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Journal Club

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Systems/Circuits

Nasal Respiration Entrains Human Limbic Oscillations and Modulates Cognitive Function

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Background & Motivation

- Animal studies – Breathing rhythms drive oscillatory activity in the olfactory systems of rodents and other small animals.
- Regulate cortical excitability, olfactory coding, memory, and behaviour.
- Direct evidence for respiratory-linked oscillations in humans is lacking.

Research Question: Does natural breathing synchronize electrical activity in human olfactory and limbic brain areas?

Methods

Participants:
- 7 patients with temporal lobe epilepsy (3 women) and 1 additional patient for the emotion judgment task.
- 107 healthy subjects (aged 18–30) for behavioral experiments.

iEEG Data Collection:
- Electrodes targeted piriform cortex (PC), amygdala, and hippocampus.
- Electrodes – localized via pre-/post-operative MRI & CT scans.
- CAR for consistency.

Respiratory Measurements:
- Respiration measured via nasal pressure sensors and abdominal breathing belts.
- Behavioral tasks in healthy subjects: Pneumotachometer for airflow rate measurement & abdominal breathing belts.

Experimental Protocol:
- Patients sat quietly with eyes open, breathing naturally for 15-minute blocks.
- Tasks paused if patients fatigued or interrupted.

Methods

Behavioural Tasks

- **Emotion Recognition Task**
  - Subjects categorized fearful vs. surprised faces during different breathing conditions (nasal (24), oral (18), control (28; Nasal with mouth held open)).
  - Fearful or Surprised faces and happy vs neutral (gender discrimination task)
  - Button press Reaction Times vs **respiratory phase***.

- **Visual Object Memory Task**
  - Participants encoded & retrieved images while respiratory phase was tracked.
  - Memory accuracy and reaction times were compared across **inspiration vs. expiration**.

*respiratory phase, determined by estimating the angle of the Hilbert transform of the respiratory signal.

Devices Used

1. **Pressure Sensor (Piezo, Nasal Cannula)**
    - Used in iEEG experiments for airflow pressure measurement.
    - Acts as an **open system**, highly sensitive to airflow changes.
    - Detects **peak inspiratory flow** for synchronization with neural data.

2. **Abdominal Breathing Belts (Siemens, Biopac RX-TSD221-MRI)**
    - Used for both nasal and oral breathing experiments.
    - Measures **chest/abdomen expansion** rather than airflow.

3. **Pneumotachometer (4719 Series, Hans Rudolph)**
    - Used for nasal breathing control condition.
    - Measures **airflow rate** directly, providing precise respiratory phase tracking.

Data Processing

1. **Respiratory Peak Detection**

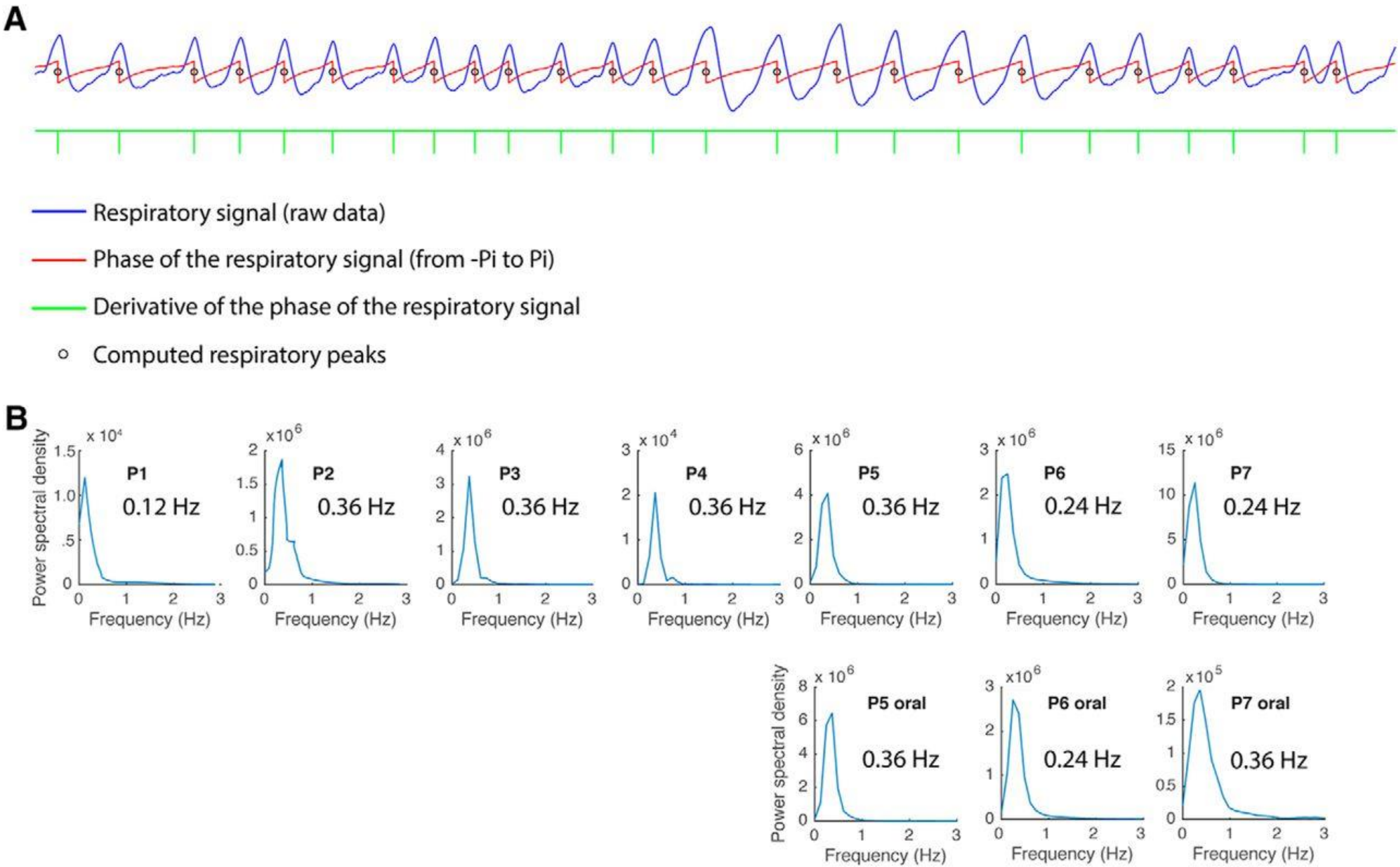
- Hilbert Transform applied to detect **inspiratory peak flow**.
- Phase discontinuities used for precise timing.

2. **Breathing Rate Analysis**

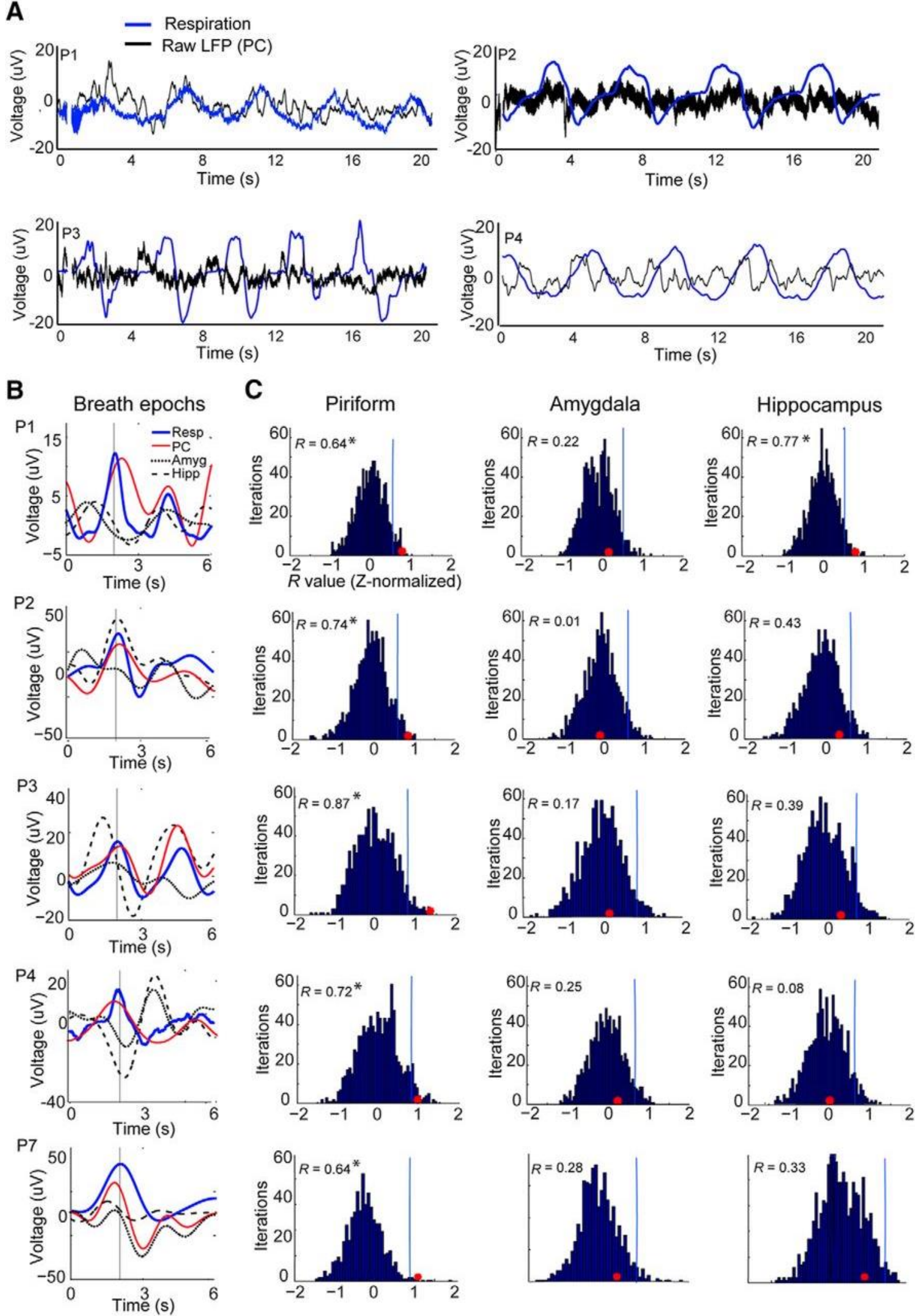
- **Fast Fourier Transform (pwelch function)** used to confirm dominant breathing rate (0.24–0.36 Hz or 14.4–21.6 breaths/min).

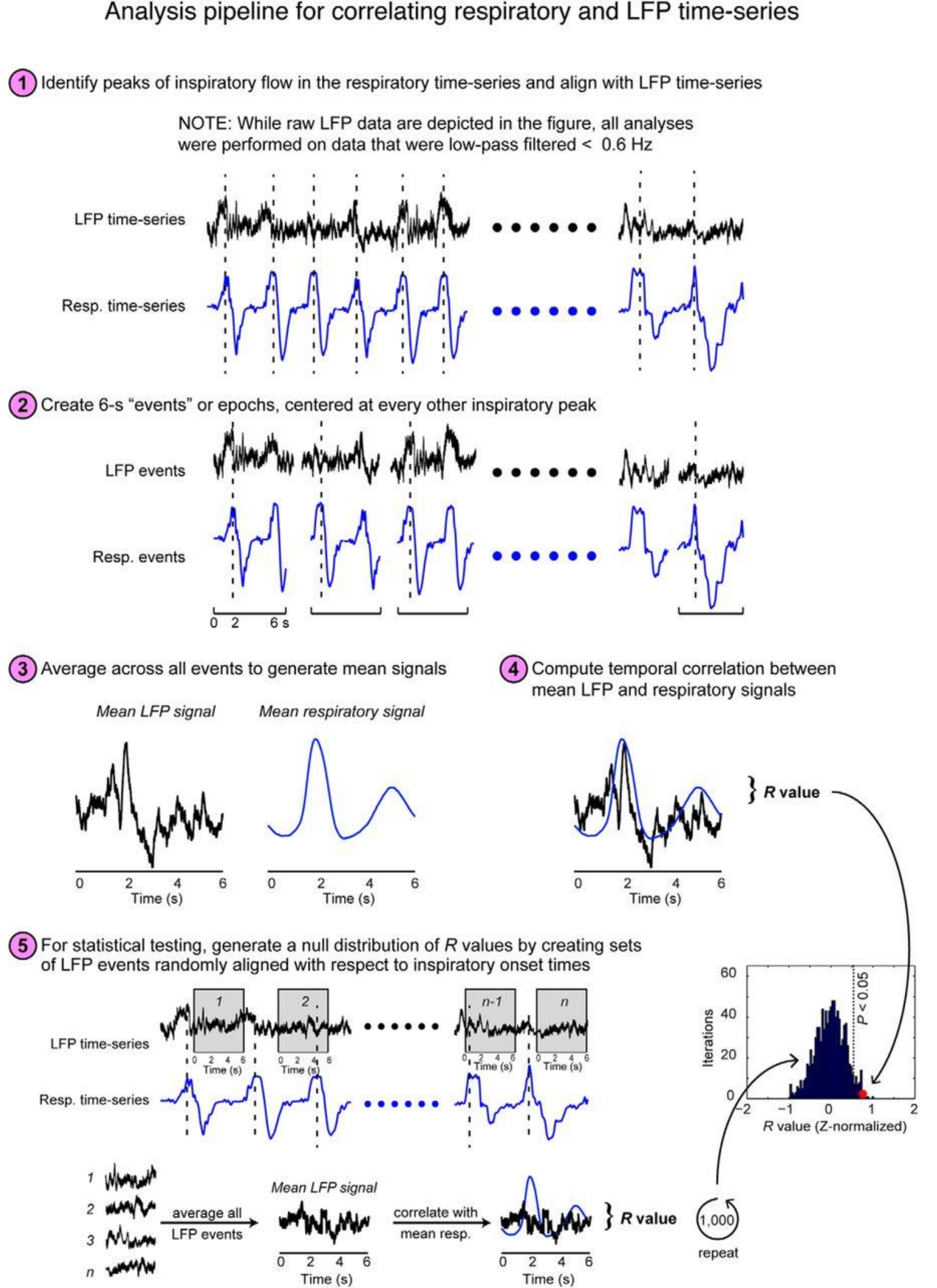
3. **Neural Signal Processing (LFP Data)**

- Band-pass filtering (0.08–0.6 Hz) to extract **slow respiratory oscillations**.
- Spectrogram analysis (1–200 Hz) for **higher-frequency oscillations**.
- **Phase-Amplitude Coupling (PAC)** assessed using Modulation Index (MI).



A
Respiratory signal (raw data)
Phase of the respiratory signal (from -Pi to Pi)
Derivative of the phase of the respiratory signal
Computed respiratory peaks
B
P1
0.12 Hz
P2
0.36 Hz
P3
0.36 Hz
P4
0.36 Hz
P5
0.36 Hz
P6
0.24 Hz
P7
0.24 Hz
P5 oral
0.36 Hz
P6 oral
0.24 Hz
P7 oral
0.36 Hz
Power spectral density
Frequency (Hz)

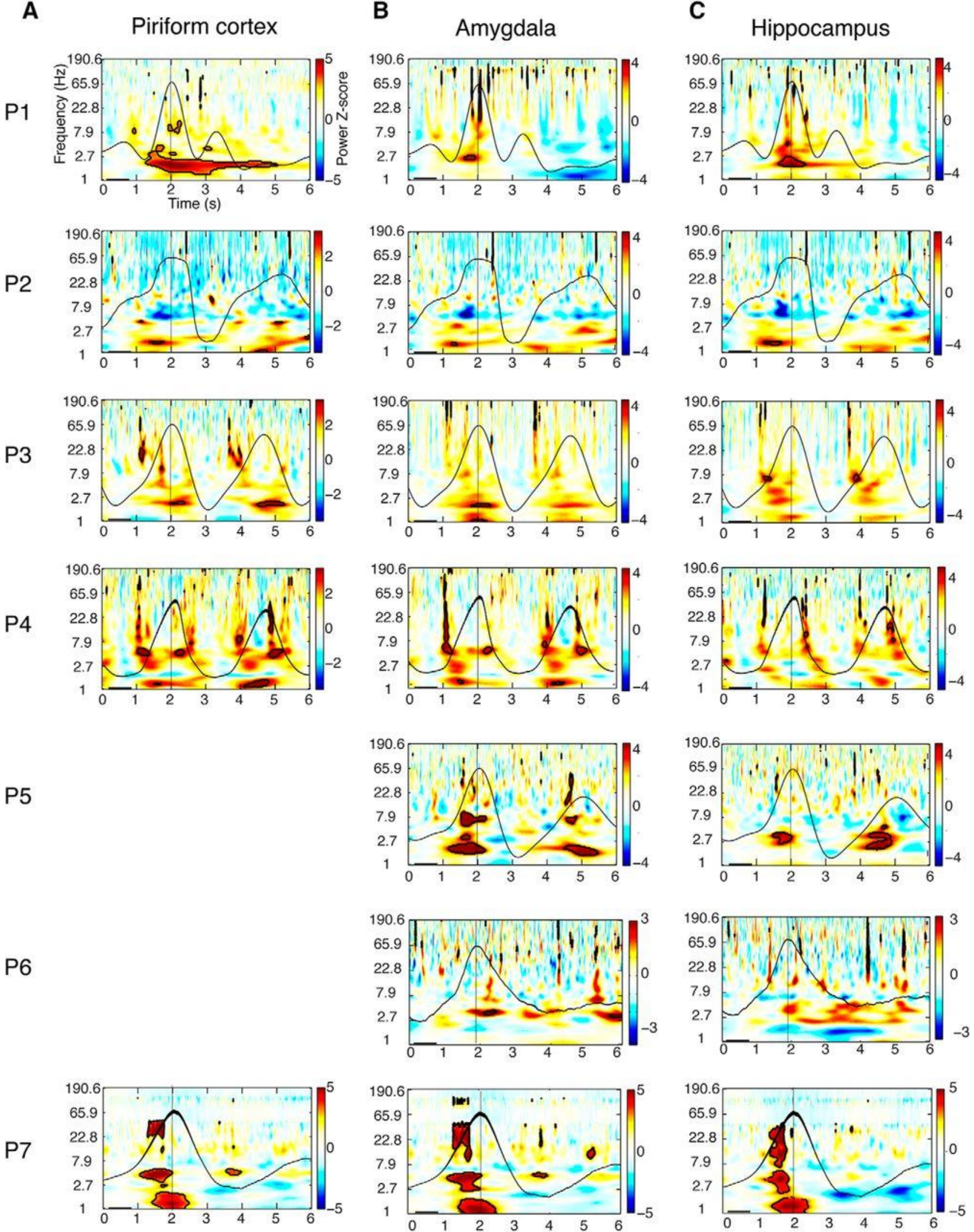

A
Respiration
Raw LFP (PC)
P1
P2
P3
P4
Voltage (uV)
Time (s)
B
Breath epochs
Resp
PC
Amyg
Hipp
P7
C
Piriform
Amygdala
Hippocampus
Iterations
R value (Z-normalized)
R = 0.64*
R = 0.22
R = 0.77*
R = 0.74*
R = 0.01
R = 0.43
R = 0.87*
R = 0.17
R = 0.39
R = 0.72*
R = 0.25
R = 0.08
R = 0.64*
R = 0.28
R = 0.33


Analysis pipeline for correlating respiratory and LFP time-series
1 Identify peaks of inspiratory flow in the respiratory time-series and align with LFP time-series
NOTE: While raw LFP data are depicted in the figure, all analyses
were performed on data that were low-pass filtered < 0.6 Hz
LFP time-series
Resp. time-series
2 Create 6-s "events" or epochs, centered at every other inspiratory peak
LFP events
Resp. events
3 Average across all events to generate mean signals
Mean LFP signal
Mean respiratory signal
Time (s)
4 Compute temporal correlation between
mean LFP and respiratory signals
R value
5 For statistical testing, generate a null distribution of R values by creating sets
of LFP events randomly aligned with respect to inspiratory onset times
LFP time-series
Resp. time-series
average all
LFP events
Mean LFP signal
correlate with
mean resp.
R value
1,000
repeat
Iterations
P < 0.05
R value (Z-normalized)

Results – Phase-locked oscillations

- **Piriform Cortex (PC):** Slow oscillations were **synchronized with natural breathing** across all patients.

- **Amygdala**: Low correlation between neural and respiratory signals (R = 0.01–0.25). No significant respiratory entrainment in most patients.
- **Hippocampus**: Low correlation (R = 0.08–0.43) in four patients, with only one showing significant respiratory entrainment (R = 0.77).

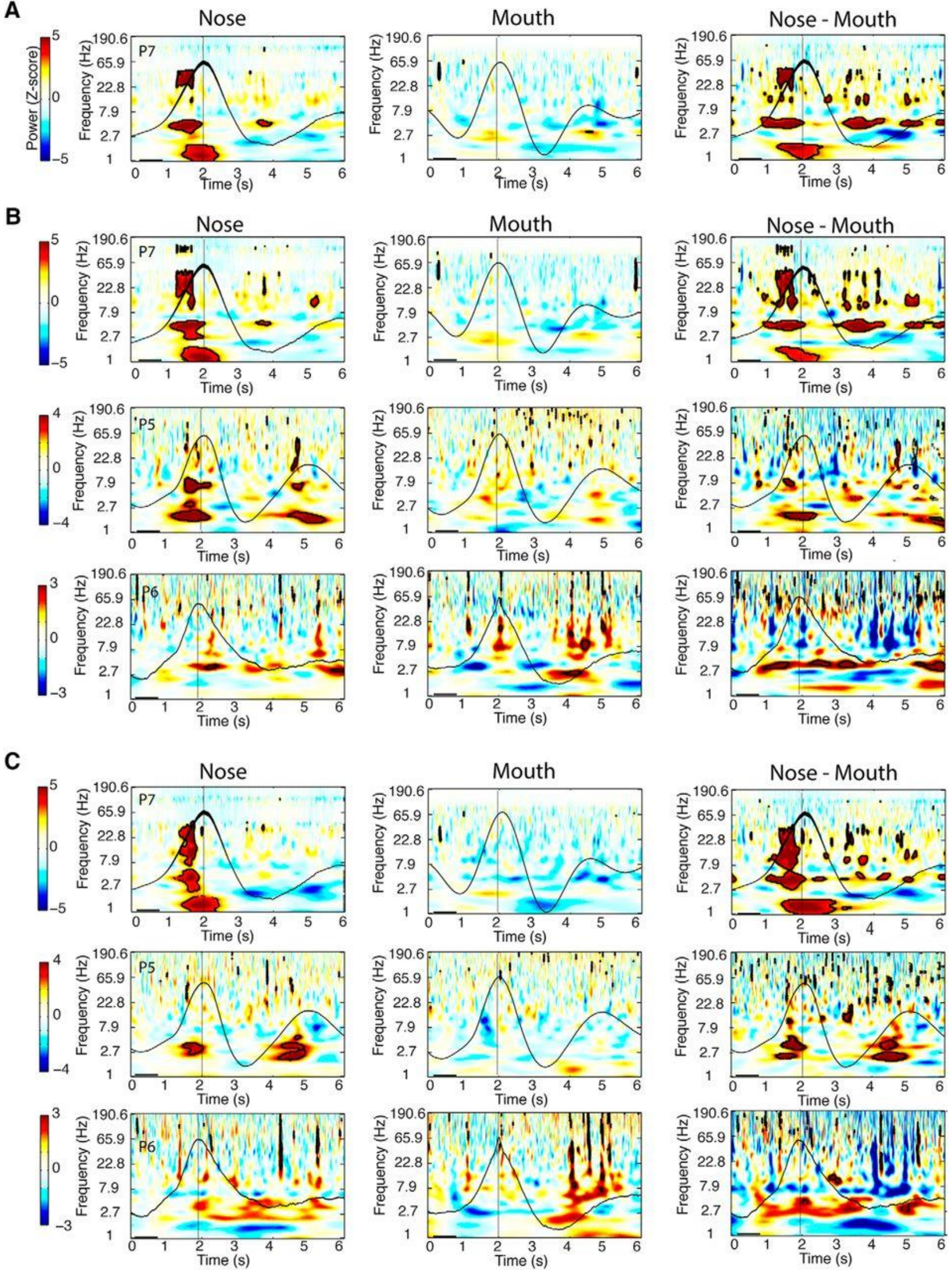

A
Piriform cortex
B
Amygdala
C
Hippocampus
P1
P2
P3
P4
P5
P6
P7
Frequency (Hz)
Time (s)
Power Z-score

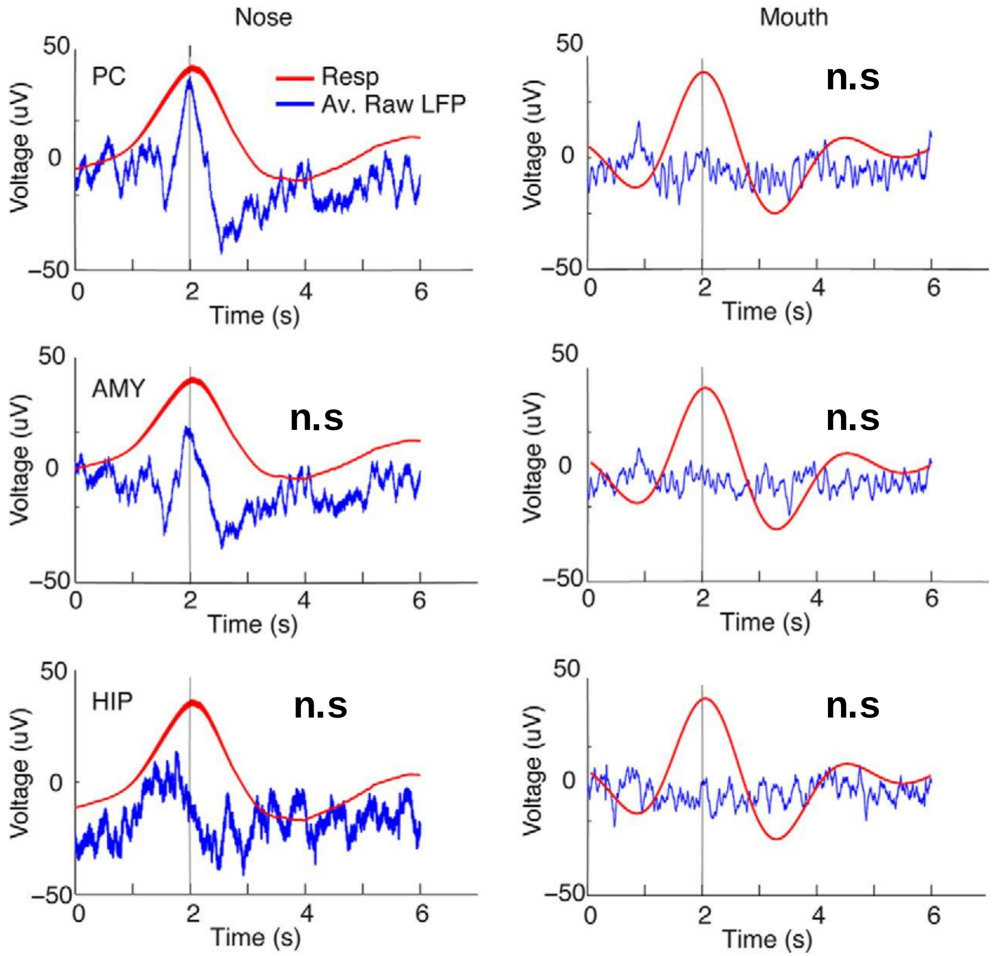
Results – Respiratory Phase-Modulated Oscillatory Power

- **PC**: **Delta (0.5-4 Hz)**, **Theta (4-8 Hz)**, and **Beta (13-30 Hz)** power consistently increased during inspiration.

- **Amygdala & Hippocampus**: Similar increases in **delta range** power in all patients. Inconsistent changes in **theta** and **beta** oscillations across patients.

- Respiratory phase-modulated oscillations in the **medial temporal lobe** extend beyond olfactory regions to limbic areas, especially at low frequencies.


A
Nose
Mouth
Nose - Mouth
P7
Power (Z-score)
Frequency (Hz)
Time (s)
B
P5
P6
C


Nose
Mouth
PC
Resp
Av. Raw LFP
n.s
AMY
HIP
Voltage (uV)
Time (s)

Patient 7

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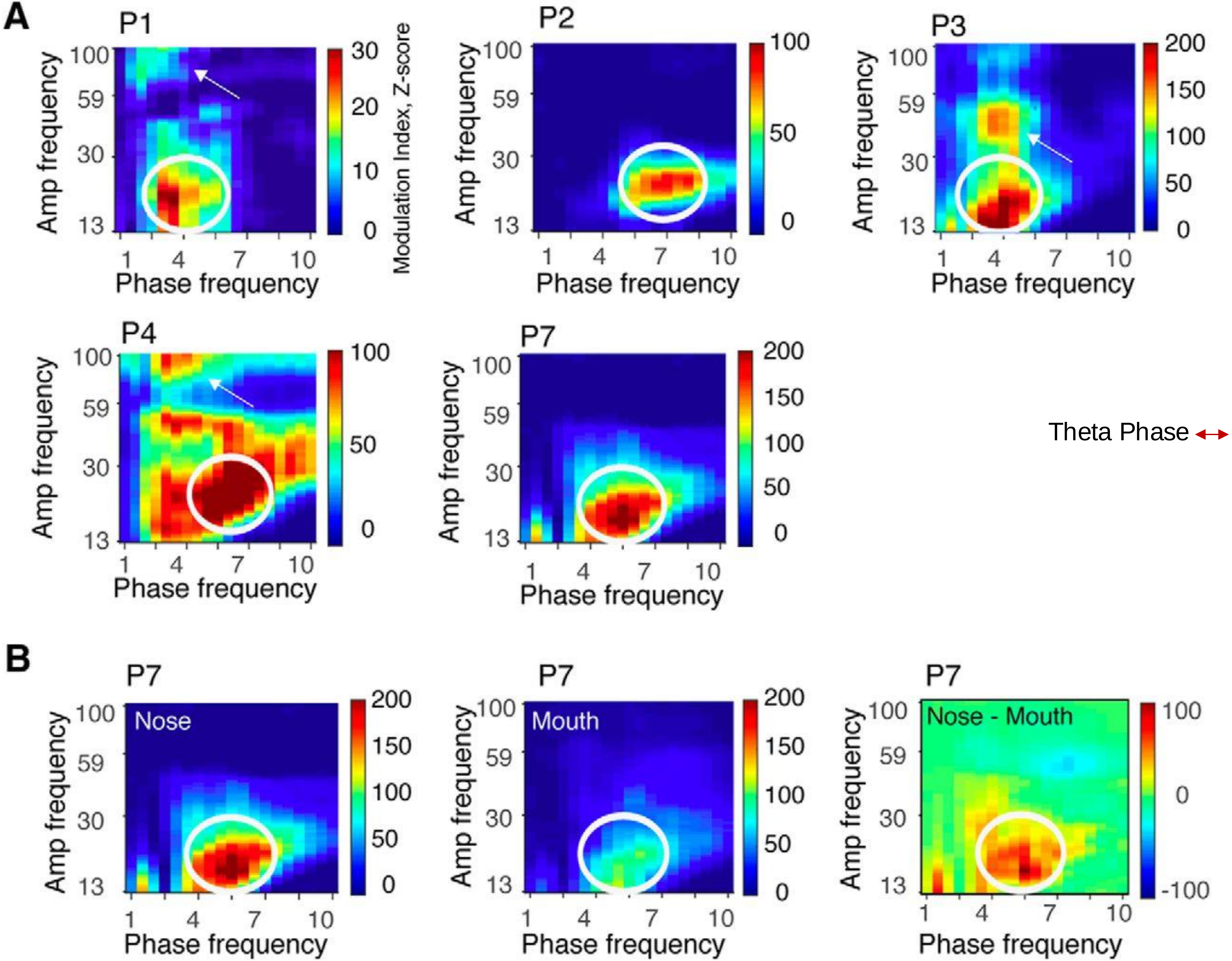


Theta Phase ↔ Beta Power

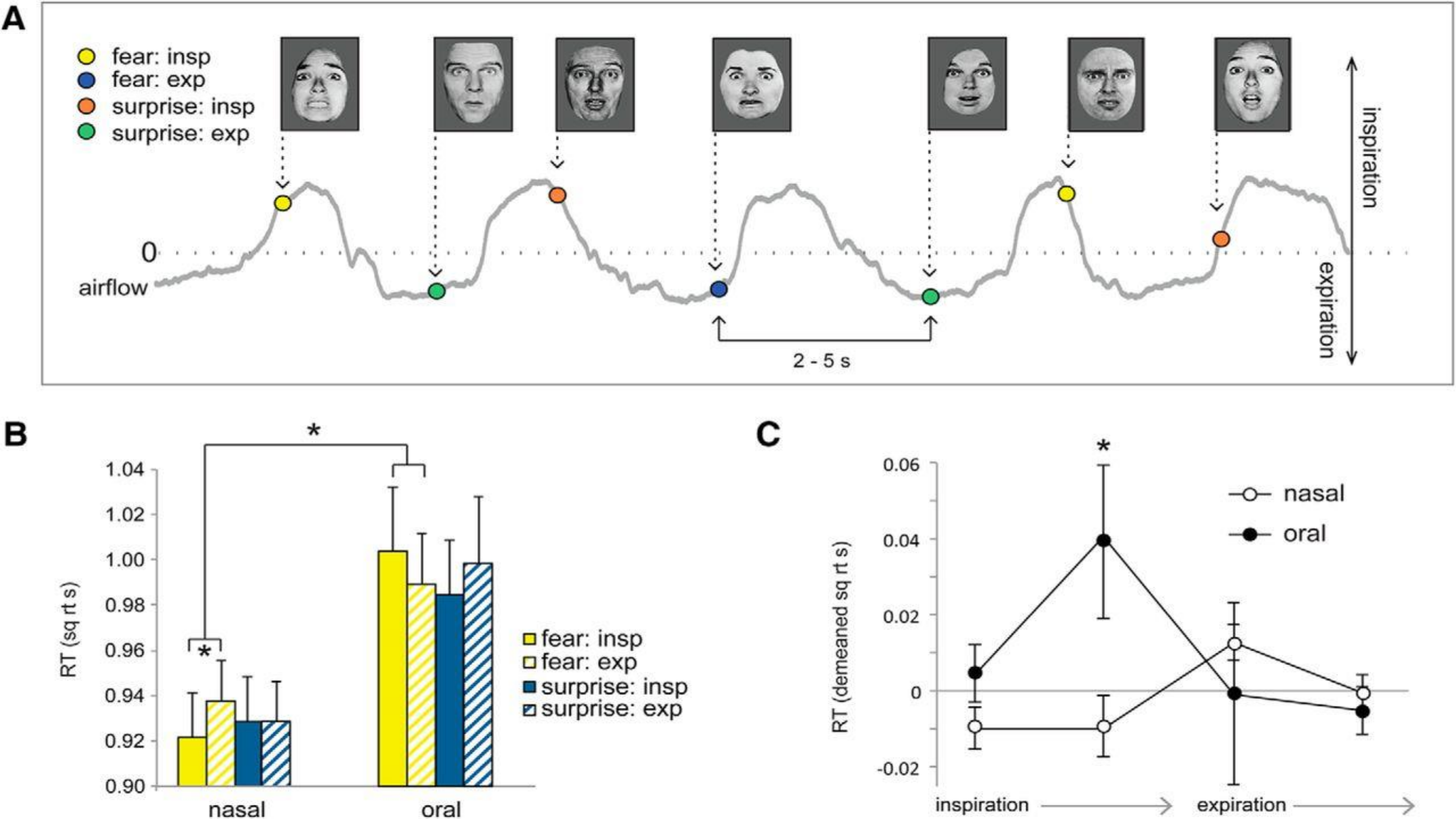
Results – Nasal vs Oral Breathing

- **Nasal breathing**: Strong respiratory entrainment of delta, theta, and beta oscillations in PC, amygdala, and hippocampus.

- **Oral breathing**: Significantly reduced respiratory entrainment in these regions.

- **PC**: Significant **theta-beta** (5/5) and **theta-gamma** (3/5) coupling observed during nasal breathing.
- **Oral breathing** reduced phase-amplitude coupling, reflecting the decrease in respiratory entrainment.

- **Nasal airflow** likely drives respiratory entrainment, with **PC** being the key brain region where oscillations are induced, propagating to downstream limbic structures.


A
fear: insp
fear: exp
surprise: insp
surprise: exp
inspiration
expiration
0
airflow
2 - 5 s
B
RT (sq rt s)
1.04
1.02
1.00
0.98
0.96
0.94
0.92
0.90
*
*
nasal
oral
fear: insp
fear: exp
surprise: insp
surprise: exp
C
RT (demeaned sq rt s)
0.06
0.04
0.02
0
-0.02
*
nasal
oral
inspiration
expiration

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Results – Respiration Modulation in Emotion Tasks

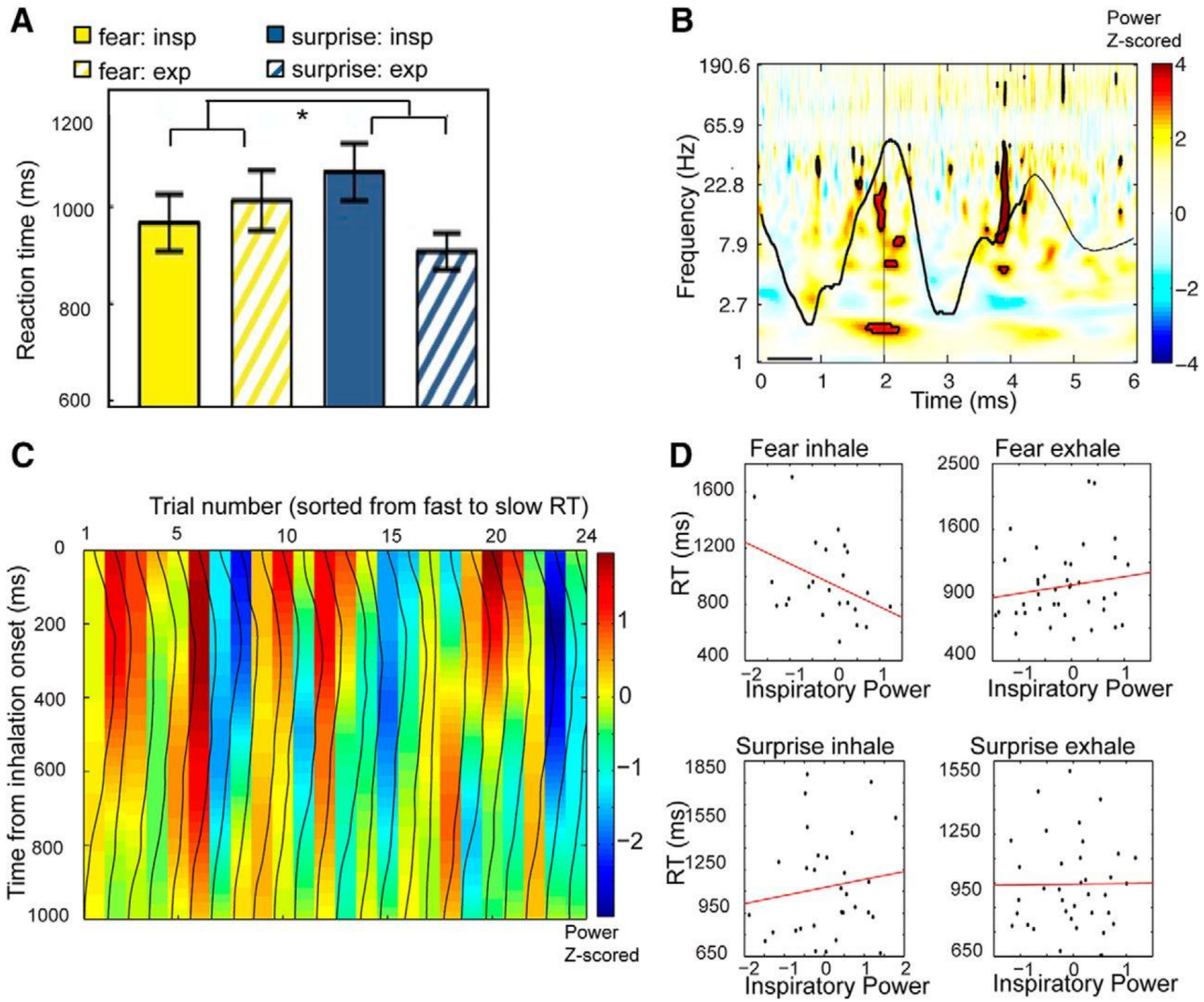
- Faster response times during **inhalation** compared to exhalation for **fearful faces**, but no effect for **surprised faces.**
- **Oral Breathing**: No RT phase differences for either emotion. Overall, **faster RTs with nasal breathing**.
- **Nasal Breathing with Mouth Open**: RT differences for fearful faces remained during **inhalation** vs **exhalation**, showing nasal breathing influences RT independent of attentional load.
- **Accuracy**: No significant difference in accuracy for either emotion between breathing phases.

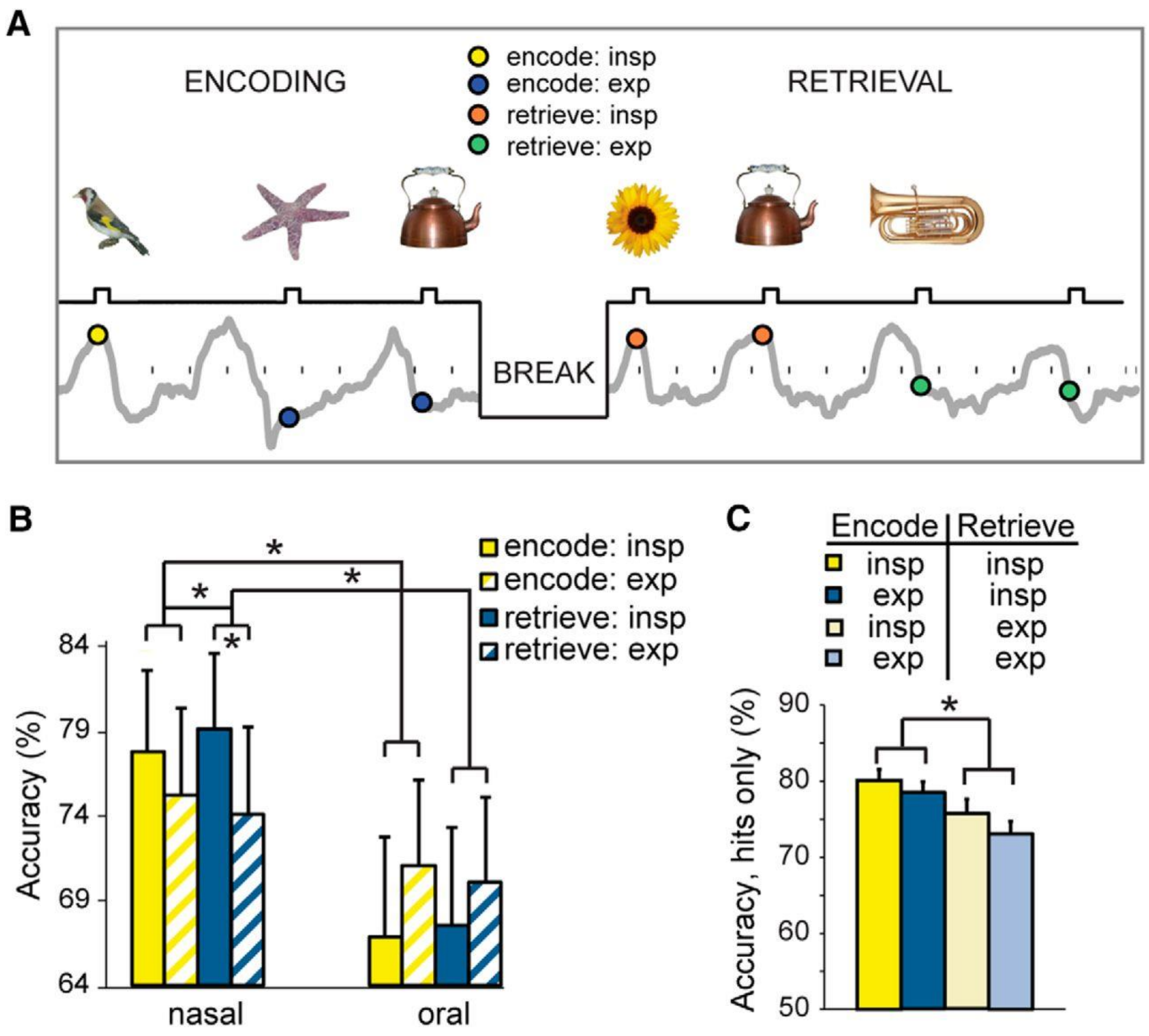
Results – Amygdala Inspiratory Power and Emotion Judgment

A patient (P8) identified fearful vs. surprised faces.

• Faster identification of fearful faces during **inspiration**.
• Significant interaction between **respiratory phase** and **emotion** (p = 0.03).
• **LFP Analysis**: Increased **delta power** during inhalation correlated with **faster response times** for fear.

Inhalation-related amygdala oscillations enhance emotional task performance.




A
ENCODING
encode: insp
encode: exp
retrieve: insp
retrieve: exp
RETRIEVAL
BREAK
B
*
*
*
*
encode: insp
encode: exp
retrieve: insp
retrieve: exp
Accuracy (%)
84
79
74
69
64
nasal
oral
C
Encode | Retrieve
insp insp
exp insp
insp exp
exp exp
Accuracy, hits only (%)
90
80
70
60
50
*

Results – Object Recognition Task

- Higher retrieval accuracy during **inspiration** compared to **expiration**.
- No effect for oral breathing.
- **Stronger impact of inhalation during encoding and retrieval**.

2x2 Factorial Design (Phase and Encoding; Phase and Retrieval)

- **Inspiratory retrieval** led to higher accuracy.
- No significant effect of encoding phase alone.
- No interaction between encoding and retrieval phases.

- Open Mouth controls – attentional demands did not have an effect in memory performance.

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Discussion

- Oscillations in PC (extending to Amygdala, Hippocampus) are in phase with the natural cycle of breathing.

- Inspiratory phase is associated with increased Delta power.
- Cross coupling between Theta phase and Beta power.
- Such effects are gone with mouth breathing (controlled for attentional demands).
- Therefore, Nasal breathing route serves as a common clock to organize spatiotemporal excitability broadly throughout the brain.

- Respiratory phase modulates limbic-based behaviors (emotion/memory)

- Cognition to Breath vs Breath to Cognition