JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Functional Mediation Analysis

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Innovations in Design, Analysis, and Dissemination:
Frontiers in Biostatistical Methods

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Hi everyone, it is a pleasure to be here. My name is Yenny Webb-Vargas, I come from the Johns Hopkins Bloomberg School of Public Health, and I will be talking about functional mediation analysis

How does the brain processes pain?

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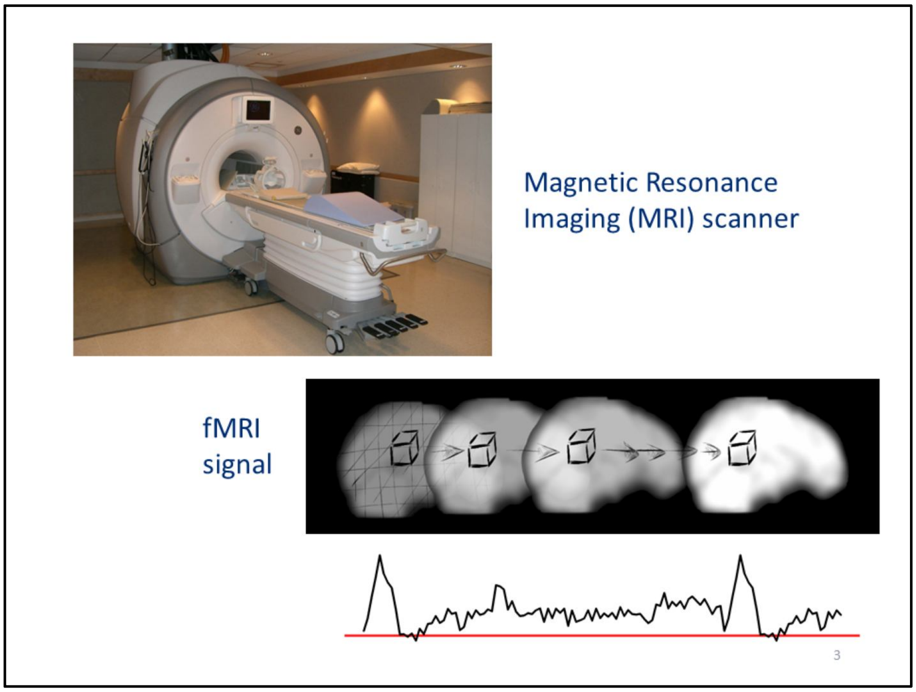
For today, our question is: how does the brain processes pain?



One way to learn what is going on in a person’s brain non-invasively is to use a magnetic resonance imaging scanner. We put a person inside the MRI scanner and measure different physical changes that happen when applying large magnetic fields. We can have a measure of brain activity that we can track over time. In order to do so, the machine “divides” the brain volume into small cubes, and tracks the signal across time. Therefore, we get a time series.

How does the brain process thermal pain?

How do different regions communicate in response to pain?

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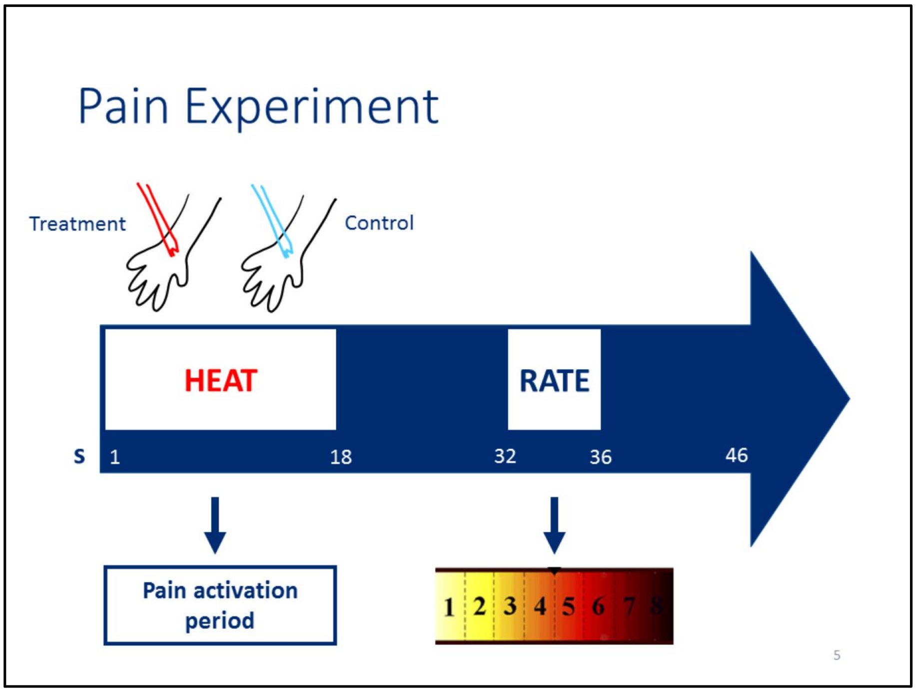
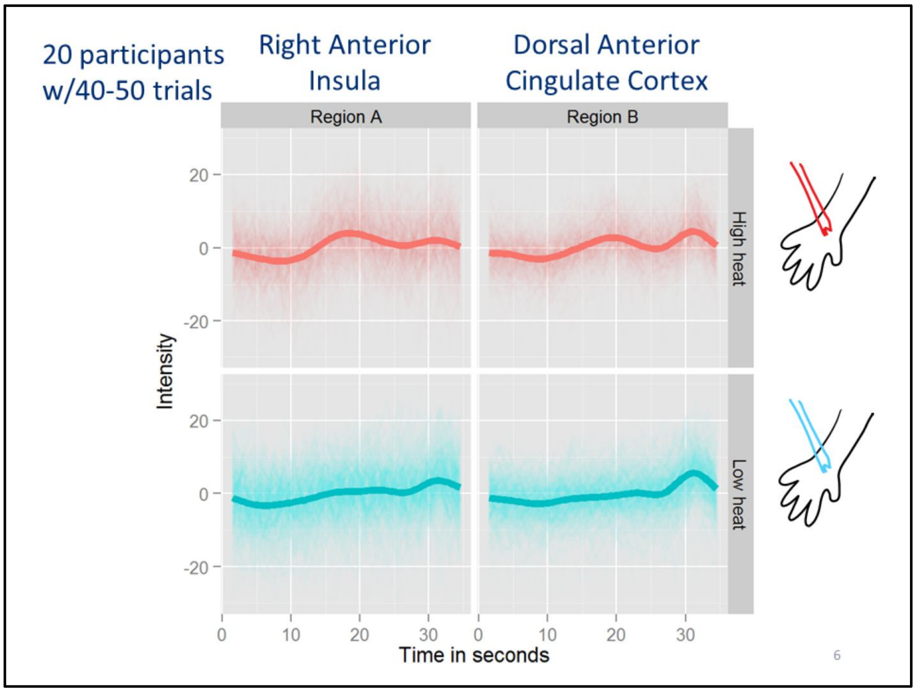
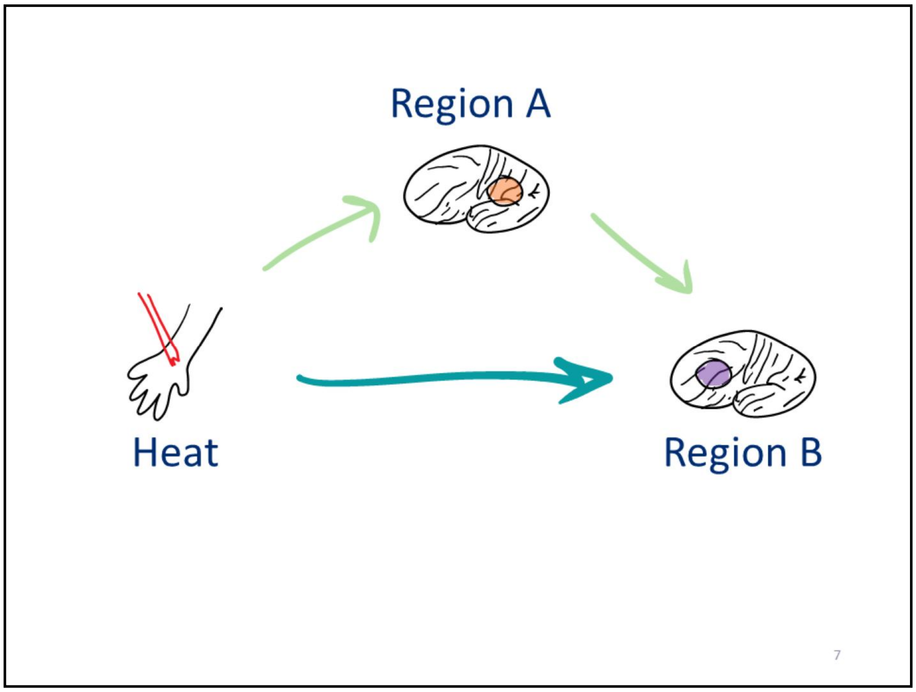
In order to learn about the pain process, we will focus on asking how two different brain regions communicate in response to pain



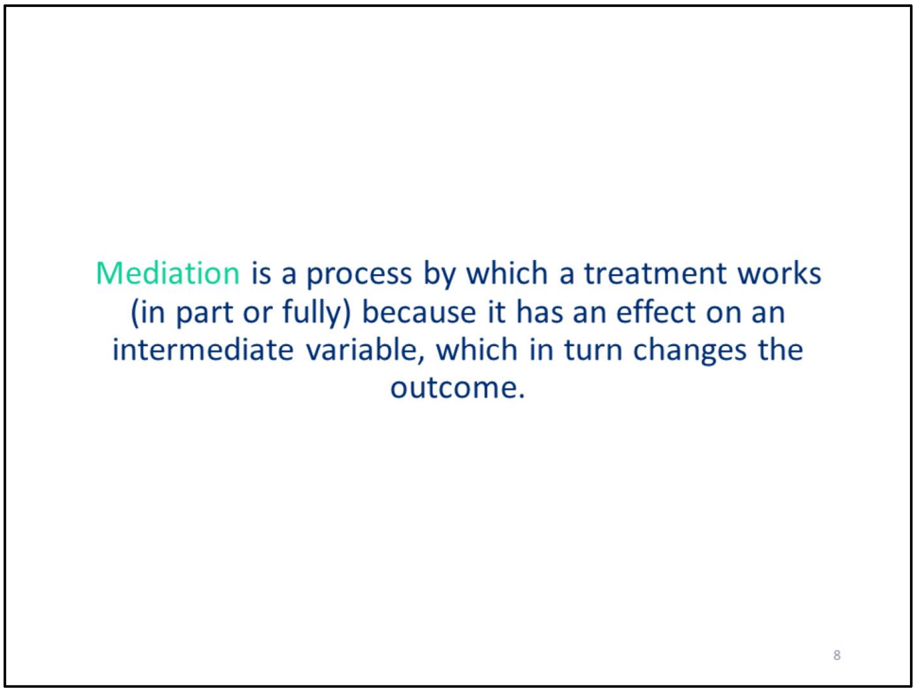
Here is an schematic of the pain experiment. People were put in the MRI scanner and for 18 seconds, their arm was touched with a small metal plate. The metal plate would be hot under treatment or warm under the control condition. Then, after some seconds, they were asked to rate the pain they felt using a continuous scale (with a nob).



This is the data that I have. I have 20 participants, each underwent 40 to 50 trials, and here I plot the time series, using a smooth function to show the mean. In the X axis we have time (in seconds), and on the Y-axis we have the intensity of the fMRI signal. The rows are separated into high and low heat, and in the columns we have the two regions that are of interest. The right anterior insula plays the role of region A, while the dorsal anterior cingulate cortex plays the role of region B. There is literature that informs us that events in Region A precede events in region B.



So, we have that the heat may be affecting region A and region B, then region A may also be affecting region B. So, if the heat makes changes in region A, then those changes may make further changes in region B



Mediation is a process in which a treatment is working, in part or fully, because it is changing an intermediate variable, which in turn changes the outcome

The intermediate variable is called a 'mediator'

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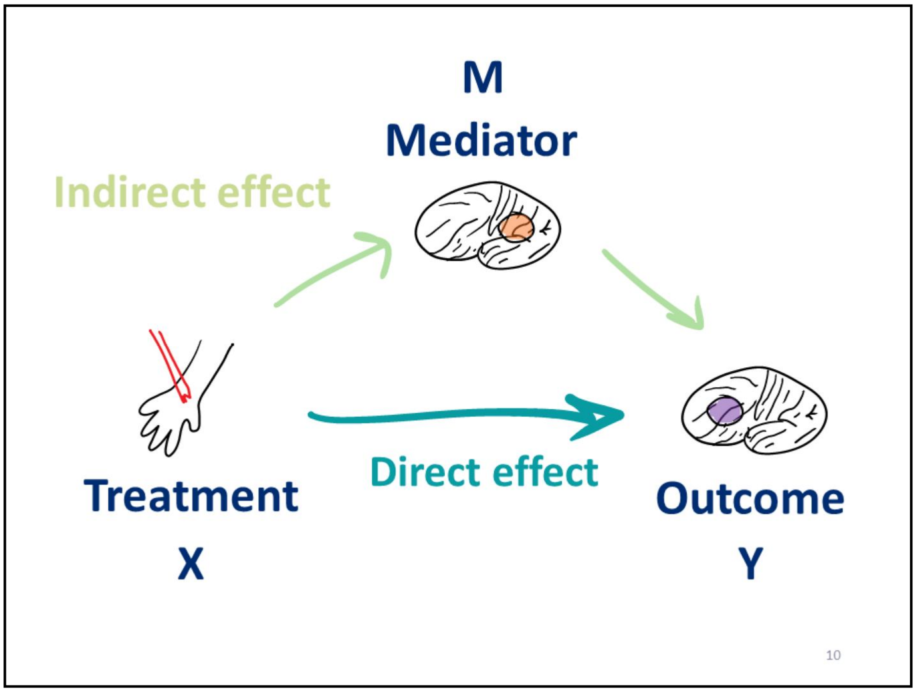
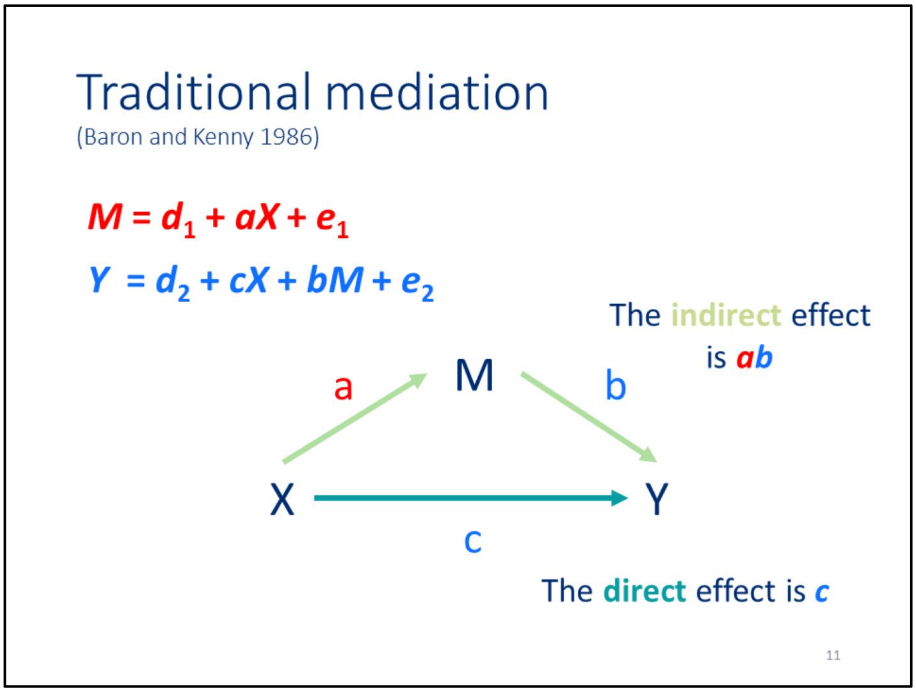
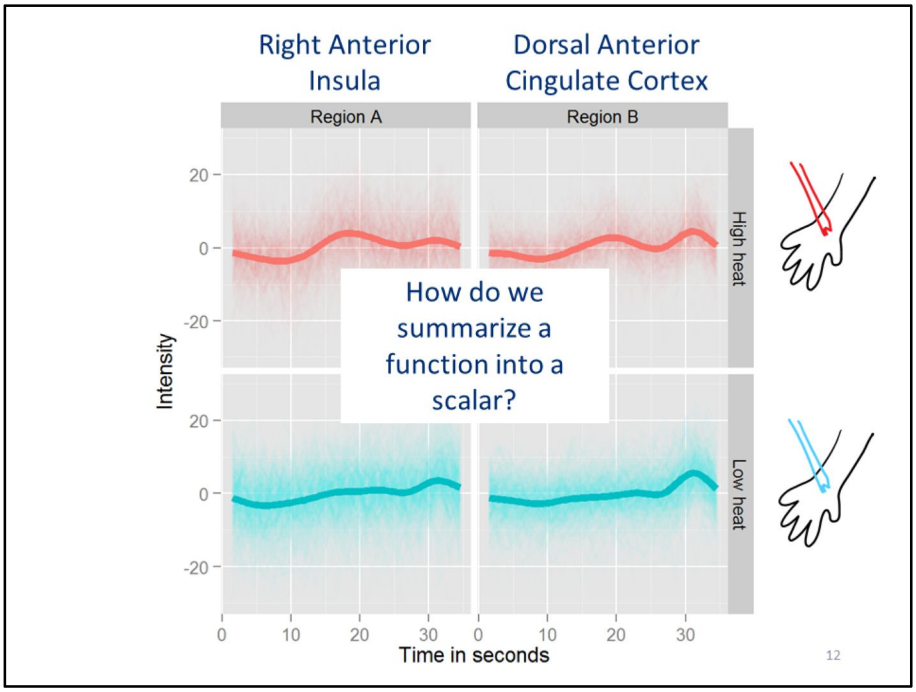
We call the intermediate variable a 'mediator'



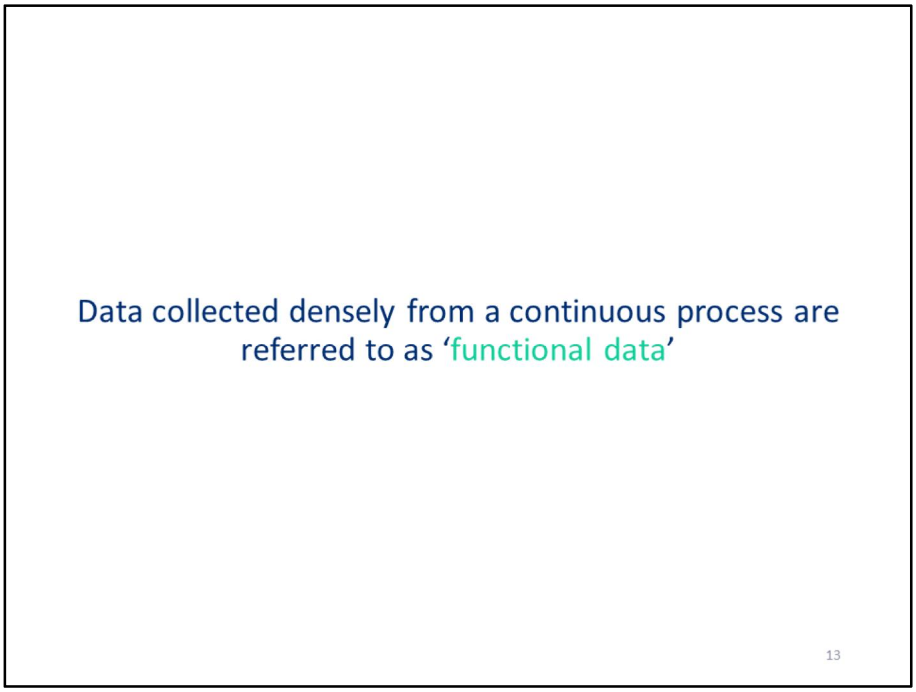
So, we have that the heat affects both region A and B, and the changes done in region A may affect region B as well. So the heat is our treatment, activation in region A is our mediator, and activation in region B is our outcome. The effect of the treatment that happens because it changed the mediator, which in turn changed the outcome, is called the indirect effect, while the effect of the treatment that doesn't involve changing the mediator is the direct effect



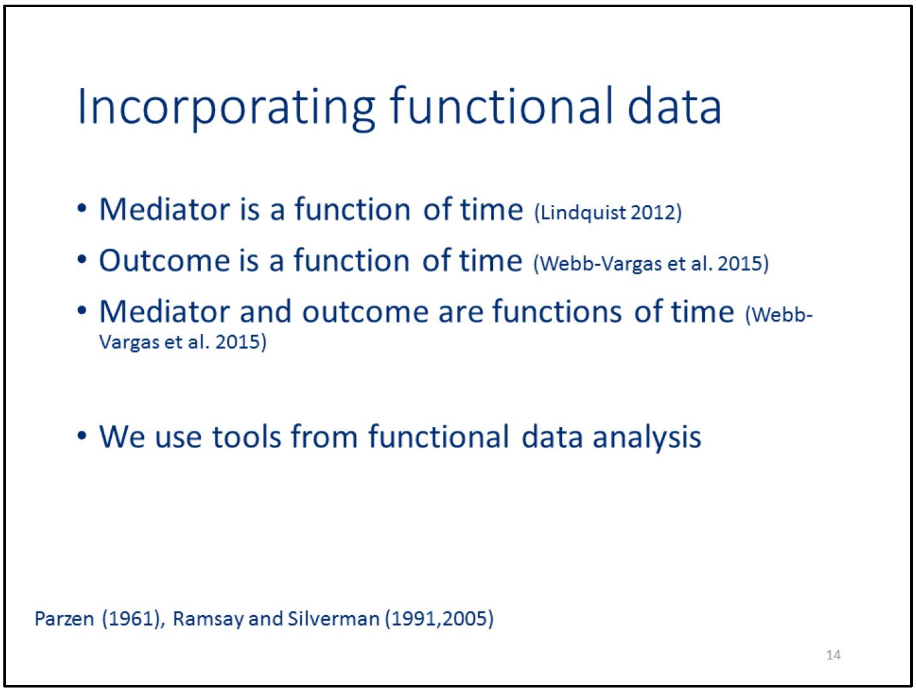
Traditional mediation addresses this with two models (or one jointly). We first pose a linear model to estimate the changes that the treatment X has on the mediator M (which is the a coefficient), then we pose a model for the effect of the treatment and mediator on the outcome. The coefficient b represents the effect of the mediator holding the treatment fixed, while coefficient c represents the effect of the treatment for a fixed level of the mediator. Here, the indirect effect is the effect of the mediator on the outcome (b) scaled by how much it changes due to the treatment (a)



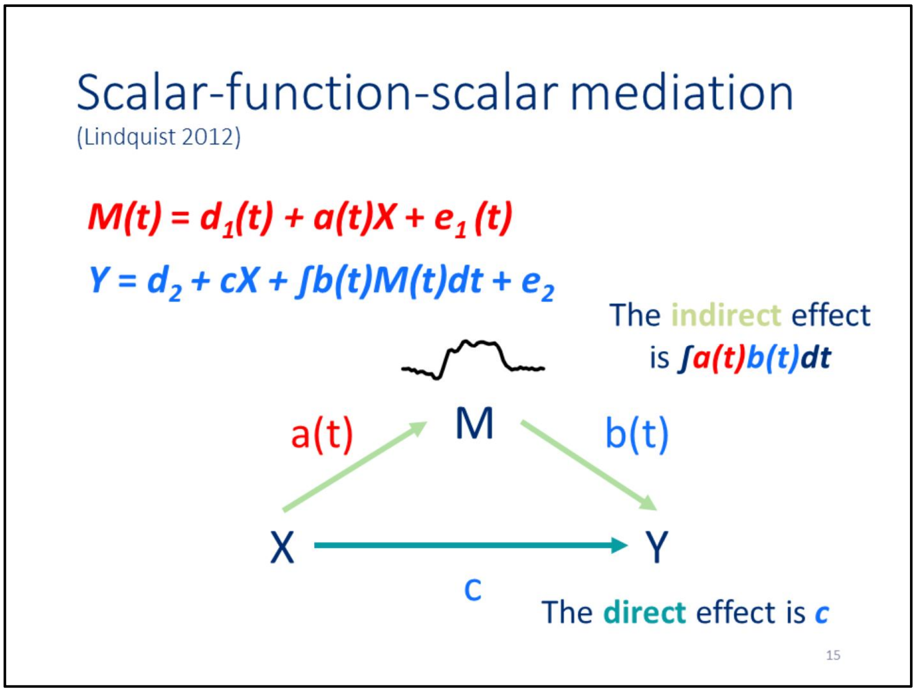
Going back to our problem. We have these time series, these functions of time. How do we summarize these into a scalar?



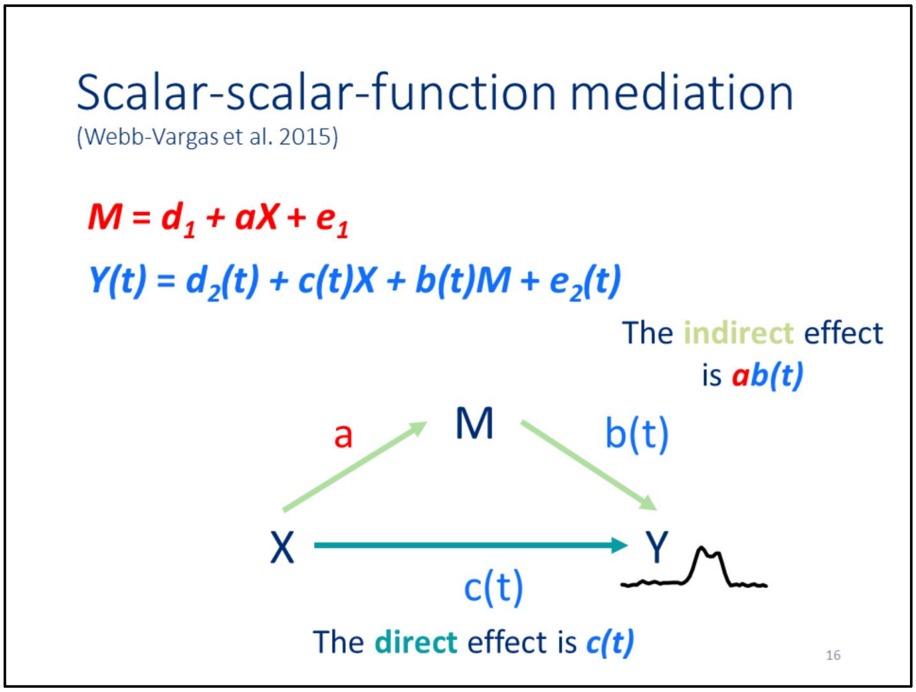
Data collected densely from a continuous process are referred to as ‘functional data’, as they can be functions of time or space.



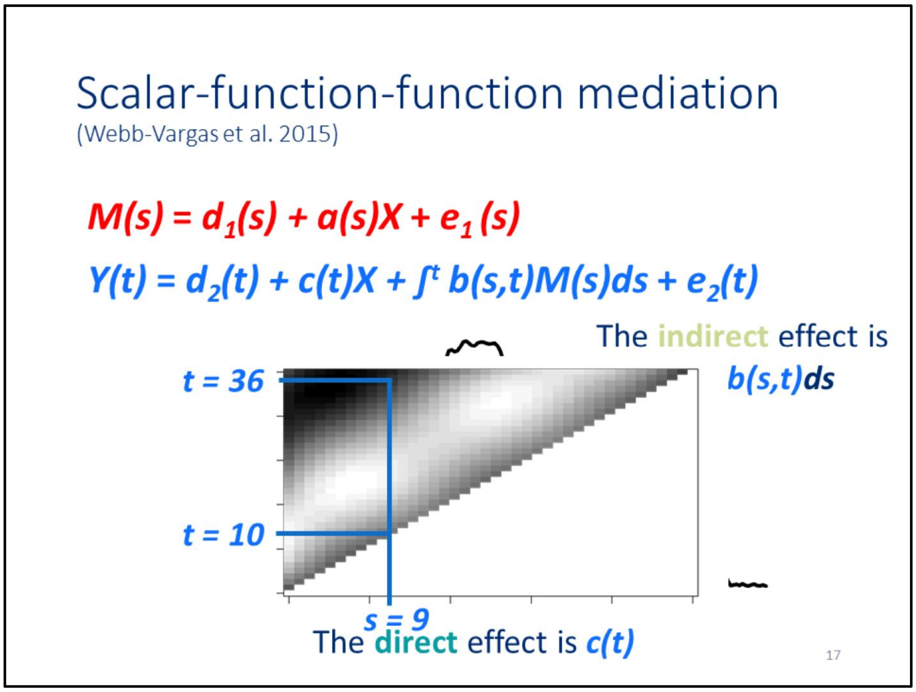
In order to incorporate functional variables in our mediation models, Lindquist used tools from data analysis to handle a functional mediator. My work extends this to having a functional outcome, and having both mediator and outcome as functions, like what we need today. Functional data analysis had some starts in the sixties, and James Ramsey and Bernard Silverman have made superb contributions and have brought it to more audiences.



So, what Linquist did is represented here. He defined a model at every point in time t for the mediator, so the effect of the treatment on the mediator is a function. Then, he summarized the effect of the mediator on a scalar outcome by taking a sum of the effect of the mediator on the outcome. Here, the effect of the mediator, the weights, are different at each time point. This looks like multiple regression, and the difference is that b is made to be a smooth function of time (the order of the covariates will matter, whereas in multiple linear regression it doesn't). Now, the indirect effect is the product of the a and b functions, and the direct effect is c.



The first extension I did was to include a functional outcome. Here, I use a linear model relating the scalar treatment and mediator, then use a functional model for the outcome. Here, the effect of the treatment on the mediator is a, and the effect of the mediator on the outcome at time t is b of t. Therefore, the indirect effect is a times b of t, and the direct effect is c of t. We have a direct and an indirect effect that are functions of time



This is the setup of our brain connectivity problem. We have a scalar treatment, a functional mediator and a functional outcome. We will basically be mixing the previous models. We define a functional model for the mediator as before. As we will have a different time scale for the mediator and the outcome, we use s for the mediator and t for the outcome. Then, a of s represents the effect of the treatment on the mediator. We now define another functional model, the one for the outcome. In this model, c of t represents the effect of the treatment for a fixed level of the mediator at time t, while the b function represents the effect of the mediator Here, we will summarize the effect of the mediator on the outcome by integrating the history of M up to the time t in consideration. The b coefficient is now a surface, with s on the x-axis and t on the y-axis. For example, it we look at the outcome at time 10, t is 10, and we will have a function of s that takes values from s equal 1 to s equal 9. Notice that the function changes for each time point of the outcome, so the weight that the first nine seconds of the mediator is different when we are looking at the outcome at time 36. Given these models, our mediation effects are both functions of time and the indirect effect is an integral, just like before, but now we are collapsing what happens over the s domain, and the direct effect is just c of t.

Estimation

- Outcome model (scalar-on-function and function-on-function)
  - Use functional generalized additive models (McLean et al., 2014; Ivanescu et al., 2014)
- Mediator model (function-on-scalar)
  - Linear models with smoothing (Fan and Zhang, 2000)

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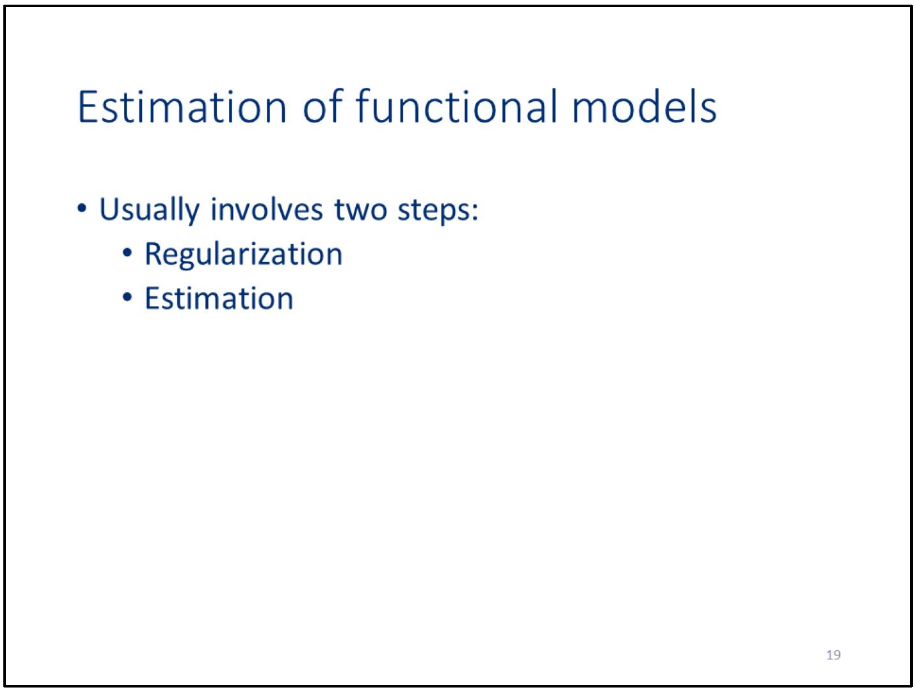
The models with functional outcomes can be written as functional generalized additive models, and there are tools to fit these, while the model for a functional mediator can be estimated very quickly by using linear models at each time point and then smoothing over them



In more detail, estimation of functional parameters typically uses two steps, or some similar form

Regularization

- Project onto a space defined by known basis functions
- Basis are known functions of time
  - B-Splines
  - Wavelets
  - Functional principal components

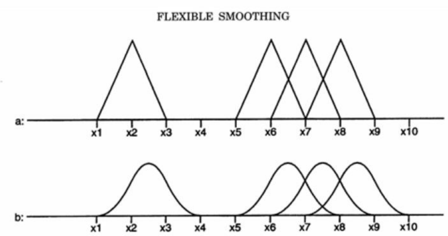
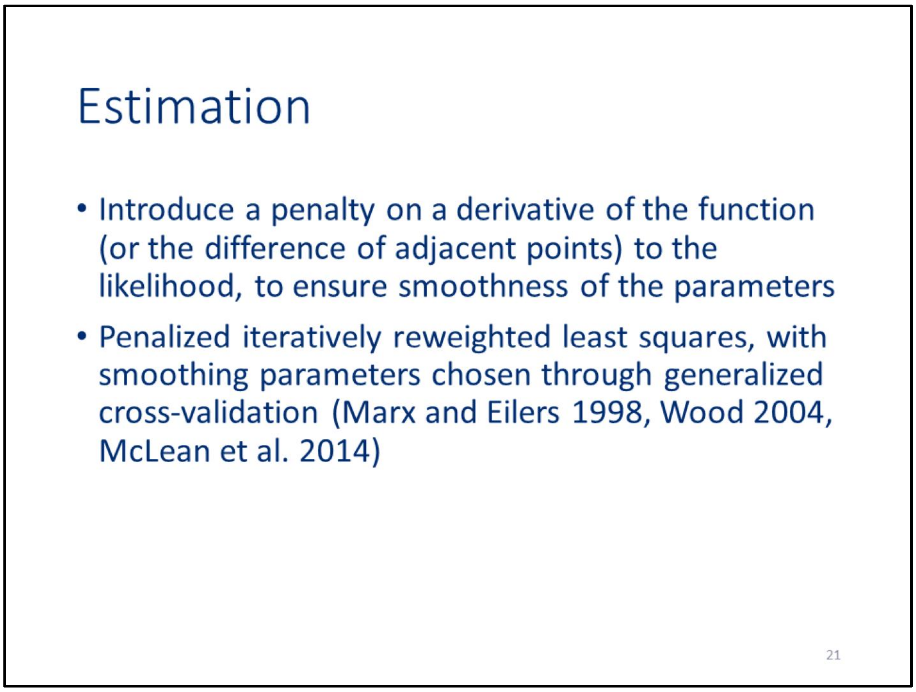


FIG. 1. *Illustrations of one isolated B-spline and several overlapping ones (a) degree 1; (b) degree 2.*

Eilers & Marx 1996

In the regularization step, the problem of having to define a function at an infinite number of time points can be solved by deconstructing the function into a sum of know mathematical functions. This is what we mean when we say we project onto the space defined by these known mathematical functions. These can be b-splines, wavelets, or functional principal components. In the figure, I show linear splines and quadratic splines, and we can use these as building blocks to construct our function to estimate, or to decompose our observations.



Once we have this representation, we use it to define a likelihood, and we add a penalty to ensure that the function is smooth, like penalizing the derivative of the function, or the difference between two adjacent points.

Then, we do penalized iteratively reweighted least squares, and choose the smoothing or penalization parameters using cross validation. The smoothing parameters are crucial for the identification of the estimates in the model.

Statistical Inference

- The product of functional coefficients has a complex variance structure
- We use resampling methods (bootstrap) for inference for mediated effects

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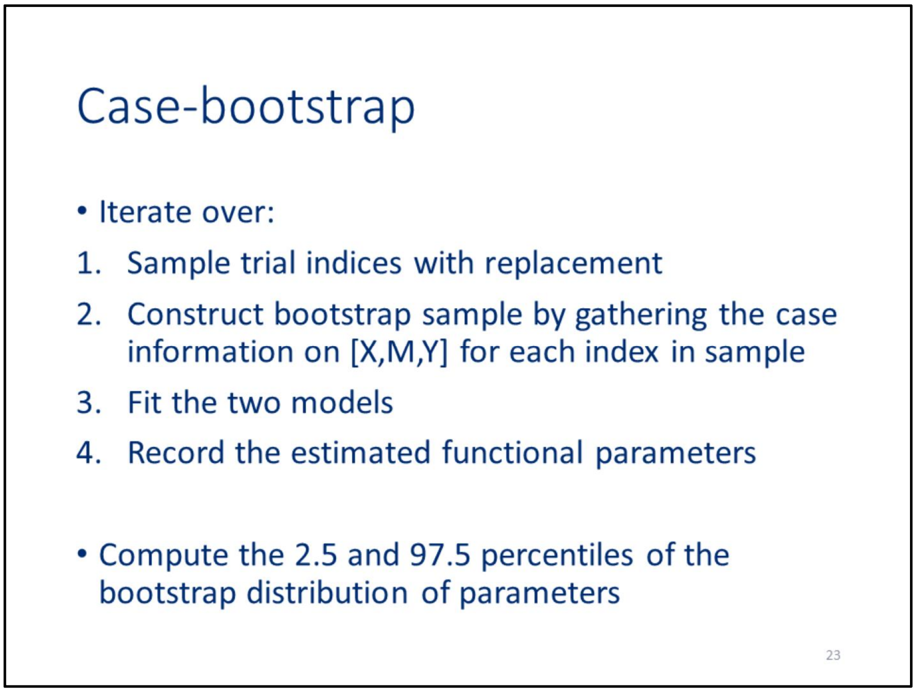
Finally, to do inference, we use resampling methods, in this case, the bootstrap



To perform the bootstrap we will do many iterations of. 1. sample trial indices with replacement. Then go to the sample and get the information associated with those indices, the whole information for that case (the treatment, and the two time series). We fit the models, and record our estimated parameters. Then, we compute the 2.5 and 97.5 percentiles of the bootstrap distribution

How do brain regions communicate in response to pain?

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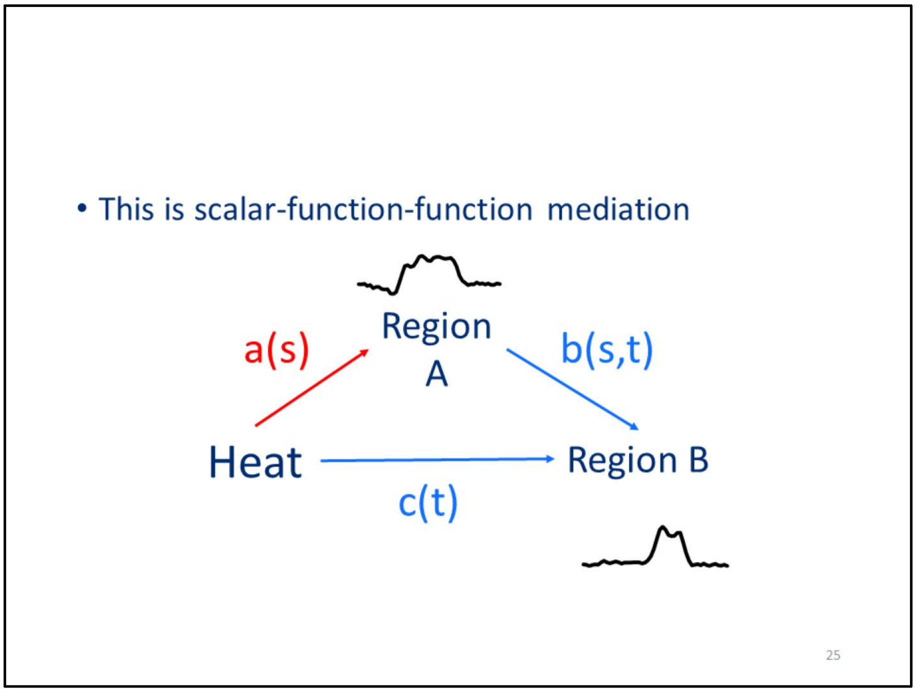
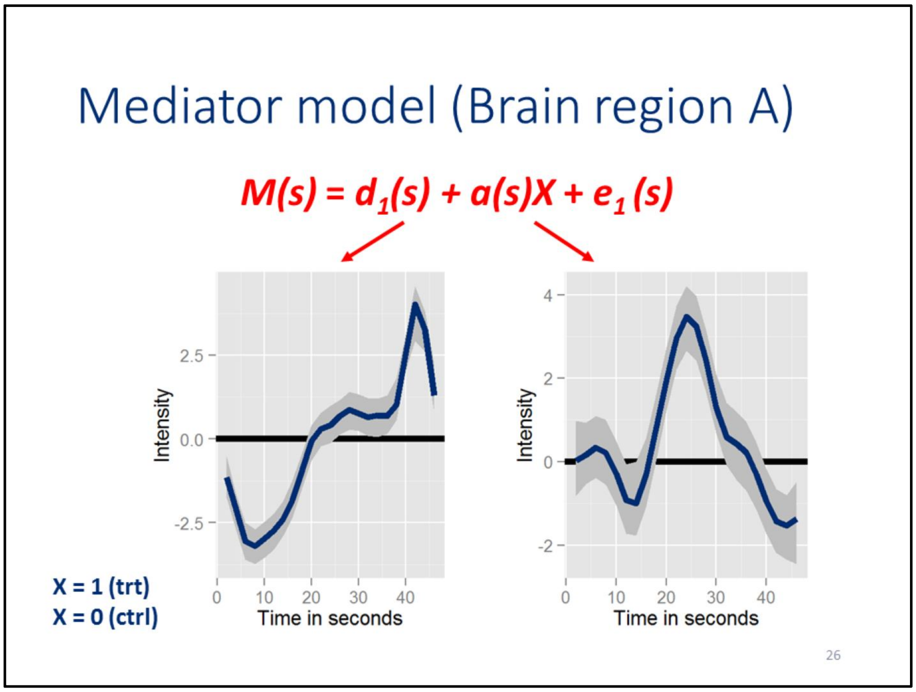
We return to our question of interest, how do brain regions communicate in response to pain

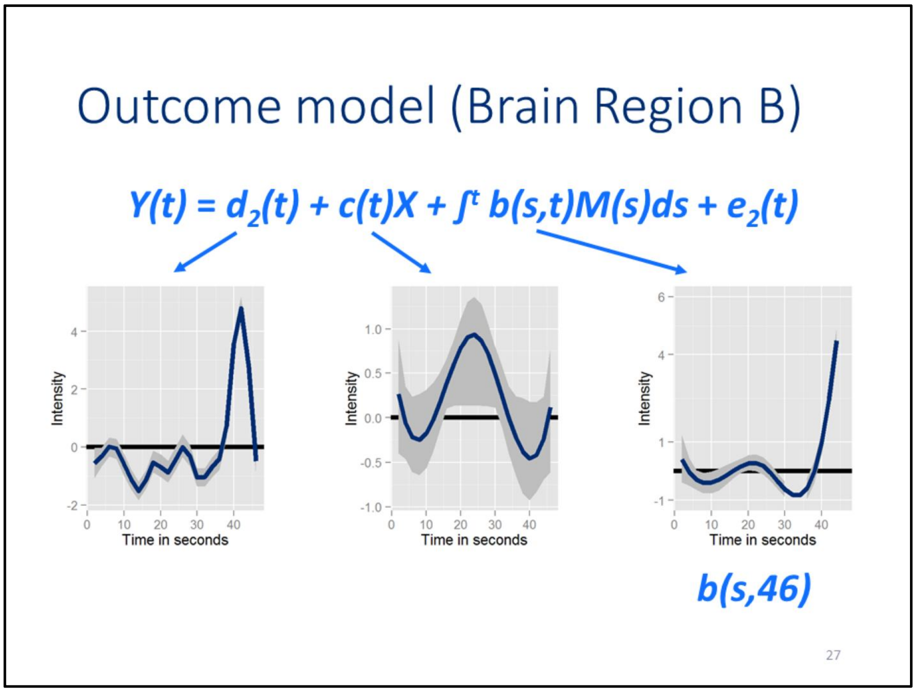


Our problem can be represented by scalar-function-function mediation. Here, the heat is the treatment, activation in region A is the mediator, and activation in region B is the outcome. We are interested in the a, b and c functions



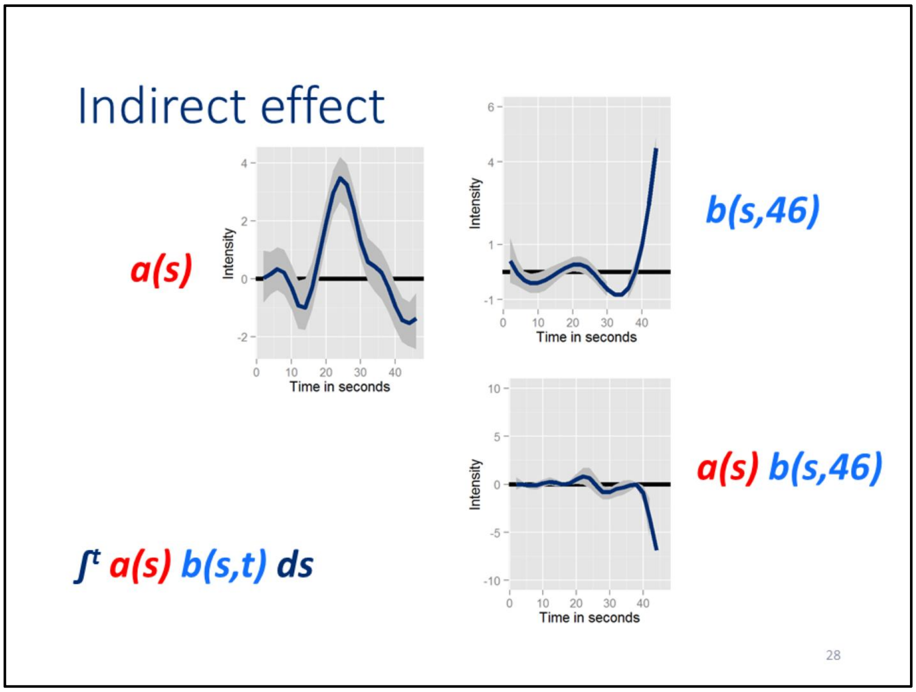
Here are the results from the mediator model for brain region A. Here, X is zero under control and one under treatment. Then, d1 represents the mean activation in brain region A under warm touch, whereas the a function represents the change that we observe among trials under hot touch. One big drawback of fMRI data is that our measure of brain activation is lagged and slow, that is, the neurons can be firing for an instant, and the brain signal will take about 10 seconds to start, then rise, then return. This is what we see in the a function.

For the mediator model, I used 15 cubic b-splines with penalty on the second derivative

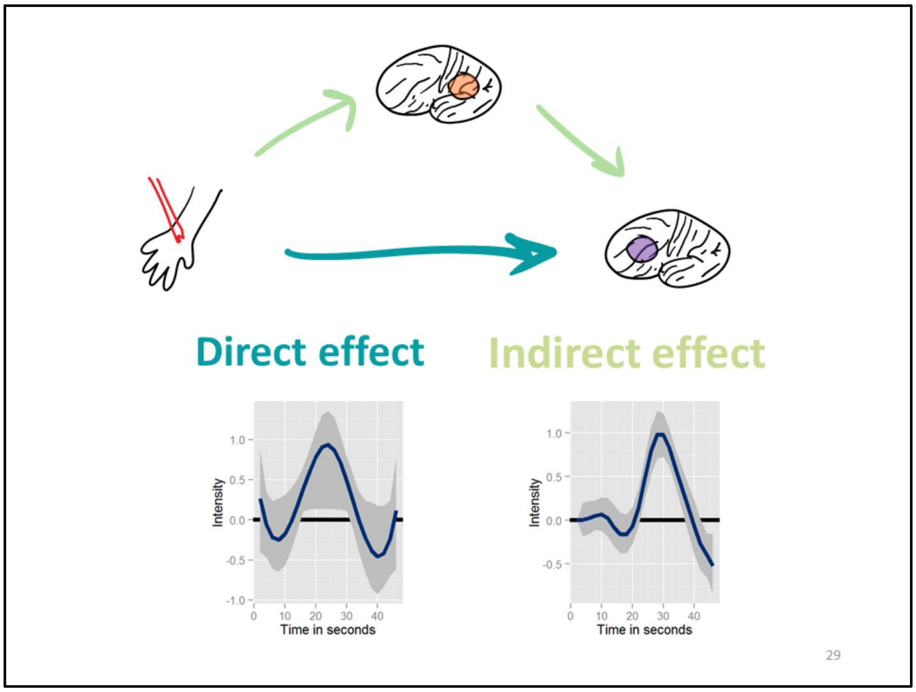


As for the outcome model for brain region B. The d2 and c functions look similar to the previous one, but these are a bit different. These functions are the residual variation in Y once we fix the brain activation in the mediator. In order to see better what the beta surface is, I present slices for particular timepoints of Y. We can see how the most recent history in activation in region A is associated with a higher response in activation in region B.

For the intercept, I used 20 cubic P-splines with penalty in the second order derivative. For the effect of the treatment (X) on the outcome, I used five cubic P-splines with penalty in the second derivative. For the function-on-function coefficient, I used a tensor product smooth using 5 cubic P-splines with second derivative penalties for both margins.



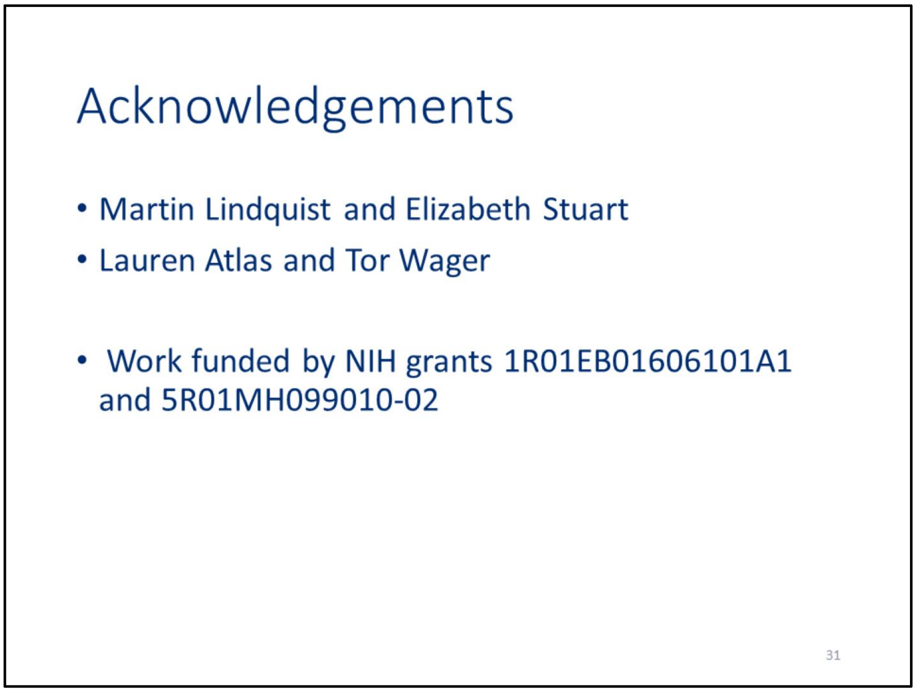
Now, let's construct the indirect effect. We take the a function of the changes in activation in region A associated with the treatment, then the effect of region A on region B, and here is how it looks. We will integrate over S to get the indirect effect at a particular time point



In summary, the direct effect has a peak at time 25, while the indirect effect has a peak at around time 30. Moreover, the effect of the heat on brain region B (holding the mediator constant) is very similar to the effect of heat on region A. We can see that they are being activated in a similar manner, but the indirect effect is showing that, beyond what the treatment is doing, region A has a lot to say about what happens later in region B.

Assumptions

- Biological
  - The BOLD signal captures brain activation
  - There is no feedback (Brain Region B doesn’t influence region A)
  - There is no measurement error in the BOLD signal
- Model
  - There are no confounders of trt-med, trt-out, med-out relations
  - There are no post-treatment confounders of med-out relation
  - The relations are linear at each time point
  - The effect of the mediator on outcome is the same for trials under trt and under ctrl (no trt-med interaction)
- Estimation
  - The number of basis components is correct
  - The smoothing penalty is correct



I thank my advisors Martin Lindquist and Elizabeth Stuart, the people who ran the brain connectivity pain trial, and the NIH for supporting my work.

Thank you!