

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Project summary

This controlled experimental study investigates the effects of hypnosis on stress regulation and executive performance in medical students exposed to experimentally induced psychological stress. Medical training is characterized by high cognitive demands and sustained stress exposure, which may negatively impact executive functioning and emotional regulation. Hypnosis has demonstrated potential in modulating stress responses and autonomic activity, yet its integrated effects across cognitive, subjective, and physiological domains remain insufficiently characterized.

The primary objective of this study is to evaluate whether a standardized hypnosis intervention can improve executive performance under stress and modulate autonomic stress responses. Secondary objectives include assessing changes in perceived stress and anxiety associated with negative memory recall.

This study is a controlled, parallel-group experimental study with repeated within-subject measurements conducted in final-year medical students exposed to a stress induction paradigm based on negative autobiographical memories related to their medical education.

Participants were allocated (using a non-random allocation procedure; sequential enrollment) to either a hypnosis intervention group (INT) or a breath-focused attention control group (CTRL).

The INT group was enrolled first to reach the planned within-subject sample size; the CTRL group was subsequently recruited as an active comparator to control for time and practice effects.

Outcome measures include executive performance assessed through the Tower of London Revised task, subjective stress and anxiety measured using Visual Analog Scales, and autonomic parameters including electrodermal activity, skin conductance responses, heart rate, and heart rate variability. Psychophysiological recordings are obtained across multiple experimental phases including baseline, stress induction, intervention, and repeated stress exposure.

The study adopts a multilevel framework integrating behavioral, subjective, and physiological markers of stress regulation. It is hypothesized that hypnosis will reshape multilevel stress response and enhance executive performance compared with the control condition.

Most hypnosis studies in this population focus on subjective outcomes, with limited integration of executive performance and autonomic markers across repeated stress exposures. This protocol addresses this gap using a multimodal within-session perturbation design

Protocol title and identification

Protocol Title

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Clinical Trial Registration

ClinicalTrials.gov Identifier NCT06778109, (Initial Release:12/29/2024).

The study was initially registered on ClinicalTrials.gov as a single-arm protocol (NCT06778109). Following editorial feedback during journal submission, an active control arm (breath-focused

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

attention) was added. This comparator was not part of the original preregistered design; therefore, between-group analyses are reported as exploratory analyses, while primary within-subject hypotheses remain consistent with the registered protocol.

Recruitment Status

Completed

Sponsor and funding

This study received no external commercial funding. The research was supported by institutional resources of the hosting academic institution.

Research site

The study was conducted at:

Department of Medicine, Istituto Anestesia e Rianimazione

University of Padua

Full Address Via Vincenzo Gallucci, 13 - 2° piano

City Padua, Country Italy

All experimental sessions including stress induction hypnosis intervention cognitive testing and psychophysiological recordings were performed at this site.

Investigators and research responsibilities

Principal Investigator

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Study conception and design overall protocol supervision psychophysiological and computational data analysis including machine learning and Bayesian modeling manuscript drafting and scientific coordination

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Co-Principal Investigator

Annalisa Boscolo-Department of Medicine

Participant recruitment intervention delivery psychophysiological data collection and contribution to manuscript drafting

Group members

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Psychophysiological recordings cognitive assessments and data acquisition

Moscardi Otello-Department of Medicine

Psychophysiological recordings cognitive assessments and data acquisition

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Enrico Facco-Department of Neuroscience

Data acquisition contribution to data interpretation and manuscript drafting

Supervisors

Paolo Navalesi-Department of Medicine, Director of U.O.C. Istituto Anestesia e Rianimazione

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[Rationale and Background Information](#)

Stress and anxiety are closely related dimensions of human functioning that significantly influence performance, executive abilities, emotional regulation, and overall quality of life^{1,2}. High levels of stress are known to impair cognitive flexibility, decision making, and attentional control, while simultaneously increasing vulnerability to anxiety and emotional dysregulation³. These effects are particularly relevant in high responsibility professional contexts where optimal cognitive performance is required⁴.

Medical doctors, especially those involved in invasive procedures, emergency care, and high acuity clinical environments, are frequently exposed to sustained psychological stress. Chronic exposure to stressors in these settings has been associated with burnout, impaired decision making, and reduced psychophysical well being. Importantly, vulnerability to stress does not begin in professional life but emerges early during medical education.

Evidence indicates that medical students experience progressive deterioration of mental health throughout their training⁵. Elevated levels of stress and anxiety have been linked to sleep disturbances, relational difficulties, substance misuse, and increased risk of depression and suicidal ideation. Academic overload, performance pressure, and limited opportunities for psychological recovery contribute to a sustained stress burden. Students often report feelings of guilt when engaging in leisure activities, perceiving constant academic demands as incompatible with personal well being⁶. Collectively, these factors position medical education as a critical period for stress related cognitive and emotional vulnerability.

Given the detrimental impact of stress on both well being and executive functioning, increasing attention has been directed toward interventions capable of modulating stress responses while preserving or enhancing cognitive performance. Among mind body approaches, hypnosis has demonstrated potential in influencing emotional regulation, autonomic activity, and cognitive processes⁷⁻⁹. However, most existing studies have examined isolated outcomes, such as subjective stress or analgesia, with limited integration of cognitive and physiological domains.

Furthermore, stress responses are inherently multidimensional and shaped by individual appraisal processes; the Transactional models of stress and coping emphasize that emotional and physiological responses depend not only on the external stressor but also on subjective interpretation, perceived threat, and coping resources¹⁰. Consequently, standardized laboratory stressors may elicit heterogeneous responses, whereas personally meaningful stress memories can produce functionally comparable psychophysiological activation across individuals.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

In this context, the present study was designed to investigate whether hypnosis can modulate multilevel stress response and executive performance in medical students exposed to stress induction based on negative autobiographical experiences related to their medical training. By integrating subjective, cognitive, and autonomic measures, the study aims to address a critical gap in understanding the systemic effects of hypnosis on stress regulation and performance under psychologically meaningful stress conditions.

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Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

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Goal

The overall goal of this study was to investigate whether hypnosis represents an effective intervention to modulate stress responses and enhance executive functioning in medical students exposed to experimentally induced work-related stress.

Primary objective

To determine whether hypnosis improves executive functioning in medical students following stress induction, as measured by performance on the Revised Tower of London (TOL-R).

Secondary objectives

1. To assess whether hypnosis reduces perceived stress and anxiety (VAS stress, VAS anxiety, PSS-10).
2. To evaluate the effects of hypnosis on autonomic physiological markers, including heart rate (HR), heart rate variability (RMSSD), electrodermal activity (EDA), skin conductance responses (SCR) and % of time in SCR.
3. To determine whether hypnosis modulates psychophysiological responses to repeated stress exposure, by enhancing HRV and by changing SCR and EDA activity.
4. To explore the interaction between cognitive, subjective, and physiological outcomes using multimodal analyses (network analysis and Bayesian approaches).
5. To examine whether physiological and subjective changes can discriminate hypnosis and control participants through logistic regression and machine-learning classification models.

Study Design

This study was designed as a **controlled, interventional experimental study** aimed at evaluating the effects of hypnosis on executive functioning, stress perception, and psychophysiological responses in medical students exposed to experimentally induced stress.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

From a methodological standpoint, the study can be classified across multiple complementary dimensions:

- **Field of research:** Behavioral and psychophysiological clinical research within medical education.
 - **Study type:** Interventional experimental study.
 - **Allocation:** Non randomized group comparison (Hypnosis intervention vs breath-focused attention control).
 - **Control:** Active control condition matched for duration, structure, and attentional engagement.
 - **Temporal design:** Longitudinal, repeated-measures design.
 - **Analytical framework:** Within-subject (pre–post) and between-group comparisons.
 - **Setting:** Laboratory-based experimental assessment conducted in a controlled university environment.
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Overall structure

Participants were allocated using a non-random allocation procedure (sequential enrollment) to one of two study arms:

1. **Intervention group (INT):** Hypnosis session following stress induction.
2. **Control group (CTRL):** Breath-focused attention session matched in duration and procedural structure.

Both groups underwent identical assessment procedures, with the exception of the hypnotic induction and the Hypnotic Induction Profile (HIP), which was administered only in the intervention group at the end of the protocol.

Experimental framework

The protocol followed a **repeated stress exposure paradigm** consisting of four sequential experimental phases:

1. **Baseline assessment (resting state)**
 - Physiological monitoring
 - Cognitive and subjective measures
2. **First stress induction**
 - Autobiographical recall of a negative medical training experience (2 minutes)
3. **Intervention phase**
 - Hypnosis (INT) or breath-focused attention (CTRL) — 8 minutes
 - Pleasant imagery recall
4. **Repeated stress induction**
 - Re-exposure to the same negative autobiographical memory (2 minutes)

Physiological signals were recorded across all phases, while cognitive performance and subjective stress/anxiety were reassessed post-intervention.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Research population and sampling frame

The study population consisted of final-year medical students enrolled at the University of Padua (Italy). Participants were prospectively recruited on a voluntary basis between February 6 and October 1, 2025.

Recruitment targeted students approaching entry into clinical practice, a population considered at heightened vulnerability to work-related stress due to increasing clinical responsibility and limited professional experience.

Inclusion criteria

Participants were eligible if they:

- Were enrolled in the final year of medical school.
 - Were aged ≥ 18 years.
 - Provided written informed consent.
 - Had no prior experience with hypnosis.
 - Were able to understand and comply with study procedures.
-

Exclusion criteria

Participants were excluded if they reported:

- Cardiovascular diseases affecting autonomic regulation.
 - Psychiatric or neurological disorders.
 - Ongoing pharmacological treatments influencing heart rate, sweating, or stress responses.
 - Substance abuse.
 - Prior hypnotic training or therapy.
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Withdrawal criteria

Participants could withdraw at any time without penalty. Withdrawal criteria included:

- Voluntary discontinuation.
- Inability to complete experimental procedures.
- Emergence of psychological discomfort during stress recall.
- Technical failure in physiological recordings preventing analysis.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

No incentives were contingent on completion.

Duration of participation

Each participant completed the full protocol within a **single experimental session** lasting approximately 60–90 minutes, including:

- Baseline recording (TOL-R, VAS-A/S, PSS-10 scale and physiological data)
 - Stress induction phases
 - Intervention/control procedure
 - Post-intervention assessments
 - Physiological monitoring
 - HIP assessment (INT group only)
-

Study timeline

- **Recruitment period:** February – October 2025
 - **Data collection:** Concurrent with recruitment
 - **Total study duration:** Approximately 8 months
-

Rationale for design choice

A controlled experimental design with repeated stress exposure was selected to:

- Elicit ecologically valid stress responses.
- Assess intervention effects on both initial and repeated stress reactivity.
- Differentiate subjective, physiological, and cognitive outcomes.
- Strengthen causal inference through comparison with an active control condition.

The inclusion of multimodal outcomes and longitudinal within-session measurements allows integrated assessment of executive functioning, autonomic flexibility, and perceived stress modulation.

Methodology

Overview

The study employed a controlled experimental methodology to investigate the effects of hypnosis on executive functioning, perceived stress, anxiety, and psychophysiological responses in medical students exposed to experimentally induced work-related stress.

All procedures were conducted in a standardized laboratory setting under supervised conditions to ensure methodological consistency across participants.

Study setting

Experimental sessions were conducted in a quiet, temperature-controlled room within the Istituto di Rianimazione, University of Padua, Italy.

Participants were seated comfortably and monitored throughout all experimental phases. Environmental disturbances (noise, interruptions, lighting variability) were minimized to reduce confounding influences on psychophysiological recordings.

Interventions

Hypnosis intervention (INT group)

Participants assigned to the intervention group underwent an 8-minute standardized hypnosis session administered by a trained operator experienced in clinical and experimental hypnosis procedures.

The hypnotic induction followed a structured protocol including:

1. **Focused attention induction**
Participants were guided to focus attention on breathing and bodily sensations.
2. **Progressive relaxation**
Verbal suggestions facilitated muscular and mental relaxation.
3. **Pleasant imagery recall**
Participants were invited to relive a previously discussed positive autobiographical experience (e.g., relaxing at the beach, resting under trees).
4. **Deepening suggestions**
Suggestions aimed at enhancing absorption, calmness, and emotional detachment from stressors.

The hypnotic procedure was standardized in duration, tone, and structure across participants to ensure procedural consistency.

Control intervention (CTRL group)

Participants in the control group underwent an 8-minute breath-focused attention exercise designed to match the hypnosis condition in:

- Duration
- Posture
- Environmental setting
- Attentional engagement

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

The procedure involved guided attention to the breath without hypnotic suggestions, imagery, or dissociative instructions.

This active control condition was selected to control for non-specific effects such as relaxation, expectancy, and attentional focus.

Stress induction procedure

Psychological stress was experimentally induced through autobiographical recall.

Participants were asked to recall and mentally relive a previously discussed negative personal experience related to medical education or clinical training.

Each stress induction phase lasted 2 minutes and occurred twice:

1. Pre-intervention
2. Post-intervention (repeated stress exposure)

This paradigm was selected to elicit ecologically valid stress responses grounded in individual appraisal processes.

Experimental procedures and timing

The protocol consisted of four sequential phases:

1. **Baseline (“Listening State”)**
 - Resting physiological recording
 - Initial subjective and cognitive assessment
2. **First stress induction**
 - Negative autobiographical recall (2 min)
 - Physiological recording
3. **Intervention phase**
 - Hypnosis or breath-focused attention (8 min)
 - Pleasant imagery recall
 - Physiological recording
4. **Repeated stress induction**
 - Same negative recall (2 min)
 - Physiological recording

At the end of the session, cognitive performance and subjective measures were reassessed.

Detailed informations for reproducibility of the experimental procedure

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

The stress induction procedure involved asking each participant to recall a personally negative experience during their medical education. Once the participant had identified and mentally accessed this past event, they were instructed to focus their attention on it for a fixed duration of two minutes. Throughout this period, they received periodic reminders to maintain focus on the recalled experience.

CTRL group procedure

Participants in the control group were instructed to focus exclusively on their breathing, paying attention to the air flowing in and out of the body. A brief reminder to return attention to the breath (“air in, air out”) was provided every 10 seconds. This procedure lasted for 8 minutes and did not include any additional imagery, suggestions, or bodily cues

Hypnosis procedure

Before the hypnotic session all participants agreed to relive a previous pleasant experience of their life. Then, hypnosis was induced in a sitting position using the eye-roll^{1,2}, followed by suggestions of progressive relaxation, focus on breathing and left arm levitation (like in HIP administration);. Then, they were suggested to imagine their thought written on a blackboard, let them go by wiping them off, and go back to the previous experience agreed upon.

Eventually, they were dehypnotized reversing the sequence of eye-roll steps used for induction.

Hypnosis script structure

Now look toward me. As you hold your head in that position, look up toward your eyebrows — now,

toward the top of your head.

Close your eyes, while holding your eyes upward. Take a deep breath, hold Now, exhale, let your eyes

relax while keeping the lids closed... You feel a pleasant sensation of relaxation... Concentrate yourself in

this sensation of progressive relaxation... And let your body float...

Imagine a feeling of floating, floating right down through the bed. There will be something pleasant and

welcome about this sensation of floating.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

And this relaxation spreads to your eyelids, which get heavier and heavier... As if you were going to sleep,

but you remain awake, sliding down inside yourself, into a pleasant hypnotic trance... In a cool state of

peace.... This relaxed, pleasantly numb feeling is spreading throughout your whole body... From your

eyelids to your face... neck... arms... legs... your whole body... You are perfectly relaxed, limp...

Bring your attention to your nostrils... perceive the air flowing towards your lungs... It is fresh... An intense

and pleasant sensation ... You can also follow the flow of air from your lungs to the nostrils... And realize

that the exhaled air is warm and wet... It is very different for the inhaled one...

The inhaled air is reach of oxygen... While the exhaled air is reach of carbon dioxide and water vapor...

When you are breathing, the oxygen reaches your lungs... and then spreads to all the cells of your body...

bringing new energy... wellbeing...relaxation...

Now, if you wish to relax more and more... And reach a state of perfect wellbeing and bliss... You do not

need to do anything special... Only let yourself be pleasantly rocked by your own breath ... with its unceasing, regular rhythm... like high and ebb tide... and at each respiratory act you will more and more

relaxed... and in a deeper trance... spontaneously... pleasantly... automatically...

And now you can go backward in time using a moviola, where all your life is recorded ... and you can

go back and see your previous experience

but before

Imagine your thoughts written on a blackboard. I will slowly count from zero to three.

Zero. Take the eraser and gently wipe away the first thought.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

One. Wipe away the next thought, letting it dissolve completely.

Two. Continue erasing, allowing the board to become clearer and quieter.

Three. The blackboard is now empty. Your mind is calm and still.

If any thoughts are still present, allow them to slowly appear on the blackboard. Take the eraser again and gently wipe them away, one by one. Continue writing and erasing at your own pace, slowly and patiently, until nothing remains and the board is completely blank.

When your mind is truly empty, without thinking about it consciously, you will give me a small signal with your left finger.

From this quiet space, return to the experience we previously agreed upon.

Now, imagine yourself taking a slow walk along the seashore.

Feel the sand beneath your feet, notice the steady rhythm of your steps, and listen to the waves moving in and out.

The air is fresh, and the scent of salt fills your breath.

Imagine stepping into the sea and beginning to swim.

Take your time, completely immersed and when you feel the right moment allow your body to be supported by the water, letting yourself completely go.

Feel the gentle movement of the sea around you, carrying you effortlessly.

As you surrender to the water, your senses become more vivid: the coolness on your skin, the soft sounds surrounding you, your breathing becoming slower and deeper.

The more you relax the more you arm floats.

You are being cradled by the sea, immersed in a deep sense of peace, safety, and calm

This calm spreads through your entire body, reaching every part of you.

[Expanding and exploring sensation and peace]

When the experience is complete, and all these positive sensations are fully integrated, your arm will naturally and comfortably return to its resting position, bringing with it a lasting sense of balance, relaxation, and inner clarity.

And now it is time to come back to the present time ... in one minute I shall count from 3 to 1 ... at 3 you

will be ready ... at 2 you will your eyes will again roll upward with your eyelids closed and at 1 you will

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

slowly open your eyes ...

3 ... 2 ... 1

Hypnotherapists

Enrico Facco, author of the paper, Male

Senior Scholar, Studium Patavinum – Dept. of Neurosciences, University of Padua, Italy.

Professor of Anesthesiology & Intensive Care

Specialist in Neurology.

Teacher, Inst. Franco Granone - Italian Center for Clinical and Experimental Hypnosis, Turin (Italy) from 2007.

Member of the Executive Committee of the Inst. Franco Granone - Italian Center of Clinical and Experimental Hypnosis (CIICS) from 2012.

European Certificate of Hypnosis, delivered by the European Society of Hypnosis (ESH).

Head of Laboratory of Neurophysiology - Dept. of Anesthesiology and Intensive Care, University Hospital of Padua, from 1988 to 1998.

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Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

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1st Level Master (1-year postgraduate program) in Data analytics

2nd Level Master in Neuroimaging

1st Level Master in Biostatistic

Reference

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Outcome measurements

Cognitive performance

Executive functioning was assessed using the **Revised Tower of London (TOL-R)**, a standardized neuropsychological test evaluating:

- Planning
- Problem solving
- Inhibitory control
- Visuospatial working memory

Performance was scored across 30 problems of increasing difficulty (max score = 30).

Subjective measures

1. **Visual Analog Scale – Anxiety (VASa)**
2. **Visual Analog Scale – Stress (VASs)**
 - Digital 0–10 cm scales
3. **Perceived Stress Scale (PSS-10)**

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

- 10-item Likert self-report questionnaire assessing perceived stress over the previous month.
4. **Post-session self-evaluation**
- Better / Same / Worse vs baseline.
-

Hypnotic susceptibility

Hypnotic responsiveness was assessed in the INT group using the **Hypnotic Induction Profile (HIP)** administered at the end of the protocol to avoid expectancy bias.

Physiological measurements

Physiological data were recorded continuously across all experimental phases.

Electrodermal activity (EDA)

EDA and Skin Conductance Responses (SCR/min; %) were recorded using the eSense Galvanometer (Mindfield Biofeedback).

Measures included:

- Tonic skin conductance level
- Phasic SCR frequency
- % time in SCR activation

Automated detection algorithms identified SCR onset, peak, and recovery.

Cardiovascular parameters

Heart rate (HR) and heart rate variability (HRV) were recorded via photoplethysmography using the HRV Camera App.

Metrics:

- HR (beats per minute)
- RMSSD (parasympathetic vagal index)

Artifact correction included removal of zero values and ± 2 SD deviations.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Standardization procedures

To ensure methodological consistency:

- All sessions occurred in the same laboratory.
- Procedures followed identical timing.
- Operators used standardized verbal scripts.
- Physiological devices were calibrated before sessions.
- Participants received uniform instructions.

Flow diagram

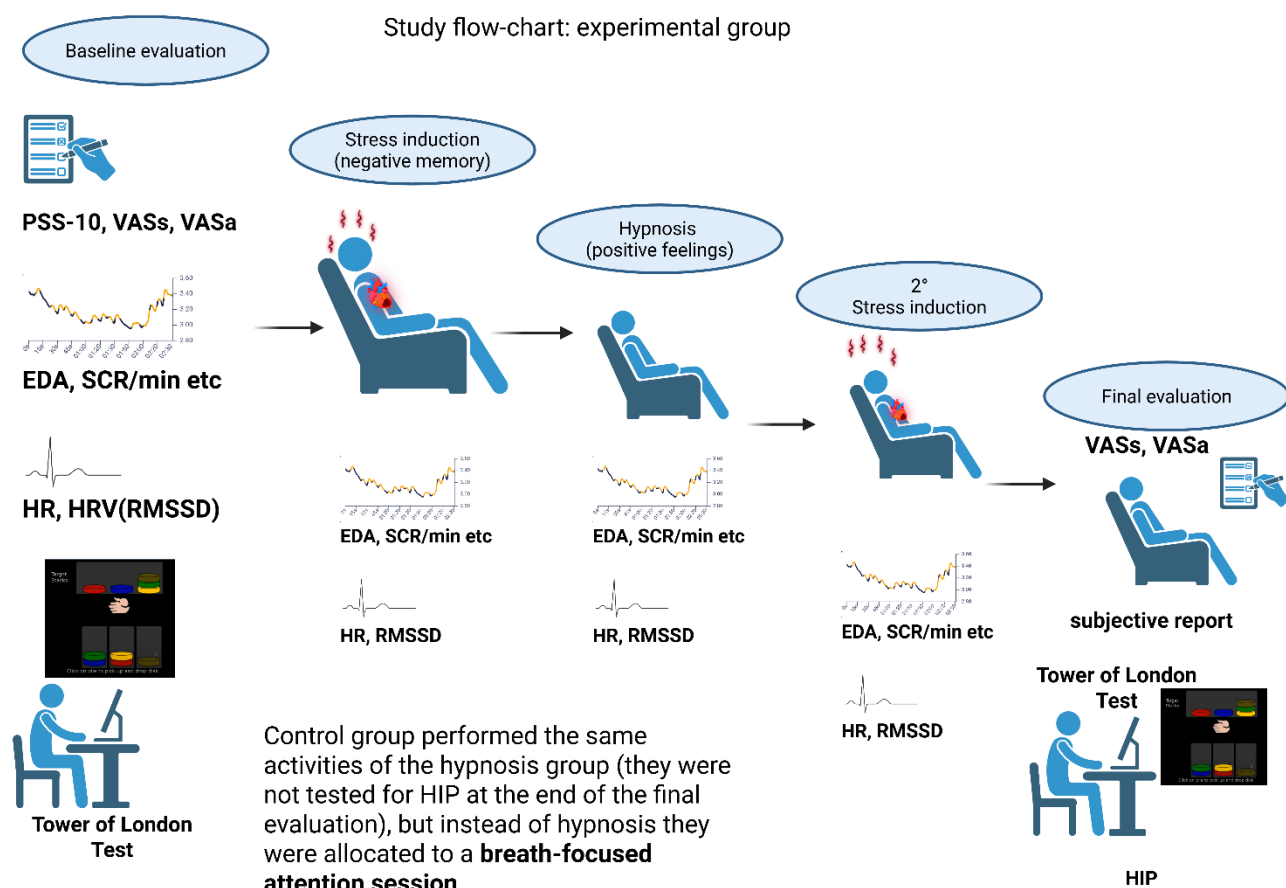


Figure 1—Study flow-chart. | BioRender

Abbreviations: TOL-R, Tower of London-Revised; VASa, Visual Analog Scale for Anxiety; VAS, Visual Analog Scale for Stress; EDA, Electrodermal Activity; SCR, skin conductance response; min, minute; HR, Heart Rate; HRV(RMSSD), Heart Rate Variability; PSS-10, Perceived Stress Scale- 10 Item Version. Created in BioRender. Science Suite Inc. dba BioRender ("BioRender") has granted CC BY open access license permission to use this Completed Graphic in accordance with

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Safety Considerations

The safety and psychological well-being of participants were prioritized throughout all phases of the study. Given the non-invasive nature of the experimental procedures, the study was classified as minimal risk. However, specific measures were implemented to monitor and manage any potential adverse effects.

Psychological and emotional safety

The primary potential risk was transient emotional discomfort associated with the stress induction procedure, which involved recalling negative autobiographical experiences related to medical training. To mitigate this risk:

- Stress recall was time-limited (2 minutes per induction).
- Participants discussed the memory with the investigator beforehand to ensure appropriateness.
- The procedure was conducted in a controlled and supportive environment.
- Participants were informed that they could interrupt or discontinue the recall at any time without consequences.

Immediately following stress induction, all participants underwent a relaxation phase (hypnosis or breath-focused attention), which functioned as an emotional down-regulation period.

Hypnosis-related safety

The hypnosis intervention was administered by a trained operator experienced in clinical and experimental hypnosis. The procedure involved standardized relaxation and imagery suggestions only and did not include regression, memory alteration, or suggestive content that could induce distress.

No adverse psychological reactions to hypnosis were observed or reported.

Monitoring and adverse event reporting

Participants were continuously monitored throughout the experimental session. Any signs of distress, discomfort, or unwillingness to proceed would have resulted in immediate interruption of the procedure.

Adverse events were defined as any unexpected psychological or physiological reaction occurring during or after participation. No adverse events requiring clinical intervention occurred during the study.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Physiological recording safety

All physiological measurements (photoplethysmography and electrodermal activity) were non-invasive and involved no electrical stimulation or risk to participants. Sensors were applied externally and removed immediately after recording.

Right to withdraw

Participants were informed of their right to withdraw from the study at any time without providing a reason and without academic or personal consequences.

Post-session well-being

At the end of the session, participants were asked to report their psychological state relative to baseline (better/same/worse). This served as an additional safety monitoring measure. No participant reported persistent worsening of emotional state.

Overall, the study procedures were deemed low risk, and all necessary precautions were implemented to safeguard participant safety and psychological well-being.

Follow-up

Given the single-session experimental design and the non-invasive nature of the procedures, no long-term clinical follow-up was required.

However, participant well-being was monitored at multiple time points to ensure psychological safety. Immediately at the end of the experimental session, all participants were asked to report their psychological state relative to baseline (better, same, or worse). This post-session assessment served to detect any residual distress following stress induction or intervention procedures.

Participants were observed for a short debriefing period after completion of the study to ensure emotional stabilization before leaving the laboratory.

Although adverse events were not anticipated due to the minimal-risk design, participants were informed that they could contact the research team after participation if they experienced delayed discomfort or emotional distress related to the study procedures.

Contact details of the principal investigator and the research team were provided within the informed consent documentation.

No adverse events requiring follow-up intervention were reported.

Overall, no formal longitudinal follow-up was deemed necessary given the minimal-risk profile and the absence of persistent adverse effects.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Data management and statistical analysis

Data management

All data were collected and stored in accordance with institutional and GDPR-compliant procedures. Each participant was assigned a unique alphanumeric study code. Identifying information (e.g., informed consent forms) was stored separately from research data in access-restricted files.

Data capture and coding.

Behavioral and questionnaire data (TOL-R, VAS stress/anxiety, PSS-10, post-session wellbeing rating) were recorded in electronic form and linked to participants only through the study code. Physiological data (HR, RMSSD, EDA, SCR/min, % time in SCR) were exported from the recording devices/apps and stored using the same coded identifiers. All derived variables (e.g., change scores: Δ RMSSD, Δ SCR, Δ VAS) were computed from coded datasets and documented in analysis scripts.

Data storage, access, and security.

Digital research data were stored on password-protected institutional computers and/or encrypted storage with access limited to authorized study personnel. Only de-identified datasets were used for analysis. Data shared for reproducibility consisted exclusively of preprocessed, de-identified datasets and analysis code.

Quality control, monitoring, and verification.

Data quality checks included (i) verification of completeness for questionnaire and behavioral measures, (ii) range checks (e.g., VAS 0–10), and (iii) inspection of physiological time series to identify recording artifacts.

Handling missing, spurious, or noisy data.

Missing values were documented and not imputed unless explicitly stated for a given analysis. Physiological recordings were preprocessed to reduce device-related artifacts by removing zero values and isolated single-point deviations exceeding ± 2 SD within each recording segment. When physiological segments were judged unreliable (e.g., sustained motion/pressure artifacts in PPG), the affected measures for that segment were excluded from analyses and the exclusion was reported.

Data retention and sharing.

Preprocessed datasets and analysis scripts supporting all statistical, network, and machine-learning analyses were made available in the Supplementary Materials to ensure full computational reproducibility. Raw physiological recordings were not publicly shared due to privacy and ethical restrictions; however, all reported results can be reproduced from the shared preprocessed data and code. For further information regarding the datasets, readers may contact the corresponding author.

Sample size justification.

An a priori power analysis indicated that a minimum of 19 participants would be sufficient to detect a within-subject pre–post difference in executive function in the intervention group (INT), assuming power = 0.80, expected effect size $d = 0.60$, and $\alpha = 0.05$. To account for potential dropouts or unusable recordings, 26 participants were recruited for INT. The control group (CTRL) was added subsequently to strengthen causal interpretation by controlling for time and practice effects;

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

therefore, no separate a priori power calculation was conducted for between-group comparisons, which were considered exploratory.

Descriptive statistics and assumptions.

Continuous variables were summarized as mean $\pm$ SD when approximately normally distributed, or median (and distribution-appropriate dispersion) when non-normal. Normality was assessed using the Shapiro–Wilk test. Categorical variables were summarized using counts and percentages.

Within-group comparisons.

Paired pre–post comparisons were performed using paired t-tests or Wilcoxon matched-pairs tests depending on distributional assumptions. Associations between variables were assessed using Pearson’s or Spearman’s correlation coefficients as appropriate.

Repeated-measures analyses across experimental phases.

To test condition effects on physiological measures (e.g., HR, RMSSD, EDA, SCR indices) across the four phases (baseline, stress induction, intervention, repeated stress induction), repeated-measures ANOVA was used when assumptions were met (normality of residuals and homoscedasticity; sphericity assessed via Mauchly’s test and corrected using Huynh–Feldt if violated). When parametric assumptions were violated, Friedman’s ANOVA was applied. Post-hoc comparisons were adjusted using Bonferroni correction.

Between-group analyses and adjustment for baseline performance.

To compare INT versus CTRL while mitigating baseline imbalance and practice effects, ANCOVA models were used with post-intervention outcomes as dependent variables, study group as fixed factor, and baseline values as covariates (e.g., TOL-R Post $\sim$ Group + TOL-R Pre; analogous models for VAS stress and VAS anxiety). Homogeneity of regression slopes was verified by testing the group $\times$ covariate interaction term.

Bayesian analyses.

Bayesian analyses were conducted to quantify evidence for intervention-related effects on executive functioning, subjective measures, and physiological outcomes. Bayes Factors (BF10) were interpreted according to Jeffreys’ scale. For non-normal data, Bayesian rank-based/robust bootstrap approaches were applied as specified in the analysis scripts.

Network analysis (exploratory).

A two-step dimensionality reduction approach was used to identify a parsimonious subset of variables embedded in the correlational structure of the dataset. Variables were retained if they showed at least five significant moderate-to-strong correlations ($r \geq 0.3$) with other variables. Sampling adequacy was assessed using the Kaiser–Meyer–Olkin (KMO) measure; variables with MSA < 0.5 were excluded, and the retained subset was required to meet overall KMO > 0.8 . A weighted adjacency matrix was constructed using a stricter edge threshold ($r \geq 0.4$), and network topology was evaluated using standard graph metrics (nodes/edges, density, average path length, diameter, betweenness and closeness centrality).

Machine learning classification (secondary exploratory aim).

To test whether a compact psychophysiological signature could discriminate INT from CTRL participants, a multivariable logistic regression classifier was specified a priori (after data collection but independent of model-fit optimization) using theoretically motivated predictors: Δ RMSSD, Δ SCR, Δ VAS stress, and post-intervention VAS stress. To estimate out-of-sample performance

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

under small-sample constraints, leave-one-out cross-validation (LOOCV) was applied. Performance metrics included accuracy, sensitivity, specificity, AUC, Brier score, and 95% confidence intervals.

Level of significance and software.

Frequentist analyses used a two-sided $\alpha = 0.05$, with multiple-comparison correction as specified above. Analyses were performed in jamovi (including Bayesian analyses via jsq and effect-size estimation via pamlj) and MATLAB for network while Python for machine-learning procedures. Scripts and preprocessed datasets are provided in the Supplementary Materials to ensure reproducibility.

Quality assurance

Although this study did not involve investigational medicinal products or invasive procedures, it was conducted according to principles consistent with Good Clinical Practice (GCP), including participant safety, protocol adherence, data integrity, and confidentiality. Given the minimal-risk, single-site laboratory setting, a formal Data and Safety Monitoring Board (DSMB) and external clinical monitoring were not deemed necessary.

Standardization of procedures

To ensure consistency across participants and reduce procedural variability:

- All sessions were conducted at a single site under comparable environmental conditions (quiet setting, seated posture, supervised recordings).
- The timing and sequence of experimental phases (baseline, stress induction, intervention/control, repeated stress induction) were standardized.
- Intervention and control procedures were delivered using standardized scripts and fixed durations (8 minutes), and stress induction was time-limited (2 minutes).
- All participants received uniform written and verbal instructions.

Training and oversight

Study personnel conducting testing and physiological recordings were trained in:

- Administration and scoring of TOL-R and questionnaire measures (VAS, PSS-10).
- Use of the EDA device and smartphone-based PPG recording procedures.
- Recognition of participant discomfort and procedures for immediate interruption if needed. The hypnosis intervention was administered by an operator trained and experienced in clinical/experimental hypnosis.

Instrument and data quality control

Quality control procedures included:

- Device functionality checks prior to sessions (EDA sensor connection and signal stabilization; PPG signal quality verification).
- Real-time supervision during recordings to minimize motion/pressure artifacts.
- Post-session inspection of physiological signals to identify recording failures or obvious artifacts.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

- Range and consistency checks for behavioral and questionnaire data.

Data management and auditability

- Participants were coded using unique study identifiers; identifiable information was stored separately from research data.
- Preprocessing steps (artifact handling, derived variable computation) were implemented using scripted workflows (jamovi outputs/specifications and Python scripts) to ensure traceability and reproducibility.
- Any exclusions of physiological segments or missing data were documented with explicit criteria.

Protocol deviations

Any deviations from the planned procedures (e.g., incomplete phases, device malfunction, participant interruption) were recorded and considered during analysis. Data affected by technical failures or poor signal quality were excluded according to predefined preprocessing criteria.

Overall, the quality assurance plan was designed to be proportionate to the minimal-risk nature of the study while ensuring methodological standardization, reliable data acquisition, and transparent, reproducible analyses.

Expected outcomes of the study

This study is expected to contribute to the advancement of knowledge in the field of stress regulation, cognitive performance, and psychophysiological functioning in healthcare trainees. Specifically, it aims to clarify whether hypnosis represents an effective, rapid, and scalable intervention capable of modulating executive functioning, subjective stress perception, and autonomic nervous system dynamics under experimentally induced work-related stress.

Scientific advancement

The study is expected to expand current understanding in several domains:

- The interaction between cognitive performance and stress regulation.
- The psychophysiological mechanisms underlying hypnotic interventions.
- The integration of subjective, autonomic, and executive-function outcomes within a single experimental framework.
- The identification of multimodal biomarkers (e.g., HRV, EDA, SCR) associated with adaptive stress responses.

By combining frequentist, Bayesian, network, and machine-learning approaches, the study may contribute methodological innovation to stress-intervention research, supporting more integrative models of performance under pressure.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Implications for medical education

If confirmed, the findings may support the integration of hypnosis-based stress regulation protocols within medical training curricula. Medical students represent a high-risk population for stress-related cognitive impairment, burnout, and emotional distress. Brief hypnotic interventions could be incorporated into resilience training, examination preparation, or simulation-based education to enhance cognitive control under stress.

Implications for healthcare professionals and systems

At the healthcare system level, improving stress management and executive functioning in future physicians may have downstream implications for:

- Clinical decision-making quality.
- Diagnostic accuracy under pressure.
- Reduction of cognitive fatigue and burnout risk.
- Patient safety outcomes in high-stakes environments.

Scalable, non-pharmacological interventions such as hypnosis could represent cost-effective tools to support workforce well-being without requiring extensive infrastructure.

Translational and clinical relevance

The protocol evaluates a brief, single-session intervention requiring minimal equipment and limited time commitment. If effective, such an approach could be translated into:

- Self-regulation training programs.
- Preventive mental health strategies for healthcare workers.
- Integration with existing approaches (e.g., biofeedback, mindfulness, resilience training).

Future research directions

The study is expected to generate preliminary evidence to inform:

- Larger randomized or multicenter trials.
- Longitudinal investigations of durability of effects.
- Neuroimaging studies examining neural correlates of hypnotic modulation.
- Predictive modeling of stress resilience using psychophysiological markers.

Overall, the anticipated outcomes may support the recognition of hypnosis as a scientifically grounded adjunctive tool for stress regulation and performance optimization in medical education and healthcare settings.

Dissemination of results and publication policy

Study findings will be disseminated through peer-reviewed publications and scientific conferences. Participants may request a summary of aggregate results. Authorship will follow international guidelines based on substantive scientific contribution. No restrictions on publication apply

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Duration of the project

The overall duration of the project was approximately 12 months, including protocol development, recruitment, data collection, analysis, and dissemination.

Participant recruitment and experimental data collection were conducted between February and October 2025.

Problems anticipated

Given the single-site, single-session design, no major operational barriers were anticipated. However, several potential challenges were considered.

Recruitment of final-year medical students could have been limited by academic workload and clinical rotations. This was mitigated by flexible scheduling and conducting sessions within university facilities.

Physiological recordings (PPG and EDA) are susceptible to motion and pressure artifacts. To address this, recordings were supervised in real time, and standardized preprocessing procedures were applied to identify and remove noisy segments.

Psychological discomfort related to autobiographical stress recall represented a potential risk. This was mitigated through time-limited exposure, supervised administration, and immediate relaxation phases following stress induction.

Finally, the relatively small sample size may limit generalizability and the stability of advanced computational models. This limitation was addressed by using conservative statistical approaches, cross-validation procedures, and transparent data sharing to support reproducibility.

Overall, no issues arose that compromised study completion within the planned timeframe or resources.

Project management

The principal investigator (LQ) oversaw study design, data analysis, and project coordination. Data collection was conducted by the research team (LQ, AB, CT, MO, EF). Advanced statistical and computational analyses were performed by LQ. All authors contributed to manuscript preparation and critical revision.

Ethical considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines for non-pharmacological research involving human participants.

Ethical approval was obtained from the Ethics Committee of the Department of General Psychology, University of Padua (Reference No. 3274/2019; approval date: 05 November 2019). The study was also registered on ClinicalTrials.gov (Identifier: NCT06778109).

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Risk assessment

Given the non-invasive and single-session design, the study was classified as minimal risk. However, specific ethical considerations were addressed.

The primary potential risk concerned transient psychological discomfort related to autobiographical stress recall. This was mitigated by:

- Prior discussion of the recalled experience with the investigator.
- Time-limited exposure (2 minutes per induction).
- Continuous supervision during the procedure.
- Immediate relaxation phases following stress induction.

The hypnosis intervention involved standardized relaxation and imagery suggestions only and did not include regression, memory alteration, or suggestive procedures capable of inducing distress.

Physiological recordings (EDA, PPG) were entirely non-invasive and posed no physical risk.

Informed consent process

All participants received detailed written and verbal information describing:

- Study aims and procedures.
- Nature of stress induction and hypnosis.
- Physiological recordings.
- Potential risks and benefits.
- Voluntary nature of participation.

Participants were given the opportunity to ask questions prior to enrollment. Written informed consent was obtained before any study procedures were initiated.

Right to withdraw

Participants were informed of their right to withdraw at any time, without providing a reason and without academic or personal consequences. Withdrawal did not affect access to educational activities or institutional standing.

Confidentiality and data protection

All collected data were pseudonymized using study codes. Identifiable information was stored separately from research data in secure, access-restricted files. Data management complied with institutional policies and applicable data protection regulations (GDPR).

Post-study support

Although adverse effects were not anticipated, participants were informed that they could contact the research team following participation if any delayed discomfort occurred

INFORMATION SHEET AND INFORMED CONSENT FORM

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Study Title:

Effects of hypnosis on stress, physiological parameters, and executive performance in medical students exposed to experimentally induced stress.

Ethics approval

This study has been reviewed and approved by the Ethics Committee of the Department of General Psychology, University of Padua (Approval Reference No. 3274/2019; approval date: 05 November 2019). The study has also been registered on ClinicalTrials.gov (Identifier: NCT06778109).

1. What is the purpose of this study?

The aim of this study is to investigate the effects of a brief hypnosis session on perceived stress, anxiety, physiological parameters, and problem-solving performance in medical students exposed to an experimentally induced stress condition.

Specifically, the study examines the relationships between:

- Subjective emotional states (stress and anxiety).
 - Peripheral physiological parameters (heart rate, heart rate variability, skin conductance).
 - Cognitive performance (executive functions).
-

2. What does participation involve?

Participation consists of a single experimental session lasting approximately 60–90 minutes.

During the session:

- Non-invasive physiological parameters will be recorded (heart rate via smartphone photoplethysmography; skin conductance via external sensors).
 - You will complete a computerized cognitive task assessing planning and problem-solving abilities (Tower of London-Revised).
 - You will be asked to briefly recall a personal stressful memory related to your medical training (experimental stress induction).
 - You will then undergo either a guided hypnosis session or a breath-focused attention exercise of equal duration.
 - Brief self-report scales assessing stress and anxiety will be completed.
-

3. Are there any risks or discomforts?

This study is non-invasive and classified as minimal risk.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

The primary potential discomfort relates to the temporary emotional engagement associated with recalling a stressful memory. This phase is brief, supervised, and followed by a relaxation procedure.

No physical risks are expected. All sensors used are external and non-invasive.

4. Is participation voluntary?

Yes. Participation is entirely voluntary.

You may decline to participate or withdraw from the study at any time without providing a reason and without any academic or personal consequences.

5. Will I be informed about the study results?

If you wish, you may request information about the overall study results at the end of the research. Individual data will remain anonymous and will not be disclosed.

6. Confidentiality and data protection

All collected data will be pseudonymized using study codes. Personal identifying information will be stored separately from research data and handled in accordance with applicable data protection regulations (GDPR).

CONSENT TO PARTICIPATE

I, the undersigned, declare that:

- I have read and understood the information provided above.
- I have had the opportunity to ask questions and received clear and satisfactory answers.
- I understand that I may withdraw at any time without consequences.
- I voluntarily agree to participate in this study.

Name and Surname: _____

Signature: _____

Date: _____

Principal Investigator: _____

Signature: _____

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Participant Information – Institutional and Data Protection Notice

You are invited to participate in this research study conducted by the Department of Neuroscience, University of Padua.

The study is promoted by:

Dr. Luca Queirolo

Department of Neuroscience – University of Padua

Via Giustiniani 2, 35128 Padua, Italy

Email: luca.queirolo@unipd.it

Dr. Annalisa Boscolo

Department of Medicine, Istituto Anestesia e Rianimazione

University of Padua

Email: annalisa.boscolobozza@unipd.it

Before you decide whether to participate, it is important that you understand why this research is being conducted and what participation involves. If you agree to participate, you will be asked to sign the informed consent form and the personal data processing authorization. You may withdraw your consent at any time without consequences.

Purpose of the study

Autonomic activation plays an important role in cognitive performance and emotional regulation. This study aims to investigate the relationship between physiological parameters, emotional states, and executive functioning under experimentally induced stress.

Peripheral physiological parameters (e.g., heart rate, heart rate variability, skin conductance) will be collected using non-invasive sensors and smartphone-based recording systems and analyzed in relation to cognitive performance and psychological measures.

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Study procedures

Participation consists of a single experimental session lasting approximately 60–90 minutes. You will complete a planning/problem-solving cognitive task and undergo physiological recordings before and after repeated stress induction and intervention procedures. The stress induction paradigm is based on a negative autobiographical memories related to your medical education

Risks and discomforts

The study involves minimal risk. The only potential discomfort is temporary emotional engagement during recall of a stressful memory. No physical risks are expected.

Voluntary participation

Participation is entirely voluntary. Refusal to participate will not result in any consequences.

Access to study results

If you wish, you may request general information about the study results at the end of the research.

Data Protection and Privacy Notice

Protocol: – No. 3274 (05 November 2019)

Data Controller:

Prof. Gastone Zanette

Data Processing:

Dr. Luca Queirolo

Department of Neuroscience – University of Padua

Email: luca.queirolo@unipd.it

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Personal data will be processed in accordance with Good Clinical Practice, EU GDPR regulations, and applicable Italian data protection laws.

Nature of the data

Your data will be coded using a unique study identifier. Identifiable information will be stored separately from research data. Only authorized study personnel will be able to link codes to personal identities.

Data processing methods

Data may be disseminated exclusively in anonymized form through scientific publications and conferences. Ethics committees and regulatory authorities may review study data solely in confidentiality-protected form.

Participant rights

You may exercise your data protection rights (access, correction, deletion, restriction of processing) by contacting the study investigators. If consent is withdrawn, your identifiable data will be deleted and no longer used for research purposes.

For further information and inquiry you can contact the following email: luca.queirolo@unipd.it

Consent to data processing

By signing this document, I authorize the processing of my personal data within the limits and purposes described above.

Participant Name (print): _____

Signature: _____

Date: _____

Hypnosis reshapes multilevel stress response and enhances executive performance in stressed medical students WHO protocol

Budget and funding

This study did not receive external commercial funding. All research activities were supported by institutional resources of the hosting academic institution. No dedicated grant funding was allocated.

Other support and collaborations

No external funding, inter-institutional financial support, or linked research grants were involved in the conduct of this study. The project was conducted as an independent academic investigation.

Financing and insurance

Given the minimal-risk, non-invasive nature of the study, no additional participant insurance beyond standard institutional coverage was required.