#536 W-PM

Functional pathway discovery using mediation analysis: Approach and application to pain

Tor Wager[1], Lauren Atlas[1], Martin Lindquist[2], Kate Hard[1], Matthew Davidson[1]

1. Department of Psychology, Columbia University, New York, NY

2. Department of Statistics, Columbia University, New York, NY

Cognitive & Affective Control Lab
http://www.columbia.edu/cu/psychology/tor/
* Download this poster at the website above

INTRODUCTION

BACKGROUND

- Many studies use regression to investigate brain-psychology relationships in voxel-by-voxel analyses. These analyses cannot test hypotheses about relationships among multiple regions and their relationship to psychological variables. Path analysis is a promising tool for identifying such relationships.
- For example, pain-related brain activity has been correlated with stimulus intensity (e.g., temperature) and perceived pain separately (e.g., Craig et al., 2000[1]), but analyses have not localized brain pathways that mediate the stimulus-report relationship.
- We have developed a framework for conducting multi-level path analyses when one link in the path (e.g., a mediating variable) is unknown, allowing researchers to make statistical parametric maps of mediation effects.
- This approach combines some of the strengths of confirmatory path modeling and the localizing power of the voxel-wise mapping approach.

KEY PROPERTIES AND COMPARISON OF METHODS

1. The ability to search for pathways rather than confirm *a priori* pathways - useful when the paths are not known
2. Test mediation hypotheses: needed to identify pathways
3. Account for differences in hemodynamic response (HRF) between brain regions [2]
4. Multilevel modeling - to properly account for intersubject variance[3]

Technique	Advantages	Search for brain regions	Identify mediators	Handle HRF diffs	Multilevel	Non-param options
Group ICA, tensor ICA	Distributed patterns	Y	N	N	N	N
Seed Analysis	Bivariate interactions w/ 1 area	Y	N	N	N	N
PPI	Single moderator of biv connectivity	Y	N	N*	N	N
Granger causality	Bivariate interaction w/ time lag/diff HRFs	Y	N	Y	N	N
DCM	Powerful modeling of multi-region activity	N	Y	Y	N	N
SEM		N	Y	N	N	N
M3	Exploratory and confirmatory	Y	Y	Y	Y	Y

MEDIATION

- Simple, three-variable form of SEM extended to the multilevel setting, making it feasible to treat linkages (i.e., connectivity between regions) as random effects.
- Uses two key concepts:
  1. Mediation/moderation in path analysis
  2. Mixed-effects (or hierarchical) models
- The M3 analysis merges the two approaches, building on recent developments in multi-level mediation analyses in psychology[4]
- Mediation provides tests of whether relationship between two variables is explained (mediated) by a third, thus establishing either a direct or indirect linkage[5]
- A test for mediation should satisfy the following criteria:
  1. X should be related to M (the *a* pathway in Fig. 2)
  2. b should be significant after controlling for X
  3. The indirect relationship (*a*b*) should be significant
     - This is generally assessed with the Sobel test, or more efficiently, with a bootstrap test[6]
- Three linear equations at the first (within-subjects) level:
  1. $y_i = c_i x + e_{y,\ i \text{ indexes subject}}$
  2. $m_i = a_i x + e_m$
  3. $y_i = b_i m + c'x + e'_y$
- If the relationship between *x* and *y* can be accounted for by an indirect relationship through *m* as described by slope coefficients *a* and *b*, then *c - c'* (the product *ab*) will be statistically different from zero.
- Second-level equations (between-subjects):
  $c_i = c + u_{0i}$, $a_i = a + u_{1i}$, $b_i = b + u_{2i}$, $c'_i = c' + u_{3i}$
- The *u*'s are between-subjects random effects
- Population inference on 2nd-level path coefficients

How to deal with HRF differences?

1) Use trial-to-trial response estimates (e.g., 'beta series'[7])
   * Used in this poster: trial-to-trial area under curve (AUC)
2) Explicitly model lags or HRF shapes

Example: Variable latency model

- Assumes HRF shape the same, up to a delay *d*
- *x* and *m* are replaced by f(*x*, d_1) and f(*m*, d_2), where f() is a time-shifting
- Equations become:
  1. $y = c * f(x, d_1) + e_y$
  2. $f(m, d_2) = a * f(x, d_1) + e_m$
  3. $y = b * f(m, d_2) + c' * f(x, d_1) + e'_y$
- d_1 and d_2, are estimated with a genetic algorithm that maximizes - log(SSE_T)

Single-trial analysis

- As an alternative to the complex and computationally intensive full deconvolution or latency models, a *single-trial analysis* can be used.
- In the single-trial analysis, the response to each trial is fitted with a set of basis functions, and certain HRF parameters, such as height, delay, width, and area under the curve (AUC) are estimated.
- Then, instead of using a BOLD signal, the mediation will use the trial-level parameters. This is illustrated below:

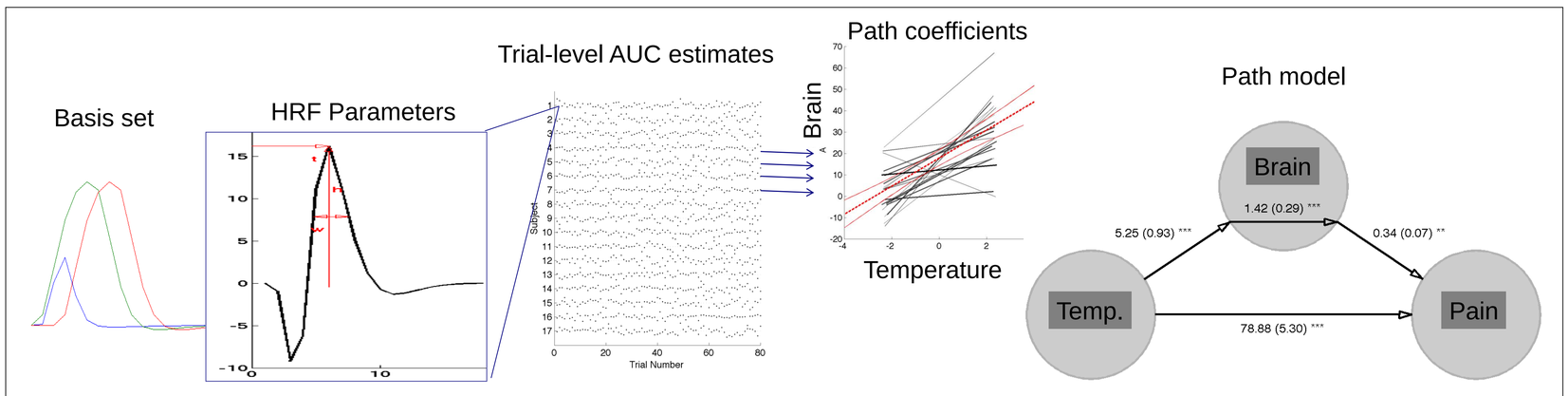


Fig. 1. Single-trial analysis. Each trial's response is fitted by a basis set (**left**), then HRF parameters are computed (**middle**), and then the resulting timeseries of trial-by-trial estimates (e.g., AUC - **right**) are used in mediation analyses.

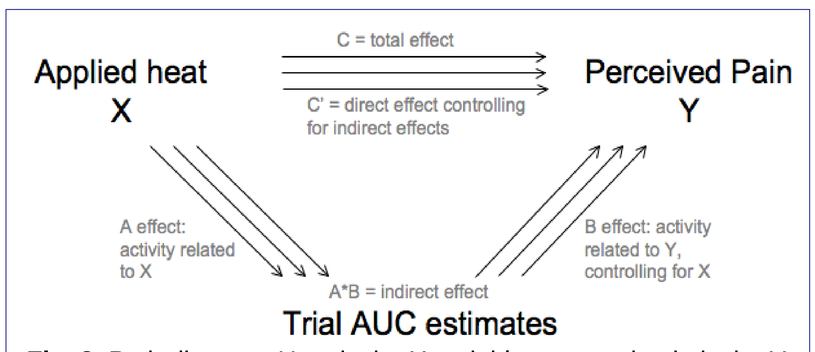
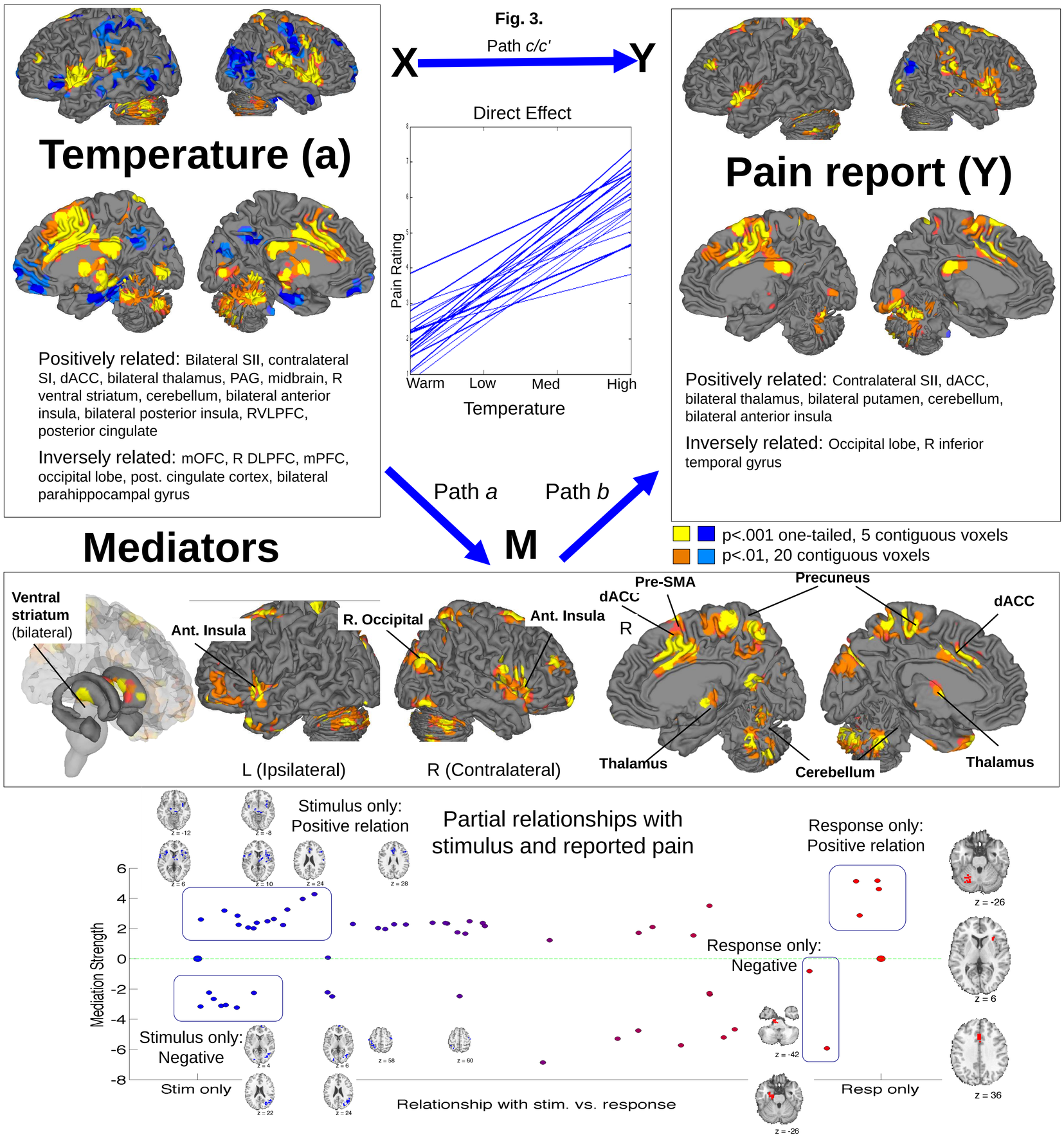


Fig. 2. Path diagram. Heat is the X variable, reported pain is the Y variable, and area-under-the-curve (AUC) estimates for each trial are the tested to see if they are mediators of the X-Y relationship.

RESULTS

• Single-trial BOLD response amplitudes were measured for 48 individual thermal stimuli of four pain intensities.
• Effective connectivity was estimated between the applied stimulus intensity, BOLD response amplitude, and reported pain across trials.
• Activity in many regions in the 'pain matrix' correlated with both stimulus intensity (path a) and reported pain controlling for intensity (path b) and satisfied the formal test of mediation, suggesting that multiple pain-responsive regions contribute to the generation of perceived pain (see Figure 1B).
• These included S1, anterior SII, anterior insula, dorsal anterior cingulate, and cerebellar nuclei.



REFERENCES

1. Craig, A.D., et al., *Thermosensory activation of insular cortex.* Nature Neuroscience, 2000. **3**: p. 184-190.
2. Gitelman, D.R., et al., *Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution.* Neuroimage, 2003. **19**(1): p. 200-7.
3. Raudenbush, S.W. and A.S. Bryk, *Hierarchical Linear Models: Applications and Data Analysis* Second ed. Methods. 2002, Newbury Park, CA: Sage.
4. Kenny, D.A., J.D. Korchmaros, and N. Bolger, *Lower level mediation in multilevel models.* Psychol Methods, 2003. **8**(2): p. 115-28.
5. Baron, R.M. and D.A. Kenny, *The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations.* J Pers Soc Psychol, 1986. **51**(6): p. 1173-82.
6. Shrout, P.E. and N. Bolger, *Mediation in experimental and nonexperimental studies: new procedures and recommendations.* Psychol Methods, 2002. **7**(4): p. 422-45.
7. Rissman, J., A. Gazzaley, and M. D'Esposito, *Measuring functional connectivity during distinct stages of a cognitive task.* Neuroimage, 2004. **23**(2): p. 752-763.