ELECTRONIC SUPPLEMENT

Medical hypnosis mitigates laboratory dyspnea in healthy humans: a randomized, controlled experimental trial

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ES1 – METHODOLOGICAL DETAILS

ES1-A. PARTICIPANTS NON INCLUSION CRITERIA

Non-inclusion criteria were: 1) any self-reported chronic somatic or psychologic disorder; 2) any self-reported current acute medical or psychological problem, including pain of any origin; 3) the regular practice of mind-body exercises or leisure activities involving intensive breathing control; 4) a tobacco consumption >2 pack-year; 4) current pain; 5) being pregnant (on a self declaration basis) or lactating; 6) any legal restriction from participation in biomedical research studies; 7) an insufficient command of the French language.

ES1-B. DETAILED DYSPNEA INDUCTION PROCEDURES

Inspiratory threshold loading (ITL). To elicit dyspnea predominantly of the excessive inspiratory effort type, the participants breathed through an inspiratory threshold loading (ITL) device consisting of an adjustable spring-loaded valve (Power breathe, UK) connected to the inspiratory limb of a unidirectional valve (Hans Rudolph 2600 medium, Kansas City, MO, USA) assembled in series with a pneumotachograph mounted on a mouthpiece [same setup and diagram as in 1]. With this type of device, the participant must generate a minimum airway opening pressure (Pao) in order to generate inspiratory flow. Inspiration ceases as soon as Pao returns below the threshold. During the familiarization procedure performed at Visit 1, the participants were asked to produce maximal inspiratory efforts from functional residual capacity against an occluded airway to determine maximal inspiratory pressure (PI,max). The valve was then connected to the inspiratory limb of the breathing circuit with an initial threshold was set at 50% of PI,max. It was then adjusted to produce visual analog scale ratings of either the affective or the sensory dimension of dyspnea of about 50% of full scale (first reached). The resulting value was used during the subsequent visits, without any adjustment.

Carbon dioxide stimulation with restricted ventilation (CO_2-rv). To elicit dyspnea predominantly of the air hunger type we used CO_2 stimulation with restricted ventilation (CO_2-rv)[procedure adapted from 2]. The participants were placed under mechanical ventilation via a face mask (Siemens Servo 900C ventilator, Solna, Sweden) set in volume-controlled mode with a 2 cmH_2O positive end-expiratory pressure. The participants were told to remain as passive as possible during mechanical ventilation, The ventilator settings were first aligned on the participants' breathing frequency, tidal volume and inspiratory time (measured beforehand during unimpeded resting breathing with the subjects wearing a nose clip and breathing through a mouthpiece connected to a pneumotachograph). If necessary, adjustments were made until the participants reported being fully comfortable with the ventilator. Ventilator settings were then frozen, and the trigger of the ventilator was set to minimize the possibility of participants triggering additional breaths. To induce air hunger, 99.9% CO_2 (Air Liquide Santé, France) was instiled into the inspiratory limb of the breathing circuit, FIO_2 being set at 50% to avoid any contribution of hypoxia to air hunger. During the familiarization procedure performed at Visit 1, CO_2 administration was adjusted to to produce visual analog scale ratings of either the affective or the sensory dimension of dyspnea of about 50% of full scale (first reached). The resulting setting was used during the subsequent visits, without any adjustment.

ES1-C. MEDICAL HYPNOSIS PROTOCOL AND SCRIPT

The hypnosis script was first drafted by the main investigator of the study (CMP) and subsequently revised by the other two hypnotherapists involved in the study (CAC, AB) and by two external experts (Prof. Marie-Elisabeth Faymonville, university of Liège, Belgium ; Dr Jean-Marc Benhaiem, responsible for the French national certification in medical hypnosis Paris, France). The script followed the following sequence.

1) Induction

'Focus on a point in the room, wherever you want. You have nothing to do other than to focus on this point. You may feel your eyelids getting heavy. This is completely normal. If you want you can close your eyes. You can feel your muscles relaxing progressively. You can feel your weight on the armchair, your back is comfortable, your head is relaxed on the cushion, your breathing is gentle and is slowing down, you can feel the air come into your mouth and go right to the depths of your lungs.'

2) Deepening (counting from 1 to 10)

'I'm going to count from 1 to 10, and as I count all the tension that remains in your body is going to disappear. 1 to 10. All muscle tension has gone. Now you feel relaxed. You may feel a soft warmth around you. You can now indicate your breathing sensations using the scales…'

3) Neutral suggestion

'Now I'm going to ask you to choose a place you find relaxing, a place where you feel at ease. It can be outside or inside, real or imaginary. Once you've chosen your place, let me know by raising your little finger. You're going to be able to enjoy this place, to observe it, go for a walk there if you like, realize how good you feel there. You can feel all the colors, the sounds, the noises, the odors. You are enjoying this moment, the calm, with no effort needed, you are savoring the moment, you want it to go on. It's satisfying to feel this good…'

Of note, the investigator continued to speak during the deepening and suggestion phases, adapting the exact words for each subject.

4) Coming out of the hypnotic state

'Now, when you feel ready, you're going to come back to us in the laboratory.'

ES1-D. REAL-TIME BIDIMENSIONAL EVALUATION OF DYSPNEA: RATING INSTRUCTIONS

The rating instructions were as follows. For the sensory visual analog scale (S-VAS), the participants were told to rate zero –"no sensation"– if they did not perceive any respiratory sensation considered to differ from what they considered normal ("*rate zero if you do not perceive anything particular with your breathing*" –in French "*cotez zéro si vous n'éprouver aucune sensation respiratoire particulière*"–) and to rate ten if the sensation was as strong as they could imagine –"maximal imaginable sensation"– ("rate 10 if what you perceive corresponds to the maximal such sensation that you can imagine" –in French "*cotez 10 si la sensation respiratoire que vous éprouvez correspond à ce que vous pouvez imaginer de plus fort*"–). For the affective visual analogue scale (A-VAS) the participants were told to rate zero –"no discomfort"– if their breathing was not the source of any discomfort ("*rate zero if your breathing is not uncomfortable at all*" –in French "*cotez zéro si votre respiration ne vous crée aucune gêne, aucun inconfort*"–) and 10 –"maximal discomfort" for the maximal imaginable intensity of breathing

discomfort ("*rate 10 if what you feel corresponds to the maximal or worst respiratory discomfort that you can imagine*" –in French "*cotez 10 si l'inconfort respiratoire / la gêne respiratoire que vous éprouvez correspond à ce que vous pouvez imaginer de pire*"–).

ES1-E. MULTIDIMENSIONAL DYSPNEA PROFILE (MDP) ITEMS

The MDP consists of 11 items, each evaluating dyspnea on a 0-10 scale for unpleasantness (A1 score, 1 item, from 0 'neutral' to 10 'unbearable'), sensory qualities (SQ score, five items [maximum score of 50]: 'my breathing requires muscle work or effort'; 'I am smothering or I feel hunger for air'; 'my chest and lungs feel tight or constricted'; 'my breathing requires mental effort or concentration'; 'I am breathing a lot'), and emotional qualities (A2 score, five items [maximum score of 50]: depressed, anxious, frustrated, angry, anxious).

ES1-F. TECHNICAL DETAILS FOR PHYSIOLOGICAL MEASUREMENTS

During each procedure (ITL or CO_2-rv), participants breathed either through a mouthpiece (ITL) or a face mask (CO_2-rv). The following variables were measured or calculated. Airway opening pressure (Pao) was measured with a differential pressure transducer (±100 cmH_2O, Validyne, Northridge, CA, USA). Ventilatory flow (V') was measured using a low resistance pneumotachograph linear from 0 to 160 L/min (Hans Rudolph série 3700, Kansas City, MO, USA), connected to a linear differential pressure transducer (±5 cmH_2O, Validyne, Northridge, CA, USA) giving access to tidal volume (V_T) after integration of flow. Inspiratory time (T_I), expiratory time (T_E), total time (T_{TOT}), breathing frequency (f_B), mean inspiratory flow (V_T/T_I), duty cycle (T_I / T_{TOT}), and Pao pressure time product (PTP) were obtained by post-hoc signal analysis. End-tidal carbon dioxide partial pressure in the expired gas ($P_{ET}CO_2$) was measured at a lateral port of the mouthpiece or mask with an infrared CO_2 analyzer (Servomex 1505, Plaine Seine Saint-Denis, France). All respiratory signals were recorded by an analog-digital converter (Powerlab, AD Instruments, Castle Hill, Australia; sampling rate 40 Hz) and analyzed with Chart software (Chart 7.3, AD Instruments, Castle Hill, Australia). Heart frequency (HF) was determined from the RR interval and the galvanic skin response (GSR) was measured with digital sensors connected to a dedicated low voltage amplifier (GSRAmp, ADInstrument, Castle Hill, Australia).

ES1-G. DETAILED DESCRIPTION OF EEG PROCESSING

Firstly, to identify nonspecific changes in brain cortical connectivity, we followed a previously described Riemannian matrix covariance analysis and applied an in-house classification algorithm to discriminate experimental conditions according to brain activity using a semi-supervised approach [3-7]. The EEG signals from each electrode were first segmented in 5-second sliding windows with a 50% overlap and band-pass filtered to enhance motor cortical activity (8-24 Hz). Artefacts were automatically removed using outlier identification. To identify changes in brain activity between conditions, reference prototypes were defined during the first 20% of a given period. This learning phase was followed by a detection phase during which the covariance matrices calculated during the two compared periods were confronted with the reference prototypes. The corresponding distance was plotted against time and compared with a rejection threshold beyond which the EEG covariance becomes statistically different from the reference value, indicating a change in brain activity. Finally, the classification performance was evaluated by a cross-validation process. The reference period of one of the conditions was divided into 10 equal parts and comparisons between nine of these parts and the data from the other condition was repeated nine times to take all combinations into account. This allowed the plotting

of receiver operating characteristic (ROC) curves, of which the areas under the curve (AUC) describe the performance of the classifier to detect a change in brain activity. An AUC of 1 indicates perfect discrimination, 0.5 indicates random discrimination, and an AUC of 0.7 or more is considered as indicating satisfactory discrimination. Secondly, to identify respiratory-specific preinspiratory potentials (PIPs), we used a previously described event-related approach [1, 6, 8, 9]. EEG recordings were segmented in 2-second windows (1500 ms before to 500 ms after the beginning of inspiration identified the PAO signal –start of the negative pressure swing–). After elimination of segments with EEG artefacts (EEG activity exceeding 20% of the baseline background signal), 70-100 segments were ensemble averaged. On the averaged plot, a pre-inspiratory potential was considered to be present when a linear relationship with a slope greater than 0.5 microvolts.s^{-1} statistically significantly different from 0 (F-test for equality of variance) was identified over the 1.5 s preceding inspiration and when the absolute maximum value during this period did not exceed 25 microvolts (suggestive of artefact). See figure 1 in [1].

ES1-H. DETAILED DESCRIPTION OF STATISTICAL ANALYSIS

The minute-by-minute S-VAS and A-VAS data were strongly non-Gaussian, because of a large number of zero values during the hypnosis intervention period. This precluded the use of two-way analysis of variance (ANOVA). We therefore analyzed S-VAS and A-VAS differences (ΔVAS) between hypnosis and visual distraction at each minute using a non-parametric approach (Wilcoxon paired tests). Holm's adjustment was applied to the P-values of the tests at the fifth minute across the six 5-minute blocks. Because the distribution of hypnosis-visual distraction differences were mostly Gaussian and the differences tended to increase linearly over time, we corroborated the above approach in a global fashion by implementing linear mixed models of the form $Y^k_i = a\,t^k + b + C_i + W^k_i$ (y^k_i=ΔVAS of subject i at time t^k, a=the slope of the ΔVAS increase with time –fixed effect factor–, b=the fixed intercept, C_i=zero mean random intercept modeling the subject effect, and W^k_i=zero mean error term). The mixed models were fitted using the maximum likelihood method. Holm's adjustment was applied to P-values of the fixed slopes and intercepts for each VAS across the six 5-minute blocks.

For the other data, we first compared inspiratory pressure values (ITL) and $PETCO_2$ values over time (one-way ANOVA for repeated measures, after verification of normality [Shapiro-Wilk's test] and equality of variances [Levene's test]). The various outcomes were compared using a two-way ANOVA with a time factor (reference, intervention, washout) and a condition factor (hypnosis, visual distraction), except for GSR that was compared using Friedman's test because of non-normality. The procedure was performed separately for ITL and CO_2, and the respective effects were not compared. Correlations between differences in VAS ratings and SHSS were studied with Spearman's test. $P<0.05$ was considered statistically significant.

In the absence of prior data that would have allowed a sample size estimate, a convenience sample of 20 participants (10 women and 10 men) was planned.

Statistical analyses were conducted with MATLAB Version 9.7.0.1261785 and its Statistics and Machine Learning Toolbox Version 11.6 (R2019b). Data are described as median and interquartile interval.

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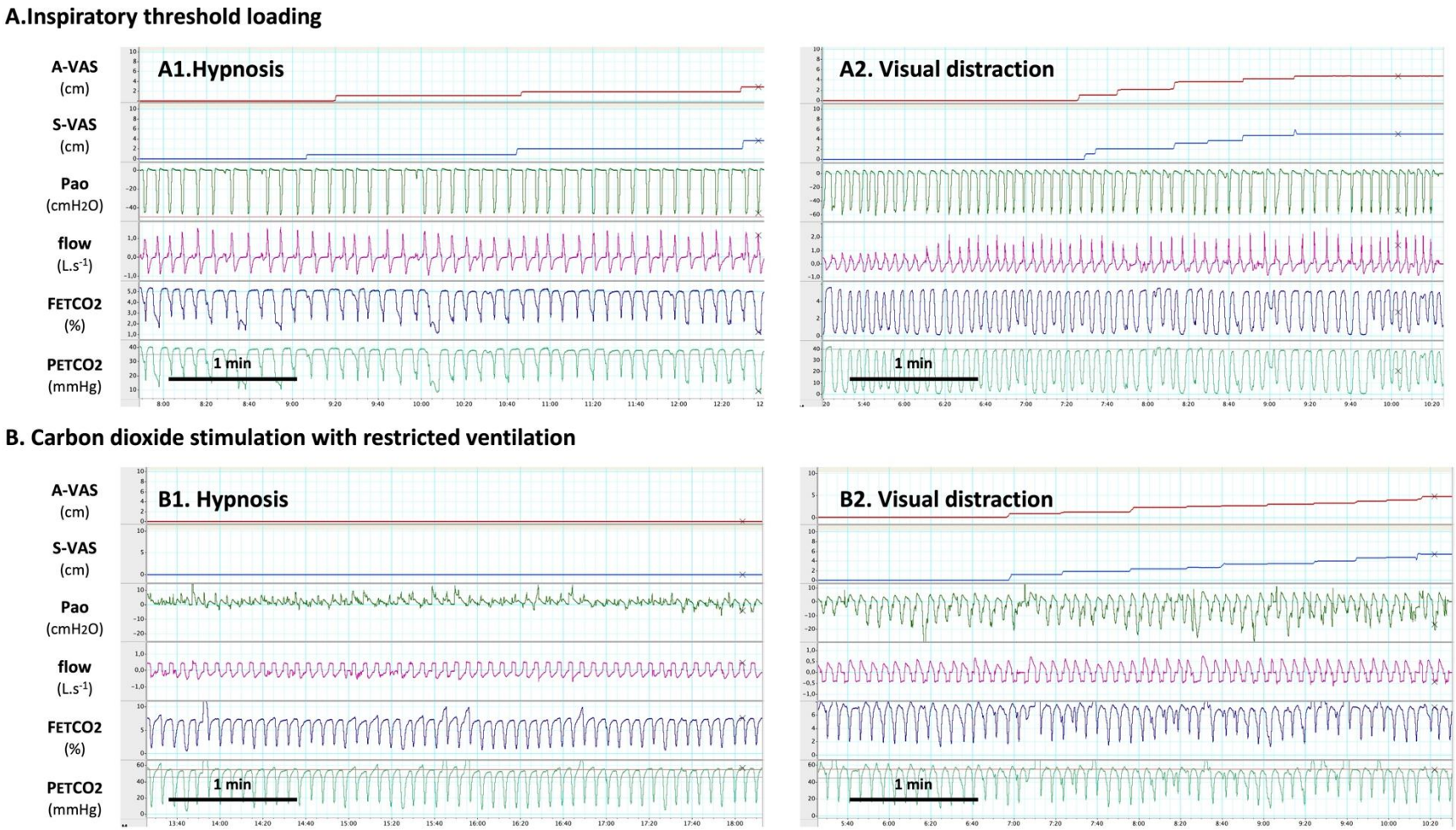
ES2 – Figure S1

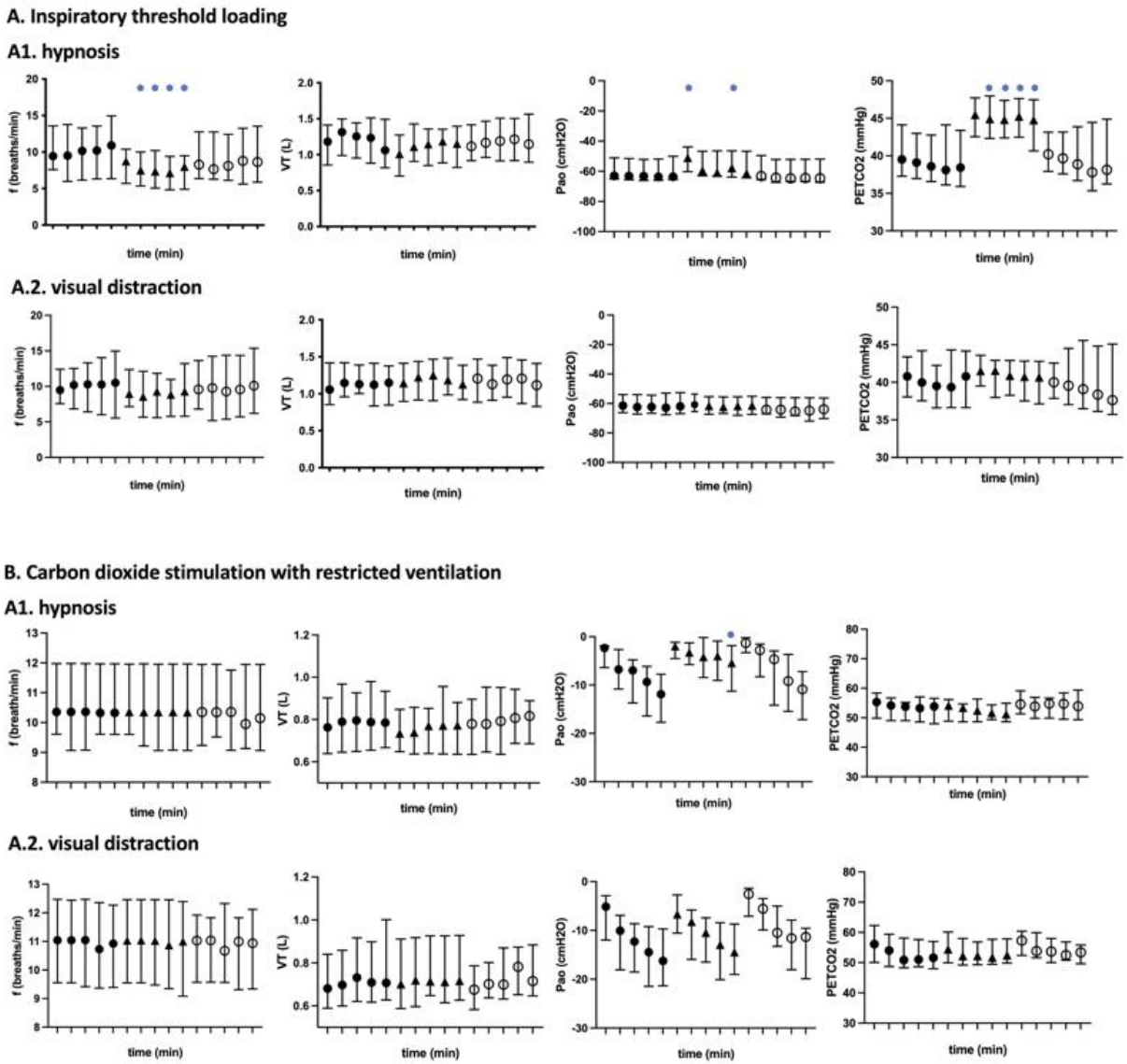
Individual examples of the responses to inspiratory threshold loading (A) during medical hypnosis (A1) and visual distraction (A2) **and to carbon dioxide stimulation with restricted ventilation** (B) during medical hypnosis (B1) and visual distraction (B2).

A-VAS:
affective dimension of dyspnea visual analog scale;
S-VAS : sensory dimention of dysnpea visual analog scale;
Pao, airway opening pressure;
$P_{ET}CO_2$, carbon dioxide end-tidal expired fraction.
$P_{ET}CO_2$, carbon dioxide end-tidal expired partial pressure.



ES3 – Figure S2

Ventilatory responses to inspiratory threshold loading (A) during medical hypnosis (A1) and visual distraction (A2) **and to carbon dioxide stimulation with restricted ventilation** (B) during medical hypnosis (B1) and visual distraction (B2).



f, breathing frequency;
VT, tidal volume;
Pao, airway opening pressure;
PETCO2, carbon dioxide end-tidal partial pressure.

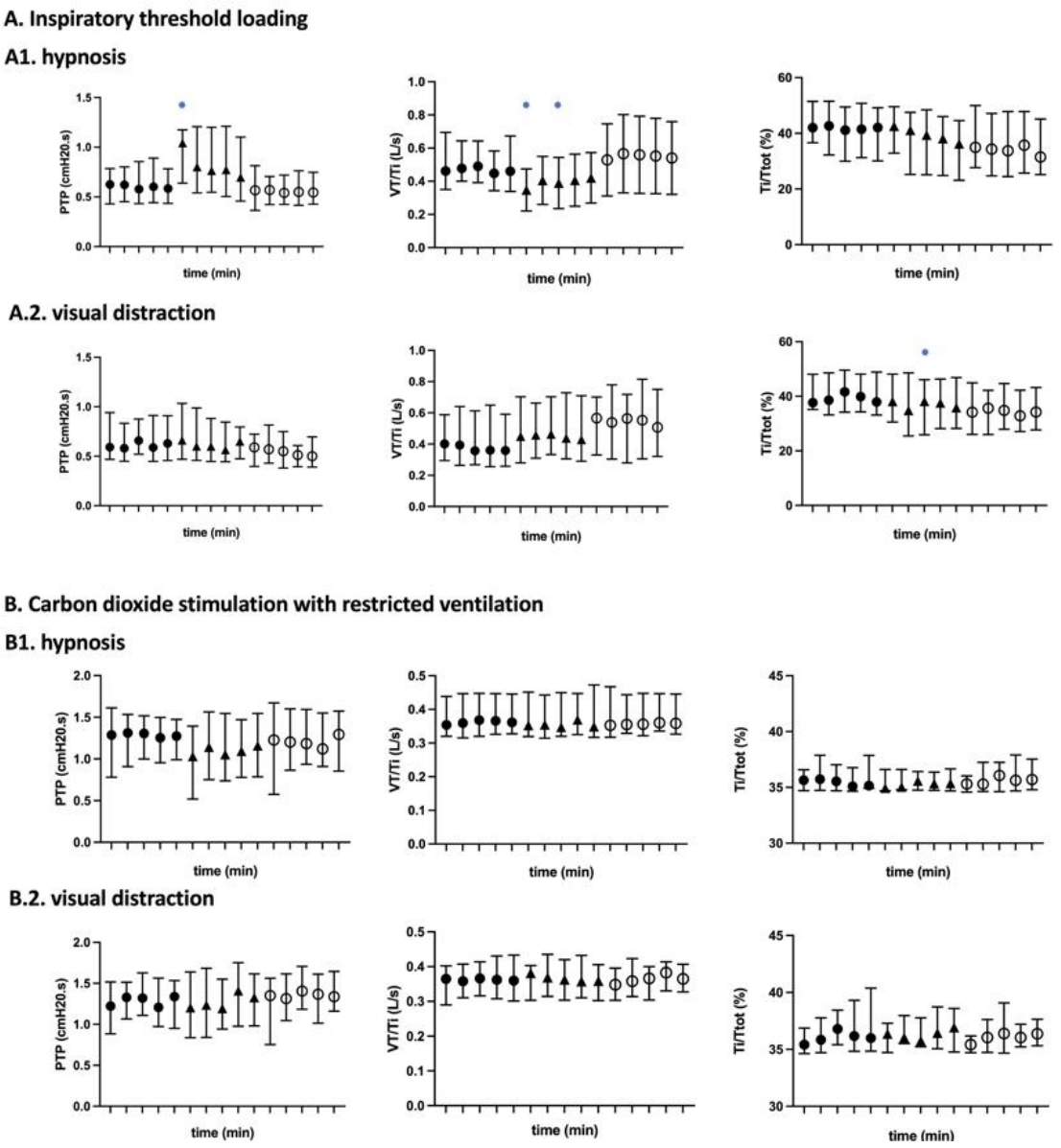
Closed circles: reference period;
Closed triangles: intervention period (either medi hypnosis or visual distraction);
Open circles: washout period.

The data are provided as medians and interquartile

*: $p<0.05$

ES4 – Figure S3

Pressure time product, mean inspiratory flow and duty cycle responses to inspiratory threshold loading (A) during medical hypnosis (A1) and visual distraction (A2) **and to carbon dioxide stimulation with restricted ventilation** (B) during medical hypnosis (B1) and visual distraction (B2).



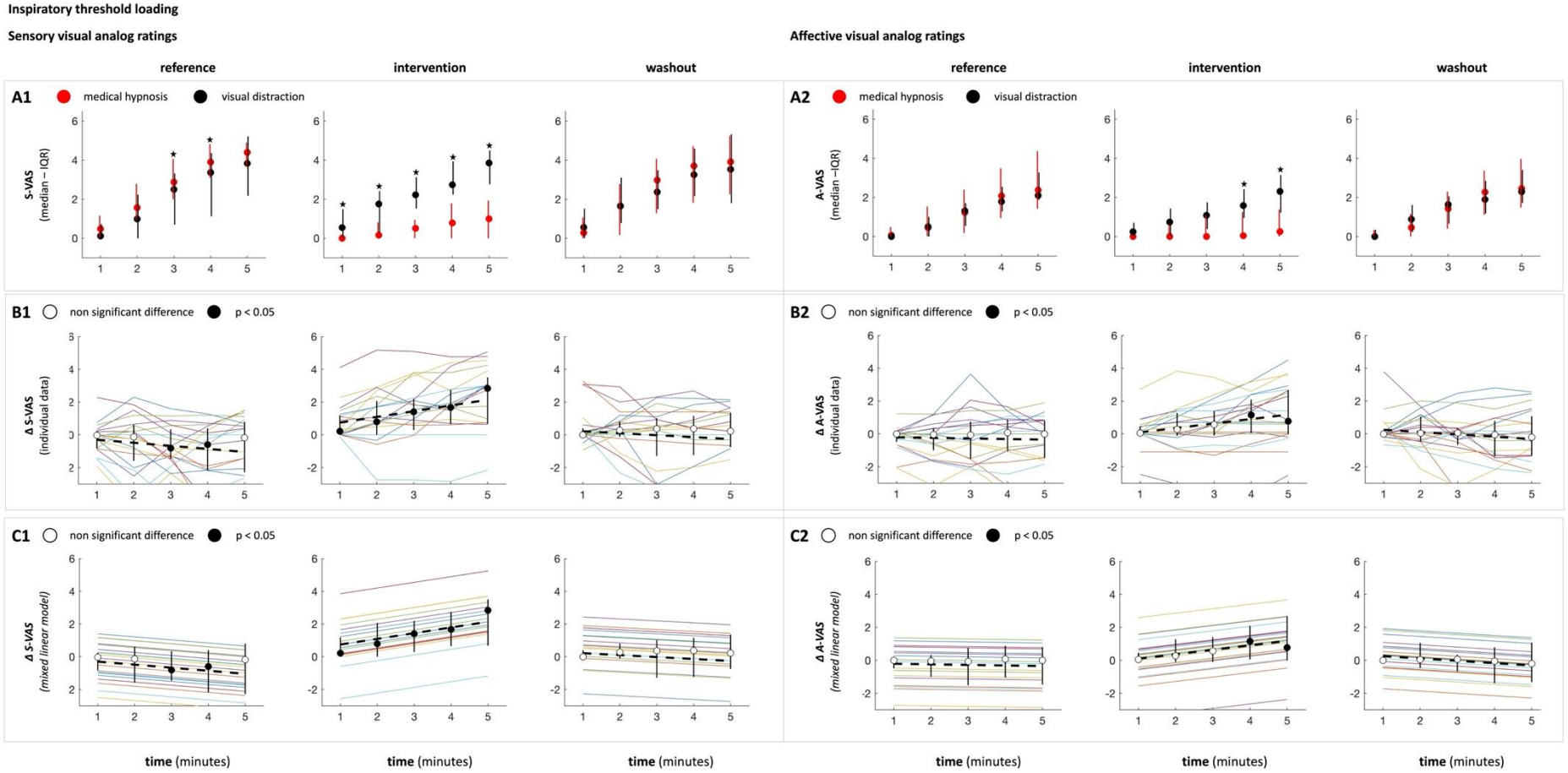
PTP, pressure time product;
VT/TI, mean inspiratory flow;
TI /Ttot, airway opening pressure;

Closed circles: reference period;
Closed triangles: intervention period (either medi
hypnosis or visual distraction);
Open circles: washout period.

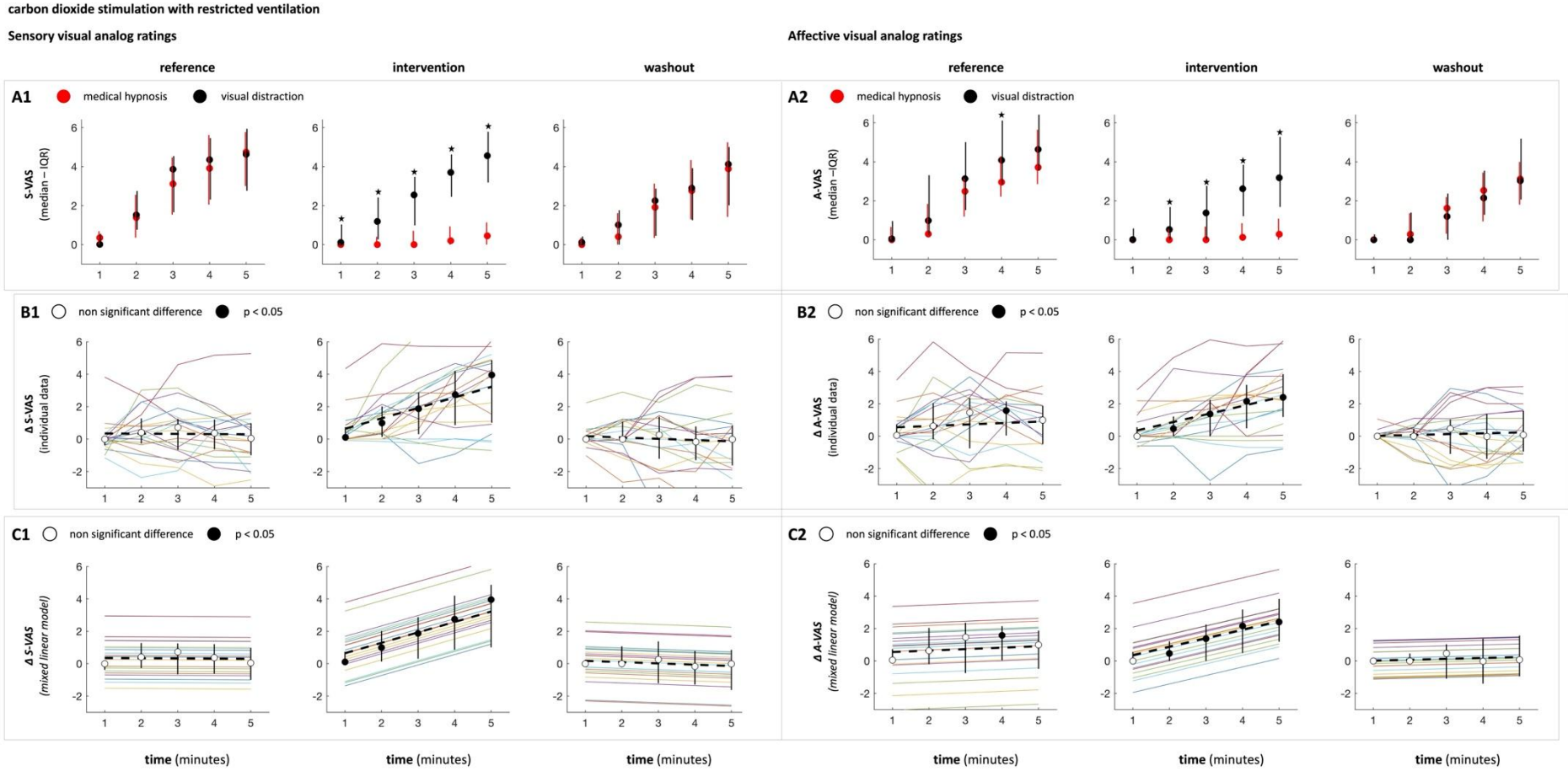
The data are provided as medians and interquartile

*: $p<0.05$

ES5 – Figure S4. Dyspnea responses to inspiratory threshold loading (left: sensory visual analog ratings, S-VAS; right: affective visual analog ratings, A-VAS). **A1-A2**: Median-interquartile range for S-VAS and A-VAS (red circles: medical hypnosis; black circles: visual distraction; *: p<0.05 beween medical hypnosis and visual distraction). **B1-B2**: Median-interquartile range for the medical hypnosis-visual distraction difference (open circles: not significant; black circles: p<0.05) with individual behaviors.**C1-C2**: Median-interquartile range for the medical hypnosis-visual distraction difference (open circles: not significant; black circles: p<0.05) with results of the mixed model analysis (see Methods).



ES6 – Figure S5. Dyspnea responses to carbon dioxide stimulation with ventilatory restriction (left: sensory visual analog ratings, S-VAS; right: affective visual analog ratings, A-VAS)**. A1-A2**: Median-interquartile range for S-VAS and A-VAS (red circles: medical hypnosis; black circles: visual distraction; *: p<0.05 beween medical hypnosis and visual distraction). **B1-B2**: Median-interquartile range for the medical hypnosis-visual distraction difference (open circles: not significant; black circles: p<0.05) with individual behaviors.**C1-C2**: Median-interquartile range for the medical hypnosis-visual distraction difference (open circles: not significant; black circles: p<0.05) with results of the mixed model analysis (see Methods).



ES7 – Table S1. Multidimensional Dyspnea Profile individual items

Inspiratory threshold loading (ITL)						
	Pre hypnosis	Per hypnosis	Post hypnosis	Pre visual distraction	Per visual distraction	Post visual distraction
SQ1	**6.5 [5-8.75]**	**5 [3-6]**	6 [5.25-7]	6 [5-7.5]	6 [4-7]	6 [4-7.75]
SQ2	2 [1-5.75]	1 [0-3]	3 [0--3.75]	2 [0-3]	1.5 [0-3.75]	2 [0-5.5]
SQ3	1.5 [025-3.75]	0.5 [0-2]	1 [0-3.75]	1 [0-4]	1 [0-3]	1 [0-4.75]
SQ4	**5 [3.25-6]**	**2 [1-4]**	4 [3-6]	3.5 [2-7]	3 [2-5]	4 [1.25-6]
SQ5	**4.5 [2-6]**	**1.5 [0.25-3.75]***	4.5 [2-6]	4.5 [2-7]	4 [2-6]	4 [2-7]
depression	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]
anxiety	2 [0-3.75]	0 [0-1]	1 [0-2.75]	1 [0-3]	0.5 [0-2]	1 [0-2.75]
frustration	**3 [0-5.75]**	**0 [0-1]**	2 [0-4]	1 [0-3]	0.5 [0-2.75]	1.5 [0-3.75]
anger	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]
fear	0 [0-0.75]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]

Carbon dioxide stimulation with restricted ventilation (CO_2)						
	Pre hypnosis	Per hypnosis	Post hypnosis	Pre visual distraction	Per visual distraction	Post visual distraction
SQ1	0 [0-2]	0 [0-1.75]	0 [0-2]	1.5 [0-4.75]	2 [0-4.5]	1 [0-3.75]
SQ2	**7 [5.25-8]**	**2.5 [1-4.5]***	5 [3-8]**	6.5 [5-8.75]	6 [4.25-8]	6 [4-7.75]
SQ3	1 [0-3.75]	0 [0-0.75]	0 [0-2]	1 [0-4]	0.5 [0-3.5]	0.5 [0-4]
SQ4	**4 [2-7]**	**0 [0-2] ***	2 [0-3.75]	3.5 [0.25-6]	3 [2-6.75]	3 [0.25-6]
SQ5	3 [0-5]	0 [0-2]	1 [0-3]	2 [0-5]	3 [0-5.75]	2.5 [0-5.75]
depression	0 [0-0.75]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]
anxiety	**4 [3-6.5]**	**0 [0-1] ***	3 [0.25-5.75] **	3.5 [1-6.75]	3 [2-5.75]	3 [1.25-6.75]
frustration	2.5 [0-4]	0 [0-1]	2 [0-3.75]	3.5 [0.25-5]	3 [0-5]	3 [0-5.75]
anger	0 [0-2]	0 [0-0]	0 [0-0.75]	0 [0-0]	0 [0-0]	0 [0-0]
fear	0 [0-1]	0 [0-0]	0 [0-0]	1 [0-3.75]	0 [0-2.5]	0 [0-3.5]

Data are provided as median and interquartile range.
Values in bold typeface indicate $p<0.05$ between pre-hypnosis and per-hypnosis ; "*": $p<0.05$ between hypnosis and visual distraction ; "**": $p<0.05$ between per-hypnosis and post-hypnosis; SQ, sensory qualifiers; SQ1: My breathing requires muscle work or effort.; SQ2: I am not getting enough air or I am smothering or I feel hunger for air; SQ3: My chest and lungs feel tight or constricted.; SQ4: My breathing requires mental effort or concentration; SQ5: I am breathing a lot.

ES8– DETAILED EEG RESULTS

EEG data were technically interpretable in 15 out of 20 participants during inspiratory threshold loading and 14 during carbon dioxide stimulation.

Nonspecific changes in brain cortical connectivity.

In response to inspiratory threshold loading in the visual distraction session of the study, the Riemannian classification provided adequate discrimination between the reference and the intervention in 12 of 15 participants, with a median area under the ROC curve describing the performance of the classification of 0.82 [0.73-0.87]), vs. 11 participants during the medical hypnosis session (0.83 [0.73-0.88]). There were no statistically significant differences between these results, indicating that both interventions consistently modified brain activity. The Riemannian classification failed to differentiate the intervention periods and the corresponding washout periods, suggesting long-lasting brain effects in spite of the return to a physiological behavior and psychophysiological responses similar to those observed during the reference period (Figures 2 and 3, Figures ES2, ES3, ES4 and ES5).

In response to carbon dioxide stimulation with restricted ventilation during the visual distraction session of the study a very similar pattern was observed: the Riemannian classification provided adequate discrimination between the reference period and the intervention period in 11 of 14 participants (area under the curve 0.81 [0.74-0.91]), vs. 10 of 14 participants during the medical hypnosis session (0.77 [0.69-0.87]). The same effect persistence was observed.

Respiratory-specific preinspiratory potentials (PIPs).

In response to inspiratory threshold loading during the visual distraction session, PIPs were present in 9 participants during the reference period, 7 during the intervention period, and 8 during the washout period. No difference in PIPs morphology and amplitude could be distinguished. During the medical hypnosis session, PIPs were present in 11 participants during the reference period, 9 during the intervention period, and 11 during the washout period. In 50% of the participants, the PIPs appeared attenuated during the intervention period (see embedded figure below).

In response to carbon dioxide stimulation with restricted ventilation during, PIPs lacked with the exception of some sporadic detections, as expected from the literature.

Example, in one participant, of preinspiratory potentials recorded in the Cz scalp EEG derivation during inspiratory threshold loading (from top to bottom, reference period, medical hypnosis, and washout). The blue lines mark the signal baseline, the red lines mark the preinspiratory potentials. It can be seen that the amplitude lf the preinspiratory potential is markedly attenuated during the medical hypnosis period, where the subsequent motor potential, visibile durint the reference and the washout periods, is lacking.