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Tracing pain pathways from stimulus to report

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INTRODUCTION

Noxious stimulus intensity and reported pain are highly correlated. However, there is rarely a perfect mapping between applied nociceptive stimulation and perceived pain.

Studies have revealed differences in activity linearly related to temperature and activity linearly related to reported pain (Craig et al., 2000) using separate linear regressions.

Temperature regression: L. posterior insula, R. anterior insula
Reported pain regression: R. anterior insula, OFC

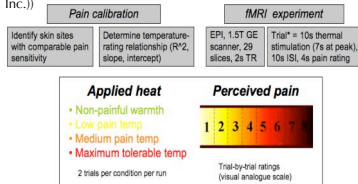
Studies have not traditionally examined brain regions involved in the pain reporting process controlling for activity related to nociceptive input.

It is likely that specific brain regions play an important role in constructing the pain experience from a given level of stimulation. These **mediator regions** may be identified using whole brain multi-level mediation analyses, to localize **pathways** that link **stimulus intensity** to **reported pain experience**.

METHODS

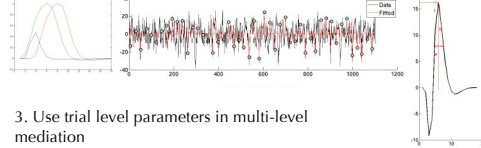
Pain calibration and experimental design

- 20 subjects (mean age = 30, 8 females)
- Thermal stimulation delivered to 3 sites on left forearm with 16mm thermode (Medoc, Inc.)



Voxelwise single trial analysis

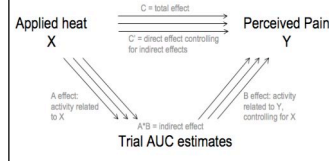
- Fit basis functions trial-by-trial width, delay, and area under the curve (AUC)
- Estimate trial-by-trial height, width, delay, and area under the curve (AUC)



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

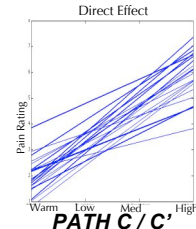
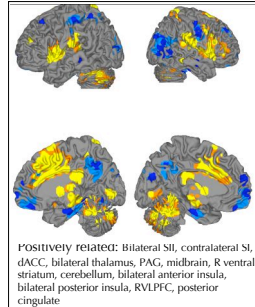


Three linear equations:

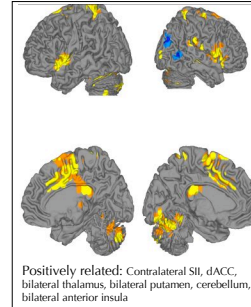
- $y = cx + e_y$
- $m = ax + e_m$
- $y = bm + c'x + e'_y$

RESULTS

Path A: Which brain regions show greater activity for higher levels of thermal stimulation?
STIMULUS-RELATED REGIONS

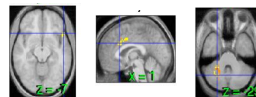
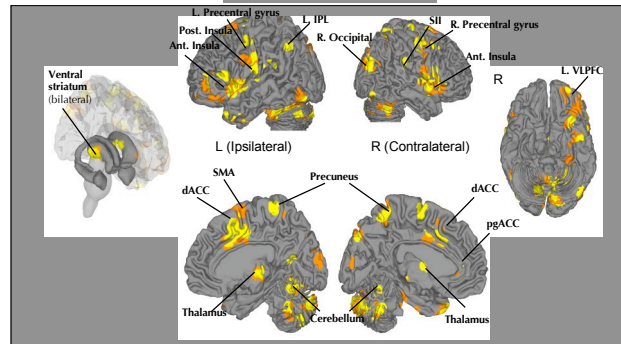


Path B: For a given level of heat, which brain regions predict magnitude of pain ratings?
RESPONSE-RELATED REGIONS



Applied Heat → Perceived Pain

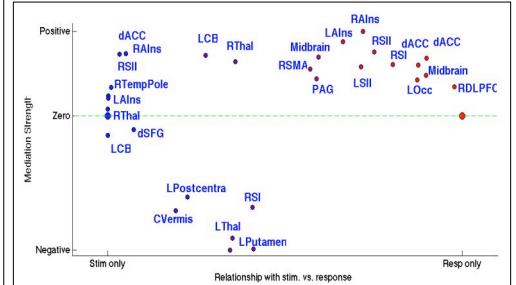
A*B: Which brain regions contribute to the relationship between applied heat and perceived pain?



Blue box: $p < .001$ one-tailed, 5 contiguous voxels
Orange box: $p < .01$, 20 contiguous voxels

RESULTS

Regression path model



Data from mediators, stimulus-related regions, and response-related regions were then extracted. Stimulus and rating vectors were included in a multiple regression model predicting activity for each region, and coefficients were sorted in order to identify the role of each region in the continuum from noxious stimulus to perceived pain.

SUMMARY

Multi-level mediation analyses identified a network of brain regions that explained a significant amount of the covariation between temperature and pain reports. Key mediators included right anterior insula, dorsal anterior cingulate cortex, and left cerebellum.

Mediation analyses also identified stimulus-related regions and response-related regions. Many key components of the traditional 'pain matrix' were identified in these path analyses.

Regions identified in the mediation analysis were then included in a linear path model illustrating the role of these regions in the pathway from noxious stimulation to the pain experience.

Future analyses will examine potential moderators of these pathways, including expectancy-related brain activity, individual difference measures, and cognitive control regions.

REFERENCES

Craig AD, Chen K, Bandy D, Reiman EM (2000). Nat Neurosci 3:184-190.

For more information on whole-brain multi-level mediation and moderation analyses, see poster B95 (tomorrow morning): **The M3 Toolbox: the Multi-level Mediation/Moderation Framework for Connectivity Analyses in fMRI Data**
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Poster reprints at
http://www.columbia.edu/cu/psychology/tor/

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