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SUPPLEMENTARY INFORMATION

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Human non-olfactory cognition phase-locked with inhalation

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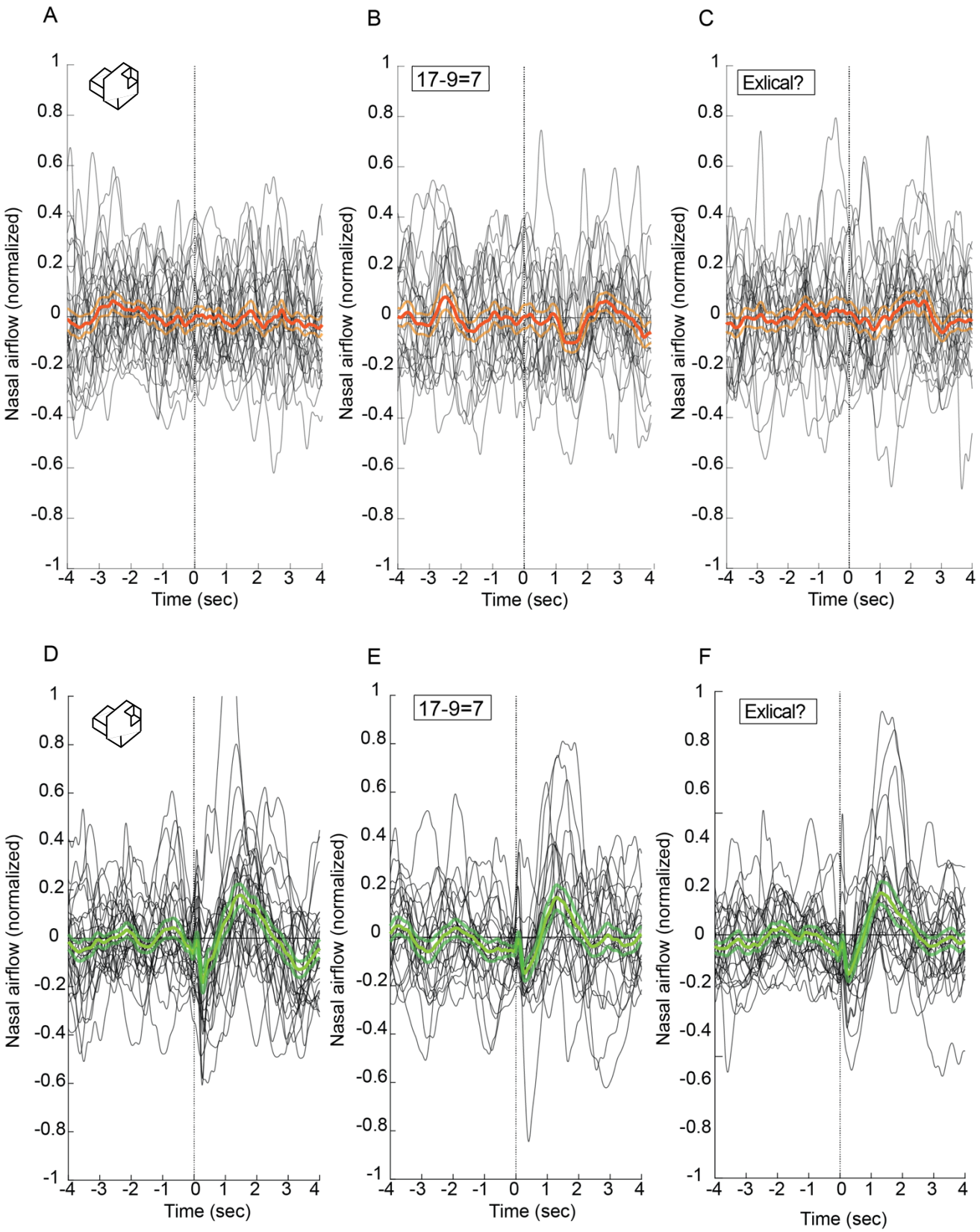
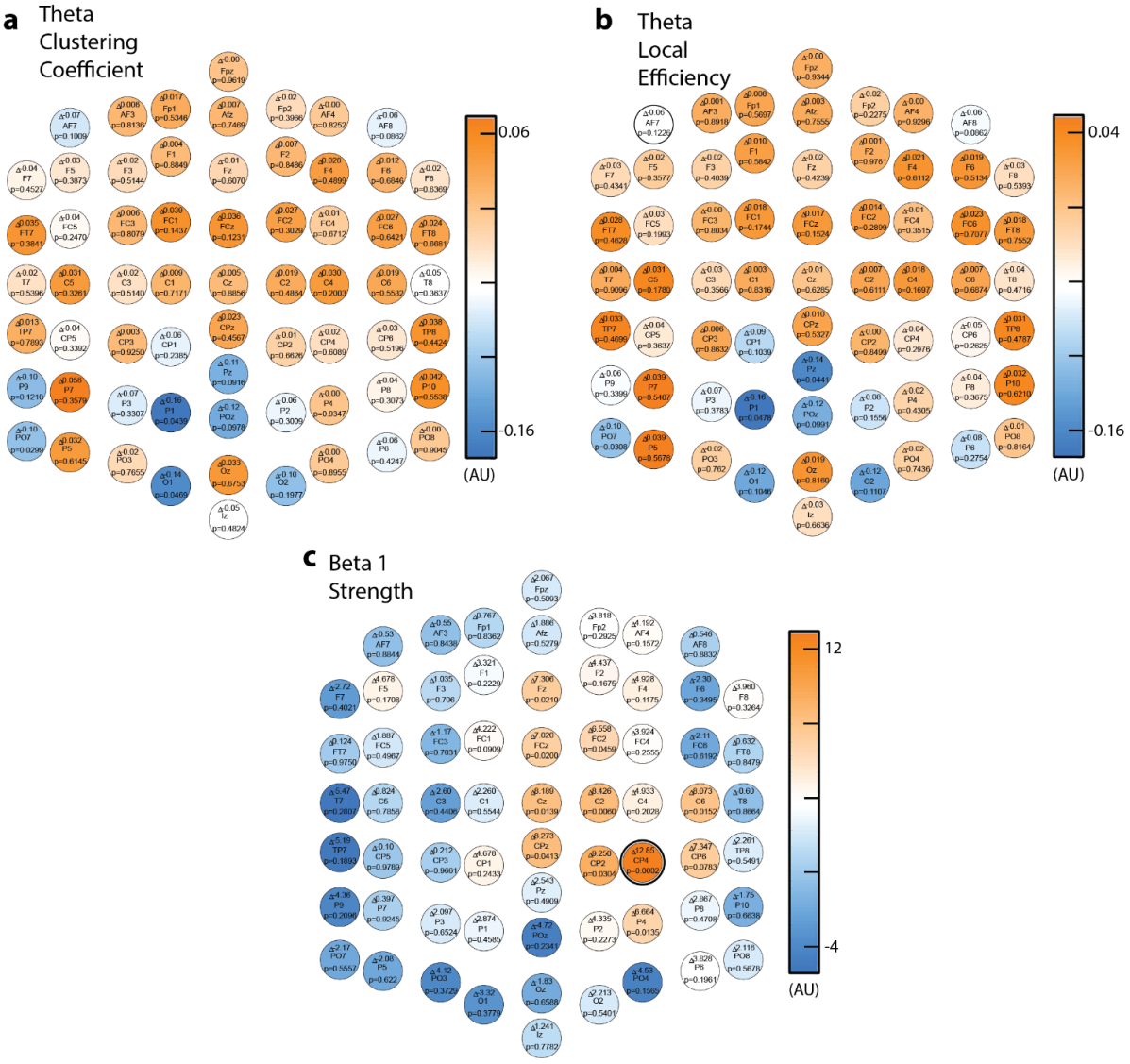

A
B
17-9=7
C
Exlical?
D
E
17-9=7
F
Exlical?
Nasal airflow (normalized)
Time (sec)

Supplementary Figure 1: Control Analysis: No nasal inhalation evident after randomly selected time point, or with response

A-C: Mean ± S.E of random time-point event-related respiratory response of all participants (orange trace) in the visuospatial (**D**), Math (**E**), and Lexical (**F**) tasks. Time 0 (dashed black line) denotes the randomly selected time-point from within the ISI. Black traces are individual mean respiration, inhalation plotted upwards. D-F: Mean ± S.E of event-related respiratory response of all participants (green trace) in the Visuospatial (n = 29) (**D**), Math (n = 26) (**E**), and Lexical (n = 24) (**F**) tasks. Time 0 (dashed black line) denotes the point in time where they initiated their answer. Black traces are individual mean respiration, inhalation plotted upwards. We observe that similar to initiating the task (Figure 1 in manuscript), answering the question is also associated with a respiratory pattern, yet a different pattern, containing a brief exhalation followed by an inevitable inhalation. To ask whether this inhalation is different from the inhalation related to task initiation, we compared the latency from time zero (either button press to initiate the task or button press to answer) to inhalatory peak and exhalatory trough within a 2000-ms time window.

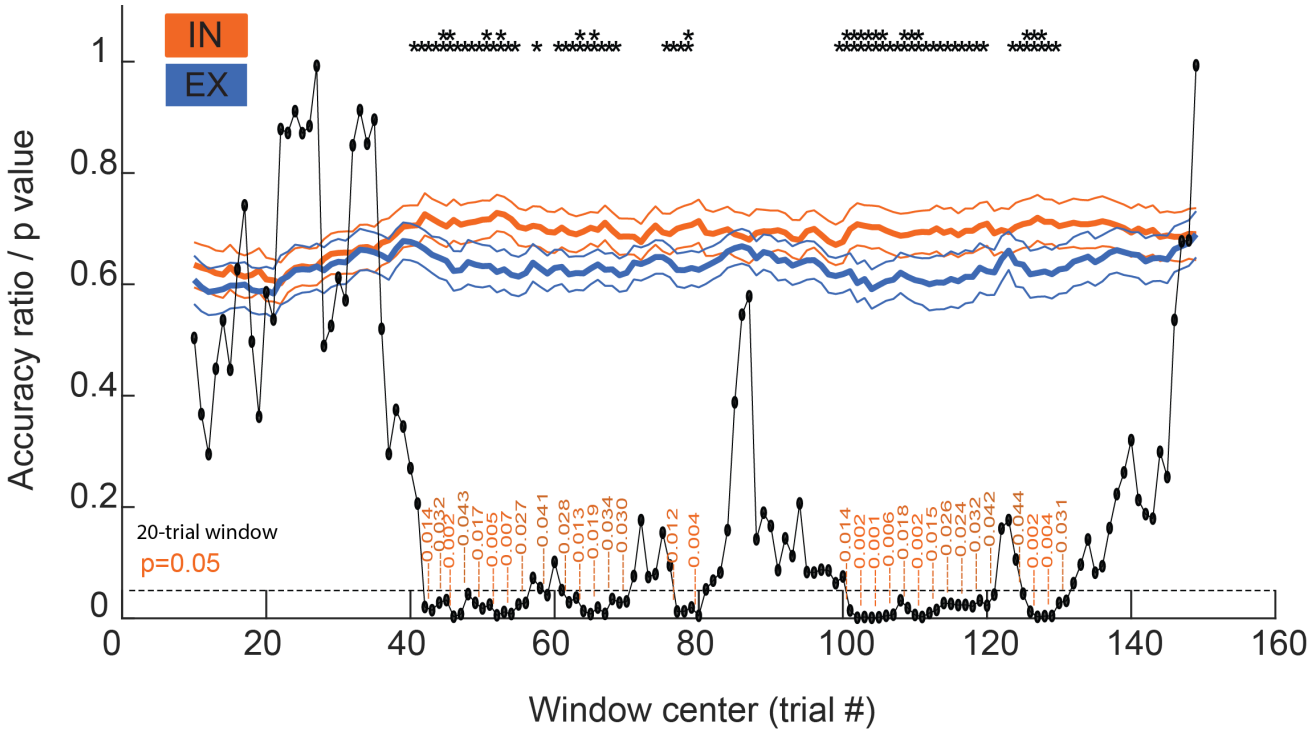
A repeated-measures ANOVA with conditions of *stage* (initiation / answer) and *maxima* (peak / trough) and a categorical predictor of *task* (visuospatial / math / lexical) uncovered a main effect of *stage* ($(F1,76) = 6.002$, $p = 0.0166$, Partial $\eta^2 = 0.073$, 90% CI = $0.007 \leq \eta \leq 0.178$), a main effect of *maxima* ($F(1,76) = 6.64$, $p = 0.0119$, Partial $\eta^2 = 0.08$, 90% CI = $0.01 \leq \eta \leq 0.188$) and a significant interaction between *stage* and *maxima* ($F(1,76) = 31.62$, $p < 0.001$, Partial $\eta^2 = 0.294$, 90% CI = $0.156 \leq \eta \leq 0.413$). No other significant main effects or interactions were observed (all $p > 0.19$). Notably, no effect of *task* was observed ($F(2,76) = 0.248$, $p = 0.781$, Partial $\eta^2 = 0.006$, 90% CI = $0 \leq \eta \leq 0.04$).

In other words, we observe that the respiratory response associated with button press at answer is different from the response associated with task initiation and that this dissociation was evident in all three tasks.



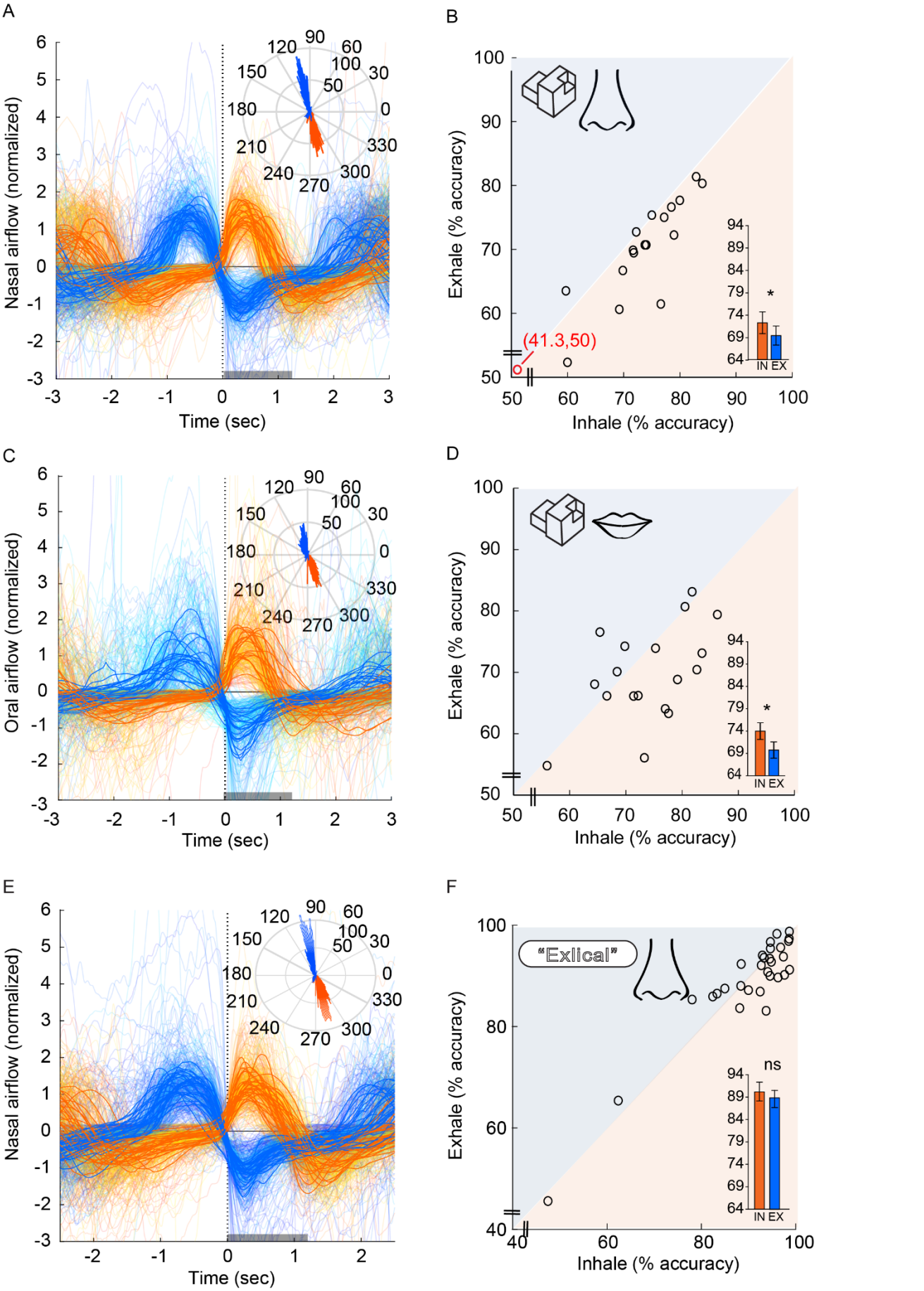
Supplementary Figure 2: Head maps depicting electrode-specific comparison of network measurements computed for EEG epochs obtained during inhalation and exhalation.

The network connectivity measurements reported in the manuscript are averaged across all nodes (EEG scalp electrodes). We also conducted a follow-up analysis of the same connectivity measurements per electrode. We focused on the average density threshold in which our results were most robust (20 in theta and 30 in beta1), conducting paired *t*-tests per electrode for values calculated for inhalation and exhalation epochs per participant (n = 28). A head map of changes in theta nodal strength per electrode uncovered a central-parietal focus around Pz which exhibited a decline in both local efficiency and cluster (Local efficiency: $p < 0.05$, Cluster: $p < 0.05$, uncorrected). This effect, however, did not survive corrections for multiple comparisons. In contrast, a head map of changes in beta1 nodal strength per electrode uncovered a right parietal focus centered around CP4 with strong modulation as a function of respiratory phase, which remained significant following FDR correction (Strength in arbitrary units (AU): IN = 51.05 ± 17.03 AU, EX = 38.20 ± 15.54 AU, $t(27) = 4.19$, $p < 0.001$ uncorrected, $p = 0.0173$ following FDR correction, , Cohen's $d = 0.79$, 95% CI = $0.23 \leq d \leq 1.32$).



Supplementary Figure 3: Difference in performance between inhale and exhale increased as the task progressed

Mean ± S.E of ongoing performance in the visuospatial task calculated from a moving average window of 20 trials (n = 29). Performance in trials phase-locked to inhalation and exhalation onset is denoted in orange and blue traces, respectively. Black dots denote p values of two-tailed paired *t* test of performance between "inhale" and "exhale". Dashed lines represent significance threshold of p = 0.05 and numerical values are p values of two-tailed paired t-test of points crossing this threshold. Note separation of performance along the session. * = $p < 0.05$, ** = $p < 0.01$. We acknowledge that this evolution of the response over time implies that we do not have full understanding of all the sources of variance in this experiment, as our theory does not explain why the inhalation advantage would not be in place from the very first trial.

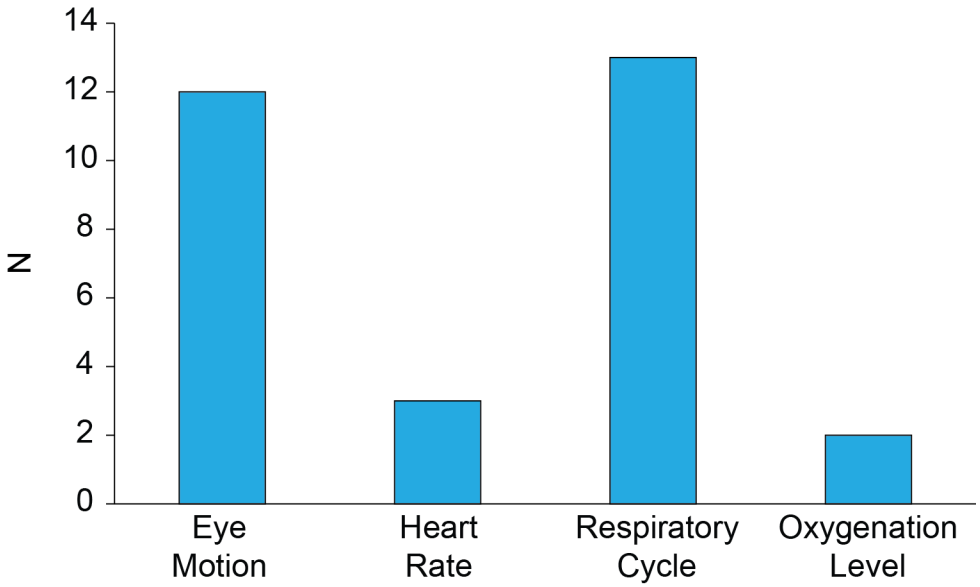

A
Nasal airflow (normalized)
Time (sec)
B
Exhale (% accuracy)
Inhale (% accuracy)
(41.3,50)
IN EX
*
C
Oral airflow (normalized)
Time (sec)
D
Exhale (% accuracy)
Inhale (% accuracy)
IN EX
*
E
Nasal airflow (normalized)
Time (sec)
F
"Exlical"
Exhale (% accuracy)
Inhale (% accuracy)
IN EX
ns

Supplementary Figure 4: Visuospatial performance remains better on inhalation, whether nasal or oral

A. Mean event-related nasal respiratory signal used to trigger trial onset time locked to inhalation (orange) or exhalation (blue). Time 0 denotes task initiation (dashed black line). Thick traces are per-subject means, fine lines denote individual trials (only one out of five trials per condition is plotted, to reduce visual encumberment, inhalation plotted upwards). Dark rectangle along x-axis represents time of stimulus on screen (1200 ms). Inlay: polar plot of respiratory phase (in degrees) at the moment of trial onset. Orange and blue bins represent trials triggered by inhalation and exhalation, respectively. **B.** Scatter plot of performance in the visuospatial task for trials presented time locked to nasal inhalation and exhalation. Each point is a participant (n = 18). The diagonal line is the unit slope line (X = Y). Thus, if points accumulate below the line (within the orange shade), performance was better during inhale. Inlay: mean group performance during inhalation (orange) and exhalation (blue). RT was not significantly different on trials initiated by inhalation or exhalation (mean Inhale: 979 ± 119 ms Exhale: 984 ± 127 ms, paired t-test: $t(17) = 0.81$, $p = 0.43$, Cohen's d = -0.04, 95% CI = $-0.61 \leq d \leq -0.04$), but performance was again significantly better in trials triggered by inhalation versus trials triggered by exhalation (mean accuracy (%) Inhale: 72.04 ± 9.80% Exhale: 69.24 ± 8.57%, Wilcoxon Signed Rank, $Z = 2.28$, $p = 0.022$, Cohen's d = 0.30, 95% CI = $-0.36 \leq d \leq 0.95$), (paired t-test: $t(17) = 2.37$, $p = 0.03$). Error bars are S.E, * = $p < 0.05$. One point at 41.3-50 shown off-location to retain equal axes with panel D. **C-D:** Same as A-B but for oral rather than nasal respiration (n = 18). We observed a similar outcome: no effect of respiratory phase on RT (mean Inhale: 936 ± 90 ms, Exhale: 934 ± 96 ms, paired t-test: $t(17) = 0.23$, $p = 0.81$, Cohen's d = 0.02, 95% CI = $-0.63 \leq d \leq 0.67$)), but again significantly better performance following oral inhalation versus exhalation (mean accuracy (%) Inhale: 74.00 ± 7.72% Exhale: 69.74 ± 7.51%, Wilcoxon Signed Rank, $Z = 1.98$, $p = 0.047$, Cohen's d = 0.55, 95% CI = $-0.12 \leq d \leq 1.21$) (paired t-test: $t(17) = 2.37$, $p = 0.029$).

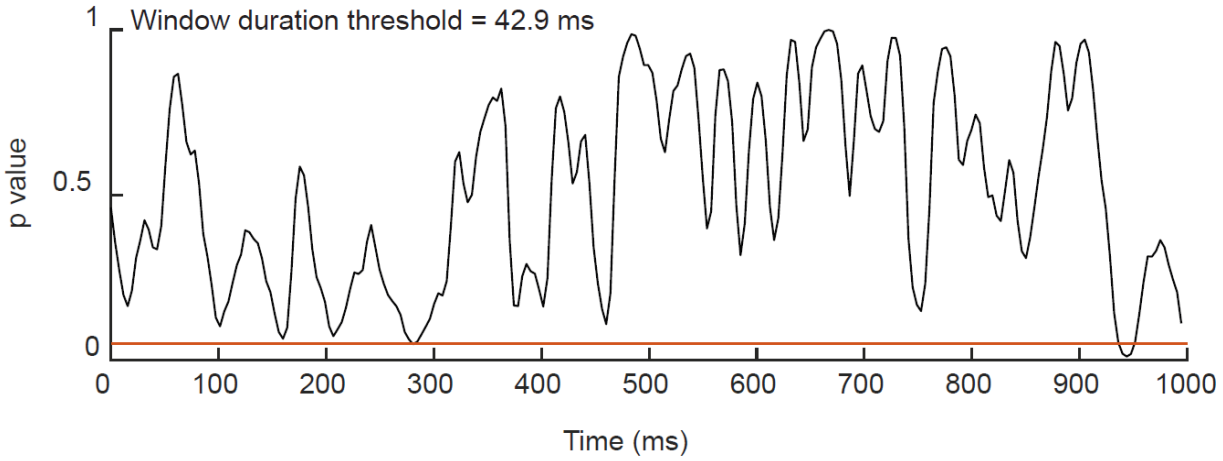
To directly compare the impact of respiratory phase on performance in nasal versus oral inhalation we entered the data from both experiments into a common analysis of variance (ANOVA) with condition of phase (inhale/exhale) and categorical predictor of path (nasal/oral) and observed a main effect of phase ($F(1,34) = 10.79$, $p = 0.0024$,Partial $\eta^2 = 0.241$, 90% CI = $0.058 \leq \eta \leq 0.413$), yet no main effect ($F(1,34) = 0.208$ $p = 0.65$, Partial $\eta^2 = 0.006$, 90% CI = $0 \leq \eta \leq 0.104$) or interaction ($F(1,34) = 0.462$, $p = 0.50$, Partial $\eta^2 = 0.013$, 90% CI = $0 \leq \eta \leq 0.129$) with path (nonparametric verification: Friedman test, Chi Square = 6.2, $p = 0.1$). In other words, participants were significantly better at a visuospatial task triggered concurrent with inhalation over exhalation, regardless of whether inhalation was nasal or oral.

E-F: Same as A-B but for the lexical decision task (n = 30). We observed no effect on performance (mean % accuracy Inhale: 90.18 ± 10.89% Exhale: 89.91 ± 10.22%, Wilcoxon Signed Rank, $Z = 1.35$, $p = 0.176$, Cohen's d = 0.03, 95% CI = $-0.63 \leq d \leq 0.68$ (two tailed paired t-test: $t(29) = 1.74$, $p = 0.0918$). Note that in this one instance, we did observe an effect for RT (mean Inhale: 866 ± 107 ms, Exhale: 848 ± 96 ms, paired *t*-test: $t(29) = 4.90$, $p < 0.001$, Cohen's d = 0.18, 95% CI = $-0.32 \leq d \leq 0.68$), yet given this control replication is the only instance with an RT effect in the manuscript, we do not further explore this front.



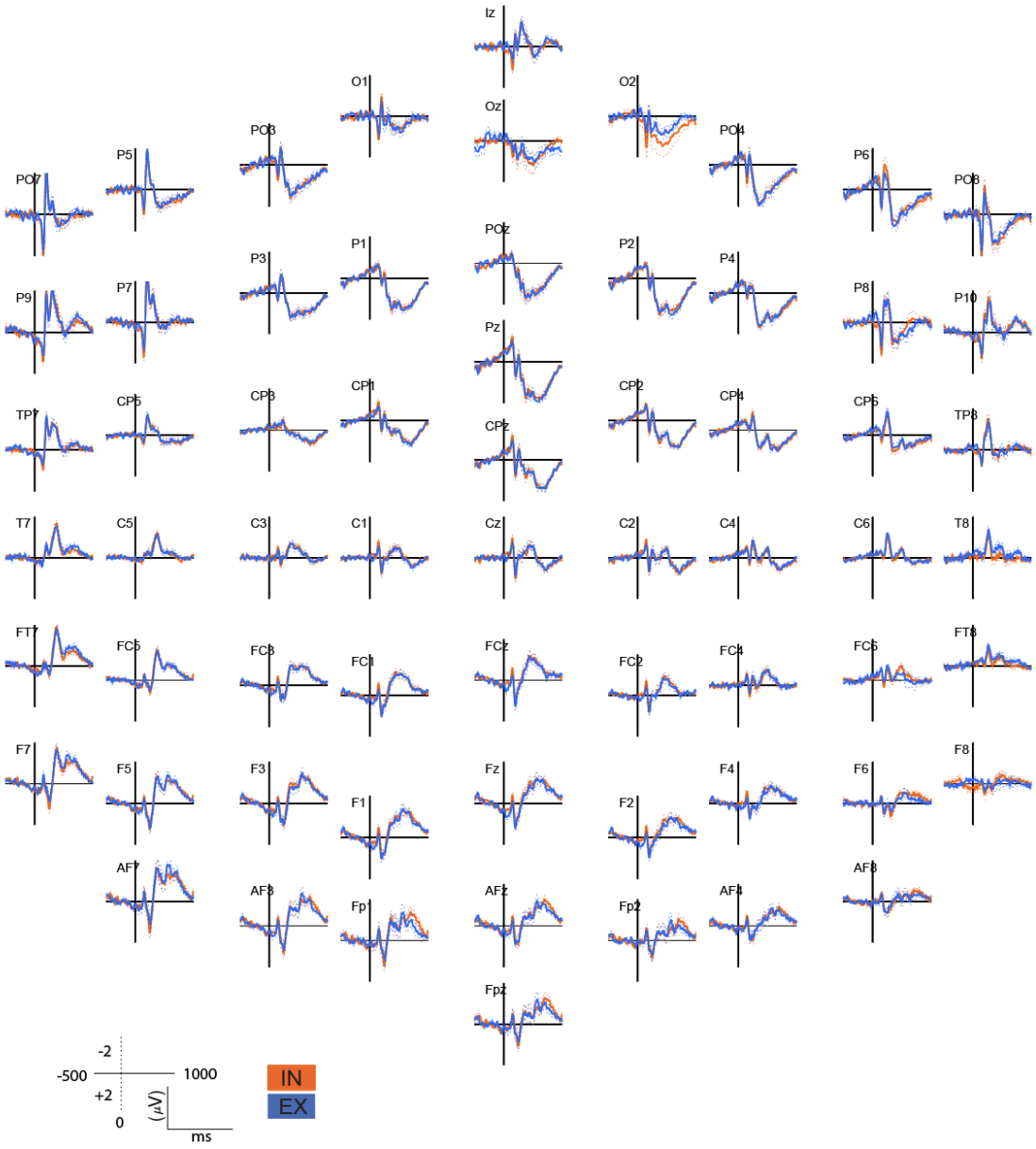
Supplementary Figure 5: Subjects were unaware of interest in respiration

All participants across experiments were questioned upon experiment completion as to what they thought we were measuring, and not one noted an interest in airflow or respiration. All notions related to cognition alone. In one control experiment with 30 participants, we also had participants write a paragraph on what they thought we were measuring or asking. Not one noted any link to respiration. We then explicitly told them that we triggered events off their physiological recording, and gave them four alternative options as to what measure we used. We observe that even when informed by us of the study method, and limited to 4 alternatives, two of which are highly implausible triggers, a similar number of participants thought we used eye motion (n = 12) rather than respiration (n = 13) to trigger events (Chi squared = 0.028, p = 0.86). Based on the exit questionnaires, and our subjective impression from interaction with participants, we think it highly unlikely that participants were aware of task design and goals. That said, we of course have no way to completely rule out subliminal awareness of task design.



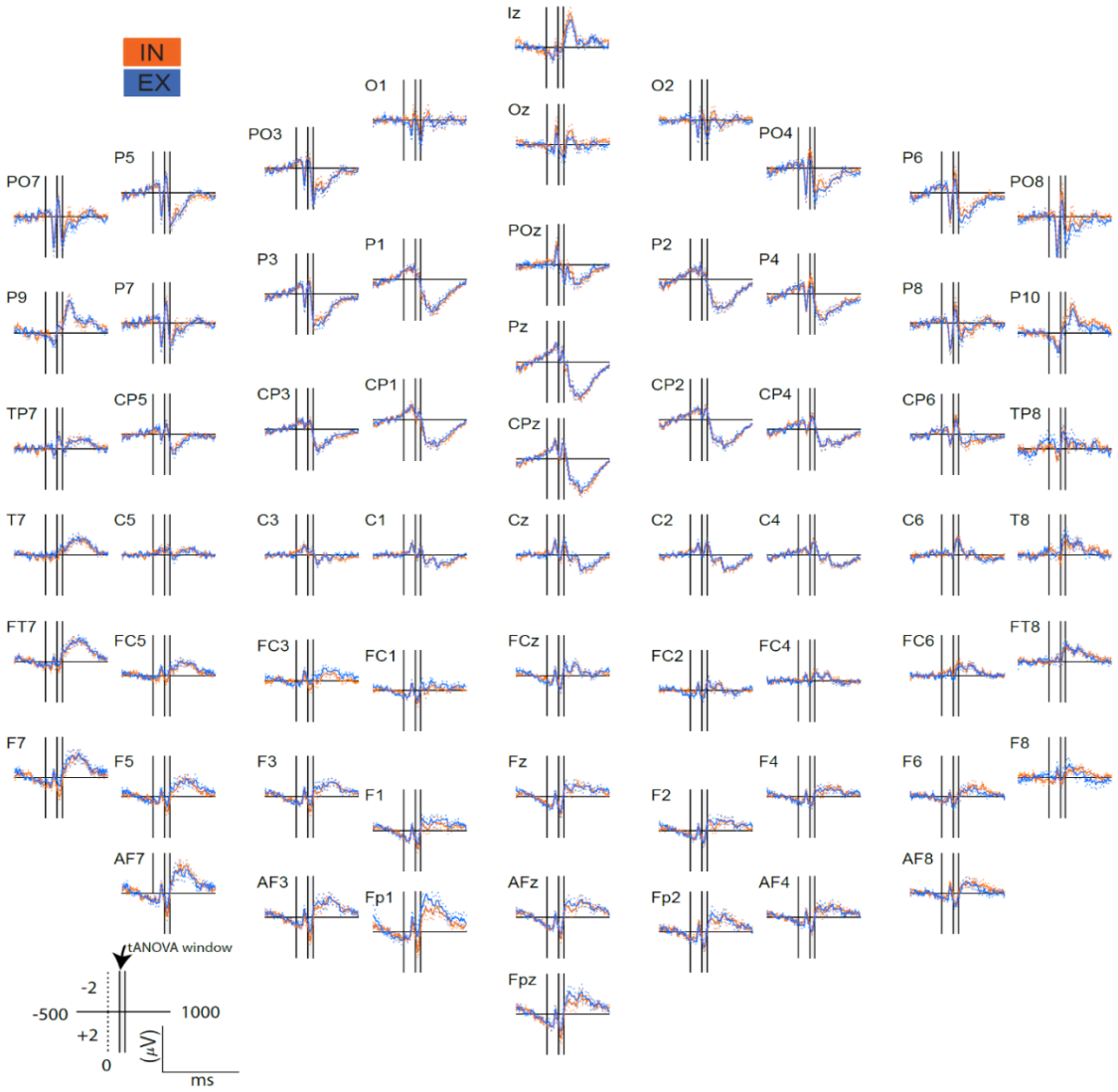
Supplementary Figure 6: No effect of respiratory phase in a tANOVA conducted on data collected during the lexical task

Point by point plot of tANOVA p value comparing inhalation- and exhalation- task-induced ERP over time (ms), (n = 26). Horizontal orange line represents significance level of p = 0.05. No consecutive significant time points qualified to meet the critical global window duration of 42.9 ms.



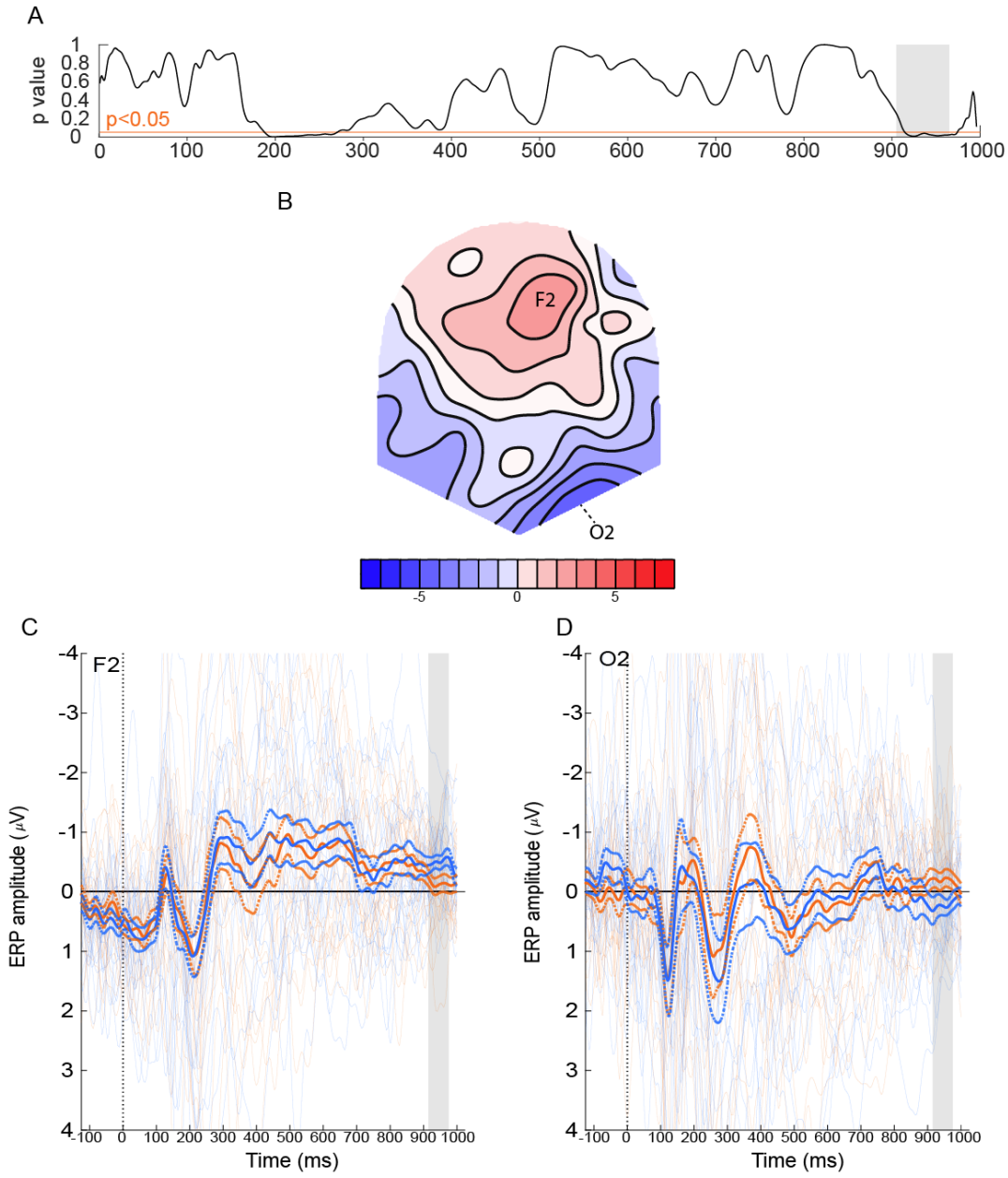
Supplementary Figure 7: Head montage of ERPs generated by the lexical task

Scalp montage of grand average ERPs evoked by the lexical task (n = 26). Plots location according to electrode coordination using the 10-20 system. Nose points towards bottom of figure. Each sub-plot is the grand mean and standard error of traces of respiratory phase-coupled ERP evoked by lexical trials presented during inhalation (orange) and exhalation (blue). Negative values are plotted upwards. Time 0 denoted by a vertical black line is surrounded by a 500 ms baseline and 1000 ms ERP signal.



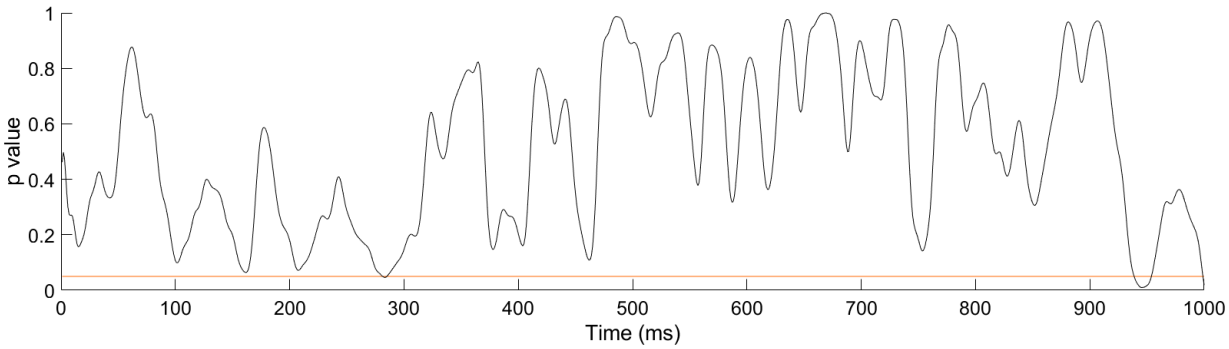
Supplementary Figure 8: Head montage of ERPs generated by the visuospatial task

Scalp montage of grand average ERPs evoked by the visuospatial task (n = 25). Plots location according to electrode coordination using the 10-20 system. Nose points towards bottom of figure. Each sub-plot is the grand mean and standard error of traces of respiratory phase-coupled ERP evoked by visuospatial trials presented during inhalation (orange) and exhalation (blue). Negative values are plotted upwards. Time 0 denoted by a vertical black line is surrounded by a 500 ms baseline and 1000 ms ERP signal. tANOVA derived significant time window is boxed by two vertical black lines at approx. 200 ms following time 0.



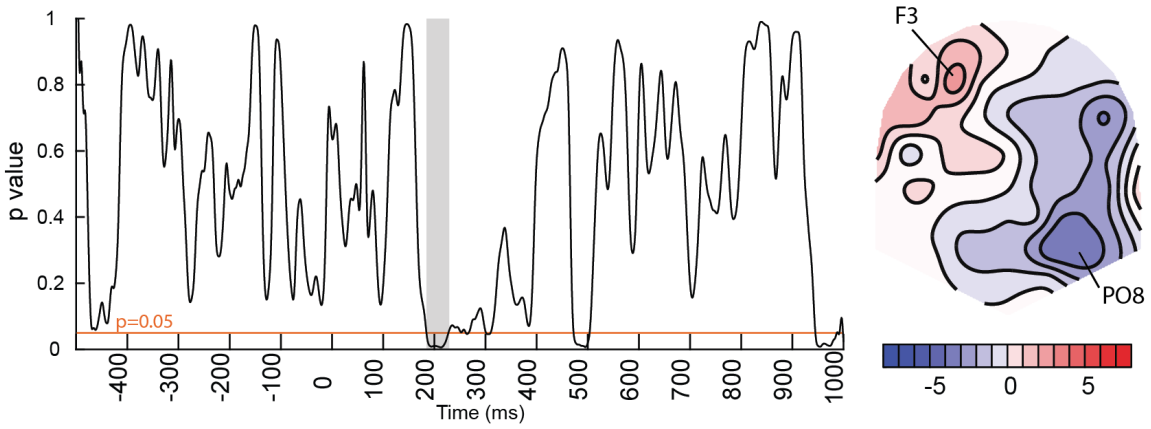
Supplementary Figure 9: A significant late ERP in the visuospatial task

A. Point by point plot of tANOVA p value comparing inhalation- and exhalation- task-induced ERP over time (n = 25). Gray rectangle around 915 and 975 ms post stimulus onset denotes significant consecutive time points. Horizontal orange line represents significance level of p = 0.05. **B-C.** Grand mean + standard error of traces of respiratory phase-coupled ERP evoked by visuospatial trials presented during inhalation (orange) and exhalation (blue) recorded from location F2 (**D**) and O2.



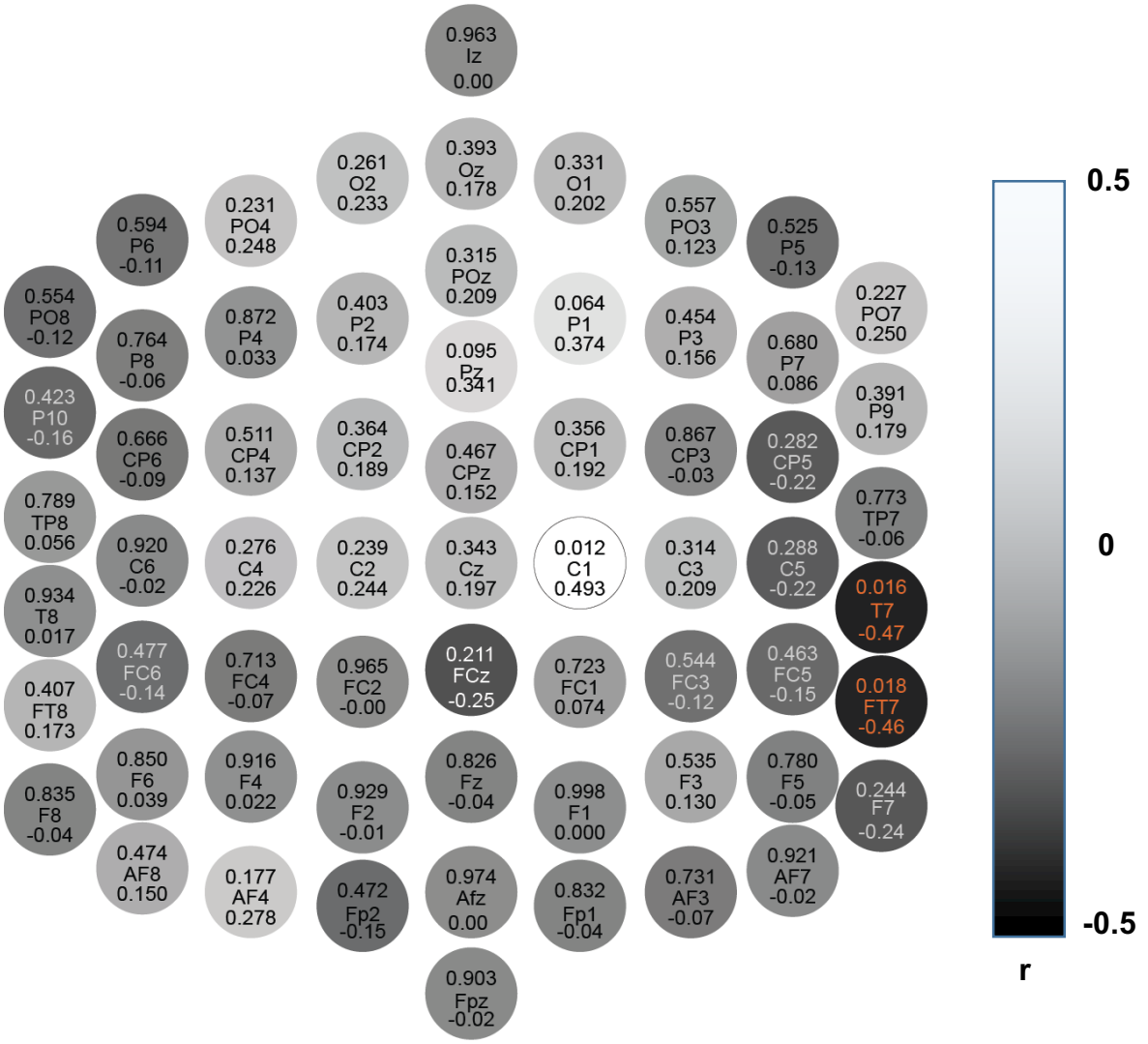
Supplementary Figure 10: No topographical ERP associated with inhalation and exhalation in the absence of a task

Point by point plot of tANOVA p value comparing EEG-derived topographical brain activity contrasting inhalation and exhalation onset over time (ms) (n = 29). Horizontal orange line represents significance level of p = 0.05. No consecutive significant time points qualified to meet critical global window duration of 42.9 ms.



Supplementary Figure 11: Respiratory phase-dependent brain response in the visuospatial task was not confounded by performance

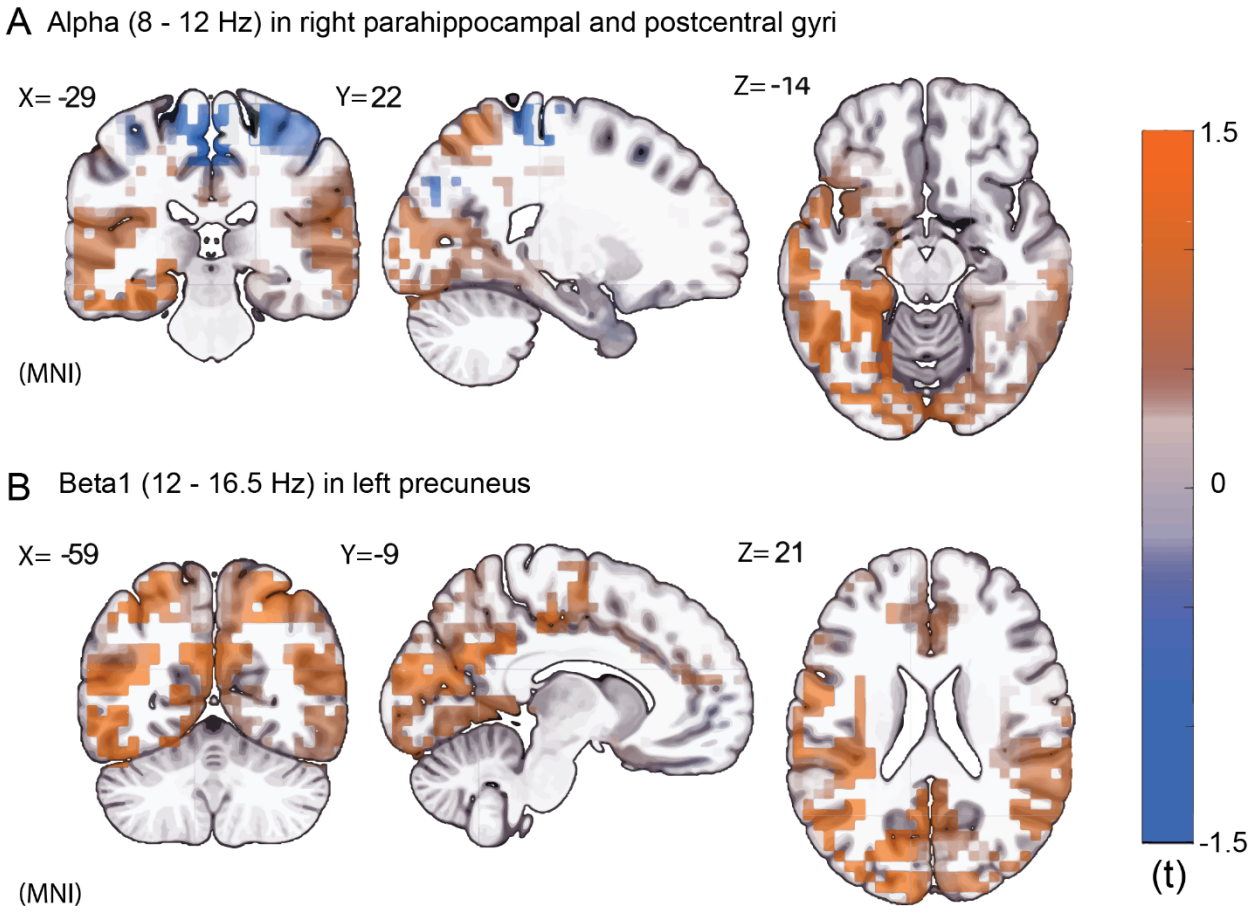
To ask whether differences in ERP are related to the overall higher performance associated with the inhalation condition, we removed successful inhalation trials and failed exhalation trials until performance was equated (This entailed removing an average of 10.8 ± 7.7 trials per participant, or 7.8% ± 5.3% of the data). **A.** Point by point plot of tANOVA p value comparing inhalation- and exhalation- task-induced ERP over time (n = 24). Gray rectangle around 185 and 229 ms post stimulus onset denotes significant consecutive time points which overlap with the main effect previously reported (tANOVA Max-Min, p = 0.0062, Cohen's d analogue = 2.04). Horizontal orange line represents significance level of p = 0.05. **B** Topographic map (t values) of main effect uncovered by tANOVA comparing respiratory phase coupled-ERP activity. Blue represents inhalation-coupled increased negativity and red represents inhalation-coupled increased positivity. Note frontal and parietal foci originating from the location of electrodes F3 and PO8 respectively. Nose points at top, apex depicts inion (Iz) electrode location. Consistent with the main findings, the largest N200 occurred at parieto-occipital electrodes (max. *t* at F3 t = 3.666, in. *t* at PO8 t = -3.521)



Supplementary Figure 12: Respiratory phase-dependent ERP signal within the N200 time window was correlated with individual differences in performance in the visuospatial task.

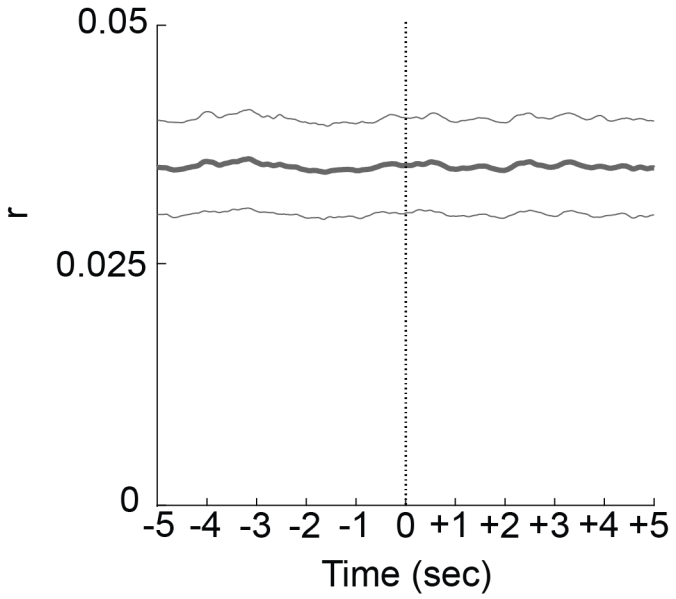
A head map showing phase-dependence between each of the 64 electrode locations (arranged according to 10-20 system) and phase-dependence of behavioral performance (n = 25). Nose is drawn downwards (see Fpz). Each circle represents an electrode (see name in circle center). p and r values are denoted at the top and bottom of each circle icon. Color codes r values between -0.5 – 0.5. The (anatomical) left temporal electrodes referred to in the results section are highlighted in orange.

Inhale vs Exhale



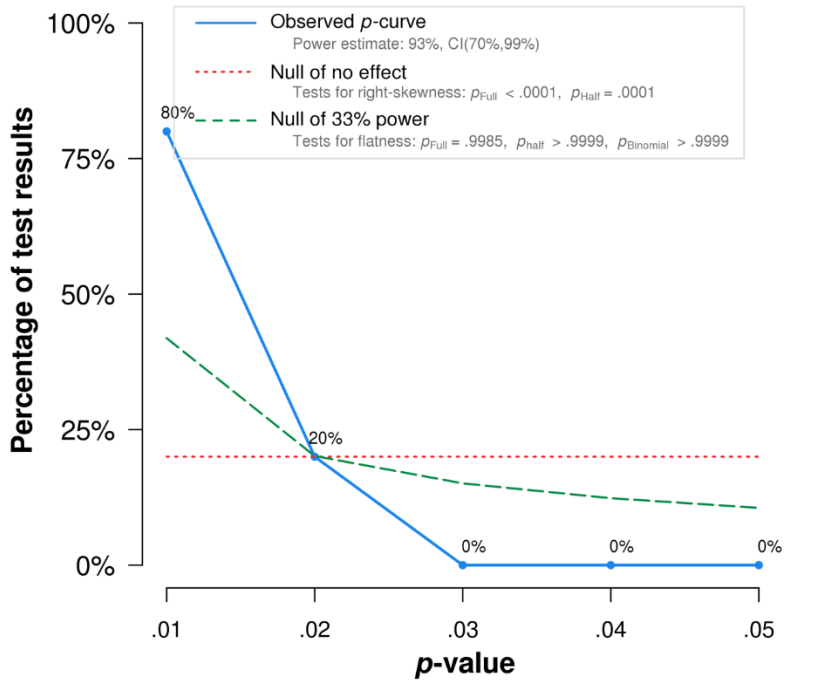
Supplementary Figure 13: sLORETA of inhalation vs. exhalation without concurrent task, focused on peak coordinates of task-coupled sLORETA analysis

A. sLORETA source localization t-maps of brain activity phase-locked to inhalation and exhalation onset within the alpha (top) and beta1 (bottom) frequency bands (n = 29). Volumetric data are centered around MNI coordinates of highest t value observed in the visuospatial ERP epochs. Hot and cold hues denote increase and decrease in activity, respectively. Note maps are not necessarily centered on maximum values of the inhale-exhale contrast but rather on coordinates derived from main results. Within this volumetric data no main effect of respiration was observed. Alpha: max(t)=2.14 at x = -15, y = -85, z = 15 (BA 18, Cuneus). Beta1: max(t) = 2.90 at x = -20, y = -75, z = 10 (BA 17, Cuneus). Critical t of $p < 0.05$ is t = 4.06.



Supplementary Figure 14 – No correlation between cardiac phase and trial onset

One may raise the possibility that some other unknown factor is orchestrating cognition and respiration. Given that heart rate is linked to both cognition and respiration, we examined whether cardiac cycle was correlated with task onset. A cross-correlation analysis between finger pulse signal and task onset reveals no link between task onset and cardiac phase. Systolic peaks were identified in a raw finger pulse trace obtained from left index finger of the participants (n = 25). Next, peak locations were used to generate a rectangular impulse vector with 125 ms long triggers representing the position of a standard QRS complex. A cross-correlation analysis was conducted on the transformed pulse and a vector of rectangular triggers representing task onset.



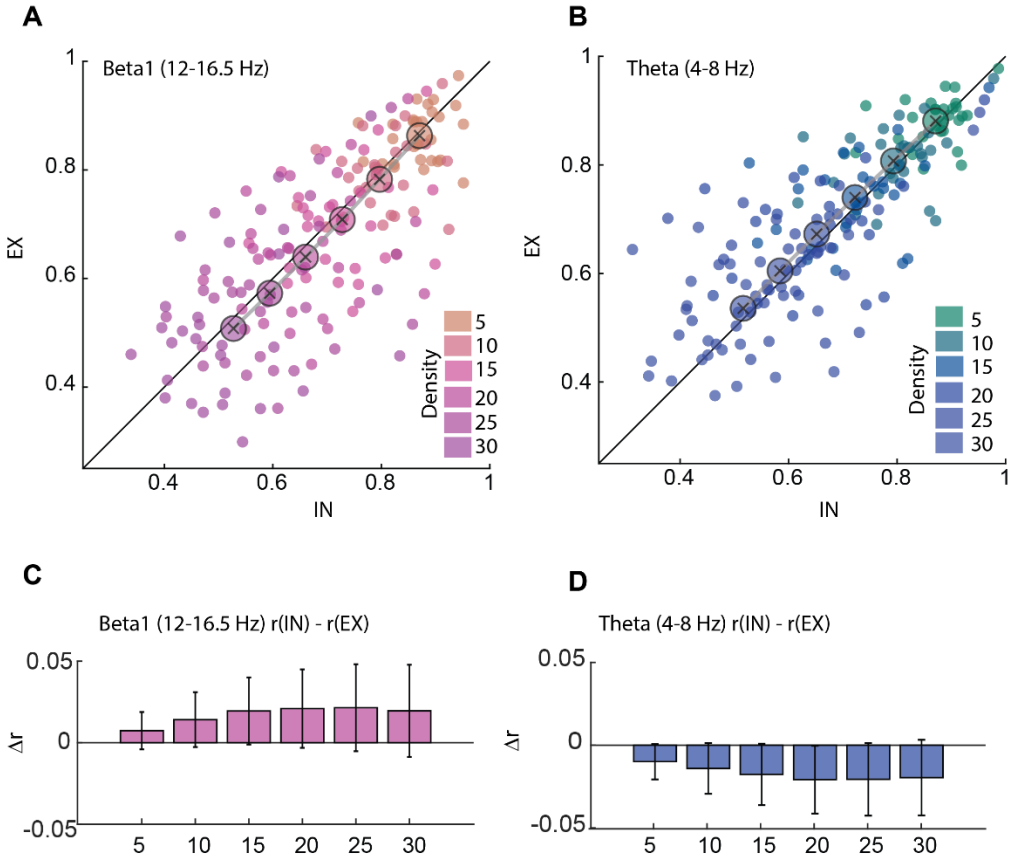
Note: The observed *p*-curve includes 5 statistically significant ($p < .05$) results, of which 5 are $p < .025$.
There were no non-significant results entered.

Supplementary Figure 15 - P-curve analysis

We analyzed the p-values in the manuscript using the p-curve method. The p-curve method was developed to estimate evidential value and power of independent studies. We applied it here, including only independent experiments, and only those derived from the main hypothesis. We stated the following main hypothesis "Conducting cognitive tasks during nasal inhalation will lead to better performance and stronger cortical responses".

Methods:

Selection criteria for the different experiments: Experiment 1: "participants inhale at task onset" the statistic relevant to the visuospatial task was t(28) = 3.77 (n = 29). For experiment number 2, we generated an omnibus ANOVA to test the effect of respiratory activity on EEG-derived cortical connectivity and used F(8,224) = 2.38 (n = 28). For experiment 3 we used the statistic representing the interaction between performance in task and respiratory phase - F(1,27) = 22.65 (n = 29). For experiment number 4 we used the statistic of the difference in EEG topographical brain activity between inhalation and exhalation t(25) = 3.34 (n = 26). For experiment 5 we used the statistic derived from the peak of the statistical map generated by sLORETA for differences between task EEG between inhale and exhale and took the most likely statistic t(26) = -4.7 (n = 27), as alpha suppression in the parahippocampal gyri area is an established finding, previously reported to be correlated with task performance.



Supplementary Figure 16 – Impact of thresholds on connectivity analysis

A. Scatter plot of mean correlation values per participant which served as cutoff values to form connectivity graphs from EEG epochs obtained during inhalation or exhalation (n = 29). Each participant is represented by five color data points, one per cutoff (5 / 10 / 15 / 20 / 25 / 30, see color legend in figure). The diagonal line is the unit slope line (X = Y). Thus, if points accumulate below the line, a higher cutoff value was applied to the connectivity matrix to retain the same average number of connections per node in inhalation epochs than exhalation. Correlation values for data filtered in the beta1 band. Larger 'X' labeled data points are the centroids of each point cloud. **B.** Same as A but with correlation values for data filtered in the theta band. **C.** A bar graph depicting difference (mean ± S.E of [IN] – [EX]) between mean r values per respiratory condition as a function of average density cutoff for data filtered in the beta1 band (All not significantly different from zero following a 1-sample t-test, all $p > 0.31$). **D.** same as C but for data filtered in the theta range. (All not significantly different from zero following a 1-sample t-test, all $p > 0.34$).

Supplementary Table 1

Network connectivity analysis

We report only effects which were observed in two consecutive average density thresholds. All statistical tests are two-tailed paired *t* tests. All values are in arbitrary units.

Frequency band (Avg. Den)	Inhale	Exhale	p value	Cohen's d	90%CI (lower)	90% CI (upper)
Theta						
Local efficiency (15)	0.733 ± 0.058	0.765 ± 0.050	0.0021	-0.58	-1.10	-0.07
Local efficiency (20)	0.787 ± 0.039	0.811 ± 0.028	0.0055	-0.70	-1.22	-0.18
Clustering coefficient (15)	0.611 ± 0.038	0.637 ± 0.036	0.0039	-0.69	-1.21	-0.17
Clustering coefficient (20)	0.658 ± 0.033	0.679 ± 0.03	0.03	-0.66	-1.18	-0.14
Beta1						
Global efficiency (25)	0.660 ± 0.02	0.672 ± 0.01	0.024	-0.75	-1.27	-0.23
Global efficiency (30)	0.717 ± 0.017	0.728 ± 0.012	0.007	-0.74	-1.26	-0.21
Strength (25)	38.82 ± 3.75	37.37 ± 3.19	0.034	0.41	-0.10	0.92
Strength (30)	44.68 ± 4.92	42.66 ± 4.14	0.027	0.44	-0.07	-0.95

Supplementary Table 2

	Binomial Test *(Share of results p<.025)*	**Continuous Test** *(Aggregate with Stouffer Method)*	
1) Studies contain evidential value. *(Right skew)*	*p*=.0313	**Full p-curve (p's<.05)**	**Half p-curve (p's<.025)**
2) Studies' evidential value, if any, is inadequate. *(Flatter than 33% power)*	*p*>.9999	*Z*=-4.58, *p*<.0001	*Z*=-3.68, *p*=.0001
	Statistical Power		
Power of tests included in *p*-curve *(correcting for selective reporting)*	Estimate: 93% 90% Confidence interval: (70% , 99%)	*Z*=2.96, *p*=.9985	*Z*=3.93, *p*>.9999

Data table on following page

Supplementary Table 3

Exp	Quoted text from original paper indicating prediction of interest to researchers	Study design	Key statistical result	Quoted text from original paper with statistical result	Results	
I	The averaged nasal airflow trace revealed that participants spontaneously opted to initiate trials concurrent with initiation of a nasal inhalation or sniff	Two cell (visuospatial vs. task-free)	Difference of means	We … observe that the tendency to sniff at task onset was significant in all tasks, Visuospatial: maximal at 1800 ms post task onset; trial = 0.52 ± 0.24 Normalized Flow Units (NFU), surrogate = 0.34 ± 0.08 NFU, t(28) = 3.77, p = 0.0007. Cohen's d = 0.97, 95% CI = 0.41 ≤ d ≤ 1.50	t(28) = 3.77, p = 0.0007. Cohen's d = 0.97, 95% CI = 0.41 ≤ d ≤ 1.50	
II	To explore the effect of respiratory phase on cortical connectivity we conducted an omnibus ANOVA with conditions of *Phase (*Inhale/Exhale*)*, *Measurement (*Strength / Betweenness centrality / Local Efficiency / Global Efficiency /Clustering Coefficient*)* and *Average Density (5/10/15/20/25/30).*	2 (phase: inhale vs. exhale) x 5 (Measurement: Strength/Betweennness/mean Loc. Eff./Glob. Eff./Clustering Coefficient) x 6 (average density: 5/10/15/20/25/30) (attenuated interaction)	Two-way interaction	We observed main effects and interactions of *Measurement* and *Average Density,* which are trivial given the different units and thresholds used for each calculation. More meaningfully, the ANOVA uncovered a three-way interaction between*, Phase, Measurement* and *Average Density,* suggesting respiratory phase affected some of the network measurements in only part of the predefined network thresholds (*Phase X Measurement X Average Density*, F(8,224) = 2.38, p = 0.017). Partial η^2 = 0.078, 90% CI = 0.007 ≤ η ≤ 0.108	F(8,224) = 2.38, p = 0.017 Partial η^2 = 0.078, 90% CI = 0.007 ≤ η ≤ 0.108	
III	We now set out to quantify behavior during the task. We then examined performance in the tasks as a function of respiratory phase.	2 (phase: inhale vs. exhale) x 2 (task: visuospatial vs verbal) (attenuated interaction)	Two-way interaction	A repeated-measures ANOVA on accuracy with conditions of *task* (visuospatial/verbal) and *phase* (inhale/exhale) revealed…. A significant interaction between *task* and *phase* (F(1,27) = 22.65 , p = 0.00006) Partial η^2 = 0.456, 90% CI = 0.208 ≤ η ≤ 0.606)	F(1,27) = 22.65 p = 0.00006 Partial η^2 = 0.456, 90% CI = 0.208 ≤ η ≤ 0.606	
IV	We probed for differences in the brain evoked response to the same cognitive task, either visuospatial or verbal, as a function of respiratory phase, either inhale or exhale.	Two cell (inhale vs. exhale)	Difference of means	in the visuospatial task, we observed a significant main effect of *respiratory phase* in a time window of 185 – 270 ms post stimulus onset (tANOVA Max-Min, p = 0.0026)	tANOVA Max-Min, t(25) = 3.34, p = 0.0026	
V	We observed that trials presented during nasal inhalation versus exhalation were associated with significant localized decreases in EEG alpha and beta1 power	Two cell (inhale vs. exhale)	Difference of means	EEG alpha power was significantly reduced in right postcentral gyrus and right parahippocampal gyrus (peak value t=-4.76, p =0.017, MNI coord. X=20, Y= -25, Z= -20, BA 35)	t(27) =-4.76, p =0.017	