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Modeling Brain Pathways using Functional Mediation Analysis

Martin A. Lindquist, Ragnheidur Haraldsdottir, Lauren Y. Atlas and Tor D. Wager

Department of Statistics, Columbia University

Department of Psychology, Columbia University

INTRODUCTION

Pathways are fundamental properties of brain organization. Thus, the ability to characterize and test pathways is critically important for understanding how psychological processes map onto brain function. Further, they provide a means for discovering links between brain activity and peripheral measures (e.g., heart rate or reported pain). In this work we discuss a set of tools for modeling functional pathways in fMRI time series data. Our approach is based on a simple three-variable path model, which can provide information on whether a region M mediates connectivity between two peripheral measures (X and Y), implying a pathway from X to M to Y.

The novel feature of our approach, compared to previous work [1], is that the data from M is treated as a continuous mathematical function of time. The class of techniques that models relationships among continuous functions, rather than observed samples, is known as functional data analysis [2]. Thus, we refer to our method as Functional Path Analysis (FPA). FPA can not only test whether brain responses are directly or indirectly related to behavioral and physiological outcomes, but also provide valuable information about the timing of these relationships.

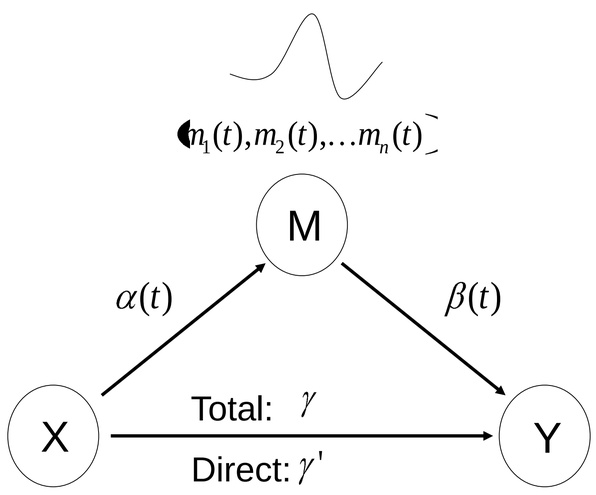


Figure 1. The basic unit of analysis in the functional mediation framework is a 3-variable system. The variables corresponding to X and Y are scalars, while the variable corresponding to M is a function. Both the α and β pathways are represented by functions, while both the total and direct relationships are scalars.

METHODS

The unit of analysis is a 3-variable path model (Fig. 1). Mediating variables (M) explain the relationship between two other variables (X and Y), implying a functional path through the mediator. In our implementation, two variables, X and Y, are scalars, while the mediating variable M is functional. In the data we present here, for example, X is a series of temperatures applied to skin, Y is the pain reported after each stimulation, and M is a time series of brain data following each stimulation (that will be treated as samples from a continuous underlying function). The relationship between the variables is expressed using the equations:

$$y_i = \gamma x_i + \varepsilon_{i,x} \quad (1)$$

$$m_i(t) = \alpha(t) x_i + \varepsilon_{i,m}(t) \quad (2)$$

$$y_i = \int_0^T \beta(s) m_i(s) ds + \gamma' x_i + \varepsilon_{i,y} \quad (3)$$

Here γ represents the total X-Y relationship, while γ' represents the direct relationship (controlling for M). In this notation the γ and γ' path coefficients are scalars, while the α(t) and β(t) path coefficients are functions that describe the relationship between variables as a function of time.

The goal of the analysis is to determine whether the observed relationship between X and Y can be explained by a path through M. Using Eqs. [1-3] the difference between direct and indirect effect can be written:

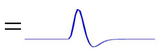
$$\gamma - \gamma' = \int_0^T \alpha(s)\beta(s) ds \quad (4)$$

The $\alpha(s)\beta(s)$ term on the right-hand side illustrates the decomposition of the γ - γ' difference across time.

A statistical test of γ - γ' is used to test whether the covariance between X and Y can be explained by M, i.e. whether the total X–Y relationship (γ) is stronger then the direct relationship controlling for M (γ'). The test is performed by testing the significance of the $\alpha(t)\beta(t)$ product using a bootstrap procedure. The $\alpha\beta$-function gives information about *where* in the time series significant mediation takes place, allowing key temporal intervals driving the mediation to be determined.

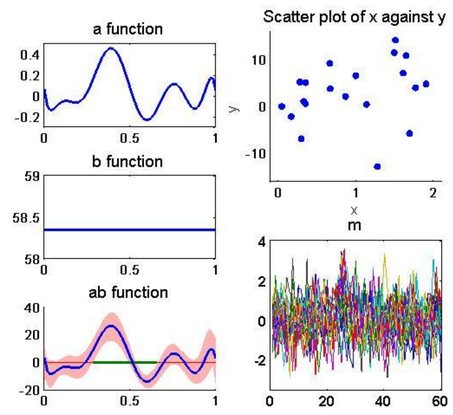
SIMULATIONS

Outline:	x	m	y	αβ(t)-effect
Simulation I	$x_i \sim unif(0,2)$	$x_i h_i + \varepsilon_i^1$	$\int_0^T m_i(t)dt + \eta_i^1$	
Simulation II	$x_i \sim unif(0,2)$	$v_i h_i + \varepsilon_i^2$, $v_i \sim unif(0,2)$	$x_i + \eta_i^2$	None
Simulation III	$x_i \sim unif(0,2)$	$x_i h_i + \varepsilon_i^3$	$x_i + \eta_i^3$	None
Simulation IV	$x_i \sim unif(0,2)$	$x_i h_i + \varepsilon_i^4$	$\int_0^{T/2} m_i(t)dt + \eta_i^4$	

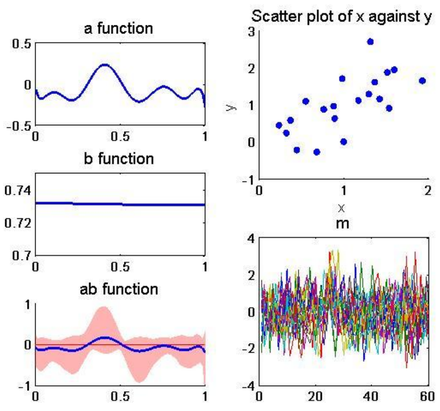
Note: $h_i =$  $\varepsilon_i^j, \eta_i^j \sim N(0,1)$

Green indicates range of expected significant functional mediation

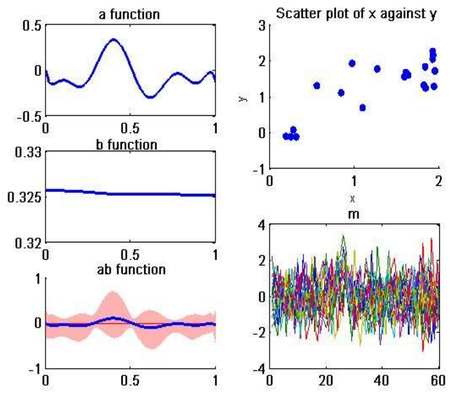
Simulation I



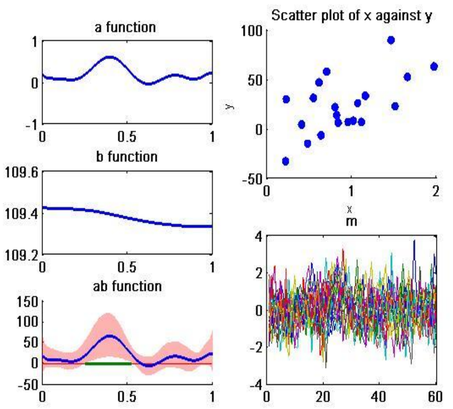
Simulation II



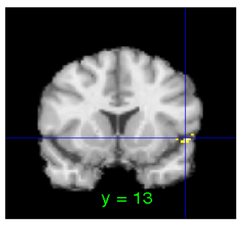
Simulation III



Simulation IV

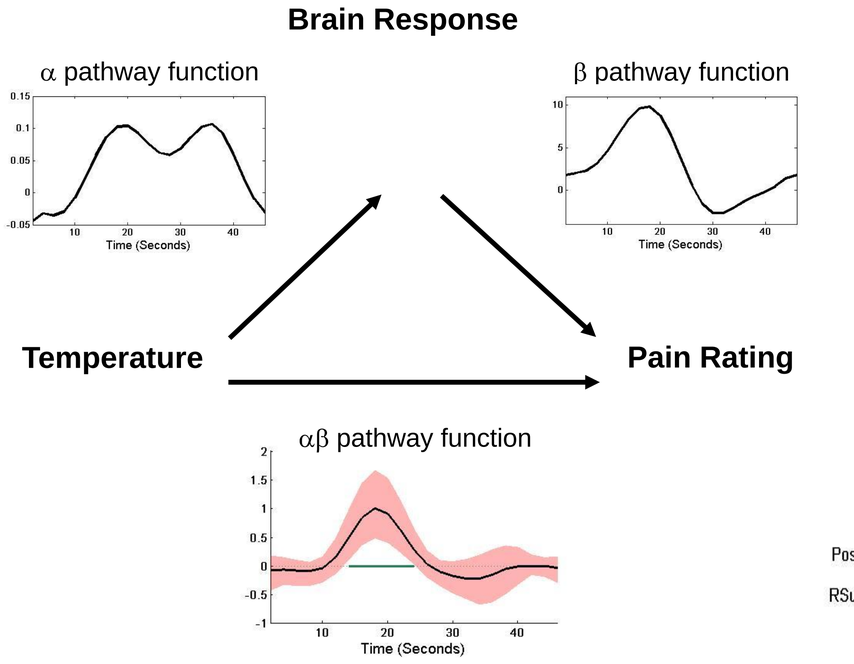


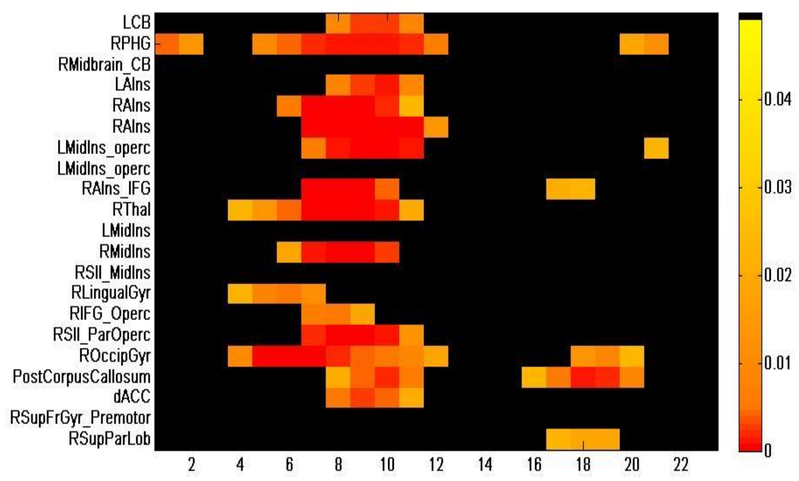
EXPERIMENTAL RESULTS



Experimental design

- Data comes from pain study (n=20) comparing brain responses to noxious heat at 4 different temperatures.
- Temperatures were chosen so that subjects were matched on subjective pain perception.
- In response to each stimulus the subjects gave subjective pain ratings.
- Data from 21 different pain-responsive regions were extracted.





Results show that activation in the right anterior insula (see brain map) mediates the relationship between temperature and pain rating. Estimates of the α(t) and β(t) pathway functions are shown on either side of the path model. These functions suggest a sustained period for which activity is modulated by temperature, and a more phasic response predicting perceived pain, controlling for temperature. A bootstrap test shows that the $\alpha\beta$(t) effect is significantly non-zero in an interval between 12-24 seconds following activation. This indicates the key time interval driving the mediation.

The plot above shows time points with significant $\alpha\beta$(t) effects from each of 21 brain regions. The results show that data in many classic "pain-responsive regions" such as the anterior insula (AINS) show significant mediation of the temperature-report relationship particularly around the end of the heat (10-12 sec). The subjective pain grows during the stimulation period, and is often maximal around the end of stimulation, which typically drives pain ratings made after the trial.

Notably, some other pain regions show significant mediation effects around the time of pain reporting, including parahippocampal cortex (PHG) and around the posterior cingulate, perhaps signaling a contribution of activity during pain recall.

IMPLEMENTATION

The path coefficients α(t) and β(t) are modeled using a b-spline basis set of order 6 with 10 knots. Eqs. [1-3] are computed using a freely available toolbox for functional data analysis (Ramsay 2005; http://www.psych.mcgill.ca/misc/fda/index.html). The test of mediation is performed using a bootstrap procedure with 1,000 repetitions. In each repetition *n* observations are chosen with replication from the observations $(x_i, y_i, m_i(t))$, i=1,…m, and the model is refit. These replications are used to determine where in the time course $\alpha(s)\beta(s)$ differs significantly from 0.

CONCLUSIONS

We present a novel approach towards path analysis that allows functional data to be incorporated. Using our method we can not only determine whether a variable mediates the relationship between two other variables, but also which time points are most crucial in driving the mediation.

REFERENCES

[1] Wager et al. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron, 59, 1037-1050.*

[2] Ramsay and Silverman. Functional Data Analysis, 2nd edition, Springer, 2005.