Placebo Analgesia Correlates with High-Frequency Heart Rate Variability

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Introduction

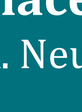
- **Increased high-frequency heart rate variability** (i.e. respiratory sinus arrhythmia) is a **proxy of parasympathetic activity** and **associated with positive health outcomes** [1].
- Placebo analgesia (i.e. pain relief) is associated with **changes in autonomic activity** [4]. The parasympathetic nervous system is a **possible contributor to placebo analgesia** due to its internal regulatory properties [3].
- Individual differences in **emotion regulation and autonomic flexibility** are hypothesized to be associated **with greater placebo responses** [2,3,5].
- In this exploratory study, we manipulated subjects' **analgesic expectations** of inert skin creams and administered pain to **isolate and quantify placebo responses.**

Methods & Materials

Participants: N = 17 Participants, aged 19-42 (M=26.35, SD = 6.26), 11 female
Conditions: **Cream/Expectation** (None, Control, Placebo), **Heat** (Low Heat, Med Heat, High Heat)

Procedure/Task Design:

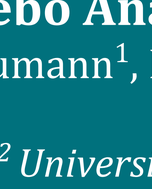
Initial Heat, No Creams (Pre)
- Patient received low, medium, and high heat on their left forearm
- Rated pain on VAS 10-point scale
- ECG measured throughout study



Conditioning

	Expectation:	Reality:
Control	Level 7	Level 7
Placebo	Level 7	Level 3

"To test if it's working, we'll administer your level 7"



ECG measured throughout experiment

Time

Placebo & Control Blocks (Counterbalanced)
- Patients receive 2 blocks with stimulus expectancy cues and 2 without.
- 4 blocks per condition
- 8 trials per block

Measures: **Respiratory Sinus Arrhythmia** or RSA (the variability in ECG due to breathing) using Mindware™ HRV analysis toolbox, **Subjective Pain** reported using 10-point Visual Analogue Scale (VAS)

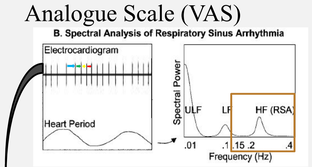
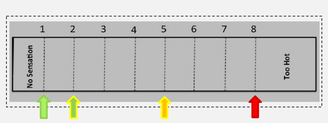


Diagram of the spectral analysis used to derive RSA from ECG signal, taken from .12hz to .4hz



Visual Analogue Scale (VAS) used by participants to communicate their acute pain

Distance between peaks of each QRS complex and the variability of those distances correspond with RSA.

Statistical Methods: One-way repeated measures ANOVA, correlations, and a mixed effects model.

Results & Figures

Descriptive Statistics & Correlations for RSA

Measure	Mean	St. Deviation
RSA Pre	6.72	1.066
RSA Placebo	6.79	1.195
RSA Control	6.78	1.199

Correlation Table

Measure	RSA Pre	RSA Placebo
RSA Pre		
RSA Placebo	.902**	
RSA Control	.935**	.960**

** = P<.05, ** = P<.001*

One-Way Repeated Measures ANOVA of RSA by Expectation of Treatment (Pre, Placebo, Control):

Effect	Expectation of Treatment	Mean	Std. Deviation	df Sphericity Assumed	df Greenhouse-Geisser	F	Sig. Sphericity Assumed	Sig.Greenhouse-Geisser
RSA	Pre	6.727	1.086	2	1.648	.186	.871	.790
	Placebo	6.790	1.195	2	1.648	.186	.871	.790
	Control	6.768	1.199	2	1.648	.186	.871	.790

Results non-significant, p-value = .831 if sphericity is assumed, p = .790 using Greenhouse-Geisser

Descriptive Statistics & Correlations for Placebo Responses

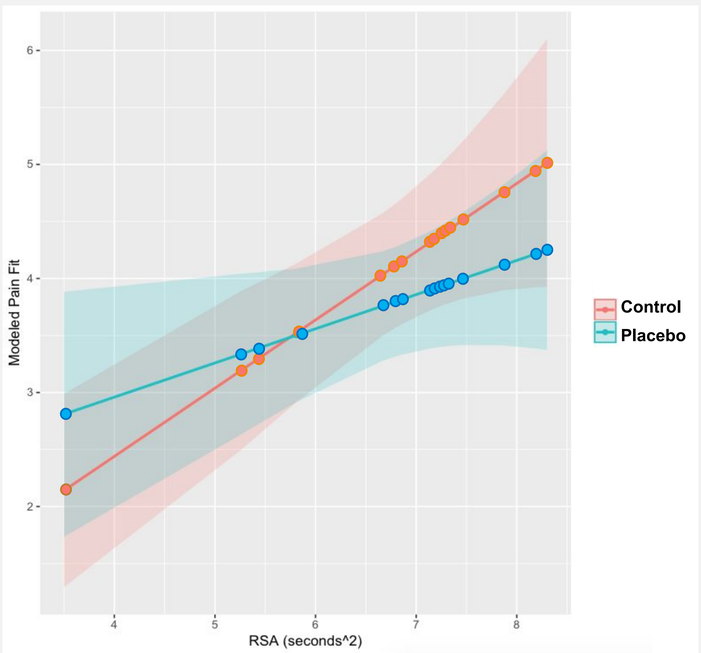
Measure	Mean	St. Deviation
Low Heat (Control - Placebo)	.122	.556
Medium Heat (Control - Placebo)	.612	.948
High Heat (Control - Placebo)	.155	.998

Correlation Table

Measure	RSA Pre	RSA Placebo	RSA Control
Low Heat (Control - Placebo)	.120	.258	.109
Medium Heat (Control - Placebo)	.542*	.588*	.483*
High Heat (Control - Placebo)	-.006	.113	.094

** = P<.05, ** = P<.001*

Mixed Effects Model of RSA & Pain:



Results were significant with B = .30(.12), t(93.15) = 2.40, p =.018. N = 17

Conclusions

- Novel evidence demonstrates the **correlation between placebo analgesia** and **individual RSA**, such that **higher RSA correlates with a greater placebo response**.
- Contrary to the literature, we found **RSA did not change significantly** between conditions (Pre, Control, Placebo).
- These results provide further evidence for an **autonomic aspect of the placebo response**, specifically **parasympathetic activity.**
- It is unclear whether RSA and the parasympathetic nervous activity it represents is **directly affecting pain scores** or whether it is **only symptomatic of the reduction of pain scores** that drive the change.
- Provides a biological basis for further investigation into the psychological mediators of increased RSA, such as **emotion regulation,** and their role in **placebo analgesia**.
- Raises the possibility for future studies to determine the **direction of causality between RSA & placebo analgesia** and other mediating variables driving the correlation.

References

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