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COPAHS Study: protocol of a randomised experimental study comparing the effects of hypnosis, mindfulness meditation, and spiritual practices on experimental pain in healthy adults

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ABSTRACT

Background There has been an increasing interest in studying the potential benefits of so-called complementary and alternative approaches for pain management, such as hypnosis and mindfulness-based interventions. More recently, researchers have been interested in studying the effects of spiritual practices on pain experience as well. These practices may increase pain tolerance, result in a positive re-appraisal of pain and influence other psychological variables that are known to be associated with pain experience. The purpose of this study is to evaluate and compare the immediate effects of self-hypnosis, mindfulness meditation, and a spiritual intervention relative to a control condition for increasing pain tolerance and reducing pain intensity and pain-related stress, in response to experimental painful stimulation.

Methods and analysis Recruitment is anticipated to start in November 2020. This is a randomised quantitative experimental mixed-design repeated-measures study with three assessment points: baseline (T0), pre-test (T1) and post-test (T2). Eligible healthy adults will be randomised to one of the four study conditions. Interventions will be a 20-minute audio-guided practice of either self-hypnosis, mindfulness meditation, or Christian prayer. Participants in the control group will not be instructed to use any specific strategy during the painful stimulation. Participants will be submitted to a first cycle of Cold Pressor Arm Wrap. They will then listen to a 20-minute audio recording inducing one of the three interventions, or, in the case of the control group, to a 20-minute audio recording of text from a natural history textbook. Primary outcomes are pain intensity and pain tolerance. Pain-related stress as measured by salivary cortisol level and heart rate variability are secondary outcomes.

Ethics and dissemination This study was approved by ISPA—University Institute's internal Ethics Committee for Research on 3rd December 2018 (reference I/010/12/2018). Findings will be published in peer-reviewed indexed journals and presented at conferences.

Trial registration number ClinicalTrials.gov registry (NCT04491630). Stage: pre-results.

Strengths and limitations of this study

- This is an innovative study comparing the effects of three 20-minute interventions (self-hypnosis, mindful meditation, Christian prayer) relative to a control group of healthy participants experiencing experimentally induced pain.
- Standard Protocol Items Recommendations for Interventional Trials and Consolidated Standards of Reporting Trials checklist guidelines were followed, to ensure quality in all aspects of study planning, execution and reporting.
- Strengths of the study include the random allocation and specific efforts to limit bias (blinded outcome assessment, standardisation of intervention and collection of concomitant treatment).
- The primary limitation of this study is the limited generalisability of potential findings to populations with chronic pain and experiencing acute pain in natural context.

INTRODUCTION

Background and rationale

Pain is a universal experience.[1] It is also a homeostatic and adaptive mechanism, essential for survival.[2–4] Without pain, an injury or serious health condition could go unnoticed, potentially leading to the death of the organism.[5 6]

At the same time, pain is also an unpleasant and distressing experience that can undermine well-being,[7 8] and is a primary reason for seeking medical care.[9] Although minor acute pain can be readily managed, moderate-to-severe acute pain may require a level of care that may not be available in many treatment settings.[10] Even when standard treatments are available, a large number of patients

continue to report severe acute pain.[11 12] Relatedly, about 20% of patients with acute pain are not satisfied with the pain treatment provided to them.[13] If not appropriately treated, severe acute pain is known to contribute to negative cardiovascular, immunological, gastrointestinal, renal, muscular, sleep and psychological complications.[10 14] The presence of severe acute pain also puts patients at risk for the development of chronic pain.[10 14] All of this evidence supports the importance of patient access to effective acute pain management treatments.

Given its subjective and complex nature, effective pain management frequently requires more than analgesics.[14] Pain is a multidimensional experience that cannot be merely explained by the physiological mechanisms that underline its experience.[3 15 16] Pain is influenced by a number of biological (eg, physiological aetiology, severity of physical damage), psychological (eg, pain-related beliefs and pain coping responses), social (eg, social support) and spiritual/religious (eg, meaning in life, religiosity) factors.[17–25] Not surprisingly, multidisciplinary treatment programmes that address the multifaceted nature of pain, including its psychosocial dimensions, are more effective than unimodal treatments that focus only on biomedical factors.[26–28] Given this evidence, multidisciplinary treatments that include instruction and encouragement in the use of psychological, social and spiritual coping may be useful.[14 29]

Two psychological coping responses that are commonly taught in such programmes are self-hypnosis (SH) and mindfulness meditation (MM). Both SH and MM have evidence supporting their efficacy with acute, chronic and experimentally induced pain.[30–40] Both interventions can be used independently or together, and have been shown to: (a) induce brain states that are hypothesised to be associated with a decrease in the processing of nociceptive input as well as adaptive cognitive processes such as acceptance and openness to suggestion; and (b) affect pain-related cognitive content—such as pain-related beliefs and cognitive pain coping responses.[37 38 40 41] Both SH and MM have also been shown to have weak-to-strong effects on pain intensity and on pain tolerance,[31 32 35 38 39] with the magnitude of the effects varying as a function of: (a) previous experience in using either of these strategies (being a novice vs being a long-term practitioner of MM); (b) outcome expectancies; (c) hypnotic suggestibility (for SH), (d) trait absorption and (e) pretreatment (pain) acceptance.[38 40 42–44] It is also possible that, as Tang *et al* have hypothesised,[45] dispositional or baseline mindfulness—that is, a long-lasting and pre-existent tendency towards mindfulness of consciousness—affects brain processing, the ability to practice MM, as well as the effects of MM. In support of this hypothesis, a recent study examined the moderation effect of baseline mindfulness on the effects of MM, cognitive therapy and mindfulness-based cognitive therapy for chronic low back pain.[46] The authors found that non-reactivity (ie, a facet of baseline mindfulness that refers to active detachment from negative emotions and thoughts), but not observation (ie, a facet of baseline mindfulness that refers to how one sees, feels, and perceives the internal and external world around oneself and selects the stimuli requiring one's attention), moderated the effects of both MM and mindfulness-based cognitive therapy. Those participants with lower baseline non-reactivity reported greater improvement in physical function as a result of MM, while those with higher baseline non-reactivity reported greater improvement in mindfulness-based cognitive therapy. However, we are not aware of any other studies that have examined the moderating role of baseline mindfulness on the effects of MM.

Recent research on the role that spirituality (the extent to which an individual searches for meaning and purpose in life, as well as feelings of transcendence and of being connected to a higher power)[20] and religiosity (the degree of an individual's engagement with the belief system and with individual and group practices of a given religion)[20] —have on pain experience suggests that at least some individuals spontaneously engage in spiritual and religious practices when experiencing pain as a way to cope.[47–49] Moreover, higher levels of spirituality and religiosity (S/R) are hypothesised to have a buffering effect against stressors.[47 50 51] Both spiritual (eg, spirituality-based meditation) and religious practices (eg, prayer) that might reduce stress may account for these buffering effects.[50] Although there is a growing interest in evaluating the potential benefits of spiritual and religious practices on pain experience,[52–57] and on identifying the mechanisms that explain their buffering effects on pain experience,[58] to date, only a limited number of studies have focused on these issues. This is especially true for religiosity and for religious practices. Findings from the limited number of studies that have been conducted suggest that S/R and spiritual and religious practices may play a role in influencing pain (eg, pain tolerance and pain intensity) and pain-related outcomes (eg, pain-related distress).[19 20 47 50 54–56 59–61] These practices are thought to increase pain tolerance, determine a positive re-appraisal of pain and modulate psychosocial variables (eg, meaning of pain, beliefs and attributions, coping and mood) that are associated with pain experience.[22 47 60 62]

However, these studies have focused primarily on clinical populations with chronic pain. There are only limited findings regarding the effects of S/R and religious practices, such as Christian prayer (CP), on acute pain.[57 63] One of the few studies examining the effects of being or not being religious and of religious practices on acute experimentally induced pain was conducted by Wiech *et al*.[57] These authors presented a group of 12 practising Christian Catholics and a group of 12 self-described non-religious participants to either a religious stimulus (ie, looking at an image of the Virgin Mary) or a non-religious stimulus (ie, looking at a matched image without religious connotation). Statistically significant and large condition and Group X Condition interaction effects were found, suggesting that the religious practice of contemplating a religious image has an effect on pain intensity, and that

the magnitude of this effect might be moderated by individuals' religion and/or religiosity.

Research focusing the effects of religious practices (eg, prayer) on pain, and on the mechanisms explaining the effects of these practices, is a critical, understudied, next step in this field of research. The findings from this research could inform both clinicians and the public about how religious practices may be used to cope more effectively with pain. Moreover, a comparison of the effects of SH, MM, and religious practices on pain experience and pain-related-outcomes, and understanding for whom these pain management practices work, may also inform the relative utility of these strategies for pain self-management ensuring their optimal implementation. This study seeks to address knowledge gaps in this area by comparing the immediate effects of SH, MM and religious practices on pain-related outcomes relative to a control condition, and assessing what individual baseline characteristics moderate the effects of SH, MM and religious practices on pain-related outcomes.

Study aims and hypotheses

The primary aim of this study (aim 1) is to compare the immediate effects of SH, MM and CP, relative to a control group (CN), for increasing pain tolerance and reducing pain intensity and pain-related stress, in response to experimental painful stimulation in a sample of healthy volunteers. Based on the research performed to date, reviewed above, we hypothesise that participants who listen to audio recordings that facilitate the use of one of the three coping responses—SH, MM and CP—will evidence greater pain tolerance and lower levels of pain intensity and pain-related stress than participants in the CN condition. Although one previous experimental study has directly compared the effects of a 3-minute practise of MM and SH on acute pain,[64] no research to date has directly compared all three (ie, SH, MM and CP). Thus, we did not have any hypotheses about possible between-strategy differences on pain outcomes. However, we do plan to evaluate possible between-group differences to examine this.

An exploratory aim of this study (aim 2) is to identify possible shared and unique predictors of response to the three treatment conditions. The possible predictors we plan to test include sex, age, religious affiliation, hypnotic suggestibility, baseline mindfulness, acceptance, pain-related beliefs, religiosity, trait spirituality, previous experience with SH, MM and CP, outcome expectancies and trait absorption. We will test for both shared and treatment-specific prediction effects for each of these variables on all three study outcomes (ie, pain tolerance, pain intensity and pain-related stress), assessed via three variables (ie, pain tolerance, pain intensity and pain-related stress that will be assessed by two psychophysiological indicators: heart rate variability (HRV) and cortisol level). The aim 2 hypotheses are to determine if: (a) the effects of SH on pain-related outcomes will be predicted by trait absorption, hypnotic suggestibility, outcome expectations (OE), and previous experience of SH; (b) the effects of MM on pain-related outcomes will be predicted by trait absorption, baseline mindfulness, acceptance, pain-related beliefs, catastrophising, OE, and previous experience of MM; and that (c) the effects of CP on pain-related outcomes will be predicted by religious affiliation, S/R, trait absorption, acceptance, pain-related beliefs, catastrophising, OE, and previous experience of CP. Due to the large number of planned analyses (see the Statistical analysis plan section, described later), and because this is the first study to our knowledge that has compared these three approaches and evaluated treatment moderators in the same study, we view the tests of shared and unique predictors of outcome as exploratory.

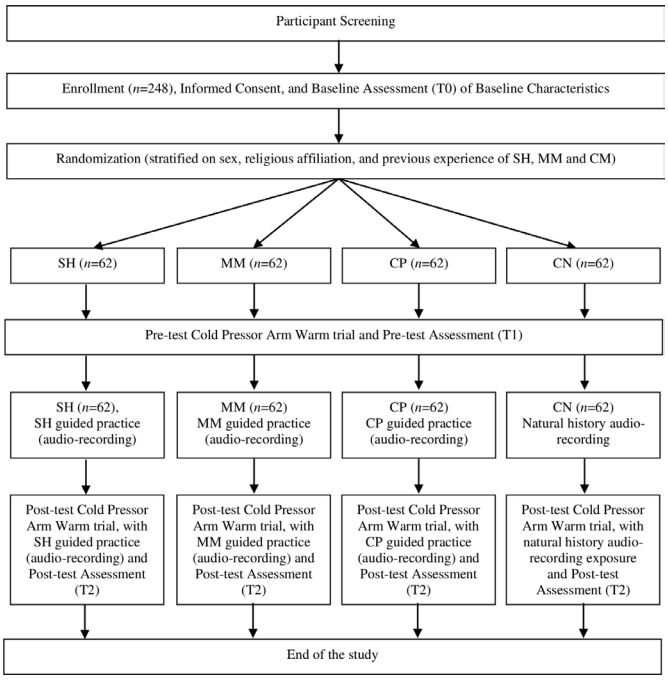

Figure 1 Flow of study procedures. CN, control group; MM, mindfulness meditation; SH, self-hypnosis.

METHODS AND ANALYSIS

Study design

The current study will use a randomised quantitative experimental mixed-design repeated-measures design. Figure 1 shows the overall flow of study procedures, while table 1 provides a brief structured summary of the study. This is a four-arm parallel prospective experimental controlled study, with one CN and three experimental conditions (SH, MM and CP), using the Cold Pressor Arm Wrap (CPAW) to induce pain.[65] The effects of the treatment conditions on the three pain-related outcomes will be compared. All participants will be assessed at three assessment points: (a) baseline (T0) to assess baseline characteristics, pre-intervention (before randomised allocation and before the first CPAW trial); (b) pre-test (T1), pre-intervention, after randomised allocation and in response to the first CPAW trial; and (c) post-test (T2),

Table 1 Structured summary of the study

Data category	Information[32]
Registry and trial identifying number	ClinicalTrials.gov (NCT04491630)
Date of registration in primary registry	29 July 2020
Source of funding	Foundation BIAL Grant for Scientific Research (grant number 188/18)
Sponsor	William James Center for Research, ISPA—ISPA–University Institute
Contact for public and scientific queries	AFV, William James Center for Research, ISPA–University Institute, Rua Jardim do Tabaco, no. 34, 1149-041 Lisbon, Portugal; +531969082988; mafvalente@gmail.com
Public and scientific title	COping With PAin Through Hypnosis, Mindfulness and Spirituality (COPAHS)
Countries of recruitment	Portugal
Health condition(s) or problem(s) studied	Healthy participants; experimentally induced acute pain
Intervention(s)	Self-hypnosis; mindfulness meditation; Christian prayer; control
Key inclusion and exclusion criteria	Inclusion criteria: (a)18 years old or older; (b) read, speak and understand Portuguese; (c) willing to be randomly assigned to all four conditions Exclusion criteria: (a) history of musculoskeletal problems, cancer, heart disease, stroke, epilepsy, diabetes or Raynaud syndrome; (b) open wound, cut or fracture in any of the upper limbs; (c) alcohol or substance dependence; (d) cognitive or physical impairment, or severe psychopathology that could prevent participation
Study type	Interventional Allocation: randomised Intervention model: parallel assignment Masking: single blind Primary purpose: basic science
(Anticipated) date of first enrolment	November 20
Target sample size	196
Recruitment status	Study recruitment began on November 20
Primary outcome(s)	Pain intensity Pain tolerance
Key secondary outcomes	Pain-related stress

immediately after the treatment condition procedures (ie, SH, MM, CP or CN) and the second CPAW trial. The study results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for trials of non-pharmacological interventions.[66]

Participants

The participants will be a non-clinical sample of 196 healthy adult participants (approximately 50% men). Sample size was determined using a priori power calculation using G*Power (V.3.1), considering a mixed-design repeated-measures design, a default pre–post correlation across the pre-test and post-test of 0.5, a small-to-medium effect size (Cohen's *f*) of 0.15 for a time×condition interaction effect, a two-sided α of 0.05 and a power of 0.95. Cohen's *f* was set at 0.15 based on the results of previous research with both clinical and non-clinical populations supporting the anticipated small-to-large effects of CP ($0.34<f<0.43$), SH ($0.15<f<0.37$), and MM ($0.45<f<4.54$) in pain intensity and tolerance.[31 32 35 38 53 57] We plan to enrol 248 participants in order to ensure a final sample size of 196 completers (49 per group), assuming a conservative 20% dropout rate.

Inclusion criteria are: (a) being at least 18 years old; (b) able to read, speak and understand Portuguese; and (c) willing to be randomly assigned to all four conditions (regardless of participant's own religious affiliation). Exclusion criteria include: (a) reporting history of musculoskeletal problems, cancer, heart disease, stroke, epilepsy, diabetes or Raynaud syndrome; (b) having an open wound, cut or fracture in any of the upper limbs; (c) self-reported alcohol or substance dependence; and (d) cognitive or physical impairment, or severe psychopathology that could prevent participation.[15]

Study setting, recruitment, screening and enrolment

This study will be conducted at the William James Center for Research, at ISPA–University Institute, Lisbon, Portugal (the host institution). All participants will be non-clinical healthy adults enrolled from the host institution internal and external participant pools. Procedures, such as informed consent, assessments, experimental trials and interventions, will be conducted in person and held at one of the host institution's labs.

Recruitment is anticipated to start in November 2020. Prospective participants will be sent an approach letter and contacted via telephone 1–2 weeks after mailing. Interested participants will be screened, during a telephone call, by research staff members to determine eligibility. Inclusion and exclusion criteria will be assessed via self-report, and reasons of ineligibility will be collected for purposes of adhering to the CONSORT standards.[66]

Prospective participants who are eligible and interested to participate will be invited to participate in an informed consent process that will be conducted in person by a research staff member. These participants will be given a full description of the study aims and procedures, as well as the opportunity to clarify any doubts or concerns. Participants will be assured of the confidential and voluntary nature of participation, and that they can discontinue participation at any moment. On agreement

to participate, participants will then be asked to sign an informed consent form. Enrolled participants will complete baseline assessment (T0) in person.

Those individuals who decline to participate will be asked to provide a reason for their decline. They will also be asked basic demographic information—such as sex and age—to enable comparison between the study participants and eligible prospective participants who decline to participate.

Randomisation, allocation and blinding

After enrolment and baseline assessment, participants will be randomly assigned to one of the four conditions (SH, MM, CP or CN). Participants will be randomised in stratified blocks to ensure that subjects with each sex, religious affiliation, and previous experience in SH, MM and CP have the same chance of being allocated to one of the four conditions. Randomisation process will be performed using a computerised random sequence generator.

Participants will be blind to the study hypotheses. During informed consent, in order to maximise the odds that participants will have similar outcome expectancies regarding the different experimental conditions, prospective participants will be told that they will listen to an audio recording that previous research studied as potentially helpful for pain management, and that the purpose of the study is to assess the effects of this audio recording on discomfort associated with the sensation of coldness. Participants will also be instructed not to disclose details of the content of the audios they receive to the experimenter. The experimenter who will conduct assessments and administer the audio-recorded interventions will be blind to both the condition to which subjects are assigned and the study hypotheses. The research staff member responsible for participants' randomisation will be blind to identifying information and to the code identifying each condition.

Trial design

Participants' baseline characteristics will be assessed at baseline (T0), immediately after consent process. Pain-related outcomes will be assessed both at pre-test assessment (T1) and post-test assessment (T2).

All participants will be provided a pre-test CPAW trial to allow for the pre-test (T1) assessment. The CPAW[65] is an effective alternative approach to the traditional cold pressor test.[15] It is a secure experimental method for inducing systemic stress and pain, involving attaching an arm wrap composed of MRI-safe gelpacs cooled to 1°C–3°C to the forearm and hand of the individual. The CPAW has been shown to result in increases in post-test cortisol releases.[65]

Baseline cortisol level will be measured, and baseline HRV will be calculated based on a 5 min resting period before pre-test. The participants will have the cold arm wrap attached at 3°C±0.5°C to the forearm and hand for as long as they tolerate the stimuli (maximum of 5 min). Pre-test (T1) assessment will be performed during (heart rate and pain tolerance) and after (salivary cortisol sample and pain intensity) the CPAW.

A second CPAW cycle will take place after a 20-minute rest interval, followed by a 20-minute interval during which participants will either listen to SH, MM, or CP induction/instruction or a natural history (CN) audio recording, which has been previously validated as a control condition.[67] This interval enables: the time for the exposure to SH, MM or CP; and to control for diffuse noxious inhibitory control.[68] The second experiment—a second CPAW cycle lasting until subjects no longer tolerate the pain (up to a maximum of 5 min)—includes a post-test (T2) assessment similar to T1. Participants will also listen to a 5-minute recording of SH, MM, CP induction/instruction or a natural history audio recording (CN) during the second CPAW cycle.

Experimental conditions/study interventions

All of the interventions will be equivalent in terms of time and structure. All four will be presented via 20-minute audio-recordings just before the second CPAW cycle, which will teach them and allow them to practice the three active responses (SH, MM or CP) or provide them with the control audio recording (CN). Following this and during the second CPAW cycle, the participants in the active conditions will be invited to practise the strategy they were taught with the 20-minute audio recording, while also listening to a 5-minute recording to assist with this practice. The participants in the control condition will listen to a 5-minute natural history audio recording during the second CPAW cycle. All audio recordings will be audible only to the participant (ie, the researcher conducting the procedures will be blind to treatment condition).

To promote participant retention and adherence to intervention and assessments, a careful explanation of the study's potential social and academic relevance and benefits will be given to all participants during the consent process. Also, both the trials and assessments will be scheduled according to participants' preferences, and reminder telephone calls prior to the trial and assessments session will be made.

Intervention content

An in-depth description of the rationale for the selection of SH and MM is provided by Jensen,[34] and by Williams *et al*.[41] Both SH and MM are well-established commonly used approaches that have evidence supporting their effectiveness with acute, chronic and experimentally induced pain.[34 36 38] CP, on the other hand, is one of the S/R practices that has preliminary evidence supporting its effects on reducing pain.[59]

Specific scripts for each intervention will be developed based on theoretical and empirical foundations. Scripts for SH and MM will be developed by research team members (MJ and MD, respectively) who are experts in each of these interventions as applied to pain management. These scripts

will then be translated, adapted into Portuguese, by two independent bilingual translators and back translated by a third independent bilingual translator. Any discrepancies in the translation will be resolved during a meeting of experts in these psychological interventions and pain management. A final version will be obtained through a consensus of these experts. The back-translation of the final version of the scripts will be reviewed and approved by MJ and MD to ensure that the content of the scripts is as originally intended. To ensure that the individuals in our population understand these scripts, a pilot test will be held in a sample of 10 Portuguese adults. Scripts for CP will be adapted from the existing online biblical meditations from the Society of Jesus (www.passo-a-rezar.net), by a research team member (AF-V) which will closely collaborate on the CP script adaptation with a Portuguese CP expert from the Society of Jesus.

SH condition

After the 20-minute rest interval between the first cycle of CPAW and the second CPAW cycle, participants assigned to this condition will listen to a 20-minute recording with instructions of SH adapted from one of our team member's (MJ) proposed model.[22] First, the audio recording will introduce and orient the participant to SH. Then instruction in SH will be provided, including: (a) how to self-induce a hypnotic induction; (b) specific self-suggestions for comfort and ability to manage intense sensations; and (c) post-hypnotic suggestions that the participant will be easily able to use these hypnotic strategies on their own at a later time (ie, in this case, during the CPAW procedures that will follow). A second 5-minute audio-recording with instructions to guide the participant in SH will be provided during the second cycle of CPAW.

MM condition

After the 20-minute rest interval between the first cycle of CPAW and the second CPAW cycle, participants in the MM condition will listen to a 20-minute recording with instructions in the use and application of Vipassana MM,[69] adapted from the manual developed by one of our team members (MD).[70] First, the audio recording will focus on introducing the idea of attention to their breath, and of non-judgemental monitoring and acceptance of the all events and stimuli. Then a guided MM (body scan) experience will be provided. A second 5-minute audio recording with instructions to facilitate the MM (body scan) experience taught in the first audio recording will be provided during the second cycle of CPAW.

CP condition

After the 20-minute rest interval between the first cycle of CPAW and the second CPAW cycle, participants in this condition will listen to a 20-minute recording with CP instructions. These instructions will be adapted from the existing online biblical meditations from the Society of Jesus (www.passo-a-rezar.net). First, the audio recording will introduce and orient the participant to CP. Then, a text of the New Testament of the Bible will be read two times, followed by a brief suggestion of prayer. A second 5-minute audio recording with instructions to facilitate the CP experience taught in the first audio recording, including the recording of a text of the Bible followed by a brief suggestion of meditation and relaxing music, will be provided during the second cycle of CPAW.

CN condition

Participants assigned to the control condition will participate in all of the assessments and experimental tasks, but will not be instructed to use any particular coping strategy to cope with the aversive stimulus provided by the CPAW procedure. After the rest interval between the first cycle of CPAW and the second CPAW cycle, participants in the CN condition will listen to a 20-minute natural history audio recording.[67] The option for this recording is supported by: (a) previous research showing that individuals who were asked to listen to it found it to be a neutral, yet relaxing, passage; (b) the use of this passage as an effective control condition in previous studies.[71 72] A 5-minute natural audio recording will be provided during the second cycle of CPAW.

Study variables

Table 2 provides a summary of the study variables and measures, as well as the assessment time points for each.

Primary outcomes

The primary outcome domains that will be assessed in this study are pain intensity and pain tolerance. These outcomes will be assessed both at pre-test (T1) and post-test (T2) assessment points.

Secondary outcomes

The secondary outcomes to be assessed are psychophysiological indicators of pain-related stress, as reflected by two domains: salivary cortisol level and HRV. These outcomes will be assessed both at pre-test (T1) and post-test (T2) assessment points.

Other variables

Other variables include presumed moderators of the effects of at least one intervention on primary and secondary outcomes, covariates that are thought to potentially bias or affect the effects of interventions on outcomes, descriptive and screening variables, and manipulation check variables.

Predictors/moderators

Predictor/moderator domains that will be assessed at baseline (T0) include hypnotic suggestibility, baseline mindfulness, acceptance, pain-related beliefs, religious affiliation, religiosity, trait spirituality, previous experience with CP, SH and MM, outcome expectations and trait absorption.

Covariates

Sociodemographic variables that could influence outcomes (ie, sex and age) will be assessed at baseline (T0), immediately after consent process.

Table 2 Assessment points, outcome variables and outcome measures

Variable	Measure	Assessment points		
		Baseline	Pre-test (T1)	Post-test (T2)
Primary outcomes				
Pain intensity	0–10 Numerical Rating Scale		x	x
Pain tolerance	Length (in seconds) that an individual bears painful stimulation		x	x
Secondary outcomes				
Pain-related stress	Salivary cortisol level Heart rate		x	x
Predictors/moderators				
Hypnotic suggestibility	Barber Suggestibility Scale	x		
Baseline mindfulness	Five-Facet Mindfulness Questionnaire	x		
Acceptance	Acceptance and Action Questionnaire-II	x		
Pain-related beliefs	Survey of Pain Attitudes	x		
Trait spirituality	Spiritual Transcendence Scale	x		
Religious affiliation	Multiple choice item: 'Please indicate your primary religious affiliation(s) with the following options, if any.'	x		
Religiosity	Duke University Religiosity Index	x		
Previous experience of H, M and CP	3 Likert items	x		
Outcome expectations	Modified Credibility/Expectancy Questionnaire	x		
Trait absorption	Modified Tellegen Absorption Scale	x		
Covariates				
Sociodemographic variables	Sociodemographic questionnaire	x		
Screening variables				
Clinical history	Clinical history questionnaire	x		
Manipulation check				
Pain coping response	Open-ended item: 'What did you think or did during the experiment to deal/cope with the discomfort provoked by the cold?'		x	x

CP, Christian prayer; H, hypnosis; M, meditation.

Descriptive and screening variables

Participants will be asked to provide clinical history information (the presence of any acute or chronic illness and/or health condition, and which) both for determining eligibility and describing the sample. Additional demographic variables (listed in the Measures section) will also be assessed at this time to describe the sample.

Manipulation check

An open-ended question (regarding coping strategies employed during the CPAW trials to cope with experimentally induced pain) asked both at pre-test (T1) and post-test (T2).

Assessment measures

Primary outcome measures

To assess pain intensity, participants will be asked to rate their average pain intensity during the CPAW procedure using a 0–10 Numerical Rating Scale (NRS) of pain intensity,[15] where 0 indicates 'No pain' and 10 indicates 'Worst imaginable pain'. Previous research supports the responsivity of the 0–10 NRS as a measure of pain intensity.[15] Pain tolerance will be operationalised as the length (in seconds) that an individual is willing to experience the aversive stimulation, up to a maximum of 5 min (300 s). It will be timed by the research using a digital stopwatch.

Secondary outcome measures

Salivary cortisol level will be measured using the method and kits mentioned above and proposed by Schwabe *et al*.[73] Saliva samples will be collected immediately before and 20 min±30 s after the CPAW.[73] Salivary Cortisol Luminescence Immunoassay kits (ROCHE,

Eletroquimioluminescence-Cobas), as well as a lab refrigerator to refrigerate the salivary cortisol samples, will be used.

Heart rate will also be measured

The recorded ECG will be treated according to the guidelines of BIOPAC Systems, in order to optimise the R–R interval data for HRV analysis (www.biopac.com). The existence of artefacts and ectopic beats will be monitored. The chosen measure of HRV is the high frequency power HRV, which is influenced by parasympathetic activity. An MP150 BIOPAC system using the software Acqknowledge V.4.0 (BIOPAC Systems) and HRV analysis (http://kubios.uef.fi) will be used to measure heart rate and compute HRV and other time and frequency domains.

Measures of predictors/moderators

These will include the following:

Hypnotic suggestibility

Hypnotic suggestibility will be measured using the Barber Suggestibility Scale (BSS).[74 75] This scale entails eight test suggestions (arm lowering, arm levitation, hand lock, thirst hallucination, verbal inhibition, body immobility, post-hypnotic response and lastly selective amnesia) which are scored by the researcher: 1/2 point if there are visible signs, and additional 1/2 if the participant verbalises afterwards she/he became thirsty. The participants are also instructed to complete a subjective scoring booklet after the administration of the test suggestion, relative to the perceived experience with each suggestion. These items are answered in a 4-point type of Likert scale, from 0 ('Not light') to 3 ('Very light'). Objective scoring ranges from 0 to 8, and the subjective score ranges from 0 to 24, with higher scores indicating higher levels of hypnotic suggestibility. The BSS can be applied with or without hypnotic induction. In this study it will be used as a standard audio-taped hypnotic induction, following the script recommend by the authors of the scale.[74] The scale has shown both validity and reliability in different studies with both non-clinical and clinical samples.[74 75]

Baseline mindfulness

This will be assessed through the Portuguese version of the Five-Facet Mindfulness Questionnaire.[76] This is a self-report questionnaire composed of 39 items divided in five domains (observing, describing, acting with awareness, non-judging and non-reactivity), with higher scores indicating greater mindfulness capacities. The items are answered in a 5-point Likert scale, from 0 ('Never') to 4 ('Always'). Previous research supports the validity and reliability of both the original[76] and Portuguese[77] versions of the Five-Facet Mindfulness Questionnaire.

Acceptance

Acceptance will be measured by using a Portuguese modified version of the 7-item Acceptance and Action Questionnaire-II (AAQ-II).[78] The items of the 7-item AAQ-II are answered in a 7-point type of Likert scale from 1 ('Never true') to 7 ('Always true') that assess a single domain of acceptance. Higher scores indicate higher degree of acceptance. Previous research supports the validity and reliability of the English and Portuguese versions of the AAQ-II.[78 79]

Pain-related beliefs

Pain-related beliefs will be assessed through the Portuguese version of the 35-item Survey of Pain Attitudes (SOPA-35).[80] An official Portuguese version of the SOPA-35 is available from the publisher of the SOPA. The SOPA-35 is a 35-item self-report questionnaire assessing seven pain-related beliefs or domains: pain control, disability, medical cure, solicitude, medication, emotion and harm. Participants are asked to specify their degree of agreement with each statement in a Likert scale from 0 ('This is very untrue for me') to 4 ('This is very true for me'). Seven scores (one per pain-related belief) are computed, with higher scores indicating greater agreement with each belief. Previous research supports the validity and reliability of the original version of the SOPA-35.[80] The study of the psychometric properties of the Portuguese SOPA-35 is in progress.[81]

Trait spirituality

The Spiritual Transcendence Scale (STS) will be used to assess spirituality as trait. The STS consists of 24 items divided into 3 domains: prayer fulfilment, universality and connectedness.[82] Respondents are asked to rate their degree of agreement with each statement in a Likert scale, from 1 ('Completely disagree') to 5 ('Completely agree'). Previous research supports the validity and reliability of both the original[82] and Portuguese[83] versions of the STS.

Religious affiliation

To assess religious affiliation, participants will answer one multiple choice question ('Please indicate your primary religious affiliation among the following options, if any'). Participants will be asked to choose from a list of possible answers: Animist, Buddhist, Christian Anglican, Christian Baptist, Christian Calvinist, Christian Lutheran, Christian Orthodox, Christian Catholic, Other Christian, Hinduist, Islamic, Jewish, Shinto, Taoist, Other, Non-religious Agnostic, Non-religious Atheist, None of the previous options, Prefer not to answer.

Religiosity

The Duke University Religiosity Index (DUREL) is a 5-item measure that will be used to assess three major dimensions (corresponding the scale's three domains or subscales) of religious involvement: organisational religious activity, non-organisational religious activity, and intrinsic or subjective religiosity.[84] Higher scores on the three subscales and on the total score of the measure indicate higher religiosity. The original version of this measure is a valid and reliable measure of religiosity.[84] The study of the psychometric properties of the Portuguese version of DUREL is in progress. Preliminary findings indicate that

the Portuguese version of DUREL is valid and reliable in a sample of Portuguese individuals with chronic pain.[85]

Previous experience of SH, MM and CP

To assess previous experience with SH, MM and CP, specifically, participants will be asked to first indicate (yes/no) if they have ever practised SH, MM or CP. If the answer is 'Yes,' they will then be asked to indicate how often they currently practise SH, MM and CP in 3 Likert items developed by the research team, from 0 ('Rarely or never') to 4 ('More than once a day').

Outcome expectations

A modified version of the Credibility/Expectancy Questionnaire (CEQ) will be used to measure outcome expectations and rationale credibility relative to each of the interventions at the baseline.[86] This measure consists of 6 type of Likert items divided into 2 domains—outcome expectations and rationale credibility. Previous research supports the validity and reliability of both the original version of the CEQ.[86] For the purpose of this study, the items of the CEQ will be adapted to fit the purposes and design of this study. The study of the psychometric properties of a Portuguese modified version of the CEQ will be performed in the context of this study.

Trait absorption

The Modified Tellegen Absorption Scale (MODTAS) will be used to assess trait absorption.[87] This scale is composed of 34-item Likert (from 0—'never' to 4—'very often') divided into 5 domains (synesthesia, altered states of consciousness, aesthetic involvement, imaginative involvement, extra-sensory perception) that are grouped in a single second-order factor. Previous research supports the validity and reliability of the MODTAS.[87 88]

Measures of covariates

A sociodemographic questionnaire will be developed by the research team and will ask participants to provide, among others, information regarding their sex and age.

Measures of descriptive and screening variables

A clinical history questionnaire will be developed by the research team to assess variables needed to screen the participants' eligibility. This will consist of a list of different acute and chronic illnesses and/or health conditions. Participants will be asked to indicate the illnesses and/or health conditions that they currently have. In addition, to collect information needed to describe the sample, the above-mentioned sociodemographic questionnaire will also ask participants to provide information regarding their education level, marital status, area of residence, employment status, household's income and religious denomination.

Manipulation check

To assess the coping strategies employed by participants to cope with the pain induced through CPAW, participants will answer one open-ended question ('What did you think or did during the experiment to deal/cope with the discomfort provoked by the cold?'). Participants will be presented this question and asked to provide their answer in writing. Answers will be coded by two independent researchers who will be blinded to the treatment condition, considering if SH, MM, CP or other coping strategy were used to cope with the pain.

Assessment procedures

All data collection procedures will be performed by a trained research assistant who is blind to the study hypotheses and to experimental condition. To maximise the quality of the self-report data, only one research assistant will obtain all measures, and this individual will be trained by a psychologist experienced in psychological questionnaire-based assessment.

Adverse events and safety monitoring

The findings from previous research indicate that unanticipated adverse effects associated with either the interventions, the CPAW procedures or the assessment procedures are unlikely. However, their occurrence will be closely monitored and recorded. For example, participants may experience fatigue while completing assessments at T0. Participants will also be told they are free to skip any questions and stop the assessment at time. Also, although participants will likely experience discomfort and pain during CPAW procedures (as these are what the procedures are designed to induce), they will be told that they can discontinue the CPAW procedures at any time for any reason they choose, and will also be instructed to take off the arm wrap if it feels too uncomfortable for them to continue. Given the short duration and minimal risks of this study, a formal data monitoring committee was deemed unnecessary.

Statistical analysis plan

Results will be considered statistically significant for a p value lower than 0.05. Because data collection will be completed in person, we do not anticipate significant amounts of missing data. In the event that some data are missing, missing data analysis will be conducted to determine potential patterns in missing values or if missing values are random. Missing value replacement will be performed through the multiple imputation of Markov chain Monte Carlo method.[89]

For analysis of the qualitative data, participants' answers to the manipulation check open-ended question will be coded in accordance with a directed qualitative approach.[90] An initial coding scheme will be developed a priori according to past research and used to categorise the units of analysis. Mutually exclusive emerging categories concerning the latent and manifest content of each pre-existing category (SH, MM, CP, other coping strategy) will be identified. The content excerpts (previously defined as unit of analysis) will be compared with the main a priori categories. Complementarily, inductive analysis will be conducted in units of analysis that do not

fit the theoretically guided categories; for these, inductively created codes will be conceived.[91] Coding decisions will be assessed by comparing the answers' excerpts with the definitions of the categories and with other answers' excerpts within existing categories. The trustworthiness will be assured by the continued comparison in the coding process, focusing both theory-guided and inductively created categories, but also through the inter-rater reliability coefficient. Thus, at the end of the coding process, 10% of the questions randomly selected will be coded by the two independent researchers, trained in the coding matrix and blinded to the treatment condition (considering if SH, MM, CP or other coping strategy were used to cope with the pain). Inter-rater reliability (Cohen's kappa coefficient, *j*) will be computed, with a *j* lower than 0 indicating no agreement, a *j* between 0 and 0.20 indicating slight agreement, a *j* between 0.21 and 0.40 indicating fair agreement, a *j* between 0.41 and 0.60 indicating moderate agreement, and a *j* between 0.61 and 0.80 or higher indicating, respectively, substantial or almost perfect agreement.[92] The final coding of the participants' answers will be achieved by consensus. Categories will then be dummy coded, with 1 indicating that the participants used a given coping strategy and 0 indicating that participants did not use a certain coping strategy.

Descriptive statistics (ie, frequencies, percentages, means, SDs, as appropriate) will be computed to describe the sample and study variables at each assessment point. The distributions of the outcome data will also be evaluated (ie, by computing skewness and kurtosis) to determine if they meet criteria for the planned analyses. If they do not, the variables will be transformed (eg, using square root transformations) to normalise the data prior to analyses. Then, to test mean differences between four groups over the T1 and T2 assessment points, we will perform a series of mixed-design repeated-measures analyses of variance (ANOVAs), with the four pain-related outcomes as dependent variables, and sex, time of assessment (T1 and T2) and condition as independent variables. Effect size measures (partial eta squared) and statistical power (1–β) will be computed and reported. If the study variables do not meet the assumptions for ANOVA analyses and cannot be transformed to meet those assumptions, we plan to employ the Wilcoxon test.

Secondary exploratory analyses will involve a series of hierarchical multiple regression analyses with the four outcome variables as the criterion measures, and experimental condition, predictor/moderator variables, time and their interactions as independent variables. We will examine both direct prediction effects (ie, the extent to which the predictor/moderator variables prospectively predict outcome across all of the treatment conditions) and moderator effects (ie, the extent to which the ability of the predictor/moderator variables to predict outcome varies as a function of treatment condition). All moderation analyses will consider the entire sample and will be done using PROCESS macro for IBM SPSS Statistics V.25. We will compute post-hoc correlation coefficients (continuous variables) or t-tests (dichotomous variables) to help explain any statistically significant moderator (ie, Moderator X Condition) effects that emerge. Data analysis will be conducted using IBM SPSS Statistics V.25.

Patient and public involvement

The development of the research question and choice of the outcome measures took into consideration the findings from previous findings present in the literature regarding the experience of patients with chronic pain and regarding the effects of SH, MM, and spiritual and religious practices on pain-related outcomes in people with chronic pain. The study itself does not involve patients. Patients were not directly involved in the development of the design of the study. Patients will not be involved neither in the recruitment and conduction of the study, nor in the assessment of the burden of the interventions. Study results will be published in peer-reviewed indexed journals and presented at pain international scientific meetings. A full report of the study results will also be made available at the funding agency website, which is open to the public and will be made available to study participants.

ETHICS AND DISSEMINATION

The present study was reviewed and approved by ISPA–University Institute's internal Ethics Committee for Research (ISPA-UI ECR) on 3rd December 2018 (reference I/010/12/2018). The study will be compliant with international ethical principles and guidelines for studies involving human subjects. Compliant with Helsinki Declaration and with national and European legislation and with the European Union (EU) General Data Protection Regulation (EU Regulation 2016/679 of 27th April 2016). Participants will read and sign an informed consent form for participation in the study and for data collection and storage. The informed consent form will include a detailed description of the study aims and procedures. Informed consent will be obtained prior to any data collection or study procedures. Participants will be encouraged to discuss any concerns, any questions raised will be addressed by the research team. Participants will be assured confidentiality and anonymity. Participants' decision to stop any procedures at any time will be honoured.

Data processing activities within the study will be carried out in accordance with the updated data protection rules as specified in the EU General Data Protection Regulation which replaces the Data Protection Directive 95/46/EC. Identifiable information (II) will be linked to a unique study participant's ID. II and the key linking the participant ID to the former will be stored in a password-protected database, accessible only to the research team and staff members. Study data will be coded with the participant ID and stored in a password-protected computer database. Study data will be accessible only to the research team members.

Any modification to the study protocol will be submitted to review and approval of ISPA-UI ECR. Study findings will be published in peer-reviewed indexed journals and presented at pain international scientific meetings.

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Contributors AF-V conceived the study idea, and together with FP and RC, developed the design of the study. MJ and MD, respectively, created the hypnosis and mindfulness meditation intervention manuals that will be employed to develop the intervention scripts and audio-recordings. MJ and JP-R substantially contributed to the review and refinement of the study design and protocol. AF-V planned the data analysis. All authors participated in the drafting of this manuscript and critically reviewed and approved the final version. AF-V, FP and RC will conduct the study procedures. AF-V is the principal investigator.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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