Amygdala and medial Prefrontal Cortex anatomo-functional dialogue in primates

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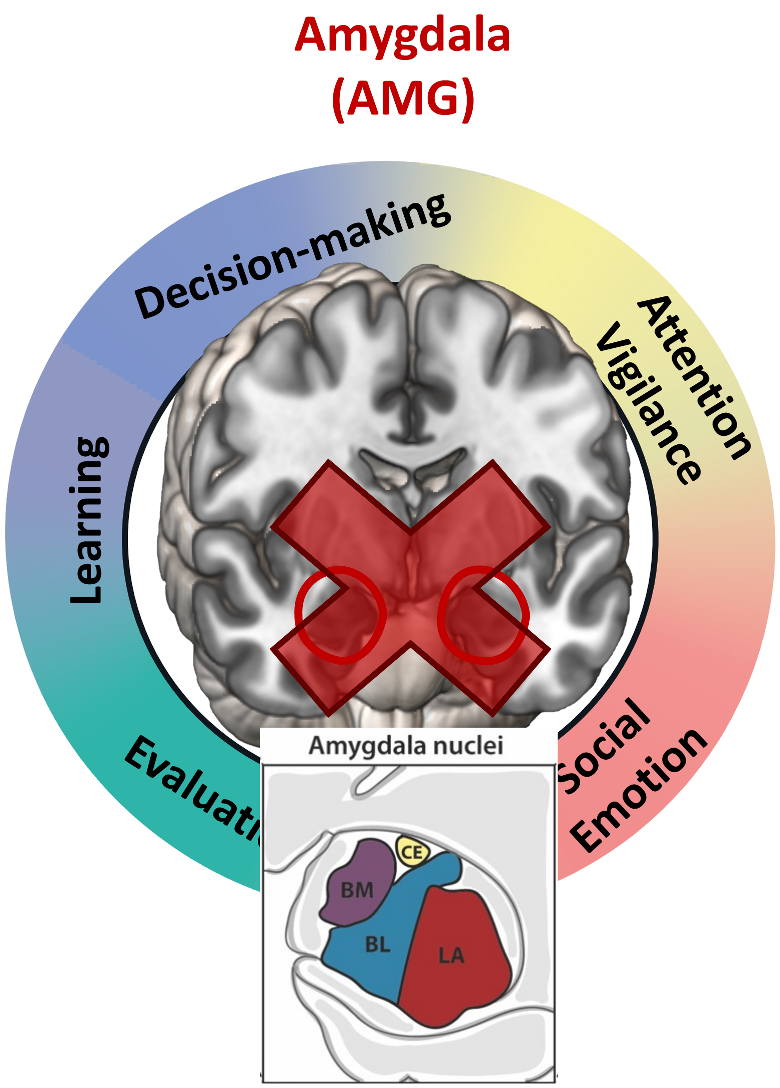
The AMG-mPFC network: why?



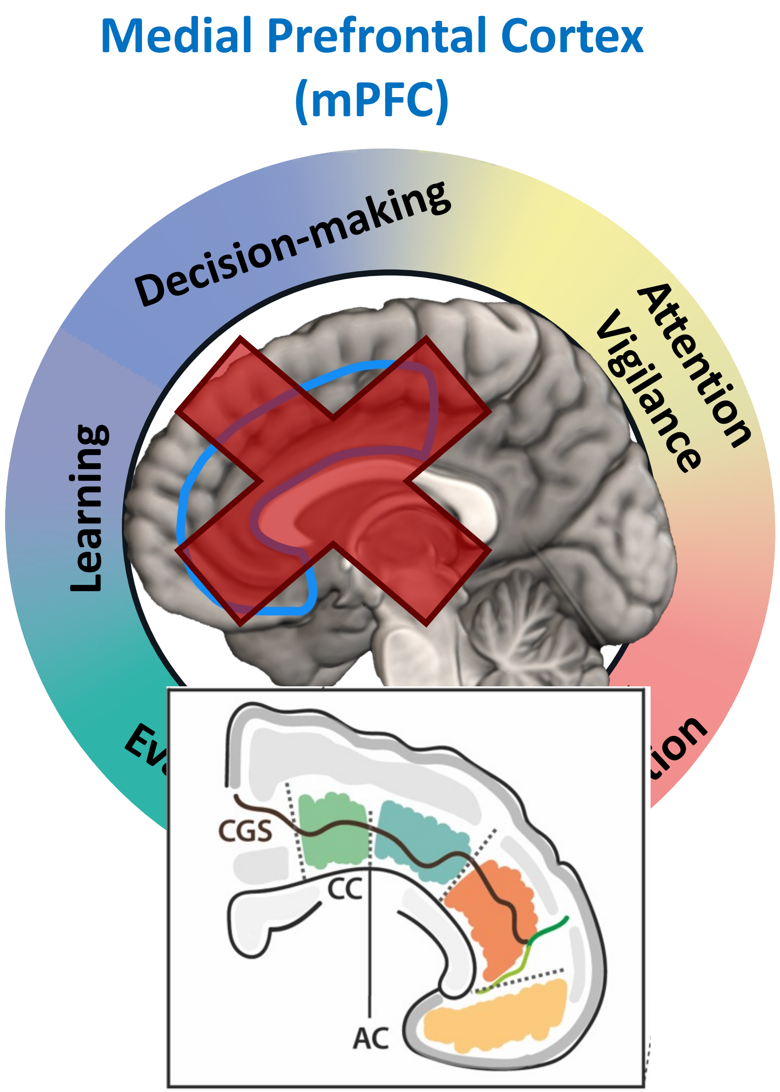
Central pivots in the brain, involved in a range of **complementary functions** related to :

Behavioral adaptation

(Gothard 2020; Klein-Flügge et al., 2022; Muray et al., 2021; Gangopadhyay et al., 2021)

Impaired in numerous of **neuropathologies:** anxiety, autism, depression, OCD, etc.

(Likhtik & Paz 2015; Kim et al., 2011; Li et al., 2021; Jalbrzikowski et al., 2017)



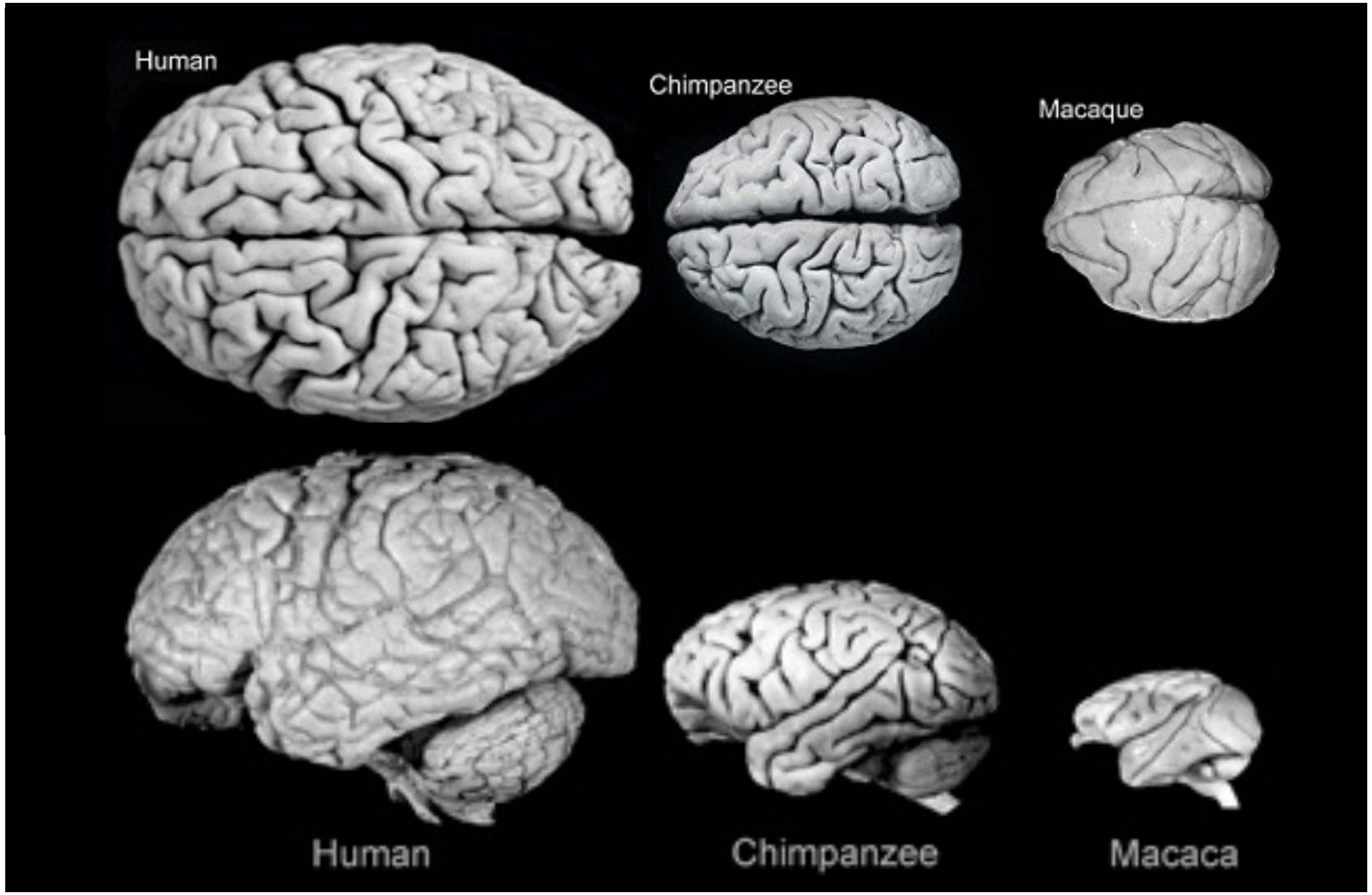
Plan

1 – Background: AMG and mPFC and their homologies/differences between human and macaques

2 – Study 1: Differential functional organization of amygdala-medial prefrontal cortex networks in macaque and human

3 – Study 2: The impact of transcranial ultrasound stimulation of the AMG on the AMG-mPFC FC *(preliminary results)*

Human brain expansion

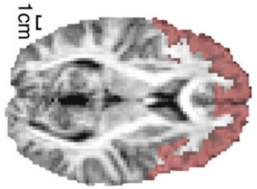


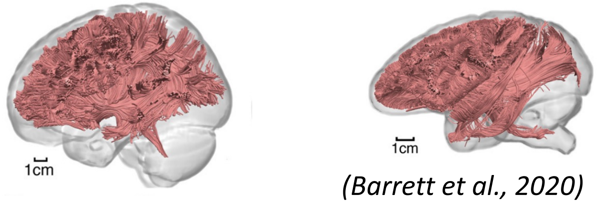
What are the consequences on the PFC/mPFC and the AMG?

In the prefrontal cortex ?

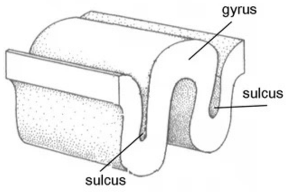
Human **Macaque**

Morphology:

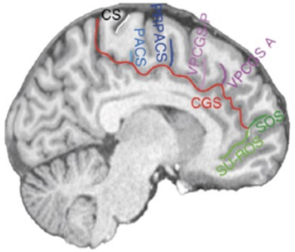


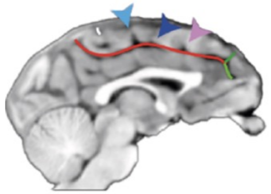


(Barrett et al., 2020)



- ❑ **Sulci**
  Precursors found in non-human primates

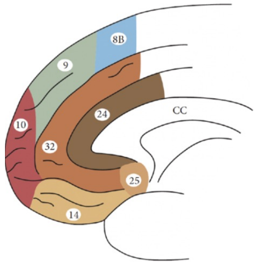


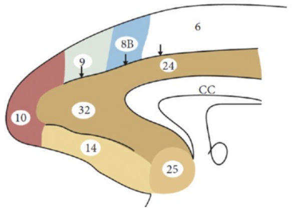


(Amiez et al., 2019)

Structure:

- ❑ Conserved cytoarchitecture*





(Petrides & Pandya 1994)

* Layer organization of the cortex

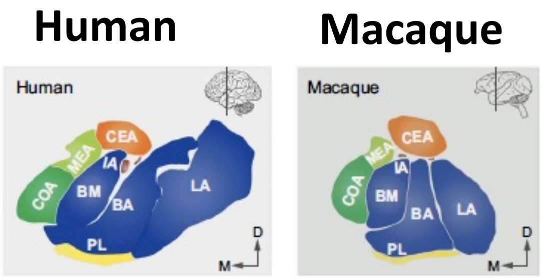
Morphology:

- ❑ **Volume**
  Cortex
  White matter tracts

- ❑ **Sulci**
  Differential organizations

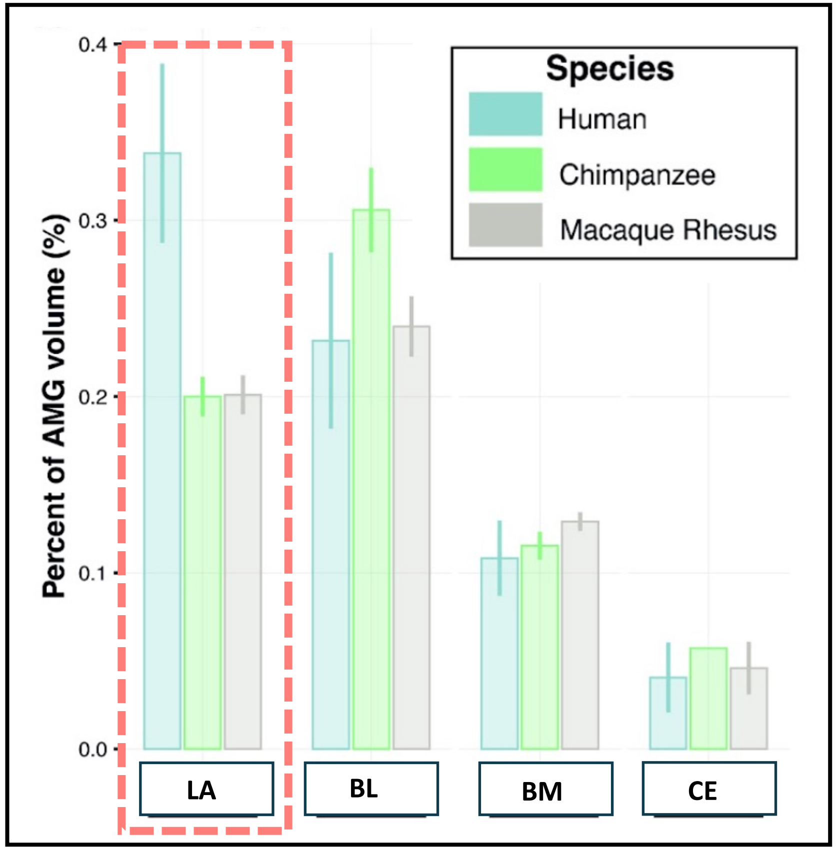
In the amygdala ?

Structure
Similar across species (mammals)



(Chareyron et al., 2011; Yu et al., 2023)

Morphology
Preserved centromedial part (i.e., CE)



Morphology
Difference in laterobasal part (i.e., LA, BL and BM)

- ❑ **Nuclei volume**

LA-specific expansion in humans

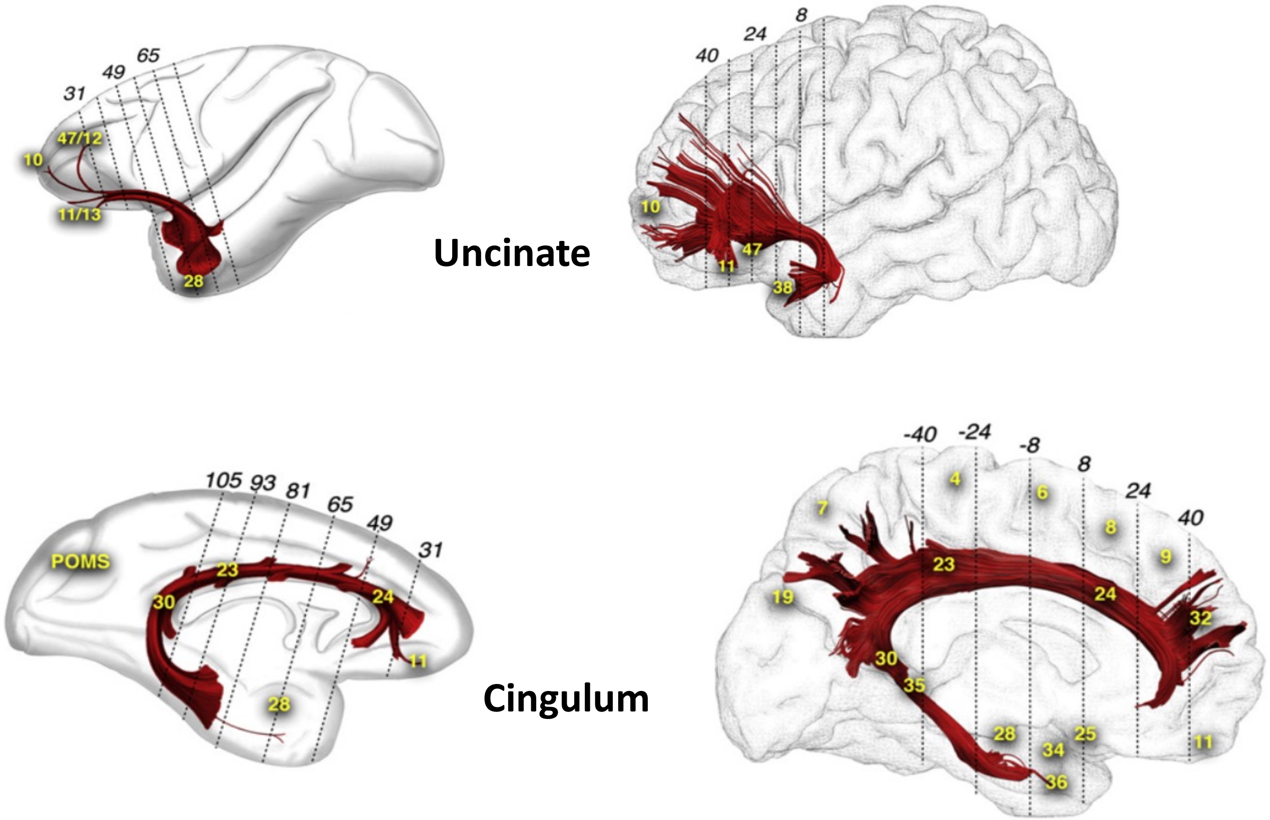
*(Review **Giacometti** et al., 2023, CRNEUR)*

Their connectivity?

Structural connections: tractography (DTI)

white fiber bundles connecting AMG and mPFC comparable between macaque and human

Macaque **Human**

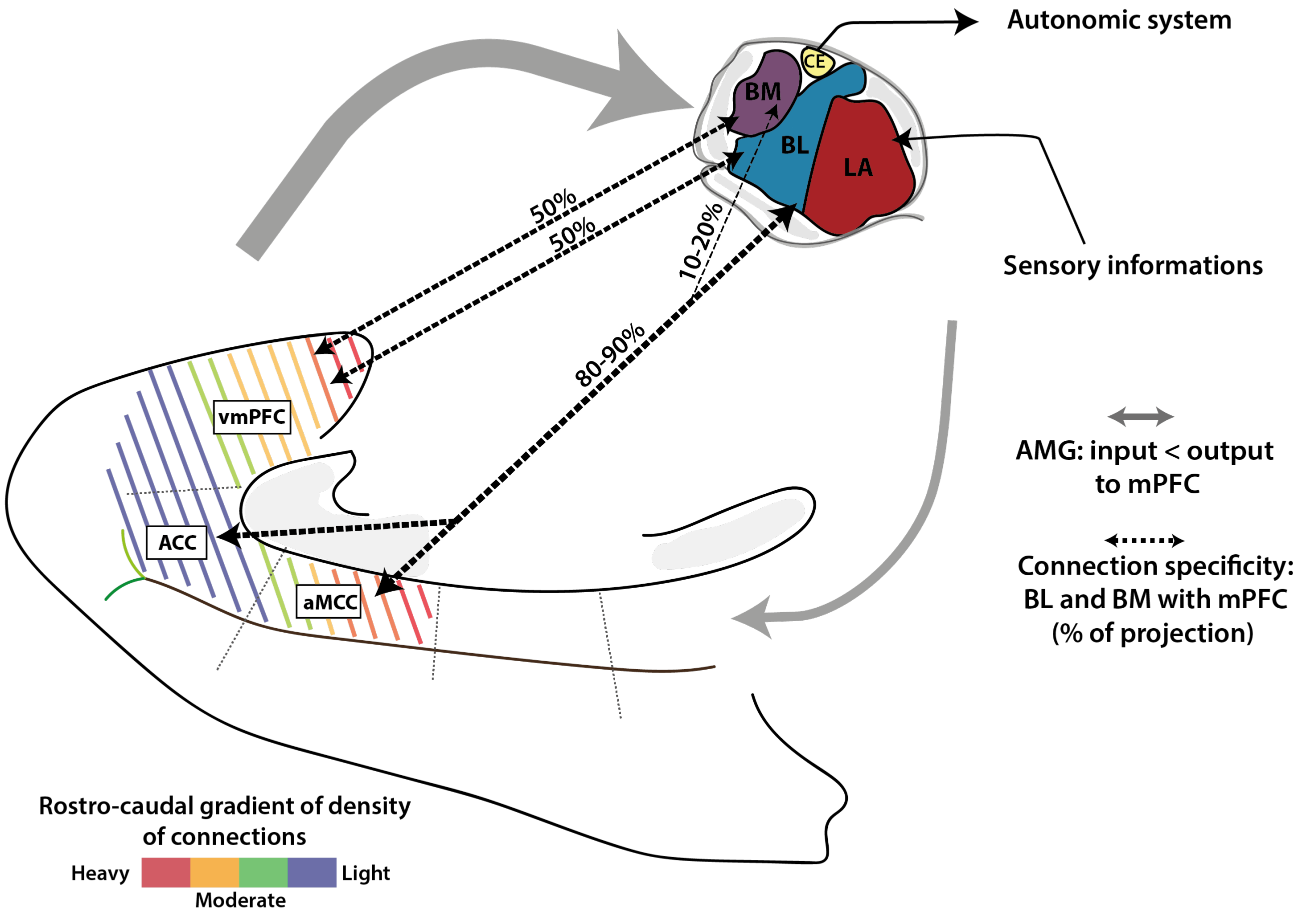


(Thiebaut de Schotten et al., 2012, Folloni et al., 2024, preprint)

Their connectivity?

MACAQUE – Microscopic scale

Ex-vivo tracers: **Intricate structual connexions at the nuclei level**



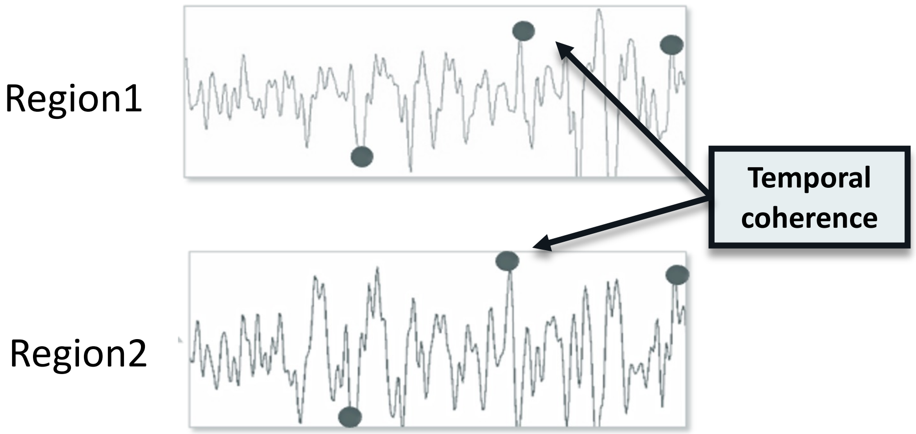
(Review: ***Giacometti*** *et al., 2023, CRNEUR, based on Ghashghei et al., 2007; Sharma et al., 2020; Roy et al., 2008, etc.)*

Their connectivity?

HUMAN – Macroscopique scale

Neuroimagery *in vivo*: **Functional connections at the subdivision level**

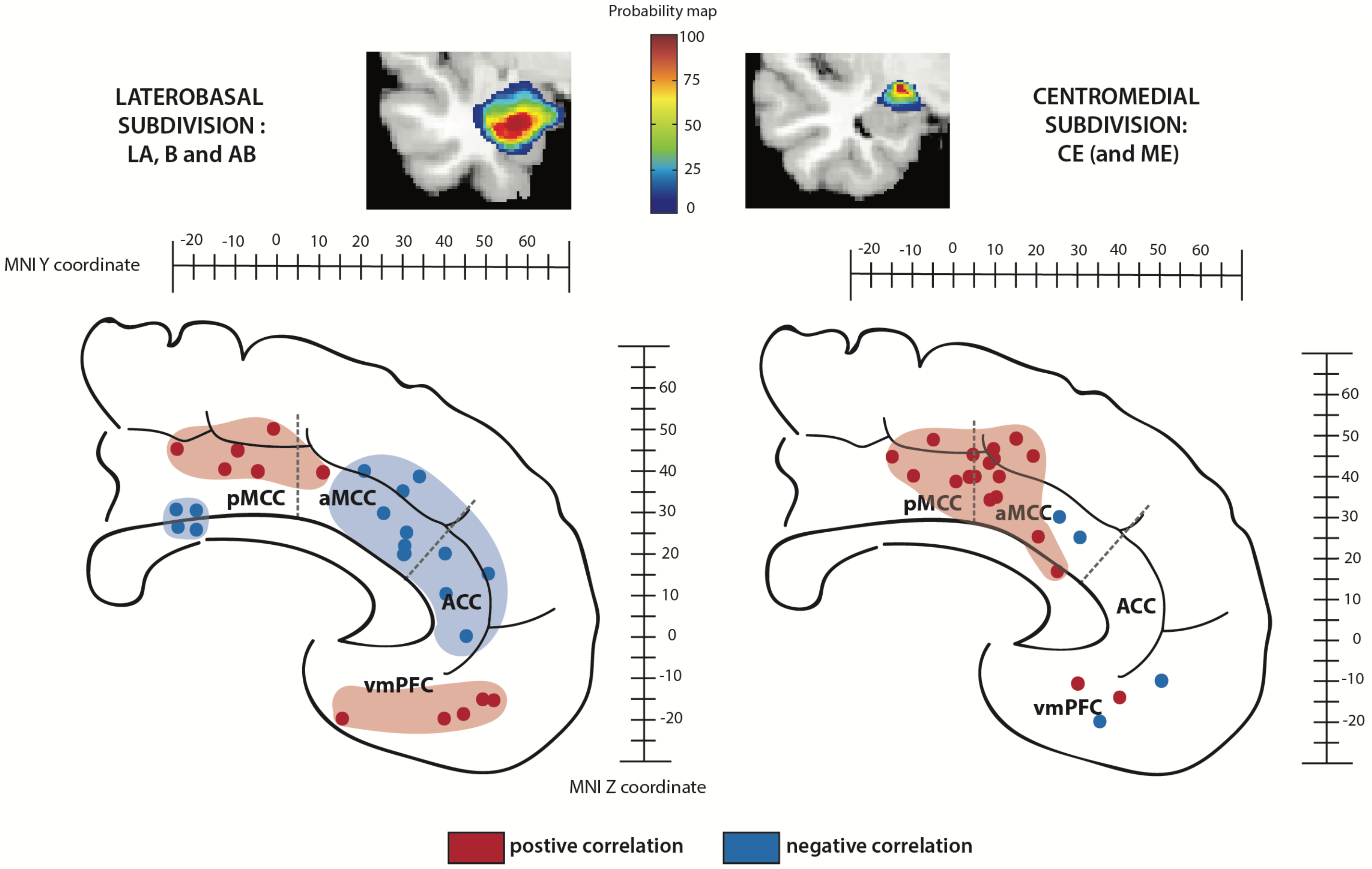
Resting-fMRI approach capture the functional dialogue



Signal BOLD (**0.01 – 0.1 Hz)**

Correlation (= functional connectivity) :

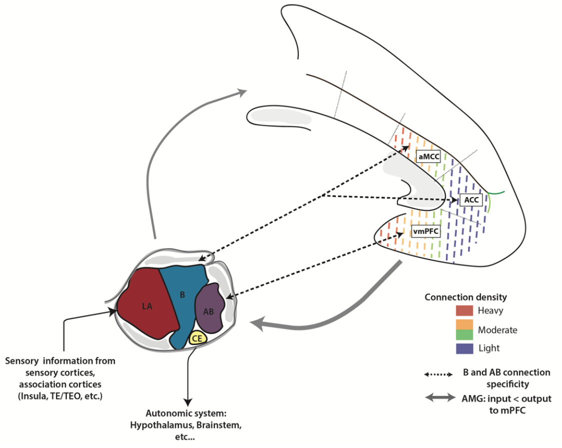
- **Positive (> 0)**
- **Négative (<0)**



(Review: **Giacometti** et al., 2023, CRNEUR, based on Ghashghei et al., 2007; Sharma et al., 2020; Roy et al., 2008, etc.)

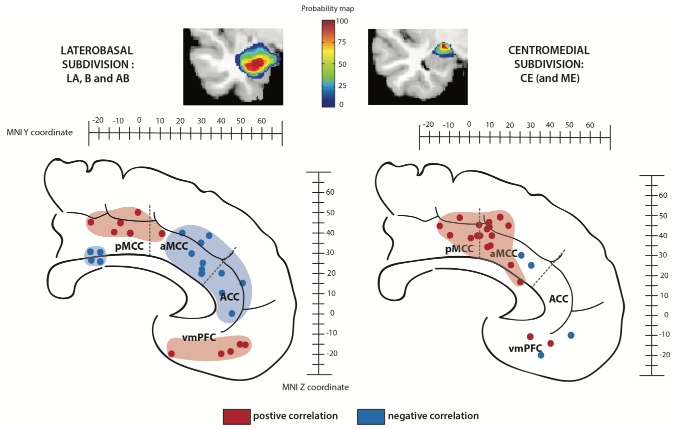
AMG-mPFC network: problematic

MACAQUE: microscopic scale



"GAP"
(Barron et al., 2021)

HUMAN: macroscopic scale



Rs-fMRI

- In macaques, the majority of rs-fMRI and comparative studies are carried out when they are under anaesthesia: *anaesthesia effect?*

Anaesthesia affect cingulo-fronto lateral network functional dynamic
(Giacometti, Dureux et al., 2022, Cereb Cortex)

- No comparative study on the complex functional relationships of the AMG-PFC network between macaques and humans: *is it comparable?*

STUDY 2

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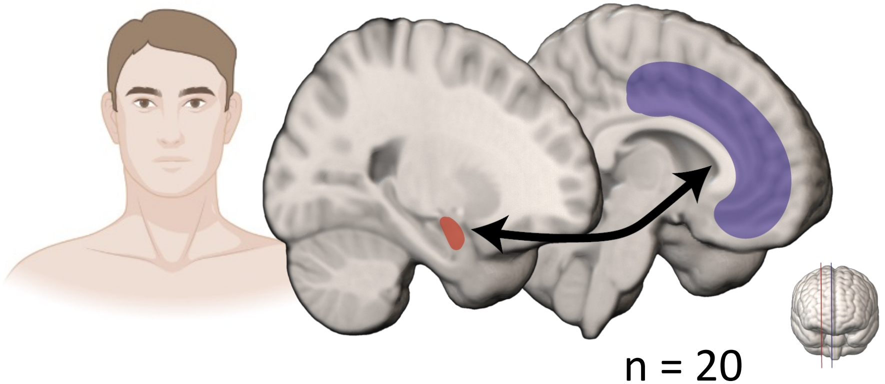
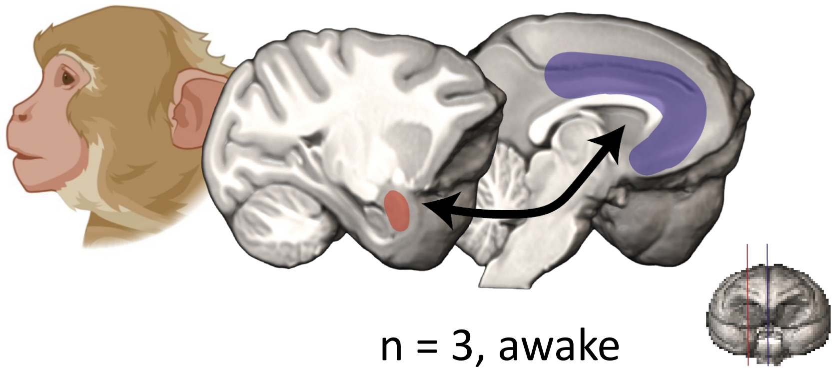
AMG nuclei and mPFC functional dialogue in humans and macaques

1) Whole AMG rs-fMRI study in anaesthetized macaque monkeys
2) No study of AM nuclei in macaque monkeys
3) No comparative study between humans and macaques on the functional relationships of AMG nuclei and mPFC regions



n = 20



n = 3, awake

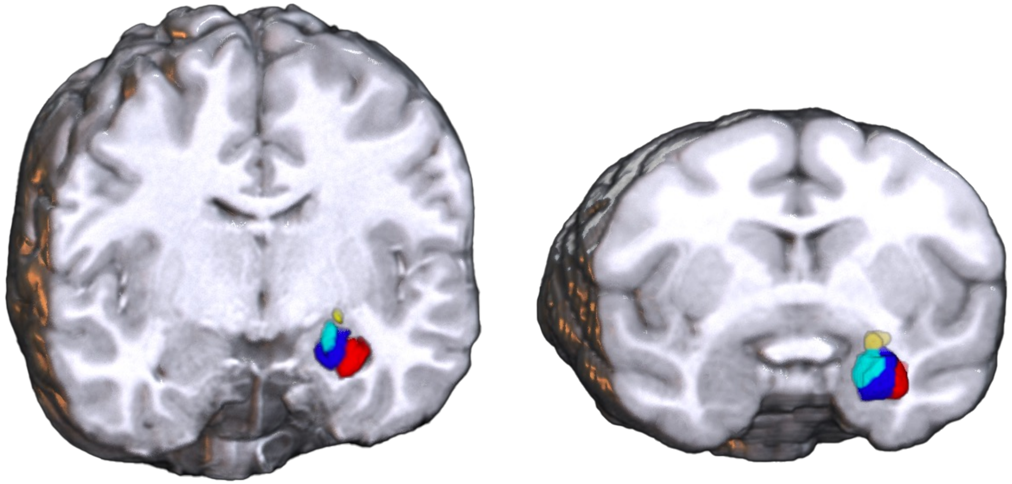
3T MRI scanner

TR= 1.5s
Voxel size = 2.5 mm3
1 run of 400vol/subject

TR= 1.8s
Voxel size = 1.8mm3
12 runs of 400vol/subject

(Giacometti et al., 2024, ComBio)

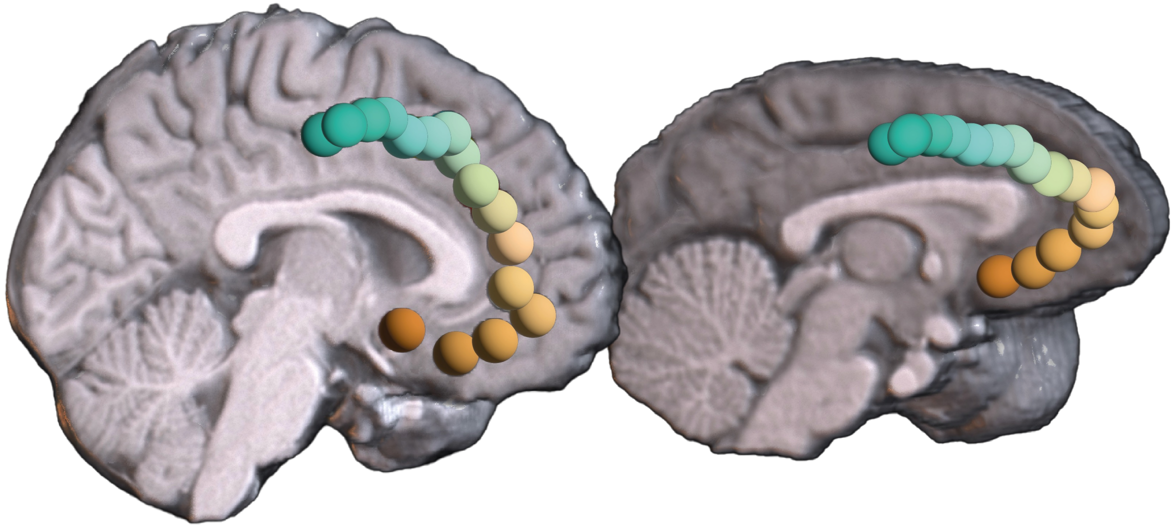
AMG nuclei and mPFC functional dialogue in humans and macaques



4 AMG nuclei

(atlas:Tyszka and Pauli 2016; Hartig et al., 2020)

- Lateral nucleus (LA)
- Basolateral nucleus (BL)
- Basomedial nucleus (BM)
- Central nucleus (CE)



16 ROIs in the mPFC :

(subject-by-suject based on local anatomical landmarks Amiez et al., 2019)

ventral to rostro-caudal

Area25 SROSp SROSm SROSa

Fork32 CgS11 CgS10 CgS9

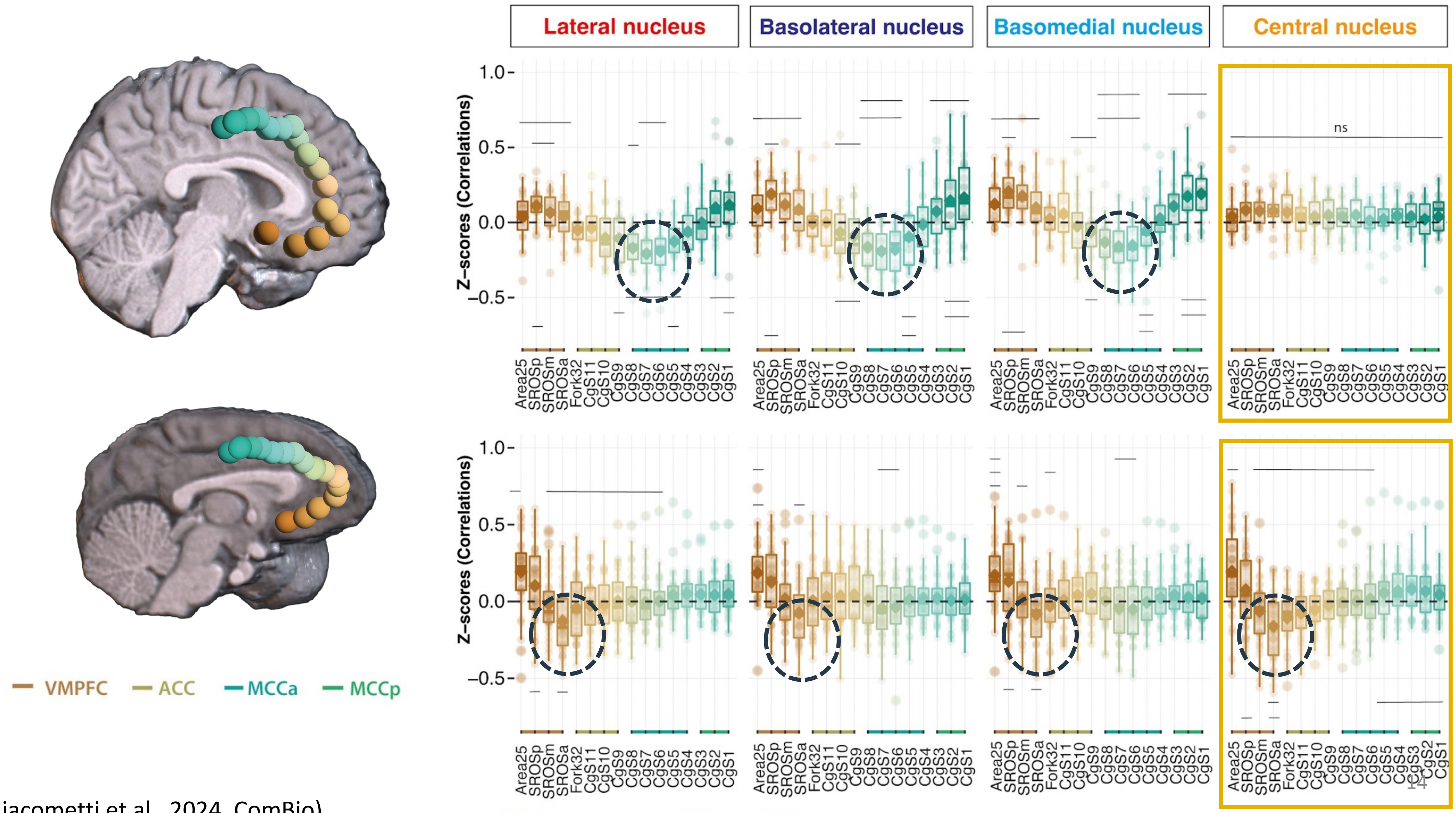
CgS8 CgS7 CgS6 CgS5 CgS4

CgS3 CgS2 CgS1

vmPFC : 4
ACC: 4
aMCC : 5
pMCC : 3

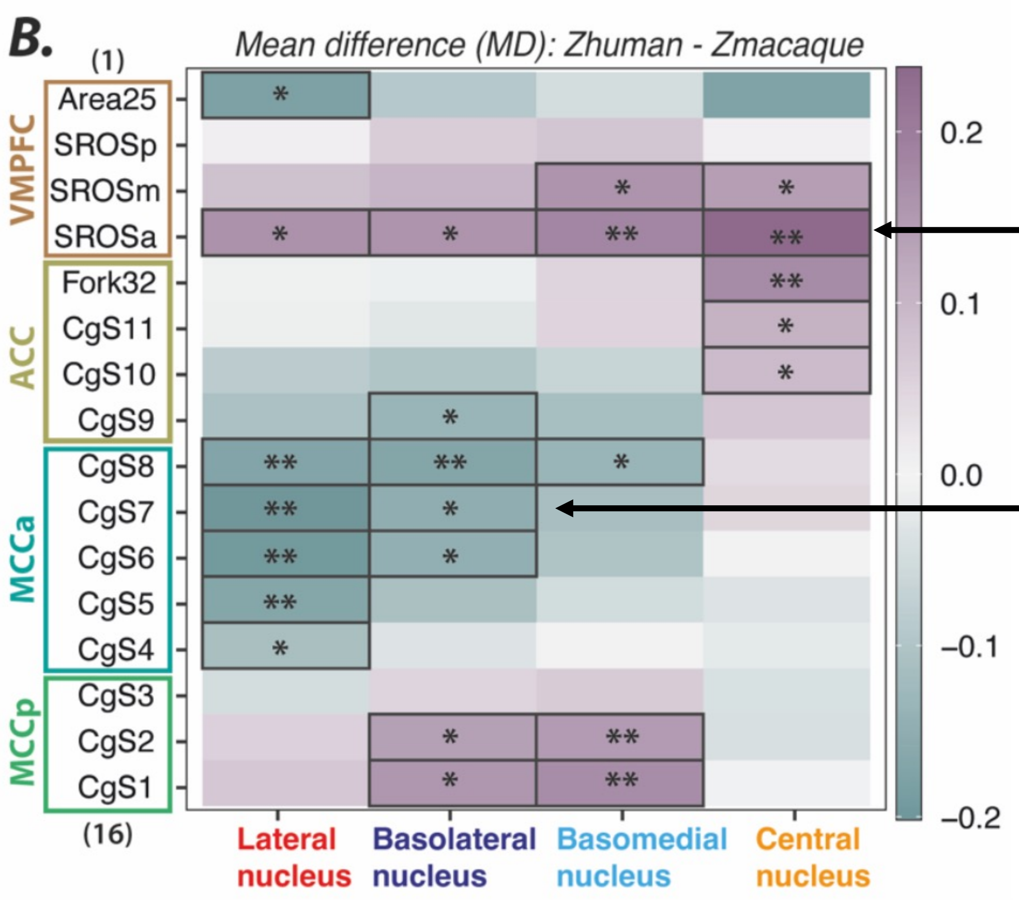
(Giacometti et al., 2024, ComBio)

AMG nuclei and mPFC functional dialogue in humans and macaques



(Giacometti et al., 2024, ComBio)

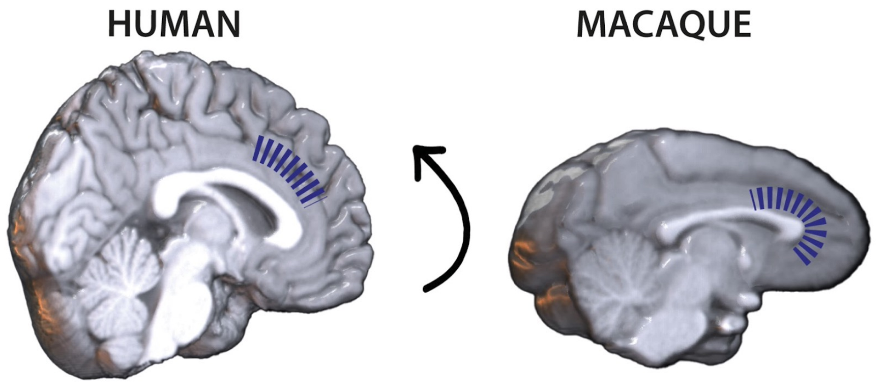
AMG nuclei and mPFC functional dialogue in humans and macaques



Negative correlation deep in macaque

Negative correlation deep in human

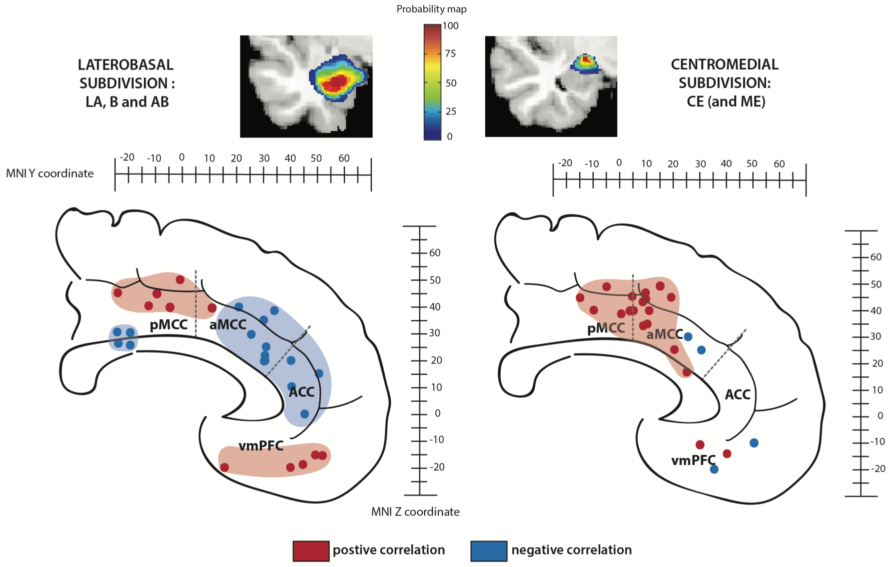
A shift in functional connectivity



(Giacometti et al., 2024, ComBio)

Take home message

- In humans, along the corpus callosum, we observed a u-shape pattern of FC between AMG nuclei, exception of CE, and mPFC charactherized by a negative correlations deep in the aMCC

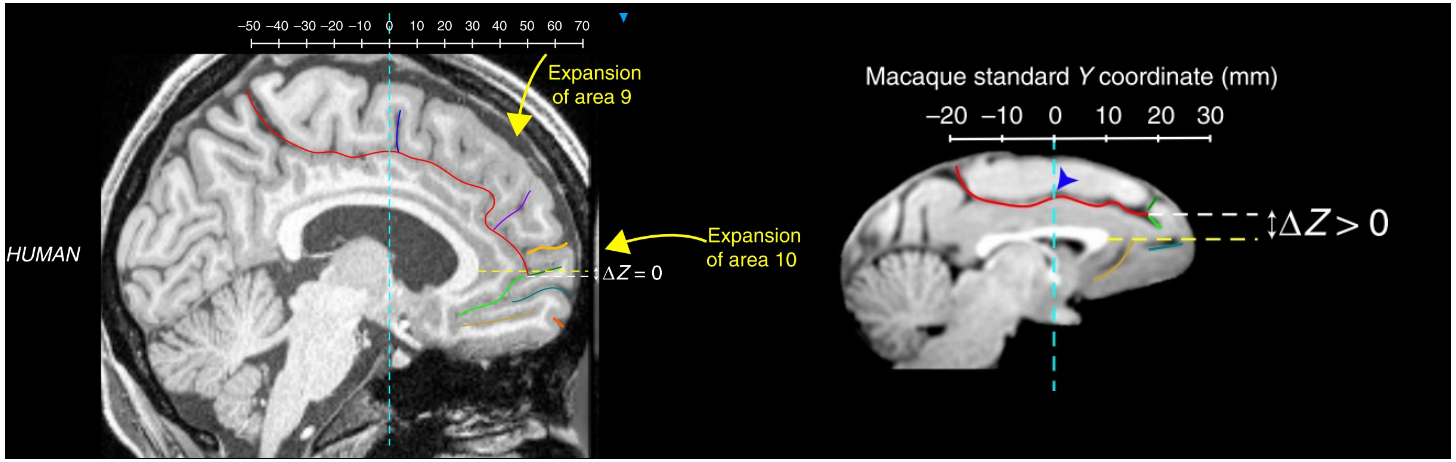


- In macaques, u-shape pattern concern all of the AMG nuclei with mPFC ROIs and is characterized by a negative deep at the limit between vmPFC/ACC

Take home message

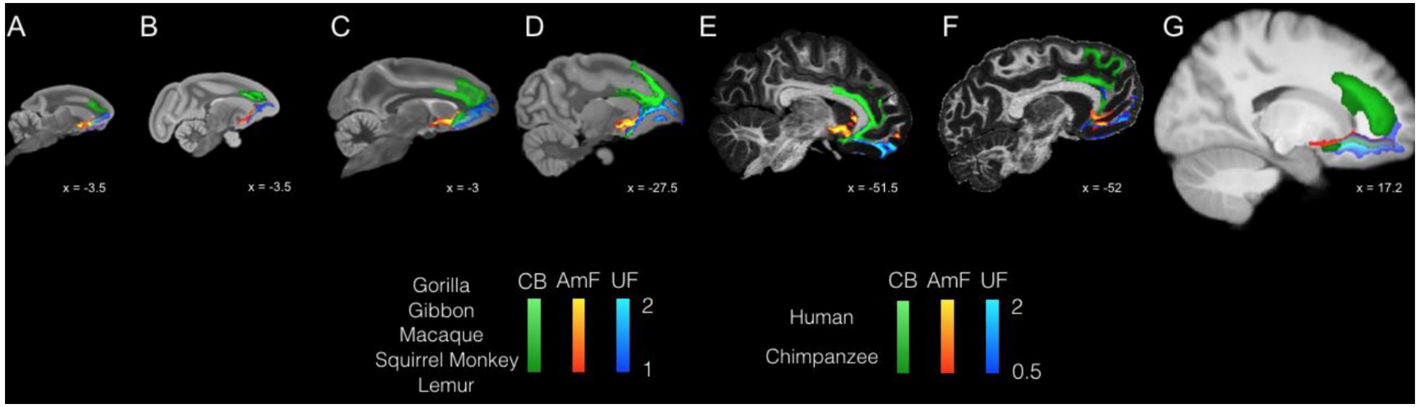
- A shift of the FC pattern between AMG and mPFC: ACC/vmPFC variability?

<u>Comparative study on medial PFC sulci organization:</u> Amiez et al., 2019



ACC/vmPFC and **sulci organization variability** between humans and macaques

<u>Comparartive study on cortico-limbic white matter bundle:</u> Folloni et al., 2024



Differences in the **innervation of subgenual cortex** across species

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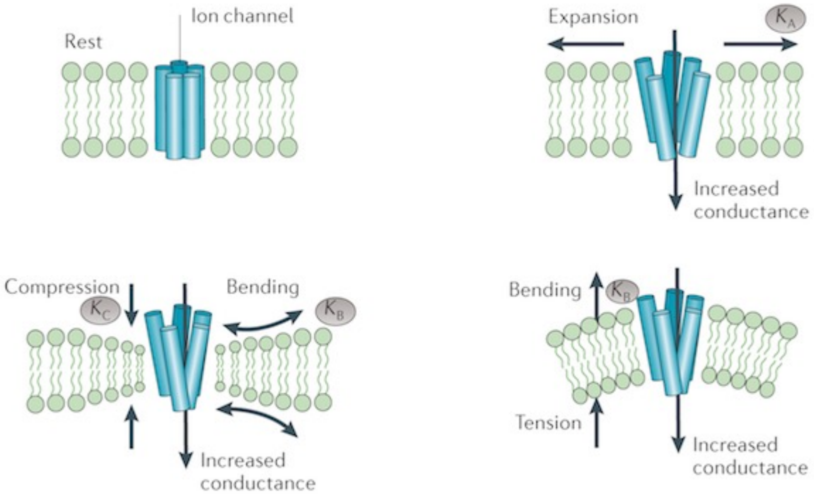
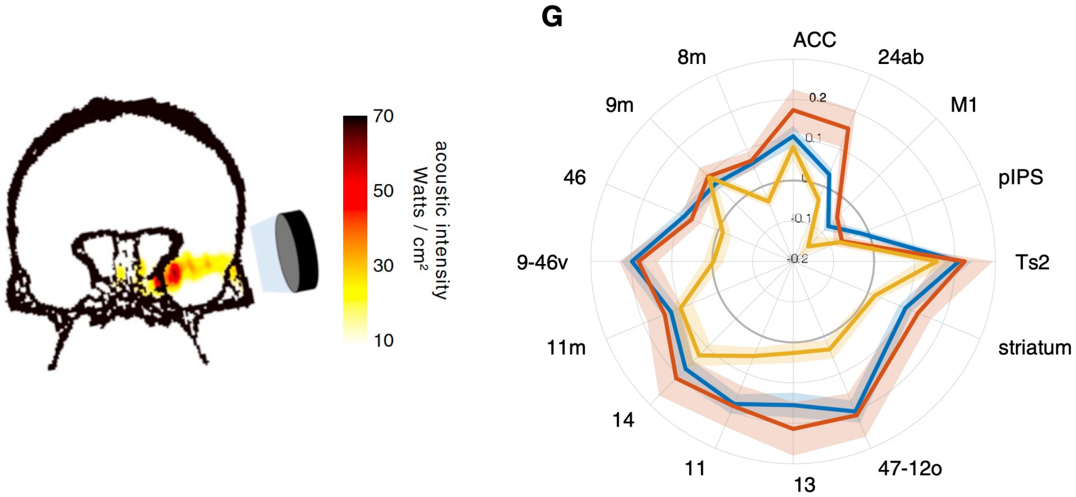
Transcranial ultrasound stimulation (TUS)

- **Non-invasive** and **reversible** perturbation technique
- Associated offline or online with an experimental protocol
- **Possible mecanism**: ultrasound waves induce a mechanic force that trigger mecanosensible channel within the cellular membrane



(Reviews see Kubanek 2018)

Previous work in anaesthetized monkeys (Folloni et al., 2019)

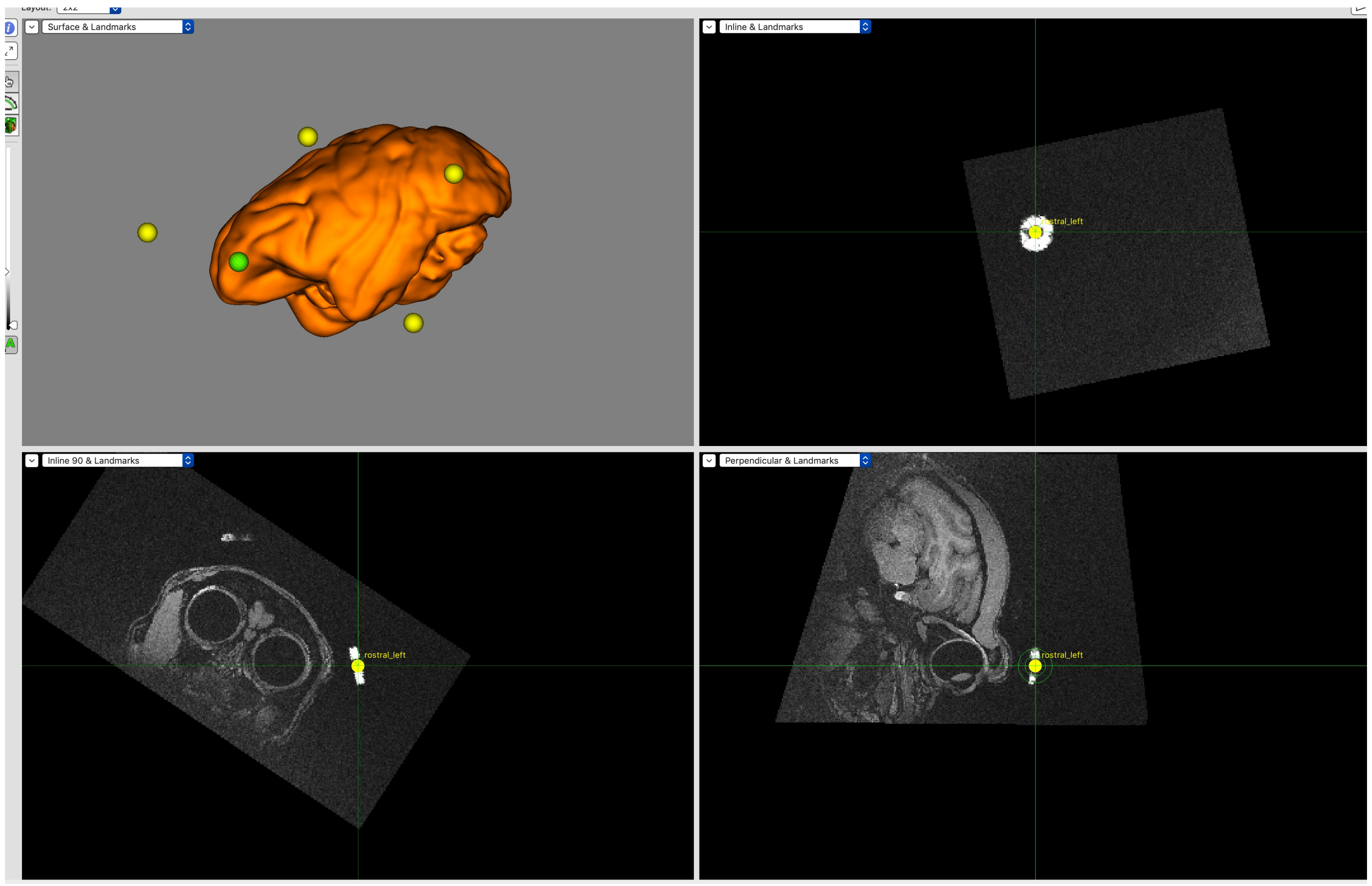


Globally **decreases the functional connectivity** of the target region: TUS AMG (yellow), sham (blue), ACC TUS (yellow)

AMG TUS effect in awake macaque monkeys?

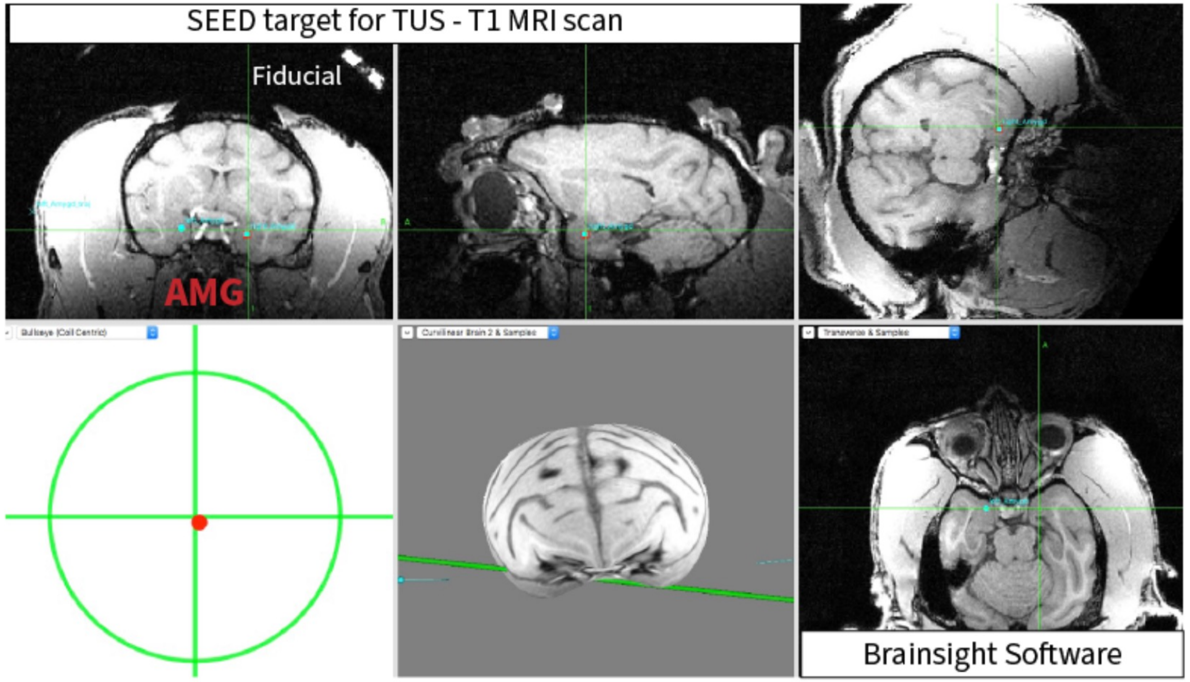
TUS on the AMG: effect on the AMG-mPFC network functional connectivity

How? Based on Folloni et al., 2019 protocol

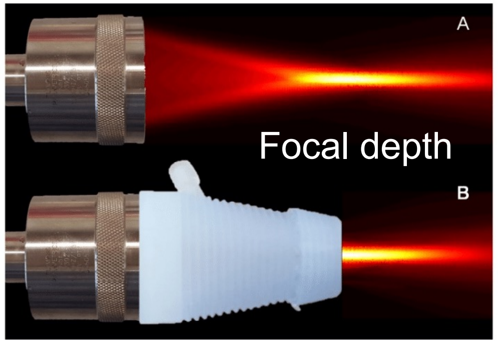


Session 1: T1 structural can
4-6 fiducial markers positionned around the monkey headpost.
It allows to delimitate and identify AMG localisation in space relative to each of the markers position.

TUS on the AMG: effect on the AMG-mPFC network functional connectivity



Transducer



Coupling Cone, filled in with degassed water

Stimulation:
Duration: 40s
Train of pulsed ultrasound (240kHz every 100ms) = 30ms ON, 70ms OFF

Session 2:
rs-fMRI + Offline bilateral stimulation of the AMG :

1) **Calibration:**
Localization in space of the monkey head (fiducial markers) and the stimulation material (transducer + region-specific coupling cone)

2) Target location and stimulation:
Guide by Brainsight software, the transducer is applied on the shaved temporal surface of the monkey head.
Once target location is secure the stimulation is applied on one side and 5/10min after on the other side.

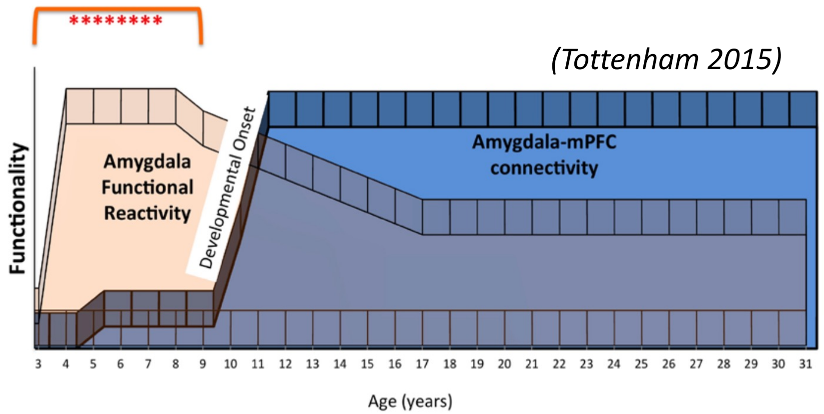
fMRI scanning session start 20-30min after stimulation

Macaque, n =2
10-8 runs of 400vol/subject
TR= 1.8s, voxel size= 1.8 mm3

Significance?

Behavioral significance of this functional connectivity pattern changes?

AMG-mPFC is an higly dynamic network charactherized by **a top-down/bottom-up balance** to react and adjust and/or regulate our behavior when facing a complex and uncertain environnement



This dynamic changes across developpement going from a "reactivity" state in childhood towards a more control state in teenagehood/aduldthood (Gee et al., 2022)

Hypothesis of a differential balance of top-down regulation and bottom-up reactivity within the AMG-mPFC network between both species ?

E.g. Adult macaques *rhesus* are characterized by behavioral traits such as aggressiveness and impulsivity that are reduced following AMG lesions (Thierry 2010; Elorette et al., 2020; Kalin et al. 2004)

> *higher AMG reactivity? Reduce top-down regulatory process?*

Aknowledgements

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Thank you for your attention !