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INTRODUCTION

•Expectancies modulate both reported pain and responses in some brain regions, yet the key brain circuitry that mediates expectancy effects on pain experience has not been identified.

–Placebo expectancy manipulations: decreases in “pain matrix” regions^{1,2}, increases in control regions, particularly rACC^{2,3,4}

–Placebo analgesia brain-behavior correlations = between-subjects only.

–Event-related (cue-based) expectancy manipulations: modulation of pain matrix and striatal regions^{5,6}

–Have not examined relationship between brain and pain reports.

•For a brain region or pathway to mediate expectancy effects on reported pain, its activity must:

- a) be influenced by expectancy.
- b) predict trial-by-trial changes in reported pain, even within a single level of noxious stimulation.
- c) statistically explain a significant portion of expectancy effects on trial-by-trial reported pain.

•We used multi-level mediation (M3) software to test this compound hypothesis, and to locate regions that formally mediate the relationship between experimentally manipulated expectancy and reported pain.

•Hypotheses

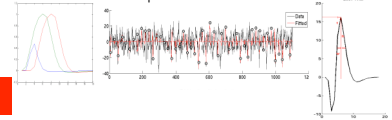
- I. Expectancies modulate pain reports.
- II. Expectancies modulate pain matrix activity (Path a).
- III. Pain matrix activity affects perceived pain (Path b).
- IV. Expectancy effects in pain matrix regions lead to changes in perceived pain (Mediation effect, A*B).
- V. Higher order regions involved in cognitive control and value processing also mediate expectancy effects on perceived pain.
- VI. Interactions among these mediators predict perceived pain.

METHODS

- 18 subjects (mean age = 25.3, 9 females)
- Thermal stimulation to 4 sites on left forearm with 16mm thermode (Medoc, Inc.)
- fMRI acquisition: 1.5T GE scanner, Spiral In-Out, 29 slices, 2s TR

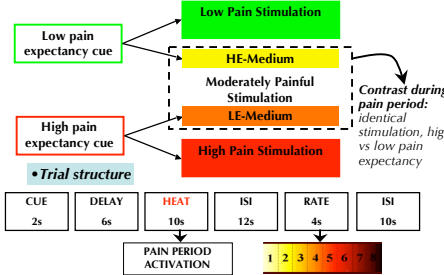
•Voxelwise single trial analysis

1. Fit basis functions trial-by-trial
2. Estimate trial-by-trial area under the curve (AUC)
3. Use trial level parameters in multi-level mediation



•Experimental design

1. Thermal pain calibration
 - Level 2 (Slightly painful)
 - Level 5 (Moderate pain)
 - Level 8 (Max tolerable pain)
2. Learning Task: Tones predict low or high pain
3. Two conditioning runs + fMRI
4. Six experimental runs + fMRI



•Whole-brain multi-level mediation

A test for mediation should satisfy the following criteria:

1. M should be related to X (a effect)
2. M should be related to Y after controlling for X (b effect)
3. The indirect relationship (a*b) should be significant

Linear equations within-subjects:

1. $y = cx + e_y$
2. $m = ax + e_m$
3. $y = bm + c'x + e_y$
4. $c = c' + a*b$

Additional between-subjects components⁷:

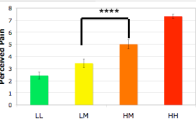
1. $\text{Mean}(a*b) = \text{mean}(a) * \text{mean}(b) + \text{cov}(a,b)$
2. $c = c' + a*b + \text{cov}(a,b)$

RESULTS

WHOLE BRAIN MULTI-LEVEL MEDIATION

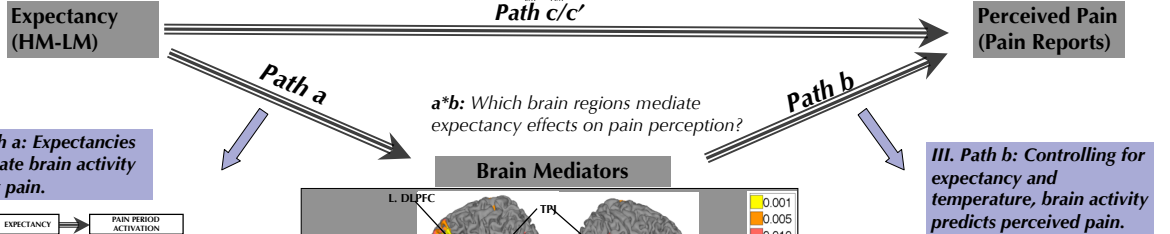
I. Expectancies modulate perceived pain.

HM>LM (p<.0001), allowing us to examine mediators of expectancy effects on reported pain within a single level of noxious stimulation.

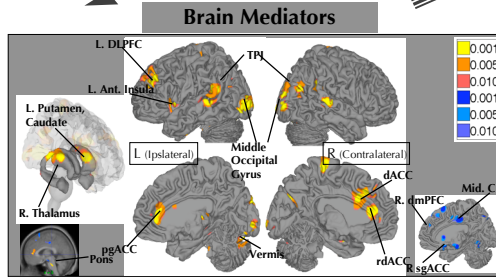
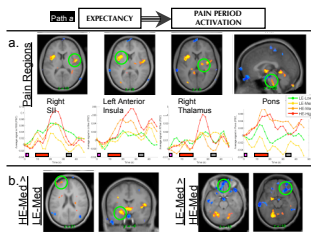


Pain Localizer - HH>LL

Region	A2	A2	A2
Bilateral Cerebellum	Y	Y	N
CB Vermis	Y	Y	Y
R. SII	Y	N	N
R. Thalamus	Y	N	Y
R. Anterior Insula	Y	Y	N
L. Anterior Insula	Y	Y	Y
R. Middle Insula	Y	N	N
L. Middle Insula	Y	N	N
dACC	N	Y	Y
PAG	N	N	N
Pons	Y	N	Y

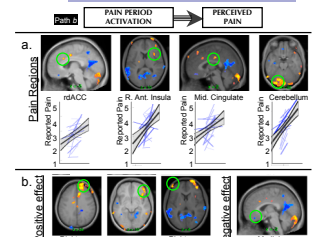


II. Path a: Expectancies modulate brain activity during pain.

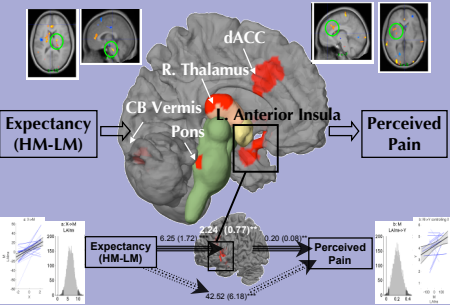


IV, V. Mediation effect: Pain matrix regions and higher order regions mediate expectancy effects on reported pain.

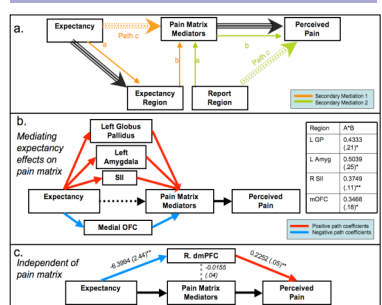
III. Path b: Controlling for expectancy and temperature, brain activity predicts perceived pain.



Pain matrix mediators



Interacting and independent pathways



SUMMARY

- Nearly all pain matrix regions are modulated by expectancy during noxious thermal stimulation (all except dACC, PAG).
- Some pain matrix regions (Insula, dACC) predict perceived pain controlling for expectancy and temperature.
- A key subset of pain matrix regions (insula, thalamus, dACC, pons, cerebellum) mediate expectancy effects on perceived pain.
- Amygdala, globus pallidus, and medial OFC mediate expectancy effects on pain matrix mediators.
- R. dmPFC mediates expectancy effects on pain independent of pain matrix activity.

References

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7. DA Kenny, J Korchmaros, N Bolger. Psychological Methods, 8(2), 115-28 (2003).