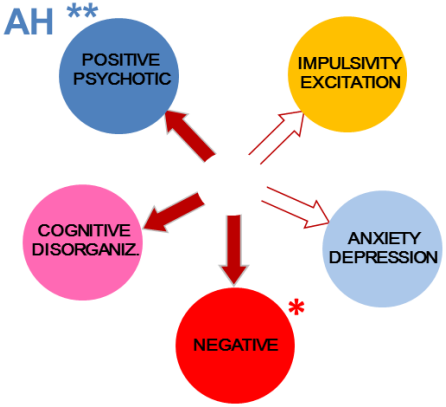
- Hypoactivity of the left prefrontal cortex
  Lawrie et al, Biol Psychiatry, 2002
  Sanfilipo et al, Arch Gen Psychiatry, 2000
- Hyperactivity of the left temporo-parietal cortex
  Sibersweig et al., Nature, 1995
- Dopaminergic alterations
  Brunelin et al, Curr Med Chem, 2013

THERAPEUTIC EFFECTS

SCH *

Brunelin et al., Am J Psychiatry. 2012
Koops et al., Front Psychol, 2015

AH **



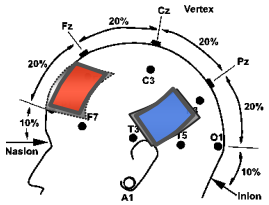
Neurophysiological correlates ?

Temporal and functional organisation of the neurophysiological correlates of fronto-temporal tDCS ?

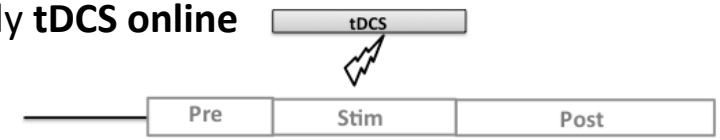
*Creating a **coherent ensemble** of the effects of the stimulation combining:*

1) Structural and functional connectivity
2) Brain activity
3) Subcortical dopaminergic transmission

- Adopt the clinicaly validated **fronto-temporal montage**

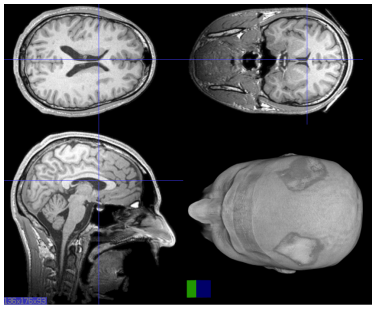


- Apply **tDCS online**

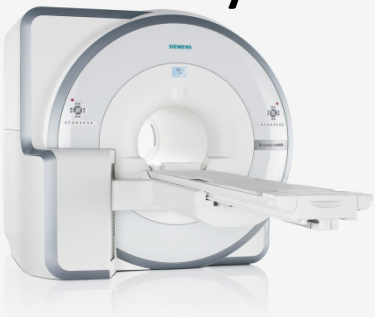


- Use of a **simultaneous imaging system**
  - ✓ Simultaneous imaging MRI & PET (MRI-PET Hybrid machine)
  - ✓ Link between connectivity, brain activity and subcortical dopaminergic transmission

Anatomical MRI

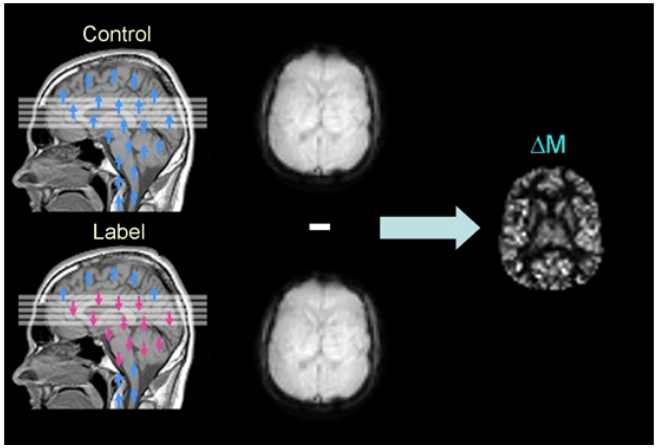


PET-MR Hybride



Brain Activity

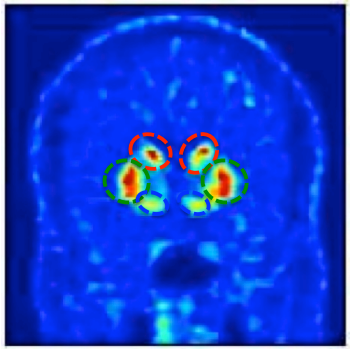
ASL



Subcortical dopaminergic transmission

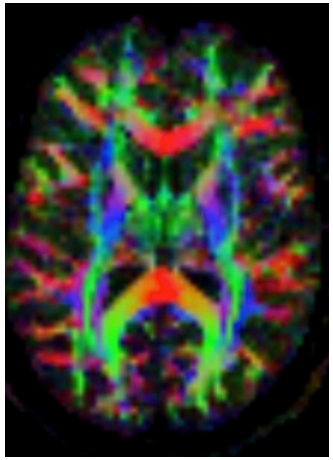
PET

([^{11}C]Raclopride)



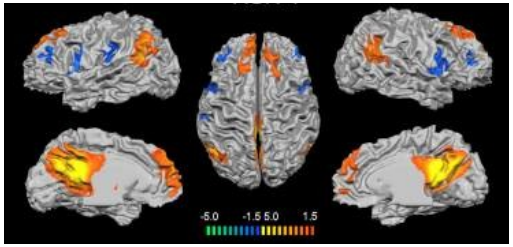
Structural connectivity

DTI



Functional connectivity

fMRI



First step in **healthy subjects**

COMBI-STIM

	ACTIVE	PLACEBO
n	15	15

FT montage
1mA – 30 minutes

1) Inclusion visit
CH Le Vinatier

2) Experimentation visit
CERMEP (morning)

Magnetic resonance imaging (MRI)

Anatomical | Functional

Pre-inclusion

Randomization

tDCS active

Positron emission tomography (PET)

Positron emission tomography (PET)

tDCS placebo

Inclusion/Exclusion Criterea, Consent, Questionnaires

T-20

T0

T40

T70

T110

T120

Questionnaires

Venous catheter insertion

Injection [^{11}C]raclopride

Perfusion [^{11}C]raclopride

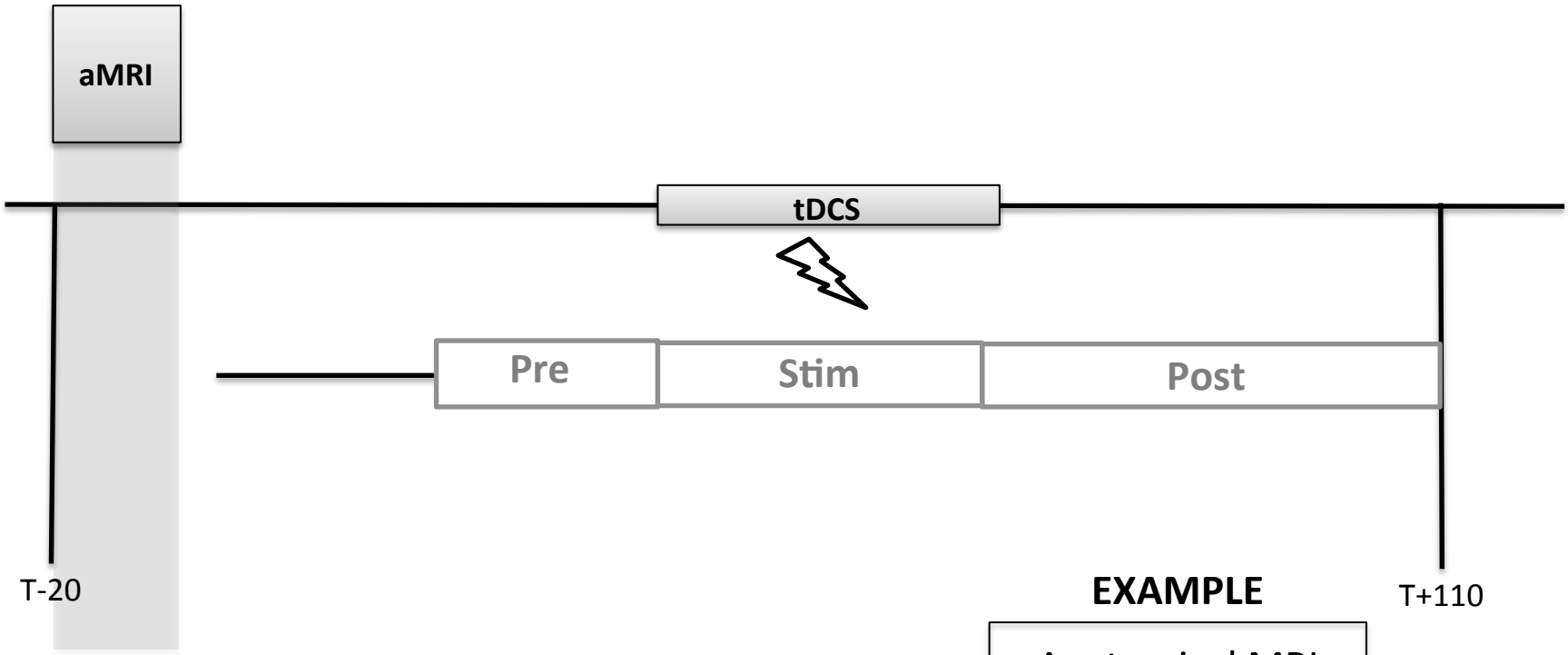
Questionnaires

9.30am

10.30am

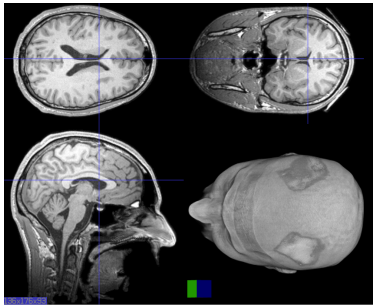
12.30am

COMBI-STIM



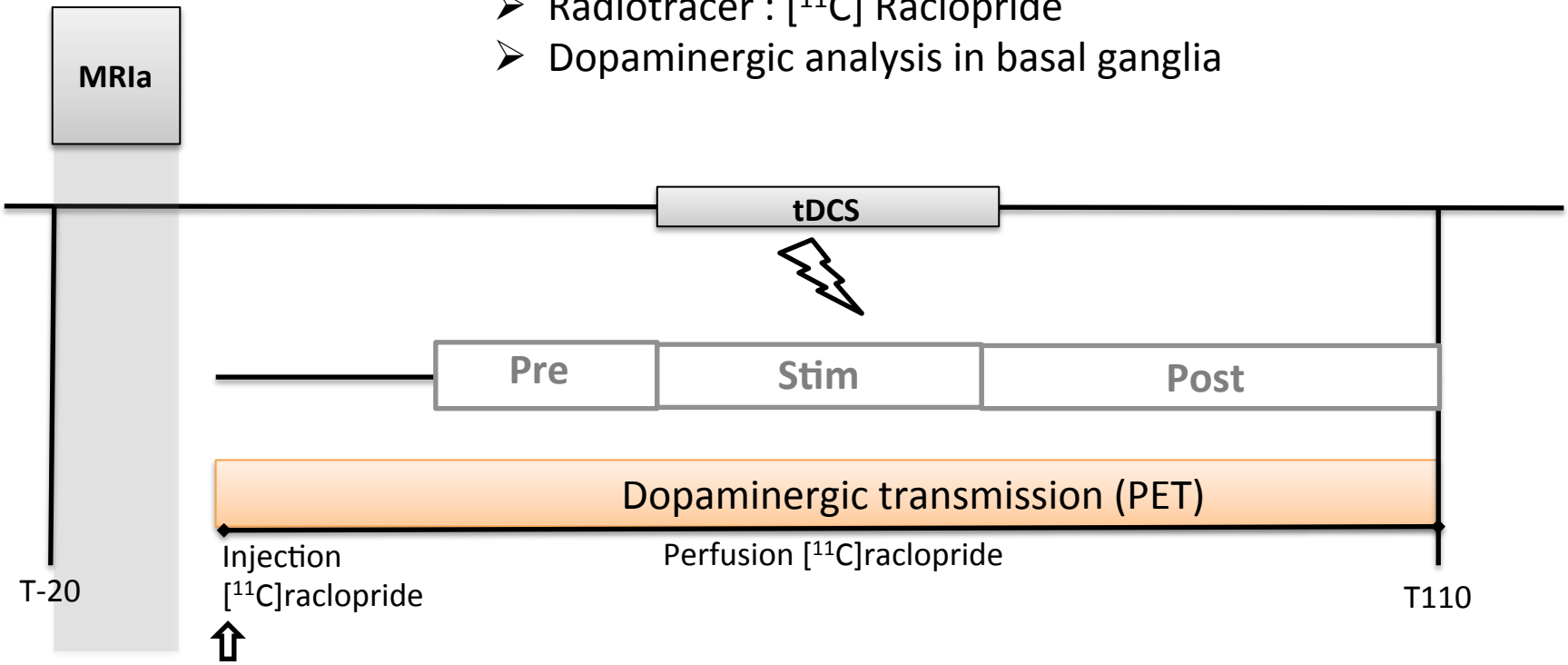
EXAMPLE

Anatomical MRI



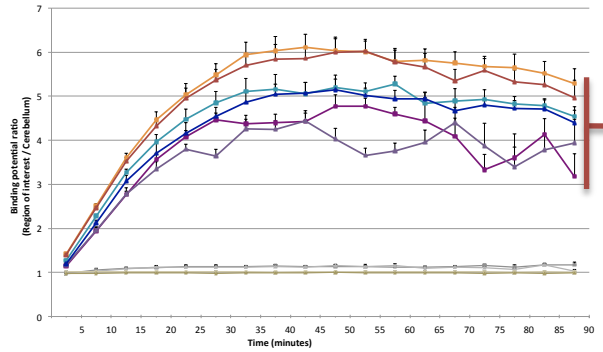
- Anatomical verification
- Coregistration with functional images
- Electrode position

- Radiotracer : [^{11}C] Raclopride
- Dopaminergic analysis in basal ganglia



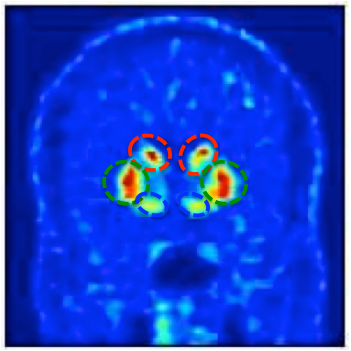
PET – Raclopride:

Dopaminergic transmission in basal ganglia
→ **Static** and **Dynamic** approach

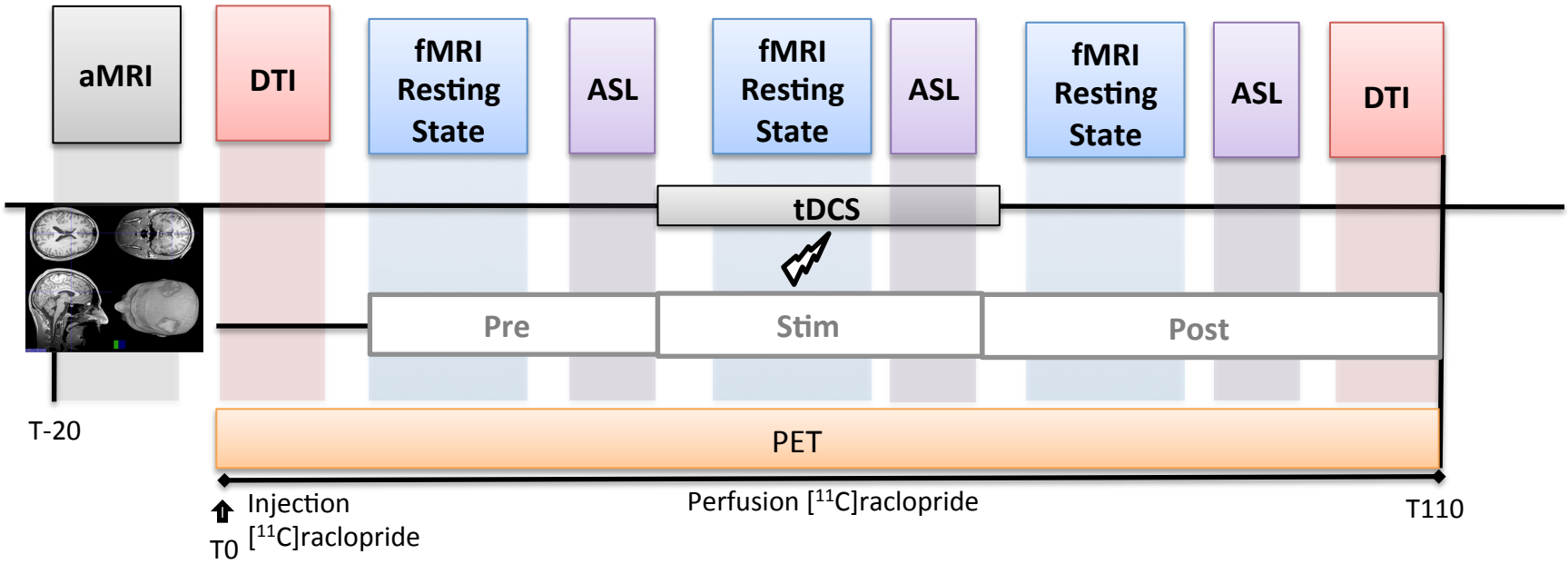


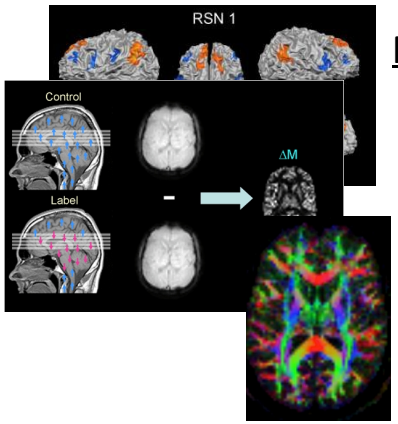
3 subcortical dopaminergic regions

- Nucleus accumbens
- Caudate Nucleus
- Putamen



COMBI-STIM





MRI – Sequences:

Resting state fMRI – functional connectivity

ASL – Brain activity

DTI – Structural connectivity

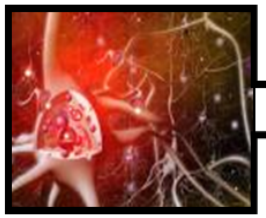
→ Region of interest analysis
- stimulated regions: **DLPFC** & **TPJ**
- connected regions: **Resting state networks** → Default Mode Network (DMN)
  Fronto-Parietal Network (FPN)
  Cingulo-Opercular Network (CON)

OUTCOME

Mesures:
Coherent ensemble

Expected results:
Imaging biomarker

NEUROBIOLOGY



Dopaminergic transmission (PET)

Structural connectivity (DTI)

NEUROPHYSIOLOGY

Functional connectivity (fMRI)

Brain activity (ASL)

Before stimulation

« Normal brain »

Pathological brain

Neurophysiological effects of fronto-temporal tDCS

Improved care for patients with schizophrenia

THANK YOU

Lyon Neuroscience Research Center

Centre hospitalier Le Vinatier

fondation neurodis

PsyR² Team

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cermep imagerie du vivant

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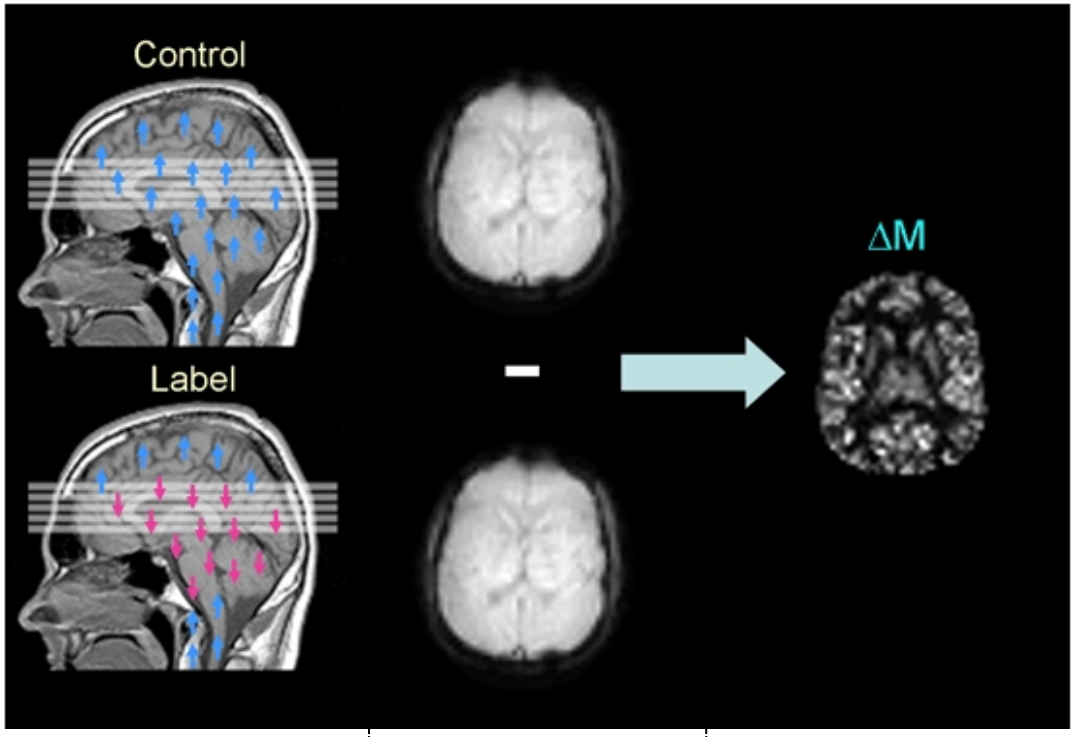
Inès Mérida
Jérome Redoute
Audrey Maurin
Elise Greusard

IRM de perfusion – Arterial Spin Labeling (ASL)

IRM

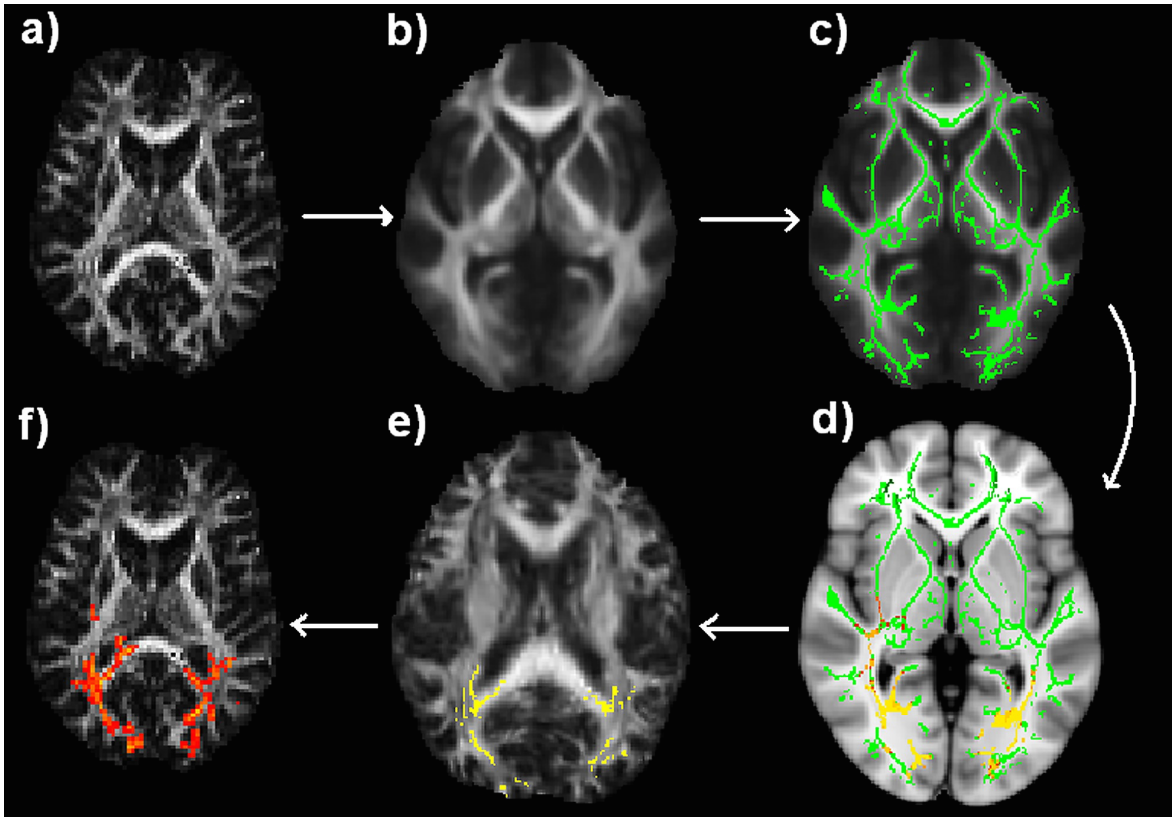


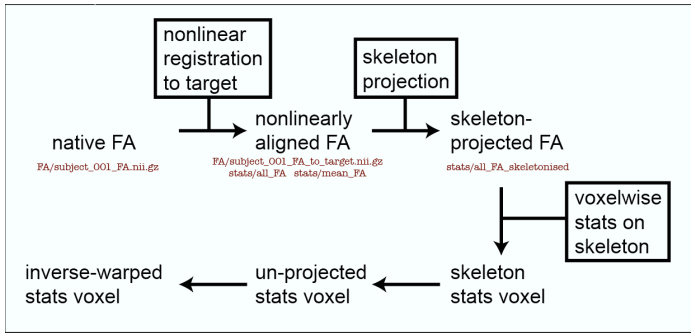
Marquage des protons du sang artériel

Elimine magnétisation statique

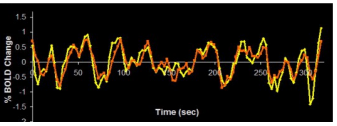
Image de perfusion

TRACT-BASED SPATIAL STATISTICAL (TBSS)





RESTING-STATE ANALYSIS



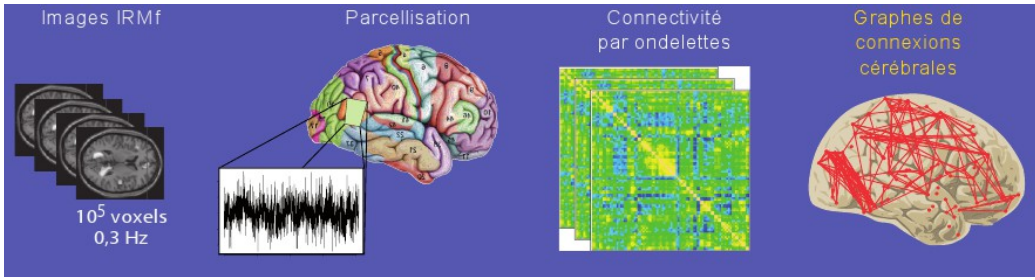
Seed-based

1- Selectionne une région
2- Extrait son décours temporel
3- Cherche parmi les autres régions celles qui ont un décours similaire

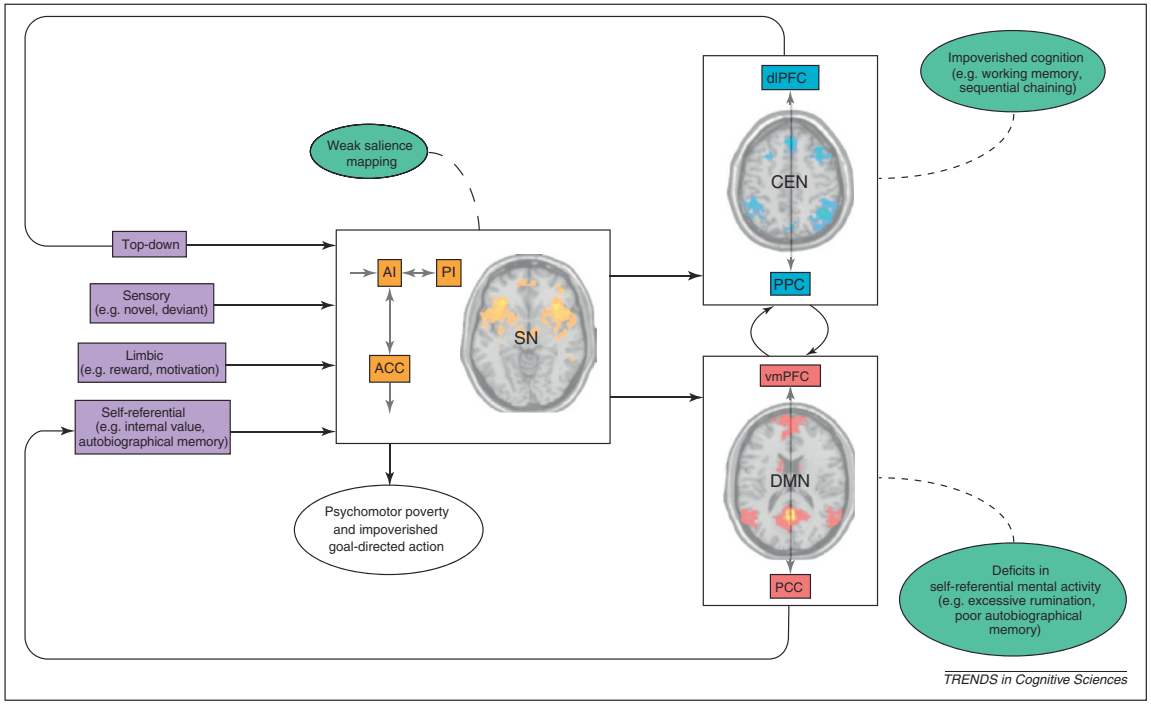
> stimulated regions: **DLPFC** & **TPJ**
> connected regions: **Resting state networks**

Default Mode Network (DMN)
→ Fronto-Parietal Network (FPN)
Cingulo-Opercular Network (CON)

Graph Analysis



(Noeuds = régions cérébrales / Arêtes = corrélation entre régions)



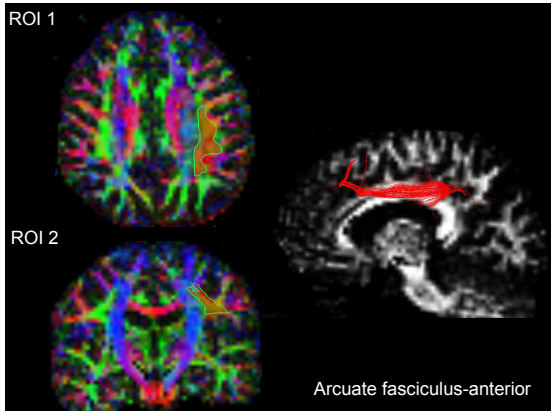
OTHER PROJECTS

Other projects
Physiopathology and impact of neurostimulation in patients with schizophrenia

Physiopathology
2 groups: With or Without auditory hallucinations

✧ Integrity of the arcuate fasciculus

Analyses DTI



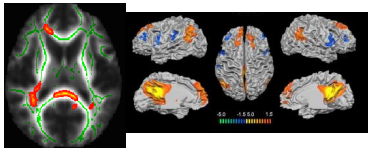
n=38 – MedINRIA software

Soumission article

Psomiades Marion, Fonteneau Clara, Mondino Marine, Luck David, Haesebaert Frederic, Suaud-Chagny Marie-Françoise, Brunelin Jérome
Integrity of the arcuate fasciculus in patients with schizophrenia with and without auditory verbal hallucinations: A DTI-tractography study
NeuroImage: Clinical, *accepted*

✧ Combined structural and functional integrity
Analyses DTI et resting state

TBSS – Graph or Seed

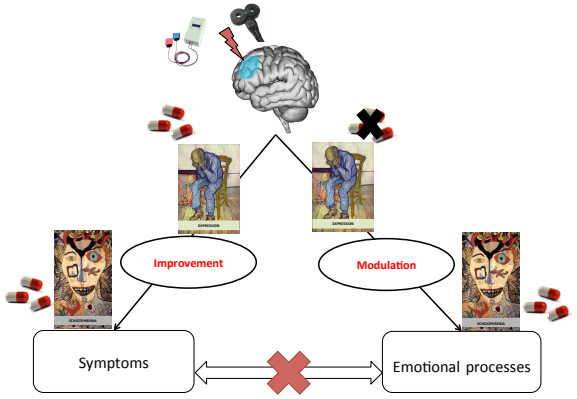


Neurostimulation
tDCS or rTMS

✧ Impact of neurostimulation on emotion processing

Review article

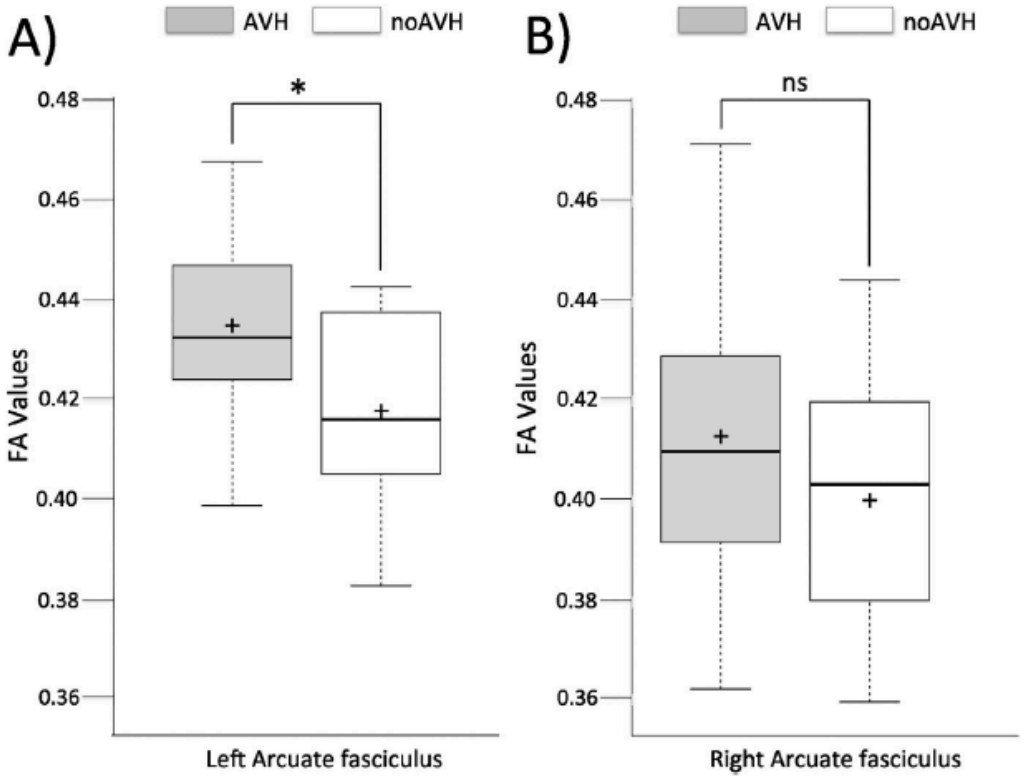
Psomiades Marion*, Fonteneau Clara*, Suaud-Chagny Marie-Françoise, Haesebaert Frédéric, Brunelin Jérôme
Neurostimulation du cortex préfrontal dorsolatéral : quels effets sur la symptomatologie et les émotions dans la dépression et la schizophrénie ?
Santé mentale au Québec ; *in press* ; *co-author



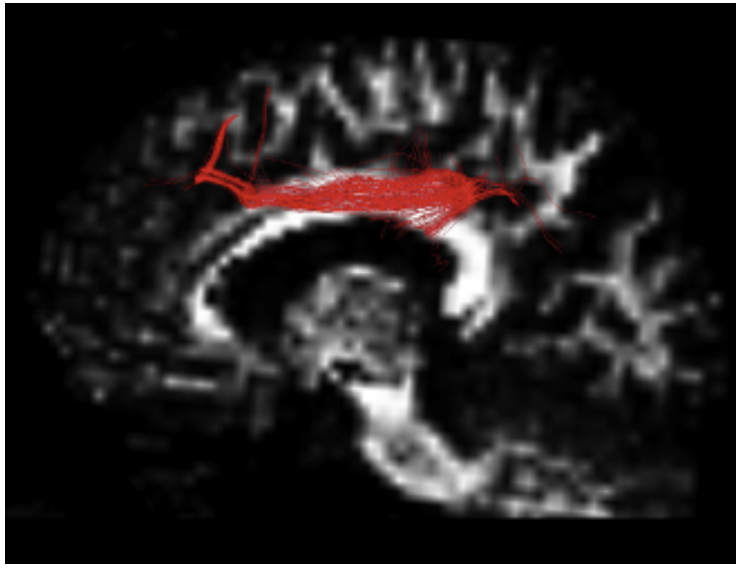
✧ After the neurostimulation cure
Combined structural and functional integrity
Analyses DTI et resting state

PHYSIOPATHOLOGY

Physiopathology in patients with schizophrenia (with or without auditory hallucinations)



Arcuate fasciculus



Link FA/AVH:
N=38 (26H+)
(r = −0.04; p = 0.80)

Psomiades et al, 2016, *accepted*