Placebo Analgesia Changes on Self-Pain and Empathy for Pain: Influences of Event-Related EEG Oscillations, Heart Rate Variability, and Personality

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Research Article

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Abstract

We induced placebo analgesia (PA), a phenomenon explicitly attenuating the self-pain feeling, to assess whether this resulted in reduced empathy pain when witnessing a confederate undergoing such pain experience. We recorded EEG and electrocardiogram during a painful control and PA treatment in healthy adults who rated their experienced pain and empathy for pain. We derived HRV changes and, using wavelet analysis of non-phase-locked event-related EEG oscillations, EEG spectral power differences for self-pain and other-pain conditions. First-hand PA produced a reduction of self-pain and self-unpleasantness, whereas we observed only a slight decrease of other unpleasantness. We derived linear combinations of HRV and EEG band power changes significantly associated with self-pain and empathy for pain changes using PCAs. We found that relative HR-slowing together with decreased midline $\theta$-band (4-8 Hz) power directly influenced self-pain reduction and, indirectly, through chained mediating effects of the Behavioral Inhibition System and Fight-Flight-Freezing System traits. In the other-pain condition, we detected a direct influence of the midline $\beta_2$-band (22-30 Hz) power reduction on the other-pain decline with a positive mediating role of Total Empathic Ability. These findings suggest that PA modulation of first-hand versus other pain relies on functionally different physiological processes involving different personality traits.

Introduction

Empathy for pain is a complex phenomenon that allows the observer to understand and share other-pain sensory and emotional qualities. Research has shown that the nervous system of people experiencing another person's pain may react as if they felt that pain themselves\textsuperscript{1}. Rizzolatti and Sinigaglia\textsuperscript{2} have suggested that the experience of empathy reproduces another person's mental state in the observer's brain through a resonance system, like that mirror mechanism. Within this framework, several studies have shown that empathic pain shares a neural substrate with first-hand pain in the pain matrix\textsuperscript{3,4}. Among EEG/MEG and transcranial magnetic stimulation (TMS) studies, a frequently confirmed finding is that observing noxious, compared with neutral body events, produces the so-called suppressions of mu (7-12 Hz) and $\beta$ (13-30 Hz) oscillations\textsuperscript{5–8}, known to reflect the sensorimotor activity. Avenanti and colleagues\textsuperscript{9–11}, using TMS, found smaller motor evoked potentials when participants attended video clips displaying needle injections than seeing touch at the exact location, suggesting motor inhibition in the sensorimotor cortex.

In contrast, in a later study, Riečanský and colleagues\textsuperscript{12} found increased motor readiness and activation in the sensorimotor cortex, as expressed by increased central $\beta$ (13-30 Hz) and mu (7-12 Hz) desynchronization when participants saw videos depicting painful needle injections than non-painful control conditions. Indeed, they later observed that the activation of the sensorimotor cortex became more robust with increasing illusory ownership of the observed hand\textsuperscript{13}. More recently, Riečanský et al.\textsuperscript{14} suggested that the facilitation of movement they had observed with needle-in-hand reflects an increased readiness for a defensive motor reaction of active avoidance (fear) or escape behavior.
In sum, research focusing on the effects of empathy on information processing produced heterogeneous results. To demonstrate shared neural functions of first-hand pain and empathy for pain, we should first highlight shared neural activity to self and other-pain modulation induced by a placebo analgesia (PA) treatment. PA is the effect of pain reduction that follows the administration of an inert treatment recommended as a potent pain killer\textsuperscript{15,16}.

Then we should demonstrate that the PA modulation of shared neural activity is causally linked to both self-pain and empathy for pain changes. In addition, the influence of individual pain sensitivity-related traits on self-pain and dispositional empathy traits on other-pain changes should also be evaluated (see\textsuperscript{17} for a detailed commentary).

**Personality dispositional factors**

Research has highlighted that personality traits such as Carver's and White's behavioral activation scale\textsuperscript{18}, optimism\textsuperscript{19}, and reward sensitivity\textsuperscript{20} are positively associated with higher placebo responses. Lyby and colleagues\textsuperscript{21} demonstrated that individuals higher in dispositional pain-related fear had decreased PA responding in the subjective report and event-related potentials. Later these authors showed that informing in advance participants that they would receive electric shocks increased their pain-related fear that reduced the PA effect\textsuperscript{22}. In line with these findings, we have recently observed smaller reductions in pain ratings and smaller decreases in the P2 and P3 amplitudes of the ERP elicited by electric stimuli in higher fear-related trait scorers\textsuperscript{23}.

The individual dispositional effect on PA responding can be studied using the more recent revision of J. A. Gray's original Reinforcement Sensitivity Theory (rRST)\textsuperscript{24-26}. The rRST has postulated three major neurobiological systems controlling approach and avoidance behaviors. The behavioral approach system (BAS), activated by all forms of appetitive stimuli. The behavioral inhibition system (BIS), linked to anxiety and triggered by all forms of goal conflict, whose function is to inhibit ongoing behavior and scan the environment. Research has demonstrated the EEG $\theta$ (4-8 Hz) activity as linked to goal conflict\textsuperscript{27} and BIS\textsuperscript{28}. Finally, the fight-flight-freeze system (FFFS) is the primary system responsible for fear responses. Fear is activated only when the threatening object is sufficiently distant to be avoided (active avoidance or flight). Freezing is triggered to avoid attracting the attention of the predator. If a threat requires an attack, then both BIS and the FFFS are activated for a fight\textsuperscript{24}. Research on fear conditioning in humans has highlighted increased $\gamma$ oscillations at the occipital and prefrontal regions, increased $\delta$ oscillations at the posterior and lateral-frontal areas, and decreased $\alpha$ and $\beta$ oscillations at the parietal and occipital regions, with the presence of such oscillations in the somatosensory cortex and insula\textsuperscript{29}. Still, links between neuroticism-related traits and placebo responses are less consistent\textsuperscript{30,31}. There is still limited experimental evidence of the link between anxiety and fear-related personality traits on PA responding, including its underlying neurophysiological functioning. One of the potential causes of inconsistent findings coming from original studies is that in the Carver and White BIS/BAS scales\textsuperscript{18}, anxiety and fear are conflated with the BIS measure, making it challenging to differentiate BIS from FFFS. As a possible
solution to this problem, Corr and Cooper have proposed the Reinforcement Sensitivity Theory of Personality Questionnaire (RST-PQ)\textsuperscript{32} to measure BAS, BIS, and FFFS. The last two traits are conceptualized as two interacting systems with different functional properties and distinct neuropsychopharmacological bases.

**The present study**

Rutgen and colleagues\textsuperscript{33}, eliciting ERPs to painful electrical stimuli, found that PA reduces measures of self-pain, other-pain, and the P2 amplitude of the ERPs. Their findings demonstrated that the modulation of the first-hand pain in an equivalent mode also modulates empathy for pain. In our recent attempt to replicate and extend Rutgen et al.\textsuperscript{33} findings, we obtained that PA treatment reduced self-pain together with P2 and P3 peak amplitudes but not empathy for pain, indicating that different neural processes govern empathy and direct pain experiences.

In a previous study of our own, we examined the influence of reward sensitivity (RST-PQ), heart rate (HR) dynamics, and EEG-delta activity during tonic pain reduction by a PA treatment\textsuperscript{20}. We found that a linear compound of HR slowing and enhanced EEG delta activity to PA treatment explains a substantial portion of the variance in PA responding. Additionally, we found that the Reward-Interest facet of the BAS and Involuntariness in pain reduction positively mediated this link.

Based on the above-reported observations, the main aim of the present exploratory study was to extend our previous ERP\textsuperscript{23,33}, and HR\textsuperscript{20} placebo findings to event-related EEG oscillation and HR variability (HRV) changes as induced by phasic painful stimulations. We aimed to highlight the mutual influence of HRV indexes and non-phase locked event-related oscillations (1–40 Hz) on self-pain and empathy for pain changes. In line with earlier literature findings\textsuperscript{12–14}, we expected a link between changes in $\beta$ and $\alpha$ activities induced by PA treatment and self-pain changes. We also expected to disclose significant associations of BIS and FFFS motivational personality traits, as measured by the RST-PQ, with self-pain and other-pain changes. Finally, using conditional process analyses, we expected to disclose, among the above-mentioned physiological factors, those that directly influence self and empathy pain changes and the role of FFFS (fear, active avoidance) and BIS (passive avoidance) in this relationship. We predicted that people high in BIS and FFFS scores should display smaller reductions of self-pain and empathy for pain, and vice versa, for lower levels in these traits. Finally, we also included measures of dispositional empathy facets, as obtained by the Empathy Component Questionnaire\textsuperscript{34} (ECQ), hoping these measures may serve as variables influencing the relationship between physiological factors and other-pain changes. We expected that higher levels of empathy traits should be associated with higher empathy pain and unpleasantness reductions induced by the PA treatment.

Finally, we demanded to see if our previous PA findings obtained for tonic pain\textsuperscript{20} are valid for phasic pain. We expected that HR slowing and enhanced slow event-related EEG oscillations would be associated with PA-induced pain reduction.

**Methods**
Participants. Participants were 63 neurotypical right-handed university student volunteers, aged between 18 and 29 years (32 women: M = 21.56, SD = 2.41, men: M = 23.03, SD = 2.63). We excluded one male participant from data analyses because we detected outliers in his data. Thus, only data from 62 participants were analyzed.

The experimental protocol was conducted under the Helsinki Declaration (1964) and approved by the Institutional Review Board (IRB) of the Department of Psychology of Sapienza University of Rome (protocol number 0001291 issued on 07/12/2017). Informed consent was obtained from each participant (see Supplementary Information, section S1, for more details).

Questionnaires. The participants completed the RST-PQ\textsuperscript{32} measuring three major systems: the BAS, BIS, FFFS. The BAS is composed of the following facets: Goal-Drive Persistence (BAS-GDP), Reward Interest (BAS-RI), Reward Reactivity (BAS-RR), and Impulsivity (BAS-I). The total BAS (BAS-TOT) measure is obtained by summing the BAS-GDP, BAS-RI, BAS-RR, and BAS-I scores.

We also administered the ECQ\textsuperscript{34} consisting of five facets. From The ECQ facets, we derived the following principal scores (see\textsuperscript{34}): Cognitive Empathy (CE), Affective Empathy (AE), Empathic Drive (ED), Total Empathic Ability (TEA), and Cumulative Total Empathy (CTE) scores. More details are provided in Supplementary Information, section S1. Participants also completed the state anxiety form of the State-Trait Anxiety Inventory (STAI-Y1)\textsuperscript{35}.

Experimental trials and treatments. To investigate pain-related empathy, we benefit from a known paradigm developed by Singer and colleagues\textsuperscript{36}. Rutgen et al.\textsuperscript{33} and ourselves\textsuperscript{23} employed this paradigm to test empathic experience wherein the object of empathy experience was a real person seated on the left side of the participant chair (see Fig. 1). In the self-pain condition, participants were exposed to individually calibrated, short-lasting painful electric stimuli (duration from 18 to 30 ms) and non-painful electric stimuli delivered to the back of their right hand. In the other-pain condition, participants experienced empathy for the pain of the confederate seated next to which we delivered painful stimuli and non-painful electric stimuli to the back of her right hand. Each of the self-pain and other-pain conditions took about 24 min, where painful stimuli were delivered respectively to the participant and the confederate in random order. We used the e-prime 2.0 system to program the self-pain and empathy for pain trials (the trial structure, stimulation, and timing are provided in Fig. 1; see supplementary materials, section S2 for more details). In the self-pain condition, participants rated, after the presentation of a painful stimulus their experienced pain and unpleasantness on a numerical 7-point Likert scale (from 1 = “not at all” to 6 = “very painful”) to obtain a numerical pain score (NPS) and unpleasantness score. Equivalently, participants used the same 7-point Likert scale to rate the inferred unpleasantness experienced by the confederate. Pain and unpleasantness ratings were presented in a quasi-random order. To evaluate the level of relative pain and unpleasantness reduction induced by placebo treatment, we calculated numerical pain and unpleasantness difference scores (NPDSs and NUDSs) by subtracting NPSs, and NUSs rated during placebo from scores rated during pain. We used these difference scores for statistical analyses.
Procedure. This experiment consisted of two sessions conducted over two days. Participants first signed approved informed consent forms on the first session and then completed the RST-PQ and EPQ. The participant and the confederate were invited for electrophysiological recordings on the second experimental day. The confederate was always a female, as well as the experimenter. Before EEG recordings, each participant underwent a psychophysical pain calibration procedure to determine sensory and pain thresholds making possible a reliable electrical stimulation intensity for painful and no painful stimuli. Details are provided in\textsuperscript{23} and in the Supplementary Information, section S2. After the calibration procedure, participants were exposed to two experimental testings: a control pain condition and a PA treatment. In the control condition, participants experienced pain without any prescription. In the PA condition, each participant had to ingest a placebo pill and then participate in a pain manipulation procedure known to reduce the first-hand experience of pain (Supplementary Information, S2). The PA treatment made it possible to test whether it modulates empathy for pain. Control and PA treatments turned up in a counterbalanced order across participants. The confederate did not receive any medication, and all participants were purposely informed about this. The partner was seated next to the participant's left side with the mandatory request to fix their gaze to the ground to prevent direct observation of the other. In addition, each participant also received a mandatory injunction to maintain a fixed eye on the screen and avoid directing the gaze to the confederate. The testing session in total took about 1.9 hours. At the end of the experiment, we dismissed participants after filling the state anxiety inventory (STAI-Y1).

A power increase relative to baseline level can be observed in response to all stimuli during pain compared to placebo treatments. This increase is much more pronounced in the self-pain between 100 to 250 msec. The maximum relative increases during the pain of TF power were at 7 Hz, 11 Hz, 18 Hz, 31 Hz, and 39 Hz, as shown by the arrows in the upper-right panel. The power increases can be observed at all midline electrodes but are more assertive at central locations.

EEG Recordings and Wavelet Analysis. EEG activity was recorded from 30 scalp sites according to the extended 10-20 system, with the addition of two earlobes electrodes (A1, A2) using 32-tin electrodes stretch Lycra cap with a ground electrode mounted between FPz and Fz (Electro-Caps, Eaton, OH, USA). The NuAmp acquisition system (Neuroscan Acquire 4.3, Compumedics Neuroscan Inc, Charlotte, North Carolina 28269, USA) with an online notch filter at 50 Hz. The reference electrode was at the linked earlobes \([(A1+A2)/2]\). The electrode impedance was kept less than 5 kΩ. The EEG was recorded in DC mode (sampling frequency = 1000 Hz, gain = 200, bandpass = 0.01–100 Hz: Butterworth zero-phase filter with 24 dB/octave roll-off) with an online 50 Hz notch filter. Both vertical and horizontal eye movements and eye blinks were monitored. Trials contaminated by eye blinks, eye movements, or electromyographic (EMG) activity exceeding ±75 µV at any electrode were excluded from the analyses. Then, the EEG signals were downsampled to 250 Hz and transformed to standard average reference to obtain reference-free recordings. We removed horizontal and vertical EOGs and EMG artifacts by extracting 1 to 3 out of 30 independent components (IC; using Infomax algorithm, Brain Products; Vision Analyzer 2.2.2, Gilching, Germany). We reconstructed the EEG trace into discrete, single-trial 1000 ms artifact-free epochs (from
(33 to 36) that were time-locked to the offset of painful electric-train stimulus delivered to the participant and to the onset of red-spark visual cue for the painful stimulus delivered to the confederate (see Fig. 1) with a 500-ms prestimulus baseline. For each treatment, we first calculated ERPs in self-pain and other-pain conditions. We subtracted ERPs in each stimulus condition from the corresponding EEG epoch to remove the phase-locked EEG activity from the EEG data.

A time-frequency (TF) representation based on the continuous Morlet wavelet transform (CMWT) of every single EEG epoch (explored frequencies: 1-40 Hz, 1 Hz step) was used to identify non-phase-locked (stimulus-induced) power modulations of oscillatory activities (for details see Supplementary Information, S3). To enhance EEG changes time-locked (but not phase-locked) to stimulus onset, the CMWT was applied to each trial. The Resulting TF power maps were then averaged across trials for each subject and within each pain condition. These maps express the average oscillation power as a function of time and frequency.

We considered the mean TF real power of the prestimulus period (between -500 and -50 ms) as a baseline level. For each frequency step, these baseline levels were subtracted from the prestimulus and post-stimulus power. Grand averages of induced TF representations of the power values at electrode Cz are displayed in Fig. 2 for the first-hand pain and other conditions. We obtained significant t-values (see right side of Fig. 2) for the following five EEG dominant sub frequencies and time-intervals: $\delta$ (4-8 Hz, 50-250 ms); $\alpha$ (9-13 Hz, 100-200 ms); $\beta_1$ (14-21 Hz, 100-200 ms), $\beta_2$ (22-32 Hz, 100-180 ms), $\gamma$ (33-40 Hz, 120-180 ms). We first obtained the maximum amplitude for each of these frequency bands of interest and the associated frequency (7, 12, 18, 31, and 39 Hz, respectively). We then computed the current source density (CSD, $\mu$V/m²) transforms of extracted wavelet waveforms at each frequency of interest mentioned above (for more details, see Supplementary Informations S3). We used the CSD transform as a spatial filter to identify the topographical source at maximum amplitude for each waveform of interest$^{38}$. These CSD maps indicated that midline frontal (Fz), central (Cz), and parietal (Pz) are sensitive sites to experimental manipulations (Fig. 3).

Color current source density maps ($\mu$V/m²) are reported at the bottom for each frequency of interest (7, 11, 18, 31, and 39 Hz) and the time corresponding to each maxima amplitude for each frequency.

**HR recordings.** We recorded the electrocardiogram (ECG) using two beryllium copper electrodes (1.5 cm in diameter) with a sample rate of 100 Hz. We processed the continuous ECG recording signal with Kubios HRV Analysis 3.0.2 software$^{39}$ to obtain the HRV measures used in the present study. Based on our previous HRV findings$^{20}$, we selected time domain, frequency domain, and sample entropy measures.

**Reduction of physiological variables.** We derived Control minus Placebo difference scores ($\Delta$) in the R-R time interval that we labeled as $\Delta$THR (ms), the standard deviation of normal-to-normal R-R interval ($\Delta$SDNN, ms), Low-Frequency power ($\Delta$LF power, 0.04-0.15 Hz), and High Frequency ($\Delta$HF power, 0.15-0.4 Hz), LF/HF ratio, Sample Entropy ($\Delta$S-Entr). More details on HR recordings and HRV are available in$^{39}$ and Supplementary Information, section S3.
For the EEG oscillation measures, to reduce skew, we derived Control minus Placebo difference scores of natural log transformation of TF mean power calculated for each of the $\delta$, $\alpha$, $\beta_1$, $\beta_2$, and $\gamma$ frequency bands across Fz, Cz, and Pz leads.

We performed five varimax-rotated Principal Components Analyses (PCAs) to reduce data dimensionality, one for each of the five frequencies of interest and separately for self-pain and other-pain conditions, on the HR and EEG frequency indices (see Supplementary Information, section S4). Each of the five PCA involved six HRV difference indices, as reported above, and three EEG Control minus Placebo difference indices as obtained across Fz, Cz, and Pz midline scalp sites of interest. These analyses served to select (i) the EEG indices loading above the threshold of 0.40 in a factor together with HVR indices, (j) to reduce problems of multicollinearity, for each EEG frequency of interest, in the subsequent analyses. Results of these preliminary analyses for self-pain and other-pain for $\delta$, $\alpha$, $\beta_1$, $\beta_2$, and $\gamma$ EEG frequency bands of interest are reported in Table 1.

For the self-pain condition, each of these separated PCAs (varimax rotation) yielded a three orthogonal factors solution (eigenvalues >1) that were exported as standardized factor scores and used for the correlation analyses. In terms of HRV changes, common to all these analyses was the first factor loading on frequency domain HRV difference scores ($\Delta$) that we labeled as “S$_\Delta$fHRV” (S stands for self-pain). Additionally, we obtained a combined factor loading on $\Delta$SDNN and sample entropy changes that we labeled as “S$_\Delta$SDNN & $\Delta$S-Entr.” In terms of EEG band power changes, we obtained two factors, one loading on $\beta_1$ power and the other on $\beta_2$ power, obtained at midline sites (Fz, Cz, and Pz) that we labeled as “S$_\Delta$Midl-$\beta_1$Pow” and “S$_\Delta$Midl-$\beta_2$Pow”. We also obtained the following composite factors including HRV measures and $\delta$, $\alpha$, and $\gamma$ power changes: “S$_\Delta$tHRV & $\Delta$Midl-$\beta$Pow,” “S$_\Delta$SDNN & $\Delta$S-Entr & $\Delta$Cz-$\alpha$Pow,” “S$_\Delta$tHRV & $\Delta$CzPz-$\alpha$Pow,” and “S$_\Delta$tHRV & $\Delta$CzPz-$\gamma$Pow” (see loadings in boldface reported in the upper section of Table 1). Descriptive statistics for these factors are reported on the left side of Table 2.

Similar separate PCAs on physiological difference data performed for the other-pain condition yielded a three orthogonal factors solution. In terms of HRV changes, common to all these analyses was the first factor loading mainly on frequency domain HRV difference scores, and we labeled it as “O$_\Delta$fHRV” (O stands for other-pain). We also obtained a combined factor loading on time HRV and sample entropy changes labeled “S$_\Delta$tHRV & $\Delta$S-Entr.” In terms of EEG band power changes, we obtained four factors loading on $\delta$, $\beta_1$, $\beta_2$, and $\gamma$ powers, across the three midline sites (Fz, Cz, and Pz) and labeled respectively as “O$_\Delta$Midl-$\delta$Pow,” “O$_\Delta$Midl-$\beta_1$Pow,” “O$_\Delta$Midl-$\beta_2$Pow,” and “O$_\Delta$Midl- $\gamma$Pow.” For the $\alpha$ band, we also obtained a factor including the $\alpha$ power differences at Fz and Cz leads that we labeled as “O$_\Delta$FzCz-$\alpha$Pow.” All these factors can be derived from loadings in boldface reported in the lower section of Table 1. Descriptive statistics for these factors are reported on the right side of Table 2.

**Statistical analyses.** We first calculate partial Pearson correlation coefficients separately for the self-pain and other-pain conditions to determine the association of NPDSs, NUDSs, RST-PQ, and ECQ personality traits with difference scores (Pain Control minus PA) on physiological factors. The potential contribution
of gender and state anxiety difference scores (control minus placebo) was partially out from these correlations. We also calculated a partial Pearson correlation matrix (gender scores were partially out) among personality traits of interest and NPDSs and NUDSs. The probability levels were corrected by applying the false discovery rate correction (FDR) method to control false-positive errors. Among physiological factors significantly correlated with a personality trait, we want to select the best predictors of this trait by avoiding collinearity among them. Thus, we first assess collinearity diagnostics using the Proc Reg procedure available in the SAS-9.4 system. We then solved the collinearity problem by implementing the Elastic Nets method provided by the Proc Glmselect procedure available in the same statistical system. This analysis can overcome the limitations on the variable selection, usually presented in other available similar methods. It can select more than one variable and achieve a better model prediction (see, e.g., ). Separately for self-pain and other-pain conditions, we applied the above-described method to select physiological factors as predictors of pain and unpleasantness difference scores (i.e., $S_{NPDSs}$ and $S_{NUDSs}$, $O_{NPDSs}$ and $O_{NUDSs}$). We set a significance level at $p=0.05$ after FDR correction. We tested multiple and simple mediator models evaluating the role of personality traits as mediators for the influence of the selected physiological factor on NPDSs and NUDSs. We tested this effect by using the conditional process analysis. The PROCESS macro (www.afhayes.com) tests model-6 (with two personality mediators) or model-4 (with one personality mediator) in all regression analyses.

Results

Pain and unpleasantness. The repeated measures ANOVA on pain scores of self-pain condition, with Gender as a between subjects factor, yielded a main effect for Gender ($F(1,60) = 4.21, p < 0.05, \eta^2_p = 0.065$) that indicated a higher pain sensation in women compared to men (M = 5.2, SD = 0.95 vs M = 4.7, SD = 1.11). In addition we observed a significant effect for Treatment ($F(1,60) = 19.92, p < 0.0001, \eta^2_p = 0.249$) indicating Placebo treatment was effective in pain reduction (M = 5.2, SD = 1.18 vs M = 4.7, SD = 1.15). The interaction of Gender by Treatment was not significant ($F(1,60) = 1.14, p = 0.290, \eta^2_p = 0.019$). A similar ANOVA on unpleasantness scores provided a significant effect for Treatment ($F(1,60) = 8.94, p < 0.01, \eta^2_p = 0.130$), showing a lower unpleasantness to Palcebo as compared to Control treatment (M = 4.9, SD = 1.30 vs M = 4.4, SD = 1.30).

The ANOVA on pain scores for the other-pain condition did not show any significant effect (all $Fs < 1$). A similar analysis on unpleasantness scores of the other-pain condition disclosed a main effect for Treatment ($F(1,60) = 5.26, p < 0.05, \eta^2_p = 0.081$) which showed a small but significant unpleasantness reduction during Placebo as compared to Control treatment (M = 4.5, SD = 1.28 vs M = 4.9, SD = 1.32, respectively).

Personality scores. In Table 3 are reported descriptive statistics in women and men participants for the RST-PQ, ECQ, STAI-Y1, numerical pain, unpleasantness scores, and their Control minus Placebo changes for self-pain and other-pain treatments. We also calculated t-tests (FDR correction) between women and
men participants for these measures. The FFFS trait was the sole to be significantly higher in women than men. Additionally, self-pain scores were higher in women than men (see Table 3).

**Correlations among personality traits and pain rating measures.** The partial correlation matrix (the effects of gender were partial out) among personality and pain ratings is reported in Table 4. It is important to note that, among personality traits of interest, FFFS was significantly and negatively correlated with S_NPDS in the self-pain condition ($p < 0.05$). A post-hoc within-subject t-test disclosed that there was a significant pain reduction in low FFFS scorers ($M = 5.1$, $SD = 1.2$ vs $M = 4.3$, $SD = 1.2$; $t (30) = 4.39$, $p < 0.001$, respectively for Control vs Placebo), whereas in high FFFS scorers pain reduction did not reach the significance level ($M = 5.4$, $SD = 1.2$ vs $M = 5.1$, $SD = 1.0$; $t (30) = 1.93$, $p = 0.063$, respectively).

Additionally, in the other-pain condition, TEA was positively correlated with relative placebo induced pain changes (i.e., O_NPDS, $p < 0.01$, Table 4). A within-subject t-test on O_NPDSs indicated that during PA treatment there was a significant pain decrease in high TEA scorers ($M = 5.2$, $SD = 1.0$ vs $M = 4.7$, $SD = 1.3$; $t (24) = 2.70$, $p = 0.013$, respectively for Control vs Placebo), whereas in low TEA scorers there was no pain reduction ($M = 4.7$, $SD = 1.1$ vs $M = 4.9$, $SD = 1.2$; $t(36) = -1.41$; $p = 0.166$, respectively).

**Correlations of physiological factors with personality and pain rating measures.**

Partial correlations showed that BIS was the only personality trait significantly and positively associated with physiological difference scores of $S_\Delta tHRV \& \Delta Midl-\vartheta Pow$, $S_\Delta tHRV \& \Delta CzPz-\alpha Pow$, and $S_\Delta tHRV \& \Delta CzPz-\gamma Pow$ factors obtained for the self-pain condition (S). These same physiological factors were significantly and negatively associated with S_NPDSs. In addition, S_NUDSs were significantly and negatively correlated with $S_\Delta tHRV \& \Delta Midl-\vartheta Pow$ and $S_\Delta tHRV \& \Delta CzPz-\gamma Pow$ factors (see the left side of Table 5).

We found the AE trait significantly and negatively correlated with the $O_\Delta tHRV \& \Delta S-\text{Entr}$ factor obtained for the other-pain condition. Additionally, TEA trait was positively correlated with $O_\Delta Midl-\beta_2 Pow$ and $O_\Delta Midl-\gamma Pow$ factors, indicating that higher TEA scores were associated with reduced $\beta_2$ and $\gamma$ power scores during placebo relative to control treatment. Further, O_NPDSs were negatively associated with $O_\Delta fHRV$, $O_\Delta Midl-\vartheta Pow$, and $O_\Delta Midl-\beta_2 Pow$ (right side of Table 5).

**Self-Pain: Physiological factors predictors of BIS, pain, and unpleasantness changes.** To select among the three physiological factors significantly correlated with BIS (i.e., $S_\Delta tHRV \& \Delta Midl-\vartheta Pow$, $S_\Delta tHRV \& \Delta CzPz-\alpha Pow$ and $S_\Delta tHRV \& \Delta CzPz-\gamma Pow$; see the left side of Table 5) those that better predict BIS scores, we first assess collinearity diagnostics using variance inflation factors $vif$, tolerance $tol$, and collinearity $collin$ options of SAS-9.4 regression procedure with the three physiological factors differences as predictors of BIS scores. This analysis suggests we exclude the factor $S_\Delta tHRV \& \Delta CzPz-\gamma Pow$ from further analyses since we found high levels of collinearity of this factor with the other two.

To further combat the multicollinearity, we then tested the multiple regression model using the elastic nets method with Akaike's information selection criterion$^{43,44}$, using as predictors of BIS the two remaining factors. This analysis yielded both factors of $S_\Delta tHRV \& \Delta Midl-\vartheta Pow$ and $S_\Delta tHRV \& \Delta CzPz-\gamma Pow$. 

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αPow as potential predictors of BIS (F(2,59) = 9.01, p < 0.01, $\omega^2_p = 0.190$; R-Square = 0.234; Glmselect procedure, SAS-9.4\textsuperscript{45}).

The three physiological factors mentioned above were significantly correlated with self-pain difference scores (i.e., S_NPDS, see the left side of Table 5). We want to select, among the three physiological measures, those that best predicted S_NPDSs and to avoid multicollinearity among them. We used the same multiple regression procedure reported above, including multiple regression and the Elastic Nets method with Akaike's information selection criterion\textsuperscript{43,44}. This method yielded the $S_{\Delta tHRV} \& \Delta Midl-\deltaPow$ factor as the most reliable predictor of pain reduction (S_NPDS; ($F(1,60) = 23.16, p < 0.001$, $\omega^2_p = 0.278$; R-Square = 0.279). More details are reported in sections S5-1, S5-2, and S5-3 of Supplementary Information for the above analyses.

A similar method used for the selection, among two potential physiological predictors of unpleasantness reduction scores (S_NUDSs; see left side of Table5) yielded again the $S_{\Delta tHRV} \& \Delta Midl-\deltaPow$ as the sole reliable predictor of S_NUDS ($F(1,60) = 8.28, p < 0.01, \omega^2_p = 0.120$; R-Square = 0.121).

**Self-Pain: Physiological influence on placebo pain changes.** Considering that the $S_{\Delta tHRV} \& \Delta Midl-\deltaPow$ factor was significantly correlated with both BIS and S_NPDS (left side of Table 5), BIS was significantly correlated with FFFS and the latter with S_NPDSs (Table 4), we tested a serial multiple mediators model by entering BIS and FFFS as potential mediators of the causal influence of $S_{\Delta tHRV} \& \Delta Midl-\deltaPow$ on the outcome S_NPDS. This analysis allowed us to investigate the direct and indirect effects of “$S_{\Delta tHRV} \& \Delta Midl-\deltaPow$” on S_NPDSs while modeling a process in which this physiological factor causes BIS, which causes FFFS, which in turn causes S_NPDSs as the final consequent (pp. 143–156; model 6)\textsuperscript{42}. The model included the state anxiety changes and gender as covariates (see the upper-half section in Table 6 and Fig. 4). The total effect of “$S_{\Delta tHRV} \& \Delta Midl-\deltaPow$” on S_NPDSs (including the mediating role of BIS and FFFS) was significant (p < 0.001) as well as the direct effect of “$S_{\Delta tHRV} \& \Delta Midl-\deltaPow$” on S_NPDSs (p < 0.001; coefficients in Table 6). In addition, we did not detect significant effects of the covariates on the S_NPDS outcome, although the influence of gender on FFFS was significant and negative (p = 0.002, Table 6), showing higher FFFS scores in women (N =32) than men (N = 30) (M = 28.9, SD = 4.2 vs M = 22.9, SD = 6.4; t(60) = 4.36, p < 0.001). We obtained bias-corrected bootstrap confidence intervals for indirect effects through chained serial multiple mediators. We used 10,000 bootstrap samples for 95% bias-corrected confidence intervals. We obtained two causal chains of indirect effects labeled “Ind-1” and “Ind-2”. The Ind-1 did not reach the significance level, whereas the Ind-2 chain was significant and negative, given that the bootstrap confidence interval was entirely below zero, respectively (ranged from -0.0057 to -0.0003). The Ind-2 effect was the specific indirect effect through the BIS, which, in turn, influenced the FFFS and then NPDSs. This effect was estimated as 0.2035 x 0.1399 x -0.0589 = -0.0017 and was significantly negative since the bootstrap confidence interval was entirely below zero (-0.0057 to -0.0003). We depicted both Ind-1 and Ind-2 effects in Fig. 4.
**Other-Pain: Physiological factors predictors of TEA and placebo pain changes.** We found two physiological factors that were significantly correlated with TEA scores (i.e., $O_{\Delta \text{Midl-}\beta^2\text{Pow}}$ and $O_{\Delta \text{Midl-}\gamma^\text{Pow}}$; see the right half side of Table 5). We used the same multiple regression procedure reported above to select the best TEA predictors and avoid multicollinearity. We also used the Elastic Nets method with Akaike's information selection criterion\(^{43,44}\) to further control multicollinearity. Both analyses selected the $O_{\Delta \text{Midl-}\beta^2\text{Pow}}$ variable as the most reliable predictor of TEA ($F(1,60) = 7.46, p < 0.01, \eta^2_p = 0.120; \text{R-Square} = 0.111$; for more details see Tables S5-4 in Supplementary Information).

We found three physiological factors, namely $O_{\Delta f \text{HRV}}$, $O_{\Delta \text{Midl-}\vartheta^\text{Pow}}$, and $O_{\Delta \text{Midl-}\beta^2\text{Pow}}$, that were significantly correlated with $O_{\text{NPDSs}}$ (right half of Table 5). To select among these three factors those that better predict $O_{\text{NPDSs}}$ scores and to detect collinearity, we used the same collinearity diagnostic method described above. We found that collinearity among these variables was not significant. Additionally, a multiple regression using the Elastic Nets method with Akaike's information selection criterion retained all the three physiological factors as reliable predictors of $O_{\text{NPDSs}}$ ($F(3,58) = 4.80, p < 0.01, \eta^2_p = 0.199; \text{R-Square} = 0.198$; see Tables S5-5 in Supplementary Information).

**Other-Pain: Physiological influence on placebo pain changes.** Considering that the $O_{\Delta \text{Midl-}\beta^2\text{Pow}}$ factor was significantly correlated with $O_{\text{NPDSs}}$ and TEA (see right half of Table 5), TEA facet was significantly associated with $O_{\text{NPDSs}}$, and this physiological factor was one of the predictors of both $O_{\text{NPDSs}}$ and TEA, we test the causal effect of this $\beta^2$ power factor on $O_{\text{NPDSs}}$. We used a simple mediation model entering the $O_{\Delta \text{Midl-}\beta^2\text{Pow}}$ as a potential causal factor that directly influences $O_{\text{NPDSs}}$, and, indirectly, through its influence on TEA trait as a potential mediator, causing $O_{\text{NPDSs}}$ as the final consequent\(^{42}\) (pp. 85–122; model 4). We included in the model state anxiety changes and gender as covariates. This mediation analysis disclosed that direct and indirect effects were significant (see the lower-half section of Table 6 and Fig. 5). The total effect of $O_{\Delta \text{Midl-}\beta^2\text{Pow}}$ on $O_{\text{NPDSs}}$ was significant ($p < 0.01$, Fig. 5), as well as the direct effect of $O_{\Delta \text{Midl-}\beta^2\text{Pow}}$ on $O_{\text{NPDSs}}$ ($p < 0.05$; bottom of Table 6) and its indirect effect (Fig. 5). This model indicated that relative reductions on midline $\beta^2$ power (i.e., higher positive values in the $O_{\Delta \text{Midl-}\beta^2\text{Pow}}$ factor) directly produced relatively higher positive $O_{\text{NPDSs}}$, i.e., relatively smaller pain sensations during Placebo treatment. The indirect positive effect of the TEA trait mediates this influence (Fig. 5). In addition, we did not detect significant effects for the covariates on the $O_{\text{NPDSs}}$ outcome, except for the influence of Gender on TEA trait that was significant and negative ($p = 0.042$, bottom-left of Table 6), indicating a slight tendency for higher TEA scores in women than men (Women, $N = 32$, $M = 37.5$, $SD = 5.3$; Men, $N = 30$, $M = 35.8$, $SD = 3.6$).

**Discussion**

One of the main aims of the present study was to manipulate the first-hand experience of pain, devoted to enhancing expectation for pain reduction, and test whether this experience also affects empathy for pain. Current results disclosed that PA treatment (i.e., a compound of manipulation of pain sensation and verbal suggestion inducing PA) effectively reduced both first-hand pain and unpleasantness sensations,
with women experiencing slightly higher pain levels than men. However, the phenomenon of empathic analgesia was not found significant for the other-pain scores, although we saw it as effective, albeit weakly, in reducing other unpleasantness. Additionally, after controlling for gender, we did find a significant negative association between FFFS trait (but not BIS) and self-pain reduction during PA. This effect indicated that Placebo treatment in low FFFS participants effectively reduced pain sensation, whereas pain reduction did not reach the significance level in high FFFS participants. The fact that we failed to find a significant correlation of self-pain reduction with BIS, while, on the other hand, this relation was substantial for FFFS, is not surprising. Indeed, observations in earlier studies showed that subjects higher in dispositional pain-related fear had reduced PA responding\textsuperscript{21,46−49}. Mostly, there is experimental evidence in these participants that the anticipation of a painful shock increases subjective fear\textsuperscript{50}. This finding demonstrates a substantial impairment of mechanisms underlying PA in high FFFS individuals who are highly disposed to fear, mainly when an anticipatory cue, indicating that they would receive a painful electric shock, induces a potential fear.

Further, we found a significant positive link between TEA trait and other-pain rating changes (Table 4), demonstrating a considerable pain decrease after PA treatment in high TEA but not in low TEA scorers. Unpleasantness did not show substantial differences in high TEA scorers. Interestingly, these findings align with Singer and Lamm's suggestions\textsuperscript{51} that empathy is a highly flexible phenomenon influenced by several factors as stable empathy traits of the empathizer and its interpersonal relationship with the other. Our observations indicate that individual differences in empathic ability traits can account for empathy for pain.

In sum, the present self-pain findings parallel those previously observed by Rutgen et al.\textsuperscript{33}, whereas our other-pain rating finding aligns with Rutgen et al.’s one only in higher TEA trait individuals. We did not detect any significant effect of situational empathy for the emotional component of other pain, i.e. when participants evaluate the unpleasantness of the other. Research using ERP and startle data has shown that the induction of fear completely abolished the effect of the placebo intervention\textsuperscript{21,22,49}. Thus, we think that fear of pain may have reduced the placebo effect, especially for empathic pain and unpleasantness.

The self-pain reduction correlated negatively with changes on three physiological factors. Each of these associations indicated that higher self-pain reduction was associated with (1) longer R-R time intervals (time-HRV) and (2) reduced midline $\delta$-band activity, (3) enhanced centroparietal $\alpha$ activity, (4) reduced centroparietal $\gamma$ activity (left side of Table 5). These observations corroborate and extend previous EEG research findings that phasic pain stimuli suppress $\alpha$ oscillations\textsuperscript{52,53}, enhanced $\delta$ activity\textsuperscript{54}, $\gamma$ activity\textsuperscript{55}. However, multiple regression analyses using the elastic nets method yielded a factor encompassing higher R-R time intervals and reduced midline EEG $\delta$ activity as the only effective capture of meaningful information in predicting placebo pain reduction. This finding extends original findings linking HR dynamics with attention and mood during stress\textsuperscript{56} and our PA findings obtained for tonic pain\textsuperscript{20}. Our observation of a joint covariation of enhanced R-R time interval and reduced $\delta$ activity aligns with
growing research suggesting that HRV reflects the brain-heart interaction\textsuperscript{57}. Notably, Thayer and colleagues’ findings suggest an essential link among cognitive performance, HRV, and prefrontal neural function that is important for physical health and mental stability. Thus, our observation that a relatively longer R-R interval and a smaller midline $\delta$ power during PA treatment causes higher pain reduction aligns well with Thayer’s and Lane’s neurovisceral model of emotion regulation\textsuperscript{58}. In line with this model, our present findings suggest that pain relief is consequent to the activation of the parasympathetic system rather than reduced activation of the sympathetic system, given that vagal influences on cardiac control are much faster than sympathetic ones. The organism facilitates higher self-regulation of pain/distress control when the immediate vagal effect is enhanced. Additionally, we obtained significant associations of self-pain relief with relatively higher EEG $\alpha$ and smaller $\gamma$ power (see the left half of Table 5). We think that these current findings complement previous reports showing that brief noxious stimuli induce a complex spectral spatial-temporal response pattern characterized by three primary frequency responses: $\delta$\textsuperscript{59}, $\alpha$\textsuperscript{60}, fast-$\beta$ and $\gamma$\textsuperscript{61} in the suprasylvian region and ACC along with the frontoparietal operculum and insula. However, the present study indicated that the factor including the covariation of $\delta$ and time-HRV changes was the most reliable predictor of placebo self-pain relief. This finding adds new information and parallels previous observations suggesting that enhanced $\delta$-band (4–7 Hz) and $\gamma$-band (>28 Hz) activities are likely expressions of prestimulus\textsuperscript{62} and consequent stimulus pain processing\textsuperscript{63}.

Finally, conditional process analysis disclosed that a factor composed of time-HRV and midline $\delta$ power difference scores obtained in the self-pain condition had a significant direct influence on PA response, indicating that longer inter-beat interval and smaller midline $\delta$ power changes significantly influenced higher pain reduction (Tab. 1, Tab. 6 and Fig. 4). This analysis also disclosed an indirect effect linking these physiological changes with lower BIS and then lower FFFS scores that, in the chain, induced an increased placebo analgesic effect (see the ‘ind-2’ path in Fig. 4 and upper-half section in Tab. 6). As far as we know, this is the first study disclosing the mutual influence of time-HRV and midline $\delta$ power during PA of phasic pain with the mediating serial role of BIS and FFFS traits. To our knowledge, these findings linking both BIS and FFFS traits with pain reduction during PA are new and merit to be discussed. We think at least two reasons may account for the lack of research on FFFS as a modulator of PA responding. The first lies in the fact that BIS has is usually measured with the BIS/BAS questionnaire\textsuperscript{18} that includes items of both the FFFS and BIS but does not provide a measure of the FFFS\textsuperscript{64}. The inclusion of active and passive avoidance items into the BIS may account for inconsistent findings in studies relating the BIS scale to placebo and nocebo effects\textsuperscript{65}. The second reason is that most previous studies reporting a relationship between BIS and PA use tonic pain stimulation rather than phasic stimulation (for review, see\textsuperscript{66}), and research using a phasic stimulus did not provide trait measures related to fear. In the present study, a visual cue anticipated each painful electric stimulus (i.e., an orange spark delivered on 5 s before delivering a pain stimulus, see Fig. 1) that may have induced participants to activate both fear of pain and pain to the painful stimulus onset. Since we found an inverse relation between FFFS scores and PA responses, we think that this finding complement Peter Lyby and colleagues findings that higher fear of pain trait reduces placebo analgesic responding\textsuperscript{49} and later findings that
induced fear abolished a weak PA and most pronounced in subjects who were highest in measures of fear of pain. Mainly, our current new finding aligns with the rRST conceptualization that BIS (anxiety) and FFFS (fear) are separated systems governing defensive behavior. Some research has suggested that the ‘direction’ of defensive behavior can distinguish FFFS from BIS. The FFFS is active with avoidance of the threatening stimulus (defensive avoidance), while the BIS is active when the threatening stimulus is met (defensive approach). If the situation requires an attack on the threat (fight), both the BIS and the FFFS are activated. Our current finding linking a reduction of EEG $\delta$ to PA with lower BIS is in line with original and more recent J. A. Gray conceptualization suggesting that activation of the BIS generates a particular EEG rhythm in the septohippocampal system (SHS), namely the $\delta$ rhythm. More recent experimental work supports the association of higher $\delta$ power reactivity with response execution during goal conflict in higher BIS participants.

In terms of ECQ personality traits, simple mediation analysis highlighted that lower midline $\beta$ power directly influenced more pronounced other-pain reduction and indirectly through the positive mediation of TEA scores. The indirect positive influence disclosed that a higher empathic ability trait could account for higher empathy for pain reduction (see Fig. 5). Since we found that different physiological factors influenced self-pain and other-pain reductions (see Figs. 4 and 5), we believe that the placebo empathy analgesia engages top-down modulated neural processes functionally different from those committed by a first-hand PA treatment. These are new findings, considering that the available research evidence does not yet allow more precise assignment of the different components to the various modulations of pain (see Ploner et al.’s review). Additionally, the present PA empathy findings seem to be compatible with previous findings showing that the observation of other’s pain increased activation in the sensorimotor cortex, as expressed by increased central $\beta$ (13-30 Hz) activity, reflecting an increased readiness for a defensive motor reaction of active avoidance (fear) or escape behavior.

**Limitations.** The present study has some limitations that deserve consideration. First, the current findings cannot generalize to the clinical population since we obtained them from healthy and young participants. Mainly, our electrophysiological correlations may not be paralleled by placebo analgesia findings derived from pain patients or participants who have suffered severe or chronic pain. Second, we administered the ECQ alone and missed using an available scale specifically developed to measure empathy for others’ pain. Third, in this study, we have provided measures of empathic ability trait derived from previous psychological and neuroscience research, ignoring that empathy results from a complex process requiring several intermediate processing stages. This limitation makes it difficult to determine the locus of any effect that influences the empathic response. We agree with the alternative proposal by Coll and collaborators explaining empathic response as individual differences in ‘emotion identification’ (i.e., the ability to identify another’s emotional state) and the degree to which the identification of another’s emotional state causes’ affect sharing’ in the self. This approach may account for mixed results from previous research concerning the effects of empathy on information processing. In sum, future research should point to (1) generalizing experimental findings into clinical application, (2) understanding how event-related brain-oscillations changes relate to higher-order empathic responses (i.e., emotion
identification, affective sharing, and emotion regulation), and how empathic responses promoted approach-related prosocial behaviors.

**Declarations**

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**Author contributions**

VDP and AV conceived and designed the study. VDP contributed to the methods and procedure. Trial structure, physiological recordings, and the pre-processing of ECG and EEG signals were carried out by AV. VDP performed oscillatory signal analyses, statistical analyses and drafted the manuscript. VDP contributed to the literature research, interpretation of data findings, and revised the manuscript. Both authors read and finally approved the version of the manuscript to be published.

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**Competing interests.** The authors declare no competing interests.

**Additional information**

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**Tables**

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

**Figures**

Figure 1
Structure and timeline for self-pain and other pain trials. An arrow cue (1000 ms) indicated the target of the upcoming electric stimulation (self, other). The arrow was followed by an anticipation cue (1500 ms) indicating the intensity of the upcoming electric stimulation (blue flash indicates a non-painful stimulus, orange flash indicates a painful one). After a waiting interval of 3500 ms, a delivery cue (1000 ms) was presented concurrently with stimulus train delivery (duration from 18 to 30 ms): red flash represents a painful stimulus, green flash represents a non-painful one. After 3000 ms, pain and unpleasantness ratings were collected (max 8000 ms) in about one-third of all trials.

**Figure 2**

Grand averages across participants of single trials time-frequency (TF) estimation of non-phase locked (induced) oscillation power obtained by using the norm of the Morlet transform of EEG time-series recorded at CZ as elicited at the offset of painful electric train stimulus. Time is presented on the x-axis, stimulus offset being indicated by the vertical bar at 0 msec. The frequency between 0 and 40 Hz is presented on the y-axis. Normed output spectral power values are coded on a color scale, the highest energy values appearing red and lower values blue. Data are baseline referenced, thus providing levels of positive power values relative to a reference period (from -500 to -50 ms). EEG changes for the pain and placebo analgesia treatment during each self-pain (upper-panel) and other-pain (lower-panel) conditions. Right panels display the t-test differences between the two conditions. A power increase relative to baseline level can be observed in response to all stimuli during pain compared to placebo treatments. This increase is much more pronounced in the self-pain between 100 to 250 msec. The maximum relative increases during the pain of TF power were at 7 Hz, 11 Hz, 18 Hz, 31 Hz, and 39 Hz, as shown by the arrows in the upper-right panel. The power increases can be observed at all midline electrodes but are more assertive at central locations.

**Figure 3**

Wavelet-extracted oscillatory amplitude waveforms at frequency layer of 7, 11, 18, 31, and 39 Hz from the averaged wavelet-transformed single trials of the self-pain (upper-quadrant) and other-pain (lower-quadrant), respectively for pain (A, C) and placebo analgesia (B, D) treatments (painful electric-train onset at time 0 ms). Color current source density maps (µV/m²) are reported at the bottom for each frequency of interest (7, 11, 18, 31, and 39 Hz) and the time corresponding to each maxima amplitude for each frequency.

**Figure 4**

The serial multiple mediator model’s schematic panels link the physiological factor of “S_ΔtHRV & ΔMidl-ϑPow” to pain reduction induced by PA treatment in self-pain condition (S_NPDS). Direct effect
and indirect effects (Ind) of BIS through FFFS traits on S_NPDS are reported. The thickness of the arrows indicates the strength of the link between variables. Gender and State-Anxiety changes are included as covariates.

**Figure 5**

Simple mediator model testing midline $\beta_2$ (22-32 Hz, 100-180 ms) power factor changes “O_ΔMidl-$\beta_2$Pow” induced by PA treatment in the other-pain condition as the independent variable influencing other-pain changes (O_NPDS) through the mediation of Total Empathy Ability trait (TEA). Direct and indirect effects (Ind) are reported. The thickness of the arrows indicates the strength of the link between variables. Gender and State-Anxiety are entered as covariates.

**Supplementary Files**

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- Table1.PCAOK.xlsx
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