WOULD TRAINING AIMED TO IMPROVE PAIN REPORTING RELIABILITY AFFECT THE PLACEBO RESPONSE?

Ehab Matta[1], Liat Honigman[1], Israa Asaad[1], Roi Treister[1]

[1]The Clinical Pain Innovation Lab, The Cheryl Spencer Department of Nursing, Faculty of Social Welfare & Health Sciences, University of Haifa, Haifa, Israel.

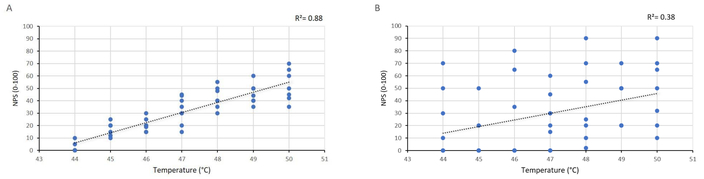
Background and Aims

- The perception of pain is the result of a complex multifaceted process, affected and modulated by physiological, psychological and social factors [1]. In accordance, pain perception and pain reports are highly variable, both within and between subjects, and often not tightly related to the severity or pathology [2,3].
- Individuals differ in their tendency to exhibit within-subject variability of pain scores, both in experimental and clinical pain, and that this characteristic is clinically relevant [3].
- The Focused Analgesia Selection Test (FAST), is a recently developed method which capture within-subjects variability of pain reports in response to administration of repeated experimental noxious stimuli of various intensities in blinded manner [4].
- The within-subjects variability assessed by the FAST reflects, at least in part, subjects' ability to reliably report pain [4].
- Recent studies applying the FAST procedure in chronic pain population demonstrated that subjects who perform well in the FAST, (i.e. demonstrating low variability/good reliability) are able to better report changes in their clinical pain [5,6] and are demonstrating lower variability of their day-to-day clinical pain reports [5].
- In addition, we developed the Evoked Pain Training (EPT), which is based on the FAST procedure, plus feedback aimed to improve subject's ability to reliability report pain [5].
- In a previous study, in clinical setting, the EPT resulted in improved reliability of pain reports and lower placebo response [5].
- The aims of the current study were to assess: (1) if in experimental laboratory settings, subject's ability to reliably report pain could be improved by training; and (2) if trained subject will demonstrate lower placebo response.

Methods

- One hundred healthy subjects ≥ 18 years were recruited into a randomized double-blind study, which comprised of a total of 6 laboratory visits and take 4 weeks to complete.
- The trial included two-stages: (1) a parallel study design in which half of the subjects underwent training (EPT) and the other half participated in a control arm; (2) a cross-over study, in which all subjects participated in a two study arms: receiving drug (ibuprofen) and placebo.
- In the first study phase, in the EPT arm, which comprised of 3 laboratory visits, subjects received feedback on reliability of pain reports in response to noxious stimuli of various intensities.
- Subjects performance in the FAST are assessed by calculating the relations between stimuli intensities and subjects pain reports. Specifically, we are calculating the correlation coefficient (R2) and Intra-class-correlations (ICC) and coefficient-of-variance (CoV).

Figure 1. Examples of FAST results obtained for a (A) "accurate" vs. (B) "non-accurate" pain reporter.



- In the second study phase, experimental noxious stimuli used to induce pain, which was assessed before and after receiving treatment/placebo. The efficacy of the treatment is calculated, for each study arm (drug and placebo) as change in pain (in response to the experimental stimuli) before and 1 hour after treatment.

- **Two Quantitative Sensory Testing (QST) devices were used:**
  1. The Thermal Sensory Analyzer II, a computerized device capable of producing and recording responses to thermal stimuli.
  2. The AlgoMed device, a computerized device capable of producing and recording responses to pressure stimuli.

- **Statistical Analyses:** Data was processed and analyzed by using the SPSS software version 23. Descriptive statistics was used to summarize all data. Repeated measure ANOVA was used to assess the effects of training (EPT) on subjects' ability to reliably report pain (aim 1). Spearman correlations were used to assess relations between subjects' ability to reliably report pain and efficacy results (aim 2).

Results

- All 100 subjects were recruited to the study and completed their first visit.
- Nine subjects were discontinued (n=9), and 13 not yet completed the study.
- Demographic characteristics are detailed in **table 1**.
- In **table 2**, the results of the first study phase are summarized. As can be seen, subjects' ability to reliably report pain in the EPT group statistically significantly improved.

Table 1. Demographic characteristics at the baseline

Characteristics	Total n = 100	EPT n = 48	Control n = 52	P Value
Age (years)				0.834
Mean ± SD	25.3 ± 5.7	25.4 ± 5.9	25.1 ± 5.6	
Range	18–49	18-49	18-43	
Sex, n (%)				0.381
Male	42 (42%)	18 (37.5%)	24 (46.2%)	
Female	58 (58%)	30 (62.5%)	28 (53.8%)	
Religion, n (%)				0.942
Jewish	48 (48%)	23 (47.9%)	25 (48.1%)	
Druze	11 (11%)	4 (8.3%)	7 (13.5%)	
Muslim	24 (24%)	11 (22.9%)	13 (25%)	
Christian	8 (8%)	5 (10.4%)	3 (5.8%)	
Atheist	3 (3%)	2 (4.2%)	1 (1.9%)	
Other	2 (2%)	1 (2.1%)	1 (1.9%)	
BMI				0.798
Mean ± SD	23.11 ± 4.55	22.99 ± 4.6	23.22 ± 4.5	
Range	16.8-38.7	16.8-38.7	17.1-37.9	

EPT, Evoked Pain Training; BMI, Body Mass Index.

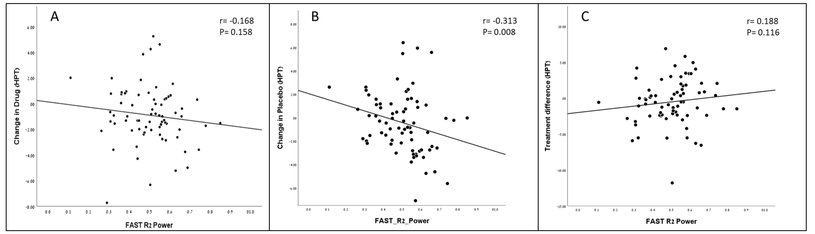
Table 2. Summary of the FAST results at baseline and EPT visits

EPT	Baseline	Visit 1	Visit 2	Visit 3	P Value
R^2 Linear					0.000
Mean (SD)	0.60 (0.12)	0.69 (0.09)	0.70 (0.06)	0.71 (0.09)	
Median	0.62	0.71	0.71	0.71	
Range	0.26-0.84	0.51-0.87	0.54-0.81	0.49-0.84	
ICC					0.000
Mean (SD)	0.68 (0.11)	0.76 (0.11)	0.80 (0.08)	0.81 (0.08)	
Median	0.69	0.78	0.83	0.84	
Range	0.32-0.89	0.52-0.92	0.64-0.92	0.67-0.92	
CoV					0.017
Mean (SD)	0.66 (0.33)	0.56 (0.25)	0.56 (0.23)	0.55 (0.23)	
Median	0.60	0.52	0.56	0.51	
Range	0.13-1.67	0.14-1.16	0.18-1.07	0.17-1.14	

Abbreviations: CoV, coefficient of variation; ICC, intraclass correlation coefficient; SD, standard deviation; (Baseline n=99; EPT n=29).

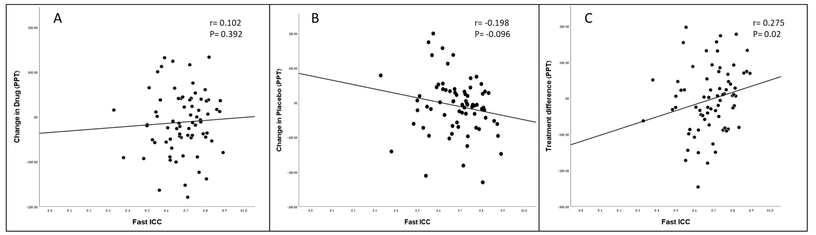
- Examples for the effects of the training on efficacy results (stage 2) are given in the two panels:
  - In panel 1, the efficacy results, based in heat pain thresholds (HPT) are described. In figure A, correlation between the effect of drug and subjects' ability to reliably report pain (R2 power) are described. In figure B, the same relations, but with the placebo response are described, and in figure C, the relations with the treatment difference (effect of drug minus effect of placebo). Significant relations were seen only with the placebo response.

Panel 1. Relations between pain reporting accuracy and efficacy results, as captured by the Heat Pain Threshold (HPT) model



- In panel 2, similar results are seen, this time with pressure pain threshold (PPT) as a model.

Panel 2. Relations between pain reporting accuracy and efficacy results, as captured by the Pressure Pain Threshold (PPT) model



Conclusions

- Our aims were achieved: the training improved subjects' ability to reliably report pain, and this ability was correlated with subjects' responses to placebo.
- Subjects who are less reliable in reporting pain, which demonstrate large fluctuations in their pain, are more likely to benefit from clinical care that is aimed to augment the placebo response.
- Additional research is ongoing to illuminate the clinical relevance of our findings.

Acknowledgment

- Funding for this project was provided by EFIC Grunenthal Grant (E-G-G) And financial aid for traveling grant provided by Galilee Medical Center, Israel.

References

1. Merskey N, IASP Press. 1994; 41-43
2. Bačkonja & Farrar, Pain Med. 2015 Jul;16(7):1247-50.
3. Ballantyne & Sullivan, N Engl J Med. 2015 Nov 26;373(22):2098-9.
4. Treister R et al J Pain Res. 2017 Feb 9;10:319-326.
5. Treister R et al PloS One. 2018 May 24;13(5):e0197844.
6. Treister R et al Pain. 2019 Feb; 1-7