Received: 10 December 2021 | Revised: 10 September 2022 | Accepted: 2 October 2022

DOI: 10.1002/ejp.2045

EJP European Journal of Pain

ORIGINAL ARTICLE

Virtual reality hypnosis in the management of pain: Self-reported and neurophysiological measures in healthy subjects

Floriane Rousseaux[1,2] | **Rajanikant Panda**[3,4] | **Clémence Toussaint**[5] | **Aminata Bicego**[1,2] | **Masachika Niimi**[3] | **Marie-Elisabeth Faymonville**[1,6] | **Anne-Sophie Nyssen**[1,2] | **Steven Laureys**[3,4] | **Olivia Gosseries**[1,3,4] | **Audrey Vanhaudenhuyse**[1,6]

[1]Sensation & Perception Research Group, GIGA Consciousness, University of Liege, GIGA (B34), Quartier Hopital, Liege, Belgium

[2]Laboratory of Cognitive Ergonomics and Work Intervention, University of Liege, ULiege (B32), Quartier Agora, Liege, Belgium

[3]Coma Science Group, GIGA Consciousness, University of Liege, GIGA (B34), Quartier Hopital, Liege, Belgium

[4]Centre du Cerveau, University Hospital of Liège, Liege, Belgium

[5]Oncomfort SA, Wavre, Belgium

[6]Algology Interdisciplinary Center, University Hospital of Liege, CHU Sart Tilman, Domaine Universitaire du Sart Tilman, Liège, Belgium

Correspondence
Audrey Vanhaudenhuyse, Algology Interdisciplinary Center and Sensation & Perception Research Group, GIGA Consciousness, Domaine Universitaire du Sart Tilman, B35, B4000 Liege, Belgium.
Email: avanhaudenhuyse@chuliege.be

Abstract

Background: Virtual reality hypnosis (VRH) has emerged as a new and promising option for pain management. Nonetheless, neural dynamics of pain modulation during VRH have not been investigated yet. The aim of this study was to measure the effects of VRH on pain, combining neurophysiological and self-reported measurements.

Methods: Eighteen healthy subjects underwent noxious electrical stimulations in both normal wakefulness and VRH conditions. Dissociation, absorption, time perception, anxiety, pain intensity and unpleasantness, heart rate variability and breathing were reported for each condition. EEG signals were analysed using event-related potentials (ERP) and time–frequency response (TFR) time-locked to stimuli. Neurophysiological features were correlated with self-reported data.

Results: VRH condition was associated with lower pain and higher dissociation. VRH significantly decreased amplitudes of N100 and P200 ERP components, reduced EEG power between 1 and 5 Hz from 100 to 560 ms, and increased EEG power from 5 to 11 Hz from 340 to 800 ms. These findings were observed at frontal, central and posterior electrodes. Heart rate variability was significantly higher and breathing frequency reduced with VRH. Correlations were found between the self-reported level of pain and ERP components.

Conclusion: VRH modulates cerebral pain processes and body physiology, leading to reduced pain levels. These findings offer a first insight on the analgesic mechanisms of VRH and suggest that VRH is an effective approach to reduce experimental pain.

Floriane Rousseaux and Rajanikant Panda contributed equally to this manuscript.

Olivia Gosseries and Audrey Vanhaudenhuyse shares the senior position

Significance: VRH decreases experimental pain perception, increases subject level of dissociation and modulates cerebral pain processing mechanisms. Pain can be managed with analgesic medication but also through complementary interventions. Among these, hypnosis and virtual reality (VR) are known to reduce pain for patients and healthy individuals. In recent years, an innovative technique combining hypnosis and VR has been proposed to help patients in managing pain. However, to our knowledge, no study has focused on the underlying mechanisms of this VR/hypnosis combination. We showed that VR combined with hypnosis decreases experimental pain, increases dissociation and influences EEG modulation.

1 | INTRODUCTION

Patient pain is usually managed with analgesic medication. However, there are currently strong incentives and growing interest in developing complementary non-pharmacological approaches for pain management. Among them, virtual reality hypnosis (VRH), an innovative technique for delivering clinical hypnosis to patients through virtual reality (VR), is increasingly used and has been proven to considerably reduce pain in clinical practice (Rousseaux, Bicego, Ledoux, et al., 2020).

On the one hand, clinical hypnosis is a one-to-one delivered technique inducing "A state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion" (Elkins et al., 2015). This approach has been successfully used for decades in various clinical settings to help patients to manage their pain (Bicego et al., 2021; Defechereux et al., 2000; Rousseaux et al., 2020b). The effectiveness of hypnosis has been further confirmed by experimental research demonstrating its analgesic effects, both at subjective and neurophysiological levels (Vanhaudenhuyse, et al., 2020; Vanhaudenhuyse et al., 2009). On the other hand, virtual reality (VR), which is a computer-generated environment that immerses the user in an artificial world, is another tool allowing to reduce pain, as shown in a recent neurophysiological study (Lier et al., 2020).

It is commonly agreed that hypnosis modifies the processing of painful stimulation by inducing a state of dissociation, while VR analgesia relies rather on distraction, allowing subjects to focus their attention away from nociceptive inputs. Interestingly, by comparing the impact of both techniques on thermal pain perception in healthy participants, Patterson et al. (2021) reported that pain intensity was lower during hypnosis relative to VR, revealing a larger analgesic effect of hypnosis (Patterson et al., 2021). Yet, the ability of subjects to dissociate and to respond to hypnotic suggestions (i.e., hypnotizability level), and thus to benefit from hypnotic analgesia, strongly varies between individuals (Vanhaudenhuyse, et al., 2020). In this context, it is noteworthy that adding VR to hypnosis allows to reduce of pain in a large number of individuals, even in subjects with a lower level of hypnotizability, probably as it enhances attentional focus and offers visual stimuli (Enea et al., 2014).

In other words, VRH appears a promising tool to give access to dissociation and optimal analgesia to a larger number of patients. While VRH is increasingly used to treat procedural and postoperative, its analgesic effects have been exclusively demonstrated based on healthcare providers' and patient's narrative, as well as on self-reported data. Thus, the question about the effect of combining VR and hypnosis remains completely open. The goal of the current study was to complement those data by objectivizing the effects of VRH in response to painful stimulation. To do so, we investigated the impact of this novel approach on neural correlates of pain response. EEG and additional neurophysiological measures were recorded in healthy volunteers receiving painful stimuli during both VRH and a control condition.

2 | METHODS

2.1 | Objectives

We hypothesized that the self-reported level of pain intensity as well as the neurophysiological responses induced by those stimuli will be decreased in the VRH condition as compared to the control condition. In addition, we hypothesized that physiological parameters (i.e., heart rate and respiration) will be slowed down with VRH. Finally, we also hypothesized that ERPs and physiological measurements will be directly related to the subjective reports of pain perception, anxiety, absorption and dissociation.

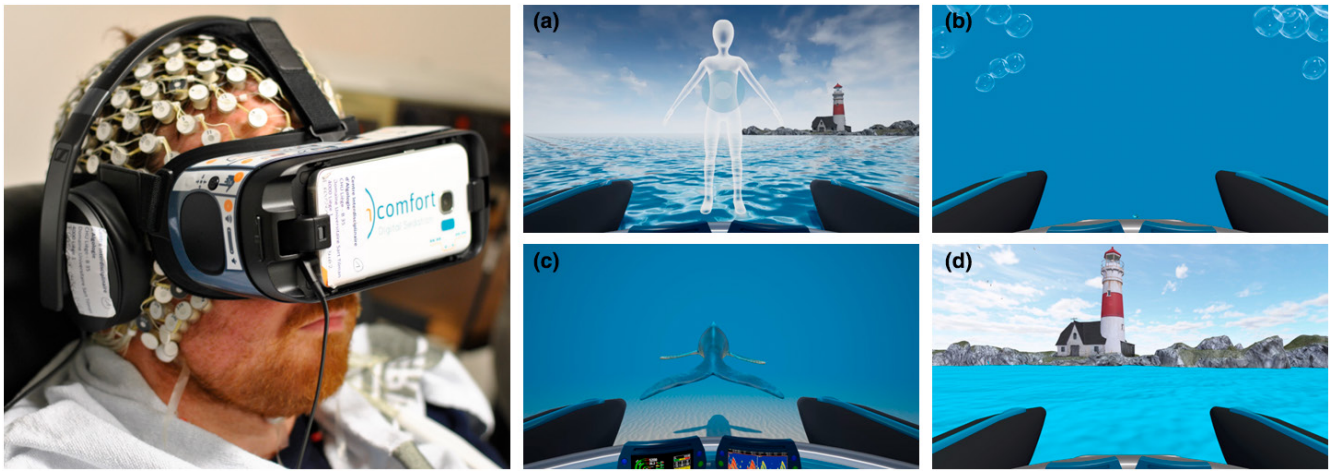

FIGURE 1 Experimental setup (left) including a VRH system and its software (right). VRH (Oncomfort's aqua®) session starts with (a) an induction phase based on hypnotic techniques, (b) a guidance phase where the subject dives in an underwater world, (c) a deepening phase during which the subject follows a whale during an underwater journey, and (d) a re-alerting phase during which the subject is brought back from the deep sea.

2.2 | Participants

Eighteen voluntary participants were recruited from September 2nd, 2019 to November 30th, 2020 in Liège (Belgium) (mean age (±SD) = 27.22 (±4.03), 10 women, 8 men). Inclusion criteria: healthy subjects, >18 years old, French speaking, no phobia of deep water, no claustrophobia, no psychiatric or neurological disease including chronic pain, no allergy to cutaneous electrodes, no head or face wounds, and no medication that could affect the autonomic nervous system. All the included subjects had sufficient auditory and visual acuity for an effective use of the device. An incentive of 15 euros per hour was offered for their participation.

2.3 | Ethics

The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liege, in accordance with the General Data Protection Regulation (GDPR), and with the 1964 Helsinki declaration and its later amendments. Written informed consent to participate in the study was obtained from all the participants. This study was preregistered with an analysis plan on Clinicaltrials.gov. Number: NCT04107558.

2.4 | Procedure

This prospective study used a randomized two-arm crossover design. Because of the nature of the device, the trial was not blind to subjects and researchers. Subjects were positioned lying on a comfortable chair and demographic data were collected. Then, measuring devices were set up: high-density EEG (256 electrodes, EGI, Electric Geodesics) and body physiological sensors (input box of EGI, Electric Geodesics), consisting of two electrodes on the chest for electrocardiogram (ECG), two electrodes on the left leg for the EMG, and two effort belts, on the chest and on the belly, for breathing signal.

The electrical pain stimuli were delivered through two rectangle electrodes Natus © (20/25 mm) to stimulate the ulnar nerve of the right arm's cubital tunnel and were triggered using Digitimer DS7A and DG2A devices (Digitimer Ltd) that generate electrical pulse noxious stimuli. Electrical pulse intensity calibration was performed for each participant. During this calibration procedure, subjects were asked to indicate their level of pain on a 10-point visual analogue scale (VAS, 0–10). First, an electrical pulse of very low intensity (i.e., 1 mA) was delivered. Intensity was then increased until reaching a self-reported score of 8, based on a staircase method (i.e., stimuli are presented in ascending and descending order, meaning that when the subject's response changes, the direction of the stimulus sequence is reversed); this individual calibrated intensity was kept for the whole experiment.

During the experiment, each subject was exposed to two conditions in a randomized order: an experimental condition of 16 min of VRH (Oncomfort's Aqua®) and a control condition of 16 minutes with eye open. The VRH session started with an induction phase (3.52 min) based on hypnotic techniques, a guidance phase (1.24 min) where the subject dived into an underwater world, a deepening phase (10.44 min) during which the subject followed a whale during an underwater journey, and a re-alerting phase (1 min) during which the subject was brought back from the deep sea (Figure 1). During

the control condition, subjects were instructed to look at a cross on the wall and to let their thoughts come and go. During each condition, EEG activity and body physiological parameters were recorded. The first 5 min of each condition allowed to obtain baseline-resting state (without noxious stimuli). The following 13 min corresponded to the noxious stimulation phase: 60 individually calibrated electrical stimuli were administrated. The Digitimer does not allow automatic stimulus with jittered inter-stimulus interval. Therefore, we recorded two sets of stimuli (i) 30 automatic stimuli with fixed inter-stimulus interval (10 s), and (ii) 30 manual pressing stimuli with jittered inter-stimulus interval between 10 and 15 s. The first 30 stimulations delivered automatically corresponded to the first 5 min of deep hypnosis in the narrative, while the last 30 stimulations delivered manually corresponded to the five last minutes of deep hypnosis in the narration. We recorded these two sets of stimulations to check for the reliability of the ERP components in the manual delivered stimulation. The level of anxiety was assessed before each condition. Ratings of pain intensity, pain unpleasantness, absorption, dissociation, anxiety and perception of time were assessed once after each condition, representing global scores for all 60 stimuli and the entire condition (Figure 1).

2.5 | Subjective assessments

After both VRH and control conditions, the following questions were asked to the subject in the following order.

2.5.1 | Pain intensity

To evaluate pain perception, a VAS was used. This scale ranges from 0 to 10, where 0 is no pain at all and 10 is the worst imaginable pain. Subjects were asked the following question: "Could you estimate on a 0 to 10 scale, the degree to which you experienced pain? 0 means no pain at all and 10 is the worst pain you can imagine".

2.5.2 | Pain unpleasantness

Participants reported their pain unpleasantness on a VAS where 0 is not unpleasant at all and 10 is most unpleasantness imaginable. Subjects were asked the following question: "Could you estimate on a 0 to 10 scale, the degree to which the pain you felt was unpleasant? 0 is not unpleasant at all and 10 is the most unpleasant you can imagine."

2.5.3 | Anxiety

The same VAS scale was used for anxiety where 0 is no anxiety at all and 10 is the worst anxiety imaginable. Subjects were asked the following question: "Could you estimate on a 0 to 10 scale, the degree to which you feel anxiety? 0 is no anxiety at all and 10 is the most anxious you can imagine."

2.5.4 | Absorption

Subjects were asked the following question: "Could you estimate on a 0 to 10 scale how deeply you felt absorbed and felt your attention focused on the session you have just experienced? 0 means you were not absorbed at all in the experience; 10 means you was fully absorbed in the experience" (Vanhaudenhuyse et al., 2019).

2.5.5 | Dissociation

Subjects were asked the following question: "Could you estimate on a 0-to-10 scale if you felt a dissociation between your bodily sensations and the actual environment? 0 means you were in the reality, in this room; 10 means that you completely escaped in your subjective experience, totally disconnected from the here-and-now reality" (Vanhaudenhuyse et al., 2019).

2.5.6 | Time perception

Subjects were asked to estimate the duration (in minutes) of each session.

2.6 | Materials

EEG was recorded using a high-density 256 electrodes along with body physiological parameters (ECG, EMG and breathing) using the polygraph devise of EGI (EGI, Electrical Geodesics).

The Digitimer High Voltage Stimulator model DS7A (Digitimer Ltd) was used to provide constant high voltage pulses of brief duration for transcutaneous stimulation of nerves. Short pulse durations have been used to minimize any discomfort such as weakness, amnesia or seizure. As the current density of the chosen electrode was lower than 2 mA rms/cm^2, there was no risk of burns at the stimulation site. The Digitimer electrical stimulus generator device (DS7A) was kept at 500 μs

with 300 V, meaning that the pulse duration was 0.5 ms with a maximum compliance of the stimulation set to 300 V. The electrical pulse intensity calibrated for each subject ranged from 4 to 8 mA. To deliver the first 30 automatically electrical pulse noxious stimuli, the following parameters were set in the electrical pulse generator device (DG2A): pulse mode = free run, repetition: 0.1 Hz (i.e., 10 s of inter-stimulus interval), delay: 10 ms, output = OUT-2 (i.e., to deliver the electrical stimulation as a double pulse) (Ree et al., 2020). For the last manually delivered electrical pulse noxious stimulation, the following parameters were set: pulse mode = train, delay: 10 ms, output = OUT-2, and manual inter-stimulus interval = 10–15 s (Matre et al., 2015).

VRH was provided using a head-mounted display (Sedakit™, Oncomfort SA). This VRH device is composed of a smartphone plugged in a VR headset, an audio headset and integrated software (Medical device Class IA). This device is non-invasive, with only a skin contact. The VRH session used was "Aqua 16" developed by Oncomfort SA. The intended use of the device is the reduction of pain and anxiety, and enhancement of patient's comfort during medical procedure. The Aqua® VRH session is an immersive virtual experience that combines a virtual 3D video with music, sounds and/or voice recording based on a hypnotic scenario recorded in French by a trained hypnotherapist. Visual experience is carefully synchronized with the hypnotic script and allows subject to induce and maintain a relaxed state with a disconnection from their external surrounding. The Aqua® VRH session follows the standard phases of hypnosis. During the induction phase, subjects are over the surface of the sea. They are invited to focus their attention on their breath, and to induce progressive relaxation in their body. The guidance phase brings the subjects slowly under the water. During the deepening phase, subjects follow a soothing underwater experience with specific suggestions regarding their comfort and relaxation. The re-altering phase brings the subjects progressively back into reality, concomitant with return to normal body sensations When the VRH device is removed, the subjects naturally return to normal perceptions (see Video S1 for experimental setup and VRH session demo).

2.7 | Data analysis

EEG signals, body physiological parameters and self-reported data (pain intensity, pain unpleasantness, anxiety, absorption, dissociation and time perception) were analysed at the individual level and at the condition level for both conditions (control and VRH). EEG and body physiological measures were then correlated with the self-reported data.

2.7.1 | EEG analysis

The EEG signal pre-processing, pain stimulus-related artefacts removal and post-processing (ERP and time–frequency response [TRF] analysis) were carried out using fieldtrip software (Oostenveld et al., 2011). The EEG signal sampling rate was kept as originally recorded, at 500 Hz. Butterfly band pass filter was applied with a low cut-off frequency of 1 Hz and a high cut-off frequency of 30 Hz with a 50 Hz notch filter to remove power line interference. Then, the EEG recordings were segmented into −500 to 2000 ms epochs time-locked to electrical stimulus onset. Baseline correction from −0.200 to 0 ms was applied for each channel. We have used dependent component analysis (ICA) denoising using 'runica' as implemented in the fieldtrip software to minimize the physiological, electrical stimulus-related, muscular and ocular artefacts. We carefully visually inspected the independent components (ICs) based on the spatial map and its temporal signal, and the IC components representing noise association (i.e., ocular artefacts, movements, electrical stimulus and muscle artefacts) were discarded. Noise channels that were previously removed were reconstructed using spherical spline interpolation based on clean EEG signal. Finally, the pre-processed and artefacts removed signal were re-referenced to the average reference. The ERP component and time–frequency response analysis were performed for each individual subject and each condition on the clean EEG signal. The ERP analysis was performed for the following three sets of electrical pain stimuli data as events of interest: (i) the first 30 stimulations, (ii) the last 30 stimulations and (iii) all 60 stimulations. The ERP analysis was carried out by averaging the epochs using the "ft_timelockanalysis" function. Then, analysis was performed on those averaged epochs for each condition using the "ft_timelockgrandaverage" function of the Fieldtrip software (Oostenveld et al., 2011). Following the ERP analysis, we assessed the power spectrum of pain stimulus response using TFR as implemented in Fieldtrip software. All 60 stimulus epochs from −500 to 2000 ms time-locked to electrical stimulus onset with −0.200 to 0 ms for baseline correction were averaged for all channels, for each condition and for each individual using "ft_freqanalysis" function with the following parameters: 'mtmconvol' method, hanning taper, frequency of interest of 1:1:30 Hz, frequency time window of 0.5 Hz. Then, a group TFR analysis was performed for each condition using "ft_freqgrandaverage" function (Oostenveld et al., 2011). Finally, group analysis

comparing VRH and control conditions for both ERP and TFR was carried out using cluster-based permutation tests.

2.7.2 | Body physiology analyses

The ECG and breathing analysis were carried out using the MATLAB signal processing toolbox (MATLAB. R2020b. Natick, Massachusetts: The MathWorks Inc.).

The ECG signal was filtered from 0.5 to 50 Hz. Artefacts were removed based on overall ECG signal amplitude and on the number of zero crossings per second. Signal amplitude smaller than 2.5 mV and between 1.3 and 4 zero-crossing per second (corresponding to 40–120 beats/min) were considered as within the normal physiological range (Clifford et al., 2006). Heart rate variability was then extracted based on R-peaks. The R-peaks were detected for each individual signal using the Pan and Tomkins algorithms (Palaniappan et al., 2020). A rolling window was used to remove peaks that occurred in a time period of 450 ms or less between neighbouring peaks. NN intervals, defined as the time interval between two successive R peaks, were then computed based on remaining R peaks. The RR interval list was segmented into 2 min segments with a shift of 30 s. Segments with insufficient NN intervals were discarded. We finally evaluated heart rate (HR), standard deviation between successive NN intervals and root mean square of the successive differences (RMSSD) for each segment. Those values were averaged across the two conditions (Shaffer & Ginsberg, 2017).

Breathing was analysed based on chest movements. The signal was filtered from 0.5 Hz to 50 Hz. Artefacts were removed based on signal amplitude and the number of zero crossings per second. Signal amplitude smaller than 2.5 mV and between 0.16 and 0.6 zero-crossing per second (corresponding to 5–18 breaths per minute) were considered as within the normal physiological range (Hung et al., 2008). Maxima and minima were detected for each individual signal using a peak detection algorithm. Inspiration time was defined as the time interval between a minimum and a maximum, while expiration was defined as the time interval between a maximum and a minimum. Inspiration and expiration duration were computed. The number of breathing cycles per minute, as well as the variability between duration of breathing cycles were then derived.

2.8 | Statistical analysis

2.8.1 | Self-reported data statistics

The normality of the dependent variables was inspected graphically with histograms and quantile-quantile plots and was tested by using the Shapiro–Wilk test. Continuous variables were reported as means (±standard deviation) or medians (interquartile range) for skewed distributions, while the number and percentages were given for qualitative variables. Homogeneity of the sample was assessed with chi-squared test for qualitative and dichotomous variables (e.g., sex) and with a one-way analysis of variance (ANOVA-1) or the non-parametric Kruskal–Wallis test for the quantitative variables (e.g., dissociation levels). A repeated measures ANOVA test was used to compare the evolution of the parameters (e.g., anxiety levels) between conditions (control and VRH) and anxiety before and after each condition (or Wilcoxon for paired samples when variables followed a non-normal distribution). All p-values were further corrected for multiple testing using Bonferroni correction and effect sizes were assessed using Cohen's d. Results were considered as statistically significant at the 5% critical level ($p < 0.05$). Analyses were performed using R 3.5.3 (R Core Team), the package Rcommander (Rcmdr) and SAS 9.4 (© SAS Institute Inc.,) (Fox et al., 2019).

2.8.2 | EEG and body physiological data statistics

To compare ERP between conditions (i.e., control and VRH), we performed a cluster-based permutation test as implemented in the fieldtrip software (Oostenveld et al., 2011). We used the Monte Carlo method, dependent samples T-statistic, parameter chosen was distance neighbours method, neighbourdist = 4, cluster alpha = 0.05 and the number of randomization was 1000 in the permutation test. The cluster-based ERP analysis provides clusters of time-points and brain regions that significantly differ between conditions. The amplitude of ERP components was extracted using AUC for the significant time-points previously identified. Finally, these ERP component amplitudes were correlated with the self-reported data.

To compare TFR between conditions (control and VRH), we also performed a cluster-based permutation test, considering the 1–30 Hz frequency band and from time-points ranging from 0.05 to 1 s based on noxious stimulus onset. We used Monte Carlo method, dependent samples T-statistic, parameter was 'powspctrm', cluster alpha = 0.05 and number of randomizations = 1000 in the permutation test. The cluster-based TFR analysis provides clusters of frequencies, time-points and brain regions that significantly differ between conditions.

Wilcoxon paired tests were used to compare body physiology (ECG and breathing) data between the two conditions.

Finally, ERP component amplitudes, TFR values and physiological measures were correlated with self-reported

data based on difference score (i.e., score in the VRH condition minus score in the control condition) using Spearman correlations (uncorrected for multiple comparisons). More specifically, we took the average ERP of every significant cluster of electrodes for central, frontal and posterior electrodes. Then for each component (N100 and P200), we considered area under the curve, resulting in one single value for each component for each subject and condition. Then we took the difference between the control vs. VRH. This difference was then correlated with behavioural scores.

3 | RESULTS

3.1 | Self-reported data

Pain intensity was significantly lower in the VRH condition compared to the control condition ($p^{adj} = 0.02$). Similarly, pain unpleasantness was lower in the VRH condition compared to the control condition ($p = 0.03$), but this difference did not reach statistical significance after Bonferroni correction ($p^{adj} = 0.23$). Dissociation was also significantly higher in the VRH compared to the control condition ($p^{adj} = 0.01$). There was no significant difference between conditions for anxiety, absorption and time perception (Figure 2 and Table 1).

In the control condition only, the anxiety increased during the noxious stimulation phase ($p = 0.047$) even if this difference did not reach statistical significance after Bonferroni correction ($p^{adj} = 0.094$). There was no significant difference in anxiety between pre- and post-session for the VRH condition (Figure 2d and Table 2).

3.2 | EEG data results

Three subjects out of 18 were discarded due to excessive movement artefacts in the data. Two subjects displayed strong head and neck movement's artefacts at the time of noxious stimuli and one subject recording was disturbed by high noise during the entire recording. Therefore, the group-level analysis to compare between conditions (control vs. VRH) was carried out on 15 subjects (mean age ± SD = 27.02 ± 4.13, 7 women).

3.2.1 | Event-related potentials

The ERP components were similar between the three analyses. The ERP components in each condition (i.e. control/VRH) and between conditions (control vs. VRH) were similar for all three sets of stimulus data. Detailed results can be found in the Appendix S1. For the combined 60 stimulations, we found significant differences ($p < 0.05$) between the control and VRH conditions for three clusters. Decreases in the ERP amplitudes were measured from 100 to 150 ms, 250 to 300 ms and 300 to 350 ms at the electrodes located in frontal, central and posterior regions of the scalp. The 100–150 ms corresponds to N100 ERP components for central and parietal electrodes and P100 for frontal electrodes. Both the 250–300 ms and 300–350 ms corresponds to one ERP component, that is P200 for central and parietal electrodes and N200 for frontal electrodes (Figure 3).

When considering the frontal electrodes cluster, we found significant differences between control and VRH conditions for P100 (ERP amplitude in 100–150 ms) and N200 (ERP amplitude in 250–350 ms) components. The P100 amplitude was significantly lower during the VRH condition (1.26 ± 2.0 μV) compared to the control condition (4.21 ± 4.7 μV) ($p = 0.0265$), and the N200 was significantly lower during VRH condition (−2.02 ± 0.99 μV) compared to control condition (−4.64 ± 3.26 μV) ($p = 0.0030$) (Figure 3, top left).

When considering the central electrodes cluster, we found significant differences between control and VHR conditions for N100 (ERP amplitude in 100–150 ms) and P200 (ERP amplitude in 250–350 ms) components. The N100 amplitude was significantly lower in the VRH condition (−1.13 ± 1.7 μV) as compared to the control condition (−2.95 ± 2.2 μV) ($p = 0.0044$), and the P200 amplitude was significantly lower in the VRH condition (1.44 ± 0.6 μV) compared to the control condition (3.00 ± 1.9 μV) ($p = 0.0021$) (Figure 3, top middle).

When considering the posterior electrodes cluster, we found significant differences between control and VHR ERP for the P200 (ERP amplitude in 300-350 ms) component. The P200 amplitude was significantly lower in the VRH condition (0.52 ± 0.8 μV) compared to the control condition (1.80 ± 1.6 μV) ($p = 0.0017$) (Figure 3, top right).

3.2.2 | Time–frequency response (TFR)

Cluster-based permutation test for TFR showed a cluster of reduced power spectral density in VRH as compared to control condition (negative cluster) and a cluster of increased power spectral density in VRH compared to control condition (positive cluster) (Figure 4, top). The negative cluster was localized in the low frequencies (1–5 Hz) and early time range (100–560 ms) after stimulus onset ($p = 0.01$). The 1–5 Hz frequencies correspond to delta (between 0.5 and 4 Hz) and early part of theta (between 4 and 8 Hz) frequency bands. The negative

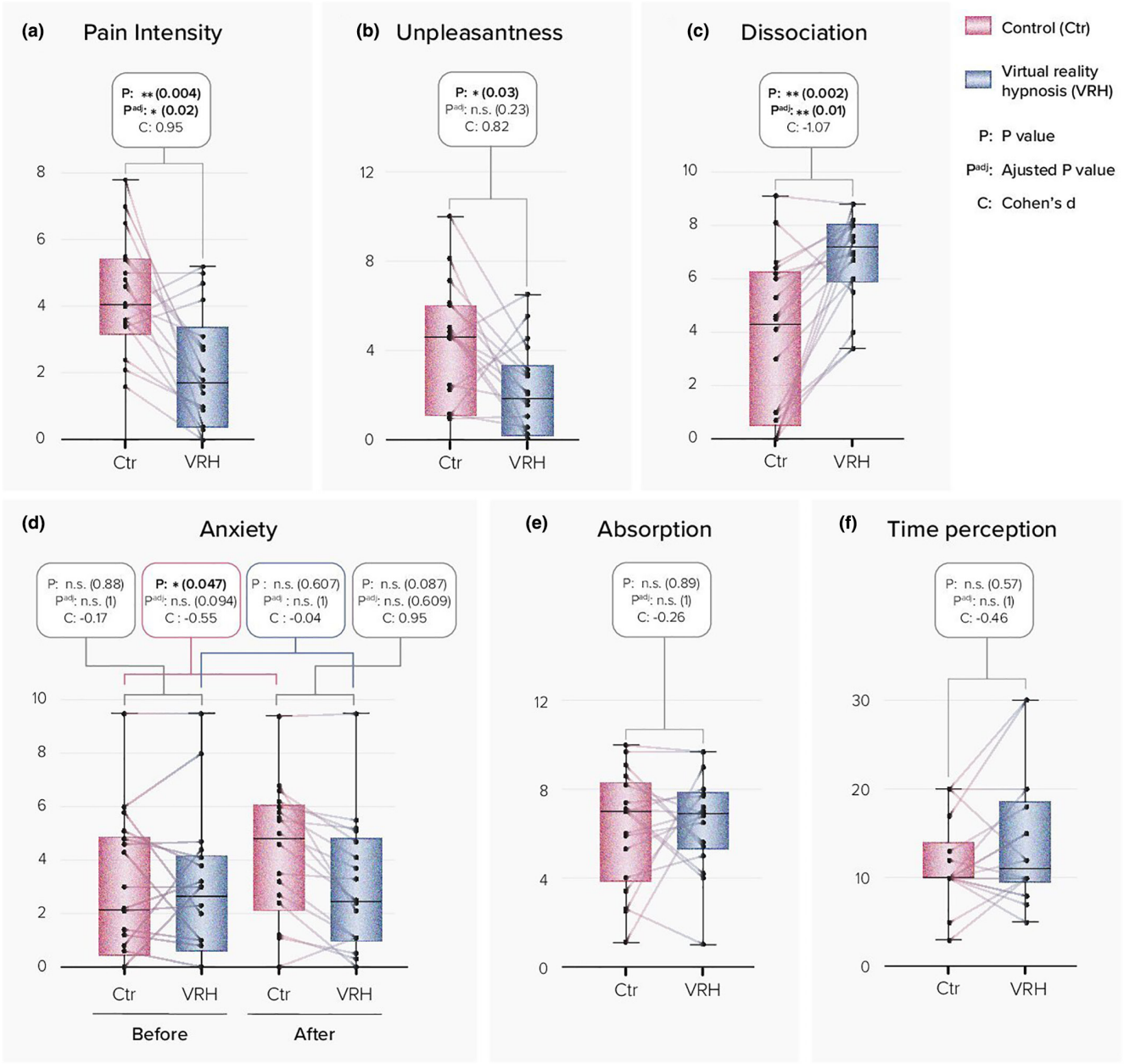

FIGURE 2 Self-reported data results in both control (ctr) and VRH conditions: Pain intensity (a), unpleasantness (b), dissociation (c), anxiety (d), absorption (e) and time perception (f), using boxplots. Box limits represent 25th to 75th percentiles; line represents median; whiskers delimit minimum and maximum. All individual values are represented by dots.

cluster TFR topology showed that this cluster was localized around bilateral frontal, midline and occipital electrodes (Figure 4, middle). The increased positive cluster was noted in the high frequencies (5–11 Hz) and late time range (340–800 ms) after stimulus onset ($p = 0.04$). The 5–11 Hz frequencies correspond to late theta and alpha (between 8 and 12 Hz) frequency bands. The positive cluster TFR topology showed that this cluster was localized around midline, frontal and posterior electrodes were significantly increased at this frequency and time range (Figure 4, bottom).

3.3 | Results of body physiological data

3.3.1 | Heart rate and heart rate variability

Heart rate variability was significantly higher in the VRH condition (137 ± 64 ms) compared to control (97 ± 10 ms) ($p = 0.017$) (Figure 5a). Mean heart rate was significantly higher in the VRH condition (60.2 ± 3.2 bpm) compared to the control condition (58.3 ± 2.8 bpm) ($p = 0.048$). Moreover, heart rate variability significantly decreased following noxious stimulations compared to baseline and

TABLE 1 Paired samples T-test for all self-reported data between conditions. Results were considered as statistically significant at the 5% critical level ($p < 0.05$) (in bold).

	Control condition	Virtual reality hypnosis	*p*	Adjusted *p*	Cohen's d
Anxiety before	2.86 ± 2.71 2.15 [0–9.5]	2.82 ± 2.7 2.65 [0–9.5]	0.88	1	−0.17
Anxiety after	4.20 ± 2.6 4.80 [0–9.4]	2.9 ± 2.5 2.45 [0–9.5]	0.087	0.609	0.95
Pain Intensity	4.16 ± 1.94 4.05 [0–7.8]	2.07 ± 1.78 1.7 [0–5.2]	**0.004**	**0.02**	0.95
Unpleasantness	4.06 ± 2.85 4.6 [0–10]	2.14 ± 1.99 1.85 [0–6.5]	**0.03**	0.23	0.82
Absorption	6.22 ± 2.61 7 [1.1–10]	6.58 ± 2.16 6.9 [1–9.7]	0.89	1	−0.26
Dissociation	3.70 ± 3.06 4.3 [0–9.1]	6.77 ± 1.74 7.2 [3.4–8.8]	**0.002**	**0.01**	−1.07
Time perception	11.67 ± 4.77 10 [3–20]	13.89 ± 7.24 11 [5–30]	0.57	1	−0.46

Note: Mean ± SD: SD, Standard Deviation; Median [IQR]: IQR, Interquartile Range. Adjusted P with Bonferroni correction.

TABLE 2 Paired samples T-test for anxiety for each condition (before and after condition). Results were considered as statistically significant at the 5% critical level ($p < 0.05$) (in bold).

	Anxiety before	Anxiety after	*p*	Adjusted *p*	Cohen's d
Control condition	2.86 ± 2.71 2.15 [0–9.5]	4.20 ± 2.6 4.80 [0–9.4]	**0.047**	0.094	−0.55
Virtual reality hypnosis	2.82 ± 2.7 2.65 [0–9.5]	2.9 ± 2.5 2.45 [0–9.5]	0.607	1	−0.04

Note: Mean ± SD: SD, Standard Deviation; Median [IQR]: IQR, Interquartile Range. Adjusted *p* with Bonferroni correction.

was negatively correlated with the ERP component at frontal electrode (r = −0.41, $p = 0.027$) (Figure 5).

3.3.2 | Breathing

Breathing frequency was significantly lower in the VRH condition (9.8 ± 1.2 cycles/min) compared to the control condition (11.06 ± 1.16 cycles/min) ($p = 0.032$). Breathing variability was lower during VRH condition (2.97 ± 1.25) compared to control condition (3.51 ± 2.6) ($p = 0.044$) (Figure 5).

3.4 | Correlation of EEG and body physiological data with self-reported data

The self-reported level of pain intensity was positively correlated with both ERP components at central electrode (rs = 0.40, $p = 0.007$), and negatively correlated with the high-frequency power content (6–12 Hz) at the same location (rs = −0.49, $p = 0.024$). A significant correlation was also found between the self-reported level of dissociation and both ERP components measured at frontal electrode (rs = −0.41, $p = 0.007$), and with the low-frequency (1–6 Hz) power content at both frontal (rs = −0.55, $p = 0.010$) and parietal (rs = −0.37, $p = 0.011$) electrodes (Figure 6).

4 | DISCUSSION

Studies have shown that virtual reality hypnosis is an innovative non-pharmacological approach that significantly decreases pain perception (Patterson et al., 2004, 2021). However, its analgesic effect has been exclusively demonstrated based on healthcare providers' and patient's reported data and has not been objectivized so far. This is the first study investigating brain responses to painful stimulations with VRH. We observed a significant reduction in pain perception during VRH compared to the control condition, along with a significant reduction in peak ERP amplitudes of N100 and P200. We noted a reduced EEG power between 1 and 5 Hz from 100 to 560 ms

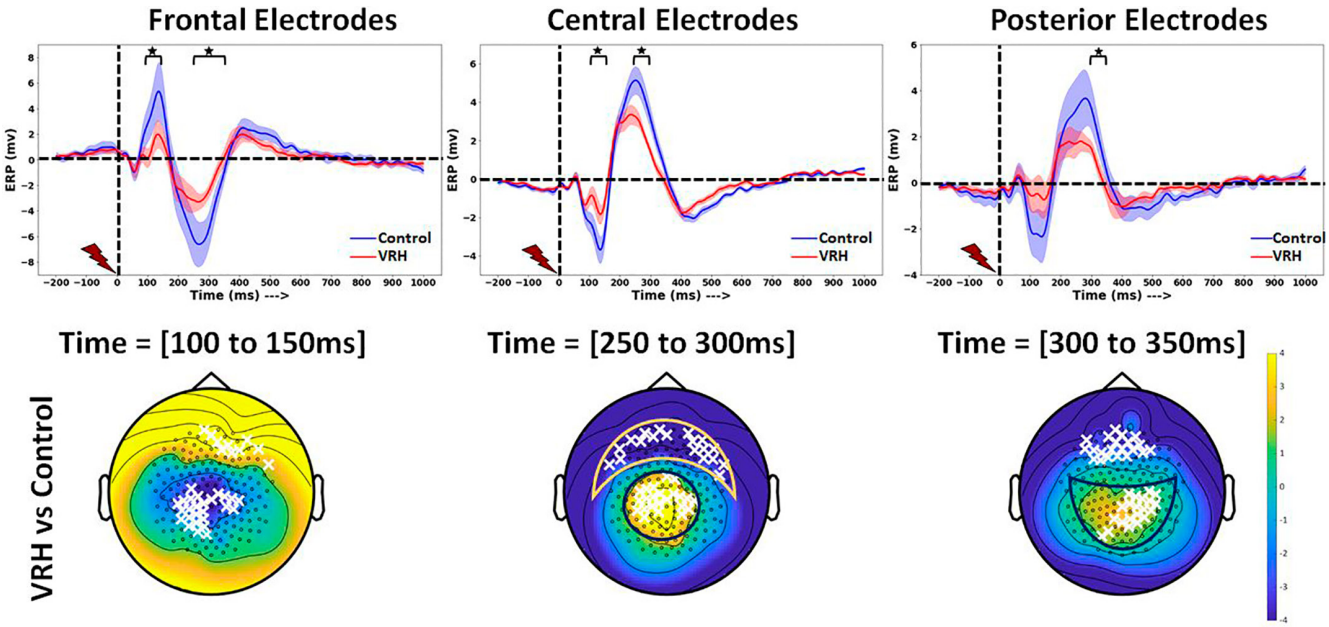

FIGURE 3 ERP graph (top) and topoplot (bottom) for VRH (red graph) and control (blue graph) conditions for the 60 stimulations. The ERP graph for frontal (top-left), central (top-middle) and posterior (top-right) electrodes. The solid lines of ERP graph represent the averaged ERPs and the shaded lines represent 95% confidence interval for control (blue) and VRH (red) conditions. The thunder symbol in x-axis represents the onset of the noxious stimuli. Topological ERP components (bottom) showed significant differences between control and VRH conditions using cluster-based permutation analysis. The ERP components showed significant differences between control and VHR conditions in N100 (100–150 ms) and P200 (250–300 and 300–350 ms) for three clusters (frontal, central and posterior electrodes). The crosses indicate significant clusters ($p < 0.05$). Yellow colour in the topoplot represents regions with reduced positive ERP components and blue colour represents regions with reduced negative ERP components.

after stimulus onset (early response) and an increased EEG power between 5 and 11 Hz from 340 to 800 ms after stimulus onset (late response) during VRH. All those findings were observed at frontal, central and posterior. The self-reported level of pain intensity was significantly correlated with both ERP components, and with the 6–12 Hz power content at central electrode. At the physiological level, VRH significantly increased heart rate variability while reducing breathing frequency. Subjects also reported higher levels of dissociation in the VRH condition compared to control. A significant correlation was found between the self-reported level of dissociation and both ERP components at frontal electrode, and with the 1–6 Hz power content at both frontal and parietal electrodes.

The main finding of this study was the objectivation of the impact of VRH on perceived pain intensity, confirming previous results from self-reported measures in clinical settings (for review see Rousseaux, Bicego, Ledoux, et al., 2020). This was first illustrated by the modification of N100 and P200 ERPs components following painful stimulations, and further supported by the significant correlation between those ERPs component and the self-reported level of pain. The relevance of the N100-P200 as an objective measure of pain perception has similarly been highlighted in several studies investigating laser-evoked EEG (Matre et al., 2015; Ree et al., 2020).

More particularly, N100 is known to reflect the sensory discriminative dimension of pain that is processed by sensory cortices and thalamus, while P200 is linked to the affective emotional dimension and is thought to be processed in the dorsal anterior cingulate cortex (dACC) and insula (De Benedittis, 2020; De Ridder et al., 2021). Overall, those two components relate to the conscious detection of nociceptive stimulus through which pain emerges (Lee et al., 2009). Since the intensity of the stimuli was equal during the whole experiment and the N50 component, which represents the early stage of sensory processing related to the ascending nociceptive input (Lee et al., 2009), was similar in both conditions, our observation of reduced N100 and P200 suggests that VRH alters pain experience through the modulation of sensory and perceptual pain processing. Moreover, we might hypothesize that this modification of supra-spinal mechanisms involved pain processing also modulates "top-down" attentional mechanisms as we have highlighted a reduction EMG response during VRH.

For the first time, we found that the pain response in the VRH condition was characterized by late power increase in the 5–11 Hz frequency band. The power content of this specific frequency band around central electrode was significantly correlated with the perceived pain intensity. Interestingly, the 6–12 Hz positivity occurs within the

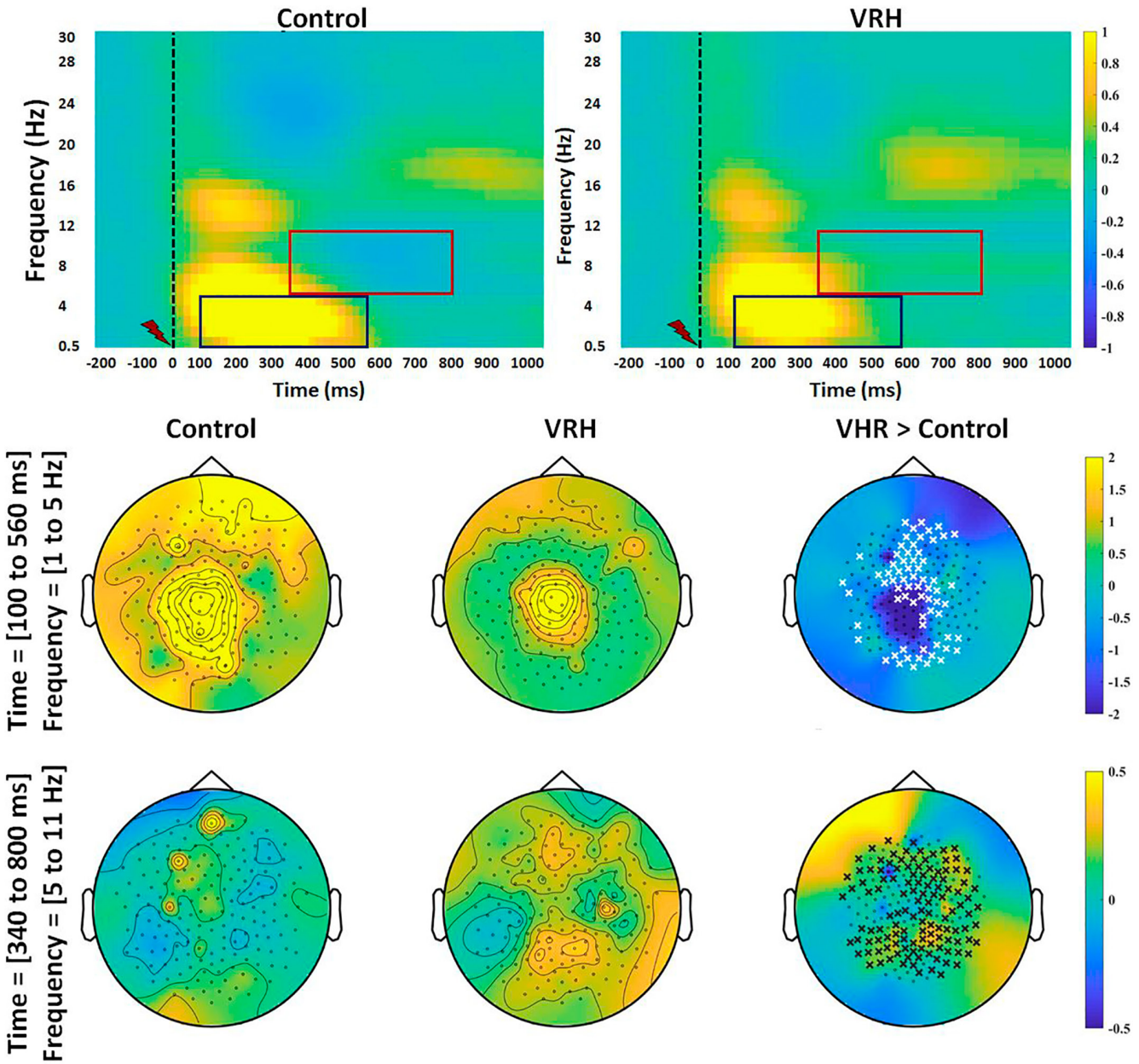

FIGURE 4 Time–frequency response (TFR) analysis. Whole brain TFR for control (top left) and VRH (top right) conditions. The x-axis of whole brain TFR represents time in ms and y-axis represents frequency in Hz. The black box indicates reduced power-spectrum in VRH (frequency 1–5 Hz, time 100–560 ms, $p = 0.01$) and the red box indicates increased power spectral in VRH (frequency 5–11 Hz frequency, 340–800 ms time, $p = 0.04$). In the middle and bottom raws, TFR topological differences are presented. TFR topoplots for the negative cluster represents 1–5 Hz frequencies from 100 to 560 ms after stimulus onset ($p = 0.01$) (middle raw). Positive cluster TFR topoplots represent 5 Hz-11 Hz frequencies from 340 to 800 ms after stimulus onset ($p = 0.005$) (bottom raw). The cross symbols in the right-side topoplots represent electrodes that have significant TRF difference in the VRH condition compared to the control condition (white crosses represent decrease and black crosses represent increased TFR during VRH).

time window of the P200 components, which is related to conscious access to sensory stimulation. In a review, authors hypothesized that such synchronization reflects ACC-mediated inhibitory effect that prevents conscious access to nociceptive stimuli. This same process is commonly acknowledged to explain the role of ACC in hypnotic analgesia. A similar increase in alpha activity was also reported in a laser-evoked pain study and was associated with cognitive or memory task-related processes (Iannetti et al., 2008).

In summary, the current study has shown that VRH modifies brain processes underlying pain processing. While this aspect was not the main focus of our study, we might hypothesize that the likely underlying mechanism

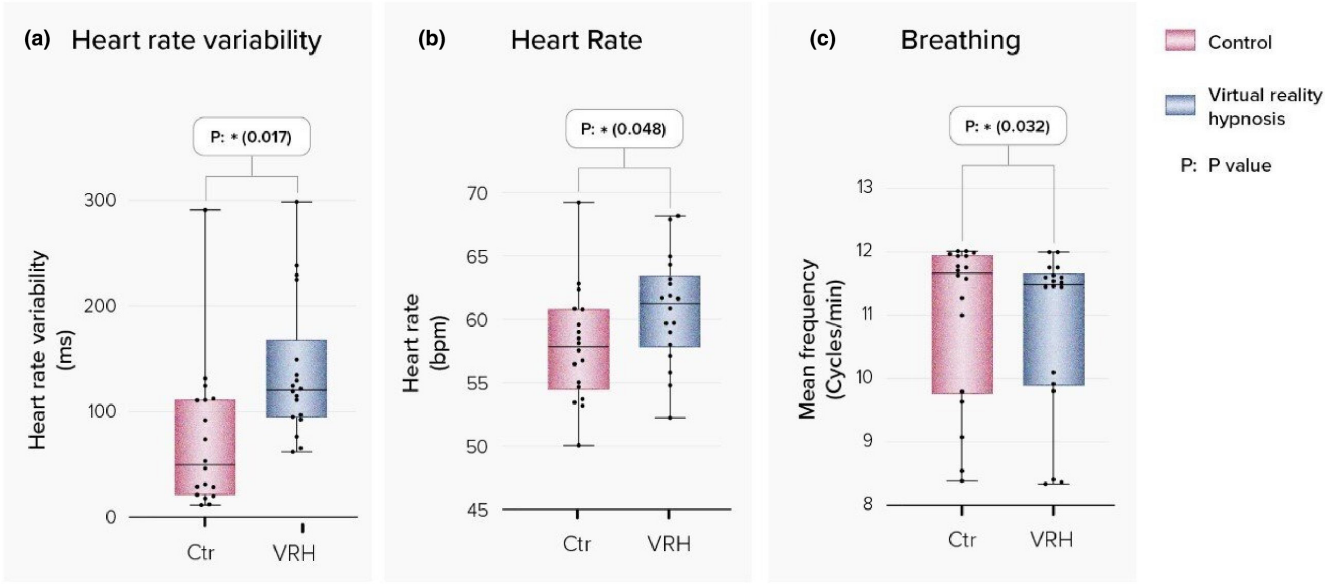

FIGURE 5 Body physiological parameters for both control (ctr) and VRH condition: Heart rate variability (a), heart rate (b) and breathing (c), using boxplots. Box limits represent 25th to 75th percentiles; line represents median; whiskers delimit minimum and maximum. All individual values are represented by dots.

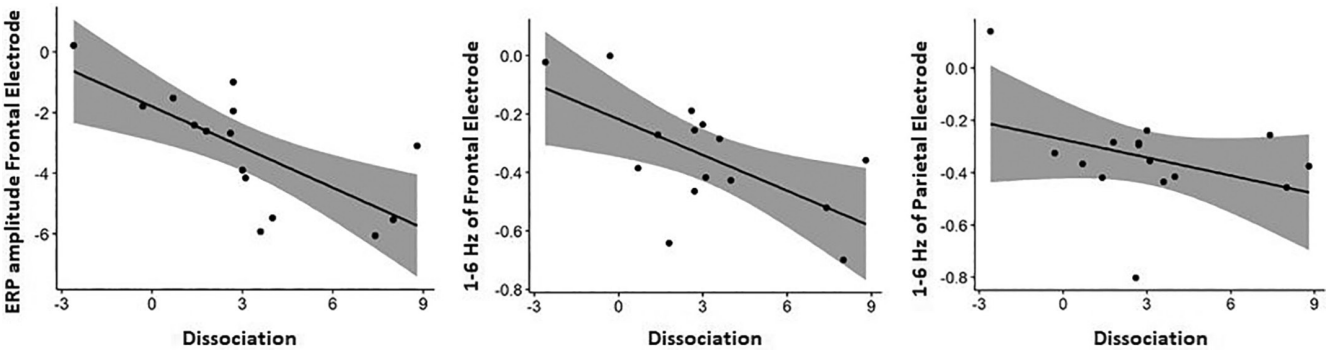

FIGURE 6 Correlations between (1) the self-reported level of dissociation and both ERP components measured at frontal electrodes, (2) the self-reported level of dissociation and the low-frequency (1–6 Hz) power content at frontal electrodes, and (3) the self-reported level of dissociation and the low-frequency (1–6 Hz) power content at parietal electrodes.

for this modification is dissociation. Several points support this hypothesis. First, subjects have reported significantly higher dissociation levels in the VRH condition as compared to the control condition, supporting that, similarly to hypnosis, VRH induces dissociation. Second, higher levels of dissociation were associated with reduced N100 and P200 components, which directly relate to pain perception. Physiological results also strengthen this hypothesis as lower respiratory rate and higher heart rate variability were previously observed during hypnosis (Dunham et al., 2021).

However, neurophysiological correlates of dissociation are still unclear. In the current study, we highlighted that the pain response in the VRH condition was characterized by early power decrease in the 1–5 Hz frequency band, which was larger in subjects reporting higher levels of dissociation. Such transient decreases in EEG power are generally associated with event-related desynchronization of cortical processes and are thought to reflect latent cerebral mechanisms (Iannetti et al., 2008).

So far, pieces of evidence regarding dissociation mainly come from hypnosis studies. The hypnotic state was previously characterized by an increase in delta activity, reflecting an increased independence of brain regions and a state of dissociation (Li et al., 2017; Panda et al., 2018). This dissociation is characterized by an increased frontal–parietal activity modulation that entails a disruption in the cognitive attention, which can influence the perception of environmental stimulations during hypnosis. Assumptions on the effect of hypnosis on the theta frequency band are more contradictory. While some studies report an increase in theta activity reflecting the intensification of attentional

processes, others have found a decrease in theta activity during hypnosis (Fingelkurts et al., 2007). Those discrepancies might be linked to inter-individual variability response to hypnotic suggestions (Fingelkurts et al., 2007).

Interestingly, our 1–5 Hz frequency band differs from the standard delta and theta frequency bands, as it encompasses part of both. It is also known that brain activity works in opposite direction during task/stimulus condition compared to rest. This could explain why our findings of decreased (inhibition) delta and theta power after noxious stimulations could be linked to a dissociative state.

The current study omits the interesting question of the direct comparison between VRH, VR and hypnosis. However, this comparison seems of low relevance as the goal of this study was to objectivize the reduction of pain perception induced by VRH. More than just a superposition of clinical hypnosis and VR, VRH uses images and sounds to illustrate and support the hypnotic script. VRH therefore overcomes the main limitations of clinical hypnosis (need for specific trained professionals, the requirement for continuous patient-side presence, patient's language proficiency, heterogeneity of response to the hypnotic suggestions of patients) (Cornelis et al., 2019) while offering the same level of analgesia (Patterson et al., 2010). We still acknowledge that a direct comparison would be really interesting to investigate specific brain processes responsible for VRH-induced analgesia.

This study represents a first step in the objectivation of VRH-induced modulation of pain perception and it has several limitations. First, this study was performed in an age-homogeneous sample while previous studies demonstrated that the analgesic effect of VR is influenced by individual characteristics such as age (Lier et al., 2020). Second, VRH is challenging to blind. A proposition for future studies could be to implement a fixed environment with a fixation point into the VR glasses. Third, we observed a trend of non-significant increase anxiety in the control condition that could have been due to set-up differences between both conditions, as the VR set-up itself isolates subjects from the environment. Inserting the VR headset into the control condition could prevent this bias. Fourth, self-reported data were measured once for each condition while EEG and other physiological data are measured continuously. This methodology is certainly not optimal, especially for pain ratings, since it provides only one global score per condition. This solution was however chosen to not disturb the VRH experience by asking questions. Finally, the control condition was assessed without the headset and VRH device on the head. Even though there are studies where the EEG recording is performed with VR headset for active condition and without VR headset for baseline condition (Cattan et al., 2019; Tarrant et al., 2018), one may argue that the recording during this condition might have been less noisy and thus introducing an important flaw in the EEG analysis. We should however highlight that the differences observed between conditions were not limited to the electrodes under the headset but were observed in frontal, central and posterior regions of the scalp. Nevertheless, we should keep in mind that the analysis we have used here is centred on a whole-brain average reference, such that weaker or noisier signal at any site in the VRH condition might have affected overall sensitivity in that condition. Future studies should take this limitation into consideration and systematically add a control condition during which subjects are wearing all the headset device, without any VRH immersion.

Future studies with larger number of subjects should be carried out to generalize the findings of the current work. Moreover, the long-lasting effects of pain should be investigated, as well as inter-subjects variability of responses to VRH. Finally, future studies should compare the potential additive effects of the combination of hypnosis and VR to VR and hypnosis intervention alone, both at the behavioural and brain levels, in both clinical and experimental settings.

5 | CONCLUSION

VRH modulates cerebral pain processing as reflected in reduced N100 and P200 ERP components, resulting in decreased pain perception and modified body physiology. We highlighted two specific EEG frequency bands which reflect states of effective cognitive processing, focused attention and enhanced somatic and emotional control. Findings objectivize the effect of VRH-induced analgesia during interventional condition offer first insight into the mechanisms of action of VRH. Overall, this suggests that VRH is an effective and quantifiable approach to reduce pain in a non-pharmacological way.

AUTHOR'S CONTRIBUTION

AV and OG are guarantors. Design and conception of the study: all authors. Project supervisors: AV, OG. Acquisition of data: AV, FR, MN, RP. Statistical analysis: RP, FR, CT. Interpretation of data: RP, FR, OG, AV. Writing up of the first draft: FR, RP, CT. Revision of the draft: all authors. Revision of the final draft: OG, AV. Read and approved the final manuscript: all authors.

ACKNOWLEDGEMENTS

The authors would like to thank the Algology Interdisciplinary Center (University Hospital of Liege) and all the volunteers who participated in the study.

FUNDING INFORMATION

Thanks to the University and University Hospital of Liege, the Benoit Foundation (Brussels, Belgium), the Non-Fria Grant (Liege, Belgium), the Belgian National Funds for Scientific Research (FRS-FNRS), the European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 945539 (Human Brain Project SGA3), the BIAL Foundation, the fund Generet of the King Baudouin Foundation and AstraZeneca Foundation. RP is a research fellow, OG is a research associate and SL is a research director at FRS-FNRS.

CONFLICT OF INTEREST

Oncomfort SA gave a financial contribution for this study and provided the VRH material. Marie-Elisabeth Faymonville and Steven Laureys are part of the scientific board of Oncomfort (www.oncomfort.com). Clémence Toussaint is employee at Oncomfort. Other authors report no conflicts of interest in this work.

ORCID

Rajanikant Panda https://orcid.org/0000-0002-0960-4340
Steven Laureys https://orcid.org/0000-0002-3096-3807
Olivia Gosseries https://orcid.org/0000-0001-9011-7496
Audrey Vanhaudenhuyse https://orcid.org/0000-0002-4288-9237

REFERENCES

Bicego, A., Monseur, J., Collinet, A., Donneau, A.-F., Fontaine, R., Libbrecht, D., Malaise, N., Nyssen, A.-S., Raaf, M., Rousseaux, F., Salamun, I., Staquet, C., Teuwis, S., Tomasella, M., Faymonville, M.-E., & Vanhaudenhuyse, A. (2021). Complementary treatment comparison for chronic pain management: A randomized longitudinal study. *PLoS One*, *16*, e0256001.

Cattan, G. H., Andreev, A., Mendoza, C., & Congedo, M. (2019). A comparison of mobile VR display running on an ordinary smartphone with standard PC display for P300-BCI stimulus presentation. *IEEE Transactions on Games*, *13*(1), 68–77.

Clifford, G. D., Azuaje, F., & McSharry, P. E. (2006). *Advanced methods and tools for ECG analysis. Engineering in medicine and biology*. Artech House.

Cornelis, F. H., Monard, E., Moulin, M.-A., Vignaud, E., Laveissiere, F., Ben Ammar, M., Nouri-Neuville, M., Barral, M., & Lombart, B. (2019). Sedation and analgesia in interventional radiology: Where do we stand, where are we heading and why does it matter? *Diagnostic and Interventional Imaging*, *100*, 753–762.

De Benedittis, G. (2020). Hypnosis: From neural mechanisms to clinical practice. *OBM Integrative and Complementary Medicine*, *5*(3), 039. https://doi.org/10.21926/obm.icm.2003039

De Ridder, D., Adhia, D., & Vanneste, S. (2021). The anatomy of pain and suffering in the brain and its clinical implications. *Neuroscience and Biobehavioral Reviews*, *130*, 125–146.

Defechereux, T., Degauque, C., Fumal, I., Faymonville, M. E., Joris, J., Hamoir, E., & Meurisse, M. (2000). L'hypnosédation, un nouveau mode d'anesthésie pour la chirurgie endocrinienne cervicale. Étude prospective randomisée. *Annales de Chirurgie*, *125*, 539–546.

Dunham, C. M., Burger, A. J., Hileman, B. M., Chance, E. A., & Hutchinson, A. E. (2021). Bispectral index alterations and associations with autonomic changes during hypnosis in trauma center researchers: Formative evaluation study. *JMIR Formative Research*, *5*, e24044.

Elkins, G. R., Barabasz, A. F., Council, J. R., & Spiegel, D. (2015). Advancing research and practice: The revised APA division 30 definition of hypnosis. *The American Journal of Clinical Hypnosis*, *57*, 378–385.

Enea, V., Dafinoiu, I., Opriş, D., & David, D. (2014). Effects of hypnotic analgesia and virtual reality on the reduction of experimental pain among high and low hypnotizables. *The International Journal of Clinical and Experimental Hypnosis*, *62*, 360–377.

Fingelkurts, A. A., Fingelkurts, A. A., Kallio, S., & Revonsuo, A. (2007). Cortex functional connectivity as a neurophysiological correlate of hypnosis: An EEG case study. *Neuropsychologia*, *45*, 45–1462.

Fox, J., Bouchet-Valat, M., Andronic, L., Ash, M., Boye, T., Calza, S., Chang, A., Grosjean, P., Heiberger, R., Pour, K.K., Kerns, G.J., Lancelot, R., Lesnoff, M., Ligges, U., Messad, S., Maechler, M., Muenchen, R., Murdoch, D., Neuwirth, E., Putler, D., Ripley, B., Ristic, M., Wolf, P., Wright, K. (2019). *Rcmdr: R Commander*. R package version 2.5-2. https://cran.r-project.org/web/packages/Rcmdr/index.html

Hung, P. D., Bonnet, S., Guillemaud, R., Castelli, E., & Yen, P. T. N. (2008). Estimation of respiratory waveform using an accelerometer. In *2008 5th IEEE International Symposium on Biomedical Imaging: From Nano to Macro* (pp. 1493–1496). IEEE.

Iannetti, G. D., Hughes, N. P., Lee, M. C., & Mouraux, A. (2008). Determinants of laser-evoked eeg responses: Pain perception or stimulus saliency? *Journal of Neurophysiology*, *100*, 815–828.

Lee, M. C., Mouraux, A., & Iannetti, G. D. (2009). Characterizing the cortical activity through which pain emerges from nociception. *Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *29*, 7909–7916.

Li, X., Ma, R., Liangjun, P., Lv, W., Xie, Y., Chen, Y., Pengyu, Z., Chen, J., Wu, Q., Cui, G., Peng, Z., Zhou, Y., & Xiaochu, Z. (2017). Delta coherence in resting-state EEG predicts the reduction in cigarette craving after hypnotic aversion suggestions. *Scientific Reports*, *7*(1), 2430.

Lier, E. J., Oosterman, J. M., Assmann, R., de Vries, M., & van Goor, H. (2020). The effect of virtual reality on evoked potentials following painful electrical stimuli and subjective pain. *Scientific Reports*, *10*, 9067.

Matre, D., Hu, L., Viken, L. A., Hjelle, I. B., Wigemyr, M., Knardahl, S., Sand, T., & Nilsen, K. B. (2015). Experimental sleep restriction facilitates pain and electrically induced cortical responses. *Sleep*, *38*, 1607–1617.

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience*, *2011*, 1–9.

Palaniappan, Y., Vishanth, V. A., Santhosh, N., Karthika, R., & Ganesanw, M. (2020). R - peak detection using altered pan-Tompkins algorithm. In *Proceedings of the 2020 IEEE International Conference on Communication and Signal Processing. ICCSP*.

Panda, R., Gosseries, O., Vanhaudenhuyse, A., Demertzi, A., Piarulli, A., Faymonville, M.-E., & Laureys, S. (2018). Neural correlates of modified subjective state of consciousness induced by hypnosis using EEG-connectivity approach. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/conf.fnins.2018.95.00100

Patterson, D. R., Hoffman, H. G., Chambers, G., Bennetts, D., Hunner, H. H., Wiechman, S. A., Garcia-Palacios, A., & Jensen, M. P. (2021). Hypnotic enhancement of virtual reality distraction analgesia during thermal pain: A randomized trial. *The International Journal of Clinical and Experimental Hypnosis*, *69*, 225–245.

Patterson, D. R., Jensen, M. P., Wiechman, S. A., & Sharar, S. R. (2010). Virtual reality hypnosis for pain associated with recovery from physical trauma. *The International Journal of Clinical and Experimental Hypnosis*, *58*, 288–300.

Patterson, D. R., Tininenko, J. R., Schmidt, A. E., & Sharar, S. R. (2004). Virtual reality hypnosis: A case report. *The International Journal of Clinical and Experimental Hypnosis*, *52*, 27–38.

Ree, A., Nilsen, K. B., Knardahl, S., Sand, T., & Matre, D. (2020). Sleep restriction does not potentiate nocebo-induced changes in pain and cortical potentials. *Eur J Pain U K*, *24*, 110–121.

Rousseaux, F., Bicego, A., Ledoux, D., Massion, P., Nyssen, A. S., Faymonville, M. E., Laureys, S., & Vanhaudenhuyse, A. (2020). Hypnosis associated with 3d immersive virtual reality technology in the management of pain: A review of the literature. *Journal of Pain Research*, *13*, 1129–1138.

Rousseaux, F., Bicego, A., Malengreaux, C., Faymonville, M.-E., Ledoux, D., Massion, P. B., Nyssen, A.-S., & Vanhaudenhuyse, A. (2020). *Can hypnosis be used in intensive care units? Médecine Intensive Réanimation*.

Shaffer, F., & Ginsberg, J. P. (2017). An overview of heart rate variability metrics and norms. *Front Public Health*, *5*, 5.

Tarrant, J., Viczko, J., & Cope, H. (2018). Virtual reality for anxiety reduction demonstrated by quantitative EEG: A pilot study. *Frontiers in Psychology*, *9*, 1280.

Vanhaudenhuyse, A., Nyssen, A. S., & Faymonville, M. E. (2020). Recent insight on how the neuroscientific approach helps clinicians. *OBM Integrative and Complementary Medicine*, *5*(2), 028. https://doi.org/10.21926/obm.icm.2002028

Vanhaudenhuyse, A., Boly, M., Balteau, E., Schnakers, C., Moonen, G., Luxen, A., Lamy, M., Degueldre, C., Brichant, J. F., Maquet, P., Laureys, S., & Faymonville, M. E. (2009). Pain and non-pain processing during hypnosis: A thulium-YAG event-related fMRI study. *Neuroimage.*, *47*(3), 1047–1054. https://doi.org/10.1016/j.neuroimage.2009.05.031.

Vanhaudenhuyse, A., Ledoux, D., Gosseries, O., Demertzi, A., Laureys, S., & Faymonville, M.-E. (2019). Can subjective ratings of absorption, dissociation, and time perception during "neutral hypnosis" predict hypnotizability?: An exploratory study. *The International Journal of Clinical and Experimental Hypnosis*, *67*, 28–38.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rousseaux, F., Panda, R., Toussaint, C., Bicego, A., Niimi, M., Faymonville, M.-E., Nyssen, A.-S., Laureys, S., Gosseries, O., & Vanhaudenhuyse, A. (2023). Virtual reality hypnosis in the management of pain: Self-reported and neurophysiological measures in healthy subjects. *European Journal of Pain*, *27*, 148–162. https://doi.org/10.1002/ejp.2045