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Neural mechanisms of expectancy-based pain modulation: Whole brain mediation analysis using fMRI

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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:

- be influenced by expectancy.
- predict trial-by-trial changes in reported pain, even within a single level of noxious stimulation.
- 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

- Expectancies modulate pain reports.
- Expectancies modulate pain matrix activity (Path a).
- Pain matrix activity affects perceived pain (Path b).
- Expectancy effects in pain matrix regions lead to changes in perceived pain (Mediation effect, A*B).
- Higher order regions involved in cognitive control and value processing also mediate expectancy effects on perceived pain.
- 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

Experimental design

1. Pain calibration

Level 2 (Slightly painful) Level 5 (Moderate pain) Level 8 (Max. tolerable pain)

2. Learning Task: Tones predict low or high pain, counterbalanced across subjects; S informed of cue-pain pairings, must correctly identify 90% of tones to proceed 2s

3. Two conditioning runs + fMRI

4. Six experimental runs + fMRI

Low pain cue → Low Pain (Level 2) LL
Low pain cue → Med Pain (Level 5) LM
High pain cue → Med Pain (Level 5) HM
High pain cue → High Pain (Level 8) HH

Contrast HM vs LM during pain period: identical stimulation, high vs low pain expectancy

Voxelwise single trial analysis

- Fit basis functions trial-by-trial
 - Estimate trial-by-trial area under the curve (AUC)
 - Use trial level parameters in multi-level mediation
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Whole-brain multi-level mediation

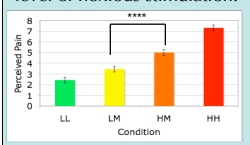
- A test for mediation should satisfy the following criteria:
- M should be related to X (a effect)
 - M should be related to Y after controlling for X (b effect)
 - The indirect relationship (a*b) should be significant
- Three linear equations:
- $y = cx + e_y$
 - $m = ax + e_m$
 - $y = bm + c'x + e'_y$

RESULTS

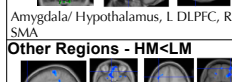
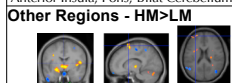
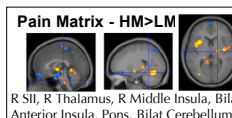
WHOLE BRAIN MULTI-LEVEL MEDIATION ANALYSIS

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.

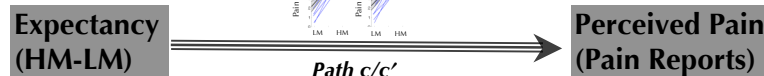


II. Path a: Expectancies modulate brain activity during pain.

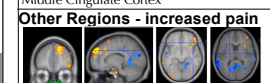
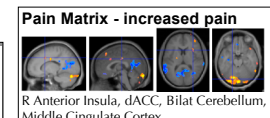
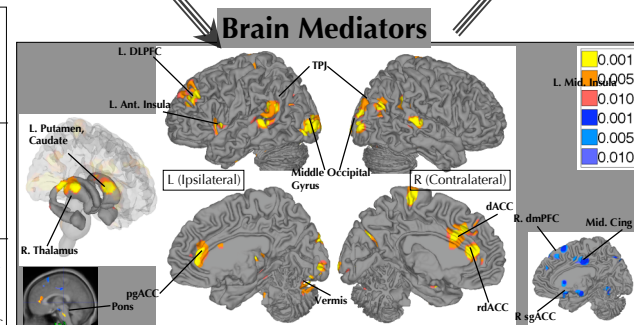


Pain Localizer - HH>LL

Region	Δ2	B2	ΔB2
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	Y
Pons*	Y	N	Y

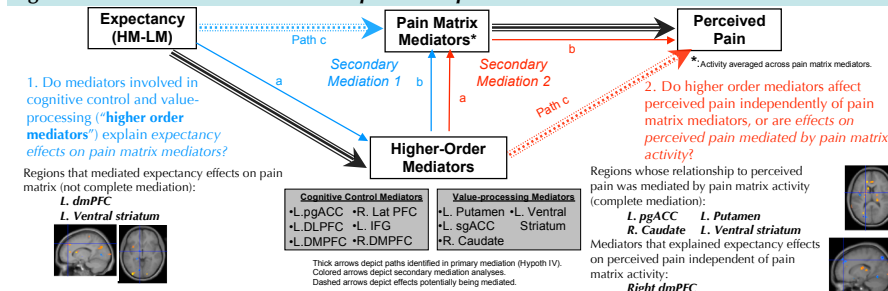


III. Path b: Controlling for expectancy and temperature, brain activity predicts perceived pain.

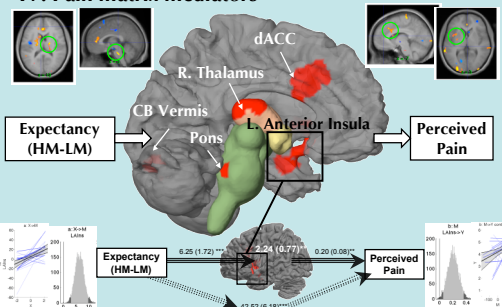


IV, V. Mediation effect: Pain matrix regions and higher order regions mediate expectancy effects on reported pain.

VI. Secondary mediation analysis: Expectancy-based interactions between pain matrix and higher-order mediators contribute to perceived pain.



IV. Pain matrix mediators



SUMMARY

- Most 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.
- Pain matrix and higher order regions mediate expectancy effects on perceived pain.
- Some higher order regions (striatum, L dmPFC) mediate expectancy effects on the pain matrix.
- Some higher order regions (striatum, L pgACC) modulate pain via connections to pain matrix.
- R. dmPFC mediates expectancy effects on pain independent of pain matrix activity.

References

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