

Cerebral contributions to pain independent of nociception

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Introduction

- The dominant view of pain over the last decade has primarily focused on **nociceptive brain circuits** that carry and process nociceptive information.
- It is becoming established that **non-nociceptive brain circuits** such as ventromedial prefrontal cortex are functionally important in pain¹, but their relationships with pain have not been systematically quantified.
- Here, we analyzed 7 studies ($N = 242$) to address the following questions:
 - Are there regions that don't respond to painful stimuli, but make direct contributions to pain experience and reports?
 - Can we quantify their contributions to pain alongside the traditional 'pain processing' circuits?
 - Which combination of systems mediates psychological modulation effects, including expectancy, agency, certainty, placebo?

Methods

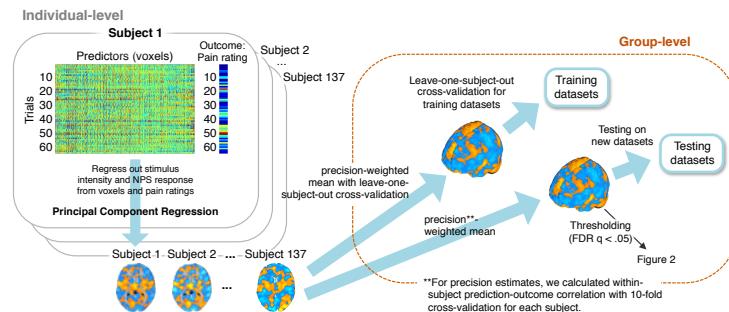
MEGA-ANALYSIS

- Combined single-trial (single painful epoch) images
 - 7 studies, $N = 242$ (124 F) participants
 - 3 to 6 levels of painful heat per study
 - $N = 13,005$ trial-level images, each with associated stimulus intensity (thermal pain) and pain rating.
- '**MEGA-analysis**' increases power and robustness of brain maps, and allows increased power to control for variables naturally correlated with pain (e.g., stimulus intensity)
- Split data into **training** dataset (Studies 1-4, $n = 137$)—to develop a pain-predictive brain signature—and **testing** data (Studies 5-7, $n = 105$) to evaluate predictive accuracy and other properties.

Table 1. Study demographics and task characteristics

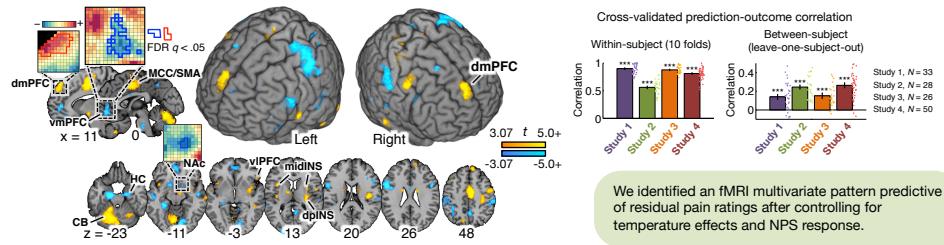
Study number	N	Gender	Ages Mean (SD)	Training/ Testing dataset	Stimulus Duration (seconds)	Stimulated locations (thermal)	Number of trials per subjects	Mean number of excluded trials (high VIFs)			Other experimental manipulations
								Number of trials per subjects	Number of intensity levels	Other experimental manipulations	
Study 1	33	22 F	27.9 (9.0)	Training (Somatic pain)	12.5	Arm	97	6.8	6	Reappraisal	
Study 2	28	10 F	25.2 (7.4)	Training (Somatic pain) Testing (Vicarious pain)	11	Arm, Foot	81	6.1	3	Cue	
Study 3	26	9 F	27.8 (7.5)	Training	10	Arm	48	3.8	4	N/A	
Study 4	50	27 F	25.1 (6.9)	Training	11	Arm	48	5.7	3	Placebo, cue	
Study 5	59	31 F	20.8 (3.0)	Testing	15	Arm	16	0	2	Placebo	
Study 6	17	9 F	25.5	Testing	10	Arm	64	2.1	3	Cue	
Study 7	29	16 F	20.4 (3.3)	Testing	10	Arm	64	1	2	Agency, Certainty	
Total	242	124 F		Training n = 137 Testing n = 105							

Fig. 1. Developing a pattern map that is predictive of pain above and beyond stimulus intensity



Results: Neuroimaging

Fig. 2. fMRI pattern-based prediction model for Pain Above and Beyond Stimulus Intensity (PABSI)



We identified an fMRI multivariate pattern predictive of residual pain ratings after controlling for temperature effects and NPS response.

Fig. 3. Stimulus intensity mediators (SIMS) vs. independent contributors (SIIPS)

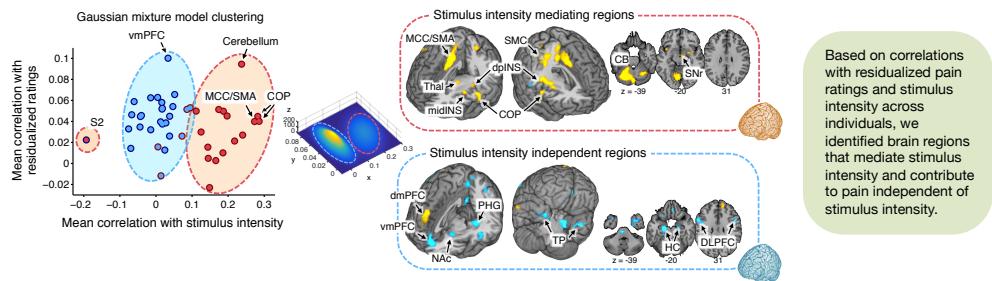
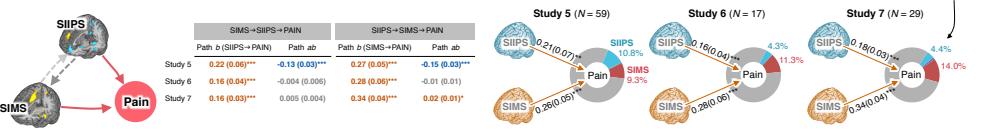
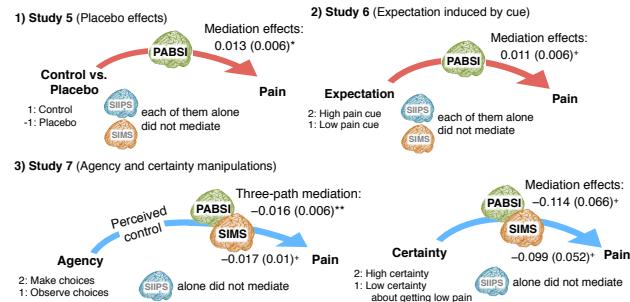


Fig. 4. Separate contributions of mediators and independent contributors



Stimulus intensity mediating system (SIMS) and Stimulus intensity independent pain system (SIIPS) make separate and comparable contributions to the overall pain experience.

Fig. 5. Mediation of psychological modulation



The full prediction model (PABSI) mediated all the psychological modulation effects in testing datasets, and the SIMS alone mediated the agency and certainty effects in Study 7. However, SIIPS alone mediated none of the psychological modulation effects.

Conclusion

- We identified a distributed fMRI pattern that is predictive of pain above and beyond stimulus intensity (PABSI), which can be divided into two sub-system, stimulus intensity mediating system (SIMS) and stimulus intensity independent pain system (SIIPS)
- The PABSI mediated all the psychological pain modulation effects in the testing datasets. We can further examine which sub-system contribute to the mediation effects.
- The PABSI sheds light on multiple pain systems in the brain, and provide a new brain measure for pain.



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