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## Respiratory modulation in the brain: deep in the cells

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► **To cite this version:**

Corine Amat, Maxime Juventin, Mickael Zbili, S. Garcia, Nathalie Buonviso, et al.. Respiratory modulation in the brain: deep in the cells. FENS 2022, 2022, Paris, France. hal-03758949

**HAL Id: hal-03758949**

**<https://hal.science/hal-03758949v1>**

Submitted on 30 Aug 2022

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# Respiratory modulation in the brain: deep in the cells

## Introduction

In recent years, several studies have shown the respiratory rhythm can drive the Local Field Potential (LFP) from numerous brain areas. Hence, beyond its primary vital function, the respiratory rhythm could be used by the brain as a master clock promoting communication between distant brain areas.

However, outside the olfactory system it is not known if respiration-related oscillation (RRo) could exist in the membrane potential (MP) of neurons, neither if it can structure spiking discharge.

To fill this gap, we co-recorded MP and LFP activities in different non-olfactory brain areas: median prefrontal cortex (mPFC), primary somatosensory cortex (S1), primary visual cortex (V1), and hippocampus (HPC), in urethane-anesthetized rats.

## Methods

Experiments were performed on freely breathing anesthetized rats.

Intracellular activity (or MP) was recorded with micropipettes filled with a solution of 2M potassium acetate (Resistance 45-120 Mohms).

All recordings were obtained in spontaneous conditions, without any kind of stimulation.

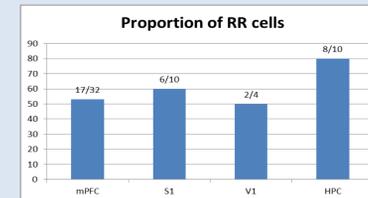
Respiration was monitored using a pressure sensor placed at the entrance of the right nostril.

To precisely quantify Respiration Related Oscillation (RRo) of MP, we developed a cycle-by-cycle method for detecting the respiratory cycles at which MP oscillated at the respiratory rhythm. This algorithm finally led to a RR encoding of MP for each respiratory cycles (RR cycle, No RR cycle). The same method was used to encode LFP.

## Results 2

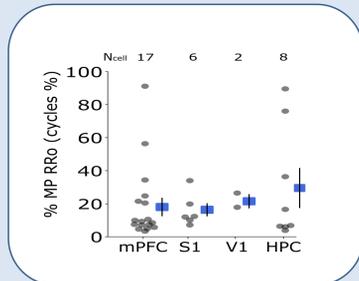
### Brain-wide quantification of Membrane Potential Respiratory-Related oscillations (MP RRo)

#### Proportion of Respiratory-Related (RR) cells across structures



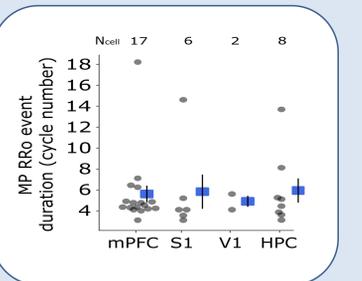
Most of recorded cells exhibit a Respiratory Related (RR) MP.

#### MP RRo cycle probabilities across structures



The percentage of MP RRo cycle varied greatly:  
- from cell to cell in a same structure  
- and between structures.

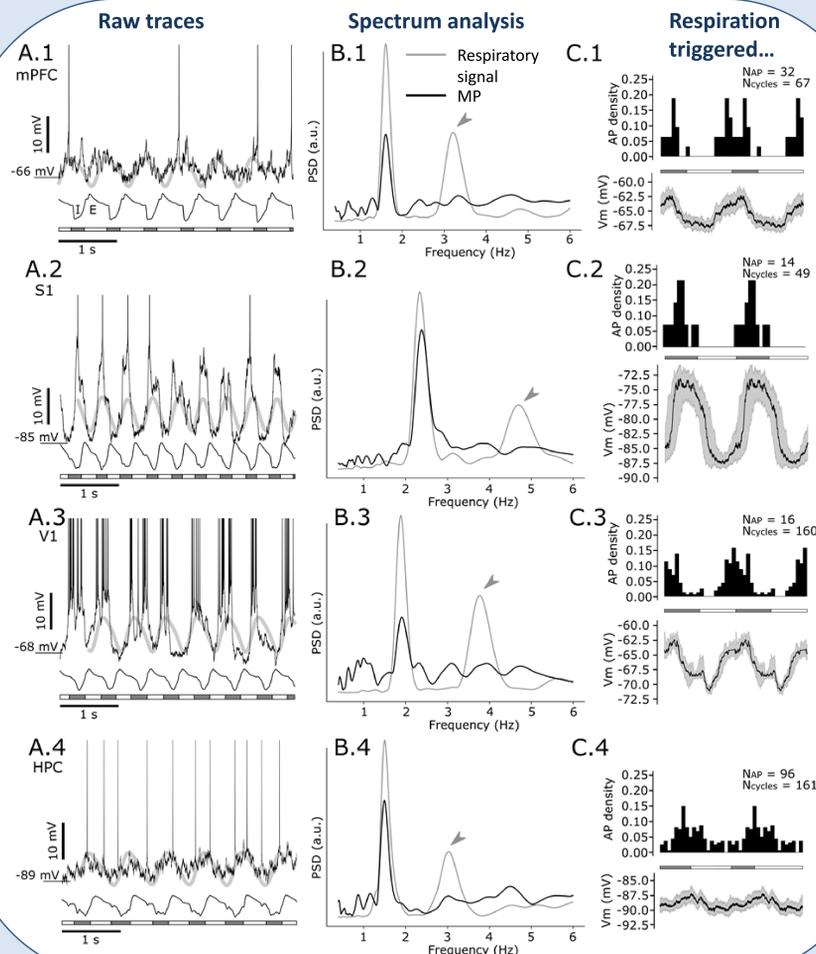
#### MP RRo episode duration across structures



The average number of consecutive MP RRo cycles was around 5, regardless of the structure.

## Results 1

### Respiratory rhythm can entrain neuron activity in widespread brain areas



... discharge histogram

... MP waveform

**A** : In the 4 areas, we found cells with a respiration-related oscillation (RRo) in their MP and a RR spiking discharge. The filtered respiratory signal (light grey) fits the raw traces of MO oscillations.

**B** : The power spectral density analysis of the MP signal (Black) exhibits a clear power peak at the respiratory frequency (grey). This confirms that MP correlates with respiratory rhythm.

**C** : AP occurrences are clearly related to respiratory cycle. **MP RRo and firing pattern are similarly phase-locked to respiration**, suggesting a strong correlation between MP RRo and the associated firing. To visually reinforce oscillatory behavior, plots have been duplicated.

#### Relationship between MP RRo and spiking discharge:

For cells exhibiting MP RRo and enough spike activity, we determined if the spikes occurring during MP RRo cycles were also synchronized to the respiratory rhythm (RR discharge pattern).

| % cell : MP RRo/Discharge RR |             |
|------------------------------|-------------|
| mPFC                         | 80% (n=4/5) |
| S1                           | 80% (n=4/5) |
| V1                           | 50% (n=1/2) |
| HPC                          | 25% (1/4)   |

Neocortical areas show stronger respiratory coupling between MP and spiking activity than hippocampus.

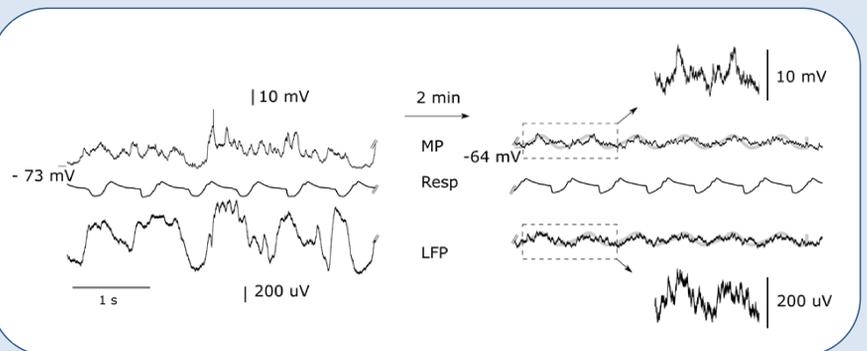
For all structures, the No RRo MP was mostly associated with the No RR discharge pattern (not shown)

We observed that both MP and spiking discharge could be RR-entrained in all recorded areas.

## Results 3

### Membrane Potential (MP) and LFP respiratory-related modulations are partly coordinated

#### Raw traces of a same cell

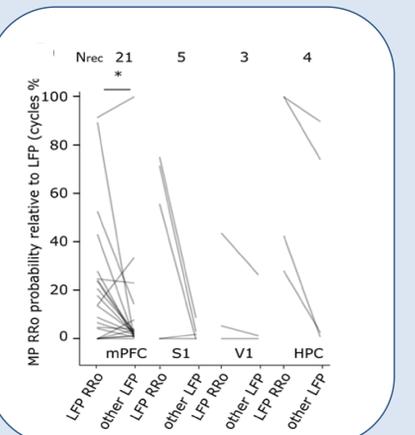


LFP and MP do not display RRo → 2 min later → LFP and MP display RRo

We encoded with the same detection method both MP and LFP. Then we computed the probability for MP to be RR-correlated as a function of LFP dynamics.

Probability for MP to be Respiratory-Related (RR) is higher when the LFP is also RR

#### MP RRo conditional probability given LFP dynamics



Columns "LFP RRo" represent the probability to observe MP RRo when LFP is also RRo. Columns "other LFP" represent MP RRo probability when LFP is no RRo.

## Conclusions

Using respiratory cycle by respiratory cycle analysis, we observed that respiration could modulate both MP oscillations and spiking discharges in all recorded areas.

A strong coupling exists between MP and spike discharge in PFC, S1 and V1.

Further quantifications revealed RRo episodes were transient in most neurons (5 consecutive cycles in average).

RRo development in MP was largely influenced by the presence of respiratory modulation in the LFP.

By showing the respiratory rhythm influenced brain activity deep to the MP of non-olfactory neurons, our data support the idea that respiratory rhythm could mediate long-range communication to set the dynamics of large-scale networks on a same slow rhythm.

As a conclusion, these findings reinforce the idea that the respiratory rhythm is a fundamental component of the neuronal network dynamics, and should not be overlooked.