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CLINICAL TRIAL REPORT

Immediate Effects of Hypnosis, Mindfulness Meditation, and Prayer on Cold Pressor Outcomes: A Four-Arm Parallel Experimental Study

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Purpose: Previous research supports the usefulness of hypnosis (HYP), mindfulness meditation (MM), and prayer as pain self-management strategies in adults with chronic pain. However, their effects on acute pain have been less researched, and no previous head-to-head study compared the immediate effects of these three approaches on pain-related outcomes. This study compared the immediate effects of HYP, MM, and Christian prayer (CP) on pain intensity, pain tolerance, and stress as assessed by heart rate variability (HRV).

Participants and Methods: A total of 232 healthy adults were randomly assigned to, and completed, a single 20-minute session of MM, SH, CP, or an attention control (CN), and underwent two cycles (one pre- and one post-intervention) of Cold Pressor Arm Wrap (CPAW). Sessions were audio-delivered. Participants responded to pre- and post-intervention pain intensity measurements. Pain tolerance (sec) was assessed during the CPAW cycles. HRV was assessed at baseline, and at pre- and post-intervention CPAW cycles. The study protocol was pre-registered at the ClinicalTrials.gov registry (NCT04491630).

Results: Small within-group decreases in pain intensity and small increases in pain tolerance were found for HYP and MM from the pre- to the post-intervention. Small within-group improvements in the LH/HF ratio were also found for HYP. The exploratory between-group pairwise comparisons revealed a medium effect size effects of HYP on pain tolerance relative to the control condition. The effects of CP were positive, but small and not statistically significant. Only small to medium, though non-significant, Time × Group interaction effects were found.

Conclusion: Study results suggest that single short-term HYP and MM sessions, but not biblical-based CP, may be useful for acute pain self-management, with HYP being the slightly superior option. Future research should compare the effects of different types of prayer and examine the predictors and moderators of these pain approaches' effects on pain-related outcomes.

Keywords: hypnosis, mindfulness meditation, prayer, experimental pain, cold pressor arm wrap

Introduction

Pain is an almost universal experience.[1] Despite its survival value, acute pain is usually unpleasant and can be highly distressing.[2–7] If inadequately managed, acute pain can have negative impacts on numerous health domains, including sleep quality, cardiovascular and immunological function, and psychological function.[8,9] Inadequately managed acute pain can also increase the risk of developing chronic pain.[8,9] Thus, access to effective acute pain management is of primary importance.[9,10]

Because pain is a complex experience influenced by biological (eg, extent of physiological damage, sex), psychological (eg, pain-related beliefs, pain-coping responses), and social (eg, social support, gender) factors,[11–17] adequate pain management requires more than biological treatments alone, such as analgesic medications.[8] Ideally, individuals at risk

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for acute pain would have resources readily available to self-manage their pain. Such resources may include approaches that would address the multidimensional factors that influence pain,[18–20] including psychological, social, and spiritual methods.[8,21]

Previous evidence supports the efficacy of hypnosis (HYP) and mindfulness meditation (MM) for reducing acute, chronic, and experimentally induced pain.[22–25] Even brief (ie, single-session) training in HYP and MM has demonstrated efficacy for improving a variety of pain-related outcomes, such as pain intensity and pain tolerance, in people experiencing acute pain and experimentally induced pain.[23,24,26–28] However, the magnitude of the beneficial effects of these approaches appears to be only moderate,[29] a result that might be attributed, at least in part, to interindividual variability in baseline psychological, social, and physiological factors.[17,30,31] For example, epidemiological and clinical findings worldwide suggest women seem to be at greater risk than men to experience pain.[17] Findings from laboratory studies on experimentally induced pain indicate that women tend to show lower pain thresholds and pain tolerance and to report higher pain intensity, across stimulus modalities and body regions.[17] However, inconsistent findings have emerged with respect to the magnitude of the sex and gender differences.[17] More importantly, findings suggest that sex and gender may partially account for interindividual variability in the response to pharmacological pain treatments, although research on its relevance in explaining interindividual variability in the response to non-pharmacological pain management approaches, such as hypnosis and mindfulness, is less understood.[17]

Recently, there has been a growing interest in how spiritual and religious factors and practices may be associated with pain experience.[11,32–34] Spirituality may be defined as a sense of connectedness with a higher being or power and a sense of, or search for, life meaning and purpose. Being of a specific religion, on the other hand, has to do with a shared common way of searching for such a connectedness, meaning, and purpose by a group of individuals with a common set of beliefs and practices, with the term religiosity referring to the degree of engagement with this shared belief system and practices. Research has found that all three – spirituality, religion denomination, and religiosity are associated with (1) pain-related outcomes (eg, pain intensity and pain tolerance); (2) the meaning attributed to pain and its impact; and (3) the way one copes with pain; while also potentially (4) informing individuals' resilience; and (5) buffering the effects of pain on stress.[11,32–39] There is also evidence that some individuals spontaneously engage in spiritual and religious practices (eg, spiritual meditation, prayer) to manage pain[35,40] which, in turn, seem to buffer the effects of pain on stress.[39]

While the evidence supporting the beneficial effects of these religious and spiritual practices – such as prayer – on pain-related outcomes is promising, prior research examining these factors is limited.[11,41] Further, most of the research undertaken to date has been limited to a small number of observational studies,[35] quasi-experimental studies that lack either a control group or random allocation of participants,[42–44] or a small number of methodologically medium quality randomized controlled trials conducted.[45–49] Much of this research has also been limited to clinical populations of Muslim individuals living in Iran. The only study focusing on the effects of Christian prayer on acute pain suggests that, at least for practicing Christian Catholic participants, a simple religious practice such as contemplating the image of the Virgin Mary, may have a beneficial effect on pain intensity.[50]

Given the limited evidence regarding the effects of prayer as a pain management strategy, further research is needed to determine if the promising results from Muslim individuals living in Iran would replicate in individuals from different countries and religious denominations. Findings from such research would also inform clinicians and individuals about if, and how, such practices might be used as effective pain self-management methods. In addition, though prior research supports the efficacy of both HYP and MM for improving pain-related outcomes, the utility of brief interventions with a single short training session of these approaches has not yet been adequately studied in head-to-head randomized controlled experimental studies. It would also be useful to know if the effects of prayer are similar to or different from HYP and MM, which are similar to prayer in many ways (ie, all three are self-management approaches that involve the engagement of cognitive processes that can be used by individuals in any acute pain situation).

Given these considerations, the primary aim of this study was to compare the immediate effects of a 20-min single-session of hypnosis (HYP), mindfulness meditation (MM), and Christian prayer (CP), relative to an attention control group (CN) on pain tolerance (co-primary outcome), pain intensity (co-primary outcome), and a physiological index of

stress level as assessed by heart rate variability (HRV; secondary outcome) metrics in healthy volunteers submitted to cold pressor arm wrap (CPAW) painful stimulation.

We hypothesized that relative to the control participants, those participants randomized to receive brief training in HYP, MM, or CP would evidence (1) significantly (within-group) improved cold pressor outcomes in the post-intervention relative to the pre-intervention (ie, an increase in pain tolerance, decrease in pain intensity, and decreases in stress as measured by HRV) and (2) significantly improved cold pressor outcomes than participants in the CN condition (ie, higher pain tolerance, lower pain intensity, and lower stress as measured by HRV). Because no prior research has directly compared the immediate effects of HYP, MM, and CP in a single study, we did not have any a priori hypotheses regarding possible between active treatment condition differences on cold pressor outcomes.

Materials and Methods

Research Design

This is a randomized four-arm parallel prospective experimental mixed-design repeated-measures design study. It compared the effects of three experimental conditions – hypnosis (HYP), mindfulness meditation (MM), and Christian prayer (CP) – with those of an attention control condition (CN). All interventions were similar in terms of time and structure. They consisted of 20-minute audio recordings teaching and allowing participants to practice one of the three active responses to painful stimulation (HYP, MM, or CP) or providing a control condition audio-recording (CN; see Figure 1). Data collection took place over a period of approximately 14 months until February 2022. Prior to any study participants' enrollment, the study protocol was approved by Ispa – University Institute internal Ethical Review Board for Research on December 3rd 2018 (reference I/010/12/2018), as well as preregistered at ClinicalTrials.gov (identifier: NCT04491630, available at https://clinicaltrials.gov/ct2/show/NCT04491630). The study protocol complied with the Declaration of Helsinki. Details of the overall design are available in the study protocol published elsewhere.[51]

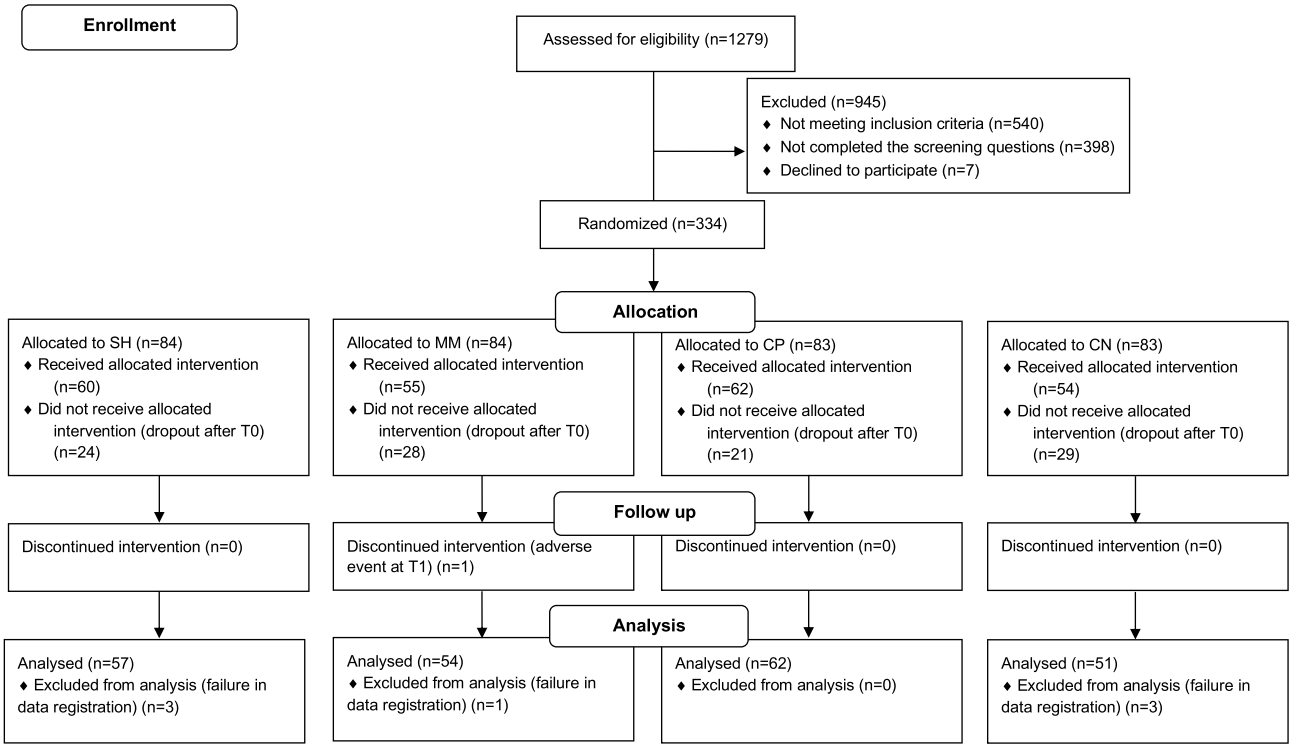

Figure 1 CONSORT 2010 flow diagram.

Participants

The study took place at the facilities of the Psychology Laboratory of the William James Center for Research at Ispa – Instituto Universitário in Lisbon, Portugal. Study participants were healthy adult individuals living in Portugal and speaking, reading, and understanding Portuguese. Participants were recruited from the internal (students in their first year of the bachelor's degree in Psychology) and external (prospective participants from the general population who indicated interest in receiving information about the active studies of the host institution) pool of participants of the Psychology Laboratory of the William James Center for Research at Ispa – Instituto Universitário. Power was estimated for the primary planned statistical analysis associated with the primary aim of this study. The minimum sample size recommended to detect a significant effect in a mixed-design repeated measures analysis of variance (ANOVA) was determined a priori through power calculation using G*Power (v. 3.1). We considered a default pre-post intervention correlation of 0.50. Based on the evidence of previous research of small to large effects of HYP, MM, and CP on pain intensity and pain tolerance, we considered a small effect size (Cohen's *f*) of 0.15 for a Time × Condition interaction effect as well as a two-sided α of 0.05 and a power of 0.95.[24,26,27,50,52,53] This calculation resulted in a minimum sample size required to detect a Time × Condition interaction effect of 196 participants (49 per study condition).

Inclusion criteria were being (1) 18-years-of-age or older; (2) able to read, speak, and understand Portuguese; and (3) willing to be randomly assigned to any of the four conditions. Individuals were excluded if they: (1) self-reported history of cancer, heart disease, stroke, Raynaud syndrome, epilepsy, diabetes, or musculoskeletal condition; (2) had an open wound, cut, or fracture in any of the upper limbs; (3) self-reported alcohol/substance dependence (self-reported history of substance dependence, or self-reported substance abuse in the previous three months); or (4) had a cognitive or physical impairment (at least two errors at the 6-item Screener),[54] or significant psychopathology (eg, suicidal ideation with intent in the previous 6 months, active psychosis or hallucinations, current intake of antipsychotic medication to treat a psychotic or bipolar disorder) that could interfere with being able to participate in the study.[55] Participants from the internal pool received course credit and a €10 voucher for their participation, whereas participants in the external pool received a €20 voucher for their participation. A total of 1279 individuals initially volunteered to participate in this study. Eight hundred and eighty-one of these (88%) completed the screening questions and 540 (61%) were ineligible: 2 (0.4%) were younger than 18-years-of-age; 4 (0.7%) did not read, speak, and understood Portuguese; 32 (6%) were not willing to be randomly assigned to all four conditions; 73 (14%) had history of musculoskeletal problems, cancer, heart disease, stroke, epilepsy, diabetes, or Raynaud syndrome; 45 (8%) had an open wound, cut, or fracture in any of the upper limbs; 170 (32%) reported alcohol or substance dependence; and 214 (40%) had cognitive or physical impairment or severe psychopathology that could prevent participation. Of the 341 eligible individuals, 334 accepted to participate in the study and were randomly assigned to one of the study conditions. Of these, 232 (40%) completed all study procedures. Valid participation in the study procedures was verified, and valid data were available for 224 participants who were included in the study sample (see Figure 1).

One-hundred and nine eligible individuals elected not to complete all the study procedures. Eighty individuals dropped out after the eligibility screening, and the remaining 29 dropped out after the baseline assessment and before the first CPAW trial. The study sample significantly differed from the group of eligible individuals who elected not to complete the study procedures, in terms of gender [$x^2(1333) = 11.60$, $p < 0.001$] and mean age [$t(331) = 4.39$, $p < 0.001$], with the study sample being, on average, younger and having a higher proportion of men than the sample who did not complete the procedures. No significant between-group differences were found relative to individuals' religious denomination [$x^2(1333) = 11.60$, $p < 0.001$].

Measures

Sample Baseline Characteristics

Participants completed a questionnaire developed by the research team assessing sociodemographic characteristics (eg, sex, age, education level, marital status, employment status, household income) and self-reported religious denomination. Participants also completed a clinical history questionnaire to screen for their eligibility in accordance with the criteria described above.

Co-Primary Outcome Measures

Co-primary outcomes for the study were pain tolerance and pain intensity. Pain tolerance was defined as the time (in seconds up to 300s, ie, 5 minutes) that participants were willing to experience the noxious stimulation as assessed by the research assistant using a digital stopwatch. Participants were aware of the maximum allowable tolerance time prior to completing the CPAW. Perceived average pain intensity experienced during the noxious stimulation was assessed, at the end of each CPAW trial, using a 0–10 Numerical Rating Scale of pain intensity (0–10 NRS)[55] ranging from 0 ("No pain") to 10 ("Worst imaginable pain"). Validity and responsivity of the 0–10 NRS of pain intensity has been demonstrated by previous research.[55]

Secondary Outcome Measures

The secondary outcome of this study was HRV, a physiological marker of stress.[56–58] HRV was calculated by the software Kubios HRV analysis (http://kubios.uef.fi) after ECG having been recorded by an MP150 BIOPAC system with the software Acqknowledge 4.0 (BIOPAC Systems, Inc) at a sampling rate of 1.000 Hz. The ECG was filtered between 0.5 and 3.5 Hz, and the template correlation function was applied. Subsequently, a tachogram was generated and artefacts removed. The calculated parameters of HRV were square root of the mean squared differences of successive interbeat intervals (RMSSD), standard deviation of interbeat intervals (SDNN), percentage of adjacent pairs of normal-to-normal intervals differing by more than 50ms (pNN50), high frequency power obtained by fast Fourier transform (HF-FFT) and autoregressive modelling (HF-AR) expressed in ms^2, and low-to-high frequency ratio obtained with fast Fourier transform (LF/HF-FFT) and autoregressive modelling (LF/HF-AR).

Additional Measures

The preregistered measures not analyzed here include those needed to address the secondary and exploratory aims of the study, including tests for identifying outcome predictors and moderators (including, but not limited to, outcome expectations, and previous experience of HYP, MM, and CP) of the effects of HYP, MM, and/or CP on the primary and secondary outcomes (see ClinicalTrials.gov identifier: NCT04491630). A second manuscript is planned that will report the findings from the analyses to address the study's secondary aims.

Changes Relative to the Study Preregistration

We initially planned to evaluate salivary cortisol levels as an additional measure of pain-related stress. However, given the necessity of complying with the Directorate-General of Health of Portugal's recommendations to prevent the spread of SARS-CoV-2 and to maximize the safety perception of prospective participants at all times, no salivary samples were collected. Thus, the research team was unable to assess salivary cortisol levels as originally planned.

Procedures

A detailed description of the study procedures is provided elsewhere.[51] In short, prospective participants were screened for eligibility via self-report. Eligible participants were provided a full description of the study aims and procedures, given the opportunity to clarify any concerns, and assured of the confidential and voluntary nature of their participation. After providing informed consent, study participants completed the baseline assessment measures (T0; pre-intervention, before randomized allocation and before the first CPAW trial), except for the baseline HRV, administered via Qualtrics online platform. Participants were then randomly assigned to one of the four study conditions in stratified blocks, considering sex and religious affiliation (self-reporting having a religious denomination vs not self-reporting having a religious denomination or self-reporting being agnostic or atheist), using a computerized random sequence generator as described in the study protocol.[51] To increase the odds of comparable outcome expectancies, the study participants were told that all four conditions had previous evidence supporting their efficacy. Participants were blinded to the study hypotheses.

The participants were then administered the first (T1) CPAW trial to assess the study's primary and secondary outcomes prior to listening to the audio recordings associated with their assigned condition.[59] CPAW is an alternative procedure to the cold pressor test and used as an aversive experience to induce pain and stress.[55] The MRI-safe gelpacs used to conduct the CPAW were cooled to 1°–3°C and wrapped around participants' forearm and hand. Participants were

instructed to maintain the arm wrap as long as they could tolerate it, up to a maximum of 5 minutes. They were informed they could withdraw the arm wrap at any time, but if they tolerated the noxious stimulation for over the established limit, the research assistant would stop the CPAW trail at the established 5-min maximum. Individuals rated the average pain intensity experienced during the noxious procedure once they reached their pain tolerance or 5 min had elapsed, whichever came first. After a 20-min rest interval, the participants listened to a 20-min audio recording of guided HYP, MM for pain management, and CP, or, for those allocated to the CN condition, a 20-min audio recording of text from a natural history book, as detailed below.[60] Noise-cancellation headphones were used for this purpose. After the exposure to the intervention, participants were then administered a second CPAW trial (T2), during which participants listened to an up to 5-minute HYP, MM, CP, or natural history reading (CN) audio recording, consistent with their group allocation. Immediately after they reached their pain tolerance or at five minutes, whichever was shorter, the audio recording was stopped and both pain tolerance and average pain intensity during the aversive stimulus were again assessed.

Baseline (T0) HRV was computed based on a five-minute resting period before the first CPAW trial. Pre-intervention (T1) and post-intervention (T2) HRV were calculated based on the ECG recordings during the period of exposition to the painful stimulation. The heart rate recordings were treated accordingly with BIOPAC Systems, Inc. (www.biopac.com) recommendations. A research assistant monitored the existence of artefacts and ectopic beats and computed the HRV indexes using Kubios HRV software v. 3.4.3 (http://kubios.uef.fi).

The baseline (T0), pre-intervention (T1), and post-intervention (T2) assessments, as well as the administration of the audio-recorded interventions and of the painful stimulation, were conducted by a research assistant (experimenter) who was blind to participants' allocation and study hypotheses. Self-report study measures, including pain intensity, were administered via Qualtrics platform. Pain tolerance and HRV values were entered by the research assistant in a Qualtrics platform. As the research staff was blinded to experimental conditions, the participants were explicitly told not to disclose which audio recording they heard.

Study Conditions Protocols

Interventions consisted of 20-minute audio recordings delivered just before the second CPAW cycle and after a 20-minute rest period after the first cycle of CPAW. All audio-recordings were recorded by the same clinician (FP) so that all four conditions had the same voice. In the case of the three experimental conditions, the respective audio recordings instructed participants and permitted them to practice HYP, MM, or CP in response to painful stimulation. Participants in the active conditions were instructed in the audio recordings to practice the pain management strategy taught during the second CPAW cycle while listening to a second 5-minute audio recording to assist with such practice.

Participants in the HYP condition listened to a recording of a clinician (FP) delivering a standard hypnotic script which was adapted by two research team members (FP and MJ) from the hypnosis scripts developed by the last author (MJ).[61] The audio included instructions on how to self-induce hypnosis, suggestions for comfort and the management of intense sensations, and a suggestion that the individual would be able to easily use HYP on their own during the T2 noxious procedures.

Participants in the MM condition listened to a recording of a clinician (FP) instructing individuals in the use and application of Vipassana MM.[62] The script of the MM audio recording was adapted from the MM scripts developed by the third author (MD).[63] It introduced the idea of attention to one's breath, as well as of acceptance and non-judgmental monitoring of all sensations, followed by a guided body scan experience.

Individuals in the Christian Prayer condition listened to a recording of the same clinician (FP) instructing individuals to follow a guided biblical-based meditation. Biblical-based meditation is a common type of prayer and practice of scriptural reading, with hundreds of years of tradition on Western Christianity. The effects of this type of prayer have been studied rarely (Jarego et al, under review). As much as 84% of the Portuguese population – the population from which the sample of this study was taken from – self-identifies as being Christians (81% Christian Catholics), even if, in recent years, Portugal has become more secularized, and religion plays a very limited role in the everyday life (eg, only 19% of the Portuguese population attends church regularly).[64] The CP script was adapted by the first author (AFV) in close collaboration with an experienced CP expert from the existing on-line biblical meditations available from the

Society of Jesus (www.passo-a-rezar.net). After introducing and orienting individuals to CP, the audio recording provided a reading from the New Testament of the Bible, read twice, followed by a brief suggestion of prayer.

Finally, individuals in the control condition were provided with natural history audio-recording of a section from White's *Natural History of the Antiquities of Selborne*.[60] The rationale for the selection of this reading is based on prior research that has found it to be neutral, though relaxing, and based on the fact that it has been successfully used as a control condition.[65,66] These participants were not directed to use any specific strategy in response to the CPAW stimulation.

Data Analysis

After invalid data were removed, the sample consisted of 225 participants. Due to the inability to analyze a subgroup of n = 1, analyses excluded one participant who identified their gender as "other", resulting in final analysis sample size of 224. Three participants out of the remaining total sample of 224 participants (1%) were missing all heart rate variability data at T1. Missing value replacement was performed using Markov chain Monte Carlo multiple imputation (MCMCMI; 20 imputations). However, the MCMCMI resulted in numerous invalid values for the imputed variables (ie, negative values). In response to these invalid imputed values, the three participants with missing data on the T1 HRV variables were excluded from analyses using HRV data, resulting in the sample size for HRV analyses being 221. This deviation from the protocol was considered acceptable given the small number of participants with missing data.

Descriptive statistics were calculated for all variables. We then used 2 × 2 × 4 mixed design ANOVAs to test the study hypotheses with respect to the two co-primary outcomes of pain intensity and pain tolerance. The repeated-measures predictor variable was time (T1 vs T2). The between-subject predictor variables were gender (female vs male) and group (HYP vs MM vs CP vs CN). For the repeated-measures analyses, multivariate tests (Wilks' λ) were used because they do not assume sphericity. Univariate analyses were used for the between-subjects analyses.

For the secondary outcome of HRV, we used 3 × 2 × 4 doubly multivariate mixed design ANOVA. Multivariate tests were used to assess the effects of the predictor variables on the seven HRV variables (RMSSD, SDNN, pNN50, HF-FFT, LF/HF-FFT, HF-AR, and LF/HF-AR) combined before evaluating the univariate effects. The repeated-measures predictor variable was time (T0 vs T1 vs T2), and the between-subjects predictor variables were gender (female vs male) and group (HYP vs MM vs CP vs CN). When possible, multivariate tests (Wilks' λ) were used because of the lack of reliance on the assumption of sphericity. For the univariate repeated-measures analyses, Greenhouse-Geisser-adjusted *df* were used. Polynomial contrasts were used to evaluate possible linear and quadratic trends in the repeated-measures factor.

For both the primary and secondary outcomes analyses, we followed-up on significant omnibus tests using pairwise comparisons of estimated marginal means. We estimated effect sizes for all ANOVAs using η_p^2. All post-hoc pairwise comparisons used Bonferroni adjusted α's to protect against Type-I error inflation of multiple related comparisons. Effect sizes of pairwise differences were estimated using Cohen's *d*. All analyses were conducted using IBM SPSS v28 and used a two-tailed α = 0.05, unless stated otherwise.

Results

Sample Characteristics

Table 1 summarizes the demographic characteristics of the sample. On average, the participants in the sample were relatively young (*M* = 28.89 years, *SD* = 11.82) and were primarily female (n = 157, 70%) and single (n = 179, 80%). In terms of education, the largest group of participants completed secondary education (n = 104, 46%). The current employment status of the largest group of participants was full-time student (n = 109, 49%) followed by full-time employment (n = 69, 31%). The largest group of participants identified as not religious (either agnostic or atheist; n = 80, 36%), followed by those who identified as Catholic (n = 69, 31%). Over one-quarter of the sample either reported that they preferred not to identify a religious denomination or had missing data on this item (n = 61, 27%). The effect sizes of the differences among the groups were all very small to small (see Table 1).

Co-Primary Outcomes

Table 2 summarizes the mean pain intensity and pain tolerance scores for the total sample and by the study group.

Table 1 Demographic Characteristics of the Sample

	Total Sample (N = 224)	CP (n = 62)	MM (n = 54)	HYP (n = 57)	CN (n = 51)
Age (n = 222), *M* (*SD*)	28.89 (11.82)	27.95 (10.32)	29.33 (13.83)	30.52 (12.72)	27.74 (10.16)
Gender, n (%)					
Female	157 (70.1)	44 (71.0)	38 (70.4)	41 (71.9)	34 (66.7)
Male	67 (29.9)	18 (29.0)	16 (29.6)	16 (28.1)	17 (33.3)
Marital status, n (%)					
Single	179 (79.9)	51 (82.3)	43 (79.6)	46 (80.7)	39 (76.5)
Married	32 (14.3)	7 (11.3)	8 (14.8)	8 (14.0)	9 (17.6)
Divorced or separated	13 (5.8)	4 (6.5)	3 (5.6)	3 (5.3)	3 (5.9)
Education level, n (%)					
3rd cycle of primary education (9th grade)	4 (1.8)	2 (3.2)	1 (1.9)	1 (1.8)	0 (0.0)
Secondary education (12th grade)	104 (46.4)	33 (53.2)	22 (40.7)	27 (47.4)	22 (43.1)
Bachelor's degree or equivalent	66 (29.5)	17 (27.4)	17 (31.5)	19 (33.3)	13 (25.5)
Master's degree or equivalent	46 (20.5)	9 (14.5)	14 (25.9)	10 (17.5)	13 (25.5)
Doctoral degree or equivalent	4 (1.8)	1 (1.6)	0 (0.0)	0 (0.0)	3 (5.9)
Employment status, n (%)					
Full-time	69 (30.8)	18 (29.0)	15 (27.8)	19 (33.3)	17 (33.3)
Part-time	31 (13.8)	6 (9.7)	6 (11.1)	10 (17.5)	9 (17.6)
Student	109 (48.7)	32 (51.6)	29 (53.7)	23 (40.4)	25 (49.0)
Unemployed or unpaid family worker	13 (5.8)	6 (9.7)	3 (5.6)	4 (7.0)	0 (0.0)
Retired	2 (0.9)	0 (0.0)	1 (1.9)	1 (1.8)	0 (0.0)
Religious denomination, n (%)					
Catholic	69 (30.8)	20 (32.3)	19 (35.2)	14 (24.6)	16 (31.4)
Other Christian	4 (1.8)	0 (0.0)	0 (0.0)	2 (3.5)	2 (3.9)
Other religious denomination	10 (4.5)	5 (8.1)	2 (3.7)	2 (3.5)	1 (2.0)
Not religious (agnostic or atheist)	80 (35.7)	22 (35.5)	19 (35.2)	23 (40.4)	16 (31.4)
Prefer not to answer/missing	61 (27.2)	15 (24.2)	14 (25.9)	16 (28.1)	16 (31.4)

Pain Intensity (0-10 NRS)

Because none of the interaction effects were significant for pain intensity (see Table 3), only main effects were examined. The main effect of time was significant, Wilks' $\lambda = 0.93$, $F(1, 216) = 15.20$, $p < 0.001$, $\eta_p^2 = 0.07$ (medium effect), such that average pain intensity during the post-intervention CPAW (T2; $M = 4.87$, $SD = 2.46$) was significantly lower than average pain intensity reported during the pre-intervention CPAW (T1; $M = 5.57$, $SD = 2.54$) across the four groups combined, $M_{diff} = 0.69$ [0.34, 1.05], $p < 0.001$, Cohen's $d = -0.26$ [−0.39, −0.12] (small effect). The main effect of gender was also significant, $F(1, 216) = 17.98$, $p < 0.001$, $\eta_p^2 = 0.08$ (medium effect), such that male participants ($M = 4.62$, $SD = 1.94$) reported significantly lower pain intensity than female participants ($M = 5.82$, $SD = 1.94$), $M_{diff} = -1.20$ [−1.76, −0.64], $p < 0.001$, Cohen's $d = -0.62$ [−0.91, −0.33] (medium effect). The main effect of group, however, was not statistically significant (Tables 3 and 4).

To better characterize and understand any potential simple effects related to the primary hypothesis (ie, the Time × Group interaction), effect sizes (Cohen's *d*'s) of the simple effects of group within time point and time within group were examined (see Table S1). Because the Time × Group interaction was not significant and these were not a priori planned analyses, these comparisons were treated as purely exploratory. At post-test (T2), the differences between HYP and MM, CP, and CN conditions were small (Cohen's *d*'s between −0.29 and −0.45) with individuals in the HYP condition reporting lower pain intensity than the other groups. All other between-group differences at post-test were very small (ie, *d*'s <0.20; Table S1). Individuals in the HYP and MM condition reported small decreases in pain intensity from pre-test (T1) to post-test (T2; Cohen's *d*'s = −0.22 and −0.49, respectively). Individuals in the CP condition reported very small decreases in pain intensity (Table S1).

Table 2 Means (Standard Deviations) of Outcome Variables

	Total Sample (N = 224)	CP (n = 62)	MM (n = 54)	HYP (n = 57)	CN (n = 51)
Primary Outcomes (Pain-Related Measures)					
Pain Intensity (0–10)					
Pre-Test (T1)	5.77 (2.35)	5.85 (2.25)	5.74 (2.42)	5.72 (2.45)	5.76 (2.34)
Post-Test (T2)	5.15 (2.34)	5.52 (2.35)	5.17 (2.42)	4.49 (2.25)	5.41 (2.25)
Pain Tolerance (s)					
Pre-Test (T1)	202.52 (114.68)	211.76 (113.01)	200.89 (115.02)	210.49 (112.41)	184.12 (119.89)
Post-Test (T2)	231.62 (102.71)	227.85 (105.78)	237.24 (100.16)	261.44 (78.31)	196.94 (116.64)
Secondary Outcomes (Heart Rate Variability Measures)					
RMSSD					
Baseline (T0)	32.50 (28.41)	31.38 (23.54)	39.06 (41.33)	26.98 (16.64)	33.10 (26.83)
Pre-Test (T1; n = 221)	47.01 (35.57)	48.86 (38.43)	53.36 (50.20)	43.21 (22.76)	42.13 (21.83)
Post-Test (T2)	50.77 (26.74)	54.39 (31.79)	52.44 (23.93)	45.98 (24.72)	49.95 (24.84)
SDNN					
Baseline (T0)	38.02 (21.06)	36.11 (19.71)	43.36 (26.34)	34.21 (16.76)	38.96 (20.07)
Pre-Test (T1; n = 221)	49.88 (25.70)	50.17 (29.30)	55.02 (30.48)	47.64 (20.13)	46.45 (20.22)
Post-Test (T2)	53.53 (23.00)	52.85 (24.26)	56.55 (23.29)	51.79 (23.87)	53.10 (20.33)
pNN50					
Baseline (T0)	9.96 (12.96)	9.75 (13.17)	12.62 (14.84)	7.86 (11.45)	9.75 (12.01)
Pre-Test (T1; n = 221)	19.15 (16.12)	18.47 (14.87)	22.24 (18.25)	18.81 (16.43)	16.98 (14.71)
Post-Test (T2)	24.29 (18.36)	25.25 (19.85)	26.98 (17.17)	21.54 (17.90)	23.33 (18.25)
HF-FFT					
Baseline (T0)	549.03 (954.01)	476.43 (519.48)	794.72 (1553.49)	369.04 (481.44)	578.30 (895.93)
Pre-Test (T1; n = 221)	1103.51 (2420.33)	1393.07 (3942.99)	1324.77 (2092.41)	868.00 (1145.09)	773.17 (843.98)
Post-Test (T2)	1319.82 (1432.74)	1297.76 (1482.27)	1560.46 (1523.97)	1136.62 (1282.31)	1296.61 (1438.49)
HF-AR					
Baseline (T0)	589.46 (988.82)	507.13 (552.61)	808.20 (1578.00)	446.67 (613.37)	617.54 (918.30)
Pre-Test (T1; n = 221)	1117.74 (1902.21)	1288.67 (2917.49)	1354.27 (1790.48)	962.70 (1070.35)	824.65 (923.01)
Post-Test (T2)	1795.36 (6144.48)	2779.58 (11,396.71)	1594.13 (1639.60)	1162.06 (1197.97)	1519.71 (1920.73)
LF/HF-FFT					
Baseline (T0)	2.90 (2.72)	2.32 (1.70)	2.78 (2.27)	3.41 (3.39)	3.14 (3.19)
Pre-Test (T1; n = 221)	2.76 (4.18)	2.61 (4.62)	2.01 (1.89)	3.79 (5.63)	2.59 (3.25)
Post-Test (T2)	2.15 (3.10)	2.00 (3.82)	1.84 (1.87)	2.31 (2.59)	2.46 (3.69)
LF/HF-AR					
Baseline (T0)	2.71 (2.26)	2.23 (1.64)	2.67 (2.12)	3.15 (2.72)	2.83 (2.43)
Pre-Test (T1; n = 221)	3.13 (8.12)	4.07 (14.31)	2.04 (1.78)	3.35 (4.09)	2.91 (4.57)
Post-Test (T2)	2.03 (2.55)	1.74 (2.91)	1.78 (1.64)	2.42 (2.56)	2.20 (2.84)

Pain Tolerance (Seconds)

None of the interaction effects for pain tolerance were significant (see Table 3), so only the main effects were examined. The main effect of time was significant, Wilks' $\lambda = 0.93$, $F(1, 216) = 15.93$, $p < 0.001$, $\eta_p^2 = 0.07$ (medium effect), such that participants demonstrated higher pain tolerance during the post-intervention CPAW (T2; $M = 239.09$, $SD = 108.96$) than during the pre-intervention CPAW (T1; $M = 212.6$, $SD = 123.4$), $M_{diff} = 26.48$ [13.40, 39.56], $p < 0.001$, Cohen's $d = 0.32$ [0.19, 0.45] (small effect). The main effect of gender was also significant, $F(1, 216) = 11.92$, $p < 0.001$, $\eta_p^2 = 0.05$ (small effect), such that male participants ($M = 250.14$, $SD = 96.29$) demonstrated significantly higher pain tolerance than female participants ($M = 201.57$, $SD = 96.62$), $M_{diff} = 48.57$ [20.84, 76.29], $p < 0.001$, Cohen's $d = 0.48$ [0.19, 0.77] (small effect). The main effect of group was not significant (Tables 3 and 4).

Table 3 Primary Outcomes Mixed-Design ANOVA Results (N = 224)

	Wilks' λ	*F*	$df_{between}$	df_{within}	*p*	η_p^2
Dependent variable: Pain intensity						
Repeated-Measures Tests						
Time × Group × Gender	0.992	0.550	3	216	0.649	0.008
Time × Group	0.975	1.810	3	216	0.146	0.025
Time × Gender	0.995	1.058	1	216	0.305	0.005
Time	0.934	15.200	1	216	< 0.001	0.066
Between-Subjects Tests						
Group X Gender		0.304	3	216	0.822	0.004
Group		0.589	3	216	0.623	0.008
Gender		17.982	1	216	< 0.001	0.077
Dependent variable: Pain tolerance						
Repeated-Measures Tests						
Time × Group × Gender	0.995	0.327	3	216	0.806	0.005
Time × Group	0.971	2.136	3	216	0.097	0.029
Time × Gender	0.996	0.880	1	216	0.349	0.004
Time	0.931	15.925	1	216	< 0.001	0.069
Between-Subjects Tests						
Group ×Gender		0.583	3	216	0.627	0.008
Group		1.570	3	216	0.198	0.021
Gender		11.921	1	216	< 0.001	0.052

Table 4 Pairwise Comparisons of the Significant Main Effects on Primary Outcomes (N = 224)

	M_{diff} [95% CI]	$S.E._{diff}$	*p*	Cohen's *d* [95% CI]
Pain intensity				
T2 - T1	−0.694 [−1.045, −0.343]	0.178	< 0.001	−0.256 [−0.389, −0.123]
Male - female	−1.201 [−1.759, −0.643]	0.283	< 0.001	−0.622 [−0.913, −0.329]
Pain tolerance				
T2 - T1	26.482 [13.402, 39.562]	6.636	< 0.001	0.320 [0.185, 0.454]
Male - female	48.566 [20.841, 76.290]	14.066	< 0.001	0.483 [0.193, 0.772]

Note: Pairwise comparisons used estimated marginal means.

As with the other co-primary outcome of pain intensity, effect sizes (Cohen's *d*'s) of pairwise differences representing simple effects of the Time × Group interaction were examined as an exploratory analysis. These exploratory analyses are summarized in Table S2. Individuals in the HYP condition demonstrated higher pain tolerance than participants in the other three study conditions (small differences from CP [$d = 0.36$] and MM [$d = 0.27$]; medium difference from CN [$d = 0.66$]). Individuals in the CN condition demonstrated lower pain tolerance than the other three groups (small differences from CP [$d = -0.28$] and MM [$d = -0.37$]). All other between-group simple effects were very small at post-test (*d*'s <0.20; Table S2). Individuals in the MM condition demonstrated a small increase ($d = 0.34$) and those in the HYP condition demonstrated a medium increase ($d = 0.60$) in pain tolerance from pre- to post-test. Individuals in both MM and CP conditions reported very small increases in pain tolerance (Table S2).

Secondary Outcome (Stress Level as Measured by Heart-Rate Variability)

Table 2 summarizes the mean scores for the seven HRV measures (RMSSD, SDNN, pNN50, HF-FFT, LF/HF-FFT, HF-AR, LF/HF-AR) for the total sample and by study group.

The multivariate three-way interaction between time, gender, and group was not significant for HRV (see Table 5). The multivariate Time × Group and Group × Gender interactions were also not significant. The multivariate main effect of group was not significant (Table 5).

The two-way multivariate interaction between time and gender was significant, Wilks' λ = 0.87, $F(14, 200) = 2.11$, $p = 0.013$, $\eta_p^2 = 0.13$ (medium effect); however, when the component univariate interactions were probed, none of them were significant (see Table 6). Due to the lack of significant univariate interactions for any of the HRV variables, the main effects of time and gender were examined instead.

Main Effect of Time

The multivariate main effect of time was significant, Wilks' λ = 0.50, $F(14, 200) = 14.47$, $p < 0.001$, $\eta_p^2 = 0.50$ (large effect). Except for LF/HF-AR, all of the univariate main effects of time were significant (see Table 6): RMSSD, $F(1.97, 420.26) = 32.34$, $p < 0.001$, $\eta_p^2 = 0.13$ (medium effect); SDNN, $F(1.97, 419.90) = 46.50$, $p < 0.001$, $\eta_p^2 = 0.18$ (large effect); pNN50, $F(1.78, 379.90) = 101.77$, $p < 0.001$, $\eta_p^2 = 0.32$ (large effect); HF-FFT, $F(1.59, 338.23) = 10.31$, $p < 0.001$, $\eta_p^2 = 0.05$ (small effect); HF-AR, $F(1.13, 239.59) = 6.53$, $p = 0.009$, $\eta_p^2 = 0.03$ (small effect); LF/HF- FFT, $F(1.80, 382.81) = 3.62$, $p = 0.032$, $\eta_p^2 = 0.02$ (small effect).

The polynomial contrasts indicated significant quadratic effects for RMSSD, SDNN, and pNN50 (see Table 7). All of the HRV measures demonstrated significant linear effects (Table 7). Table 8 summarizes the pairwise comparisons of the estimated marginal means for the main effect of time on each HRV measure.

RMSSD

RMSSD significantly increased from baseline (T0; $M = 33.72$, $SD = 30.54$) to pre-test (T1; $M = 46.44$, $SD = 38.73$), $M_{diff} = 12.72$ [7.74, 17.70], $p < 0.001$, Cohen's $d = 0.52$ [0.38, 0.66] (medium effect), and to post-test (T2; $M = 50.65$, $SD = 28.77$), $M_{diff} = 16.93$ [11.57, 22.30], $p < 0.001$, Cohen's $d = 0.60$ [0.46, 0.74] (medium effect). The change from T1 to T2, however, was not significant (see Table 8).

SDNN

SDNN significantly increased from T0 ($M = 39.47$, $SD = 22.54$) to T1 ($M = 50.81$, $SD = 27.93$), $M_{diff} = 11.35$ [7.41, 15.28], $p < 0.001$, Cohen's $d = 0.54$ [0.40, 0.68] (medium effect), and from T1 to T2 ($M = 54.84$, $SD = 25.05$), $M_{diff} = 4.03$ [0.22, 7.84], $p = 0.034$, Cohen's $d = 0.17$ [0.04, 0.31] (very small effect). The overall change from T0 to T2 was also significant, $M_{diff} = 15.37$ [11.16, 19.59], $p < 0.001$, Cohen's $d = 0.66$ [0.52, 0.80] (medium effect).

pNN50

The increase in pNN50 from T0 ($M = 10.14$, $SD = 13.86$) to T1 ($M = 18.75$, $SD = 17.45$) was significant, $M_{diff} = 8.61$ [6.46, 10.76], $p < 0.001$, Cohen's $d = 0.77$ [0.61, 0.92] (medium effect), as was the increase from T1 to T2 ($M = 23.60$,

Table 5 Secondary Outcomes Doubly Multivariate Mixed-Design ANOVA Results (N = 221)

	Wilks' λ	F	$df_{between}$	df_{within}	p	η_p^2
Repeated-Measures Tests						
Time × Group × Gender	0.834	0.891	42	594.061	0.669	0.059
Time × Group	0.786	1.194	42	594.061	0.192	0.077
Time × Gender	0.872	2.106	14	200	0.013	0.128
Time	0.497	14.467	14	200	< 0.001	0.503
Between-Subjects Tests						
Group × Gender	0.895	1.118	21	594.942	0.324	0.036
Group	0.911	0.937	21	594.942	0.542	0.031
Gender	0.806	7.124	7	207	< 0.001	0.194

Note: The dependent variable is the multivariate combination of RMSSD, SDNN, pNN50, HF-FFT, HF-AR, LF/HF-FFT, and LF/HF-AR.

Table 6 Univariate Follow-Up Tests for Significant Results of Multivariate Tests of Secondary Outcomes (N = 221)

Dependent Variable	F	$df_{between}$	df_{within}	p	η_p^2
Predictor variable: Time × gender[a]					
RMSSD	2.022	1.973	420.262	0.134	0.009
SDNN	0.188	1.971	419.894	0.826	0.001
pNN50	2.996	1.784	379.893	0.057	0.014
HF-FFT	1.055	1.588	338.225	0.336	0.005
HF-AR	1.053	1.125	239.589	0.314	0.005
LF/HF-FFT	0.824	1.797	382.811	0.428	0.004
LF/HF-AR	0.355	1.109	236.251	0.574	0.002
Predictor variable: Time[a]					
RMSSD	32.344	1.973	420.262	< 0.001	0.132
SDNN	46.502	1.971	419.894	< 0.001	0.179
pNN50	101.767	1.784	379.893	< 0.001	0.323
HF-FFT	10.306	1.588	338.225	< 0.001	0.046
HF-AR	6.526	1.125	239.589	0.009	0.030
LF/HF-FFT	3.617	1.797	382.811	0.032	0.017
LF/HF-AR	1.685	1.109	236.251	0.196	0.008
Predictor variable: Gender					
RMSSD	0.075	1	213	0.784	0.000
SDNN	4.379	1	213	0.038	0.020
pNN50	0.531	1	213	0.467	0.002
HF-FFT	0.001	1	213	0.973	0.000
HF-AR	0.626	1	213	0.430	0.003
LF/HF-FFT	29.505	1	213	< 0.001	0.122
LF/HF-AR	10.554	1	213	0.001	0.047

Note: [a]Repeated-measures tests used Greenhouse-Geisser adjustment for degrees of freedom.

Table 7 Tests of Polynomial Contrasts of the Effect of Time on Secondary Outcomes (N = 221)

Dependent Variable	Type of Effect	$F(1, 213)$	p	η_p^2
RMSSD	Linear	57.955	< 0.001	0.214
	Quadratic	5.173	0.024	0.024
SDNN	Linear	77.570	< 0.001	0.267
	Quadratic	7.377	0.007	0.033
pNN50	Linear	147.454	< 0.001	0.409
	Quadratic	7.884	0.005	0.036
HF-FFT	Linear	39.675	< 0.001	0.157
	Quadratic	0.633	0.427	0.003
HF-AR	Linear	8.898	0.003	0.040
	Quadratic	0.825	0.365	0.004
LF/HF-FFT	Linear	8.655	0.004	0.039
	Quadratic	0.940	0.333	0.004
LF/HF-AR	Linear	13.579	< 0.001	0.060
	Quadratic	1.030	0.311	0.005

Table 8 Pairwise Comparisons of the Effect of Time on Secondary Outcomes (N = 221)

	M_{diff} [95% CI]	$S.E._{diff}$	p^a	Cohen's d [95% CI]
RMSSD				
T1 - T0	12.719 [7.737, 17.701]	2.065	< 0.001	0.521 [0.380, 0.661]
T2 - T0	16.932 [11.565, 22.298]	2.224	< 0.001	0.600 [0.457, 0.742]
T2 - T1	4.213 [−1.292, 9.717]	2.281	0.199	0.115 [−0.018, 0.247]
SDNN				
T1 - T0	11.346 [7.407, 15.284]	1.632	<0.001	0.542 [0.400, 0.683]
T2 - T0	15.374 [11.162, 19.586]	1.746	<0.001	0.660 [0.515, 0.804]
T2 - T1	4.028 [0.221, 7.835]	1.578	0.034	0.173 [0.040, 0.306]
pNN50				
T1 - T0	8.612 [6.464, 10.759]	0.89	< 0.001	0.766 [0.614, 0.915]
T2 - T0	13.462 [10.787, 16.137]	1.109	< 0.001	0.947 [0.788, 1.104]
T2 - T1	4.850 [2.804, 6.897]	0.848	< 0.001	0.437 [0.299, 0.575]
HF-FFT				
T1 - T0	477.190 [66.814, 887.566]	170.066	0.016	0.241 [0.107, 0.374]
T2 - T0	690.949 [426.250, 955.648]	109.695	< 0.001	0.519 [0.379, 0.658]
T2 - T1	213.759 [−217.208, 644.726]	178.6	0.698	0.092 [−0.041, 0.224]
HF-AR				
T1 - T0	436.550 [126.465, 746.636]	128.504	0.002	0.302 [0.167, 0.437]
T2 - T0	1323.195 [252.835, 2393.555]	443.574	0.010	0.198 [0.066, 0.330]
T2 - T1	886.645 [−204.981, 1978.27]	452.387	0.154	0.108 [−0.024, 0.241]
LF/HF-FFT				
T1 - T0	−0.069 [−0.779, 0.640]	0.294	1.000	−0.036 [−0.168, 0.096]
T2 - T0	−0.639 [−1.163, −0.115]	0.217	0.011	−0.255 [−0.388, −0.122]
T2 - T1	−0.570 [−1.209, 0.07]	0.265	0.098	−0.165 [−0.298, −0.032]
LF/HF-AR				
T1 - T0	0.307 [−1.157, 1.772]	0.607	1.000	0.051 [−0.081, 0.183]
T2 - T0	−0.595 [−0.984, −0.205]	0.161	< 0.001	−0.310 [−0.443, −0.175]
T2 - T1	−0.902 [−2.339, 0.535]	0.596	0.394	−0.136 [−0.269, −0.004]

Notes: Pairwise comparisons used estimated marginal means. [a]Bonferroni-adjusted for multiple comparisons.

SD = 19.73), M_{diff} = 4.85 [2.80, 6.90], p < 0.001, Cohen's d = 0.44 [0.30, 0.58] (small effect). The overall increase from T0 to T2 was also significant, M_{diff} = 13.46 [10.79, 16.14], p < 0.001, Cohen's d = 0.95 [0.79, 1.10] (large effect).

HF-FFT

HF-FFT increased significantly from T0 (M = 601.69, SD = 1028.33) to T1 (M = 1078.88, SD = 2641.18), M_{diff} = 477.19 [66.81, 887.57], p = 0.016, Cohen's d = 0.24 [0.11, 0.37] (small effect), and to T2 (M = 1292.64, SD = 1576.61), M_{diff} = 690.95 [426.25, 955.65], p < 0.001, Cohen's d = 0.52 [0.38, 0.66] (medium effect). However, there was not a significant change from T1 to T2 (Table 8).

HF-AR

From T0 (M = 629.49, SD = 1074.34) to T1 (M = 1066.04, SD = 2074.53), HF-AR increased significantly, M_{diff} = 436.55 [126.47, 746.64], p = 0.002, Cohen's d = 0.30 [0.17, 0.44] (small effect). The overall change from T0 to T2 (M = 1952.69, SD = 6670.81) was also significant, M_{diff} = 1323.20 [252.84, 2393.56], p = 0.010, Cohen's d = 0.20 [0.07, 0.33] (very small effect). The increase from T1 to T2, however, was not significant (Table 8).

LF/HF-FFT

For LF/HF-FFT, only the overall change from T0 (M = 3.24, SD = 2.85) to T2 (M = 2.60, SD = 3.21) was significant, M_{diff} = −0.64 [−1.16, −0.12], p = 0.011, Cohen's d = −0.17 [−0.30, −0.030] (very small effect). At T1 (M = 3.17, SD = 4.42), LF/HF FFT was not significantly different from either T0 or T2 (Table 8).

LF/HF-AR

The overall change from T0 (M = 3.01, SD = 2.36) to T2 (M = 2.42, SD = 2.62) was significant for LF/HF-AR, M_{diff} = −0.60 [−0.98, −0.21], $p < 0.001$, Cohen's d = −0.31 [−0.44, −0.18] (small effect), but the changes from T0 to T1 (M = 3.32, SD = 8.94) and from T1 to T2 were not significant (Table 8).

Main Effect of Gender

The multivariate main effect of gender was significant, Wilks' λ = 0.81, $F(7, 207) = 7.12$, $p < 0.001$, $\eta_p^2 = 0.19$ (large effect). Table 9 summarizes the pairwise comparisons of the estimated marginal means for the main effect of gender on each HRV measure. On average, male participants had significantly higher scores on SDNN (M_{male} = 51.32, SD_{male} = 19.19 vs M_{female} = 45.43, SD_{female} = 19.29), M_{diff} = 5.89 [0.34, 11.43], p = 0.038, Cohen's d = 0.31 [0.03, 0.60] (small effect); LF/HF-FFT (M_{male} = 4.01, SD_{male} = 2.54 vs M_{female} = 1.99, SD_{female} = 2.54), M_{diff} = 2.02 [1.29, 2.75], $p < 0.001$, Cohen's d = 0.80 [0.50, 1.10] (large effect); and LF/HF-AR (M_{male} = 3.68, SD_{male} = 3.23 vs M_{female} = 2.15, SD_{female} = 3.24), M_{diff} = 1.54 [0.60, 2.47], p = 0.001, Cohen's d = 0.48 [0.19, 0.77] (small effect). Male and female participants' scores on RMSSD, pNN50, HF-FFT, and HF-AR were not significantly different (see Table 9).

Sensitivity Analyses

Multicollinearity

To address the effect of potentially problematic multicollinearity among the HRV variables on the results of the doubly multivariate mixed-design ANOVA, a sensitivity analyses was conducted by replicating the ANOVA with the problematic variables (ie, those with r's >0.90: HF-FFT, HF, AR, and LF/HF-AR) removed.

The overall results of this sensitivity analysis are summarized in Table S3. For the most part, the sensitivity analysis replicated the findings of the original analysis with one exception: there was a significant multivariate Time × Group interaction in the sensitivity analysis that was not found in the original analysis, Wilks' λ = 0.83, $F(24, 598.06) = 1.65$, p = 0.028, $\eta_p^2 = 0.06$ (medium effect). When the univariate Time × Group interactions were examined, only LF/HF-FFT was significant, $F(5.39, 382.81) = 2.24$, p = 0.046, $\eta_p^2 = 0.03$ (small effect; see Table S4). The polynomial contrasts did not reveal any significant linear or quadratic trends for the HRV variables across time (see Table S5).

The post-hoc pairwise comparisons of estimated marginal means found that the only between-groups difference was between individuals in the HYP condition (M = 4.52, SD = 4.50) and MM (M = 2.11, SD = 4.43) at T1, M_{diff} = 2.41 [0.15, 4.67], p = 0.030, Cohen's d = 0.42 [0.04, 0.79] (small effect; see Table S6). Only HYP group demonstrated significant changes across time on LF/HF-FFT (Table S6). In particular, participants in the HYP condition had lower LF/HF-FFT at T2 (M = 2.61, SD = 3.28) than at T0 (M = 3.90, SD = 2.91), M_{diff} = −1.29 [−2.34, −0.24], p = 0.010, Cohen's d = −0.44 [−0.71, −0.16] (small effect), or T1, M_{diff} = −1.91 [−3.19, −0.63], p = 0.001, Cohen's d = −0.28, [−0.54, −0.01] (small effect).

Outliers

To address the impact of the presence of outliers in the HRV variables, a second sensitivity analysis was conducted. For

Table 9 Pairwise Comparisons of the Effect of Gender on Secondary Outcomes (N = 221)

	$M_{diff,\ male\ -\ female}$ [95% CI]	$S.E._{diff}$	p[a]	Cohen's d [95% CI]
RMSSD	1.000 [−6.179, 8.178]	3.642	0.784	0.037 [−0.249, 0.323]
SDNN	5.886 [0.342, 11.431]	2.813	0.038	0.313 [0.025, 0.600]
pNN50	−1.479 [−5.482, 2.523]	2.031	0.467	−0.100 [−0.386, 0.187]
HF-FFT	−6.044 [−353.572, 341.484]	176.306	0.973	−0.002 [−0.288, 0.284]
HF-AR	269.151 [−401.217, 939.518]	340.087	0.430	0.131 [−0.156, 0.417]
LF/HF-FFT	2.020 [1.287, 2.753]	0.372	< 0.001	0.800 [0.504, 1.095]
LF/HF-AR	1.537 [0.604, 2.469]	0.473	0.001	0.478 [0.188, 0.767]

Notes: Pairwise comparisons used estimated marginal means. [a]Bonferroni-adjusted for multiple comparisons.

this second sensitivity analysis, each HRV variable was Winsorized by replacing any values corresponding to $z \geq 3.00$ with the next most extreme value whose z-score was <3 (there were no values with z-scores ≤ -3.00). Table S7 summarizes the resulting means and standard deviations of the Winsorized scores as well as the number of cases Winsorized on each variable. Then, the doubly multivariate mixed-design ANOVA was replicated using the newly Winsorized scores and the results were compared to the results of the original analysis. Table S8 summarizes the results of this sensitivity analysis. The pattern of significant findings and effect sizes in the sensitivity analysis were unchanged from the original analysis.

Non-Normality

The three variables removed from the sensitivity analysis addressing multicollinearity also represented the most severe violators of the assumptions of normality among the HRV variables with skewness values ranging from 2.01 to 13.64 and kurtosis ranging from 3.95 to 197.14. Therefore, by removing these variables from the first sensitivity analysis, this analysis also partly addressed the impact of violations of the assumption of normality.

The Winsorized variables used in the second sensitivity analysis addressing outliers resulted in substantial decreases to the skew and kurtosis of all the variables. The largest skew decreased from 13.64 to 3.40 and the largest kurtosis decreased from 197.14 to 13.19. Thus, the second sensitivity analysis using the Winsorized scores also partly addressed the impact of non-normality on the original analyses.

Due to the lack of an appropriate non-parametric analog to the doubly multivariate mixed-design ANOVA, we considered the consistent pattern of findings across the two sensitivity analyses (which each provided different insights into the potential impact of non-normality) to sufficiently address the violations of the assumption of normality on the original HRV analysis. Taken together, the results of both sensitivity analyses suggest that the non-normality of some of the HRV variables had little impact on the overall pattern of results of the doubly multivariate mixed-design analysis.

Discussion

This is the first head-to-head randomized controlled experimental study comparing the immediate effects of a 20-min single-session training in the use of hypnosis, mindfulness meditation, and Christian prayer relative to an attention control condition on pain tolerance, pain intensity, and stress level as assessed by HRV metrics in healthy volunteers in response to noxious stimulation. It is also one of the few head-to-head studies comparing the latter two acute pain self-management approaches, and one of the few randomized controlled experimental studies focusing the effects of prayer on pain-related outcomes in Christian individuals both born and living outside Iran.

We anticipated that participants in the active conditions would report (1) a within-group decrease in pain intensity, increase in pain tolerance, and increase in parasympathetically mediated HRV (as a measure of autonomic nervous system activity) at post-intervention relative to pre-intervention and (2) larger decreases in pain intensity, increases in pain tolerance, and increases in parasympathetically mediated HRV in the three active treatment conditions than in the control condition. Our results provided only partial support for the study hypotheses. In general, the study findings provide evidence for an overall pattern of modest beneficial effects across all four study conditions in improving cold pressor outcomes in the post-intervention assessment relative to the pre-intervention assessment. This is especially true for hypnosis and mindfulness meditation, for which the exploratory pairwise comparison analyses revealed small-to-medium effect size improvements from pre- to post-intervention in pain intensity and pain tolerance, and additionally in hypnosis only, for one of the HRV indexes (LH/HF ratio). The exploratory between-group pairwise effect sizes also showed that hypnosis seemed to have better (and medium effect size) effects on pain tolerance as compared to the control condition. However, it is important to note that these within- and between-group pairwise comparison analyses were exploratory, given the absence of a statistically significant Group × Time interaction effect and of a between-groups main effect.

The beneficial effects of a single brief hypnosis and mindfulness meditation training found in this research are consistent with previous findings.[23,24,26–28] That is, the effect sizes found here are in the range found in a previous head-to-head randomized controlled experimental study testing the effects of one session of hypnosis and a breath and body focused mindfulness practice on cold pressor outcomes as compared to the same control condition as used in the current

study.[28] Also, consistent with these previous findings, a single short-term training of hypnosis may be somewhat superior to a similar dose of mindfulness meditation training.[28] This appears to be the case across both the body scan practice as used in this research, as well as the breath and body focused meditation used by Grover et al.[28] These findings suggest that even a brief, single-session hypnosis training may be the most useful intervention, among the different approaches tested in this study, for adult individuals – even for those without previous experience, training and practice of hypnosis – as an acute pain self-management strategy to increase pain tolerance, decrease pain intensity, and decrease HRV-assessed stress. As suggested by Grover et al, hypnosis may be more quickly learned and employed than mindfulness meditation within the context of brief learning/training protocols.[28] Mindfulness meditation, on the other hand, may result in similar or even larger beneficial effects over the long term, but may also require more practice to use effectively. Consistent with this idea, a recent systematic review focusing the effects of mindfulness meditation concludes that mindfulness might be more effective in improving pain-related outcomes when training ensures a sufficiently long practice time, is associated with the participant's personal daily practice, and is led, in-person, by a facilitator who is an experienced clinician or provider engaging in frequent mindfulness meditation personal practice.[23]

The effects of the Christian prayer condition on all outcomes were positive. However, the effects sizes were small and not statistically significant. They were also very similar to the effects observed for the control condition. These results were not anticipated given previous results found for Muslim[45–49] and Christian prayer[50] on pain intensity and/or pain tolerance in randomized controlled experimental studies. This finding might be associated with the specific content of the prayer used in this study; that is, it was a Christian biblical-based meditation focusing on the trust in God's protection and assistance in times of need and suffering. In previous randomized controlled experimental studies focusing the effects of prayer, individuals in the prayer conditions were instructed to either repeat a short adoration expression, formula, or antiphon-based prayer or use a pain-specific petition prayer directly asking the deity to help individuals endure the pain.[45,47,48,53,67] Most of these studies reported beneficial effects of these types of prayer. However, the prayer used in this study was more complex. This type of prayer, either because of the specific content or due to its complexity, may not be as beneficial as other types and simpler forms of prayer.

Another possible reason for the lack of significant effects of prayer on the pain-related outcomes on average in this study may be due to the possible moderating effects of religious affiliation of the study participants. About a third of the study participants (31% in the Christian prayer condition) described themselves as either agnostic or atheist, while only 33% (35% in the CP condition) described themselves as Christian (either Roman Catholic or other Christian religious denomination). It is therefore possible that the prayer used in this study might have had a larger beneficial effect among those describing themselves as Christian than those describing themselves as being in one of the non-Christian groups and have had little (or even opposite) effect on atheists and agnostics. For the latter, prayer might have been bothering or even distressing, leading the individuals to focus more on the pain and on the distress caused by prayer itself, negatively impacting and/or fueling the cold pressor effects. Moreover, the effects of prayer on pain-related outcomes may also be associated with a moderating effect of religiosity. Religiosity is indeed associated with both pain-related outcomes and with how individuals cope with their pain.[32] In addition, there is a considerable interindividual variability in the level of religiosity of individuals of the same religious affiliation.[68] Thus, it may be possible that the prayer used in this study might have had a larger beneficial effect among those Christian participants with greater religiosity engaging in religious practices (eg, prayer) than among those Christian (and non-Christian) with lower levels of religiosity. Secondary analyses are planned that will examine potential moderator effects, including the potential moderating effects of religious denomination and religiosity on outcomes.

Inconsistent with the study hypotheses, we found only small to medium and non-significant Time × Group interaction effects, even though the study had been powered to detect such effects. This null finding may be associated with the larger-than-expected (but still less than small) effects of the control condition and the smaller-than-expected (ranging from less than small to medium) effects of the active conditions in this study. Although the effect sizes of the control condition were in the range of those found by Grover et al,[28] who used the same control condition as the one employed here, the control condition effects were larger than those observed in other studies with more neutral control conditions – eg, repeating to oneself the sentence "The sky is blue", or doing nothing.[67] However, the control condition used in this

study did control for possible effects of listening to an audio with a relaxing voice, thereby affording the capacity to more precisely quantify the specific effects of the active conditions.

Limitations

The current study has several limitations that should be considered when interpreting its results. First, study participants were healthy individuals submitted to cold pressor noxious stimulation who were also told how long to expect the stimulus to last. By informing participants of the upper limit, this may have influenced expectancies; in other studies, participants are told there is an upper limit but not what that limit is. Though the more traditional cold pressor test and its alternative cold pressor arm wrap are thought to mimic acute and chronic pain experience,[69] the generalizability of findings to clinical populations of individuals experiencing (acute or chronic) pain is limited. Further research with clinical samples and in a clinical setting is needed. Second, the study sample is composed, for the most part, of women and young adults. They also differed significantly from the group of eligible individuals who elected not to complete the study procedures in terms of gender and age, further limiting the potential generalizability of findings even among populations of healthy individuals. Third, pain intensity ratings and pain tolerance times are potentially conflated by the experimental design used (ie, greater pain tolerance means experiencing the noxious stimulation longer, which may influence pain intensity experienced during the cold pressor arm wrap). Future researchers should consider assessing pain intensity at specific points during the noxious stimulation (eg, at 60 seconds) for all participants, to disentangle the effects of duration of exposure to the stimulus on pain intensity. Fourth, the study design also does not allow us to parse apart the potential effects of the interventions from the potential effects of repeated exposure to the stimulus, since we did not have an inert control group and we did not find a significant Time × Group interaction. Thus, time main effects may also be partially attributed to practice effects. In other words, time main effects may potentially represent not only the effects of the pain self-management approach employed, but also familiarity with the cold pressor arm wrap task and other time-related changes. Further research with an inert control and a larger sample with a priori hypothesized planned contrasts between the groups is necessary to allow to control for practice effects while also enabling (non-exploratory) pairwise comparison analyses to be interpreted with greater confidence. In addition, as previously mentioned, the dose of practice of the three active pain self-management approaches may not have been adequate to maximize the effects of the active conditions, particularly with regard to mindfulness meditation – and perhaps Christian prayer. Future research to determine the minimum dose of hypnosis, mindfulness meditation, and Christian prayer required to observe the most beneficial effects on pain outcomes is necessary. Finally, although this research study is not a clinical trial per se, but rather a laboratory experimental research study, the use of Intent-To-Treat analysis (ITT) – the most conservative approach to handling missing data – might have been useful to ensure the preservation of the original randomization and avoid potential bias associated with the dropout of randomly assigned individuals who elected not to complete all the study procedures. However, ITT was not initially planned when the study protocol was designed. Future research should plan, a priori, to use ITT and responder analyses as the primary data analyses.

Conclusion

Despite the study's limitations, the findings provide important insights into the effects of a brief single audio-recorded training session of hypnosis, mindfulness meditation, and Christian prayer on experimental pain-related outcomes. The findings suggest that both single short-term hypnosis and mindfulness meditation training, but not biblical-based CP, may be viable options for effective acute pain self-management. The findings also suggest that hypnosis might be slightly more efficacious than mindfulness meditation, and least in the short-term, and perhaps especially among novice individuals with very limited hypnosis or meditation practice/training. Future research is needed to evaluate the efficacy of brief hypnosis and mindfulness meditation training in individuals from clinical populations experiencing acute or chronic pain. Further research examining and comparing the effects of different prayer types and prayer with different contents is also warranted. Finally, future research to better understand the predictors and moderators (eg, baseline characteristics such as hypnotic suggestibility, trait mindfulness, and religiosity) of these pain self-management approaches' effects on pain-related outcomes would help to identify which of these approaches might work best for which individuals. Such analyses are planned using data from the current study and will be presented in a future report.

Abbreviations

0-10 NRS, 11-point Numeric Rating Scale; CN, Attention Control Condition; CP, Christian prayer; CPAW, Cold Pressor Arm Wrap; HF-AR, High Frequency Power obtained by Autoregressive modelling expressed in ms^2; HF-FFT, High Frequency Power obtained by Fast Fourier Transform; HRV, Heart Rate Variability; HYP, Hypnosis; LF/HF-AR, Low-to-High Frequency Ratio obtained with Autoregressive modelling; LF/HF-FFT, Low-to-High Frequency Ratio obtained with Fast Fourier Transform; MM, Mindfulness Meditation; pNN50, Percentage of Adjacent Pairs of Normal-to-normal Intervals differing by more than 50ms; RMSSD, Square Root of the Mean Squared Differences of Successive Interbeat Intervals; SDNN, Standard Deviation of Interbeat Intervals.

Data Sharing Statement

The data presented in this study are available on request from the corresponding author.

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Author Contributions

AFV is the principal investigator, obtained funding, conceived the study idea and, together with MD, MJ, FP, and RC, developed the design of the study. JPR contributed to the review of the study design. CC acquired the data. BVD performed the data analysis and, together with AFV and MJ, contributed to the interpretation of data analysis results. AFV, BVD, and MJ wrote the first draft of the manuscript. CC, MD, JPR, FP, and RC critically revised the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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