STUDY PROTOCOL

Comparison of the Effects of Virtual Reality, Hypnosis, and Their Combination on Experimental Pain, Physiological Measures, and Electroencephalographic Signatures

Short title: RVH EXPE

NCT number: to be assigned upon registration

Document date: June 21, 2026 (protocol version 3, dated June 4, 2026)

REB approval: CÉR CIUSSS-EMTL No. 2027-4393

Principal Investigator: David Ogez, PhD

Department of Anesthesiology and Pain Medicine, Université de Montréal

Hôpital Maisonneuve-Rosemont, CIUSSS de l'Est-de-l'Île-de-Montréal

5415, boulevard de l'Assomption, Montréal, Québec, H1T 2M4, Canada

david.ogez@umontreal.ca

Co-Investigators: Pascal Laferrière-Langlois, MD; Louis Morisson, MD; Pierre Rainville, PhD; Mathieu Piché, PhD; Mathieu Landry, PhD

Graduate Student: Meriem Zennouche

CONFIDENTIAL — This document is the property of Université de Montréal. No part of this document may be disclosed, reproduced, published, or used by a third party without the prior written authorization of Dr. David Ogez.

1. Background and Rationale

1.1 Problem Statement

Procedure-related pain remains a major clinical challenge across many care settings, particularly in oncology and interventional specialties, where patients undergo repeated invasive procedures whose management remains insufficiently controlled despite pharmacological advances. Pain, beyond its strictly sensory component, is a multidimensional experience involving attentional, emotional, and cognitive dimensions that contribute to its interindividual variability and functional impact. To date, gaps remain in the literature regarding studies that simultaneously compare virtual reality (VR), hypnosis (H), and their combination (VRH) within a single controlled experimental design, as well as the need to distinguish the differentiated underlying mechanisms — top-down mechanisms for hypnosis and bottom-up mechanisms for VR.

1.2 State of Knowledge

Despite the use of pharmacological analgesics, a substantial proportion of patients present significant levels of pain and distress — a phenomenon attributable to the sometimes-limited efficacy of these agents and their adverse effects (approximately 30–50% of patients according to some estimates). In this context, non-pharmacological approaches are attracting growing interest due to their capacity to modulate pain perception by targeting underlying neurocognitive mechanisms. Among these, hypnosis and virtual reality have demonstrated robust analgesic effects in both experimental and clinical contexts. Hypnosis acts through top-down mechanisms involving the modulation of expectations, attention, and interpretation of sensory experience; VR, in turn, engages bottom-up processes related to sensory immersion and attentional capture. Recent work suggests that these approaches rely on partially distinct but potentially complementary mechanisms, opening the way to combined strategies that may optimize pain modulation.

Several limitations remain in the current literature. Comparative studies between these approaches remain scarce, and few have evaluated their respective and combined effects within a single rigorous experimental protocol. Moreover, most available data originate from controlled experimental contexts whose applicability to real clinical situations, particularly during medical interventions, remains to be demonstrated. Recent data nonetheless suggest that the combination of VR and hypnosis (VRH) may produce superior analgesic effects compared to either approach used alone (estimated gains of 15–25% in some protocols), by simultaneously engaging top-down and bottom-up mechanisms. These combined effects remain poorly documented, particularly in procedural contexts where environmental constraints, cognitive load, and emotional factors are likely to influence intervention efficacy.

1.3 Methodological Recommendations and Research Proposal

The neurophysiological mechanisms underlying these effects remain insufficiently characterized. Although some studies have independently explored the brain correlates of hypnosis and VR (e.g., changes in alpha and theta oscillations), few have examined their comparative and combined neurophysiological signatures in real time. Electroencephalography (EEG) is a particularly relevant tool in this regard, as it captures the brain dynamics associated with attention, sensory engagement, and cognitive modulation of pain. Integrating EEG measures during procedures represents an opportunity to better understand the processes involved in analgesia induced by these interventions.

It is therefore essential to rely on controlled experimental designs to characterize the specific and combined effects of VR and hypnosis prior to their implementation in clinical settings. Induced pain models (calibrated electrical or thermal stimulation) allow standardization of nociceptive stimulation, control of contextual variables, and rigorous comparison of the different intervention modalities. This approach provides a methodological framework for isolating the mechanisms of action of VR, hypnosis, and VRH, while integrating both subjective measures (numeric pain rating scales, distress questionnaires) and neurophysiological measures (RIII nociceptive reflex, evoked potentials, EEG spectral analyses).

2. Study Objectives

This study aims to characterize, through a rigorous experimental protocol, the specific and combined effects of virtual reality (VR), hypnosis (H), and their combination (VRH) on the modulation of induced pain. Four main objectives structure the overall research design.

2.1 Primary Objective (1) — Pain Modulation

Compare the effects of VR, H, and VRH on the intensity and unpleasantness of experimentally induced pain. We hypothesize that VRH will produce superior analgesic effects compared to VR and H, due to the simultaneous engagement of top-down (H) and bottom-up (VR) mechanisms.

2.2 Secondary Objective (2) — Emotional Modulation

Evaluate the effects of VR, H, and VRH on emotional distress and anxiety associated with experimental pain stimulation, given that these dimensions significantly contribute to interindividual variability in the pain experience. We expect a significant reduction in emotional distress across all active conditions compared to baseline, with a more pronounced effect in the VRH condition.

2.3 Secondary Objective (3) — Physiological Modulation

Compare the effects of the three conditions (VR, H, VRH) on physiological parameters associated with the nociceptive and autonomic response. We hypothesize that the VRH condition will be associated with reduced RIII reflex amplitude and lower autonomic reactivity compared to VR and H used in isolation. This objective includes: the RIII nociceptive flexion reflex; cardio-respiratory indices (heart rate, heart rate variability, respiratory rate); and skin conductance.

2.4 Exploratory Objective (4) — EEG Profiles

Compare EEG signatures associated with the three conditions during painful stimulation, with particular attention to relevant frequency bands (alpha, theta, gamma) and functional connectivity indices, in order to identify potential predictors of response to non-pharmacological pain-modulation approaches.

3. Methods

3.1 Study Design

This study is a within-subjects experimental design with three conditions (VR, H, VRH), with counterbalancing of presentation order using a Latin square to control for order and fatigue effects. Each participant is exposed to all three conditions during a single session of approximately 140 minutes, conducted in a dedicated psychophysiology laboratory.

3.2 Sample Size and Power Calculation

Sample size was calculated using G*Power (v.3.1.9.7) for a repeated-measures design (repeated-measures ANOVA, three conditions). Based on effect sizes reported in the literature — notably Rousseaux et al. (2022), who observed moderate effects (Cohen's $d \approx 0.50$; $f \approx 0.25$) of VRH on subjective pain indices compared to isolated conditions — the following parameters were used: effect size $f = 0.25$ (moderate, conservative estimate), $\alpha = 0.05$, power $(1–\beta) = 0.80$, average correlation among repeated measures $\rho = 0.50$, non-sphericity correction $\varepsilon = 1$. These parameters yield a minimum sample of $n = 28$. To account for an estimated 20% attrition/exclusion rate (unusable EEG data, withdrawal, non-response to RIII calibration), the target sample size is set at $n = 40$.

3.3 Participants and Recruitment

The study will include adults aged 18 to 65 recruited from the general population via institutional postings (Hôpital Maisonneuve-Rosemont, Université de Montréal), emails distributed to staff and student mailing lists of Université de Montréal (Department of Psychology and Anesthesiology) and Hôpital Maisonneuve-Rosemont (research center) with approval from the relevant directors, as well as social media announcements. Potential participants will be invited to contact the research team and will undergo pre-screening (by phone or via an online REDCap form hosted by CIUSSS-EMTL) to verify eligibility. Eligibility criteria will be verified by phone interview or via a structured REDCap form, then confirmed verbally by the participant at the start of the session. No medical chart review is required.

The informed consent form (ICF) is sent to the participant before the session (by email or via REDCap) to allow at least a 48-hour reflection period. Formal confirmation of eligibility and signing of consent take place at the start of the experimental session, avoiding an additional visit. Participants are informed of the experimental nature of the induced pain, its controlled and adjustable intensity, and their right to withdraw at any time without consequence.

3.3.1 Inclusion Criteria

- Adults aged 18 to 65 years
- Fluency in French (validated French-language versions of all instruments and the hypnotic script)
- Capacity to provide free and informed consent
- General good health, without uncontrolled acute or chronic pathology
- Sufficient visual and auditory acuity (corrected as needed) to interact with the experimental equipment (VR headset, hypnotic instructions)

3.3.2 Exclusion Criteria

- History of major neurological disorders (epilepsy, severe head trauma, multiple sclerosis) or major psychiatric disorders (psychosis, dissociative disorders, active PTSD)
- Current use of medication likely to affect pain perception or CNS activity (opioids, benzodiazepines, anticonvulsants, tricyclic antidepressants, gabapentinoids)
- Alcohol or psychoactive substance use within 24 hours prior to the session
- Use of analgesics (e.g., ibuprofen, acetaminophen, aspirin) within 24 hours prior to the session
- Contraindications to VR (severe history of cybersickness, vestibular disorders, ophthalmic migraine)
- Contraindications to EEG recording (scalp lesions, incompatible cranial metal implants)
- Current or suspected pregnancy
- Skin lesions, peripheral neuropathy, or any condition precluding safe electrical stimulation of the sural nerve
- Inability to tolerate moderate painful stimulation during calibration, operationalized as: (i) inability to reach the RIII reflex threshold without exceeding a subjective intensity of 7/10, or (ii) explicit request to stop during the first three calibration steps

3.4 Experimental Procedure

The experimental procedure is structured into four main phases: (i) welcome, consent, and baseline measures; (ii) calibration of nociceptive stimulation via the RIII reflex; (iii) exposure to the three experimental conditions (VR, H, VRH) in counterbalanced order; and (iv) final evaluations and debriefing. EEG and physiological recordings are performed continuously throughout.

3.4.1 Welcome, Consent, and Baseline Measures

Upon arrival, participants are welcomed by a team member trained in experimental procedures and the management of participants in induced-pain contexts. After signing the consent form, participants complete a series of baseline questionnaires: (a) a sociodemographic questionnaire developed by the team; (b) the STAI-T (State-Trait Anxiety Inventory, trait version); (c) the TAS (Tellegen Absorption Scale, abbreviated French version); (d) baseline state measures (11-point numeric rating scales for current pain and emotional state). Hypnotic susceptibility is assessed using the HGSHS:A (Harvard Group Scale of Hypnotic Susceptibility, Form A). The EEG system (24 dry electrodes) and physiological sensors (BIOPAC: heart rate, heart rate variability, respiratory rate, skin conductance) are then installed, followed by a 5-minute resting period (eyes open then eyes closed, 2.5 min each) to obtain baseline neurophysiological and autonomic measures.

3.4.2 Calibration of Nociceptive Stimulation (RIII Reflex)

Nociceptive stimulation is delivered via transcutaneous electrical stimulation of the sural nerve using surface electrodes positioned at the ankle. Electromyographic activity is recorded from the biceps femoris muscle to capture the RIII nociceptive flexion reflex, following the standardized protocol described by Sandrini et al. Stimulation parameters: train of 5 rectangular pulses (1 ms) delivered at 300 Hz (total train duration ≈ 17 ms); inter-stimulus interval randomized between 8 and 12 seconds (~0.1 Hz) to limit habituation; maximum allowed intensity of 40 mA (conservative safety threshold); maximum total of 150 stimulations per session (calibration included). Intensity is progressively increased in 2 mA steps to determine the perception threshold, pain threshold, and RIII reflex

threshold (defined as a reproducible EMG response with amplitude exceeding two standard deviations of background noise in the 90–180 ms post-stimulation window). The intensity used during the experimental phase corresponds to 120% of the RIII threshold, typically corresponding to a moderate pain level (4–6 on a 0–10 scale). A 5-minute rest period follows calibration to limit sensitization or fatigue.

3.4.3 Experimental Conditions

Participants are exposed to the three experimental conditions in counterbalanced order (Latin square, 6 sequences). Each condition targets complementary pain-modulation mechanisms: immersive attentional distraction (VR), top-down cognitive modulation and suggestion (H), and synchronized integration of both approaches (VRH). Each condition follows a standardized sequence of approximately 12–15 minutes, comprising three phases: (1) induction/immersion (3–5 min); (2) painful stimulation (7–8 min, 30 stimulations per condition), with continuous EEG, RIII, and autonomic recording; (3) post-condition evaluation (2–3 min). A 5–10 minute rest period is provided between each condition, without stimulation, to reduce residual effects, habituation, and sensitization.

3.4.4 End of Session and Debriefing

At the end of the session, participants complete final questionnaires on their overall experience and tolerability of the procedures. The Simulator Sickness Questionnaire (SSQ) is administered immediately after conditions involving VR (VR and VRH) to document cybersickness (safety measure). A 10-minute calming period is provided before removal of the equipment, followed by a debriefing on the participant's subjective experience. Psychological support resources are available if needed.

4. Measures and Variables

The study relies on a multimodal approach combining subjective, neurophysiological, and physiological measures, collected repeatedly throughout the session, allowing intra-individual comparison of the effects of the different conditions.

4.1 Subjective Pain Measures (Objective 1)

Pain intensity is assessed using an 11-point numeric rating scale (0 = no pain; 10 = maximum imaginable pain). Unpleasantness (affective dimension) is assessed on an identical scale, distinguishing the sensory and emotional components of the pain experience, consistent with Rainville's classic approach. These measures are collected immediately after each condition.

4.2 Emotional and Cognitive Measures (Objective 2)

Emotional and cognitive dimensions are assessed using 11-point numeric rating scales administered after each condition: anxiety, emotional distress, negative affect, and perceived control over pain. Condition-specific process variables are also assessed: immersion/presence (VR and VRH), attentional absorption/engagement, and ease of following suggestions (H and VRH). Baseline measures are collected before calibration: current pain, anxiety, emotional distress, negative affect, fatigue, and vigilance.

4.3 Physiological Measures (Objective 3)

Nociception is assessed via the RIII nociceptive flexion reflex, recorded by electromyography of the biceps femoris muscle. Reflex amplitude is quantified in the 90–180 ms post-stimulation window, and aggregated indices (mean amplitude and area under the curve) are calculated for each condition. Autonomic measures are recorded continuously via the BIOPAC system: heart rate (ECG), heart rate variability (time and frequency domain), respiratory rate (chest belt), and skin conductance (palmar electrodes).

4.4 Neurophysiological Measures — EEG (Objective 4)

Brain activity is recorded continuously using a 24-channel dry-electrode EEG system at a 500 Hz sampling rate. Analyses will focus on: (i) oscillatory activity in the alpha (8–12 Hz), beta (13–30 Hz), theta (4–7 Hz), and gamma (30–80 Hz) bands; (ii) nociceptive evoked potentials (N2/P2), included only when the signal-to-noise ratio meets a minimum threshold (SNR ≥ 5 dB); and (iii) exploratory functional connectivity indices.

5. Statistical Analysis Plan

The statistical analysis plan is designed to address the four study objectives while accounting for the within-subjects structure of the data. Analyses will be conducted using R. The significance threshold is set at $p < 0.05$, with appropriate corrections for multiple comparisons (Benjamini-Hochberg for exploratory EEG analyses; Bonferroni for planned comparisons).

Descriptive analyses will first characterize the sample and data quality, including detection of outliers, verification of distributions, and identification of missing data. For the primary objective, linear mixed models will be used, with experimental condition (VR, H, VRH) as a fixed effect, participant as a random effect (random intercept), and presentation order as a control covariate. Similar analyses will be conducted for unpleasantness. Pairwise comparisons between conditions will use Bonferroni correction.

Emotional (Objective 2) and physiological (Objective 3) variables will be analyzed using the same approach. EEG data (Objective 4) will undergo spectral analyses (power in bands of interest) and event-related analyses (evoked potentials), compared between conditions using mixed models or cluster-based permutation tests. Integrative analyses will examine relationships between dimensions (correlations, regressions, mediation analyses) to explore links between subjective pain, emotional variables, physiological indices, and brain activity. Exploratory analyses may identify responder profiles (clustering, hypnotic susceptibility as a moderator).

No imputation is planned for missing data; case-by-case exclusion will be applied (e.g., unusable EEG data due to SNR < 5 dB), with the participant retained for other outcome families.

6. Ethical Considerations

This project will be conducted in accordance with the Declaration of Helsinki and the institutional standards of the CIUSSS de l'Est-de-l'Île-de-Montréal. All participants will provide free and informed consent prior to inclusion.

6.1 Consent and Reflection Period

The informed consent form (ICF) will be sent to the participant before the session (by email or via REDCap), allowing at least a 48-hour period to review it. Formal confirmation of eligibility and signing of consent take place at the start of the experimental session.

6.2 Identified Risks

Risks associated with this study are considered low to moderate, related to four components: painful stimulation (transient discomfort, possible localized bruising; minimized by individualized calibration ≤7/10 and immediate interruption if requested), virtual reality (cybersickness or transient nausea; minimized by exclusion criteria and continuous monitoring), hypnosis (mild anxiety or transient emotional response in sensitive individuals; minimized by staff training and availability of psychological support), and neurophysiological recording (mild skin irritation from electrodes; minimized by dry electrodes and hypoallergenic gel).

6.3 Protection and Safety Measures

- Individualized calibration of stimulation, maintaining intensity at a tolerable level (≤7/10)
- Continuous monitoring by a team member trained in experimental procedures and emotional response management
- Possibility of immediate interruption at the participant's request, without justification
- Planned rest periods between conditions (5–10 min)
- Strict exclusion criteria (neurological, psychiatric disorders, VR/EEG contraindications)
- Controlled, safe laboratory environment equipped for emergencies

6.4 Adverse Event Management and Reporting

Any adverse event (AE) occurring during or within 48 hours of the session will be recorded in a dedicated log. A post-session follow-up plan is in place: systematic phone contact 24–48 hours after the session to confirm the absence of residual effects; PI contact information (Dr. David Ogez, 514-252-3400 ext. 4443) provided in writing;

referral to the Hôpital Maisonneuve-Rosemont psychology service or appropriate external resources (Info-Social 811) in case of psychological distress.

6.5 Compensation

Each participant who completes the session receives compensation in the form of a prepaid Visa card, calculated based on participation time (approximately 2 hours, including screening and the experimental session). In case of early withdrawal after the session has begun, compensation proportional to time spent is provided. This amount is considered non-coercive according to Québec psychophysiological research standards. (Note: the protocol and informed consent form should be harmonized regarding the exact compensation amount — $50 CAD is stated in the protocol, $60 CAD in the informed consent form.)

6.6 Data Management and Protection

Data collection, storage, and processing comply with Québec's Act Respecting the Protection of Personal Information (Law 25) and CIUSSS-EMTL institutional requirements. Participants are assigned a unique alphanumeric code upon inclusion; all data are collected and stored in coded form. The coded database is hosted on secure CIUSSS-EMTL servers for 7 years. The correspondence key between participant identity and code is stored in a separate, password-protected file, with access restricted to authorized research team members.

6.7 Conflicts of Interest and Funding

This project is funded by the Fondation Cole. The researchers declare no financial or personal conflict of interest likely to influence the conduct or interpretation of the study. The immersive VR content provider (Super Sublime) has no role in study design, analysis, or manuscript preparation, and receives no compensation related to this project. VR headsets were purchased using research funds, with no industry partnership involved.

7. Expected Outcomes

This study aims to advance understanding of non-pharmacological pain-modulation mechanisms while generating knowledge that may inform future clinical practice, with scientific, clinical, methodological, and societal implications, including the potential development of integrative VR-hypnosis protocols for procedural pain management and the identification of predictive biomarkers of treatment response.

References

1. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain: a review of published literature. Ann Oncol. 2008;19(12):1985-1991.

2. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007;18(9):1437-1449.

3. Melzack R, Casey KL. Sensory, motivational, and central control determinants of pain. In: Kenshalo DR, ed. The Skin Senses. Springfield: Charles C Thomas; 1968:423-443.

4. Wiech K, Ploner M, Tracey I. Neurocognitive aspects of pain perception. Trends Cogn Sci. 2008;12(8):306-313.

5. Eccleston C, Crombez G. Pain demands attention: a cognitive-affective model. Psychol Bull. 1999;125(3):356-366.

6. Montgomery GH, DuHamel KN, Redd WH. A meta-analysis of hypnotically induced analgesia. Int J Clin Exp Hypn. 2000;48(2):138-153.

7. Hoffman HG, Richards TL, Coda B, et al. Modulation of thermal pain-related brain activity with virtual reality. Neuroreport. 2004;15(8):1245-1248.

8. Indovina P, Barone D, Gallo L, et al. Virtual reality as a distraction intervention to relieve pain and distress during medical procedures. Clin J Pain. 2018;34(9):858-877.

9. Jensen MP, Patterson DR. Hypnotic approaches for chronic pain management. Am Psychol. 2014;69(2):167-177.

10. Rousseaux F, Bicego A, Ledoux D, et al. Hypnosis associated with 3D immersive virtual reality technology in the management of pain: a review. J Pain Res. 2020;13:1129-1138.

11. Patterson DR, Jensen MP, Wiechman SA, Sharar SR. Virtual reality hypnosis for pain associated with recovery from physical trauma. Int J Clin Exp Hypn. 2010;58(3):288-300.

12. Rousseaux F, Dardenne N, Massion PB, et al. Virtual reality and hypnosis for anxiety and pain management in intensive care units. Eur J Anaesthesiol. 2022;39(1):58-66.

13. Vanhaudenhuyse A, Laureys S, Faymonville ME. Neurophysiological correlates of hypnotic analgesia. Contemp Hypn. 2009;26:15-23.

14. Jensen MP, Adachi T, Tomé-Pires C, et al. Mechanisms of hypnosis: toward a biopsychosocial model. Int J Clin Exp Hypn. 2015;63(1):34-75.

15. Sandrini G, Serrao M, Rossi P, et al. The lower limb flexion reflex in humans. Prog Neurobiol. 2005;77(6):353-395.

16. Shor RE, Orne EC. Harvard Group Scale of Hypnotic Susceptibility, Form A. Palo Alto: Consulting Psychologists Press; 1962.

17. Rainville P, Carrier B, Hofbauer RK, et al. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. Pain. 1999;82(2):159-171.