On the relationship between pain variability and relief in randomized clinical trials

Siddharth Tiwari[1,2], Andrew D. Vigotsky[2,3], A. Vania Apkarian[2,4]

[1] Illinois Mathematics and Science Academy, Aurora, IL
[2] Center for Translational Pain Research, Feinberg School of Medicine, Northwestern University, Chicago, IL
[3] Departments of Biomedical Engineering and Statistics, Northwestern University, Evanston, IL
[4] Departments of Neuroscience, Anesthesia, and Physical Medicine & Rehabilitation, Feinberg School of Medicine, Northwestern University, Chicago, IL

Background

- Placebo response in clinical trials - “improvement in pain due to the psychological effect of receiving treatment”
- Drug effect is measured in clinical trials; Drug effect = Drug relief - Placebo relief
- High placebo response leads to “clinical trial failure” or a small drug effect
    - EXAMPLE:
        - Drug relief: -5,
        - Placebo relief: -1 vs. -3
        - Drug effect: -4 and -2

Background (cont.)

- Current research aims to find correlates that predict placebo responders
- Pain variability: previously identified correlate of placebo response
- Previous research does not account for confounding variables (pre-intervention pain and natural history of disease)

Research Objectives

Derive the strength of the relationship between **baseline pain variability** and **relief** while controlling for the effects of **pre-intervention pain** and **natural history** between **treatment groups**.

Methods

- Used data from two clinical trials; both included no treatment (no_tx) and placebo groups, only one included a drug group (Placebo II)
- **post** ~ **pre** + **group***sd** (**group** is a factor, used for linear contrasts)
  - included pre-intervention pain as a covariate to control for pre-intervention pain
  - isolated effect by group to control for natural history by using linear contrasts
    - placebo improvement = no_tx + placebo
    - drug improvement = no_tx + placebo + drug
    - drug = drug improvement - placebo improvement = (no_tx + placebo + drug) - (no_tx + placebo) = drug

Methods (cont.)

- Calculated semipartial correlations using multiple regression model (**post** ~ **pre** + **group*sd)**
  - variance accounted for by ONE variable; reduces confounding effects

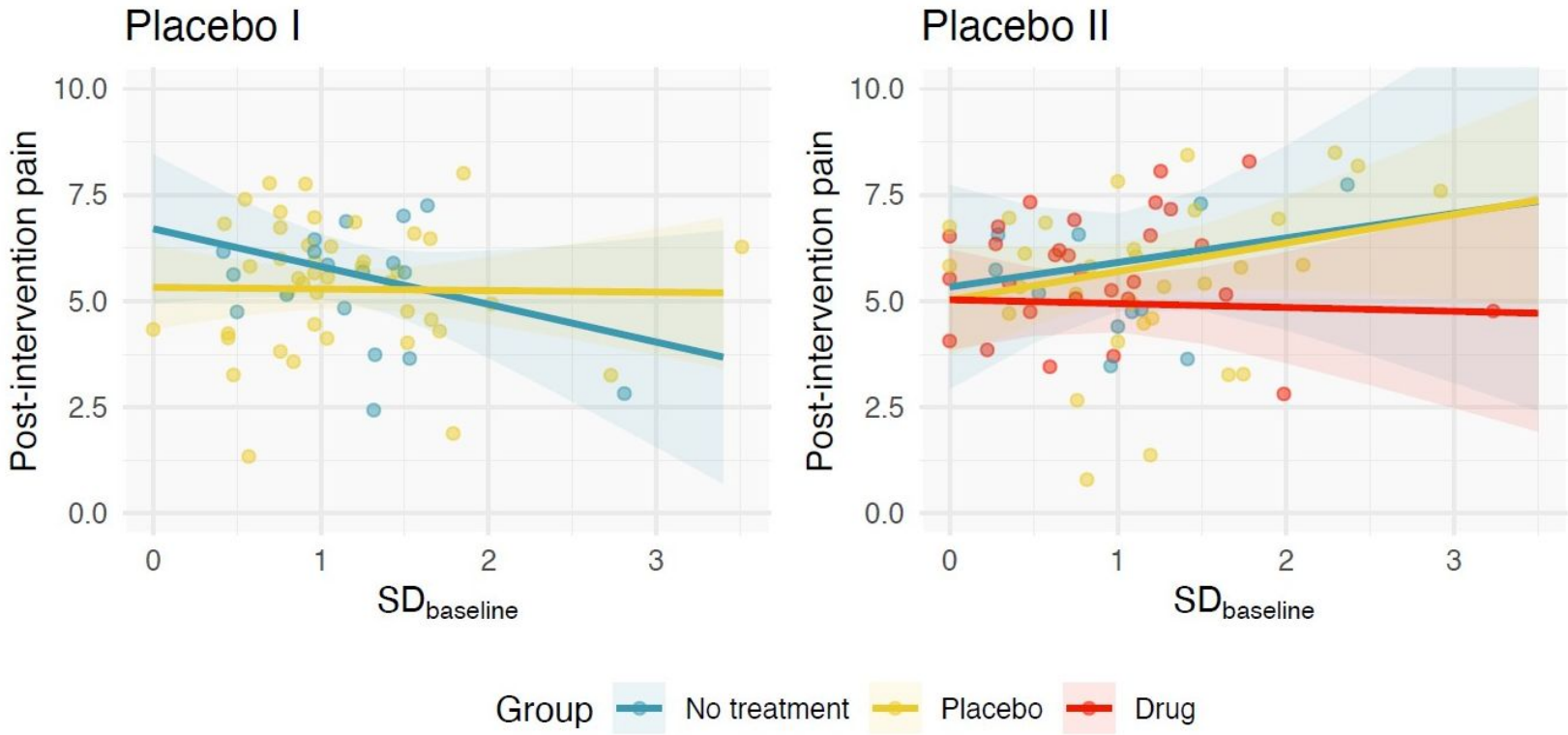
$$r_{sp} = \text{sgn}(t)\sqrt{\frac{t^2(1-R^2)}{df}}$$

r_{sp} = semipartial r
t = t-statistic (of variability)
R^2 = model coefficient of determination (global fit of the model)
df = residual degrees of freedom

Results

		r_{sp} (CI)
Placebo I	No treatment (n = 18)	−0.16 (−0.39, 0.08)
	Placebo (n=43)	0.13 (−0.08, 0.37)
Placebo II	No treatment (n=11)	0.08 (−0.11, 0.31)
	Placebo (n=32)	0.01 (−0.15, 0.20)
	Drug (n=30)	−0.11 (−0.26, 0.06)

Results (cont.)



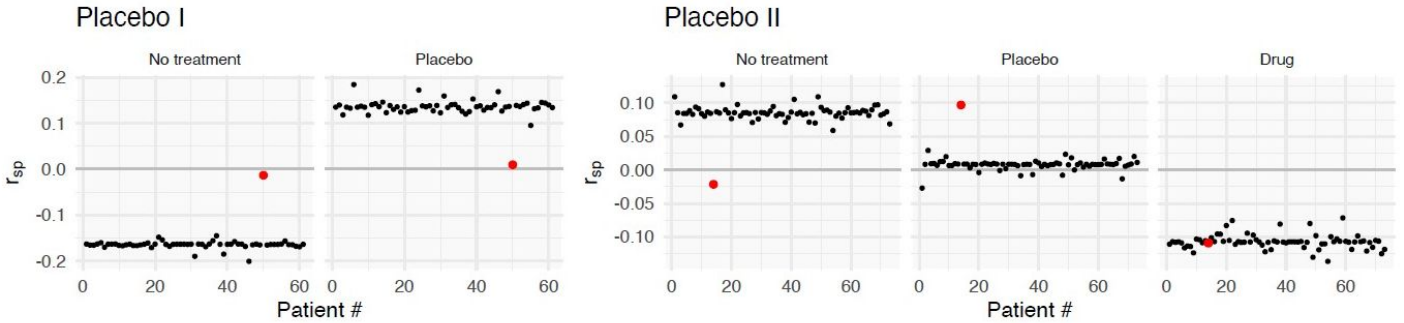
Conclusions

The relationship between pain variability and relief is weak and inconsistent; should not be used as a univariate predictor of relief in any group of a clinical trial

Acknowledgements

- Andrew Vigotsky and Dr. Apkarian
- IMSA Student Inquiry and Research Program
- Japan Super Science Fair

Sensitivity Analysis



Supplementary Figure 1. ***Influence of individual patients on the semi-partial correlations.*** Each point represents the semi-partial correlation when patient *x* is removed from the analysis. This leave-one-out analysis reveals that in both Placebo I and Placebo II, there was one participant who strongly drove the results (red points). Removing the individual in Placebo I tends to produce semi-partial correlation coefficients that are much closer to zero for both groups. Removing the individual in Placebo II to decrease the no treatment semi-partial correlation and increase the placebo semi-partial correlation. In both cases, our conclusions are unaffected since appreciable, negative semi-partial correlations do not appear in the placebo groups.

Correlations without “the model”

			r_{sp} (CI)
Within-group change score, no pre covariate	**Placebo I**	No treatment (n = 18)	−0.33 (−0.73, 0.23)
		Placebo (n=43)	0.16 (−0.23, 0.45)
	Placebo II	No treatment (n=11)	0.31 (−0.80, 0.79)
		Placebo (n=32)	0.28 (−0.09, 0.52)
		Drug (n=30)	0 (−0.27, 0.40)
Within-group, with pre covariate	**Placebo I**	No treatment (n = 18)	−0.30 (−0.61, 0.19)
		Placebo (n=43)	0 (−0.37, 0.28)
	Placebo II	No treatment (n=11)	0.68 (−0.20, 0.91)
		Placebo (n=32)	0.22 (−0.16, 0.52)
		Drug (n=30)	−0.10 (−0.40, 0.42)