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► To cite this version:

Capucine Morélot-Panzini, Cécile Arveiller-Carvalho, Isabelle Rivals, Nicolas Wattiez, Sophie Lavault, et al.. Medical hypnosis mitigates laboratory dyspnoea in healthy humans: a randomised, controlled experimental trial. *European Respiratory Journal*, 2024, pp.2400485. 10.1183/13993003.00485-2024 . hal-04646889

HAL Id: hal-04646889

<https://hal.science/hal-04646889>

Submitted on 12 Jul 2024

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Early View

Original Research Article

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Please cite this article as: Morélot-Panzini C, Arveiller-Carvallo C, Rivals I, *et al.* Medical hypnosis mitigates laboratory dyspnoea in healthy humans: a randomised, controlled experimental trial. *Eur Respir J* 2024; in press (<https://doi.org/10.1183/13993003.00485-2024>).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

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**Medical hypnosis mitigates laboratory dyspnoea in healthy humans:
a randomised, controlled experimental trial**

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CMP, CAC, SL, AB, MCN, TS: conception or design of the work; acquisition, analysis, or interpretation of data; drafting or revising critically the manuscript for intellectual content; final approval; accountable for all aspects. IR, NW, LS, CS: acquisition, analysis, or interpretation of data; drafting or revising critically for intellectual content; final approval; accountable for all aspects.

Funding:

The study was solely academically funded, and supported by a grant from *Fonds de Recherche en Santé Respiratoire* (FRSR) and *Fondation du Souffle* (FdS) Paris, France. It was also supported by a grant *Legs Poix* from the *Chancellerie de l'Université de Paris* and by the *Association pour le Développement et l'Organisation de la Recherche en Pneumologie* (ADOREPS) Paris, France.

Running head:

Medical hypnosis mitigates experimental dyspnoea

Abstract

Question. Dyspnoea persisting despite treatments of underlying causes requires symptomatic approaches. Medical hypnosis could provide relief without the untoward effects of pharmacological approaches. We addressed this question through experimentally induced dyspnoea in healthy humans (inspiratory threshold loading –excessive inspiratory effort– and carbon dioxide stimulation –air hunger–)

Material and Methods. 20 volunteers (10 women, 21-40) were studied on 4 separate days. The order of the visits was randomised in two steps, firstly "inspiratory threshold loading first" vs. "carbon dioxide first" group (n=10 in each group), secondly "medical hypnosis first" vs. "visual distraction first" subgroup (n = 5 in each subgroup). Each visit comprised three 5-minutes periods (reference, intervention, washout) during which participants used visual analog scales to rate dyspnoea's sensory and affective dimensions and after which they completed the Multidimensional Dyspnea Profile.

Results. Medical hypnosis reduced both dimensions of dyspnoea significantly more than visual distraction (inspiratory threshold loading: sensory reduction after 5 minutes 34% of full VAS vs. 8% –P=0.0042–; affective reduction 17.6% vs. 2.4% –p=0.044–; carbon dioxide; sensory reduction after 5 minutes 36.9% vs 3% –P=0.0015–; affective reduction 29.1% vs 8.7% – P=0.0023–). The Multidimensional Dyspnea Profile showed more marked sensory effects during inspiratory threshold loading and more marked affective effects during carbon dioxide stimulation.

Answer to the question. Medical hypnosis was more effective than visual distraction at attenuating the sensory and affective dimensions of experimentally induced dyspnoea. This provides a strong rationale for clinical studies of hypnosis in persistent dyspnoea patients.

Keywords

Respiratory disease; air hunger; excessive breathing effort; nonpharmacological treatment

Introduction

Dyspnoea is among the most distressing human experiences, even more so than pain, because of the fear of dying inherent to being unable to breathe. Its persistence despite treatments aimed at correcting the underlying causes is common, due to respiratory system damages that are frequently irreversible. The absence of a systematic therapeutic response to persistent dyspnoea [1], in contrast with pain, generates a feeling of helplessness in patients and caregivers, which is exacerbated by the condition being generally under-recognised by those not affected [2, 3]. Providing therapeutic approaches capable of improving persistent dyspnoea is therefore a central medical duty, anchored to compelling moral obligations [4]. Opiates can be effective in this indication, but treatments devoid of their side effects are needed. Several such approaches, pharmacological or otherwise, have been investigated, including furosemide or menthol inhalation [5, 6], trigeminal stimulation with portable fans [7, 8], musical stimulation [8], cognitive behavioral therapies [9], mindfulness [10] or virtual reality based therapy [11].

Medical hypnosis, described as a "*modified state of consciousness resulting from a change in baseline mental activity after an induction procedure and typically experienced at the subjective level as an increase in absorption, focused attention, disattention to extraneous stimuli and a reduction in spontaneous thought*" [12], and defined, in simpler terms, as "*a state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion*" [13], could also be proposed. Indeed, it can alleviate the sensory and affective dimensions of pain [14], most likely through functional changes in brain areas involved in cognitive pain processing [15]. Since pain and dyspnoea share neural pathways within the central nervous system [16, 17], hypnosis could also have positive effects on dyspnoea. A preliminary study in patients with chronic obstructive pulmonary disease (COPD)[18] showed it to be more effective than a control intervention at reducing anxiety and slowing breathing frequency, but not at reducing a unidimensional measure of dyspnoea (Borg scale)[18].

Intepreting the effects of dyspnoea interventions in a clinical context is difficult because of multidimensionality and multifactoriality, hence the interest of laboratory dyspnoea experiments. There is currently no data regarding medical hypnosis in this setting. We therefore designed the present study to test the hypothesis that medical hypnosis would alleviate the affective and sensory dimensions of acute experimental dyspnoea of both the "air hunger" and "sense of excessive breathing effort" types. We also hypothesised that hypnosis effects would

be more marked on dyspnoea's affective dimension and thus more marked for experimental air hunger, more affectively distressing than excessive breathing effort [19].

To test these hypotheses, we conducted a proof of concept study of medical hypnosis in experimental dyspnoea, with visual distraction as a comparator and with subjective and objective assessments of efficacy.

Methods

(Details on specific techniques are provided in the electronic supplement).

Ethics

This was a randomised, cross-over, open-label, controlled study conducted at a single site in Paris, France (NCT02792738). The study protocol was approved by the appropriate ethical body (*Comité de Protection des Personnes Ile-de-France VI, Paris, France*). Participants received detailed information, provided written consent before enrolment, and received a financial incentive after study completion.

Participants

Healthy individuals aged >18 were enrolled. They had no prior experience of physiology experiments or of hypnosis and their hypnotic susceptibility was unknown (*non-inclusion criteria in ESI-A*). During the 48 hours preceding the experiments, the participants were asked to refrain from consuming analgesic and anti-inflammatory medications, alcohol, caffeine, or any psychotropic substances, and to avoid sleep deprivation.

Study protocol

The study comprised an inclusion visit (Visit 1) and four subsequent visits (Visits 2-5) separated by 2-4 days (Figure 1). During Visit 1, the participants' hypnotic susceptibility was tested using the Stanford Hypnosis Sensitivity Scale. The notion of sensory vs. affective dimensions of dyspnoea was explained using a music analogy (sensory dimension: volume of the music listened; affective dimension: agreement/disagreement evoked by the music; "*if you do not like a music, it does not have to be loud to be disagreeable*") and participants were trained to answer the Multidimensional Dyspnea Profile (MDP) [20, 21]. Finally, participants were familiarised with the dyspnoea-inducing procedures, namely inspiratory threshold loading (ITL) and CO₂ stimulation with restricted ventilation (CO₂-rv). During ITL and CO₂-rv familiarisation, we aimed at obtaining VAS ratings of the affective or of the sensory dimension of dyspnoea of about 50% of full scale (see below). During the four subsequent visits, the participants underwent three 5-minute dyspnoea inductions separated by 10 minute intervals according to a "reference", "intervention" and "washout" sequence ("washout" as in

"recovery", not as in "before next session")(Figure 1). The order of the visits was randomised in two steps, firstly "ITL first then CO₂-rv" vs. "CO₂-rv first then ITL" group (n=10 in each group), secondly "medical hypnosis first then visual distraction" vs. "visual distraction first then hypnosis" subgroup (n = 5 in each subgroup). Randomisations were achieved using Microsoft Excel[®].

Procedures

Induction of experimental dyspnoea (details in ES1-B)

During the experiments, participants were seated comfortably in a semi-reclined position with their arms and heads supported.

Inspiratory threshold loading (ITL). To elicit dyspnoea predominantly of the excessive inspiratory effort type, the participants breathed through a spring-loaded threshold valve (Power breathe, UK), adjusted, during familiarisation at Visit 1, to produce visual analog scale (VAS) ratings of either the affective or the sensory dimension of dyspnoea of about 50% of full scale (first reached).

Carbon dioxide stimulation with restricted ventilation. To elicit dyspnoea predominantly of the air hunger type we used CO₂ stimulation with restricted ventilation (CO₂-rv)[procedure adapted from 19]. The participants were placed under mechanical ventilation via a face mask, with a ventilator set in volume-controlled mode and aligned on the participants' resting breathing pattern to provide full breathing comfort. During familiarisation at Visit 1, 99.9% CO₂ was progressively instilled into the inspiratory limb of the breathing circuit to induce air hunger, until a 50% VAS ratings of either the affective or the sensory dimension of dyspnoea of was reached.

Dyspnoea-relieving interventions

Medical Hypnosis. Hypnosis was conducted using a standardised script (*ES1-C*) by physicians certified in medical hypnosis (CAC, AB, CMP). The induction procedure [derived from 22] involved relaxation (the script including "*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*"), binding between the participant and the experimenter, and the establishment of a hypnotic state (considered present when roving eye movements could be observed and the subjects indicated that they felt having reached their "safe place" through a pre-arranged finger movement). This lasted for about 5 minutes, after which the experimental dyspnoea challenge started for 5 minutes, the hypnotic state being maintained throughout the exposition to the dyspnoea-inducing stimulus, the instruction to "come back" being given simultaneously with stimulus removal. Of note, the participants were responsive during the hypnotic phase, as evidenced by

their continuous rating of dyspnoea (see below). Post-hoc electroencephalographic readings confirmed the absence of sleep-related figures.

Visual distraction. Visual distraction consisted in watching an emotionally neutral extract of an animal documentary ('*March of the Penguins*', Luc Jacquet, France, 2005). To mirror the medical hypnosis procedure that included an induction period before the dyspnoea challenge, 5 minutes of viewing during free breathing preceded the 5 minutes of viewing during the dyspnoea challenge.

Psychophysiological measurements

Real-time bidimensional evaluation of dyspnoea. The participants used two separate 10 cm electronic VAS (slide control response meters, AD instruments, Castle Hill, Australia) for sensory rating (S-VAS) and affective rating (A-VAS)(*detailed rating instructions in ESI-D*). They were instructed to move the S-VAS and A-VAS cursors as needed to record any change without any instruction regarding in which order to do so. If they did not move the cursors for one minute, the experimenter prompted them to provide a rating through a pre-arranged arm touch. VAS values were averaged minute by minute.

Post-hoc multidimensional evaluation of dyspnoea. The participants filled out the MDP (*MDP items in ESI-E*) at the end of each dyspnoea induction session (ie, three times at each of Visits 2-5, Figure 1). They focused on the last 30 seconds spent under experimental dyspnoea, and MDP data were analyzed in terms of an "immediate perception response" and an "emotional response domain", in line with pain conceptual models.

Physiological measurements

During each procedure (ITL or CO₂-rv), participants breathed either through a mouthpiece (ITL) or a face mask (CO₂-rv). The following variables were measured or calculated (*technical details in ESI-F*): airway opening pressure (P_{ao}), ventilatory flow (V'), tidal volume (V_T), 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}), P_{ao} pressure time product (PTP), end-tidal carbon dioxide partial pressure in the expired gas (PETCO₂), heart frequency (HF), and galvanic skin response (GSR).

Electroencephalographic recordings (EEG)

EEG acquisition. EEG activity was recorded with eight cap-mounted active electrodes (actiCAP, Brain Products, Germany), placed in Cz, FCz (reference), Fz, AFz (ground), FP1, FP2, A1 et A2. Electrode impedance was maintained below 5 kΩ. Data acquisition used a V-Amp amplifier (Brain Products, Germany). Signals were filtered analogically with a low-pass

value of 0.05 Hz, a high-pass value of 5 Hz, and a band-stop filter centered on 50 Hz. EEG signals were amplified and digitised at 256 Hz and then processed as follows.

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 [23-27] (*detailed EEG processing in ESI-G*). Secondly, we used a previously described event-related approach to identify respiratory-specific preinspiratory potentials (PIPs) [26, 28-30] (See figure 1 in [30], and *ESI-G*).

Outcomes

The primary study outcome was the intensity of breathing discomfort (A-VAS). The sensory intensity of dyspnoea (S-VAS) was a co-primary outcome. Secondary outcomes included Multidimensional Dyspnea Profile, ventilatory variables, heart frequency and galvanic skin response.

Statistical analysis (detailed description in ESI-G)

Statistical analyses were conducted with MATLAB Version 9.7.0.1261785. Data are described as median and interquartile interval. $P < 0.05$ was considered statistically significant. S-VAS and A-VAS differences (Δ VAS) between hypnosis and visual distraction were analyzed minute by minute using repeated Wilcoxon paired tests with Holm's adjustment for multiplicity. This approach was corroborated by implementing linear mixed models fitted using the maximum likelihood method, also with Holm's adjustment of the fixed slopes and intercepts P-values. Physiological data were compared using a two-way ANOVA with a time factor (reference, intervention, washout) and a condition factor (hypnosis, visual distraction). Correlations between differences in VAS ratings and SHSS were studied with Spearman's test. Of note, 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.

Results

Study participants

Twenty healthy adults (10 women, 10 men, age 21-40) completed all 5 visits as planned.

Hypnosis sensitivity

Median [inter-quartile range] Stanford Hypnosis Susceptibility Scale was 5 [3-8] (≥ 8 –high susceptibility–: 8 cases; ≤ 4 –limited susceptibility–: 8 cases). Based on behavioral cues we considered that a hypnotic state was achieved in all participants.

Ventilatory and dyspnoeic Responses to inspiratory threshold loading

During medical hypnosis, breathing frequency decreased significantly, and PETCO₂ increased significantly for the 4 last minutes of the dyspnoea challenge (ES3-Figure S2) suggesting a reduced neural drive to breathe –in line with decreases in peak Pao and mean inspiratory flow (VT/TI)(ES4-Figure S3)–. There was no change in VT, PTP, TI/TTOT(ES3-Figure S2 and ES4-Figure S3). During visual distraction, no significant changes in breathing pattern were observed (ES3-Figure S2 and ES4-Figure S3). ITL consistently induced dyspnoea of the excessive inspiratory effort type. During the reference and washout periods, S-VAS and A-VAS ratings similarly increased over the 5 minutes of loading (Figure 2, ES5-Figure S4). This dynamics was not affected by visual distraction (Figure 2, ES5-Figure S4). In contrast, medical hypnosis significantly mitigated sensory ratings –from the first minute on– and affective ratings –at the 4th and 5th minutes– (Figure 2, Table 1; ES5-Figure S4). There was no significant correlation between dyspnoea attenuation and the Stanford Hypnosis Susceptibility Scale score. The effects of hypnosis did not vary between hypnotherapists. Medical hypnosis significantly decreased the MDP perceptual score (A1+SQ, $p=0.009$) and the MDP affective score (A2, $p=0.002$), both returning to pre-hypnosis levels during washout (Figure 4). MDP changes did not reach statistical significance during visual distraction. There was a significant reduction in the ‘work/effort’ descriptor during medical hypnosis ($p=0.0024$) but not during visual distraction, hence a significant hypnosis-visual distraction difference ($p=0.0034$)(Figure 4, ES8-Table S1).

Responses to carbon dioxide stimulation with restricted ventilation

During both medical hypnosis and visual distraction, no statistically significant changes were noted in breathing frequency, tidal volume, peak Pao, PETCO₂, PTP, VT/TI, or TI/TTOT. Carbon dioxide stimulation consistently induced dyspnoea of the air hunger type. During the reference and washout periods, sensory and affective dyspnoea ratings similarly increased over the 5 minutes of loading (Figure 3, ES6-Figure S5), with, however, a tendency to habituation (Figure 3). This dynamics was not affected by visual distraction (Figure 3, ES6-Figure S5). In contrast, medical hypnosis significantly mitigated sensory ratings and affective ratings from the first minute on (Figure 3, Table 1, ES6-Figure S5). There was no influence of suggestibility or of the hypnotherapist. Medical hypnosis significantly decreased the MDP perceptual score (A1+SQ) ($p<0.0001$) and the MDP affective score (A2) ($p=0.0007$), both scores returning to pre-hypnosis levels during washout (Figure 4). MDP changes did not reach statistical significance during visual distraction. There was a significant reduction in the "air hunger" rating during medical hypnosis ($p<0.0001$) but not during visual distraction, hence a significant hypnosis-visual distraction difference ($p=0.0005$)(Figure 4, ES7-Table S1). The ‘anxiety’

rating decreased significantly following hypnosis ($p < 0.0001$), also with a significant hypnosis-visual distraction difference ($p = 0.0005$). Overall, the effects of medical hypnosis on dyspnoea appeared more marked during CO₂ stimulation than during ITL.

Other physiological variables

Cardiac frequency decreased significantly with time during both dyspnoea-relieving interventions for both dyspnoea challenges. Galvanic skin response did not vary during hypnosis for ITL ($p = 0.73$, but valid signal in only 9 participants), but decreased significantly for CO₂-rv-induced dyspnoea ($p < 0.0001$, but valid signal in only 6 participants).

Electroencephalographic data

EEG data were technically interpretable in 15 participants during ITL and 14 during CO₂-rv. Connectivity changes occurred between the reference and the intervention period in the majority of cases (ITL: 12 participants during visual distraction, 11 during medical hypnosis; CO₂-rv: 11 and 10, respectively), indicating that both interventions modified brain state in some way. In contrast, no changes were detected between intervention and washout, suggesting long-lasting effects. Respiratory specific pre-inspiratory potentials were not significantly affected quantitatively, but appeared attenuated in amplitude during medical hypnosis in half the participants (*see ES8*).

Discussion

This study showed that medical hypnosis can alleviate the sensory and affective dimensions of experimentally induced dyspnoea in healthy humans. This was true in response to two challenges known to induce distinct dyspneic sensory modalities (inspiratory threshold loading/sense of excessive inspiratory effort vs. carbon dioxide stimulation with restricted ventilation/air hunger) and distinct affective responses [19], and to involve different brain networks. The effects of medical hypnosis were more marked for air hunger, with a relief magnitude comparable to that obtained with morphine in a similar setting [31]. Attentional distraction, otherwise reported to have mitigating effects on experimental dyspnoea [32, 33], was not associated to significant dyspnoea relief. In contrast to experimental pain studies [34], there was no relationship between medical hypnosis effects and individual hypnotic sensitivity. Of note, the electroencephalographic recordings performed in our participants did not evidence sleep-related figures during medical hypnosis. They showed that both visual distraction and medical hypnosis were associated with nonspecific brain connectivity changes, indicating that both interventions had an effect at the cortical level but without providing insight regarding the differential impact of the two interventions on dyspnoea. EEG recordings failed to demonstrate

a statistically significant difference regarding the frequency of respiratory specific pre-inspiratory potentials between visual distraction and medical hypnosis, even though these potentials appeared attenuated during medical hypnosis (ES8). One possible explanation for these EEG results could lie in medical hypnosis acting at a brain level (e.g. limbic cortex) not easily accessible to scalp recordings.

Putative mechanisms

Symptomatic interventions that relieve dyspnoea can do so by decreasing the neural drive to breathe (corollary discharge theory [35, 36]) or by altering the central processing of respiratory sensations [8, 36, 37]. In our subjects during ITL there was evidence of breathing drive reduction under medical hypnosis (decreased breathing frequency, increased PETCO₂, ES2-Figure S2; decreased VT/TI, ES3-Figure S3). Hypnosis could thus have acted on the cortical component of the neural drive to breathe associated with ITL [29] and causatively related to clinical dyspnoea in various settings [26, 27, 38]. This was supported in some participants by attenuation of pre-inspiratory potentials. During CO₂-rv, we found no indication of breathing drive reduction during medical hypnosis (ES2-Figure S2; ES3-Figure S3), yet dyspnoea relief was more marked than during ITL. This points at a "processing" type of effect, reminiscent of the effects of medical hypnosis on pain [39]. This is consistent with neuroimaging studies showing that hypnosis modulates the activity and connectivity of a large brain network [40-44] that comprises regions involved in the pathogenesis of dyspnoea, including the anterior cingulate cortex, the right insula, and the supplementary motor area as well as many others [reviewed in 45]. Our EEG results support the role of hypnosis-related brain connectivity changes, but specific brain imaging studies will be necessary to precisely describe the involved networks and possibly devise targeted interventions [46].

Dyspnoea is characteristically associated with anxiety. Yet, therapeutic approaches that relieve anxiety can help dyspneic patients independently of their effect on dyspnoea itself, as shown for hypnosis in patients with chronic obstructive pulmonary disease [18]. The known anxiety-relieving effects of hypnosis [47] were apparent in our study, in the form of a reduction in the corresponding Multidimensional Dyspnea Profile ratings that was most pronounced during CO₂-rv, described as more anxiogenic than inspiratory loading [19]. This observation aligns with the attenuation of the galvanic skin response observed under hypnosis during CO₂-rv but not during ITL.

Strengths, limitations, and questions for future research

A strength of our study was its controlled, cross-over design but the open-label aspect meant that cognitive bias favoring hypnosis over visual distraction was possible. To minimise this

risk, participants were informed that the study aimed "*to compare two interventions possibly relieving dyspnoea*" rather than "*to evaluate the effectiveness of hypnosis*". Additionally, three hypnotherapists were responsible for the hypnosis intervention to further reduce cognitive bias. Other strengths of the study include the incorporation of two models of experimental dyspnoea, the coherence of psychophysiological outcomes and physiological ones, and a dual statistical approach showing consistent results. The main limitation of the study lies in the imperfect representation of clinical dyspnoea by experimental dyspnoea models, with participants knowing the dyspnoea challenges to be time-limited and retaining control over their situation. Another limitation of our study relates to the brevity of the dyspnoea challenges that we used, that did not allow dyspnoea ratings to stabilise over time. In addition, we needed to train our subjects before the actual experiments, and observed that after training we were unable to reproduce the dyspnoea levels initially observed, hence a possible floor effect due to relatively modest dyspnoea ratings at the beginning of the dyspnoea challenge. Of note, we did not characterise our participants regarding trait or state anxiety, which could have modulated the effects of hypnosis. Finally, the size of the study population implies caution, particularly regarding secondary outcomes. However, the magnitude of the effect of hypnosis on VAS ratings exceeded minimal clinically important differences [48-50], suggesting that clinical benefits could be obtained in patients with persistent dyspnoea. However, effect duration, tachyphylaxis, or the level of hypnosis expertise required to obtain an effect cannot be predicted at this stage. These elements will condition practical applicability, and will determine whether particular strategies should be explored, from highly sophisticated ones involving cortical sensitisation [46] to simpler ones such as self-hypnosis, which has proven useful in other situations [51]. It is thus necessary design studies of medical hypnosis in patients with persistent dyspnoea in the real-world, taking care to use multidimensional outcomes [52]. To define optimal indications, such studies will need to explore the role of individual hypnotic susceptibility and the importance of protocols.

Conclusions

In conclusion, we believe that our results provide a solid proof-of-concept to pursue the study of medical hypnosis to manage persistent dyspnoea, noting that empirical clinical studies are appearing [18, 53]. If effective, medical hypnosis would have several advantages, including fast implementation, rapid effects, low cost, and lack of significant risks [see review in 54].

Acknowledgements

Dr Andrew Lane (Lane Medical Writing, France) provided professional medical writing assistance in the preparation of the manuscript in accordance with the European Medical Writers Association guidelines and Good Publication Practice. He was funded by research unit UMRS1158, Inserm-Sorbonne Université, Paris, France.

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Table 1. Comparison of the reductions in dyspnoea ratings by visual distraction and medical hypnosis at the 5th minute of the dyspnoea challenges, showing agreement between the non-parametric and the mixed-model statistical approaches.

	Visual distraction	Medical Hypnosis	Visual Distraction <i>minus</i> Hypnosis*	
			Non parametric model	Linear mixed model
<i>Sensory visual analogue scale (S-VAS)</i>				
ITL	-0.08 [-1.12 — -0.26]	-3.40 [-4.84 — -0.85]	P=0.0042	P=5.6.10 ⁻⁷
CO2	-0.30 [-1.45 — -0.74]	-3.69 [-5.14 — -1.74]	P=0.0015	P=1.6.10 ⁻¹¹
<hr/>				
<i>Affective visual analogue scale (A-VAS)</i>				
ITL	-0.24 [-0.72 — -0.32]	-1.76 [-3.30 — -0.08]	P=0.044	P=5.10 ⁻⁷
CO2	-0.87 [-2.03 — -0.18]	-2.91 [-4.46 — -2.37]	P=0.0023	P=1.6.10 ⁻¹⁰

Figure legends

Figure 1. Diagrammatic summary of the experimental protocol

SHSS: Stanford hypnosis susceptibility scale; S-VAS: sensory dyspnoea visual analogue scale; A-VAS: affective dyspnoea visual analogue scale; ITL: inspiratory threshold loading (predominantly induces 'excessive inspiratory effort'); CO₂: CO₂ stimulation with restriction of the reflex ventilatory response (predominantly induces 'air hunger'); MDP, MultiDimensional Dyspnea Profile.

Figure 2. Visual analog scale dyspnoea ratings in response to 5 minutes of inspiratory threshold loading.

Top row : sensory visual analog scale (S-VAS)

Bottom row: affective visual analog scale (A-VAS)

Red circles, medical hypnosis; black circles, visual distractions; the circles represent median values, with indication of the interquartile range; *: $p < 0.05$ between medical hypnosis and visual distraction.

Figure 3. Visual analog scale dyspnoea ratings in response to 5 minutes of carbon dioxide stimulation with ventilatory restriction.

Top row : sensory visual analog scale (S-VAS)

Bottom row: affective visual analog scale (A-VAS)

Red circles, medical hypnosis; black circles, visual distractions; the circles represent median values, with indication of the interquartile range; *: $p < 0.05$ between medical hypnosis and visual distraction.

Figure 4. Multidimensional Dyspnea Profile (MDP) post-hoc evaluation of dyspnoea in response to inspiratory threshold loading and carbon dioxide stimulation with ventilatory restriction

The participants were asked to focus on the last 30 seconds of the immediately preceding condition.

Panel A: Inspiratory threshold loading

Panel B: Carbon dioxide stimulation with ventilatory restriction

A1, respiratory discomfort; A1+SQ, perceptual score; A2, emotional score.

In each of the three panel, the first three bars correspond to the hypnosis intervention (pre, and post in white, per in black), and the three subsequent bars correspond to the visual distraction intervention (pre and post hatched, per dark grey).

* $p < 0.05$

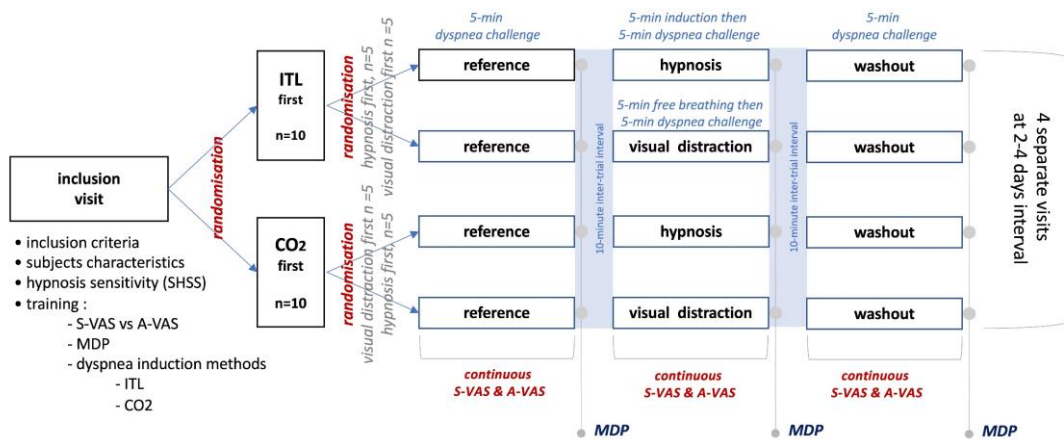


Figure 1

Inspiratory threshold loading

- medical hypnosis
- visual distraction

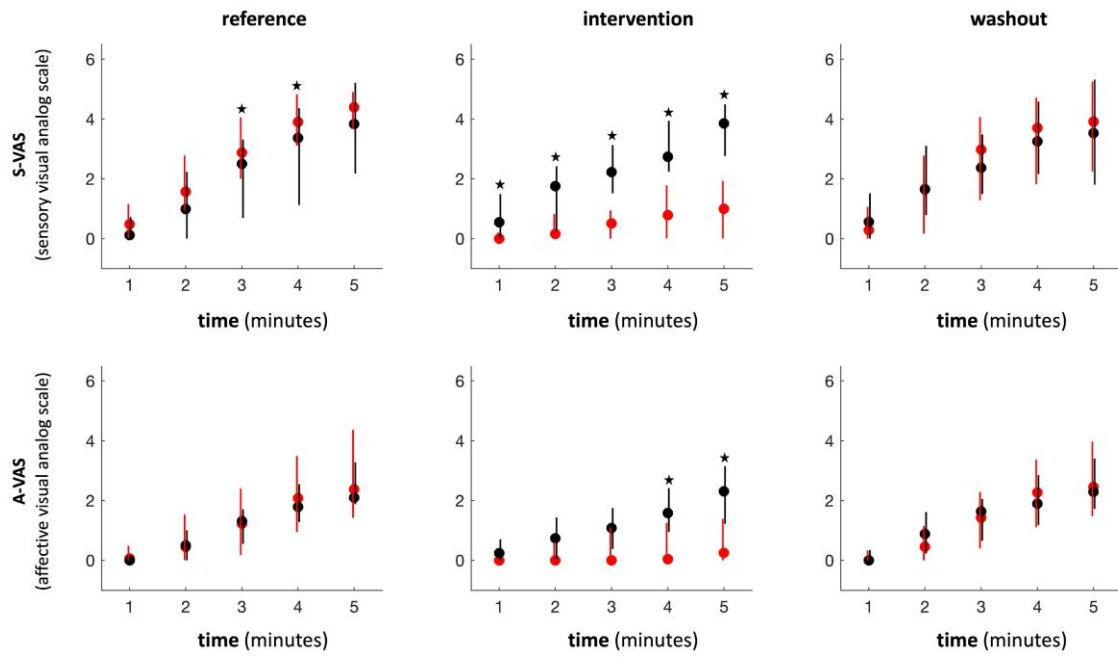


Figure 2

carbon dioxide stimulation with restricted ventilation

- medical hypnosis
- visual distraction

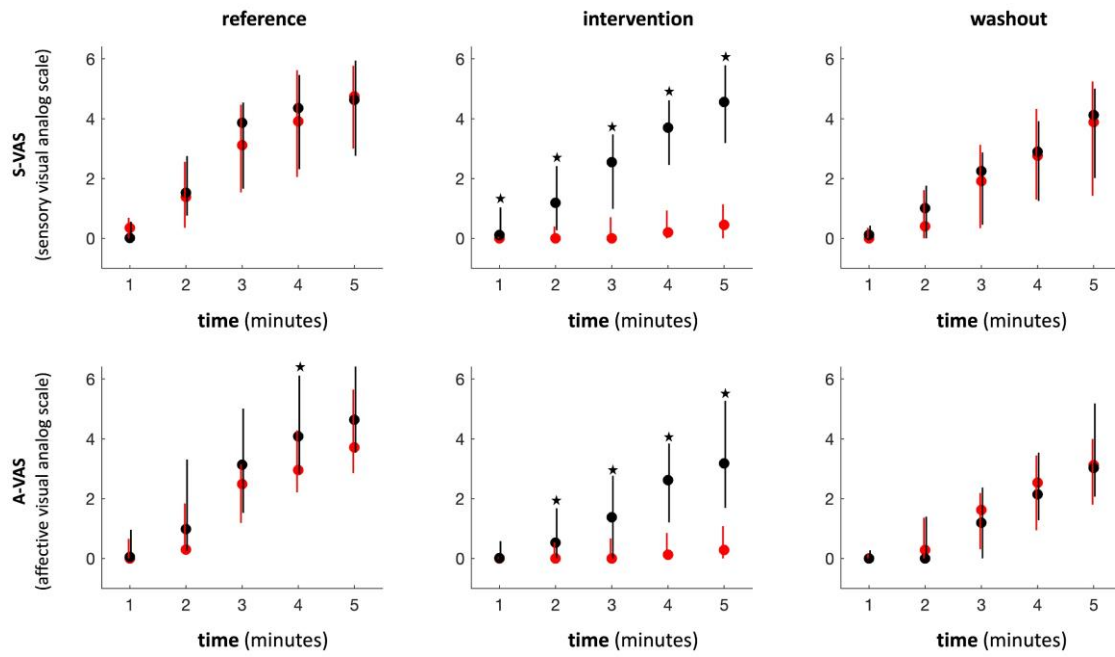
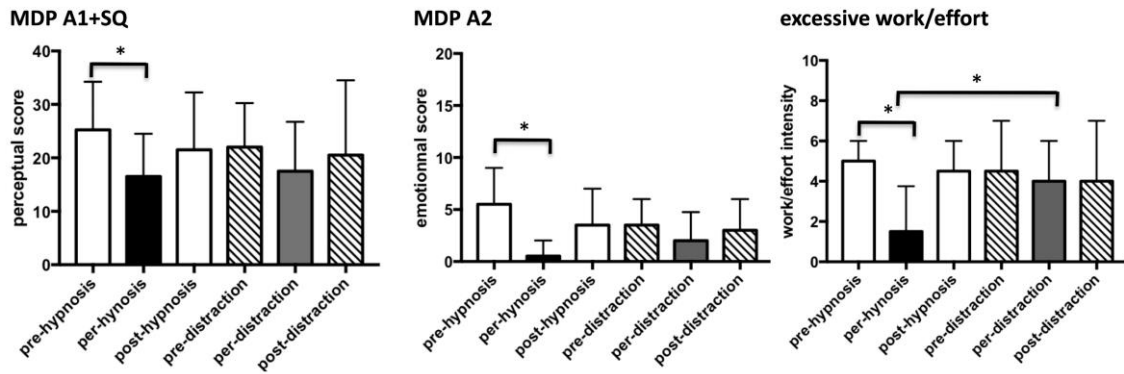


Figure 3

A. Inspiratory threshold loading



B. carbon dioxide stimulation with restricted ventilation

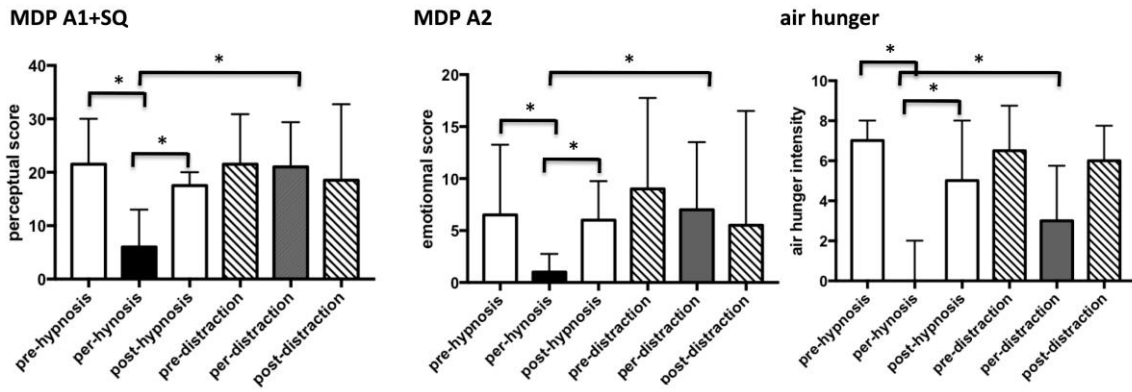
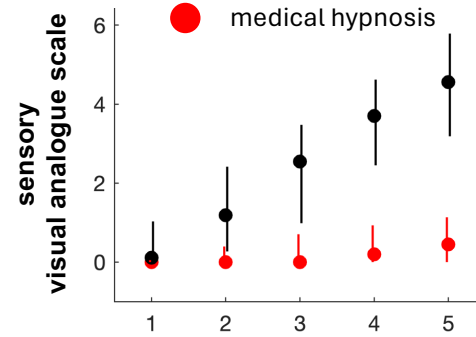
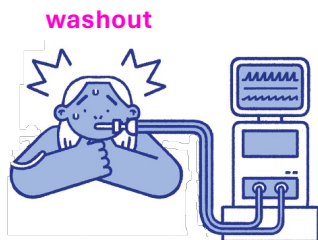
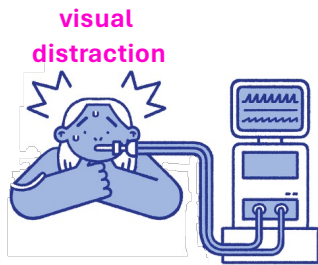
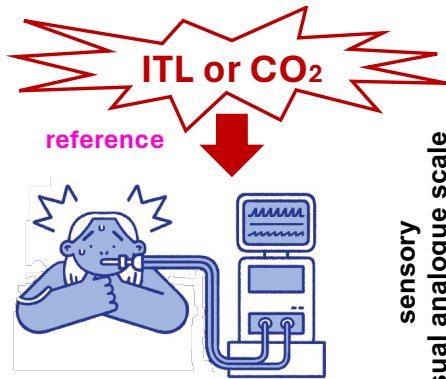


Figure 4

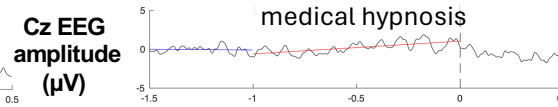
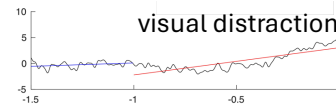
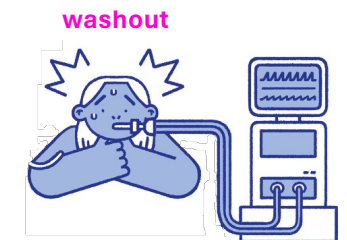
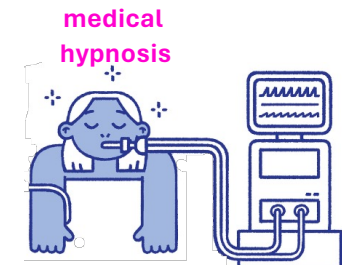
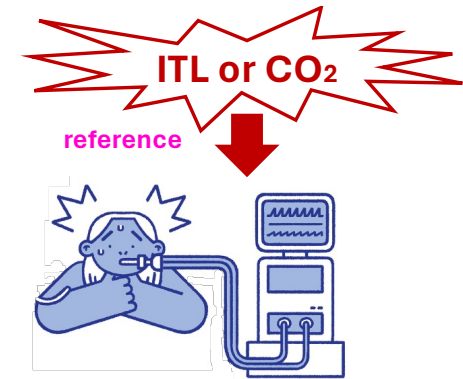
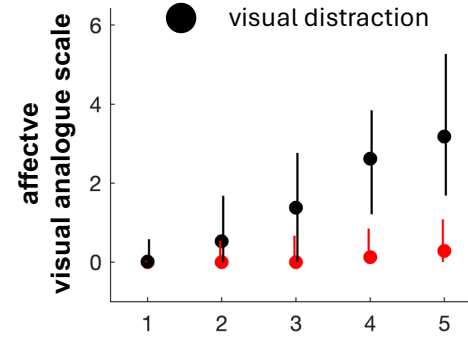
20
healthy
volunteers

experimental
dyspnea
Inspiratory
Threshold Loading
ITL
-
CO₂ stimulation
with restricted
ventilation
CO₂-rv

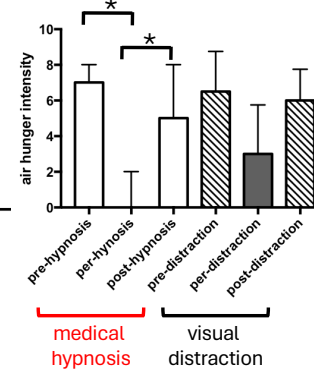
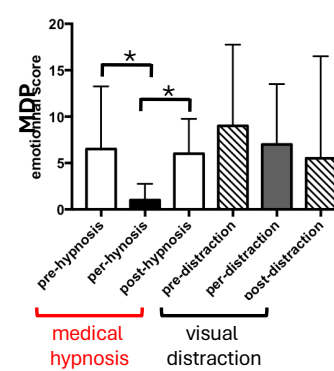
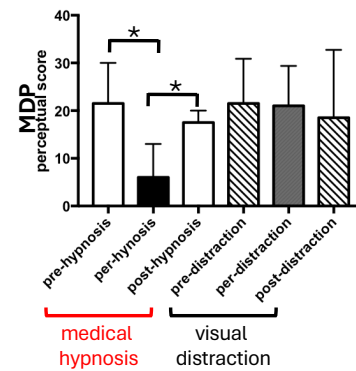
effects of
visual
distraction
vs.
medical
hypnosis



medical hypnosis reduces sensory and affective dyspnea VAS ratings (CO₂-rv)



medical hypnosis interferes with cortical connectivity –preinspiratory potentials (ITL)



medical hypnosis mitigates Multidimensional Dyspnea Profile (MDP) scores (CO₂-rv)

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 (CO₂-rv). To elicit dyspnea predominantly of the air hunger type we used CO₂ stimulation with restricted ventilation (CO₂-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 cmH₂O 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% CO₂ (Air Liquide Santé, France) was instilled into the inspiratory limb of the breathing circuit, FIO₂ being set at 50% to avoid any contribution of hypoxia to air hunger. During the familiarization procedure performed at Visit 1, CO₂ administration was 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 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 CO₂-rv), participants breathed either through a mouthpiece (ITL) or a face mask (CO₂-rv). The following variables were measured or calculated. Airway opening pressure (Pao) was measured with a differential pressure transducer (± 100 cmH₂O, 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 cmH₂O, Validyne, Northridge, CA, USA) giving access to tidal volume (VT) after integration of flow. Inspiratory time (TI), expiratory time (TE), total time (TTOT), breathing frequency (fB), mean inspiratory flow (VT/TI), duty cycle (TI / TTOT), and Pao pressure time product (PTP) were obtained by post-hoc signal analysis. End-tidal carbon dioxide partial pressure in the expired gas (PETCO₂) was measured at a lateral port of the mouthpiece or mask with an infrared CO₂ 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 (Δ VAS) 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 $Y^{k_i} = a t^k + b + C_i + W^{k_i}$ ($y^{k_i} = \Delta$ VAS of subject i at time t^k , a=the slope of the Δ VAS 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 PETCO₂ 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 CO₂, 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:

ffective dimension of dyspnea visual analog scale;

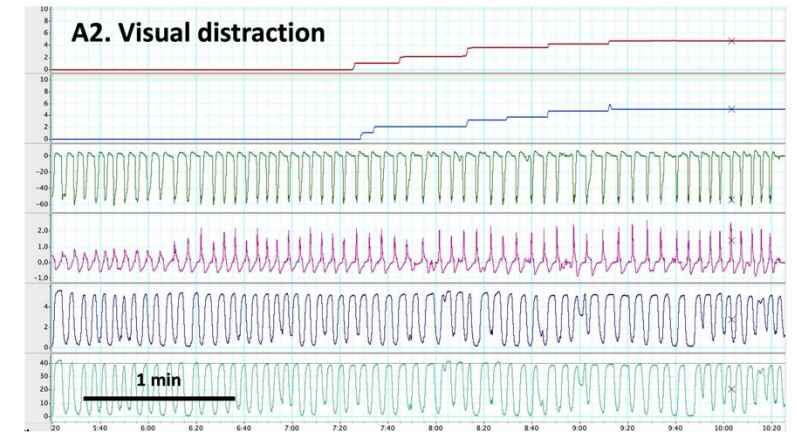
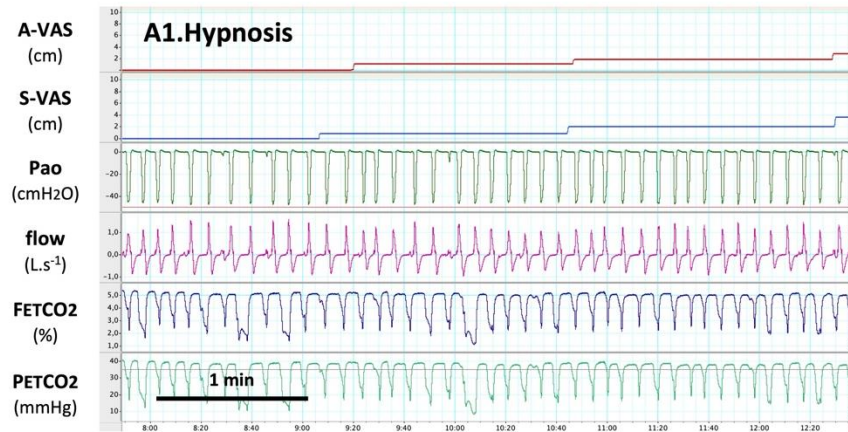
S-VAS : sensory dimension of dyspnea visual analog scale;

Pao, airway opening pressure;

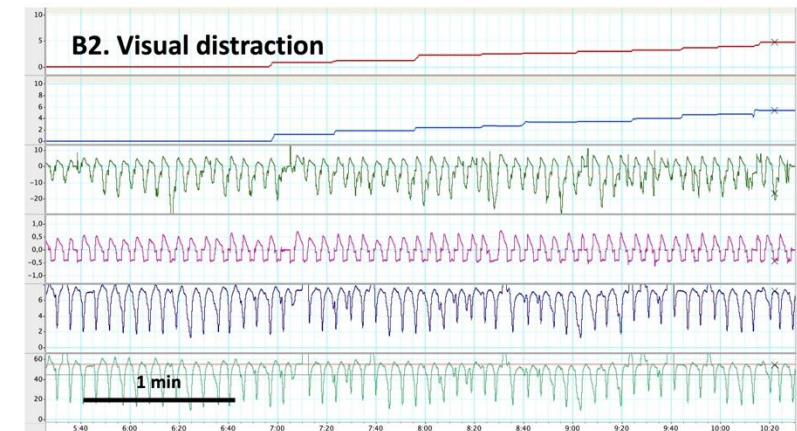
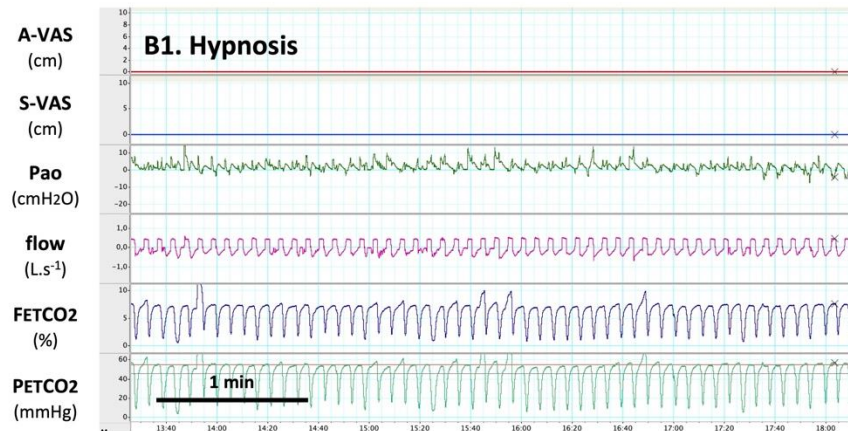
FETCO₂, carbon dioxide end-tidal expired fraction.

PETCO₂, carbon dioxide end-tidal expired partial pressure.

A. Inspiratory threshold loading



B. Carbon dioxide stimulation with restricted ventilation



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 medical hypnosis or visual distraction);

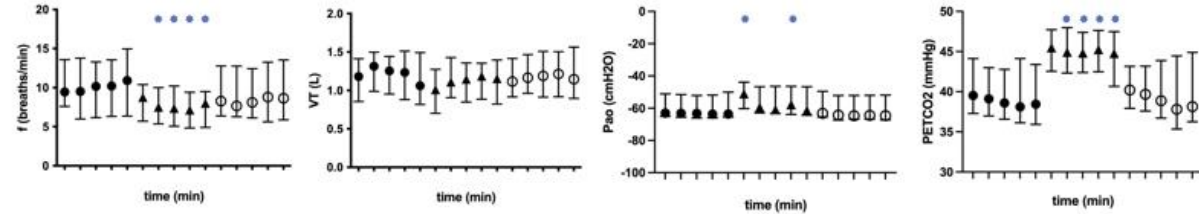
Open circles: washout period.

The data are provided as medians and interquartil

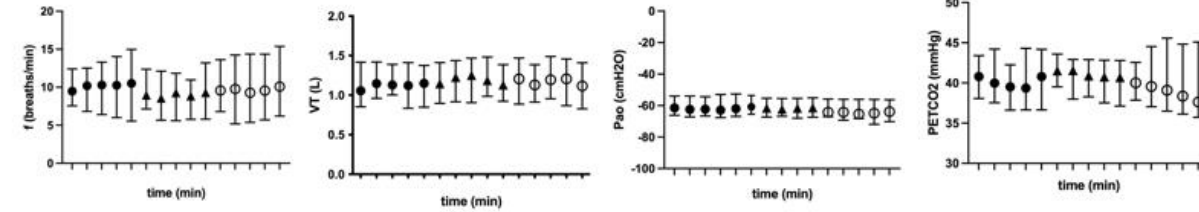
*: $p < 0.05$

A. Inspiratory threshold loading

A1. hypnosis

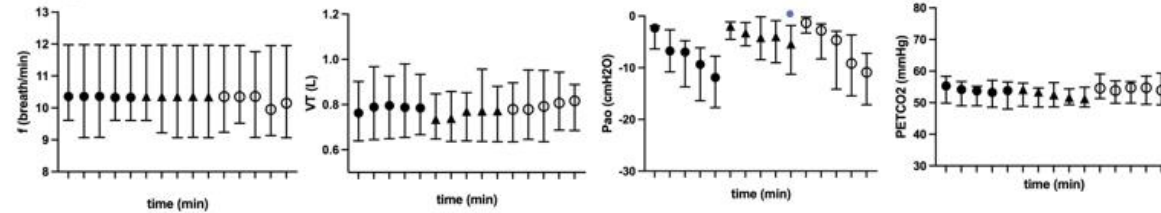


A.2. visual distraction

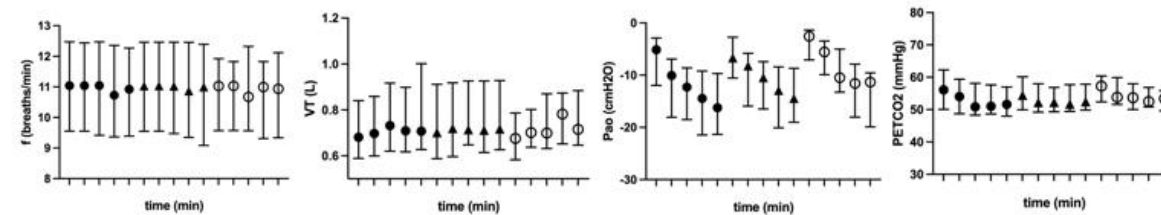


B. Carbon dioxide stimulation with restricted ventilation

B1. hypnosis



A.2. visual distraction



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;

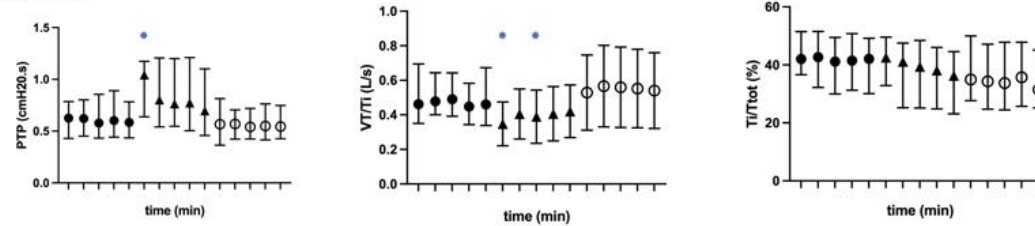
Closed circles: reference period;
Closed triangles: intervention period (either med hypnosis or visual distraction);
Open circles: washout period.

The data are provided as medians and interquartil

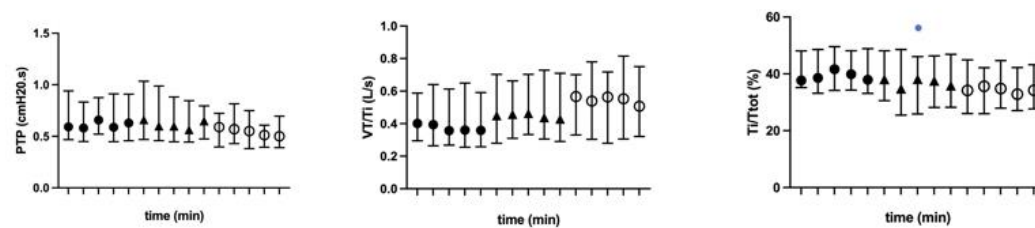
*: $p < 0.05$

A. Inspiratory threshold loading

A1. hypnosis

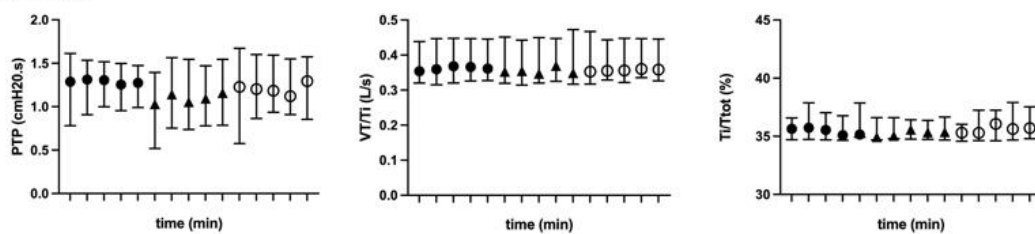


A.2. visual distraction

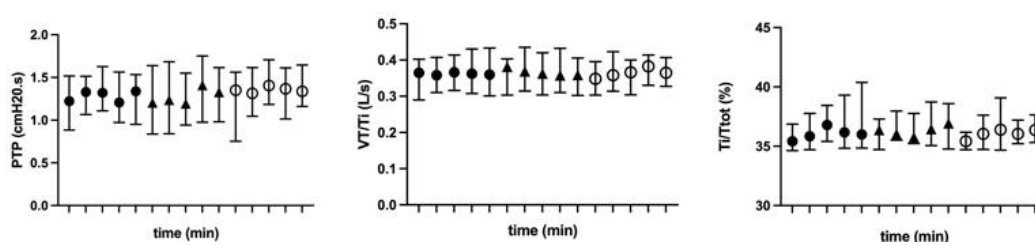


B. Carbon dioxide stimulation with restricted ventilation

B1. hypnosis



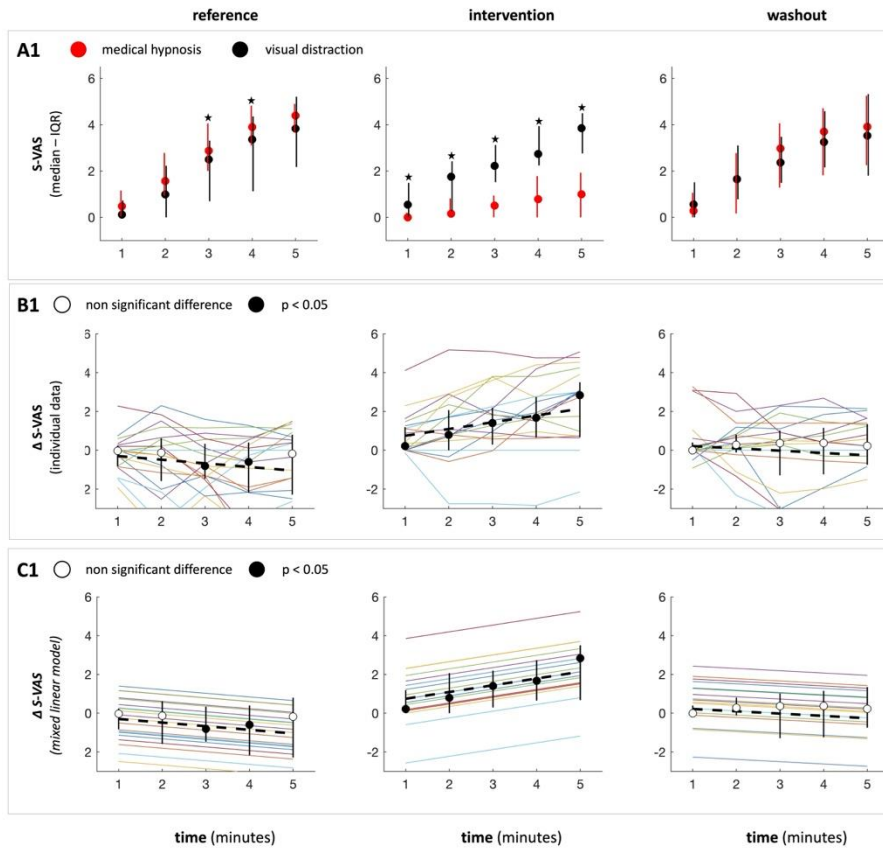
B.2. visual distraction



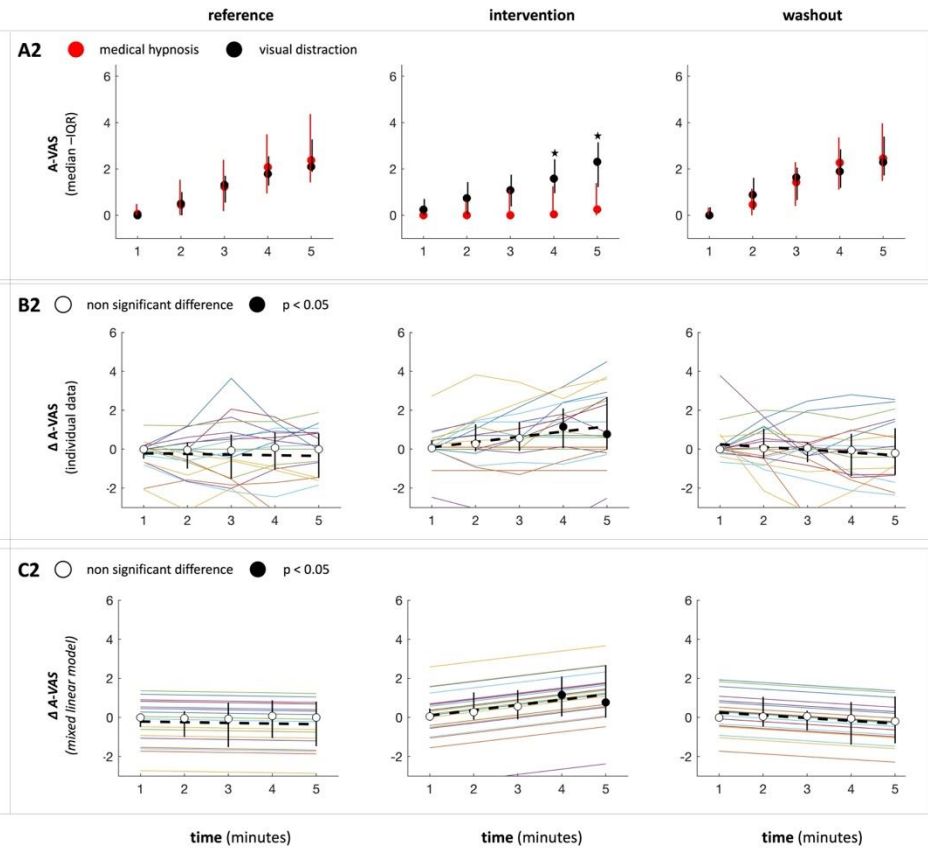
ES5 – Figure S4. Dyspnea responses to inspiratory threshold loading (left: sensory visual analog ratings, S-VAS; right: affective visual analog ratings, A-VAS). **A1-A2:** Median-interquartile range for S-VAS and A-VAS (red circles: medical hypnosis; black circles: visual distraction; *: $p < 0.05$ between 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).

Inspiratory threshold loading

Sensory visual analog ratings



Affective visual analog ratings

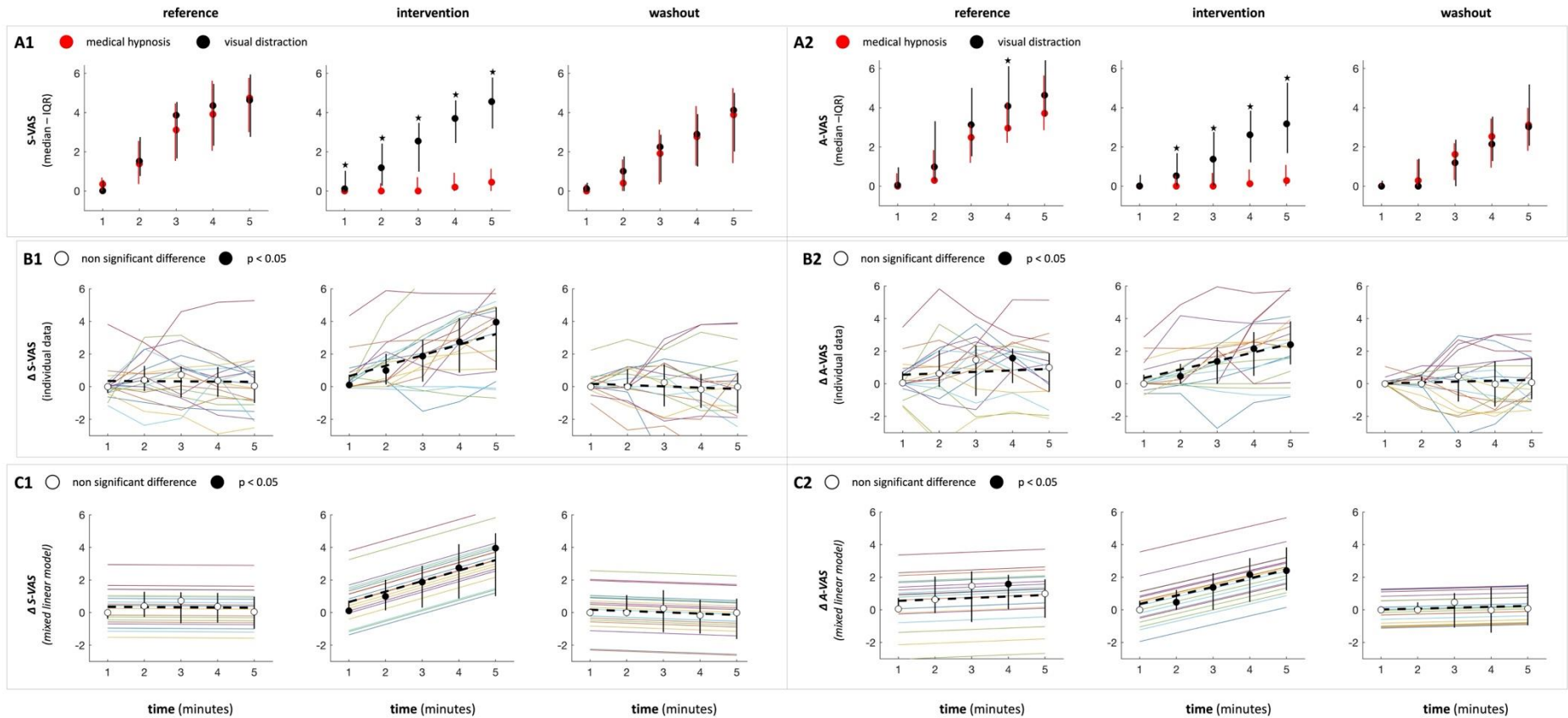


ES6 – Figure S5. Dyspnea responses to carbon dioxide stimulation with ventilatory restriction (left: sensory visual analog ratings, S-VAS; right: affective visual analog ratings, A-VAS). **A1-A2:** Median-interquartile range for S-VAS and A-VAS (red circles: medical hypnosis; black circles: visual distraction; *: $p < 0.05$ between 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).

carbon dioxide stimulation with restricted ventilation

Sensory visual analog ratings

Affective visual analog ratings



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 [0.25-3.75]	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 (CO₂)						
	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 of the preinspiratory potential is markedly attenuated during the medical hypnosis period, where the subsequent motor potential, visible during the reference and the washout periods, is lacking.

