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## **Transcranial ultrasound neuromodulation induces metabolic and resting-state changes in amygdala**

J Claron, C Giacometti, S Manickam, V Morel-Latour, C R E Wilson, F Lambertson, C Amiez, F Hadj-Bouziane, J Sallet

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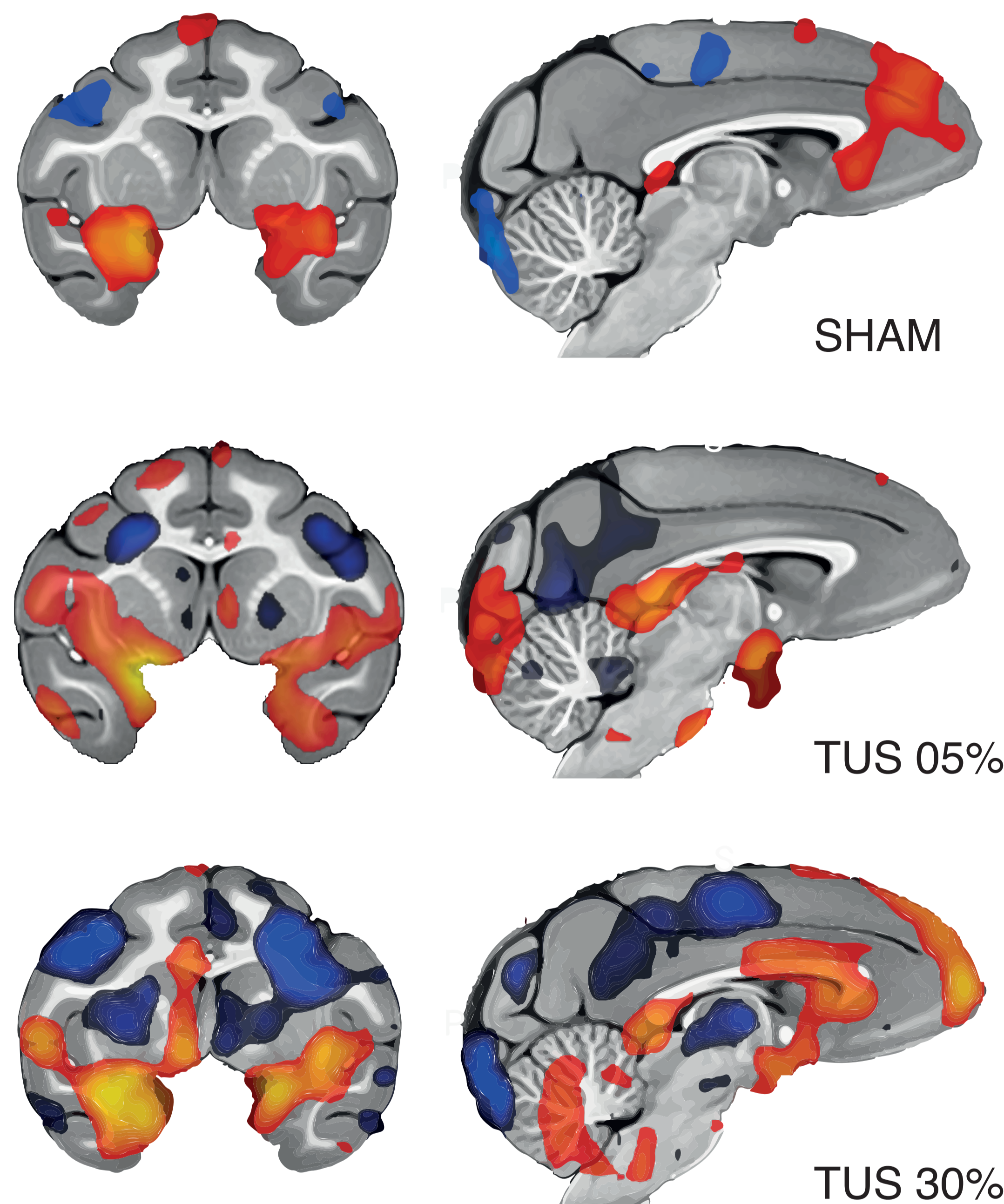


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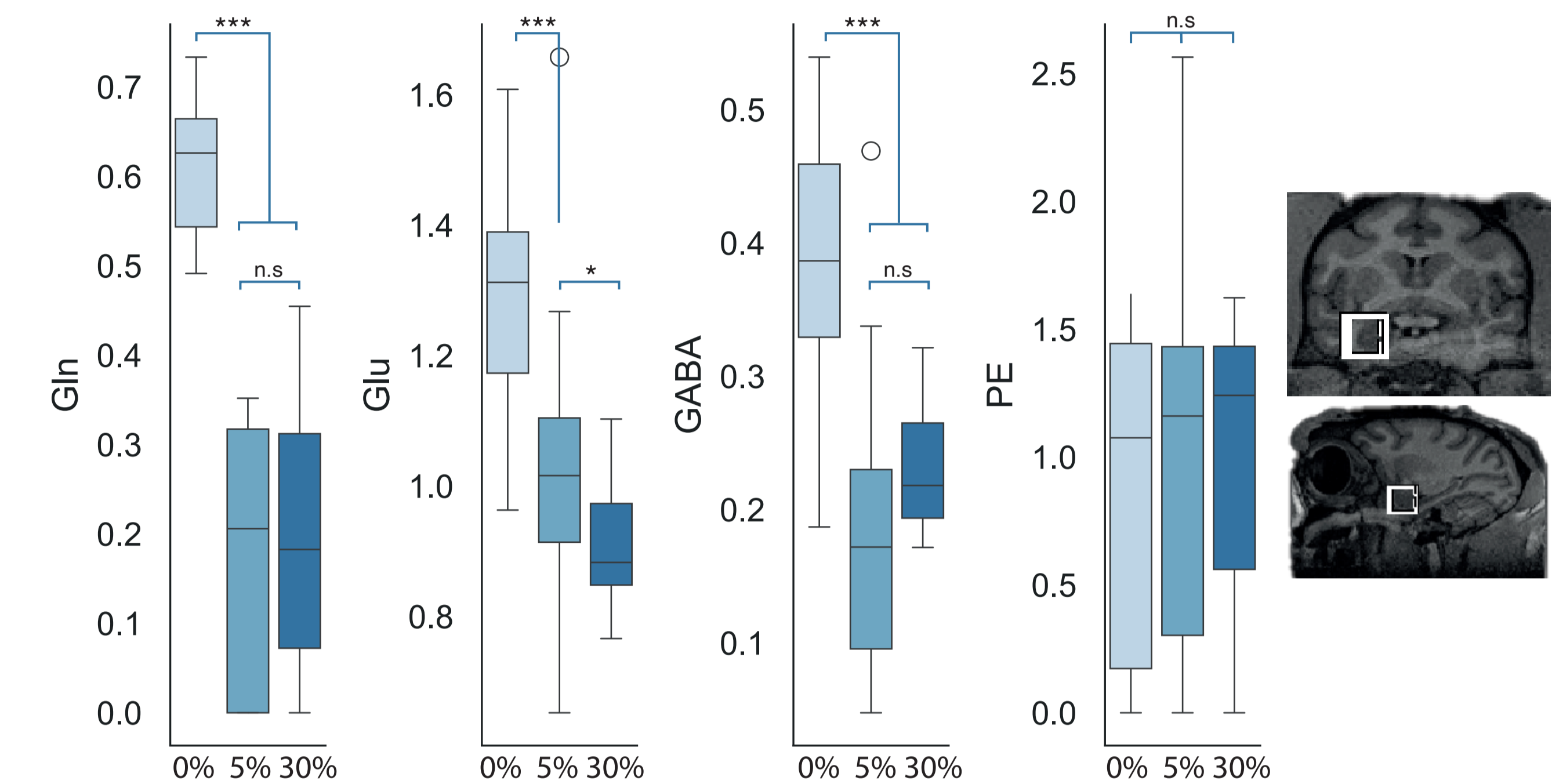
Introduction

Transcranial ultrasound neuromodulation (TUS) is a fast growing non-invasive brain stimulation method allowing reversible and local perturbation of the neuronal activity in superficial but also deep-brain structures. Although TUS efficiency at been shown at the circuit and behavioral levels [1] and can last several hours [2], its precise impact on the neuronal tissue remain a subject of ongoing investigation. Using resting-state fMRI (rs-fMRI) and MRI spectroscopy (MRS), we characterized both the functional and metabolic effects of TUS on a subcortical structure, the amygdala. In two anaesthetized non-human primates, we selectively stimulated bilaterally the amygdala nuclei using two stimulation protocols that differ on the amount of energy transmitted to the amygdala (250Khz transducer; stimulation duration : 40s; pulse duration : 100ms; Duty Cycle 5% and 30%). Our findings revealed a TUS-induced shrinkage of functional connectivity patterns of the amygdala with the rest of the brain. Additionally, we observed metabolic changes in key neurotransmitters (γ-aminobutyric acid (GABA), glutamate (Glu)) and in neurotransmitter metabolic pathways (glutamine (Gln)). We observed significant reductions of GABA, Glu and Gln with both protocols. However, our results also showed a difference between the two protocols for the Glu but not for the GABA. Altogether our findings could be explained by a greater sensitivity of inhibitory interneurons to TUS compared to excitatory pyramidal cells. These outcomes contribute to a nuanced understanding of neuromodulation and its underlying mechanisms.

resting-state f-MRI (n=1)



Magnetic resonance spectroscopy (SPECIAL) (n=2)  
 SPin-Echo full-intensity acquired localized spectroscopy



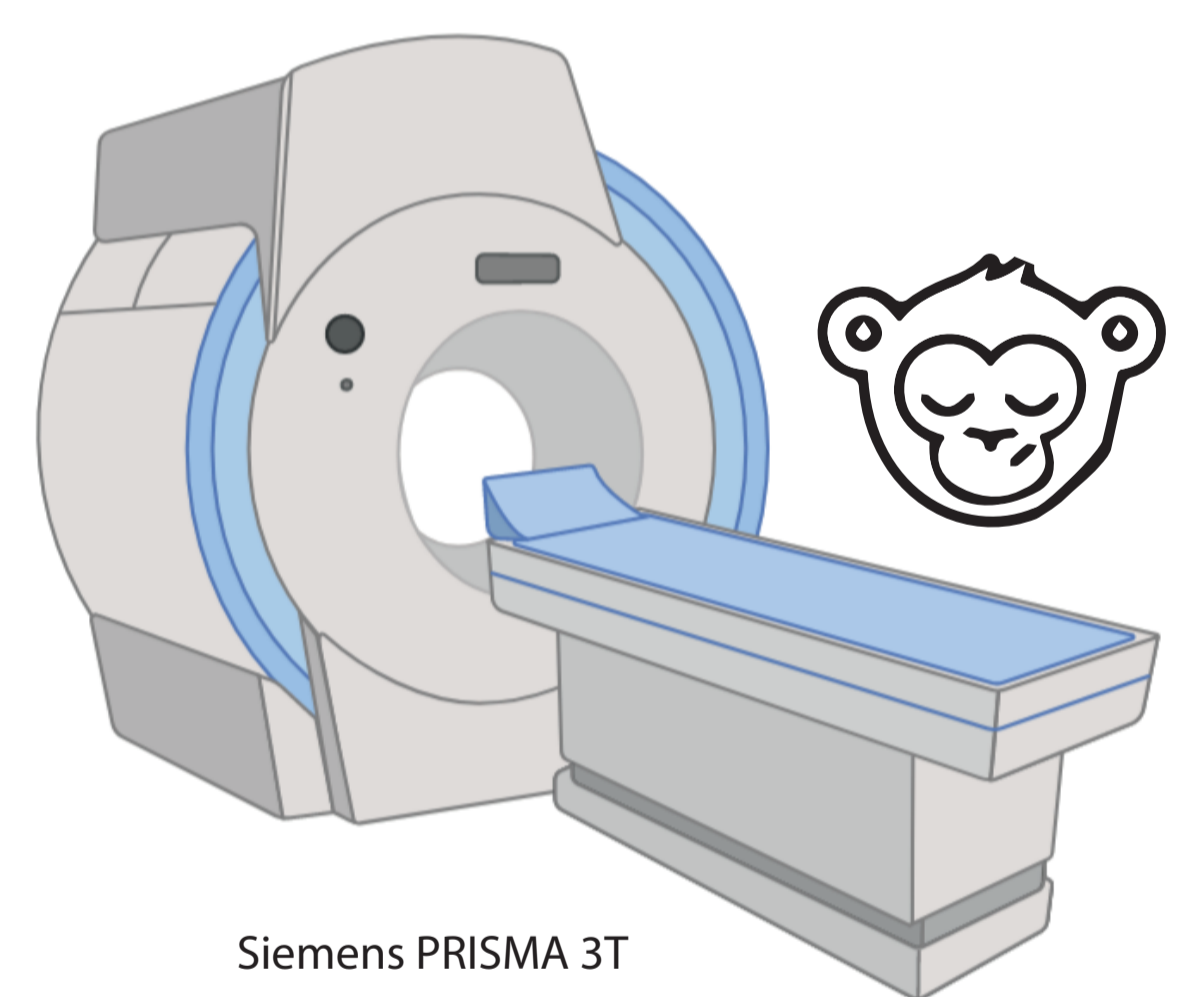
Gln : Glutamine ; Glu = Glutamate ; GABA = g-aminobutyric acid, PE = phosphatidylethanolamine  
 Scale is normalized by total creatine signal area. e.g. : [Gln]/[Cr]

Data were processed using OSPREY software on Matlab, using LCModel fitting algorithm and a 3T Siemens base for all the metabolites, goodness of fit is given though Cramér-Rao bounds

With a 1x1x1 mm<sup>3</sup> voxel on the amygdala and 8 runs of 256 averages, we observed a change in the concentration of GABA, Glutamine and Glutamate in the voxel of interest after TUS.

Whereas [Glu] seems to be dependant of TUS parameters (duty cycle : 0%, 5% or 30%) , [GABA] seems to be much more independant, indicating a possible sensitivity difference between excitatory pyramidal neurons and inhibitory interneurons.

Materials & Methods

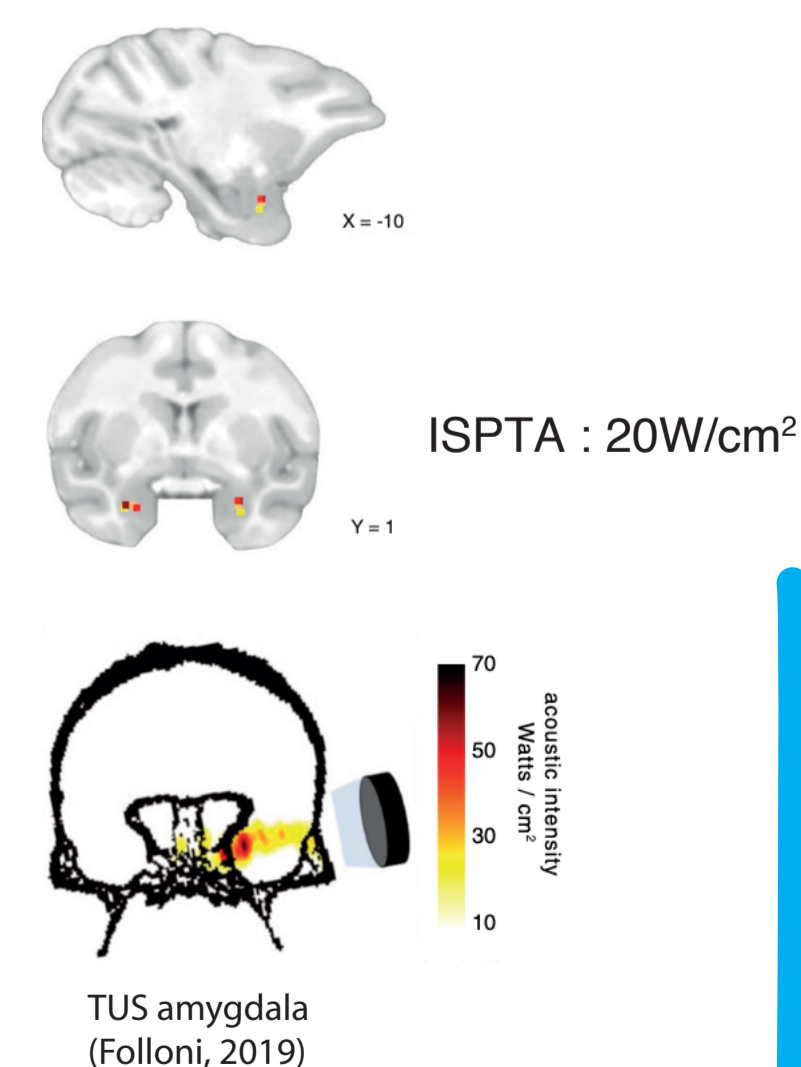
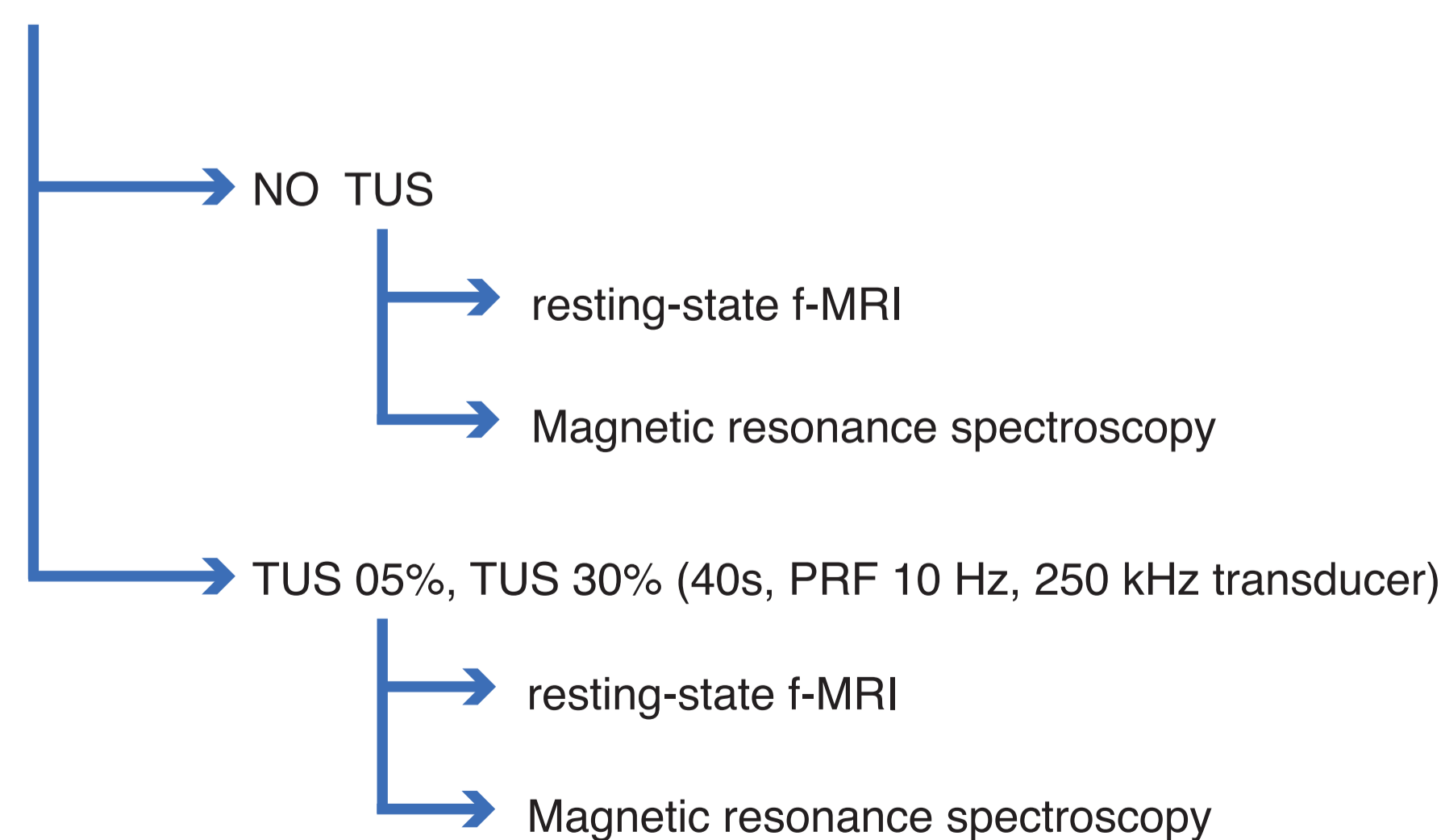


Anaesthetized monkey (isoflurane, 1% to 1.5%, for stable monitoring) N = 2

|                               | rs f-MRI | MRS   |
|-------------------------------|----------|-------|
| TR (s)                        | 1.7      | 4     |
| Voxel size (mm <sup>3</sup> ) | 1.7 iso  | 1 iso |
| Vol. per run                  | 2400     | 1024  |
| Runs                          | 2        | 2     |

- Time between TUS and MRI : ~ 30 min
- Time between L and R amygdala : ~ 5 min
- Time between induction and imaging : ~ 1h30

Siemens PRISMA 3T  
 Induction : Ketamine/Metomedidine or Zoletil



Each 2400 TRs run is subdivided into 6x400 TRs  
 Pearson's r correlation into Z-score  
 IIR filter, 0.01-0.1 Hz. Seed : bilateral amygdala

|           | SHAM | TUS 05 | TUS 30       |
|-----------|------|--------|--------------|
| mPFC      | ++   | ~      | ++           |
| preSMA    | ~    | ~      | --           |
| Insula    | ~    | ++     | ++           |
| Cingulate | ~    | ~      | -- (see [1]) |

Data were processed using a mix of AFNI, SPM, FSL and NiTime though NiType warping environment

Discussion

The offline mechanism by which TUS modulates brain activity over several hours appears to reflect an inhibitory effect on the stimulated brain area. By using both resting-state imaging and MRS, we were able to see both metabolic and vascular changes in brain patterns, indicating a correlation between ultrasound energy and sub-population of neurons. The differential impact of TUS stimulations on Glu and GABA suggests that different excitatory and inhibitory neurons might have different sensitivity to ultrasound mechanical stimulation. While those results might help to understand how TUS modulate brain activity, it's still indirect measures of brain activity, but also suggest the implication of glia into those changes, though the Gln/Glu-GABA cycle between neurons and astrocytes. From a pathology point of view, this cycle is perturbed in various diseases such as Alzheimer's, where we can imagine TUS as a way to mitigate perturbations with more perturbations.

[1] Folloni D., Manipulation of subcortical and deep cortical activity in the primate brain using transcranial focus ultrasound stimulation  
 [2] Clennel B., Transient ultrasound stimulation has lasting effect on neuronal excitability  
 [3] Mylnarik V., Localized short-echo-time proton MR spectroscopy with full signal-intensity acquisition  
 [4] Giacometti C., Differential functional organization of amygdala-medial prefrontal cortex networks in macaque and human