Heart rate variability is not associated with placebo analgesia
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Introduction
Placebo analgesia is pain reduction induced by a sham treatment. Heart rate variability (HRV) is a measure of autonomic nervous system control over the heart. Commonly used variables to analyze HRV are high frequency HRV (HF-HRV) and a ratio of low to high frequency HRV (LF/HF). HF-HRV occurs within the frequency band corresponding to respiration (15–40 Hz) and is believed to measure parasympathetic influence over the heart. LF/HF is thought to reflect the balance of sympathetic and parasympathetic influences over cardiac functioning, with lower values indicating greater sympathetic influence. Prior research has found HF-HRV is associated with decreased pain. The present study examined whether HRV metrics are associated with placebo analgesia. Specifically, we examined whether HRV is related to a change in pain ratings and the nociceptive reflex function (NFR; a physiological correlate of spinal nociceptive processing) following placebo manipulations. Participants were 139 healthy, pain-free individuals (69 females) involved in a placebo analgesia study. Participants were randomly assigned to one of three groups: a natural history control group (NH=35), or an expectation only group (E-only=33) or an expectation plus conditioning group (EC=35). An inert cream was applied on two different occasions in the same day and pain and NFR were tested before and after each application. HRV metrics were assessed between the two cream applications.

Procedure

**Session 1**
- Session 1: Pretest stimulations delivered—pain ratings and NFR assessed
  - Procedure: Patient is given instructions to relax
  - Procedure: An ANOVA was used to examine group differences in HRV metrics. A logarithmic transformation was used in the ratio of high to low frequency HRV.
  - Procedure: For our analysis, we computed a change score for both pain and NFR (post minus pre-test, for session 1 only).
  - Procedure: Correlations were computed for HRV and changes in pain, in addition to HRV and changes in NFR.

**Session 2**
- Session 2: Posttest stimulations delivered—pain ratings and NFR assessed
  - Procedure: Procedure: An ANOVA was used to examine group differences in HRV metrics. A logarithmic transformation was used in the ratio of high to low frequency HRV.
  - Procedure: For our analysis, we computed a change score for both pain and NFR (post minus pre-test, for session 2 only).
  - Procedure: Correlations were computed for HRV and changes in pain, in addition to HRV and changes in NFR.

Objective
To examine whether HRV metrics are associated with placebo analgesia.

Participants
- Healthy Participants: N=139
- Participant Characteristics:
  - Natural history control group (Age=30.8, SD=10.1; Female=51%), expectation only group (Age=34.5, SD=12.8; Female=52.3%), or an expectation plus conditioning group (EC=35%)
  - In the NH group, participants were randomly assigned to one of three groups: a natural history control group (NH=35), or an expectation only group (E-only=33), or an expectation plus conditioning group (EC=35%).
- Exclusion Criteria:
  - Age < 17 years of age
  - Current acute illness
  - Cardiovascular, neurological, and/or circulatory problems
  - Chronic pain condition (e.g., migraine, back pain)
  - Recent use of anxiolytic medication
  - Current use of anxiolytic and/or hypnotic medication
  - BMI > 35

Methods: NFR
- Nociceptive Flexion Reflex (NFR) Threshold: biceps femoris EMG activity in the 90-150 ms post-stimulus window
- NFR is a spinal-mediated protective withdrawal reflex elicited by A8 fiber activation
- NFR magnitude = mean of biceps femoris EMG in 90-150 ms post-stimulus interval minus mean of 60 ms prestimulus interval
- NFR magnitude correlates with pain ratings

Methods: HRV
- Heart Rate Variability was assessed
  - Procedure: Participant is given instructions to relax
  - Procedure: An ANOVA was used to examine group differences in HRV metrics. A logarithmic transformation was used in the ratio of high to low frequency HRV.
  - Procedure: For our analysis, we computed a change score for both pain and NFR (post minus pre-test, for session 1 only).
  - Procedure: Correlations were computed for HRV and changes in pain, in addition to HRV and changes in NFR.

Results

- Heart rate variability was not significantly correlated with change in pain ratings (HF-HRV: r = .05, p = .60)
- Heart rate variability was not significantly correlated with change in NFR (HF-HRV: r = .13; LF/HF: r = .07, although there was a trend for LF/HF to be lower in the E, C, and EC group relative to NH (p = .05)).

Conclusions
- These data suggest that placebo manipulations did not lead to differences in HRV
- HRV is not a good predictor of placebo response

Funding Source: This work was funded by a grant (HR12-100) from the Oklahoma Center for the Advancement of Science and Technology (OCAST)