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# Using Machine-Learning to Diagnose Perception, Feeling, and Action: A Study of Neuroimaging, Psychometric, and Insurance Claims Data

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Neuroscience

by

Donald Albert Vaughn Jr.

2017

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ABSTRACT OF THE DISSERTATION

Using Machine-Learning to Diagnose Perception, Feeling, and Action:
A Study of Neuroimaging, Psychometric, and Insurance Claims Data

by

Donald Albert Vaughn Jr.
Doctor of Philosophy in Neuroscience
University of California, Los Angeles, 2017
Professor Mark S. Cohen, Chair

I explored the capability of multivariate machine learning on low-signal and bioinformatic data to distinguish between different perceptual, emotional, and behavioral outcomes. In Chapter II, I designed and executed an experiment to evoke differences in empathy on the basis of religious identities as well as on general notions of ingroup and outgroup. I discovered that the act of simply learning about another's religious identity correlated with a detectable modulation in one's brain activity—most notably in regions related to empathy and sympathy—which identified subjects' religious ingroups from outgroups with 70% accuracy. In Chapter III, I used multimodal data to distinguish between control participants and patients with one of two body-image disorders: anorexia nervosa and body dysmorphic disorder. These data included psychometric scales of obsessive-compulsive behaviors, depression, anxiety, and insight; white matter connectivity patterns; and neural haemodynamic activity. My models achieved 72% accuracy in

distinguishing healthy controls from patients with anorexia nervosa or body dysmorphic disorder, and 76% accuracy in distinguishing patients with anorexia nervosa from those with body dysmorphic disorder. In Chapter IV, I extended these techniques to insurance claims data to predict the actions of patients and doctors. I discovered that the pattern of care delivered by doctors predicted the hospitalizations and use of biologic drugs in patients with inflammatory bowel disease. My diagnostic model may be used by healthcare alongside various interventions to reduce hospitalizations, decrease expenditures of insurance companies, and improve patient quality of life.

The dissertation of Donald Albert Vaughn Jr. is approved.

Jamie Feusner

Marco Iacoboni

Daniel Hommes

Mark S. Cohen, Committee Chair

University of California, Los Angeles

2017

Dedicated to Mom, Dad, David, Mark, and Jamie

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# NOMENCLATURE

| | |
|---|---|
| 5-ASA | 5-Aminosalicylic Acid |
| ACC | Anterior Cingulate Cortex |
| ADA | Adalimumab |
| AI | Anterior Insula |
| AN | Anorexia Nervosa |
| ANN | Artificial Neural Network |
| AR | Autoregressive |
| AUC | Area Under the Curve |
| AUC-ROC | Area Under the ROC Curve |
| AUC-PR | Area Under the PR Curve |
| BABS | Brown Assessment of Beliefs Scale |
| BBR | Boundary-Based Registration |
| BDD | Body Dysmorphic Disorder |
| BEES | Balanced Emotional Empathy Scale |
| BET | Brain Extraction Tool |
| BMI | Body Mass Index |
| BOLD | Blood-Oxygen-Level Dependent |
| CBC | Complete Blood Count |
| CD | Crohn's Disease |
| CPL | Characteristic Path Length |
| CPT | Current Procedural Terminology |
| CRP | C-Reactive Protein |
| CT | Computed Tomography |
| CTL | Control |
| CTZ | Certolizumab |
| DARPA | Defense Advanced Research Projects Agency |
| DRG | Diagnosis- Related Group |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DTI | Diffusor Tensor Imaging |
| ED | Emergency Department |
| EEG | Electroencephalography |
| EPV | Events per Explanatory Variable |
| ESR | Erythrocyte Sedimentation Rate |
| FEAT | fMRI Expert Analysis Tool |
| FLAME | FEAT Mixed Effects Modeling |
| FILM | FMRIB's Improved Linear Model |
| FLIRT | FMRIB's Linear Image Registration Tool |
| fMRI | Functional Magnetic Resonance Imaging |

| | |
|---|---|
| FMRIB | Oxford Centre for Functional MRI of the Brain |
| FNIRT | FMIRB's Non-linear Image Registration Tool |
| fROI | Functional network ROI |
| FSL | FMRIB's Software Library |
| FWHM | Full Width at Half-Minimum |
| GE | Gastroenterology/Gastroenterologist |
| GLM | General Linear Model |
| HAM-A | Hamilton Anxiety Rating Scale |
| HDRS | Hamilton Depression Rating Scale |
| IBD | Inflammatory Bowel Disease |
| IC | Independent Component |
| ICA | Independent Components Analysis |
| ICA-AROMA | ICA-based Automatic Removal of Motion Artifacts |
| ICD | International Classification of Disease |
| ICN | Independent Component Network |
| IFX | Infliximab |
| IRB | Institutional Review Board |
| ITI | Inter-Trial Interval |
| LatDA | Latent Dirichlet Allocation |
| LOR | Log Odds Ratio |
| MADRS | Montgomery Asberg Depression Scale |
| MATLAB | Matrix Laboratory (Mathworks, Inc.) |
| MCFLIRT | Motion-Correction FLIRT |
| MELODIC | Multivariate Exploratory Linear Optimized Decomposition into Independent Components |
| MNI | Montreal Neurological Institute |
| mPFC | Medial Prefrontal Cortex |
| MP-RAGE | Magnetization Prepared Rapid Acquisition Gradient Echo |
| MRI | Magnetic Resonance Imaging |
| MTX | Methotrexate |
| NAT | Natalizumab |
| NMF | Non-negative Matrix Factorization |
| OR | Odds Ratio |
| PCA | Principal Components Analysis |
| PE | Parameter Estimate |
| PET | Positron Emission Tomography |
| PPV | Positive Predictive Value |
| PR | Precision-Recall |
| ROC | Receiver Operator Characteristic |
| ROI | Region of Interest |

| | |
|---|---|
| SD | Standard Deviation |
| SEM | Standard Error of the Mean |
| SPM | Statistical Parametric Mapping |
| SVM | Support Vector Machine |
| TE | Echo Time |
| TMS | Transcranial Magnetic Stimulation |
| TNF | Tumor Necrosis Factor |
| TR | Repetition Time |
| UC | Ulcerative Colitis |
| UCLA | University of California - Los Angeles |
| YBC-EDS | Yale-Brown-Cornell Eating Disorder Scale |
| YBOCS | Yale-Brown Obsessive Compulsive Scale |

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Chapter III is a version of “Predicting diagnoses of anorexia nervosa and body dysmorphic disorder with multimodal neuroimaging and psychometric data,” a manuscript in preparation with authors Don Vaughn, Gigi Cheng, Teena Moody, Aifeng Zhang, Alex Leow, Michael Strober, Mark Cohen, and Jamie Feusner.

Chapter IV is a version of “Using insurance claims to predict and prevent hospitalizations and ineffective use of biologics in patients with inflammatory bowel disease,” a manuscript in preparation with authors Don Vaughn, Welmoed K. van Deen, Wesley T. Kerr, Travis R. Meyer, Andrea Bertozzi, Daniel W. Hommes, Mark S. Cohen.

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## BIOSKETCH

Don has a BA in economics from Stanford. Don has a BS in physics from Stanford. Don worked in David Eagleman's lab at Baylor College of Medicine prior to his Ph.D.

## Chapter I - Introduction

I conducted my research at UCLA under the mentorship of Dr. Mark Cohen. During this time, I worked on a number of projects related to the functional interpretation of haemodynamics, including functional near-infrared spectroscopy, bias introduced into functional magnetic resonance imaging (MRI) by compressive sensing reconstruction, and classification of attention states using functional MRI (fMRI). While working on classifying attention, I began to comprehend the major role that machine learning will play in the future of neuroscience and medicine. I avoid saying that you ***are*** your brain because so far, we have made correlative observations with regard to consciousness only. It is eminently clear, however, that you ***need*** your brain (at least for now). If you lose the pinky-finger-sized piece of cortex called the hippocampus, the brain cannot form episodic memories. If you drink a lot of alcohol, your saccades will be jerky; your volition does not seem to be able to influence the binding of ethanol to neurotransmitter receptors. A change in the brain is reflected by a change in function. As far as neuroscientists can tell, the converse is also true: a change in function is reflected by a change in the brain. This observation is the fundamental motivation behind my thesis: namely, we can employ machine learning on differences in brain function and structure to diagnose various human conditions in novel and useful ways.

Here, I present my work using linear classifiers to diagnose how we perceive, feel, and act. I used the term diagnosis in its more general definition: “to analyze the cause or nature of” human conditions (Merriam-Webster and Inc 1997). In this vein, I explored the capability of multivariate machine learning on low-signal, bioinformatic data to

distinguish between different perceptual, emotional, and behavioral outcomes. I made contributions in three categories: sensory input, emotional computation, and motor output. In the first two categories, I used neuroimaging and psychometric data; in the last case, I stretched diagnostic capabilities further by using *non*-biological data to predict both the medical outcomes of patients and the behavior of doctors.

In Chapter II, I designed and executed an experiment to evoke differences in empathy on the basis of religious identities. I extended this investigation and model beyond religion to the general notions of *ingroup* and *outgroup*. I discovered that the act of simply learning of another's religious identity, without ever meeting the person or gathering additional information, correlated with a detectable modulation in one's brain activity, most notably in regions related to empathy and sympathy. Although my manipulation of religious labeling was a small perturbation in information, it produced neural changes sufficiently robust to distinguish between each participant's perceptions from *ingroup* members versus *outgroup* members. My model also generalized to newly formed arbitrary affiliations as well as modulation to the status of existing religious outgroups. This experiment showed that neuroimaging can distinguish the status of social affiliations *within* a participant. This classification was motivated by DARPA's funding for this study to support the development of a model to diagnose large biases in empathy.

In Chapter III, I used multimodal data to distinguish between control (CTL) participants and patient participants with one of the two body-image disorders: anorexia nervosa

(AN) and body dysmorphic disorder (BDD). These data included psychometric scales of obsessive-compulsive behaviors, depression, anxiety, and insight; white matter connectivity patterns; and neural haemodynamic activity. The results supported the hypothesis that differences in visual processing accounted at least partially for the differences between patients with AN / BDD and neurotypical CTL participants. In the clinical setting, participants with AN and BDD often present with many similarities, making it difficult to diagnose AN versus BDD with certainty (Hollander et al. 1992; Ruffolo et al. 2006). Given their symptomatic overlap, they are almost certainly not mutually exclusive diseases. In the context of this diagnostic challenge, I created a two-part classification model to assess the degree of overlap. My models achieve 72% accuracy distinguishing CTL participants from patients with 76% accuracy distinguishing patients with AN from those with BDD. With clinical validation, this tool may be useful in the clinical management of participants with AN and BDD.

In Chapter IV, I used the aforementioned techniques to predict the actions of patients and doctors. My classification challenge here differed fundamentally from the previous chapters because my data were not related to neuroimaging but to insurance claims. These insurance claims had little biological information. In the data analysis, I used many variables (e.g. that the occurrence of a test or use of a medication did not convey the patient's *outcomes* from the test or use of medication). For example, the data indicated that an x-ray was performed, but not how it was interpreted by the radiologist. Similarly, the number of Inflammatory Bowel Disease (IBD)-related claims submitted by a member in a given year was known, but it was unclear if these claims were warranted

by the severity of medical conditions. Despite this ostensible lack of biological information, the data in aggregate correlated with an important latent variable—the diagnostic ability and methodology of clinicians. To some degree, the tests and treatment provided to a patient reflected the diagnostic ability of the doctors. I discovered that the pattern of care delivered by doctors, in concert with insurance company protocols, predicted the hospitalizations of and use of biologic drugs in patients with IBD. My diagnostic model may be used by healthcare to couple with various interventions to reduce hospitalizations, reduce expenditures of insurance companies, and improve quality of life among patients.

Next, I will introduce a few terms and methodologies that are fundamental to this study.

### 1.1 Neuroimaging

To make inferences about brain structure and function, it is helpful to measure brain activity. Many well-established methods use blood flow, such as functional near-infrared spectroscopy (Irani et al. 2007), MRI (Turner 2003), metabolic activity via PET scan (Turner 2003), and electrical activity using electroencephalography (EEG), electrocorticography, local field potential, and voltage clamp (Bunce et al. 2006; Villringer 1997; Mulert et al. 2004). In this thesis, I used an fMRI metric based on blood oxygenation level-dependent (BOLD) signals, which measures the ratio of oxyhemoglobin to deoxyhemoglobin by exploiting their differences in magnetic susceptibility (Kwong et al. 1992; Ogawa et al. 1990).

We used neuroimaging software, such as Statistical Parametric Mapping (SPM) and Oxford Centre for Functional MRI of the Brain Software Library (FMRIB Software Library, or FSL), to convolve the timing of events in the experiment with the empirically observed time course of the BOLD signals to generate a model of blood flow. We then used the magnitude, timing, and noise of these fits, called parameter estimates (PEs), to estimate the strength of response to each event or effect. We iterated this method across all brain-volume elements (voxels) that were collected in the neuroimaging. The method was both univariate (i.e. the response in each voxel is assumed independent from its neighbors) and linear (i.e. the haemodynamic response is from the overlap of two stimuli). We assumed that they summed together rather than interacting. This framework for processing data is known as the general linear model (GLM).

### 1.2 Classification

Classifiers are mathematical models that discriminate between different groups. In my work, this involved discriminating between either different groups of participants (e.g. participants diagnosed with AN versus BDD) or different outcomes within a participant (e.g. being stabbed with a needle versus touched with a cotton-swab). All classification methods were applied on a set of instances (examples), each with one or more features (variables). For example, when classifying participants diagnosed with AN from those with BDD, each participant was an instance; their age, gender, and white matter density were all features. Although classifiers can be applied to discriminate between multiple groups, my work utilized binary classification as two classes. To define the notion of "group" mathematically, I assigned one group the label of 0 and another group the label of 1.

Scholars used multiple methods to accomplish classification, including logistic regression, support vector machine (SVM), neural network, and decision tree (Westreich, Lessler, and Funk 2010; Dreiseitl and Ohno-Machado 2002). This study used the first two methods (Dreiseitl and Ohno-Machado 2002). A logistic regression is a process utilizing all available data points and assuming that the data will conform to a particular distribution and corresponding probabilistic interpretation (Iyer, Hosmer, and Lemeshow 1991), whereas an SVM is a process using only a few important points as the support vectors and making no assumptions about the distribution of the data beyond these points (Suykens, Vandewalle, and De Moor 2001). In other words, an SVM (Shawe-Taylor and Sun 2011) indicates the hyperplane that best divides the data. I clarify “best” in the Measuring distance section below. A logistic regression is better suited for a probabilistic interpretation, while an SVM is more appropriate when the data distribution is unknown (Boyd, Parikh, and Chu 2011).

I chose to use linear classification schemes rather than artificial neural networks (ANNs), which are, as suggested by the name, mathematical imitations of neurons . Each “neuron” receives input from multiple other neurons in the network and then computes the sum of inputs to send a signal with some probability to all of its downstream neurons (Yegnanarayana 2009). ANNs are applied successfully in computer vision (Ciresan, Meier, and Schmidhuber 2012), Google deep learning (Schmidhuber 2015), particle detection in high-energy physics (Baldi, Sadowski, and Whiteson 2014), handwriting recognition (Voigtlaender, Doetsch, and Ney 2016), and

prostheses (Li et al. 2010). Unfortunately, sufficient training of ANNs requires a large amount of input data (Hippert, Pedreira, and Souza 2001). Additionally, as a result of their interconnected design, ANNs are highly nonlinear, so it is difficult to interpret the influence of a single feature in the dataset (Dreiseitl and Ohno-Machado 2002). Since my three projects did not have sufficient examples to train ANNs, and because I was interested in interpreting the relative importance of each feature, I chose linear classification schemes instead.

### 1.2.1 Signal detection theory curves

We needed a concrete method to assess and compare the performances of classification models. One model may be sufficient to perform more accurately than multiple models, but if we place unequal value on the performance of each model with one particular outcome, multiple models will be ideal. For example, in Chapter IV I created a model to predict whether a patient will be admitted to the hospital. Considering the cost of inaccurate predictions, the cost of predicting incorrectly that someone *will* go to the hospital involves follow-up tests and office visits only. The cost of predicting incorrectly that someone will *not* go the hospital is far greater due to thousands of dollars in medical bills, surgeries, and quality-of-life disruption. Therefore, the large financial and medical impact of a hospitalization necessitates that diagnostic tests are biased in favor of predicting a hospitalization.

For the cases in which we valued each outcome equally, we measured performance by the receiver operator characteristic (ROC) that true-positives as a fraction of instances of class 1 meant identified correctly and false-positives as a fraction of instances of

class 0 meant identified incorrectly (Swets 2014). In other words, ROC measures sensitivity vs specificity. We used the area under curve (AUC) of the ROC (AUC-ROC) as a comparison metric. Despite concerns about its noisiness and application to small sample sizes (Hanczar et al. 2010; Lobo and Jiménez- Valverde 2008; Hand 2009), the machine-learning community often uses AUC-ROC for model comparison (Hanley and McNeil 1983). Perfect classifiers have 100% sensitivity and specificity corresponding to an AUC of 100%, while chance classifiers have a mean AUC of 50%.

For the cases in which we valued the outcomes of class 1 more than outcomes of class 0, we measured the performance by the precision-recall (PR) curve (Fawcett 2006) as precision versus recall, another name for sensitivity. Precision, also known as positive predictive value (PPV), was calculated as the instances of class 1 that were identified correctly divided by the number of times that the model predicted class 1. Perfect classifiers had an area under the PR curve (AUC-PR) of 100%, whereas chance classifiers had a mean AUC-PR at the frequency of class 1 in the dataset. We used AUC-ROC in two cases and AUC-PR in a third case because optimizing in ROC space does not guarantee optimal model performance in PR space (Davis and Goadrich 2006).

### 1.3 Odds ratios

In Chapter IV, I worked with the odds ratio (OR), also known as likelihood, as the probability of one outcome divided by the probability of the other (Bland 2000). If the participant had AN with probability ⅔ and BDD with probability ⅓, the OR is 2 due to the probability of AN divided by probability of BDD (⅔ divided by ⅓). In other words, it is

twice as likely that the participant has AN than BDD. An OR greater than 1 signified that the outcome was more likely than the alternative, while an OR less than 1 signified that the outcome was *less* likely than the alternative. A variant of the OR is the log odds ratio (LOR, also termed log odds or log likelihood) or simply the log of OR. The LOR was relevant because the coefficients' output from a logistic regression were log odds. For the LOR, a negative coefficient indicated that the parameter was predictive of the label 0, while a positive coefficient was predictive of the label 1.

### 1.4 Measuring distance

One important factor in quantifying the "best" hyperplane is the method of distance calculation. Let us say that you are in downtown San Diego, which, like Manhattan, has a street grid. If you are standing on 4th Ave and A St, and you assume the blocks are square, which is closer: (1) 10th Ave and A St or (2) 8th St and D St? Option (1) is 6 blocks up and 0 blocks over, while option (2) is 4 blocks up and 3 blocks over. If you walk, (1) is closer since 6 blocks are fewer than 7. If you fly, (2) is closer since *sqrt(*$3^2$ + $4^2$*)* = 5 blocks. Mathematicians quantify this concept as L1 vs L2 distance (Bellot and Krause 1988). The "best" hyperplane or regression fit may depend on the type of distance used because L1 distance is always greater than or equal to L2 distance. L1 classifiers, therefore, incur a greater distance penalty for each feature included; subsequently, more features have coefficients driven to 0 because their explanatory power does not outweigh those of other features significantly (Aggarwal, Hinneburg, and Keim 2001). I invoked this sparsifying effect of an L1 penalty regularly in my models.

## 1.5 Graph theory metrics

In a highly linear system, such as firing a gun, the finger pulls the trigger to enable the firing pin to contact with a round in the chamber, which ignites the gunpowder and expels the bullet. It is trivial to trace causality. The human brain, on the other hand, is a highly nonlinear interconnected network where causality is difficult to define, much less trace. To understand the nonlinear behavior of the brain, neuroscientists employ a graph theory, which is a branch of mathematics designed for dealing with networks (West 2001). In the analysis of white matter data of patients with AN or BDD, I used a single graph theory metric, the characteristic path length.

Path length represents the shortest distance between two nodes / vertices in a graph (Newman 2006). The mean shortest path length is defined as the shortest number of steps required to connect two nodes averaged across all unique node pairs. This is also known as the characteristic path length (CPL) (Sporns et al. 2004). In this analysis, CPL gives a numerical metric for the ease of parallel information transfer. One concern with CPL is that a population (e.g. participants with AN) may have a larger CPL simply because the population had a larger network size (van Wijk, Stam, and Daffertshofer 2010). We therefore used the normalized path length, defined as observed CPL divided by the CPL of an identically sized but randomly connected network (calculated by simulation) to measure information transfer while controlling the network scale.

## 1.6 Technical methods

*The methods described in this section are common in all chapters.*

I calculated confidence intervals for all summary statistics using a percentile bootstraps with 10,000 resamples (Dixon 2002). I performed all significance testing for a difference in the means of multiple groups using a permutation test (also known as an exact test or randomization test) with 10,000 resamples (Oden and Wedel 1975).

### 1.6.1 Feature extraction from functional data

This section details how I translated the whole-brain GLM results from fMRI data into the features of classification. For each subject and each condition, I averaged the whole-brain PEs in a region of interest (ROI) to obtain the average activation in the region (**Figure 1**). I repeated this method for all ROIs, resulting in a collection of features for the instance and condition, and then for each condition and instance, resulting in a dataset of instances by the features and conditions.

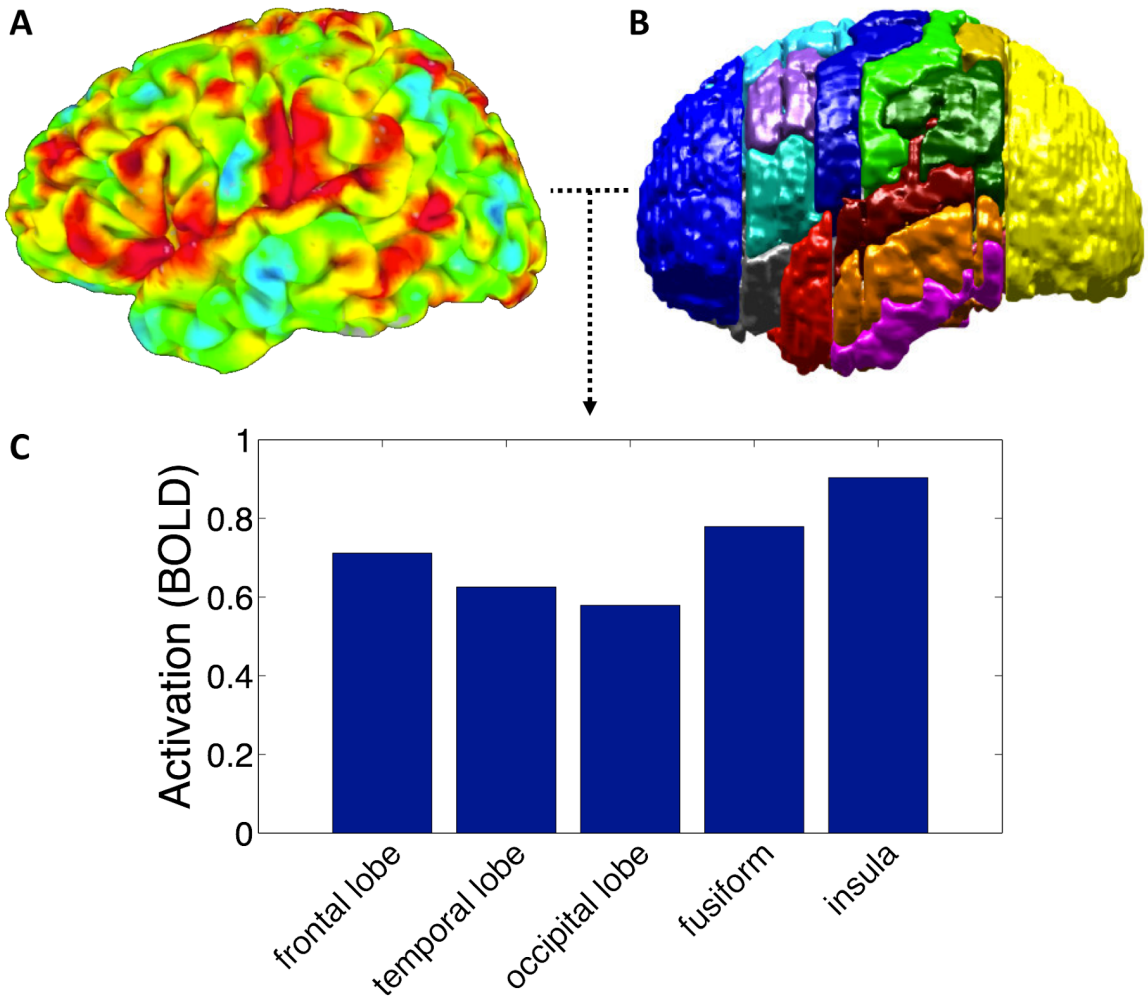



**Figure 1 - creating features from whole-brain activity.** For any given conditions and subjects, the whole-brain PEs (**A**) averaged in an ROI (**B**) averaged activation in the region. This was completed for all ROI resulting in a collection of features for the instance and condition (**C**). This method was repeated for each condition and instance, resulting in a dataset of instances by the features and conditions. *Image (B) was used under license for non-commercial use with modification.*

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Since PEs have arbitrary units, it may be difficult to compare activation across subjects. For example, a participant may respond with magnitude 5 in the visual cortex when observing one of the hands being stabbed painfully and 4 when observing a hand being touched with a cotton swab. Another participant may respond with magnitude 8 for being stabbed and 6 for being touched. The second subject responds more to both

conditions, which indicates that using the raw values would not confer any discriminatory power between stabbing and touching. Instead, if we look at a subject's response to each condition with reference to their mean response, a detectable signal will emerge. Consequently, the first subject's stab response is 0.5 units higher than their average response, and the second subject's stab response is 1 unit higher than their average (**Figure 2**). This technique is reminiscent of a paired t-test but is more general. The main difference is that I demeaned multiple instances per subject and used the resulting values together to train my classification model. I am specific about the exact methodology here because a counterfactual methodological choice could have been to take the ratio of each PEs with respect to the mean rather than the arithmetic difference.

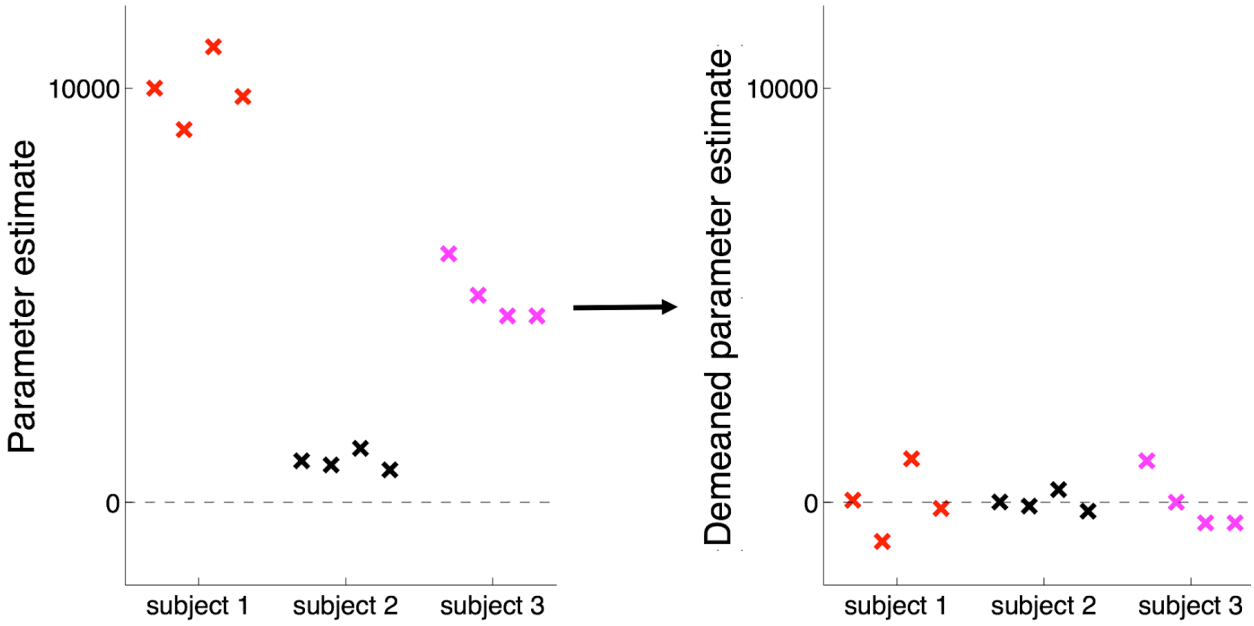



**Figure 2 - creating features from whole-brain activity.** For classification, ROI-averaged PEs from the GLM were demeaned, per subject, to bring all values into a comparable space.

### 1.6.2 Significance testing

To assess model performance, I performed cyclical leave-one-out cross-validation of the data. In this validation process, the models are trained using all-but-one exemplar and tested on the one excluded exemplar. The identity of the test exemplar was cycled such that every datapoint was used for testing only once.

To assess the significance of my predictions, I used permutation testing to estimate the empirical probability distributions of a classifier with no relationship between the potentially predictive features and the label. To disrupt any potential relationship between features and outcomes, I permuted diagnosis labels randomly without replacement while keeping input data the same. I conducted the same process of training and validation on these permuted datasets and repeated this for 10,000 permuted datasets to estimate the probability distribution of all reported summary statistics empirically. I determined the empirical *p*-value as the fraction of permuted datasets that achieved a summary statistic as, or more, extreme than that observed in the original data. Finally, I used the results of these permutations to determine the significance of feature weights.

In Chapters II and III, I used AUC-ROC as the summary statistic for assessing model performance. In Chapter IV, I used AUC-PR as the summary statistic for assessing model performance. AUC has been shown to provide a better assessment of model performance than accuracy (Bradley 1997). I performed all classifications in MATLAB using the LibLinear toolbox (Fan et al. 2008).

I was careful to avoid non-independence errors - " a violation of independence between selection and the subsequent statistical measure" (Vul and Kanwisher 2010) - as they guarantee a statistical result and thus yield no information (Culham 2006). This type of error plagued the formative years of social neuroscience research and must be avoided carefully (Vul et al. 2009). As an example, if I generated two sets of random data, subtracted one from the other to identify distinguishing features, and then used those features to see if I could classify one set versus the other, my classifier would perform better than chance, but only because I am relying on areas that I pre-selected to show the effect. As an example, in Chapter II I do not use the network found by subtracting the *ingroup* and *outgroup* conditions to classify those conditions subsequently, even though there is a priori reason to suspect those same regions may be involved.

## Chapter II - Predicting ingroups and outgroups from task-based functional neuroimaging

### 2.1 Abstract

When observers witness someone in pain, they display neural activation patterns similar to if they have experienced the pain themselves. I located the brain regions activated in this so-called empathy network and analyzed activation in observers who watched videos of hands subjected to pain. I found that the empathy network and other mentalizing regions displayed more activation when observers watched hands labeled with the observer's own religion rather than hands labeled with other religions. Multivariate activation patterns in empathy and mentalizing networks discriminated religious ingroups from religious outgroups with 70% accuracy. In two validation experiments, this model also discriminated successfully between newly formed teams. The interaction of empathy and mentalizing regions may prove to be a useful diagnostic tool in assessing bias in relationships and affiliations.

### 2.2 Introduction

To diagnose differences in empathy, I first need to define the term. Unlike quantum mechanics, diffusor tensor imaging, or special relativity, empathy is a word and concept coined by society and culture long before it appeared in a rigorous academic context. Without constraints and specifications, it is ambiguous. Over a hundred years ago, Edward Titchener introduced "empathy" from German to English as "the attempt by one self-aware self to comprehend unjudgmentally the positive and negative experiences of another self" (Cuff et al. 2016). Since then, the field of psychology developed a gradual

appreciation for the complexity of human emotional exchange and subsequently differentiated empathy from other related phenomena such as mimicry (automatic synchronization of expressions and physicality), emotional contagion (automatic "infection" by other people's emotions), and sympathy (intentional feeling for another person), among many others (Becker 1931; Hatfield, Cacioppo, and Rapson 1994; Batson 2009; Hatfield, Rapson, and Le 2009; Batson, Fultz, and Schoenrade 1987).

Here, I focused on empathy and sympathy. These concepts are often conflated (Barnett and Mann 2013; Pavey, Greitemeyer, and Sparks 2012; Wispé 1986; Eisenberg and Miller 1987) but disambiguated succinctly by Tania Singer and Claus Lamm as (1) empathy: feeling *with* someone and (2) sympathy: feeling *for* someone (Singer and Lamm 2009). In this phrasing, empathy and the often-mentioned experience sharing ("vicariously sharing targets' internal states") (Gallese, Keysers, and Rizzolatti 2004) are two words for approximately the same concept.

The most plausible causal explanation for this automatic, empathic experience sharing is the mirror neuron system. First discovered in macaques (di Pellegrino et al. 1992; Gallese et al. 1996; Rizzolatti et al. 1996), mirror neurons fire when an animal is performing an action or watching another animal perform the same action. Since social cognition and mimicry are fundamental to prosocial human behavior, it is logical that brain activation in regions associated with mimicry may also be related to social and empathetic behavior (Eisenberg and Miller 1987; Miller and Eisenberg 1988; Perry and Szalavitz 2010). Activity in the pars opercularis, a key player in the mirror neuron

system (Iacoboni et al. 2005), correlates with children's empathic behaviors and interpersonal skills (Pfeifer et al. 2008). Scholars also found that functional and structural abnormalities in this network are correlated with psychopathy (Decety et al. 2013), a diseased characterized by deficits in affective and interpersonal abilities (Ellis 1982; Hare 2003). Although it was thought originally that psychopathy was associated with a nonspecific decrease in empathy-related neural activity, more recent evidence suggests that there is a marked but multivariate difference (Decety, Skelly, and Kiehl 2013). One of the most robust diagnostic measures of differences in empathy—from psychopaths to children to normally functioning adults—involves the response to watching another person in pain.

Neuroimaging reveals that when we watch another person getting hurt, we experience activation in affective regions involved in the perception of our own pain (Botvinick et al. 2005; Hein and Singer 2008; Bruneau, Jacoby, and Saxe 2015; Singer 2004; Valeriani et al. 2008). Importantly, this empathy-related response is not constant; rather, it is modulated by one’s beliefs about the person being hurt. For example, if the observer believes that the pain recipient has acted unfairly in a simple economic exchange, the observer displays a diminished empathy response (Singer et al. 2006). Similarly, if the observer learns that the victim is receiving a large monetary compensation for undergoing the pain, empathy diminishes (Guo et al. 2011).

Modulation of empathy-associated regions occurs along the lines of group distinctions as well. In general, people are more empathic toward members of their ingroup than

toward members of an outgroup. Prior research demonstrates a neural ingroup bias for one's preferred sports team (Cikara, Botvinick, and Fiske 2011; Hein et al. 2010), for one's cognitive equivalents (Montalan et al. 2012), and for members of the same racial group (Contreras-Huerta et al. 2013; Xu et al. 2009; Azevedo et al. 2012).

Ingroup bias affects more than our neurons; it motivates our actions (and inaction) subconsciously with tangible consequences. At the simplest level, members of an ingroup are more likely to help a fellow ingroup member (Nadler, Harpaz-Gorodeisky, and Ben-David 2009). Judicial outcomes favor ingroup members (Shayo and Zussman 2011) and ingroup biases modulate how bystanders respond in emergency situations (Levine et al. 2005).

More often, however, the signs of ingroup memberships are less obvious. We are already beginning to appreciate how these biases exert influence in situations such as the court, where the jury has significant information about the people whom they subconsciously assign to their "ingroup" or "outgroup." But what if this bias can be evoked with much less information, such as a simple text label denoting a faceless stranger's religion? Then, perhaps, the ingroup/outgroup bias may be affecting everyday situations in more subtle ways that we have yet to appreciate. To what degree does the constant barrage of information suggesting micro-allegiances – perhaps appearing as symbols, text labels, clothing choices, or conversational intonation – influence neural activity and subsequent behavior? Can a text label denoting someone's religion, for instance, elicit a biased response? Understanding the influence of this allegiance

information may aid in detecting the biasing effect of narratives and eventually help prevent harmful action by people with strong biases.

Despite being one of the most strongly polarizing allegiances, the effect of religious labels on neural activity has not been widely studied; in fact, to my knowledge there is only one case. In 2014, a single EEG study found a bias in P2 (a positive deflection in the event-related potential around 200ms) and N2 (a negative deflection in the event-related potential after 200ms) amplitudes on the basis of religious identity congruency. However, it is unclear which regions drive this effect and to what degree they might be able to diagnose larger biases in empathy (Huang and Han 2014). As detailed in this chapter, I used fMRI to investigate how the neural ingroup bias extends to the identity of religious groups.

## 2.3 Methods

### 2.3.1 Participants

I recruited 135 participants (29.2 +/- 8.9 years, 63 males, 108 right-handed) with normal or corrected-to-normal vision from the Houston, TX metropolitan area and compensated the participants for their time. I excluded 8 participants' data due to errors in MRI acquisition or reconstruction and an additional 22 participants due to excessive head motion as indicated by an absolute mean displacement greater than 3.0 mm, leaving 105 participants for analysis.

To obscure the true motivation for the study, I informed participants that I was investigating the relationship between pain and memory for religions. Since I did not

disclose our true interest—understanding the neural empathetic response—this study qualifies as deceptive research. The Baylor College of Medicine IRB approved the study before its conduction. During an informal exit interview, none of the subjects reported skepticism towards its purported nature.

### 2.3.2 Behavioral Questionnaires

First, participants declared their religious identity (including agnostic or atheist) as specifically as possible. Next, participants completed five additional surveys, which collectively quantified their degree of religiosity, alignment with right wing authoritarianism, and strength of overall empathy: (1) Balanced Emotional Empathy Scale (BEES) (Mehrabian and Epstein 1972; Mehrabian 1997); (2) Davis Emotional Empathy Interpersonal Reactivity Index (Davis 1983) (3) Right Wing Authoritarianism Scale (Altemeyer 1981); (4) Religious Conviction Scale (Dawkins 2016); and (5) Religious Orientation Scale (Allport and Ross 1967). None of the surveys asked participants about the extent of empathy they feel toward members of their own or other religions, since this would have revealed the true purpose of the study.

### 2.3.3 Stimuli

I programmed all stimuli in MATLAB with PsychToolbox (Kleiner et al. 2007; Brainard 1997; Pelli 1997). Participants viewed the stimuli on a back-projected screen while lying supine in the scanner. Overall, I designed the experiments with two primary intentions: to provide the minimum amount of information on each ingroup and outgroup, and to reflect realistically the religious diversity found in communities around the world.

***Baseline block***

First, participants viewed the trials in which 6 hands, selected randomly from 12 possible versions, appeared on the screen. Each hand was similar in skin tone and apparent age but was differentiated by an arbitrary bracelet and text label that conferred a unique identity. The text label remained in association with its hand for the duration of the trial. After 2-4 seconds, the computer selected a hand randomly, as indicated by the appearance of a red border around the image. After 6 seconds, the selected image moved into the middle of the screen. The image became a video, lasting 2.3 seconds, in which the hand was either stabbed with a syringe needle or touched with a cotton swab (**Figure 3A**); the events were similar from a visual perspective (angle-of-approach and timing) but different in emotional impact (**Supplementary Figure S1**). Participants viewed multiple stabbing and touching events, separated by a blank screen for 8-12 seconds as the inter-trial interval (ITI). To reduce desensitization over the course of viewing many stabs and touches, I filmed stabbing and touching events from 6 different angles, and I shuffled the position of each hand and its associated text label for each trial.

In most versions of the experiment (see **Experiment 1,** below), participants began by observing 6 *stab* trials and 6 *touch* trials. I used the differences between the *baseline stab* and *touch* conditions as a functional localizer to generate an operational definition for the empathy network. A few participants completed alternative experiments instead (see **Experiment 2** and **Experiment 3** below).

***Experiment 1: religious affiliations***

After participants completed the *baseline* block, the hands reappeared with labels of religious groups rather than arbitrary text labels. The next 60 trials were otherwise identical to the first block. For each participant, the computer assigned religious labels to the hands randomly, but once assigned, labels remained with the same hands for the duration of the trials. Each hand was subjected to an equal number of stabs and touches, and each hand was selected for the same number of trials as each other hand. In these 60 trials, each of the 6 religions were selected for 5 *stab* and 5 *touch* trials.

I defined the *religious ingroup* condition to include trials in which the participant observed a hand labeled with their religious identity, and I defined the *religious outgroup* condition to include trials in which the participant observed a hand labeled with any religious identity other than their own. I subdivided each of these conditions further into a *touch* and *stab* condition. This yielded 6 conditions in the GLM: *baseline touch, baseline stab, religious ingroup touch, religious ingroup stab, religious outgroup touch,* and *religious outgroup stab*. The condition *religious ingroup* by itself refers to the mean of *religious ingroup stab* and *religious ingroup touch*. Similarly the condition *religious outgroup* by itself refers to the mean of *religious outgroup stab* and *religious outgroup touch*.

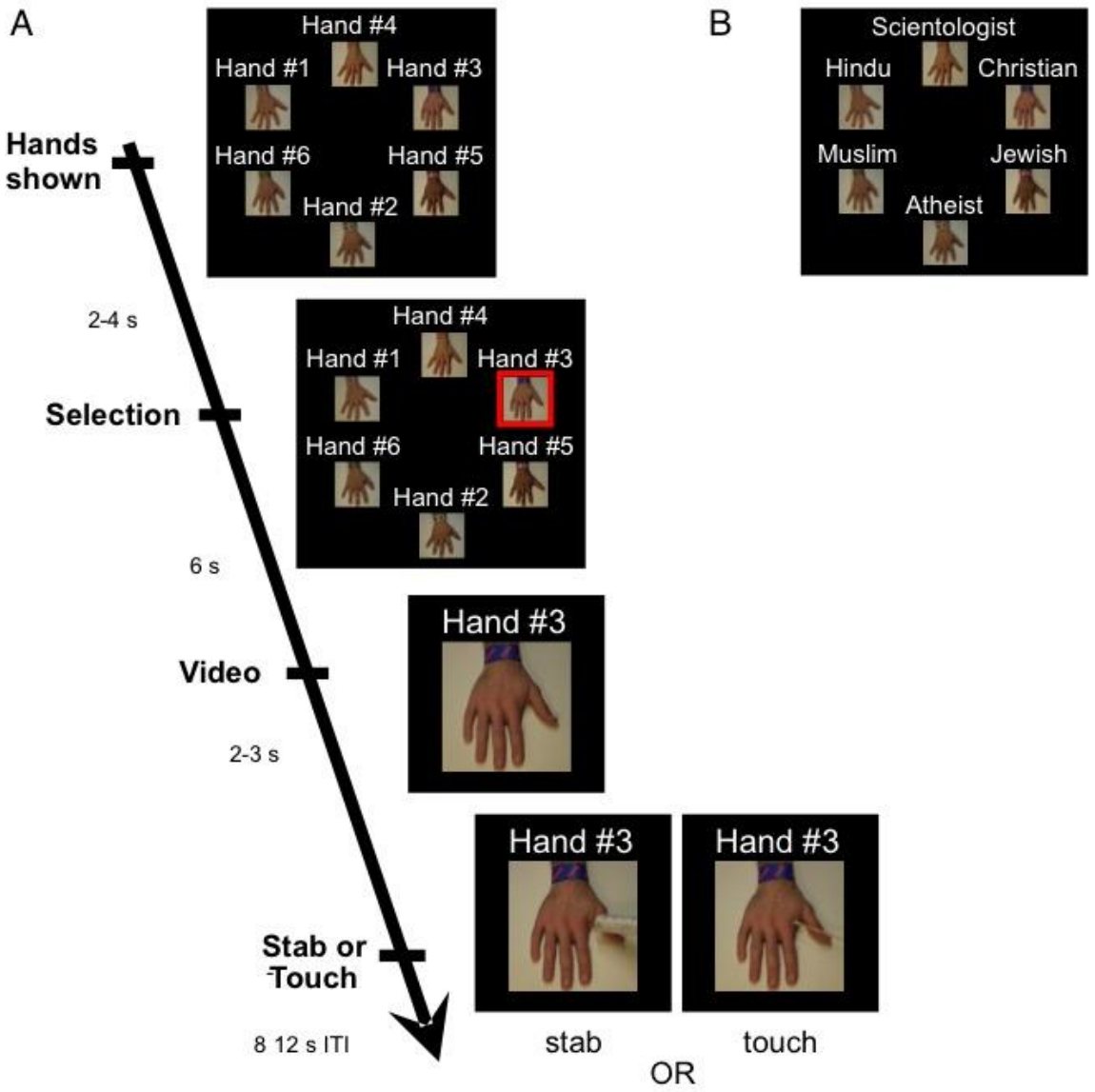



**Figure 3 - experimental design for the main empathy experiment. A.** I used the *baseline* block as the functional localizer to identify neural regions that responded more to stabbing than touching. In each trial, hands appeared with arbitrary text labels; the computer selected a hand, and that hand received either a stab or a touch. **B.** The *religious ingroup – religious outgroup* block was identical in structure and timing to the *baseline* block with the exception of religious labels.

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To reflect the varying degrees of religious diversity across different communities, I utilized three variations within the *religious ingroup – religious outgroup* block:

a. 6 hands, 6 different religious labels, ITI 8-12 s, 12 *baseline* trials, 60 *religion* trials (n = 38 participants, including 10 agnostic)

b. 6 hands, 2 different religious labels (3 Christian and 3 Atheist to boost and balance number of *religious ingroup* trials), ITI 8-12 s, 12 *baseline* trials, 60 *religion* trials (n = 11 participants, including 4 agnostic)

c. 4 hands, 4 different religious labels, ITI 14-18 s, 8 *baseline* trials, 56 *religion* trials (n = 23 participants, including 5 agnostic)

Next, I conducted two separate versions of the experiment on separate and smaller sets of participants to address ingroup bias and determined whether this could be manipulated rapidly.

***Experiment 2: flexibility of religious affiliations***

I investigated the effect of bringing a former religious outgroup member into closer alliance with an ingroup. I assigned the 6 religions arbitrarily to 2 teams, the green team and the blue team, with 3 hands each. A text box explained that a group of the 3 religions was now at war with the other 3 religions. This set of trials used 6 hands, ITI 10-14 s, 6 religions, 12 *baseline* trials, and 60 *religion* trials (n = 19, including 5 agnostic).

This experiment introduced the concept of allies. I defined the *religious ally* condition to include trials in which the participant observed hands labeled with an outgroup religion on the same blue or green team as the participant's ingroup religion. As before, I subdivided each of these conditions further into *touch* and *stab* conditions. This yielded 8 conditions in the GLM: *baseline touch, baseline stab, religious ingroup touch, religious*

*ingroup stab, religious ally touch, religious ally stab, religious outgroup touch,* and *religious outgroup stab*.

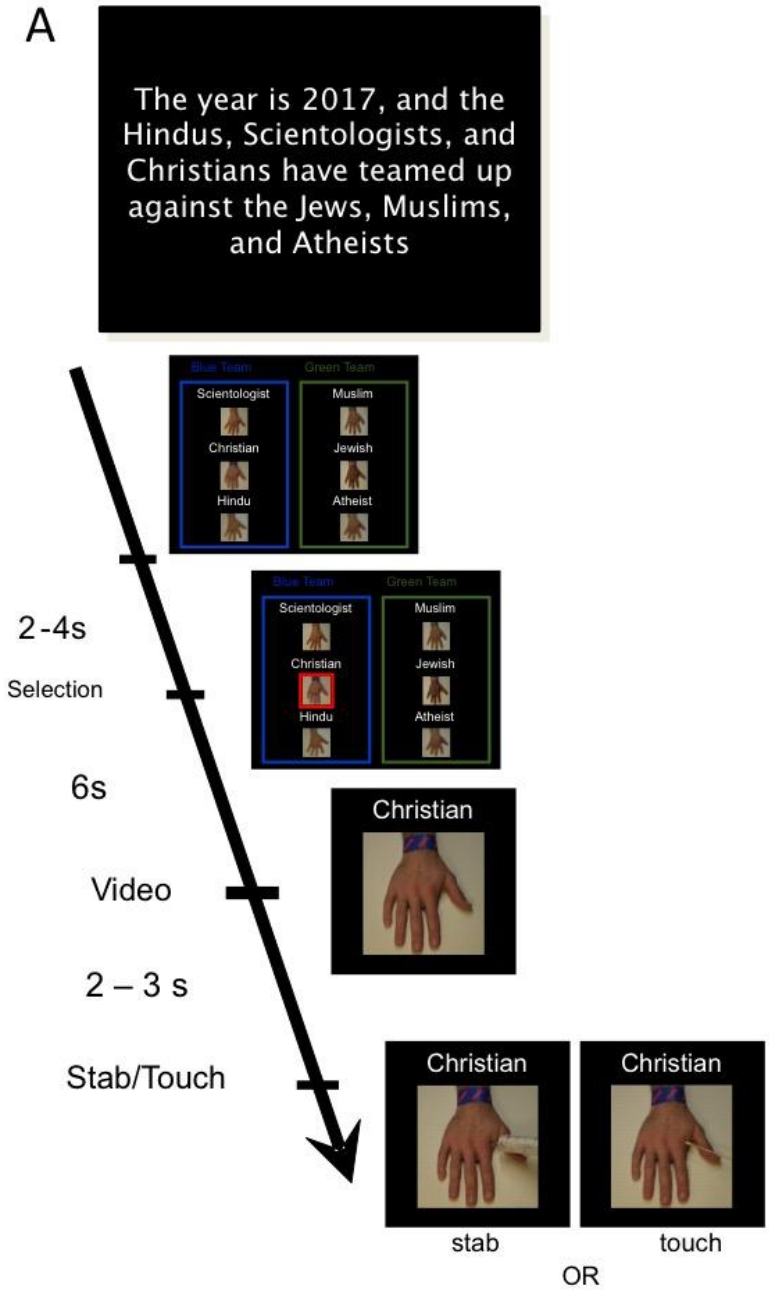



**Figure 4 - experimental design for the allegiance experiment.** The allegiance experiment was identical in structure to the main experiment except for the story presented to participants after the *baseline* block. Hands were assigned randomly to either the blue team or the green team.

***Experiment 3: arbitrary teams***

Before initiating the fMRI portion of the experiment, I used a coin toss to assign participants randomly to one of two fictional groups: “Augustinians” or “Justinians.” Since participants flipped the coin themselves, they understood that the assignment was arbitrary. I assigned heads or tails randomly for each participant. Participants received a bracelet for their “team” with the instruction to wear the bracelet during the experiment. This both reminded participants of their team identity and encouraged bonding to the identity. This set of trials used 6 hands, ITI 10-14 s, 2 groups, 12 *baseline* trials, and 60 group trials (n = 14 participants).

I defined the *arbitrary ingroup* condition to include trials in which the participant observed hands labeled with the group to which the participant was assigned; *arbitrary outgroup* included trials in which the participant observed hands labeled with the group to which the participant was not assigned. As before, I subdivided each of these conditions further into *touch* and *stab* conditions. This yielded 6 conditions in the GLM: *baseline touch, baseline stab, arbitrary ingroup touch, arbitrary ingroup stab, arbitrary outgroup touch,* and *arbitrary outgroup stab*.

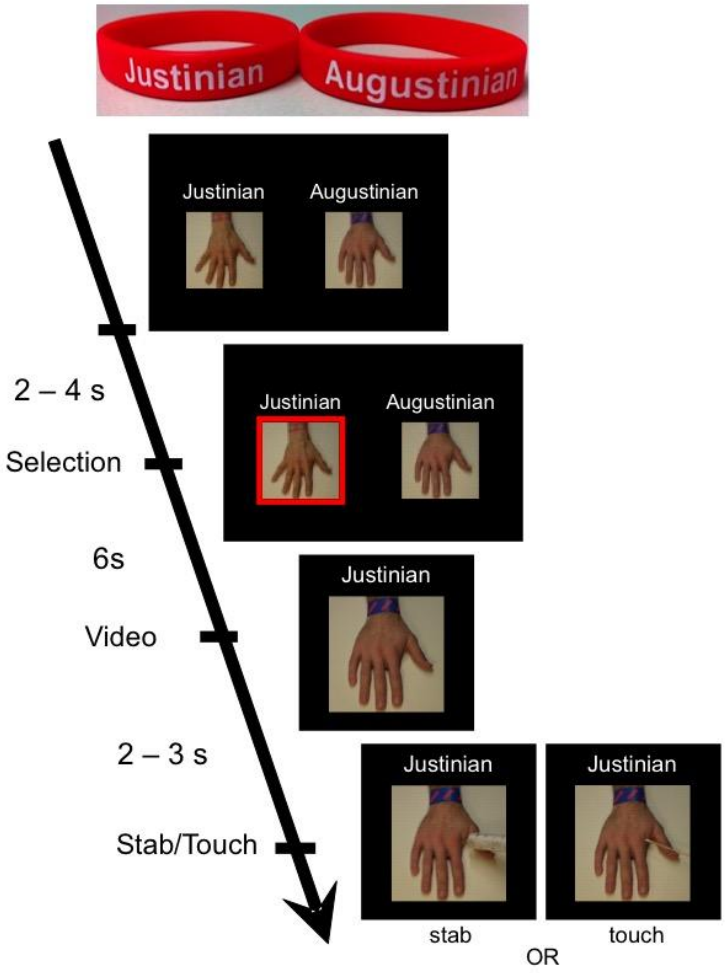



**Figure 5 - experimental design for the arbitrary assignment experiment.** The arbitrary assignment experiment was identical in structure to the main experiment, except that participants flipped a coin for random assignment to one of the two teams. They received a team wristband and later read a slide explaining that "the Augustinians and Justinians are two warring tribes."

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### *Behavioral response*

Since I led participants to believe that the study was investigating the effects of pain on memory, participants believed that they would receive evaluation frequently to test their memory of which hand had been stabbed. To buttress this impression, increase attention, and quantify alertness, I asked participants on a random 20% of trials to report which religion was associated with the selected hand 10-14 seconds after the

trial. All participants with usable fMRI data scored successfully with a response accuracy greater than 80%.

### 2.3.4 MRI data

#### *Acquisition*

I acquired data on a Siemens 3T Trio (Erlangen, Germany) scanner. First, I used an MP RAGE sequence (0.4785 x 0.4785 x 1.0 mm voxels) to create high-resolution T1-weighted scans (Mugler and Brookeman 1990). Functional image acquisition details are echo-planar imaging, gradient recalled echo; repetition time (TR) = 2000 ms; echo time (TE) = 40 ms; flip angle = 90°; 64 x 64 matrix, twenty-nine 4 mm axial slices, yielding functional 3.4 mm x 3.4 mm x 4.0 mm voxels, and one 30-45 minute run. To account for the slight initial instability in the magnetic field, the scanner software discarded the first two volumes from every participant's functional run.

To ensure the accuracy of these results, my colleague and I completed the full analysis pipeline as preprocessing, GLM modeling, and group analysis using FSL (www.fmrib.ox.ac.uk/fsl), and SPM (http://www.fil.ion.ucl.ac.uk/spm/), respectively.

#### *Preprocessing*

##### *FSL*

We used FEAT (fMRI Expert Analysis Tool) Version 6.00, part of FSL 5.0.9, to process fMRI data. We performed the pre-statistics processing, which involved motion correction using MCFLIRT (Jenkinson et al. 2002), slice-timing correction using Fourier-space time-series phase-shifting, non-brain removal using BET (Smith 2002), spatial smoothing using a Gaussian kernel of FWHM 5 mm, grand-mean intensity

normalization of the entire 4D dataset by a single multiplicative factor, and highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 30 s). We conducted all first-level analyses and model fitting in the functional space.

For group-level analyses, we registered PEs and contrasts of beta weights to the Montreal Neurological Institute (MNI)152 template brain (Tzourio-Mazoyer et al. 2002). We used FLIRT full-search, boundary based registration (BBR) for registration to high-resolution structural images (Jenkinson and Smith 2001; Jenkinson et al. 2002). We then used FNIRT (nonlinear registration) of full-search and 12 degrees of freedom, warp resolution 10 mm for registration from high-resolution structural to standard space (Andersson, Jenkinson, and Smith 2007b; Andersson, Jenkinson, and Smith 2007a).

***SPM***

I processed the fMRI data with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). I performed the pre-statistics processing, which involved motion correction realignment through 6 parameter rigid-body spatial transformation (Friston et al. 1995; Thevenaz, Blu, and Unser 2000; Collignon et al. 1995; Wells et al. 1996), segmentation (Ashburner and Friston 2005), normalization to MNI space (Ashburner et al. 1997; Ashburner and Friston 1999), and smoothing with a 8 mm full-width / half-maximum kernel.

***GLM analysis***

In both platforms, we fit a GLM (Worsley et al. 1996; Friston et al. 1994) to each participant's time-series data, including 6 standard motion regressors, individual motion outlier regressors, and a temporal high-pass filtering of signal > 128 s. In FSL, we used FILM, FMRIB's improved linear model with local autocorrelation correction (Smith et al.

2001), and root mean square intensity difference to middle volume (*fsl_motion_outliers*). In SPM, we employed the autoregressive AR(1) model during parameter estimation and motion difference to the first volume.

For each trial condition (*baseline*, *religious ingroup*, *religious ally, arbitrary ingroup, etc.*), we included a separate set of regressors for *stab* and *touch* trials, which corresponded to the onset of the video showing the hand receiving either a stab or a touch. We also included regressors to mark the following: hand selection for each condition, corresponding to the time when the hand with a particular label, religion, and group was selected; time of trial onset; time of questions asked; and time of answer selection. For each regressor, we fit a temporal derivative regressor to allow slight offsets in peak timing (Henson et al. 2002; Friston et al. 1998).

***Group analysis***

First, we identified the empathy network by contrasting the initial 6 *stab* trials with the initial 6 *touch* trials (*baseline stab – baseline touch*). In the FSL data, we used FSL FEAT mixed-effects modeling (FLAME 1) with outlier de-weighting for the group-level contrasts. We did not use outlier de-weighting for our SPM pipeline.

Next, we used a whole-brain search to identify regions outside of the pre-defined empathy network that responded more to the stabbing of a *religious ingroup* hand than of a *religious outgroup* hand. We used nonparametric statistics via permutations testing as FSL *randomize* (Winkler et al. 2014) to perform the whole-brain *religious ingroup – religious outgroup* searches. We conducted contrasts between *religious ingroup* and

*religious outgroup* on all eligible participants (n = 67; agnostics were excluded since they had no religious ingroup). From within these two networks, we extracted PEs and converted them to percent signal change, using *featquery* for FSL data and MATLAB for SPM data.

### 2.3.5 Classification methods

#### *ROI averaging*

I used the average values of the PE in different brain ROIs as features (see Introduction, **Figure 2**). I selected the regions of the empathy, relief, and mentalizing networks as features in my initial mode, which I label as the *a priori* model. For the following whole-brain analyses, I employed the ROIs from the Harvard-Oxford atlas distributed with FSL (Caviness et al. 1996; Makris et al. 2006; Desikan et al. 2006). To rule out a classification based on the label text by visual word form or other visual areas (Petersen et al. 1990; McCandliss, Cohen, and Dehaene 2003; Cohen et al. 2000), I did not use visual areas as features in my *a priori* model in which I performed all hypothesis testing. I generated the visual exclusion mask from the Harvard-Oxford atlas (**Figure 6**). Specifically, I excluded the left fusiform and right middle temporal gyrus clusters from the empathy network, the left and right angular gyri and precuneus clusters from the relief network, and the precuneus cluster from the mentalizing network. After exclusion there were 11 regions remaining, all of which were included as features in my *a priori* model.



**Figure 6 - visual exclusion mask.** A mask of areas considered to be visual. Areas of the empathy, relief, and mentalizing network overlapping with this mask were not included in the initial *a priori* model.

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### *Modeling*

I predicted religious affiliations using an L2-regularized logistic regression model with AUC-ROC as the statistic of interest (see Introduction for details). In all experiments and models, I assigned the outgroup condition the value of zero; thus, positive weights for features contributed to a prediction of ingroup (or ally in the classification *religious ally* vs *religious outgroup*). All individual weights reported are presented uncorrected. For all *ingroup* and *outgroup* classification tests of significance, I included *stab* and *touch* conditions as separate exemplars. For example, in the *religious ingroup* vs *religious outgroup* classification, each participant had 4 exemplars: *religious ingroup touch, religious ingroup stab, religious outgroup touch,* and *religious outgroup stab*.

If a classification was found to have an area under the curve significantly different from chance, I re-ran the classification. For this second calculation, I averaged together the (leave-one-out) test participant's *touch* and *stab* instances within their class. As an example, in the *religious ingroup* block, for each cross-validation fold I trained my model on the 66 participants x 4 instances = 264 instances (as identical to the above hypothesis testing). I tested on the left-out participant's instances of *religious ingroup* (mean of *religious ingroup touch* and *religious ingroup stab*) and *religious outgroup* (mean of *religious outgroup touch* and *religious outgroup stab*).

In other words, this maximum-performance classification was identical to the original classification method except that it tested on a participant's average *ingroup* activation, thereby reducing noise and improving performance. As I mentioned in the introduction and illustrated in **Figure 2**, each participant's exemplars were brought into a common space by subtracting that participant's original value from their average activation; each participant's instances were demeaned together. When I averaged the *touch* and *stab* trials together for the *ingroup* and then for the *outgroup* conditions, there were only two exemplars left. Since they were both demeaned, they were the negative of each other by definition, and summed to 0 necessarily. Consequently, there was one unique value only per participant in this classification, which was precisely what I was interested in testing: the model's accuracy (right or wrong) in predicting each participant's *ingroup* and *outgroup*. As a result, sensitivity was equal to specificity, so the ROC curves were always symmetric.

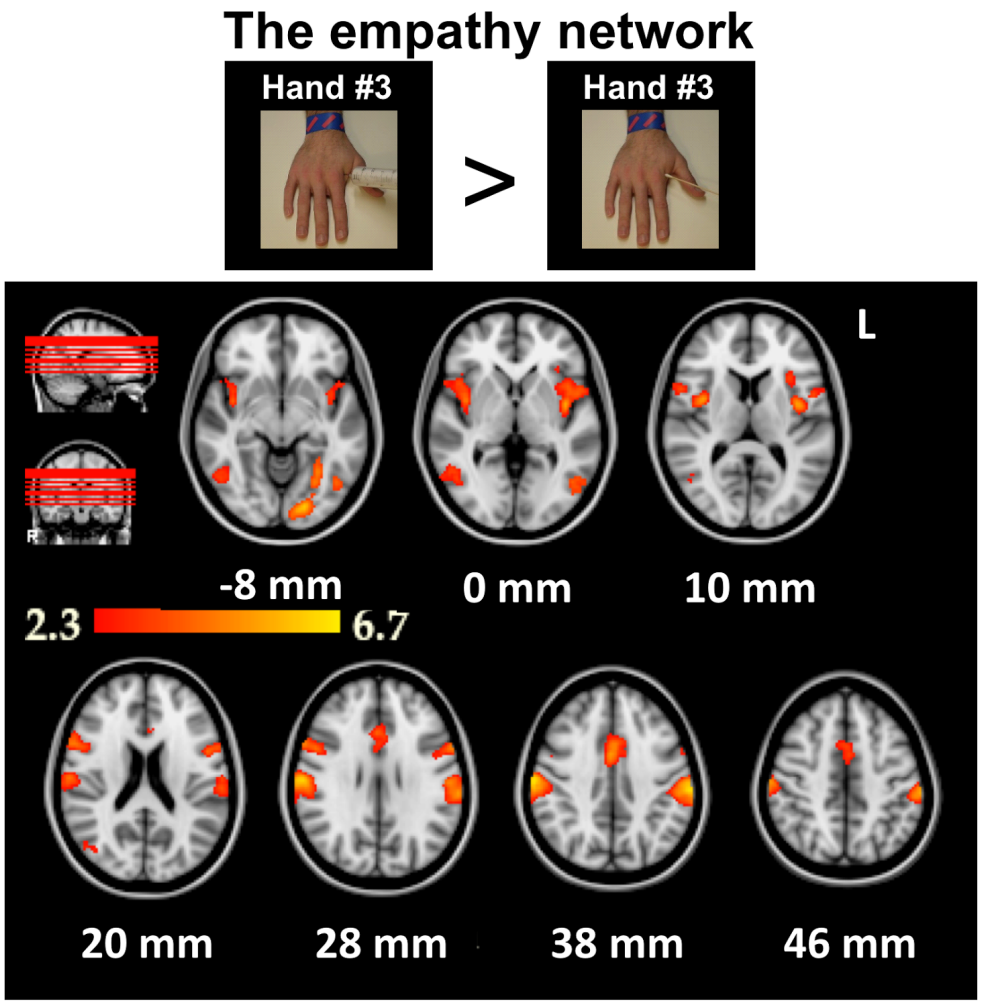
## 2.4 Results

### 2.4.1 Univariate

#### *Empathy network functional localizer*

I used the *baseline* block without religious affiliation labels from all participants in all experiments to localize empathy-related brain regions. Here, each participant observed hands receiving either a stab with a needle or a touch from a cotton swab (**Figure S1**). The whole brain contrast of *stab* > *touch* trials yielded 8 significant clusters, which I referred to collectively as the empathy network (**Figure 7**).

A




B

| Cluster | # voxels | p | X (mm) | Y (mm) | Z (mm) |
|---|---|---|---|---|---|
| left insular cortex | 1347 | 2.9E-06 | -44.5 | 5.3 | 8.5 |
| right insular cortex | 1276 | 5.3E-06 | 48.4 | 7.8 | 10.8 |
| left supramarginal | 1043 | 4.1E-05 | -58.4 | -26.1 | 33.9 |
| right supramarginal | 1022 | 5.0E-05 | 61.0 | -21.4 | 32.2 |
| ant. cingulate cortex/SMA | 907 | 1.5E-04 | -0.6 | 9.8 | 36.1 |
| left fusiform gyrus | 862 | 1.0E-09 | -23.7 | -70.7 | -12.7 |
| right lateral occipital cortex | 520 | 8.3E-03 | 49.5 | -61.7 | 0.4 |
| left lateral occipital cortex | 306 | 1.2E-04 | -47.5 | -68.5 | -1.0 |

**Figure 7 - the empathy network. A.** The contrast of *stabs* > *touches* revealed 8 significant clusters (Z > 2.3 and FWE-corrected cluster significance threshold of $p < 0.05$). **B.** Corresponding MNI coordinates represent the center of gravity of the z-statistic for each cluster.

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This network was localized consistently using ordinary least squares with SPM, FLAME, or permutations testing with the FSL *randomise* package (**Figure 8**).

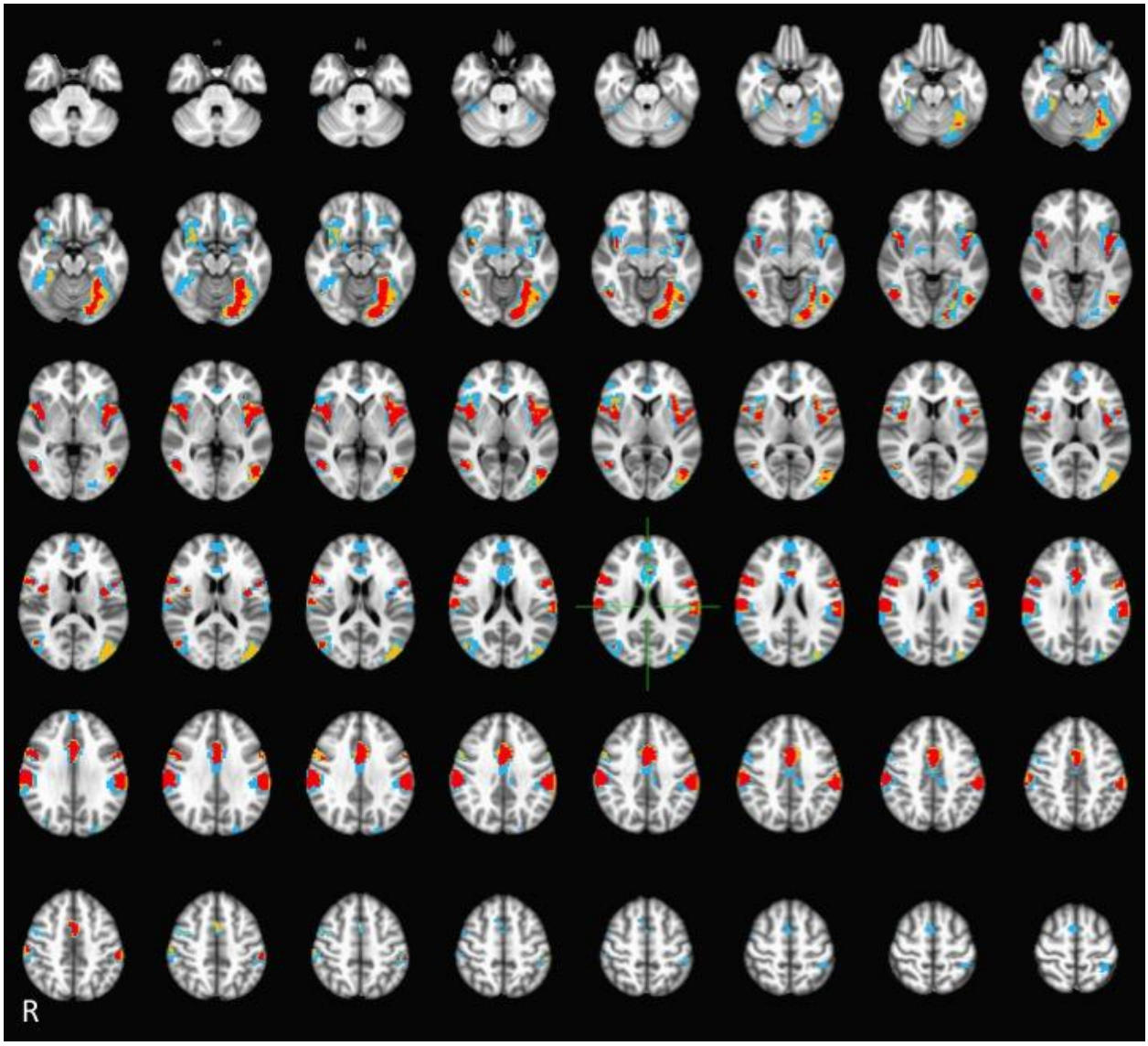



**Figure 8 - localized empathy network with multiple approaches.** The empathy network was localized similarly with various methods. Processing and analyzing data with Ordinary Least Squares with SPM, FLAME, or permutations testing with FSL *randomise* all identified a similar empathy network for the contrast *stab* > *touch*. **Red** indicates voxels found significant for all 3 approaches, **yellow** indicates significance for 2 approaches, and **blue** indicates significance for 1 approach only. Most blue regions were areas found to be significant using SPM, which may be due to a slightly larger smoothing kernel. Images are radiologic convention.

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I also defined the “relief network” operationally as the opposite contrast, *stab* < *touch*.

The whole-brain contrast yielded 8 significant clusters in this network (**Figure 9**). It is of

note that in many of the relief network ROIs, the *baseline stab* condition is less than baseline; there is deactivation.

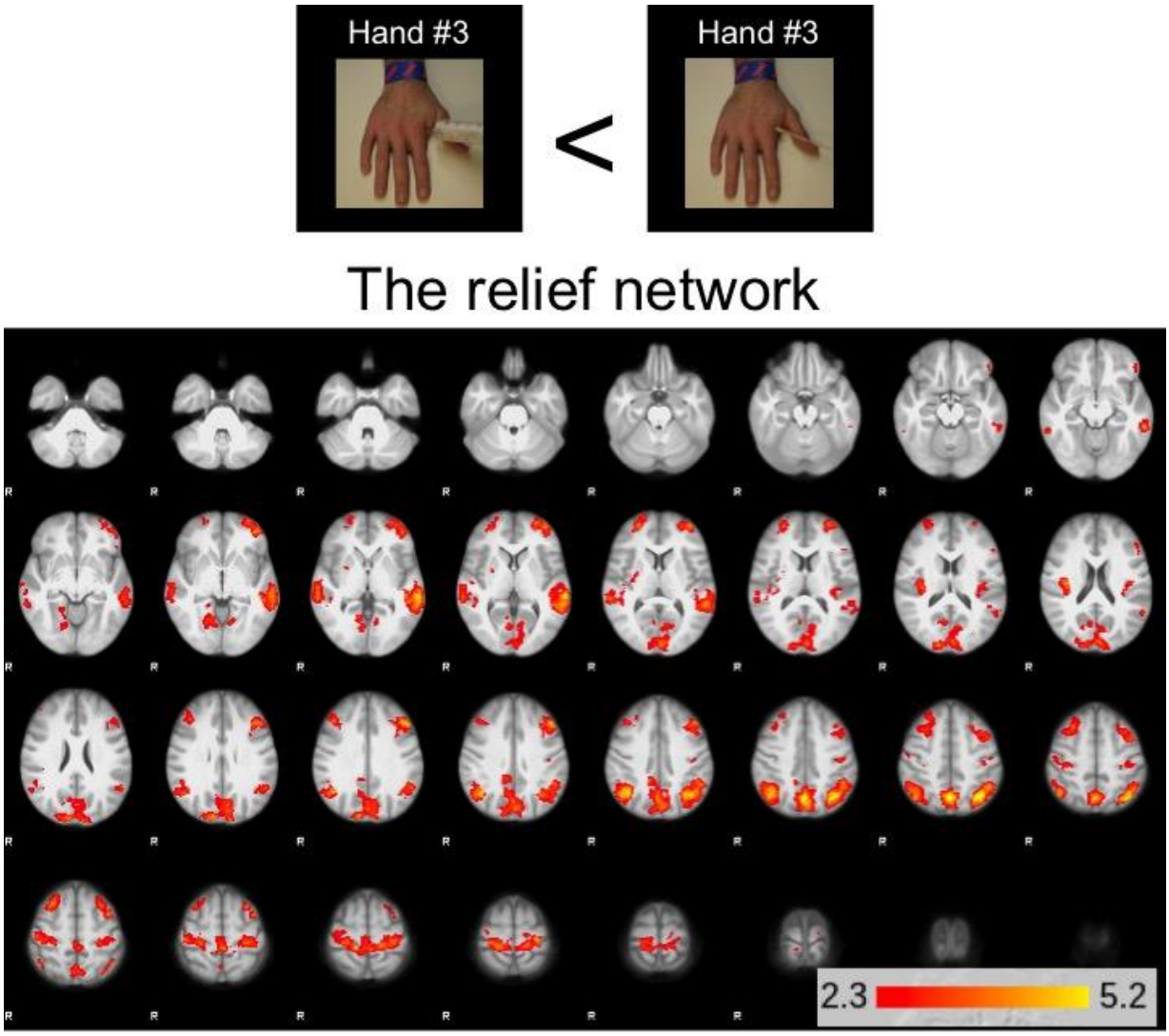



**Figure 9 - the relief network.** The contrast of *touches* > *stabs* reveals 8 significant clusters (Z > 2.3 and FWE-corrected cluster significance threshold of $p < 0.05$).

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### *Experiment 1: religious ingroups*

After establishing the *baseline* empathy network, I assessed if the religion of the stabbed hand modulated the magnitude of the neural response within the empathy

network. This analysis utilized data from the *religious ingroup* – *religious outgroup* block, in which I labeled each hand as either Christian, Muslim, Hindu, Jewish, Scientologist, or Atheist (**Figure 3B**). The average response magnitude in the empathy network was significantly higher for *religious ingroup* trials compared to *religious outgroup* trials for both *stab* ($p = 0.05$, corrected) and *touch* ($p < 0.05$, corrected) trials (**Figure 10**, n = 67).

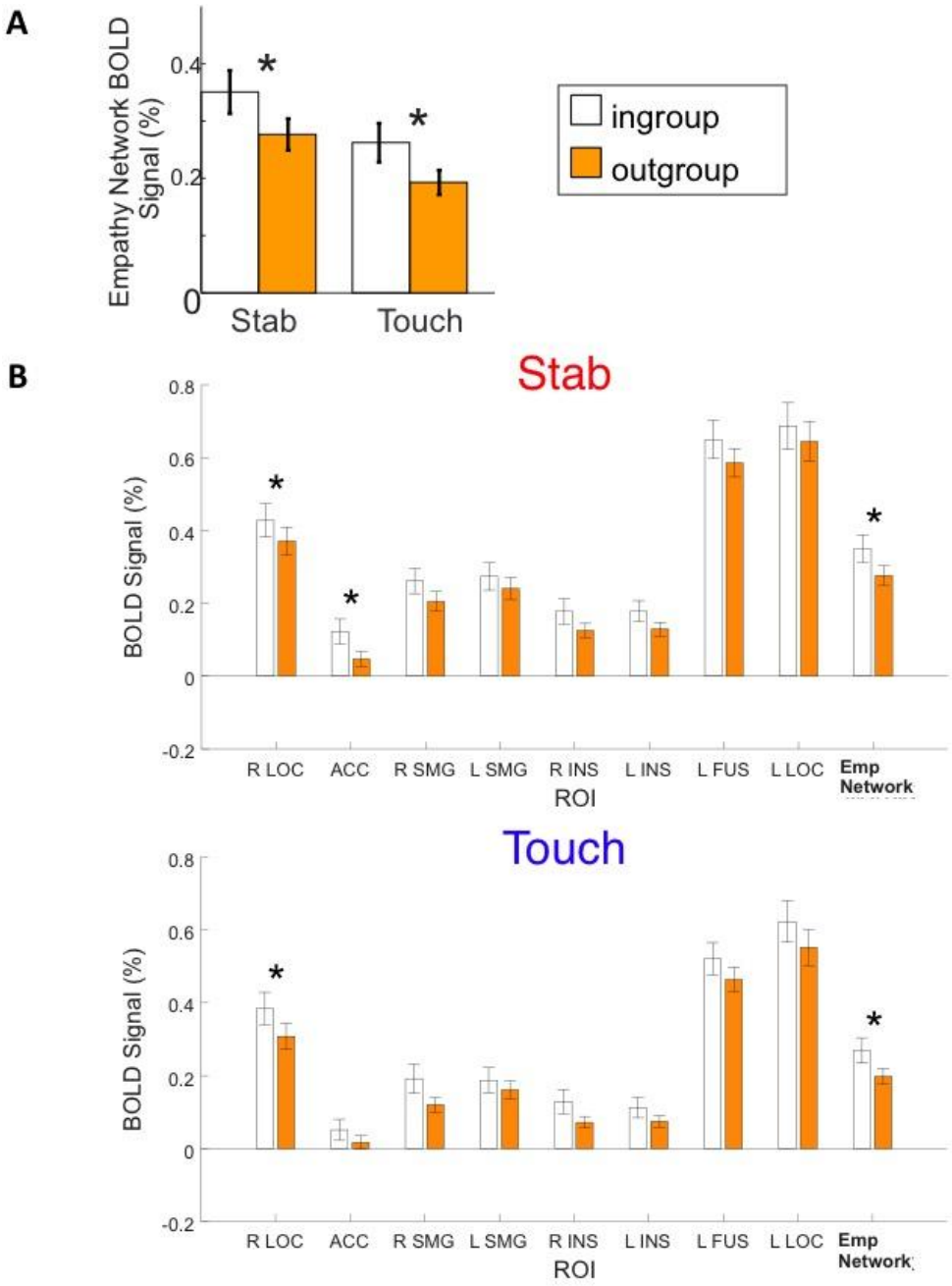



**Figure 10 - ingroup bias in the empathy network.** Within the empathy network, BOLD activity to both stabs and touches was larger for *religious ingroup*- than for *religious outgroup*-labeled hands. **A.** Within the empathy network, participants showed greater activation for their *religious ingroup* than *religious outgroup* for both *stab* ($p < 0.001$) and *touch* ($p < 0.005$) trials. Error bars are standard error of the mean (SEM). **B.** PEs from each of the empathy-network clusters in the *religious ingroup* condition for both *stab* (red) and *touch* (blue) conditions. Asterisks represent a *religious ingroup – religious outgroup* bias significantly different from 0 ($q < 0.05$, corrected for the number of ROIs in the empathy network).

A whole-brain contrast for *religious ingroup* > *religious outgroup* combining *stab* and *touch* trials yielded three clusters beyond the empathy network: the mPFC, posterior cingulate/precuneus, and superior temporal gyrus (**Figure 11A**). Since these three regions appear in many paradigms about the understanding of the perspective of others (Saxe 2006; Völlm et al. 2006; Jackson et al. 2006), we defined these ROIs together as the “mentalizing network”.

No significant voxels appeared in the contrast r*eligious ingroup* > *religious outgroup*. I found a positive correlation between participants’ scores on the Balanced Empathy Emotional Scale and activity in the left insula (**Figure 11B**). However, the activity in regions of the empathy network did not correlate with participants’ strength of religious belief or with their score on the Right Wing Authoritarian Scale.

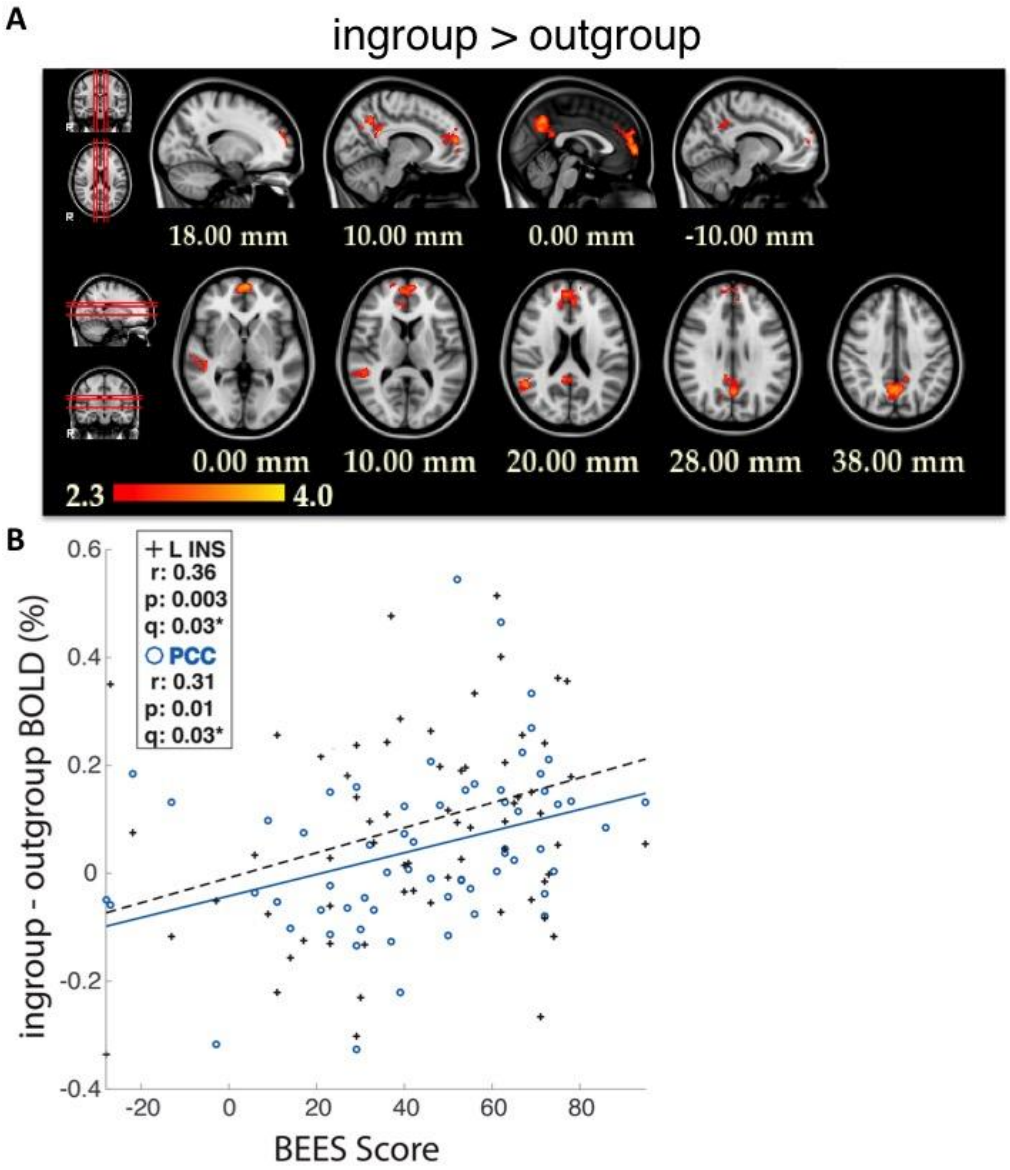



**Figure 11 - religious ingroup vs religious outgroup. A.** The whole-brain *religious ingroup* > *religious outgroup* contrast yielded three significant clusters: the ACC, posterior cingulate/precuneus, and superior temporal gyrus. No significant voxels appeared in the contrast *religious outgroup* > *religious ingroup*. **B.** Participants' normalized scores on the Balanced Empathy Emotional Scale correlated with their *religious ingroup–religious outgroup* contrast PEs in the left insula (r = 0.36, 95% confidence interval 0.17 to 0.54, $p < 0.05$ corrected) and posterior cingulate (r = 0.31, 95% confidence interval 0.04 to 0.54, $p < 0.05$ corrected).

---

The average activity in the empathy network, relief network, and mentalizing network had significantly non-zero correlations with each other (p < 10-4, $q < 10^{-3}$ Holm-Bonferroni corrected for all three comparisons, **Figure 12**). The empathy network and

relief network had a correlation of 0.56 with the 95% confidence interval 0.45 to 0.65; the empathy network and mentalizing network had a correlation of 0.61 with the 95% confidence interval 0.50 to 0.70; and the relief network and mentalizing network had a correlation of 0.82 with the 95% confidence interval 0.78 to 0.86.

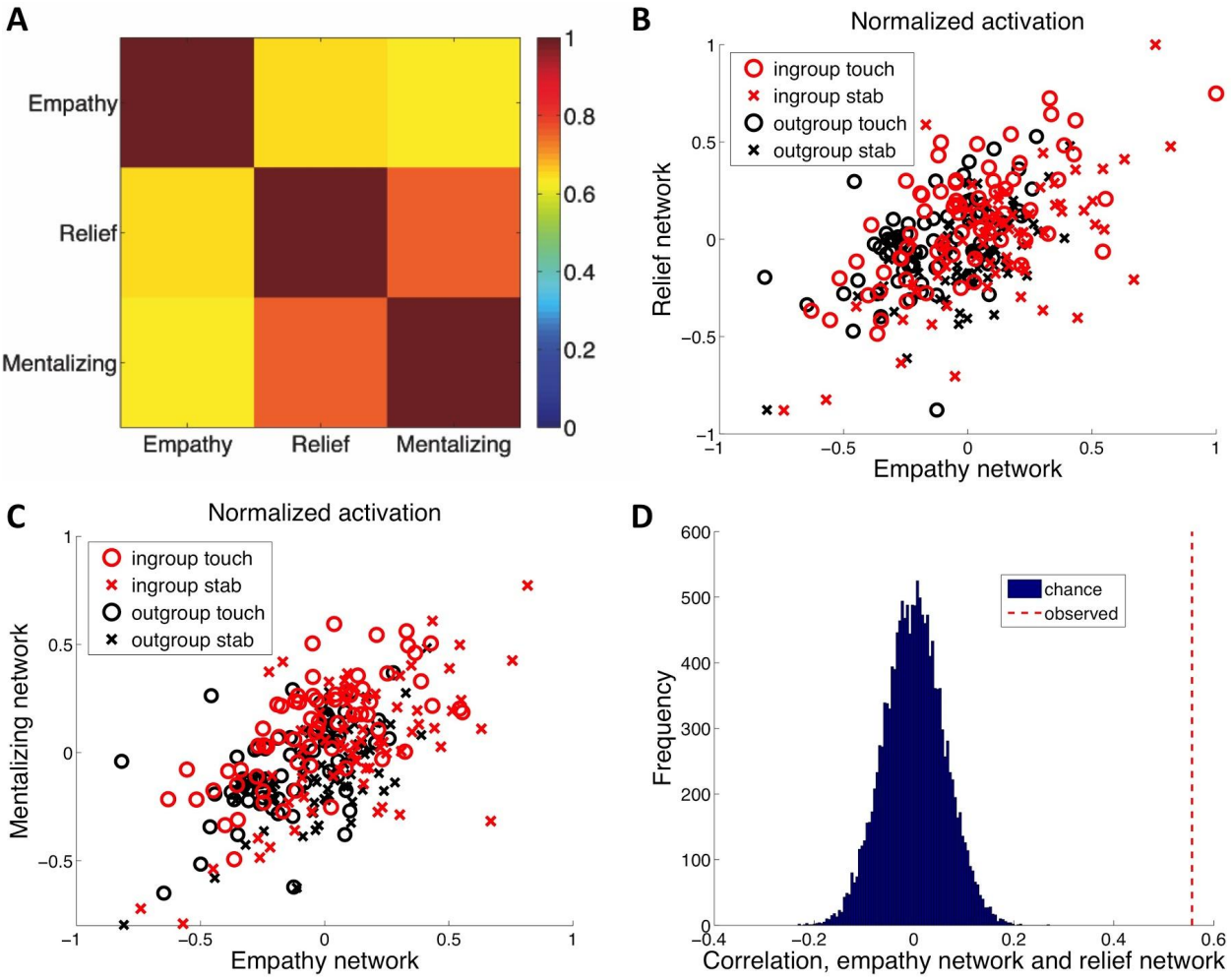



**Figure 12 - empathy, relief, and mentalizing network correlations. A.** Correlation matrix of all three networks. **B.** Normalized PEs for *religious ingroup* and *religious outgroup touch* and *stab* conditions in the empathy network and relief network. **C.** Normalized PEs for the empathy network and mentalizing network. **D.** Significance testing for the correlation of empathy network and relief network. The observed correlation is significantly different from 0 ($p < 10^{-4}$, n = 266 instances).

---

## 2.4.2 Unbalanced design

*This section details a sub point of the thesis.*

Since each participant identified with one religious ingroup only, this study design yielded a ratio of approximately 4:1 *religious outgroup* trials to *religious ingroup* trials. To account for possible frequency effects and differences in timing between trials, my colleague and I designed a control experiment, which my colleague, Ricky Savjani, executed. We swapped *religious ingroup* trial labels with the closest temporally adjacent *religious outgroup* trial labels (**Figure 13**). Since this yielded no significant *ingroup* effect, we concluded that the main results cannot be attributed to either random timing effects or to an unbalanced number of trials.

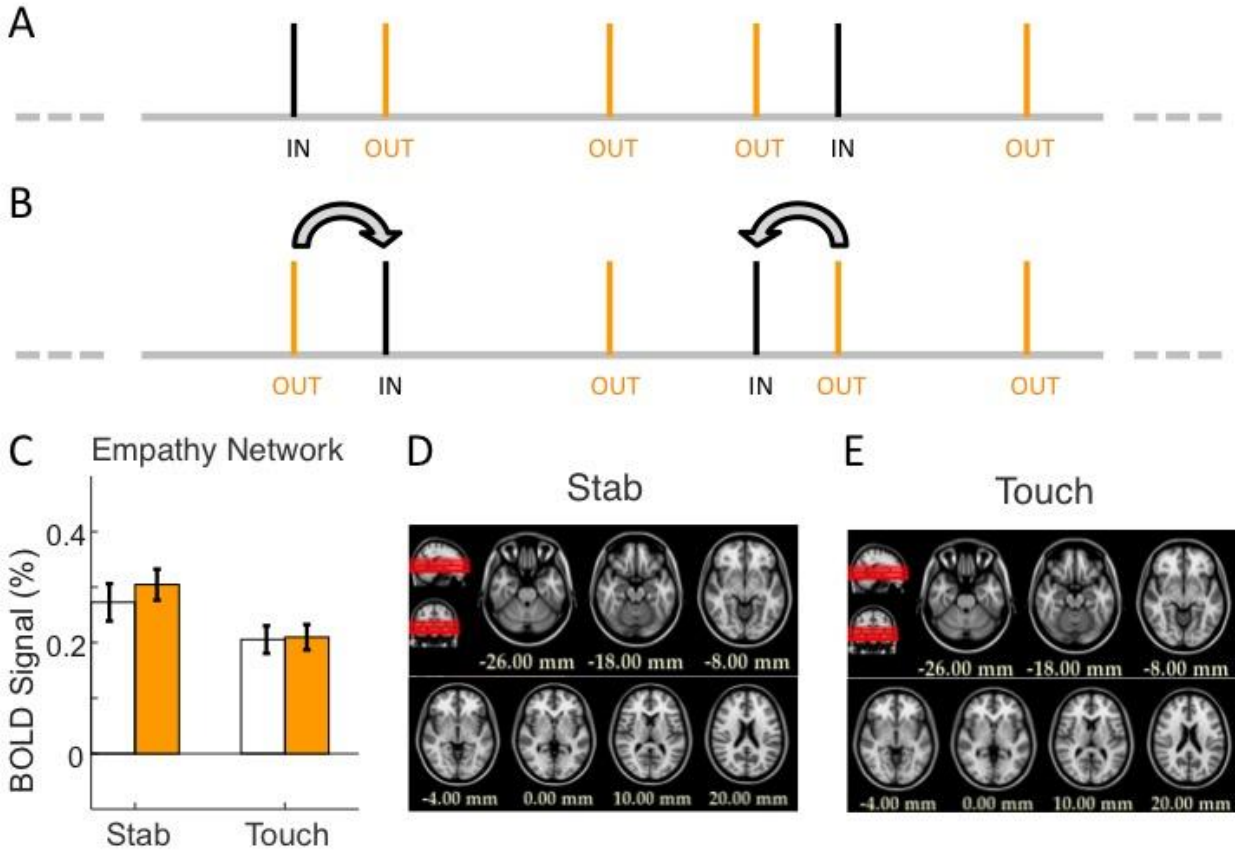



**Figure 13 - control for unbalanced number of trials. A**. The stick diagram represents a schematic of the true timing of *religious ingroup* and *religious outgroup* trials. For simplicity, condition type (*stab* or *touch*) labels are not shown. **B**. *Religious ingroup* trials were swapped with temporally adjacent *religious outgroup* trials with condition preserved. **C**. With the *religious ingroup* trials swapped, the group effect of

the empathy network is no longer observed (*stab*: $p = 0.92$, *touch*: $p = 0.59$, permutations testing). Error bars SEM. Furthermore, a whole-brain search for *religious ingroup* > *religious outgroup* effects yielded no significant voxels for either *stabs* (**D**) or *touches* (**E**).

---

### *Experiment 2: flexibility of religious ingroups*

Subsequently, I investigated the flexibility of the bias between religious ingroups and religious outgroups. When the participant learned that the 6 religions were divided into 2 teams at war with each other, 2 outgroup religions became part of the participant's "team." To represent their status as falling somewhere on the spectrum between *religious ingroup* and *religious outgroup*, I labeled these hands *religious allies*. I found that these *allies* did not elicit a neural response in the empathy network that differed significantly from the response to the *religious outgroup* members ($p = 0.40$, **Figure 14**, n = 14).

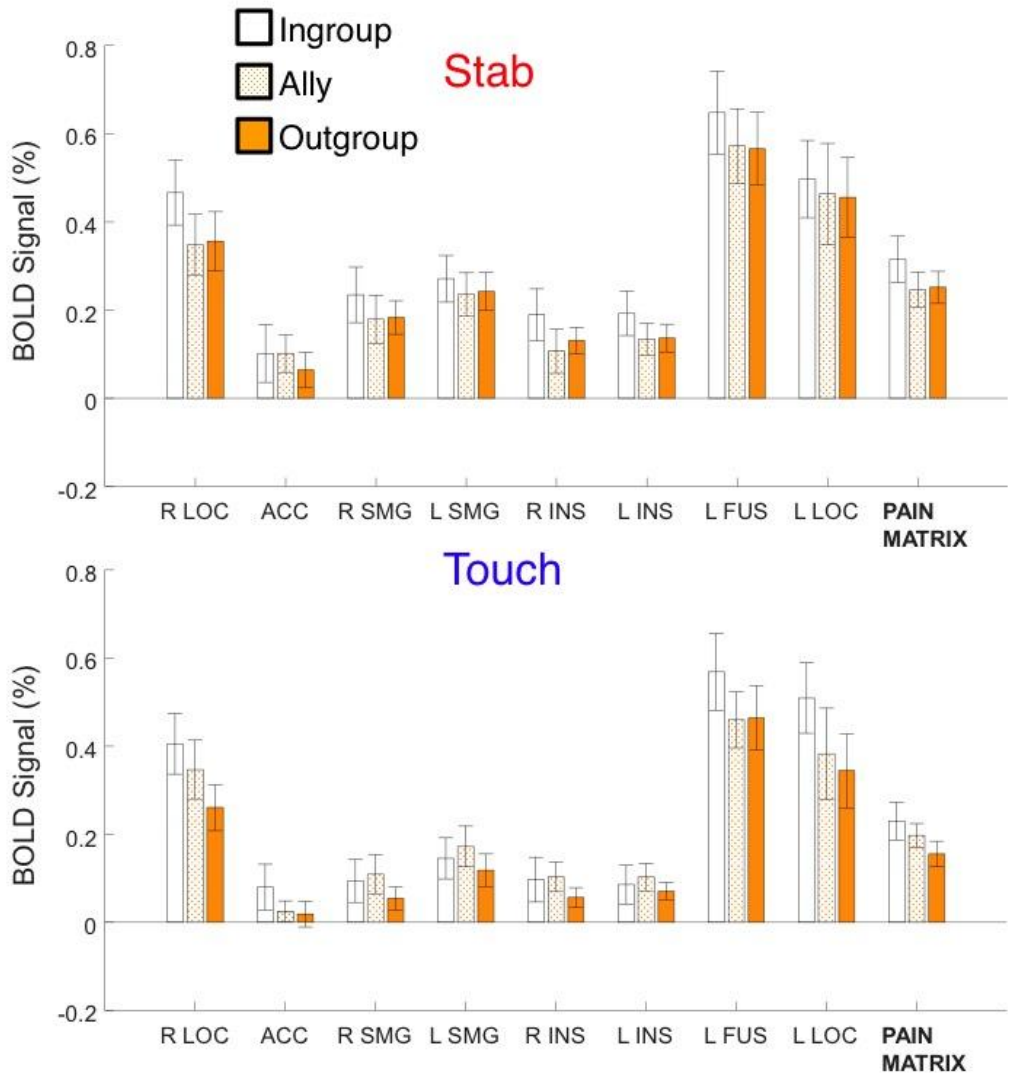



**Figure 14 - results of the forward model on Experiment 2.** PE for each condition of each ROI within the empathy network are shown for both *stab* and *touch* trials. Manipulating allegiances did not alter brain responses within the empathy network. Specifically, the mean of the *religious ally* condition did not differ significantly from the mean of the *religious outgroup* condition in the empathy network ($p$ = 0.40). Error bars SEM.

---

### *Experiment 3: arbitrary team membership*

Next, I investigated whether an ingroup/outgroup bias existed in the case of the arbitrarily assigned teams. I found that in the empathy network, the mean of the *arbitrary ingroup* condition was not significantly different from the mean of the *arbitrary*

*outgroup* condition ($p$ = 0.78, n = 14). Since I did not find a significant difference, I did not test each individual brain region for a significant difference; for completeness, however, they are shown below (**Figure 15).**

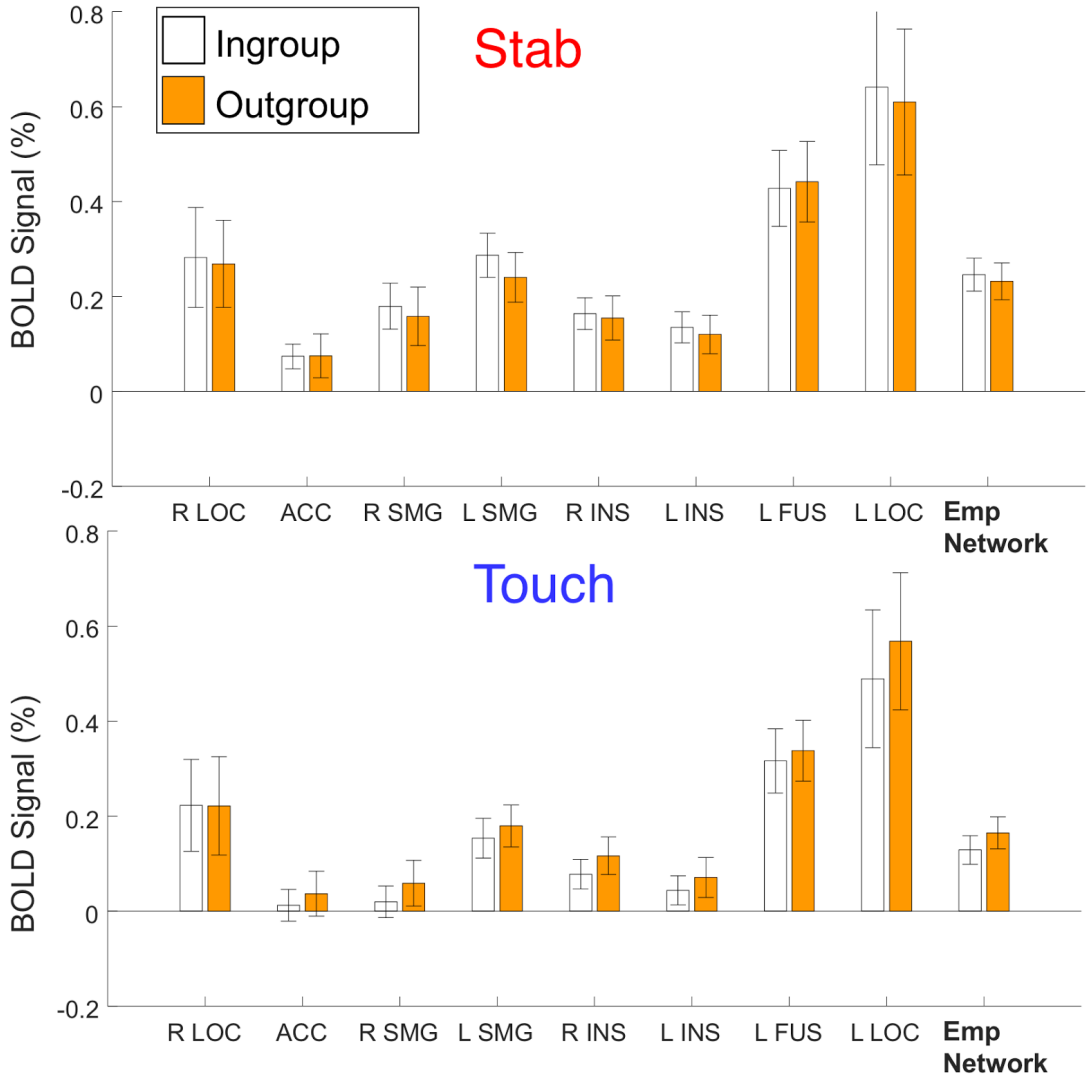



**Figure 15 - results of the GLM in Experiment 3.** PEs for each condition of each ROI within the empathy network are shown for both *stab* and *touch* trials. Arbitrary assignment to a team did not alter brain responses within the empathy network. Specifically, the mean of the *arbitrary ingroup* condition did not differ significantly from the mean of the *arbitrary outgroup* condition in the empathy network ($p$ = 0.78). Error bars SEM.

## 2.4.3 Classification

### *Touch vs stab*

I first classified the distinction between *baseline* events as unlabeled *baseline touch* and *baseline stab* conditions. I could not use the empathy and relief network activation as features because we derived them from the univariate contrast of *baseline stab* and *baseline touch.* Using activity in regions specified by the Harvard-Oxford parcellation, my classifier discriminated the *baseline touch* from *baseline stab* conditions with 98% accuracy and 99% AUC-ROC, which is significantly greater than the chance AUC-ROC of 50% ($p < 10^{-4}$, **Figure 16A**, n = 210 instances). This model distinguished a single *stab* and *touch* trial with 71% accuracy and 77% AUC-ROC (**Figure 16B**, n = 1144 instances). Including visual areas as features, the accuracy and AUC-ROC increased to 72% and 80%, respectively (**Figure 16B**).

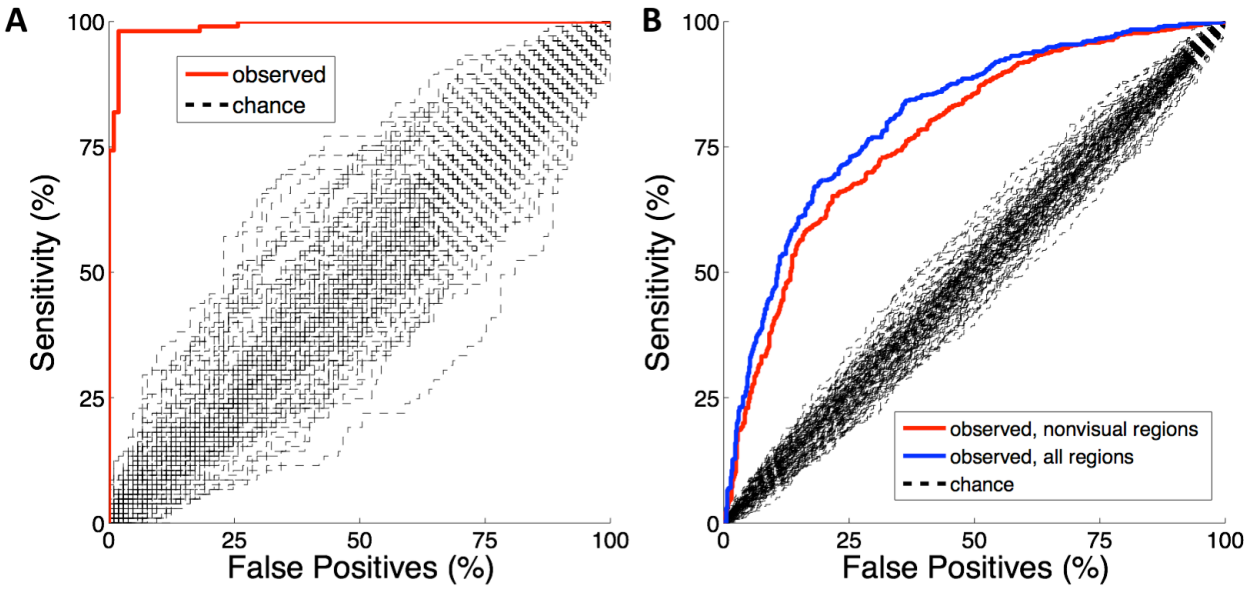



**Figure 16 - discriminating the perception of stab and touch. A.** Using non-visual regions of the Harvard-Oxford parcellation as features, my classifier distinguished a participant's *baseline stab* from *baseline touc*h conditions with 95% accuracy and 98% AUC-ROC, significantly greater than the chance

AUC-ROC of 50% ($p < 10^{-4}$, n=210 instances). **B.** Classification of *baseline stab* from *baseline touch* at the individual trial level. Chance lines are for reference only; I performed no hypothesis testing since the discriminatory power was already shown in panel **A**.

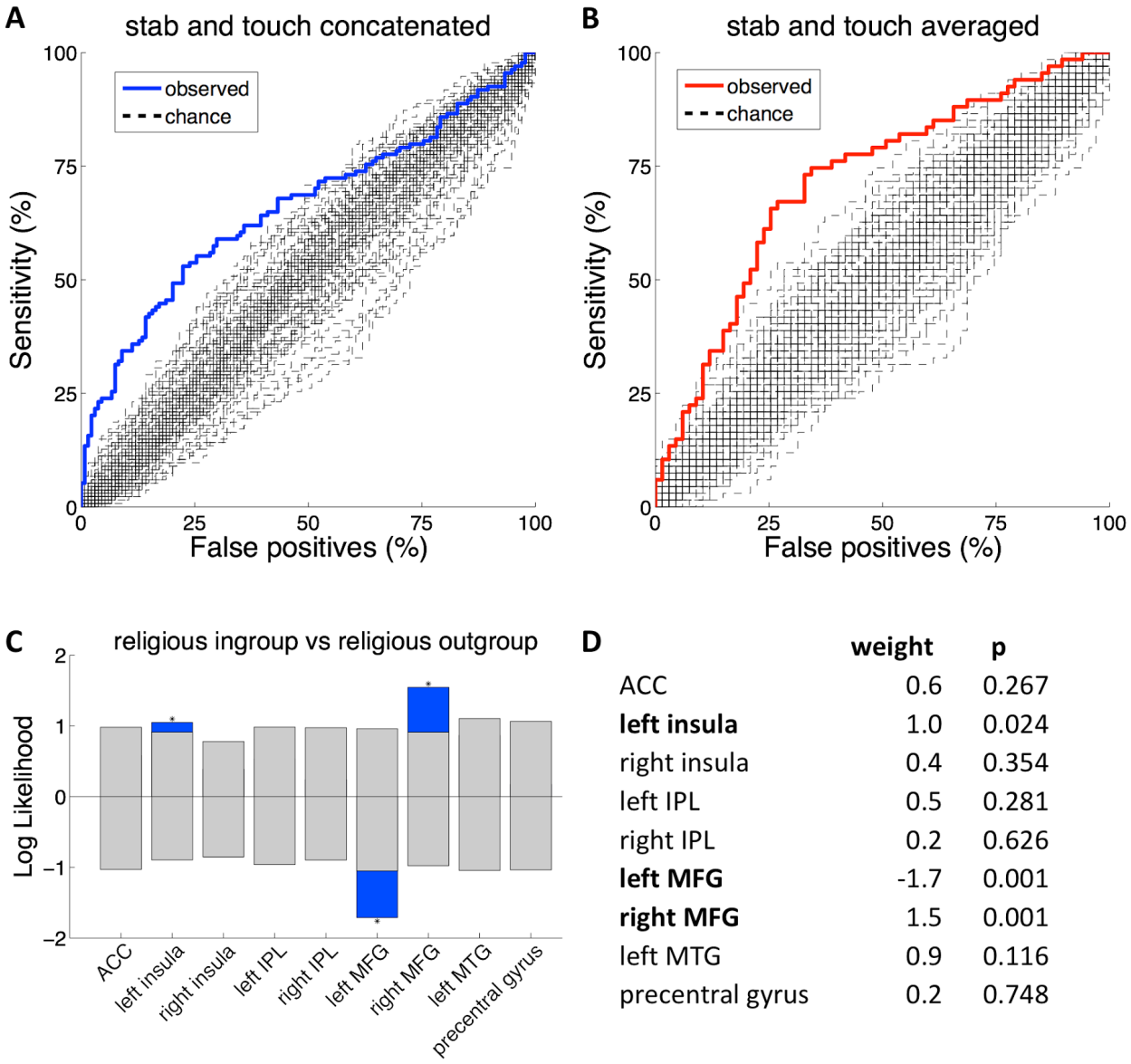
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### *Ingroup vs outgroup*

I assessed the experiment's central question: is there a consistent difference across all three experiments in the neural representation of ingroup and outgroup? I attempted to find answers using BOLD activation within the empathy network, relief network, and mentalizing network. I excluded visual ROIs because I did not want my classifier operating on the uncontrollable visual differences between conditions (a needle vs a cotton swab for *baseline stab* vs *baseline touch*, and the text of each religion for *ingroup* vs *outgroup*). Although it would indeed be interesting to examine ingroup/outgroup bias based on text alone, it is beyond the scope of this paper, and I will not discuss it further. I referred to this collection of non-visual ROIs as the *a priori* model because our univariate results informed the feature choice for classification. I trained and cross-validated the model on Experiment 1, *religious ingroup* vs *religious outgroup*, and then applied it to the validation data in Experiment 2 and Experiment 3. I did not include the mentalizing network in the classification of *religious ingroup* vs *religious outgroup* because I derived the mentalizing network from the univariate contrast *ingroup* > *outgroup*; thus, inclusion of the network would be a non-independence error.

To provide a diagnosis of ingroup-related empathic bias across *stab* and *touch* conditions, I started with the four *religious* conditions from the *religious ingroup* – *religious outgroup* block. The classifier distinguished the conditions of *religious ingroup stab* and *religious ingroup touch* from *religious outgroup stab* and *religious outgroup*

*touch* with an accuracy of 62% and 66% AUC-ROC, which is significantly greater than the chance AUC-ROC of 50% ($p < 10^{-4}$, **Figure 17A,** n = 268 exemplars). I averaged the *stab* condition and *touch* conditions within each class to calculate a single unique instance per participant and to reduce noise. The classifier distinguished *religious ingroup* from *religious outgroup* with 67% accuracy and 72% AUC-ROC (**Figure 17B,** n = 67 participants**)**. Permutations testing revealed three regions with significant contributions in the model: the right insula, left MFG (medial frontal gyrus), and right MFG (**Figure 17C**). **Figure 17D** shows the magnitude and uncorrected p-values of the model's features. To assess the distributed nature of this effect, I re-ran the model with the three significant features removed. The reduced model approached significance ($p < 0.06$) and had a reduced accuracy and AUC-ROC of 61% and 66%, respectively.




**D**

| | weight | p |
|---|---|---|
| ACC | 0.6 | 0.267 |
| **left insula** | 1.0 | 0.024 |
| right insula | 0.4 | 0.354 |
| left IPL | 0.5 | 0.281 |
| right IPL | 0.2 | 0.626 |
| **left MFG** | -1.7 | 0.001 |
| **right MFG** | 1.5 | 0.001 |
| left MTG | 0.9 | 0.116 |
| precentral gyrus | 0.2 | 0.748 |

**Figure 17 - classification of religious ingroups and outgroups using the *a priori* model. A.** A ROC curve for distinguishing the conditions of *religious ingroup stab* and *religious ingroup touch* from *religious outgroup stab* and *religious outgroup touch*. The accuracy and AUC-ROC were 67% and 72%, respectively, which is significantly greater than the chance AUC-ROC of 50% ($q < 10^{-3}$). **B**. Chance lines are for reference only; I performed no hypothesis testing since the discriminatory power was already shown in panel **A. C.** The significant weights of the *a priori* model are shown in blue and 95% null confidence intervals in grey. Stars represent a weight's empirical *p*-value is less than 0.05, uncorrected. **D.** Table of exact model weights and uncorrected empirical *p*-values; significant weights in bold.

---

To test whether this model was specific to religious ingroups and outgroups or instead pertained to ingroups and outgroups more generally, I next applied my *a priori* model (now including the mentalization network) to the validation data from Experiment 2 and

Experiment 3. The weights, now including the mentalization network ROIs, are shown in **Figure 18A**.

In Experiment 2, two hands with religious identities that were different from the participant's religion were placed on a team with the *ingroup* hand (**Figure 4**). My *a priori* model classified *religious ally touch* and *religious ally stab* conditions from *religious outgroup touch* and *religious outgroup stab* with an accuracy of 55% and an AUC-ROC of 63%, which was significantly different from the chance of 50% ($p = 0.05$, n = 56 instances). After averaging the *stab* and *touch* conditions for each participant, as before, the classifier discriminated the *religious ally* condition from the *religious outgroup* condition with 71% accuracy and an AUC-ROC of 68% (**Figure 18B, green**).

In Experiment 3, participants received a random assignment to one of the two fictitious teams (**Figure 5)**. My *a priori* model classified *arbitrary ingroup touch* and *arbitrary ingroup stab* conditions from *arbitrary outgroup touch* and *arbitrary outgroup stab* with an accuracy of 59% and an AUC-ROC of 63%, which was significantly different from the chance of 50% ($p = 0.02$, n = 56 instances). After averaging the stab and touch conditions together for each participant, the classifier discriminated the *arbitrary ingroup* condition from the arbitrary *outgroup* condition with 71% accuracy and 74% AUC-ROC (**Figure 18B, magenta**). All three independent significance tests of the model (Experiment 1, Experiment 2, and Experiment 3) were significant after multiple comparisons corrections.

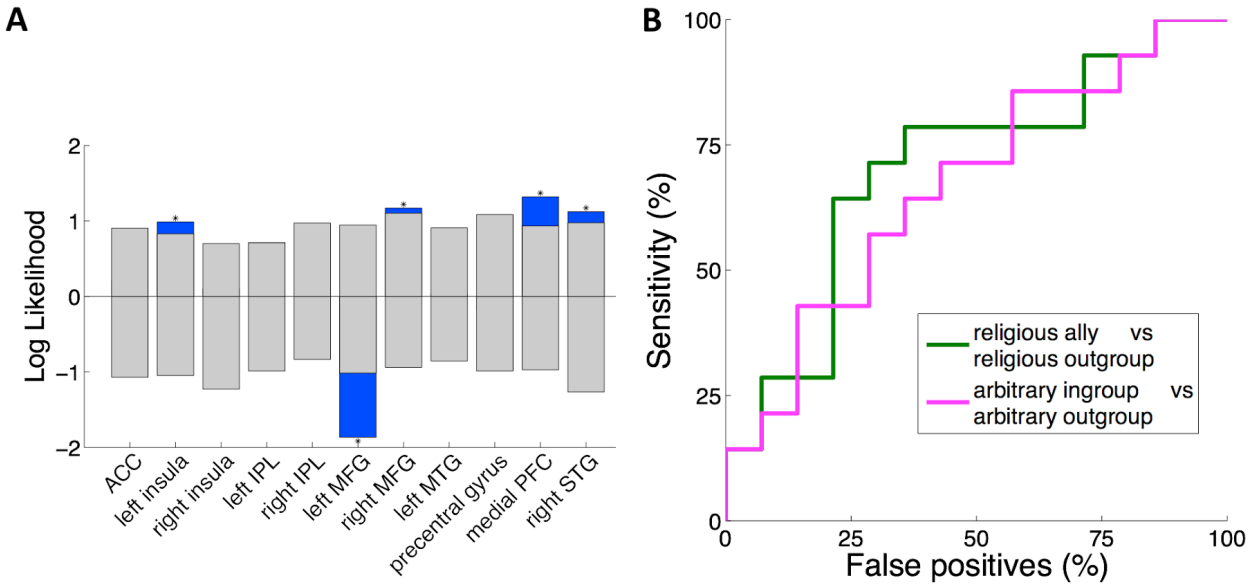
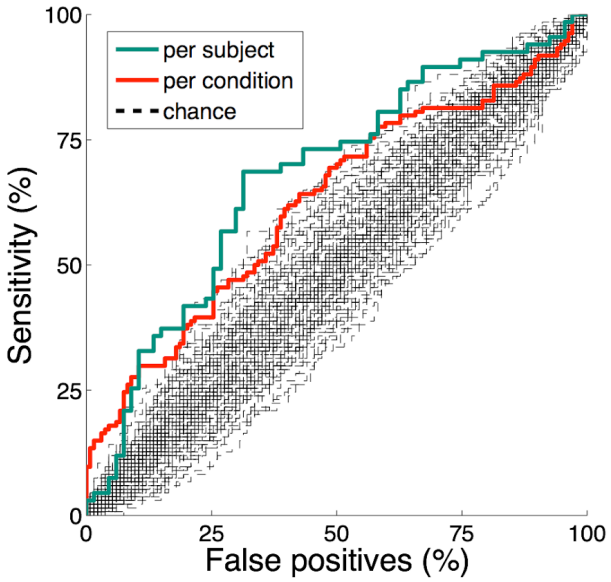



**Figure 18 - validation results. A.** Weights of the 11 non-visual regions of empathy, relief, and mentalizing networks, which comprise the *a priori* model. One or more components from each network are significant; there are no multiple comparisons corrections on the weights. **B.** Classification results at the participant-level for both validation experiments distinguishing *religious allies* from *religious outgroup* and *arbitrary ingroup* from *arbitrary outgroup* (n = 14 participants in both experiments).

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To investigate whether expanding beyond my *a priori* network improved my model's diagnostic ability, I trained a model to classify between the main *religious ingroup* versus *religious outgroup* activation in regions of the Harvard-Oxford atlas whole-brain parcellation as features. This whole-brain model had an accuracy of 59% and an AUC-ROC of 63%, which was significantly different from the chance of 50% ($p < 0.01$, n = 268 instances). After averaging the *stab* and *touch* conditions for each participant, as before, the classifier performance increased to an accuracy of 69% and an AUC-ROC of 68% (**Figure 19A**). Significant features are listed in **Figure 19B** and illustrated in **Figure 20**. Excluding visual regions, the accuracy and AUC-ROC for *religious ingroup* versus *religious outgroup* were reduced to 63% and 66%, respectively.

A




B

| | mean | p |
|---|---|---|
| **Frontal Medial Cortex** | 1.9 | 0.00 |
| **MTG Anterior Division** | 1.4 | 0.01 |
| **Left Putamen** | 1.3 | 0.00 |
| **Angular Gyrus** | 1.2 | 0.01 |
| **Left Accumbens** | 1.1 | 0.03 |
| **IFG ParsTriangularis** | 1.0 | 0.03 |
| **Occipital Fusiform Gyrus** | 0.9 | 0.05 |
| **Supracalcarine Cortex** | 0.9 | 0.03 |
| **Heschls Gyrus** | 0.8 | 0.05 |
| **Insular Cortex** | 0.7 | 0.03 |
| **Superior Parietal Lobule** | -0.9 | 0.05 |
| **Cuneal Cortex** | -1.0 | 0.04 |
| **Subcallosal Cortex** | -1.2 | 0.01 |

**Figure 19 - whole brain ingroup vs outgroup model. A.** ROC curves for the whole brain model. As with all previous assessments of significance, chance curves are per condition, and the *stab* and *touch* conditions are averaged together for the per-participant ROC curve. **B.** Model weights that are significantly different from zero. Empirical *p*-values are uncorrected.

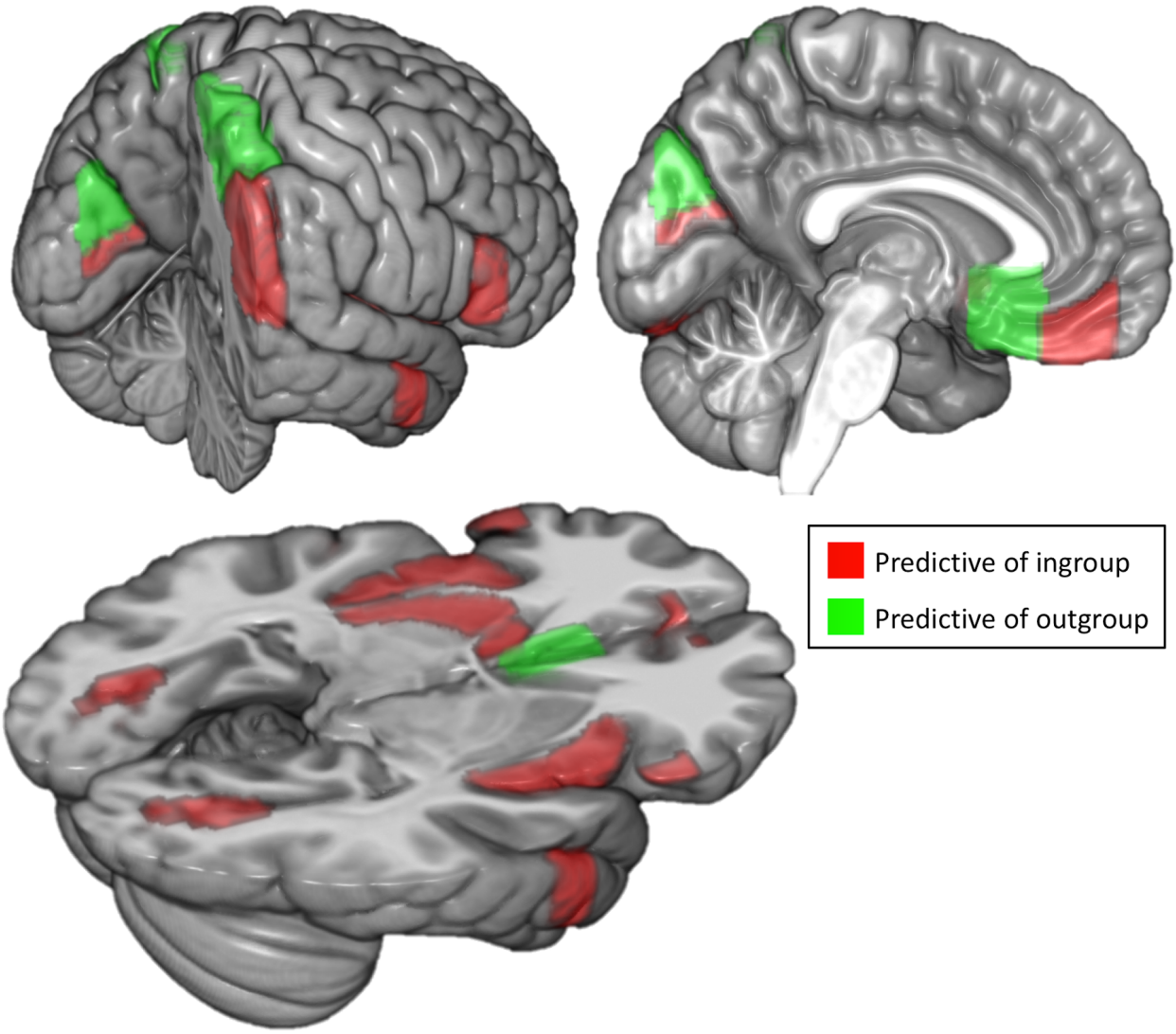



**Figure 20 - rendering of significant weights in the whole brain model.** Significant weights from the whole-brain ingroup model. All regions have an empirical *p*-value < 0.05, uncorrected.

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## 2.5 Discussion

The empathy network, which I defined operationally as *baseline stab* > *baseline touch* in my univariate analysis, is highly consistent with previous findings. It contains common affective components (Zaki and Ochsner 2012; Singer 2004; Decety 2010) including the bilateral insula and anterior / medial cingulate cortex. Sensorimotor components of the empathy network for pain are less exact because they depend on the task stimuli (Lamm, Decety, and Singer 2011). Indeed, most imaging studies on empathy for pain

have suggested the anterior insula (AI) and anterior cingulate cortex (ACC) as the main areas involved (Cheng et al. 2007; Lamm, Batson, and Decety 2007; Jackson et al. 2006; Morrison, Peelen, and Downing 2007; Saarela et al. 2007; Morrison and Downing 2007).

Nevertheless, primary and secondary somatosensory regions have demonstrated involvement in empathy for pain (Lamm et al. 2007; Bufalari et al. 2007; Cheng et al. 2008). Avenanti et al. supported this finding: they used transcranial magnetic stimulation (TMS) to show that the simple observation of a needle penetrating the hand muscle results in a reduction in the amplitude of the motor-evoked potentials (i.e. motor inhibition) (Avenanti et al. 2006; Avenanti et al. 2005). Tasks involving visual stimuli of body parts in painful situations tend to recruit the ventral premotor area and the inferior parietal lobule (Chong et al. 2008; Decety and Grèzes 1999), which are involved in processing observed action (Fogassi et al. 2005; Buccino et al. 2001; Grèzes and Decety 2001).

Picture-based paradigms, which include the presentation of photographs displaying limbs in painful situations, are likely to activate the somatosensory cortex (Avenanti et al. 2005; Avenanti et al. 2006; Bufalari et al. 2007; Cheng et al. 2008; Lamm et al. 2007; Lamm, Decety, and Singer 2011; Van Overwalle and Baetens 2009). A picture-based paradigm of mere observation of touch activates the secondary somatosensory cortex (Keysers et al. 2004; Avenanti et al. 2005). Generally, researchers also observed a subset of the inferior frontal gyrus and lateral occipital gyrus (Carr et al. 2003; Iacoboni

et al. 1999). The empathy network I localized includes all of these areas as well as the left fusiform gyrus, which may be included because the fusiform is often recruited in hand representation (Grosbras and Paus 2006; James and Engelhardt 2012). This observation is also in line with previous reports suggesting the activation of the fusiform in intentional empathy (de Greck et al. 2012; Nomi et al. 2008).

Likewise, my univariate contrast *religious ingroup > religious outgroup* yielded areas implicated in self-referential thought and mentalizing (Zaki and Ochsner 2012; Mitchell, Banaji, and Macrae 2005). The canonical mentalizing network includes the medial prefrontal cortex (mPFC), precuneus, right temporoparietal junction, temporal poles, and sometimes amygdala (Rameson, Morelli, and Lieberman 2012; Lawrence et al. 2006; Völlm et al. 2006). Some studies find the middle temporal gyrus present in mentalizing paradigms (Shamay-Tsoory 2011; Marsh et al. 2010), while others included it in the empathy network (Zaki and Ochsner 2012; de Greck et al. 2012). Similarly, some studies find that the inferior parietal lobule is recruited in both experience-sharing (Keysers et al. 2004) and perspective-taking paradigms (Decety and Lamm 2006).

There is a strong qualitative correspondence between the three networks I localized (**Figure 21A)** and the two generally accepted networks underlying affective and cognitive empathy (**Figure 21B)** (Zaki and Ochsner 2012). Note that many studies find very caudal ACC activation (sometimes even middle cingulate cortex) in empathy for pain paradigms (Singer 2004).

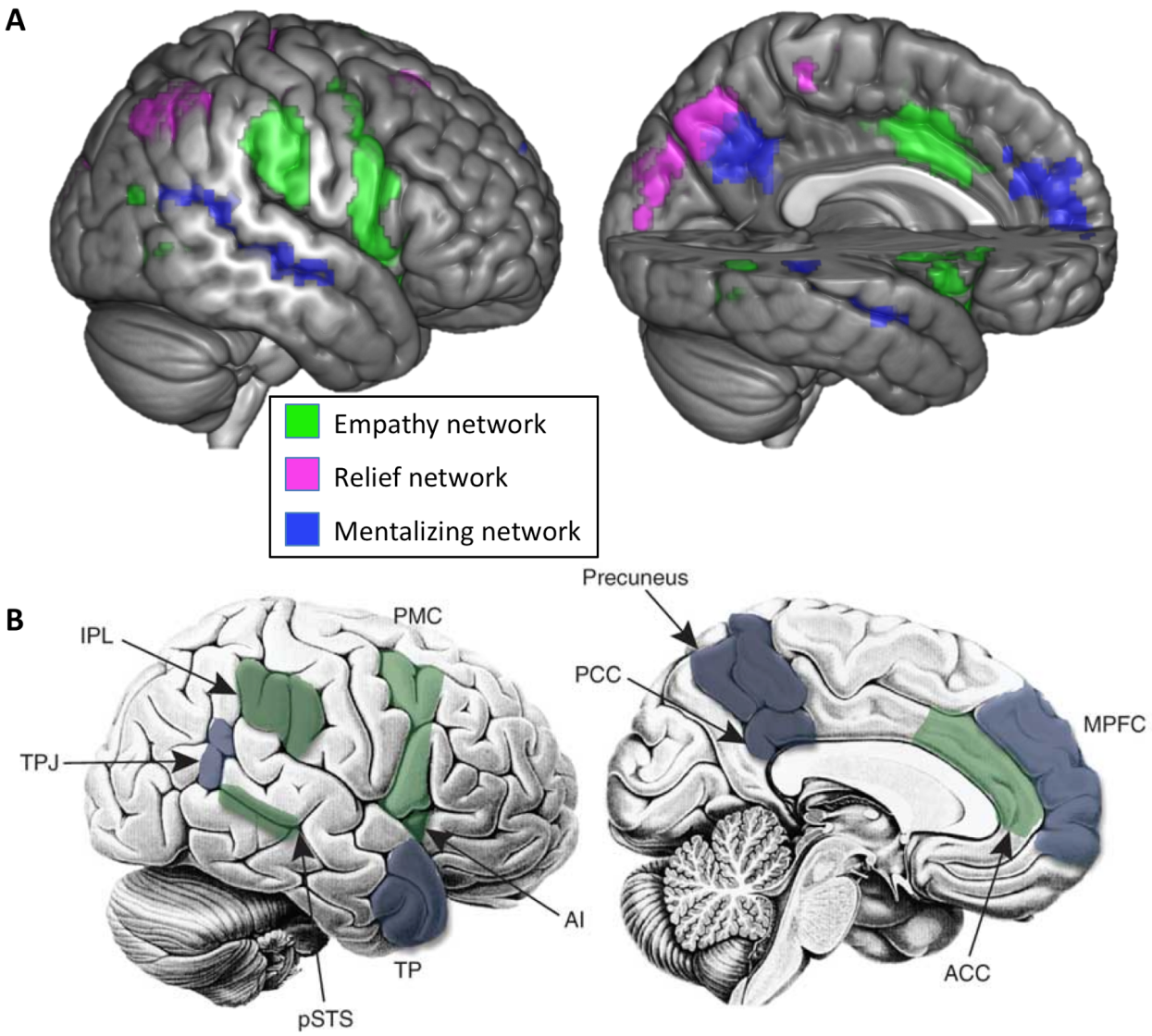



**Figure 21 - comparison of the empathy and mentalizing network with previous work. A.** The empathy, relief, and mentalizing networks localized in our univariate paradigm. **B.** Affective empathy and mentalizing networks reproduced from a 2012 *Nature Neuroscience* review article on empathy (Zaki and Ochsner 2012). The empathy network is shown in green and mentalizing in blue. Our empathy and mentalizing networks are a superset of those listed here, with the exception of the temporal pole.***Key:*** ***ACC*** *= Anterior Cingulate Cortex,* ***AI*** *= Anterior Insular,* ***IPL*** *= Inferior Parietal Lobule,* ***MPFC*** *= Medial Prefrontal Cortex ,* ***PMC*** *= Premotor Cortex,* ***pSTS*** *= posterior Superior Temporal Sulcus,* ***TP*** *= Temporal Pole ,* ***TPJ*** *= Temporal-Parietal Junction.*

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Our results expanded upon previous findings by demonstrating that a neural-empathy bias is present in religions affiliations. The ingroup bias was elicited by changing the text label written above a hand only, without any other information. Furthermore, the strength of the ingroup bias correlated with an individual's empathic rating but not with

their religious conviction. This indicated that the more a person can empathize with another, the stronger their ingroup bias. This ostensibly counter-intuitive result, informally dubbed “the dark side of empathy” by Dr. Iacoboni, has several interpretations.

There are multiple plausible explanations for the larger ingroup bias among participants with high BEES scores. It could stem from reduced activation in empathy and mentalizing regions for outgroup members: ergo, more self-reported empathy corresponds to larger bias. Alternatively, this ingroup bias may be present as a default in all humans at similar levels, but empathy acts as an amplitude modulator, and the response to both ingroup and conditions is multiplied. Highly empathic people would therefore have a larger response to both conditions, and the arithmetic difference between the two conditions would be inflated. These two hypotheses may be disambiguated in future analyses of this data, by regressing the religious ingroup and religious outgroup conditions, separately, against BEES scores. A positive correlation of BEES with religious ingroup and a negative correlation of BEES with religious outgroup would support the first hypothesis. Both correlations being positive supports the second hypothesis.

A third, non-exclusive consideration is that self-reported empathy may be biased. One pitfall of empathy questionnaires is the lack of specificity about the “other” alluded to in the questionnaires. For example, the Davis Interpersonal Reactivity Index asks, “When I see someone being taken advantage of, I feel kind of protective towards them.” When

answering empathy-related questions, perhaps participants, by default, imagine their "their own". I doubt participants would respond identically if the question were specific to their political/social/business opponents. Thus, it would not be surprising to find a correlation between self-reported empathy for one's own ingroup and a neural correlate of that bias. Studies assessing empathy as it relates to ingroup and outgroup differences should specify to whom each theoretical question is directed. The finding about more bias correlated with more self-reported BEES is further evidence that self-reported empathy is not a scalar value, but rather a vector quantity, with different magnitude for different groups.

In Experiments 2 and 3, I investigated the flexibility of religious ingroups and the generalizability of our model to arbitrarily formed groups. Specifically, can a simple story about team membership prompt the brain to generate a new representation of *allies*, bringing certain *outgroup* members into a role resembling *ingroup* members more closely? Does a similar process happen with the formation of arbitrary groups? In both cases, no significant effect appeared in the forward GLM for one of several explanations: (1) no detectable neural representational difference appeared between a *religious ally* and a *religious outgroup* member because the difference was purely semantic; (2) a representational difference may exist in some situations, but my simple narrative about team membership was insufficient to evoke the difference; (3) a representational difference existed even in my simple experiment, but I had insufficient power to detect it; or (4) the representation of ingroup and outgroups is a multivariate interaction fundamentally. My multivariate classification model distinguished *religious*

*allies* from *religious outgroup* members and *arbitrary ingroup* from *arbitrary outgroup* members successfully. Additionally, using the average activation in each of the three networks (combining the activation in each of their respective ROIs) did not distinguish the *religious allies* from the religious *outgroup* condition significantly (data not shown). These results are consistent with explanations (3) and (4): ingroup and outgroup representation is a multivariate interaction of empathy, relief, and mentalizing network ROIs, consistent with recent functional connectivity findings (Christov-Moore and Iacoboni 2016).

It is a vast over-simplification to represent the complexity of human affairs and allegiances as a one-dimensional spectrum between 100% ingroup and 100% outgroup. Yet, these results show there is utility in this sparse, low dimensional representation. I found that this one-dimensional model of ingroup and outgroup affiliations correlated with differential activity in the empathy, relief, and mentalizing networks. Furthermore, the multivariate interaction of these networks was diagnostic of ingroup – outgroup biases in religions, newly formed alliances, and arbitrarily formed teams. Bolstered by recent TMS results which suggest a causal link between these networks, empathic behavior and religious beliefs (Holbrook et al. 2016; Christov-Moore et al. 2017), we believe our paradigm and model may be used to diagnose propensities for (non-)empathic behavior, particularly in non-compliant subject populations. The applications are discussed in detail in Chapter V. Future studies may use the classification of activity in these networks as elicited by observing other individuals to assess the nature of participants.

### 2.6 Summary of work contributions

I designed all three versions of the experiment under the guidance of Dr. David Eagleman. I created and filmed the video stimuli, drafted the IRB protocols, and received their approval. I administered all surveys and ran all participants. My co-author Ricky Savjani and I each processed the data independently in FSL and SPM, respectively, and we used FSL's *randomise* to check our results and learn the process. I noted specifically the two analyses we developed together that he executed alone. My co-author and I both conducted the ROI-averaging of the functional data. He used FSL, and I used MATLAB. I performed all of the classifications analysis.

## Chapter III - Predicting diagnoses of anorexia nervosa and body dysmorphic disorder with multimodal neuroimaging and psychometric data

### 3.1 Abstract

Anorexia nervosa (AN) and body dysmorphic disorder (BDD) share distorted perception of appearance, obsessive and compulsive tendencies, and poor insight. AN and BDD are comorbid frequently. Despite many similarities, the recommended treatment strategies differ between AN and BDD. Correct diagnosis therefore is critical, particularly in early stages of the illness, to minimize risks associated with medical morbidity, mortality, and suicide. Unfortunately, distinguishing AN from BDD correctly can prove difficult in certain cases. Here, I used neuroimaging and psychometric data to predict the diagnoses for medication-free, normal-weight participants with AN or BDD compared to healthy controls (CTL). The multimodal dataset included BOLD signal changes from task-based fMRI using face, body, and house visual stimuli; path length metrics from diffusor tensor imaging (DTI); and psychometric data from the Brown Assessment of Beliefs Scale, Hamilton Anxiety Rating Scale, and Montgomery-Asberg Depression Rating Scale. My classification models distinguished CTL from participants with AN or BDD with a peak accuracy of 72% and an AUC-ROC curve of 88%, using principally a combination of participants' depression and anxiety scale scores. A second model distinguished participants with AN from participants with BDD with a peak accuracy of 76% and an AUC-ROC curve of 82%. Depression and insight scores and white matter normalized path length contributed significantly. If these models survive independent validation, they have the potential to help clinicians disambiguate

participants with AN from those with BDD, thereby clarifying the most appropriate treatment for each individual, improving their outcomes.

### 3.2 Introduction

Anorexia nervosa (AN) and body dysmorphic disorder (BDD) are DSM-5-defined pathologies (American Psychiatric Association 2013; Phillips et al. 2010; Brown, Holland, and Keel 2013) that share distorted perception of appearance (Grant, Kim, and Eckert 2002; Hartmann, Greenberg, and Wilhelm 2013; Hrabosky et al. 2009), obsessive and compulsive tendencies (Woodside and Staab 2006), and poor insight (Madsen, Bohon, and Feusner 2013; Zhang et al. 2016; Konstantakopoulos et al. 2012). BDD is characterized principally by a patient's obsession with a perceived defect in their appearance (Veale 2004; Didie, Kuniega-Pietrzak, and Phillips 2010). Prevalence in the general population is estimated to fall between 0.7% (Faravelli et al. 1997; Otto et al. 2001) and 2.4% (Koran et al. 2008). AN is characterized by restriction of energy intake, yearning to be thin, disturbance in one's perception of body weight, and low Body Mass Index (BMI) (Agüera et al. 2015; Sunday and Halmi 2003). In young females, the prevalence is an estimated 0.3% (Hoek and van Hoeken 2003) with 0.6% mortality per year (Sullivan 1995; Hoek 2006).

Individuals with BDD and with AN have elevated rates of completed suicide (Phillips and Menard 2006; Phillips 2007; Coren and Hewitt 1998; Pompili et al. 2004). Medical morbidity and mortality related to the starvation state are major risks in individuals with AN specifically (Keel et al. 2003). Treatment with cognitive behavioral therapy (Beck 1979) can be effective in BDD (Neziroglu et al. 1996; Greenberg et al. 2010; Halmi,

Mitchell, and Crow 1999), but its effectiveness in AN is minimal; family-based psychotherapy in adolescents has more empirical support (Eisler et al. 2000; Eisler et al. 2007; Lock et al. 2005). BDD responds to treatment with selective serotonin reuptake inhibitors (SSRIs), but AN does not (Phillips and Hollander 2008; Holtkamp et al. 2005). Clearly, choosing an effective treatment is predicated on proper diagnostic classification of patients.

Unfortunately, it often is difficult to separate the diagnoses of AN and BDD. Individuals sometimes present so similarly that some researchers question whether one disorder should be considered a subtype of the other (Grant and Phillips 2004; Grant, Kim, and Eckert 2002). For example, 30% of BDD patients have significant weight concerns, even if they do not have a comorbid eating disorder (Kittler, Menard, and Phillips 2007). Additionally, AN and BDD are comorbid with each other frequently (Grant, Kim, and Eckert 2002; Ruffolo et al. 2006; Rabe-Jablonska and Sobow Tomasz 2000). Approximately 33% of those with AN are diagnosed with lifetime BDD, and approximately 33% of those with BDD will have a lifetime eating disorder. It also is important to distinguish psychiatrically ill patients from non-psychiatrically ill patients. This may be particularly challenging and critical at early stages in adolescents, as behaviors consistent with normal development (e.g. overvaluing appearance, thoughts about dieting, mirror-checking) overlap with pathological symptoms of AN and/or BDD.

Neuroimaging has elucidated several features that may help distinguish AN from BDD. Recent research suggests that distorted perceptions of appearance may be linked to

abnormalities in the visual system (Madsen, Bohon, and Feusner 2013; Pallanti et al. 1998; Pietrini et al. 2011; Feusner et al. 2010; Grocholewski, Kliem, and Heinrichs 2012). A task-based fMRI paradigm showed differences between patients with AN/BDD and CTL participants in the dorsal stream and early secondary visual processing regions (Li, Lai, Bohon, et al. 2015). EEG likewise revealed differences in the latency and amplitude of P100 and N170 components in individuals with AN or BDD (Li, Lai, Loo, et al. 2015). These functional differences are underscored by the white matter tractography of the whole brain of patients with AN/BDD, in contrast with that of CTL participants (Hayes et al. 2015; Buchanan et al. 2013); BDD has a particularly stark effect on the visual system (Arienzo et al. 2013; Zhang et al. 2016). Previous work has also found that specific brain-behavior relationships correlate with these abnormalities: insight with ERP amplitude (Li, Lai, Loo, et al. 2015) and insight with DTI path length (Zhang et al. 2016).

In the context of these multimodal nature findings, I developed a classification model using the aforementioned neuroimaging and psychometric data to help clinicians disambiguate AN and BDD from each other and from the CTL participants. I performed this work under the guidance and mentorship of Dr. Jamie Feusner.

### 3.3 Methods and materials

#### 3.3.1. Participants

This study included data from 120 participants (age 22 +/- 4.5 years, 87.5% female): 33 diagnosed with AN, 44 diagnosed with BDD, and 43 healthy CTL. For semantic ease, I

defined the non-control group (non-CTL) to include all of the participants with either AN or BDD. Participants were matched for age and educational level.

Participants with AN were administered the Yale-Brown-Cornell Eating Disorder Scale (YBC-EDC) (Mazure et al. 1994), and participants with BDD were administered the Yale-Brown Obsessive Compulsive Scale (BDD-YBOCS) (Phillips et al. 1997). Participants of both patient populations took the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) and the Brown Assessment of Beliefs Scale (BABS) (Eisen et al. 1998). All participants took the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1969) and the Montgomery-Asberg Depression Scale (MADRS) (Montgomery and Asberg 1979). We verified participants' BDD diagnosis with a score greater than 19 on BDD-YBOCS and with the BDD diagnostic module (Dufresne et al. 2001). Participants with AN met all the DSM-IV criteria except for BMI less than 18.5.

Any of the following were exclusion criteria for participants: (1) any medical disorder affecting cerebral metabolism; (2) a pregnancy; (3) a neurological disorder; (4) any concurrent Axis I disorders other than dysthymia, major depressive disorder, or generalized anxiety disorder; (4) a score higher than 20 on the HDRS; (5) an assessment by Dr. Feusner that the participant was suicidal; and (6) a simultaneous diagnosis of both AN and BDD.

### 3.3.2 fMRI data

We acquired MR images from a Siemens Trio 3T scanner equipped with a 12-channel head coil. We acquired T1-weighted images with an MP-RAGE sequence and BOLD

signal changes from task-based fMRI using face, body, and house visual stimuli, henceforth referred to as the *faces*, *bodies*, and *houses* conditions, respectively. Participants engaged in a simple task of matching photographs of others' faces, bodies, and houses within separate runs. Each of these stimulus types was observed with low, normal, or high spatial-frequency content.

MRI data preprocessing involved running all individual participant data for three tasks as bodies, faces, and houses through ICA-based Automatic Removal Of Motion Artifacts (ICA-AROMA) with the option of non-aggressive de-noising (Pruim et al. 2015). Using FEAT (part of FSL), I processed participant data further with high-pass temporal filtering and nonlinear BBR registration.

Two of Dr. Feusner's lab members, Gigi Cheng and Dr. Teena Moody, executed a coherence analysis of the functional data. To create group-specific masks, they used FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) with multi-session temporal concatenation to obtain independent component (ICs) for each task (Beckmann and Smith 2004). Due to a software limitation in processing subjects with different numbers of TRs, they had to exclude one participant's data for the *bodies* condition and three participants' data for the *faces* condition. They allowed MELODIC to generate an unspecified number of ICs automatically, which resulted in 12, 9, and 10 components for *bodies*, *faces*, and *houses*, respectively. They matched the MELODIC-generated ICs to functional network ROIs (fROIs) from Shirer et al. by choosing the IC that had the highest correlation with

each network fROIs (Shirer et al. 2012). Tested fROIs included the following networks: salience, dorsal / ventral default mode, higher visual, left / right dorsolateral prefrontal cortex or executive control network, primary visual, and visuospatial. Then, they summed the ICs chosen from each task (*bodies*, *faces*, and *houses*), thresholded them at 95%, and binarized them to create a group-level independent component network (ICN) mask for each fROI. The resulting 8 ICN masks were our versions of the fROIs, derived from all participants.

Through dual regression (Zuo et al. 2010; Poppe et al. 2013), we used the group-spatial maps from MELODIC to regress into participant-specific time courses, and applied those time courses to regress into participant-specific spatial maps for each IC (Beckmann et al. 2009; Filippini et al. 2009). For every network fROI, we calculated coherence values for *bodies* by averaging the non-zero voxels within each participant's spatial map for the IC used to create the group-level ICN mask (Abram et al. 2015).

***DTI data***

The neuroimaging data also included DTI in the form of a minimally diffusion-weighted scan (the b0 image) and 64 gradient direction diffusion-weighted images with b = 1000 s/mm$^2$. Two colleagues of Dr. Feusner computed the participants' tractography, yielding CPL (the shortest path length between all pairs of nodes, averaged over all nodes) and normalized path length (see Chapter I, graph theory metrics for an introduction). I summarize their results here; see the original publication for more details (Zhang et al. 2016; Leow et al. 2013; Gadelkarim et al. 2014). They derived 87 cortical and subcortical structures from each participant's T1 imaging and continuous fiber tracking

from the diffusion-weighted results. Combining the parcellation and fiber tractography results yielded an 87 x 87 connectivity matrix of tractography relationships between these parcellations. From each participants' data, we calculated CPL of the actual data and of a random network of equivalent size and density. The ratio of observed CPL to that of a random network is the normalized path length.

***Classification***

I predicted the diagnoses using a L2-regularized logistic regression model and AUC-ROC as the statistic of interest (see introduction for details). Data are missing for participants as follows: the first eight patients with AN did not receive the BABS, one patient with BDD had no psychometric or processed fMRI data, and several participants' data were not included in either the DTI or fMRI because of atypical ventricles or acquisition errors. In total, 119 of the total participants completed the HAM-A and MADRS, 65 of the patients with AN and BDD completed the BABS, 84 of the total participants have acceptable DTI data, and 69 of the total participants have acceptable functional coherence data. Specifics on the presence of data between modalities can be found in **Supplementary Table S1**.

### 3.4 Results

In box plots below, the red bar, pink box, blue box, and dots represent the mean, SEM 95% confidence interval, one standard deviation (SD), and each participant, respectively. All tests between groups unless otherwise specified utilize a two-tailed permutation test with 10,000 resamples to calculate an empirical *p*-value.

### 3.4.1 Psychometric features

Because we gave participants either the YBC-EDC or BDD-YBOCS on the basis of their diagnosis, we therefore cannot use these questionnaire scores to differentiate between AN and BDD without creating a non-independence error. YBC-EDC and BDD-YBOCS do, however, have some overlap related to eating-related preoccupations and rituals (Hoffman et al. 2012), I reasoned that if the distributions did not differ in central tendency or variance, they could be included in the classification to capture multivariate interactions between the severity of eating disorder symptoms and the other variables. In spite of the similarities between the questionnaires, the distributions were significantly different in their mean ($p < 10^{-4}$, n = 24 AN and 43 BDD, **Figure 22A**). As such, I did not use YBC-EDC or BDD-YBOCS scores further in these analyses. BABS scores, however, were independent of diagnosis and differed significantly between participants with AN vs BDD ($p < 0.01$, **Figure 22B**).

CTL subjects had significantly lower mean HAM-A and MADRS scores (data not shown) than did subjects with AN and BDD diagnoses (both $p < 10^{-4}$, **Figure 22C**, n = 42 CTL and 77 non-CTL**).** I used HAM-A and MADRS to distinguish patients with AN from those with BDD, as well as CTL from non-CTL, subject to the dimensionality reduction discussed immediately below.

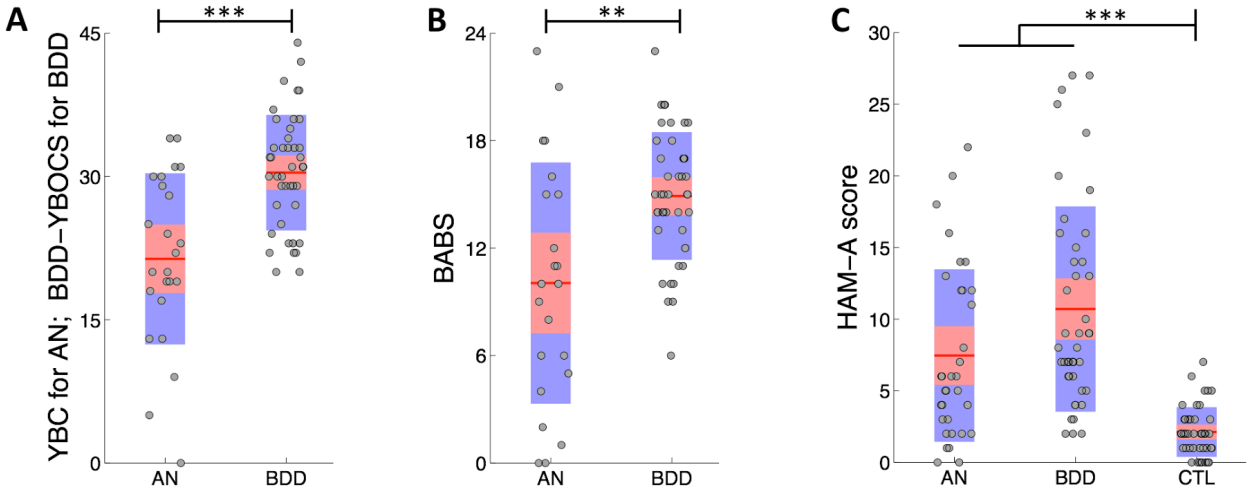



**Figure 22 - distributions of psychometric data. A.** Mean YBC and BDD-YBOCS scores from participants with AN and BDD, respectively, differed significantly and were not used for any classifications ($p < 10^{-4}$). **B.** BABS scores differed significantly in mean between participants with AN and BDD ($p < 0.01$) **C.** Mean HAM-A and MADRS scores also differed significantly between CTL and non-CTL participants ($p < 10^{-4}$).

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I observed a high Pearson correlation between the HAM-A and MADRS scores of all three participant groups (r = 0.85, 95% CI [0.79, 0.90] percentile bootstrap, **Figure 23A**). To reduce the number of redundant features, I collapsed both scales using principal components analysis (PCA). The first component explained 93% of the variance in the data (**Figure 23B**). I generated a combined metric, “MH” (MADRS & HAM-A), with each participant’s loading on this first principal component, to represent both scales.

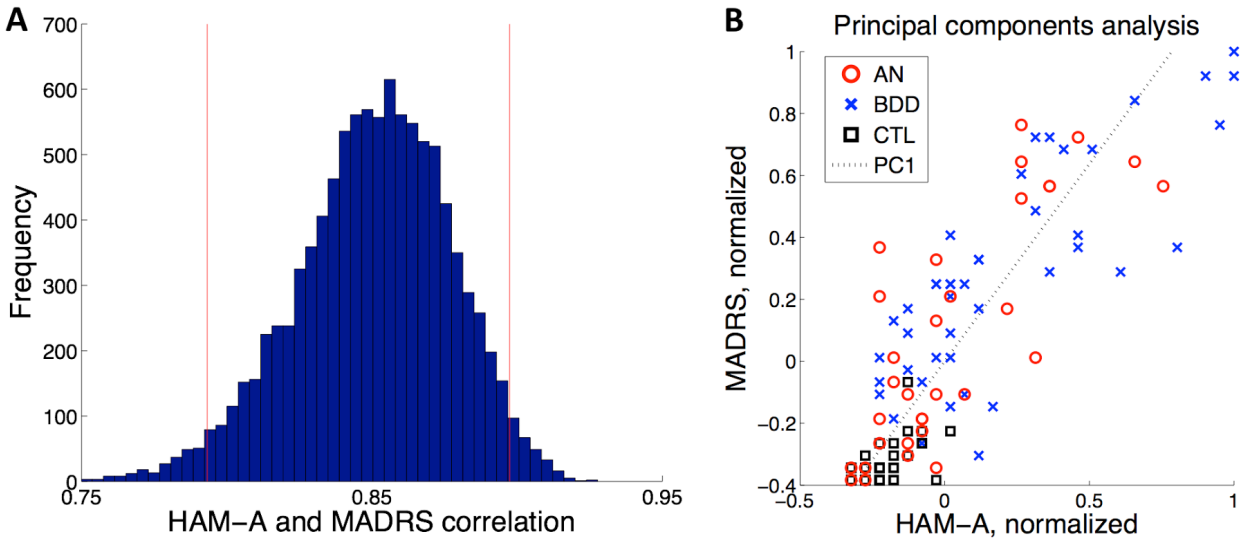



**Figure 23 - combining HAM-A and MADRS using PCA. A.** Histogram of 10,000 bootstraps of the correlation between HAM-A and MADRS. Red lines are 95% confidence interval. **B.** The first single principal component (PC1) of HAM-A and MADRS explained 93% of the variance among all participants with HAM-A and MADRS scores (n = 119). Each marker represents 1 participant.

### 3.4.2 MR features

Normalized path length differed significantly between participants with AN and participants with BDD ($p < 0.01$, n = 24 AN and 29 BDD) but notably not between CTL and non-CTL participants ($p = 0.35$, **Figure 24A**, n = 24 AN, 29 BDD, and 31 CTL). The AN group distribution was possibly bimodal, and a fraction of patients had a normalized path length similar to CTL and participants with BDD and another fraction had an even larger one. Since normalized path length is a fraction, I investigated whether this distribution was attributable to a difference in the observed CPL or to large fluctuations in the denominator (the CPL of the randomized network). The random network CPL did not differ significantly between the three populations (anova $p = 0.92$) The bimodal phenomenon appeared to stem from a larger CPL in the actual observed mean path length (**Figure 24B**), rather than from a decrease in equivalent random network CPL.

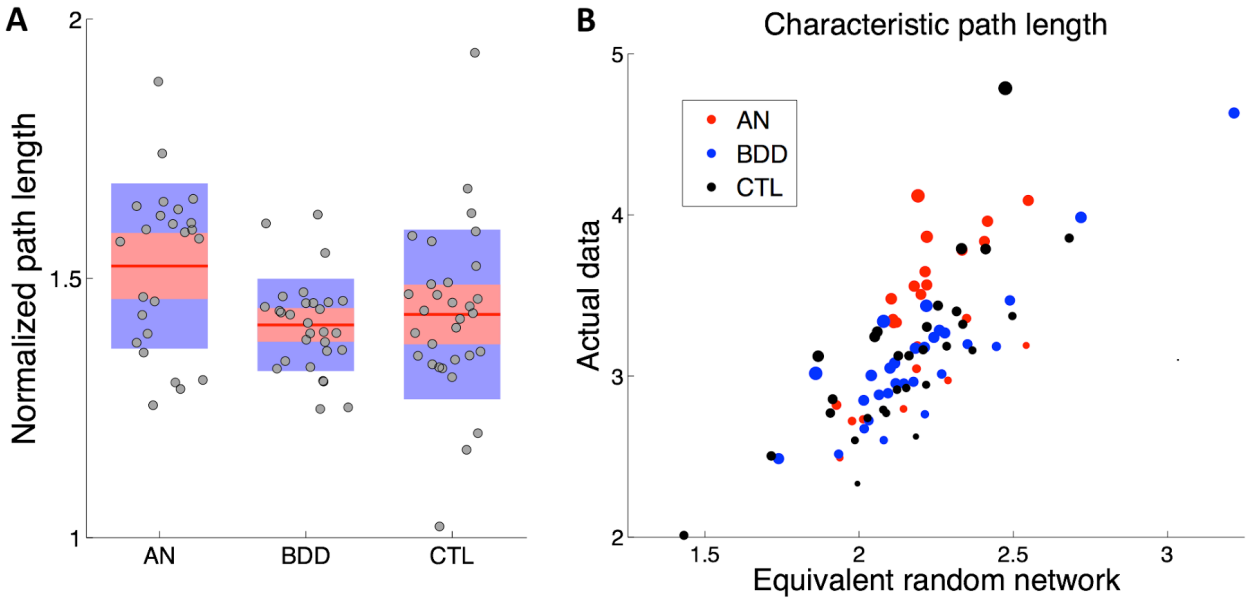



**Figure 24 - DTI path length data. A.** Box plots of normalized path length for each participant population. **B.** Relationship between actual and random CPL for all participants. Marker size reflects the normalized path length value. Each marker represents a participant.

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Because of the small sample size, I elected to use the coherence values in three hypothesis-driven regions as the primary visual, high visual, and salience networks since activation and functional connectivity had been found to be affected in AN and BDD populations previously (Moody et al. 2015). The relationship of these three features is shown in **Figure 25**.

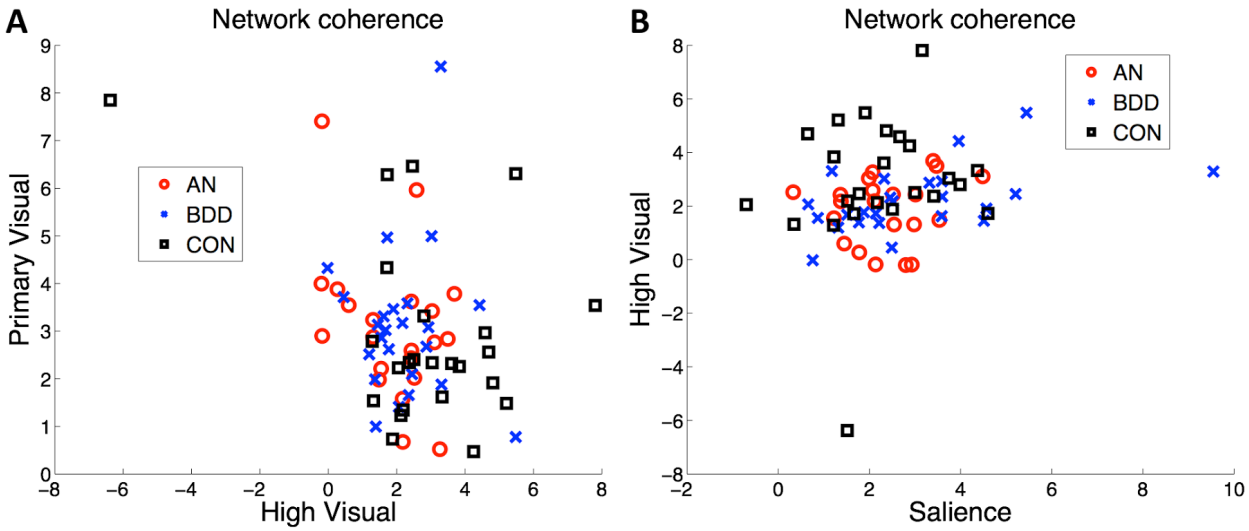



**Figure 25 - coherence in the three networks of interest. A.** Coherence values between the primary network and visual networks. **B.** Coherence values between the salience network and high visual network. Two participants were more than 3 standard deviations from the distribution. Each marker represents a participant.

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## 3.5 Classification

### 3.5.1 CTL vs non-CTL

With the justifications set forth above, I used my derived MH metric, normalized path length, and fROI coherence to classify CTL from non-CTL for a total of 56 participants (17 AN, 19 BDD, and 21 CTL). I assigned non-CTL to be the label-positive class; thus, sensitivity refers to the fraction of correctly identified non-CTL, and false positives refers to the number of control participants predicted to be non-CTL. The model achieved an accuracy of 72%, a mean PPV of 93%, and an AUC-ROC of 88%, which differed significantly from a chance AUC-ROC of 50% ($p < 0.01$, **Figure 26**). Only MH contributed to the classification significantly; its removal reduced the accuracy to 63%, the AUC-ROC to 64%, and rendered the classification non-significantly different from the chance value as measured by AUC-ROC ($p = 0.22$).

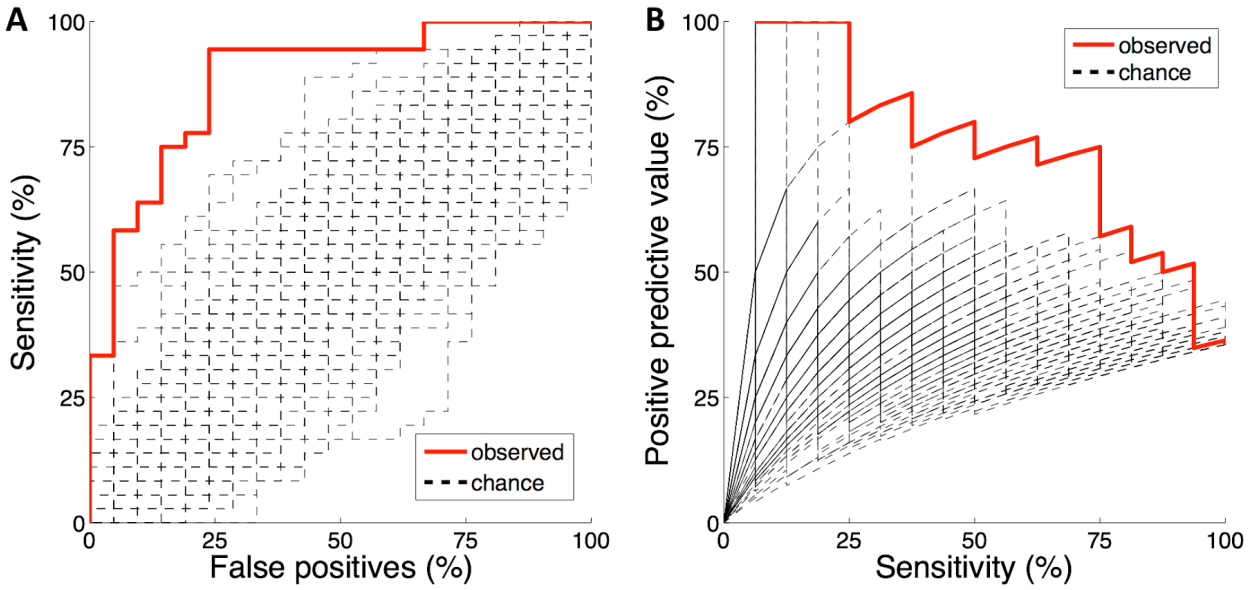



**Figure 26 - classification of CTL from non-CTL. A.** My classifier distinguishes CTL from non-CTL with an accuracy of 72% and an AUC-ROC of 88%, which is significantly greater than the chance AUC-ROC of 50% ($p < 0.01$). Sensitivity is the fraction of non-CTL identified divided by the total number of non-CTL. Only 100 null permutations are shown. **B.** The equivalent PR curve is useful when prioritizing one outcome over another. Chance curves are shown for reference only; I performed no significance testing.

### 3.5.2 AN vs BDD

Next, I investigated whether these multimodal data could distinguish the more difficult clinical task of predicting a diagnosis of AN or BDD. I assigned participants with AN to be the label-positive class; thus, sensitivity refers to the fraction of correctly identified participants with AN, and false positives refers to the number of patients with BDD predicted to have a diagnosis of AN. A model using MH, BABS, normalized path length, and coherence values had an accuracy of 70% and an AUC-ROC of 75%, which was not different from the chance value significantly ($p = 0.09$, n = 14 AN and 19 BDD). Here, there are 3 fewer participants with AN than the previous classification of controls from non-controls because those 3 participants did not have BABS scores. The coherence features were highly non-significant, so I elected to remove these features from the model, which also allowed me include 12 additional participants for whom there

was psychometric and DTI data but no functional data. A model incorporating the MH, BABS, and normalized pathlength distinguished patients with AN from those with BDD with 76% accuracy and an AUC-ROC of 82%, which is significantly greater than the chance AUC-ROC of 50% ($p < 0.05$, **Figure 27A**, n = 16 AN and 29 BDD). All three multimodal features were significant (**Figure 27B).** All three features in this model also differed significantly from 0 (MH $p < 0.05$, BABS $p < 0.05$, normalized path length < 0.01, uncorrected). To be clear, removing the coherence features did not allow the model to reach significance; rather, removing the coherence features allowed me to include 12 additional participants, each of whom had data for MH, BABS, and normalized path length data but *not* coherence data and were thus excluded from the first model. The possibility of imputing values is discussed below.

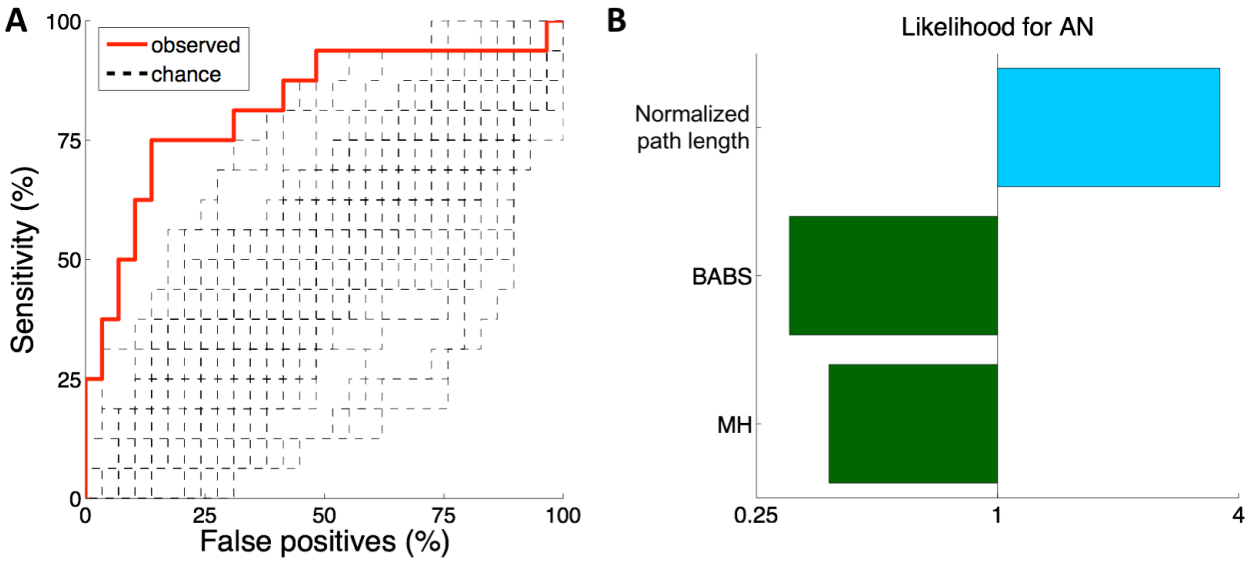



**Figure 27 - classification of patients with AN from those with BDD. A.** ROC curve for the model incorporating the MH, BABS, and normalized path length, which distinguished patients with AN from those with BDD with 76% accuracy and an AUC-ROC of 82% ($p < 0.05$, n = 16 AN and 29 BDD). **B.** OR for the 3 features in this model, all of which differed significantly from 0 ($p < 0.05$, uncorrected).

### 3.6 Discussion

A combination of neuroimaging and psychometric data predicted diagnoses of AN, BDD, or CTL. While a univariate combination of anxiety and depression scale data are adequate to distinguish CTL from non-CTL, a combination of psychometric and neuroimaging data best discriminate participants with AN from those BDD. These are not mutually-exclusive classifications; each group has overlapping, related features. A combination of both models yields a more informative clinical viewpoint and diagnostic flowchart: (1) is this potential patient neurotypical? (2) if not, how strongly does the evidence suggest they have symptoms of AN or BDD? By combining each participant's results for both models, we can see the relationship among these conditions more clearly (**Figure 28**).

This plot shows fairly strong separability between groups. If the threshold were set at 50% for both models, a few CTL participants would be misclassified as having AN, and a few participants with AN would be misclassified as CTL. It is interesting to note that none of the participants with BDD would have been misclassified as CTL. Given the high PPV in this context, if a new potential patient has a greater than 50% probability of both being non-neurotypical and having BDD, these results suggests high likelihood of a clinical diagnosis of BDD.

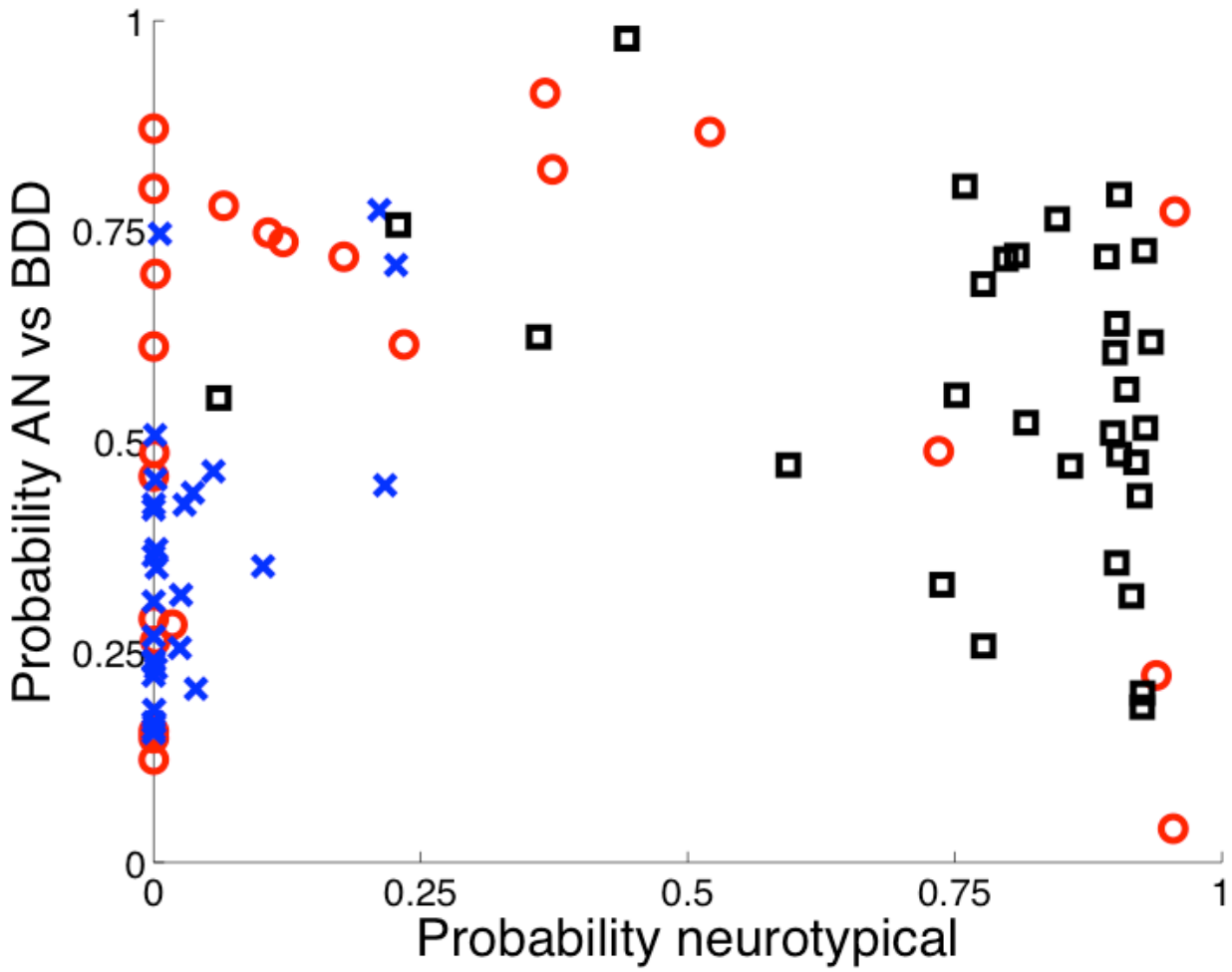



**Figure 28 - joint predictions of both models.** When synthesized, the CTL vs non-CTL model and the AN vs BDD model reveal relatively clear delineation between CTL participants (black), participants with AN (red), and participants with BDD (blue). The predictions of both models together reveal the high separability of these 3 groups. *Produced by Wesley Kerr from our ongoing collaboration.*

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My discrimination of CTL from non-CTL participants was limited by the criteria that CTL participants were required to meet. The inclusion criteria for CTL participants required the absence of a concurrent Axis I disorder; in contrast, I did allow patients with AN/BDD to have anxiety and depression comorbidities, which are common in those populations. Although I did not use scores from the questionnaires to exclude certain participants, CTL participants were more likely to have lower scores on HAM-A and MADRS questionnaire scores (the main features driving the CTL versus non-CTL

discrimination). This did not in any way diminish the power of this classifier to discriminate CTL participants from patients with AN or BDD. It did, however, limit the its applicability to the general population, not all of which meet the screening criteria satisfied by healthy CTL participants. If the general population has, for instance, higher HAM-A and MADRS scores than the CTL population, the accuracy will be reduced.

In addition, my findings were limited because of the relatively small sample size, which prevented me from dividing the data into a training group and independent validation group against which to test my model. An essential next step would be to validate my model using an independent sample of participants with AN or BDD. Ideally, this validation would have two parts. First, it would test whether my multimodal model significantly and usefully distinguishes participants who have been diagnosed with AN exclusively from those diagnosed with BDD, since they have been determined not to have both. Second, I would expect that participants comorbid with AN and BDD would be clearly differentiable from CTL. As a group, patients with comorbidity lie closer to the AN / BDD decision plane than participants with either AN or BDD. In other words, the variance in their probability estimates would be smaller than an identically sized group of participants with AN or BDD (but not comorbid). Another approach to this step would be to develop and test a 3-class classification model on a group that includes AN, AN/BDD comorbid, and BDD, which would perform better if there is an interaction effect on psychometric or neural data with AN/BDD comorbidity. To further the clinical utility of this model, the classification could be tested on adolescents at early stages of illness. If

these can be validated, my multimodal and two-stage classification model may aid in clinical disambiguation between healthy individuals and patients with AN or BDD.

## Chapter IV - Using insurance claims to predict and prevent IBD hospitalizations

### 4.1 Abstract

Inflammatory Bowel Disease (IBD) is an inflammatory disorder of the intestines that can necessitate hospitalization and the use of expensive biologics. Models predicting these interventions may improve patient quality of life and reduce expenditures of insurance companies. I used insurance claims from 2011 to 2013 to predict hospitalization for IBD and the use of biologics. I derived and optimized our model from a 2011 training set of 7,771 patients predicting their outcomes the following year. The final model then was applied to a 2012 validation set of 7,450 patients to predict their outcomes in 2013. The training models predicted both IBD hospitalization and biopharmaceutical use in the validation set significantly, with average PPVs of 17% and 11%, respectively – a more than 300% improvement over chance. Furthermore, I used topic modeling to identify four internally similar patient subpopulations. When included in our prediction model, the PPV of IBD-related hospitalization increased to 21%. I showed that using this hospitalization model, in concert with a mildly effective interventional treatment plan for the patients identified as high-risk, would both improve patient outcomes and reduce insurance plan expenditures. These results indicated a mechanism to provide personalized patient care based on insurance claims data, which is demonstrated here as a viable alternative to traditional medical data in the field of predictive medicine.

### 4.2 Introduction

Inflammatory Bowel Diseases (IBD) are disorders of the gastrointestinal tract that affect approximately one million people in the United States (Ford et al. 2011). IBD can be

subclassified into Crohn's disease (CD) or ulcerative colitis (UC). While UC is limited to the colon, CD can affect any parts of the gastrointestinal tract. These disorders may afflict some patients simultaneously. Although the life expectancy of patients with IBD is close to normal, recurring flares and serious complications including toxic megacolon and fistulas may require surgery and reduce quality of life substantially (Podolsky 1991; Sonnenberg 2007). IBD also reduces patients' work productivity significantly (Zand et al. 2015). It can be treated by a variety of immunomodulating medications, including corticosteroids, 5-aminosalicylic acids (5-ASA), thiopurines, and methotrexate, which decrease the body's overall immune response. Alternatively, IBD may be targeted by the more recently developed "biologics": compounds that target specific proteins in inflammatory pathways (Talley et al. 2011a). The introduction of these biological compounds, such as anti-TNF-α (adalimumab, infliximab, and certolizumab pegol) and α4-integrin inhibitors (natalizumab), resulted in major improvements in the quality of life of patients with IBD (Vogelaar, Spijker, and van der Woude 2009).

IBD is associated with significant costs for both patients and insurers. Total annual expenditures are estimated at $12,000 for a CD patient and $8,700 for a UC patient, of which patients pay approximately 15% out-of-pocket (Gunnarsson et al. 2011). Hospitalizations and biological treatment account for the highest portion of these costs as 13% and 72% respectively for CD and 15% and 39% for UC (van der Valk et al. 2016). Biologics are particularly costly, often exceeding $20,000 per person annually (Gleason et al. 2013). Despite their expense, doctors prescribe biologics because they are highly efficacious (Ford et al. 2011) and may reduce costs in the long run. Beyond

inducing remission in some patients with IBD, biologics may improve quality of life and work productivity, thereby reducing the indirect costs associated with IBD by almost 70% (Zand et al. 2015). The timing of treatment initiation is critical because an early therapeutic window has been shown to improve long-term outcomes (D'Haens et al. 2008; Schreiber et al. 2007; Kang et al. 2016). In this case, "patient populations need to be identified that would benefit from early use of these agents" (Panaccione and Ghosh 2010).

This type of patient identification warrants new technological approaches in predictive modeling. Researchers have used digitized databases to predict many medical outcomes successfully (Bates et al. 2014; Dhar 2014; Parikh, Kakad, and Bates 2016) including, but not limited to, 30-day hospital readmission (Donzé et al. 2013), acute ischemic stroke (Hsieh et al. 2015), and future autism diagnosis (Wall et al. 2012). Unfortunately, patient biomedical data may not be readily available due to privacy concerns (Weber, Mandl, and Kohane 2014) or may be available but incomplete or incompatible across providers and institutions (Xiaoming Wang et al. 2009). Because of these limitations related to biomedical data, recent efforts utilized insurance claims records to predict various outcomes. For example, researchers used claims data to predict the outcomes of depression treatment (Huang et al. 2014) and falls in the elderly (Homer et al. 2017).

In this study, I used insurance claims data in an effort to predict the two primary cost-drivers in IBD: hospitalizations and the use of biologics. By identifying patients at risk for

hospitalization, targeted patients could be advised to return to the clinic for early intervention and treatment optimization. By identifying patients who will need biologics, treatment could be expedited to fall within the critical therapeutic window, thereby improving efficacy and quality of life. Interventions are costly: these advanced strategies require a model to identify the subpopulations of patients who would benefit from them. To construct this model, I analysed 36 months of longitudinal insurance claims data from patients with IBD who were treated at UCLA. These data contained information pertaining to medications, test administrations, psychometric scales, office appointments, hospital visits, insurance coverages, and demographics. Except for comorbidity assessments, none of these data include biological information from the outcomes of tests, scales, or appointments; instead, they indicated simply that a visit or test occurred, and that it was paid for.

To account for different IBD subtypes and care pathways, I selected topic modeling (Blei 2012), a type of unsupervised learning, to identify patient subgroups. Originally applied to the problem of finding trends in text corpora, topic models were used effectively to extract meaningful low-dimensional representations from large data sets. Researchers adapted topic modeling techniques in a variety of areas, including social media (Hong and Davison 2010), images (Xiaogang Wang and Grimson 2008), ADHD classification (Anderson et al. 2014), and motion classification (Y. Wang, Sabzmeydani, and Mori 2007). Although this subgrouping analysis has been used in predicting automobile claims (Yeo et al. 2001), we are the first to our knowledge to leverage it in healthcare insurance.

This study addressed two questions: (1) Do insurance claims reveal patterns of care that indicate future hospitalizations and biologics use? (2) Does the hospitalization model make predictions sufficiently accurate to justify an intervention for high-risk patients based on direct cost savings alone?

## 4.3 Methods and materials

### 4.3.1 Patient data

*The data were acquired entirely by Daniel Hommes and Welmoed van Deen at the UCLA Center for Inflammatory Bowel Diseases.*

Anthem, California provided the insurance claims data, including enrollment data, and pharmacy and medical claims from 2011 through 2013. Medical claims included a unique beneficiary ID, provider ID and specialty, date of service, location of service, Current Procedural Terminology (CPT) code, up to 8 International Classification of Disease (ICD)-9 codes, and a Diagnosis-Related Group (DRG) for hospitalizations. Pharmacy claims included patient and provider ID; medication fill date, and medication name, dose, and number of days filled. Age was provided for all beneficiaries, though no gender details or other demographic characteristics were available.

I included patients if they had at least two medical claims with an ICD-9 code for IBD (555.x or 556.x) or one medical claim for IBD and one pharmacy claim for an IBD-related medication. I constructed variables for IBD-related claims, hospitalizations, Emergency Department (ED) and office visits, procedures, lab and imaging tests, medication use, disease severity, and relapse rate (van Deen et al. 2017). For each

medication, I analyzed whether it had been used, the number of times a course of medication was started, and the number of days of use. For each procedure and test, I analyzed whether the procedure / test had been performed at all and the number of times it was performed. In total, I extracted 110 potentially predictive features (**Figure 29**). Because multiple variables were derived for each medication, test, and procedure, several variables were correlated highly with one another.

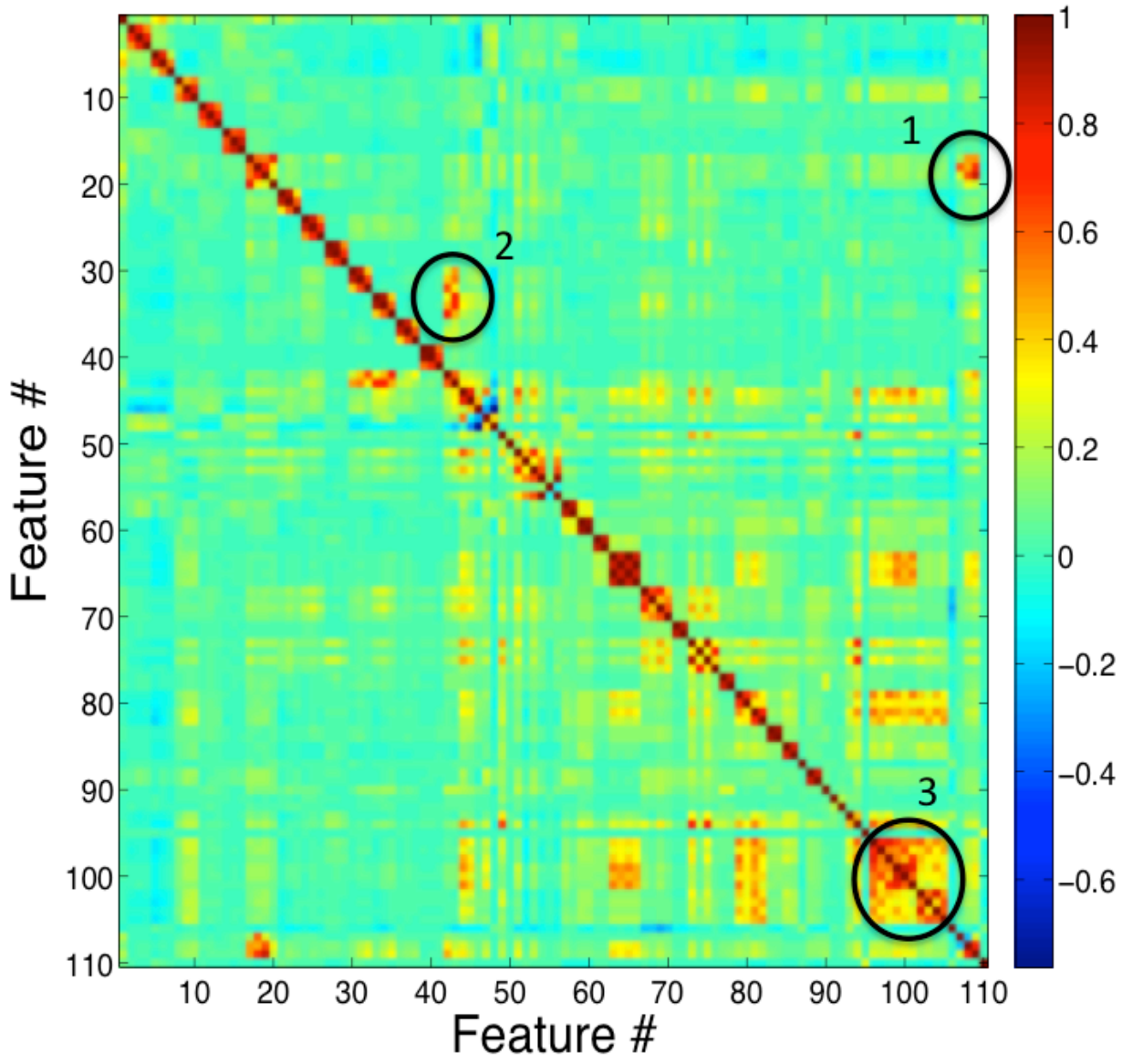


**Figure 29 - pearson correlation matrix of data features.** Pearson correlation matrix of all 110 features. Highly correlated squares on the midline correspond to features describing different aspects of the same medication: whether the medication had been used, the number of times a course of medication was started, and the number of days of use. Correlation clusters around (1) systemic steroids and disease severity metrics, (2) patients on biologics and number of insurance claims and (3) hospitalizations and ED visits.

---

To design and validate our model, I split the data into two mutually exclusive datasets. The training dataset included 7,771 patients who were enrolled continuously 2011 through 2012. I derived a model in which the variables described above from the 2011 claims data predicted two outcomes in the year 2012 as (1) the hospitalization for IBD and (2) the use of biologics. To validate our model, I then applied it to the validation dataset comprised of 7,450 patients enrolled continuously through 2012 and 2013. A total of 4,050 patients were enrolled continuously from 2011 through 2013 and were present in both datasets, comprising 54% of the validation set. I address the concern of overlapping subjects between the training and validation set in Figure 36B.

### 4.3.2 Classification

To identify predictors of future IBD-related hospitalizations, I used L1-regularized logistic regression. I used 110 features from the insurance claims data as independent variables and hospitalization for IBD (binary) as the single dependent variable. Models were run on the entire dataset, as well as within each of the identified risk-groups, and I compared the outcomes of each approach. To predict the future use of biologics, I ran one L1-regularized logistic regression model on the subset of patients not using biologics currently. Because this is already a small subpopulation of the included IBD population, I did not attempt to sub-classify this population further using topic modeling.

### 4.3.3 Grouping

I used topic modeling to identify four patient subgroups. Topic modeling is an unsupervised learning algorithm (i.e. it makes classifications without using outcome data) that uses data to identify related features in the dataset, based on which *topics* are created. Specifically, a model known as latent Dirichlet allocation, or LatDA (Blei, Ng, and Jordan 2003), was utilized for data dimension reduction and trend extraction. LatDA, proposed originally as a model for word occurrences in text documents, is a probabilistic generative model made popular due to the model's exploration of the solution space and efficacy with large data sets. More generally, topic modeling applied to any non-negative data results in a non-negative linear decomposition into the number $\mathrm{t}$ of topics or components. The LatDA model in particular can be stated as follows: Let $\mathrm{m}$ be the number of features and $\mathrm{n}$ the number of observations. Let $\mathrm{X}$ be the $\mathrm{m}$ by $\mathrm{n}$ non-negative data matrix. LatDA models this matrix via latent $\mathrm{m}$-by-$\mathrm{t}$ and $\mathrm{t}$-by-$\mathrm{n}$ nonnegative matrices $\mathrm{Y}$ and $\mathrm{Z}$ respectively with unit sum columns. That is, $\mathrm{X} \approx YZ$ via the generative process:

$$
\begin{aligned}
&Y_{:,k} \sim \mathrm{Dirichlet}(\alpha) \quad \forall\, k = 1, ..., t \\
&Z_{:,j} \sim \mathrm{Dirichlet}(\beta) \quad \forall\, j = 1, ..., n \\
&X \sim \mathrm{Poisson}(YZ)
\end{aligned}
$$

Here, $\alpha > 0 \text{ and } \beta > 0$ are model parameters that control the strength of the Dirichlet prior assumption on the distributions in the columns of $\mathrm{Y}$ and $\mathrm{Z}$. The prior is responsible for avoiding degenerate solutions containing zero entries. The third parameter, $\mathrm{t}$, specifies the number of latent factors used to model the data. The resulting model resembles another popular technique known as non-negative matrix factorization (NMF)

(Lee and Seung 1999). In particular, LatDA is NMF with the Poisson sampling assumption and added smoothing via the Dirichlet assumptions. I use a simple maximum-likelihood estimation algorithm for LatDA known as expectation-maximization (Asuncion et al. 2009).

### 4.3.4 Significance testing

To assess the significance of our predictions, I used permutation testing to estimate the empirical probability distributions of a classifier where there was no relationship between potentially predictive features and outcomes. I broke the potential relationship between features and outcomes by permuting the 2012 and 2013 outcome information randomly without replacement and by keeping the input data the same. I conducted the same process of training and validation on these permuted datasets and repeated this for 10,000 unique permutations to estimate the probability distribution of all our reported summary statistics empirically. I determined the empirical *p*-value ("*p*-hat") as the fraction of permuted datasets that achieved a summary statistic as, or more, extreme than the one observed within the original data.

### 4.3.5 Intervention

To estimate the impact of these predictive models for insurance companies, I considered a hypothetical intervention in which those patients preventable from hospitalization would be instructed to attend an office visit (**Figure 37** in the IBD hospitalization section below). I assumed that if, at the time of the office visit, these patients were using steroids only, 5-ASA only, or no medication at all, future hospitalizations could be prevented by initiating immunomodulator treatment. To account for the uncertainty about the efficacy of this intervention to prevent

hospitalizations, I varied the probability across as a wide range to determine the minimum efficacy that would result in an overall cost reduction. I assumed a consistent cost of $10,000 per hospitalization and $200 per office visit.

## 4.4 Results

### 4.4.1 Statistics

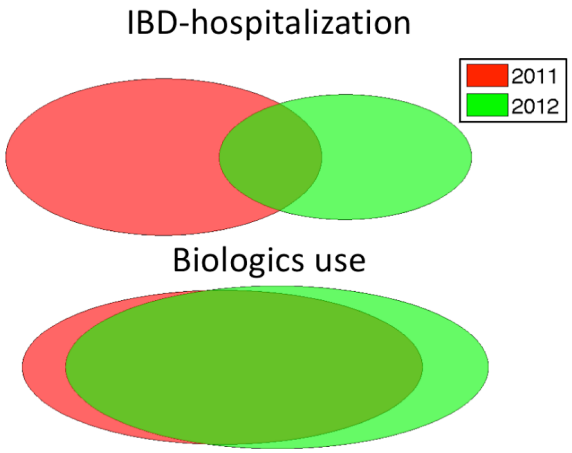
The patients in the 2011 to 2012 training set (7,771) and 2012 to 2013 validation set (7,450) had an average age of 42 +/- 14 years and were patients of this UCLA plan for an average of 1.3 +/- 0.8 years. The training and validation sets had IBD-related hospitalization rates of 8% and 5%, respectively. Of the patients hospitalized in 2011, 20% returned to the hospital in 2012. In 2011 and 2012, 16% and 18% of the patients used biologics, respectively. The majority of biologics users in 2011 remained on biological therapy in 2012 as 88% (**Figure 30A**).

### 4.4.2 Feature extraction

An important exercise in machine learning is feature extraction as a means of transforming the initial and measured data into an information-maximizing set of variables for subsequent learning (Yu and Liu 2004). In this case, the original monthly data contained temporal trends that were lost when looking at one year in isolation. To detect a latent temporal trend, I analyzed monthly hospitalization rate as a function of time elapsed since the patient joined the insurance plan (**Supplementary Figure S2**). Given that IBD is known to be seasonal, I fit these data with a first-order polynomial and 12-month cyclically repeating parabola. I discovered that the monthly IBD-hospitalization rate decreased by 0.0046% per month, which translated to a yearly IBD-

hospitalization rate decrease of 0.66% per year. This feature (time as a member of the insurance plan) was added to the data for classification.

**A**




| | 2011 | 2012 |
|---|---|---|
| **IBD-hospitalization** | 7.5% | 4.8% |
| **Biologics use** | 16.4% | 18.3% |
| **Initiation of biologics** | 4.7% | 3.5% |
| **Termination of biologics** | 12.5% | 11.3% |

**B**

| | Topic 1 | Topic 2 | Topic 3 | Topic 4 |
|---|---|---|---|---|
| **Risk level** | medium-high | low-medium | low | high |
| **Related features** | Methotrexate | certolizumab | rectal steroids | natalizumab |
| | Adalimumab | infliximab | long-term steroid use | ultrasounds |
| | Any endoscopies of small intestines | IBD surgeries | Pneumococcal vaccination | stool calprotectin tests |
| | Episodes on budesonide | Acute IBD surgeries | non-Methotrexate immunomodulators | Emergency department visits |
| **% of all patients** | 16% | 14% | 53% | 17% |
| **IBD-hospitalization Rate** | 7% | 5% | 3% | 10% |

**Figure 30 - statistics and topic modeling. A.** Frequencies of interest in training data. 2012 | 2011 shows of the frequency with which patients who had an outcome in 2011 also had the same outcome in 2012. For example, 88% of patients prescribed biologics in 2011 continued using biologics in 2012 and were thus highly likely to continue their use the following year. **B.** Topics revealed by our topic modeling analysis and their associated IBD-hospitalization rate.

### 4.4.3 Topic modeling

Topic modeling revealed 4 topics among patient claims (**Figure 30B**). The model computed a score for each patient's belongingness in each topic and assigned each patient to the single topic for which they had the highest score.

### 4.4.4 IBD hospitalization

#### *Univariate analysis*

For each of the 110 features, I fit a separate L1-regularized logistic regression of the feature onto the (binary) IBD hospitalization outcome variable. For each of these 110 models, I used average PPV (the area under the AUC-PR curve), as a metric for the usefulness of the feature in predicting IBD hospitalization. The PR curve plots positive predictive value (PPV) versus sensitivity; the average PPV is a common method to compare models. The top 20 models ranked in order of descending average PPV are listed in **Figure 32**.

Univariate predictors of IBD-hospitalization

| Feature | average precision | log odds ratio | Feature | average precision | log odds ratio |
|---|---|---|---|---|---|
| **IBD** | 15.56 | 0.03 | **claimnumber** | 10.02 | 0.00 |
| **hospdays_IBD** | 13.61 | 0.06 | **Xray** | 9.91 | 0.16 |
| **CD** | 13.02 | 0.03 | **CBC** | 8.98 | 0.02 |
| **hospitalizations_IBD** | 12.65 | 0.48 | **hospitalizations_IBD_yn** | 8.80 | 0.65 |
| **hospdays** | 12.25 | 0.02 | **UC** | 8.59 | 0.02 |
| **ERvisits_IBD** | 11.53 | 0.23 | **syststeroiddays** | 8.28 | 0.00 |
| **hospitalizations** | 11.36 | 0.19 | **RR** | 8.17 | 0.10 |
| **ERvisits** | 10.77 | 0.09 | **abdays** | 8.15 | 0.00 |
| **office_IBD** | 10.40 | 0.05 | **LFT** | 8.09 | 0.02 |
| **CT** | 10.11 | 0.18 | **IBD_acute_surgery** | 8.00 | 0.29 |

**Figure 32 - univariate analysis of IBD hospitalization.** Outcomes of a separate univariate regression on IBD hospitalization by each of 110 claims data features using training data. Several variables, most notably IBD as the number of annual IBD-related claims, yielded predictive models as measured by average PPV. The LOR is per 1 unit change in the normalized variable. The range of values for each variable is listed in **Supplementary Table S2**.

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#### *Feature reduction*

Reducing a dataset's dimensionality can improve classification (Roweis and Saul 2000). One way to accomplish this is by orthogonal transformation: reorienting the basis set along axes which explain more variance and ignoring those new axes which do not

explain a large portion of this variance (Kanjilal and Banerjee 1995). For this purpose, I applied principal components analysis (PCA) and independent components analysis (ICA) to the training data, varying the number of desired components from 1 to 110 (**Figure 32A**). Regardless of the number of components included, both PCA and ICA underperformed the original dataset consistently, so I did not pursue feature reduction further.

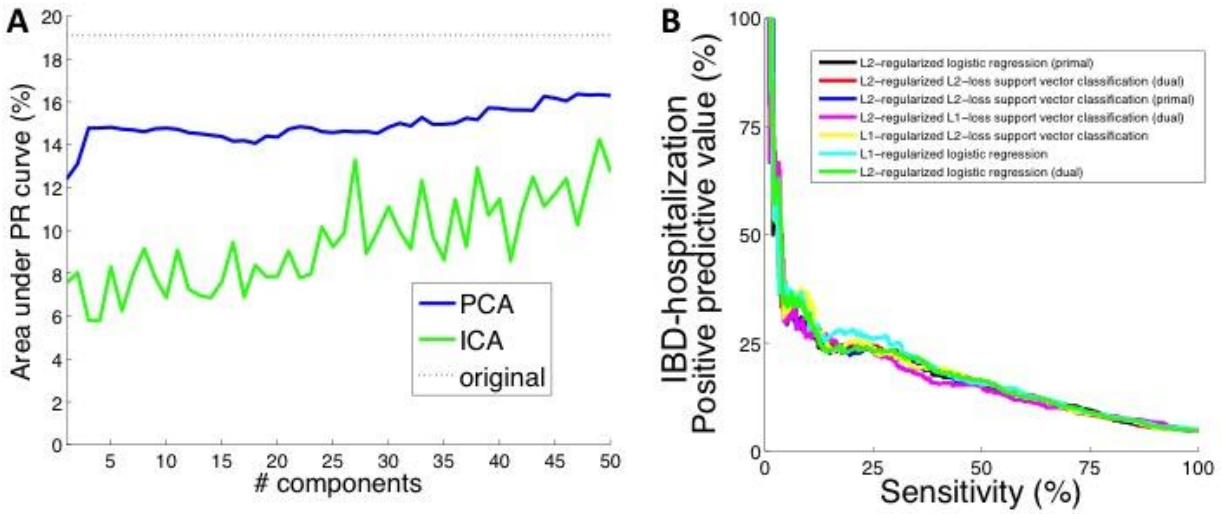



**Figure 32 - optimizing the IBD-hospitalization model. A.** The original data and its 110 features had an average PPV of 19%. The efficacy of PCA saturates never reached that of the original 110 features. ICA was even less effective on this data. **B.** PR curves for predicting an IBD-hospitalization the following year using various linear classification schemes. Multivariate classification was robust with respect to classification method.

---

### *Multivariate analysis*

I classified IBD-hospitalization outcomes using numerous linear classification schemes (**Figure 32B**). Model performance varied only slightly across both regularization and loss distance metric (L1/L2) and classification method (logistic regression versus SVM and dual vs primal). To favor sparsity (Ryali et al. 2010) and probabilistic interpretation (Liu et al. 2009), I chose the L1-regularized logistic regression method for further

analyses. The weights from this model on the training data are shown as log likelihood in **Figure 33** with stars over significant weights ($q < 0.05$, corrected).

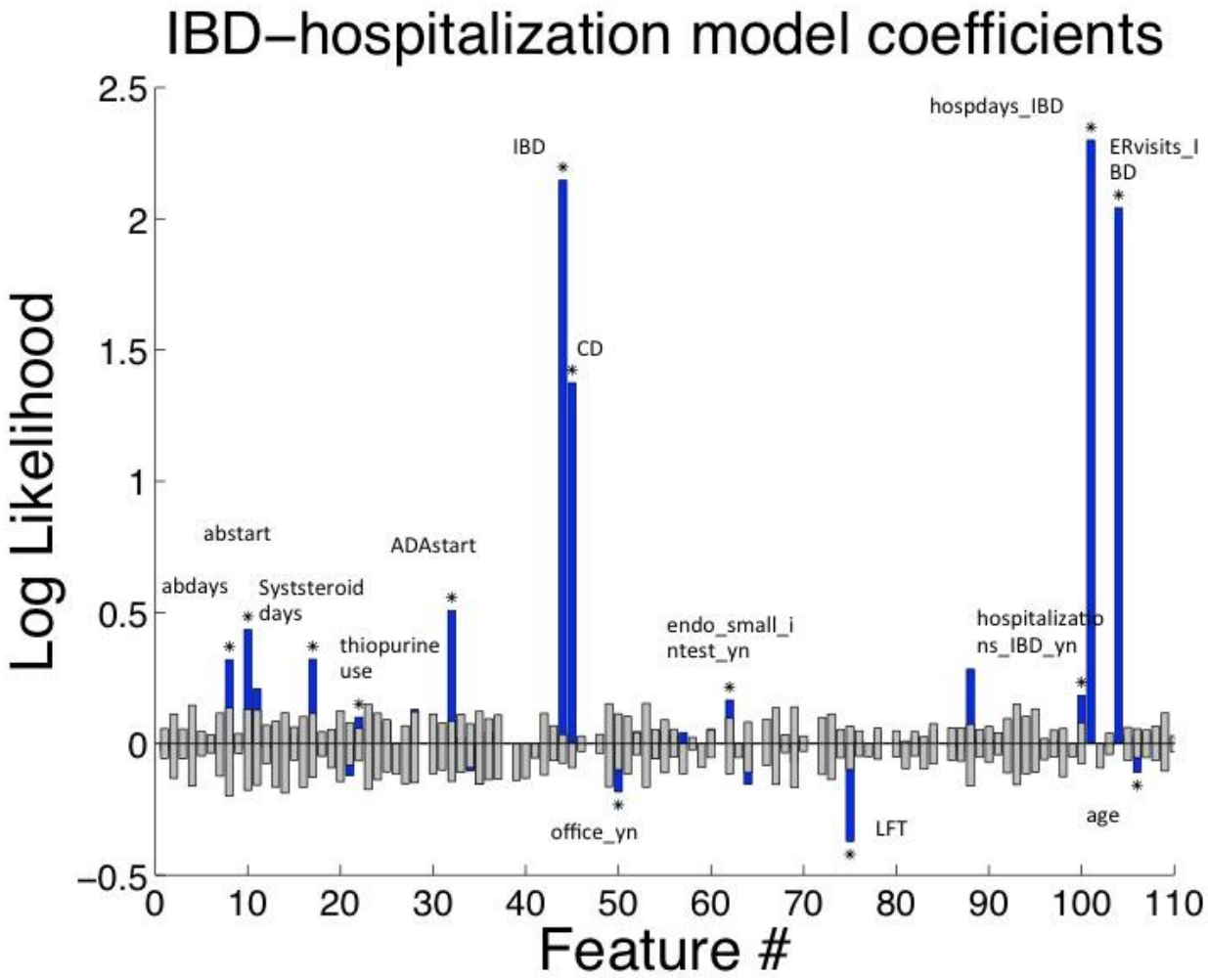



**Figure 33 - all training model weights for predicting IBD-hospitalization.** Results of an L1 logistic regression of the 110 features on IBD-hospitalization. Blue bars are actual fit, and grey bars are 95% change confidence intervals. Stars signify $p < 0.05$ after Holm-Bonferroni correction.

---

Likelihood coefficients (ORs) for IBD-hospitalization for the 11 significant weights are shown in **Figure 34.** These are the probability of going to the hospital divided by the probability of not going to the hospital per 1 unit change in the variable. For example, an IBD hospitalization predicted an IBD hospitalization the following year as 1.22 times as likely and as an increase of 22%. Similarly, an office visit predicted an IBD

hospitalization the following year as 0.83 times as likely and as a decrease of 17%. For variables that contained multiple values, it is important to consider the variable's frequency when assessing its relative importance. For example, a single IBD claim predicted an IBD hospitalization the following year as 1.01 times as likely and as an increase of only 1%. However, the average patients had 5.7 claims in a year with a SD of 8.4 and a maximum of 185. Thus, for the average patient, the number of IBD claims may have a larger influence than an IBD-hospitalization. To reflect the importance of non-binary variables, I used a black "x" to indicate the change in likelihood of an IBD hospitalization with a 1 SD change in the value.

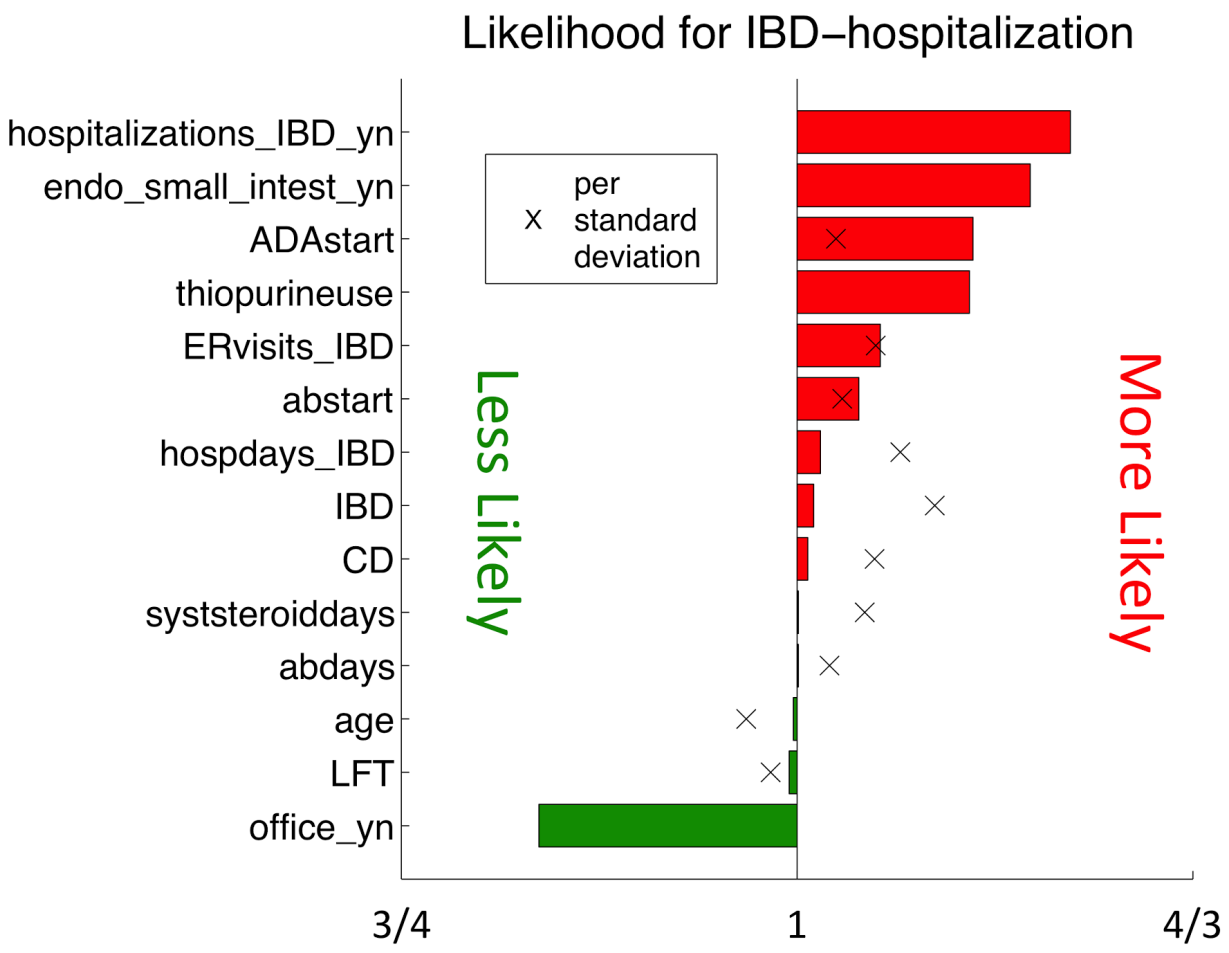


**Figure 34 - likelihood for significant features of general model.** Significant features ($p < 0.05$ Bonferroni-Holm corrected) and their relative weights from an L1-regularized logistic regression predicting initiation of biologics. Red bars reflect features positively predictive of initiation of biologics, and green bars reflect features negatively predictive of initiation of biologics.

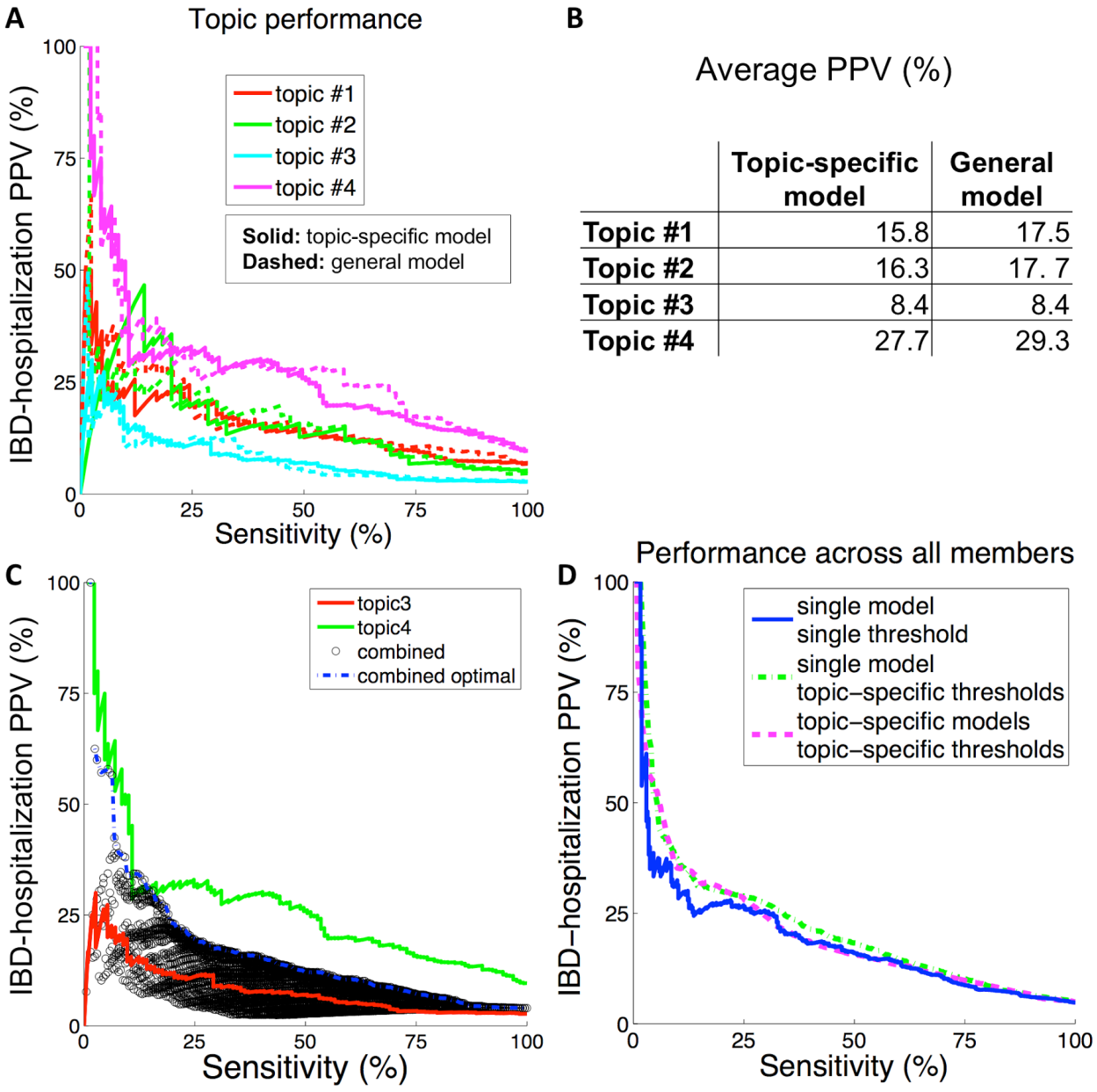
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To capture the differences between patients, I tried a completely separate modeling approach by creating a specific model for each subgroup identified by the topic modeling. This yielded four total models with one for each topic. For each topic, the topic-specific models performed slightly less well than the general model (**Figure 35A and 35B**). Topics on which the general model performed less well than others, for example Topic #3, were similarly difficult for the topic-specific model to predict.

I concluded that topic modeling does not improve model accuracy by creating a separate model for each subgroup. Rather, the value in topic modeling stemmed from its ability to identify at-risk patient groups that were otherwise overlooked by the regression modeling. In other words, topic modeling captured important interaction terms between features, which would have been missed by the main-effect nature of single and general multivariate regression otherwise.

To assess the overall combined results of the topic-specific models, I combined the results of each topic-specific model and eliminated suboptimal combinations (**Figure 35C**). Each point in the final results was the combination of thresholding of each topic model at different cutoff values. Using this method, I can compare (1) the original model, (2) the single model evaluated at different decision criteria for each topic, and (3) the topic-specific models each applied at different decision criteria (**Figure 35D**). The

single general model, thresholded differently for each topic (labeled as green), had an average PPV of 21%; the topic-specific models had an average PPV of 20%. Given their comparable performance but increased number of parameters (and thus over-fitting), the topic-specific models were not applied further.




| | Topic-specific model | General model |
|---|---|---|
| **Topic #1** | 15.8 | 17.5 |
| **Topic #2** | 16.3 | 17. 7 |
| **Topic #3** | 8.4 | 8.4 |
| **Topic #4** | 27.7 | 29.3 |

**Figure 35 - topic modeling performance. A.** Performance in each of the 4 topics. Solid lines depict the performance of the model created from the topic specifically, whereas dashed lines depict the performance of the single and general model on the topic. **B.** AUC-PR for each topic using either the model fit for the topic specifically or a general model fit to all instances of the data. The general model

outperformed the topic-specific model in all topics. **C.** A demonstration of how all the topic-specific model results were combined to compare performance across all patients. Since any threshold could be chosen for either model, there were m x n possible combinations, where m was the number of instances of topic 3 and n was the number of instances of topic 4. Points with suboptimal PPV, sensitivity, or specificity were eliminated. **D.** Using the method in (**C)**, I assessed the overall performance of each methodology on the training data. The single and general model thresholded differently for each topic (green) and outperformed the topic-specific models at most but not all) sensitivities.

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### *Validation*

To reduce the influence of overfitting, the final model applied to the validation set utilized only the 11 features that were significant in the training set after correction for multiple comparisons. This model predicted IBD hospitalizations in the validation set with an average PPV of 17%, significantly above the chance of 5% ($p < 10^{-4}$, **Figure 36A**, one-tailed percentile permutation test). After applying the general model to each topic group separately, average PPV was improved to 21%. This model performed better on continuing patients as those also present in the training data as 54% than on new patients as those present only in the validation data as 46% **(Figure 36B)**.

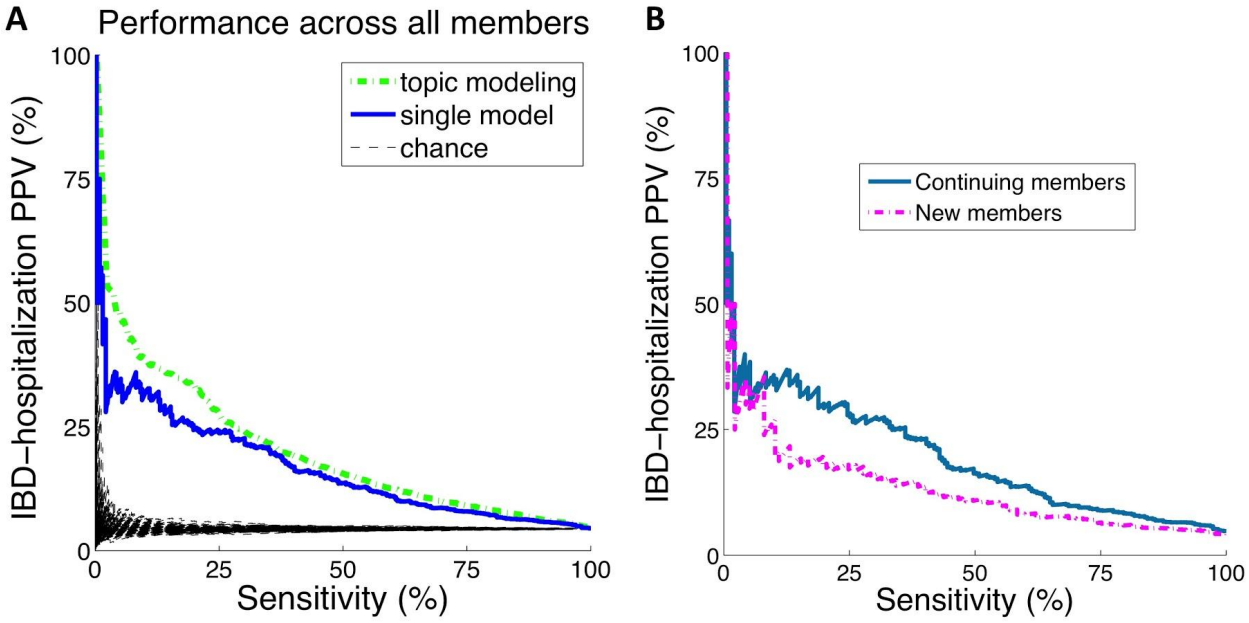


**Figure 36 - IBD hospitalization model validation. A.** PR curves for predicting IBD-hospitalization using the final 11-feature IBD-hospitalization model on the validation set ($p < 10^{-4}$, one-tailed percentile permutation test, 100 null permutations shown). The general model, applied to each topic with different thresholds (green), performed better with an average PPV of 21% versus 17% for the single model applied to all data equally (blue). This difference in performance was observed primarily at sensitivities below 25%. **B.** PR curves for IBD-hospitalization prediction performance in the validation set for both continuing and new patients. The model applied better to continuing patients ($p < 10^{-3}$).

---

### *Intervention*

Next, I used our IBD-hospitalization model's predictions to assess whether an intervention was financially feasible. I assumed that if patients used steroids only, 5-ASA, or no medication at all, a future hospitalization could be prevented by initiating immunomodulator or biologic treatment. With this criteria, I divided the IBD-hospitalization outcome validation data into intervention and nonintervention groups; a total of 4,918 (66%) of patients in the validation set were eligible for the intervention group.

To estimate the savings associated with a proposed intervention, I assumed the cost structure as $10,000 per IBD-hospitalization (Pfuntner, Wier, and Steiner 2013) and $200 per office visit. If our model predicted a true hospitalization correctly, it and its associated cost would be "prevented" with a probability *e* (**Figure 37**). To account for the significant uncertainty in the efficacy of an interventional strategy, I modeled the outcomes assuming a range of efficacy probabilities. I then used our intervention cost-savings results to determine the minimum efficaciousness needed to make the intervention a financial improvement.

| Predict IBD-hospitalization | | Actual IBD-hospitalization: No | Actual IBD-hospitalization: Yes |
|---|---|---|---|
| | **No** | $0 | $10,000 |
| | **Yes** | $200 | $200 + $10,000 * (1-e) |

**Figure 37 - proposed intervention costs.** Total cost of hospitalization and proposed intervention across all possible evidence thresholds for multiple treatment efficacies. Hospitalizations can be prevented with an efficacy *e*, which was between 0 and 1, if our model correctly predicted a patient's forthcoming IBD-hospitalization. Due to the uncertainty in *e*, it is left as free parameter.

Since each patient had some risk for IBD hospitalization, the intervention's threshold for defining "at-risk" determined the number of patients included and treated in the intervention (**Figure 38A**). If only the patients our model identified as severely at-risk were treated, a lower percentage of the total IBD hospitalizations would be treated (low sensitivity), whereas more lax criteria would yield a higher sensitivity and potentially higher cost. For a given efficacy, X denotes the minimum cost point, where the power of the model to predict IBD-hospitalizations was offset equivalently by the cost of treating false positives, since patients who were predicted incorrectly by our model would have an IBD hospitalization. Connecting the minimum points across all efficacies from 0% to 100% showed savings and prevention as a function of efficacy (**Figure 38B**). Greater efficacy therefore made it financially optimal to treat more patients, resulting in fewer hospitalizations. Our model predicted that an intervention required at least 5% efficacy to be financially advantageous with more significant returns after 20%.

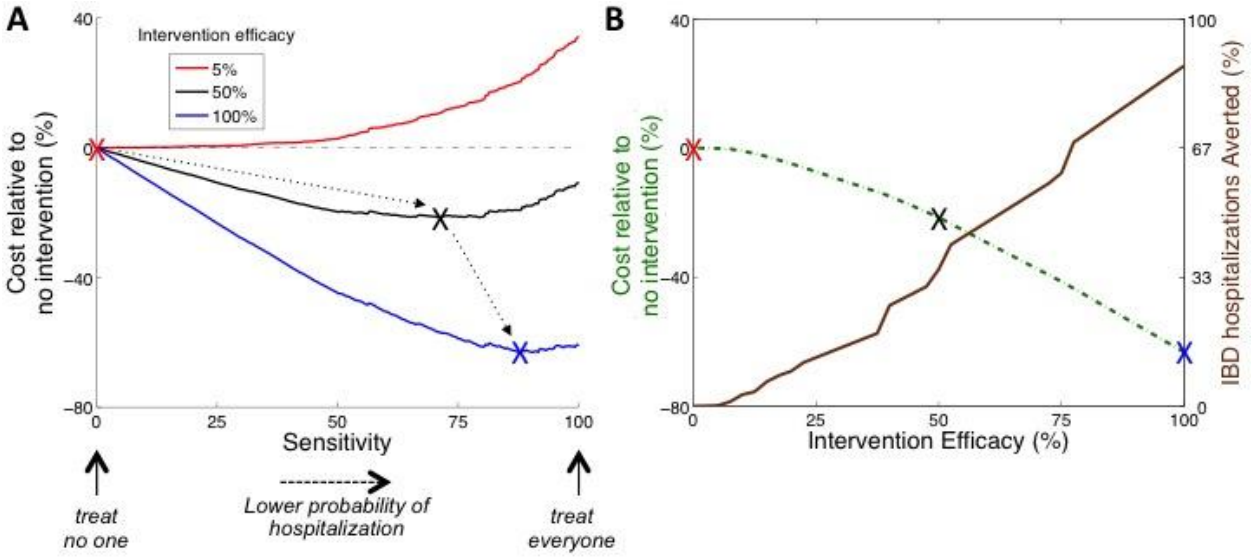



**Figure 38. IBD-hospitalization intervention results. A.** Total cost of hospitalization and proposed intervention across all possible evidence thresholds for multiple treatment efficacies. Colored X's represented the cost-minimizing solution for each intervention efficacy. At 5% efficacy, no intervention was cost-effective, whereas with 50% efficacy it was cost-effective to treat patients for whom there was strong evidence of an impending hospitalization. **B.** Patient and monetary impact as a function of treatment efficacy. Intervention was cost-optimal if intervention was at least 5% efficacious with significant savings if > 20% efficacious. The curves were not fit; and they were calculated for efficacies from 0 to 100%.

---

### 4.4.5 Biologics

I assessed our second intended outcome measure: predicting a patient's biologics use the following year. Specifically, I was interested in predicting a *change* in patient use of biologics: starting biologics if not already in use, or stopping biologics if in use currently. I focused on the former predominantly because many patients have insurance-related, non-medical reasons for stopping biologics, so discontinuation may not be of clinical relevance.

#### *Univariate analysis*

As before, I performed a univariate analysis by regressing each of the 110 features one-by-one onto the outcome: initiation of biologics (**Figure 39**). IBD was again, by itself, highly predictive. For this and all future analyses, I used an L1-regularized regression.

Univariate predictors of beginning biologics

| Feature | average precision | log odds ratio | Feature | average precision | log odds ratio |
|---|---|---|---|---|---|
| **IBD** | 13.54 | 0.03 | **hospdays_IBD** | 7.71 | 0.02 |
| **office_IBD** | 12.45 | 0.07 | **UC** | 7.59 | 0.02 |
| **CD** | 11.49 | 0.03 | **age** | 7.55 | -0.01 |
| **CRP** | 9.74 | 0.11 | **LFT** | 7.45 | 0.02 |
| **office_IBD_GI** | 9.27 | 0.07 | **syststeroidstart** | 7.44 | 0.12 |
| **syststeroiddays** | 9.27 | 0.00 | **TBtest_yn** | 7.36 | 0.67 |
| **ESR** | 9.08 | 0.08 | **thiopurinestart** | 7.08 | 0.19 |
| **RR** | 8.31 | 0.13 | **hospitalizations_IBD_yn** | 6.79 | 0.41 |
| **CBC** | 8.04 | 0.02 | **MR** | 6.69 | 0.34 |
| **hospitalizations_IBD** | 7.77 | 0.26 | **LTsteroid** | 6.68 | 0.35 |

**Figure 39 - univariate analysis of initiation of biologics.** The outcomes of a separate univariate regression on IBD hospitalization by each of 110 claims data features using the training data. Several variables, most notably IBD as the number of annual IBD-related claims, yielded predictive models as measured by average PPV. The LOR was per 1 unit change in the variable. The range of values for each variable is listed in **Supplementary Figure S2**.

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### *Model optimization*

I again performed PCA and ICA dimensionality-reduction techniques. Whereas ICA was again ineffective, PCA apparently provided a slight improvement in average PPV (**Figure 40**). Since this improvement was mild, I instead favored sparsity by using an L1-regression to reduce the final model to a subset of the original 110 features.

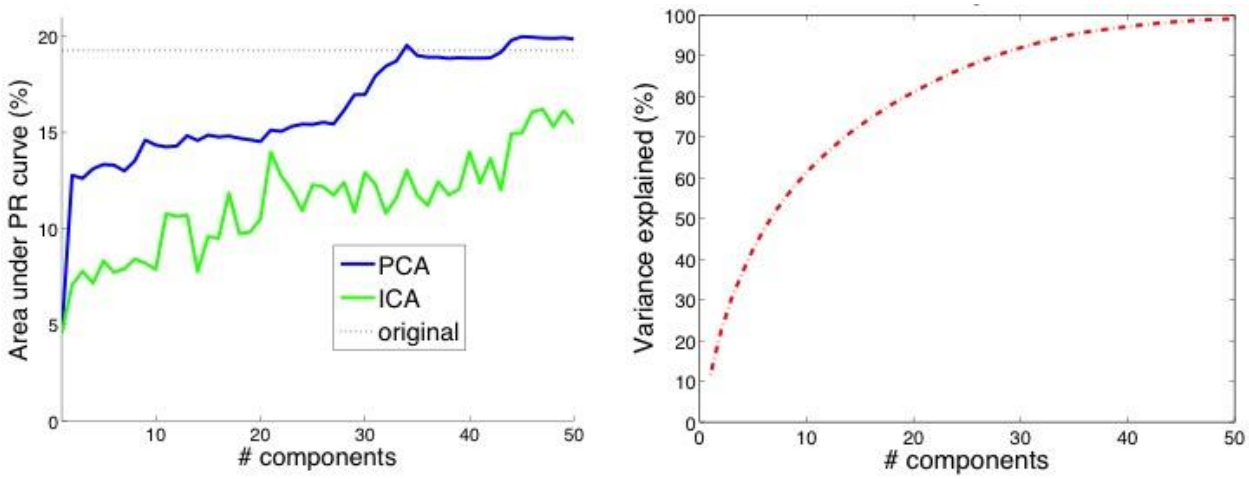



**Figure 40 - consequences of feature reduction in predicting initiation of biologics. A.** The original data and its 110 features had an average PPV of 19%. The effectiveness of PCA saturates never

reached that of the original 110 features. ICA was even less effective on this data. **B.** Variance explained in the feature data as a function of the number of PCs returned.

---

### *Multivariate analysis*

I first constructed a single, general model to predict biologics use. Patients may have very different reasons for initiating biologics versus continuing biologics from one year to the next. Since a single model could not distinguish between these reasons, I took a more specific approach. I created one model to predict biologics use for the subpopulation that was already using biologics, and a separate model to predict biologics use for patients who were not yet using them. I refer to these two as the "specific" models. The general model and the two specific models performed similarly (**Figure 41**).

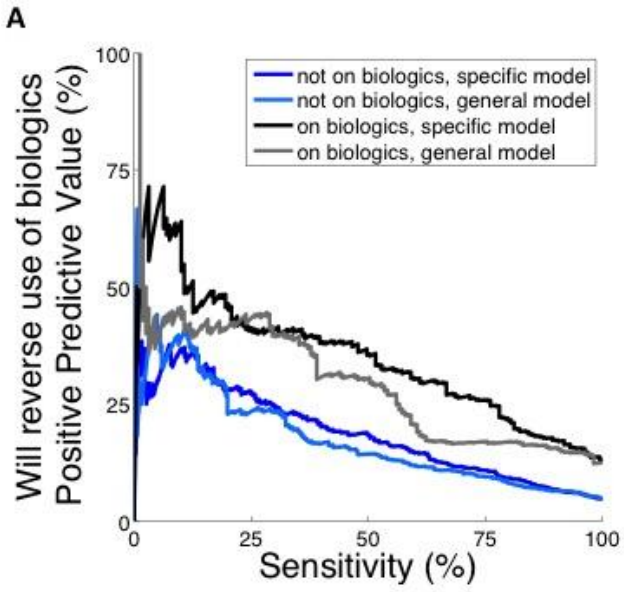



**Figure 41 - general versus specific modeling on training set data.** PR curves for both outcomes of interest in both models. Performance was similar between models for predicting which patients would begin biologics use.

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The log likelihood and null permutations of the model coefficients are provided in **Figure 42**.

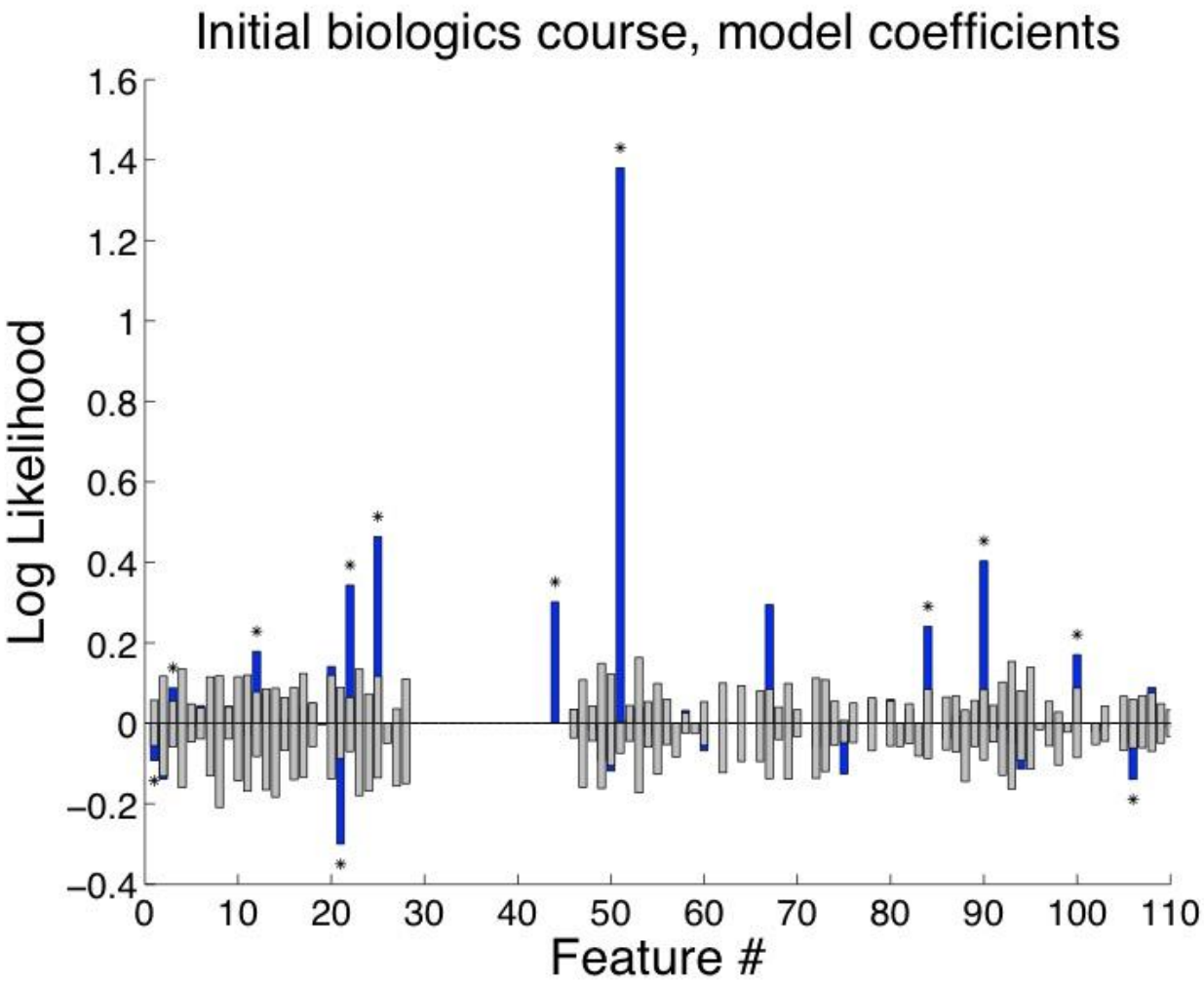



**Figure 42 - all training model weights for predicting initiation of biologics.** Results of an L1 logistic regression of the 110 features on initiation of biologics. Blue bars are actual fit; grey bars are 95% change confidence intervals. Stars signify $p < 0.05$ after Holm-Bonferroni correction. Variables 30 to 43 are features representing biologics use and are non-existent in this subgroup.

---

The significant weights after Holm-Bonferroni correction are listed in **Figure 43A** as ORs. After applying these 11 coefficients to the validation set, I saw that both models were significantly predictive of their respective outcomes ($p < 10^{-3}$ corrected, **Figure 43B**, one-tailed percentile permutation test).

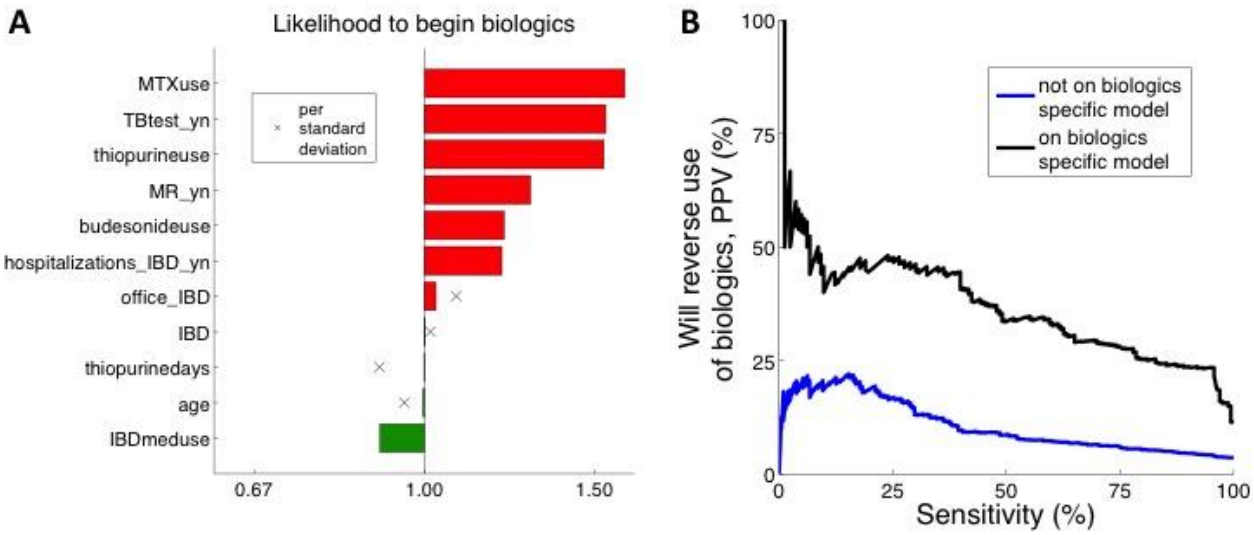



**Figure 43 - significant weights and model validation for predicting initiation of biologics. A.** Significant features ($p < 0.05$ Bonferroni-Holm corrected) and their relative weights from an L1-regularized logistic regression predicted initiation of biologics. Red bars reflect features positively predictive of initiation of biologics; green bars reflect features negatively predictive of initiation of biologics. **B.** Both models were significantly predictive of their respective outcomes ($p < 10^{-3}$ corrected, one-tailed percentile permutation test).

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## 4.5 Discussion

In this study, we focused on the two factors in IBD treatment with the most significant impacts on the quality-of-life and insurance expenditure of patients: hospitalizations and biologics use. We found that insurance claims data could make substantial and statistically significant predictions of both factors. Achieving maximum classification information in each case required fewer than 15 features from the original 110 feature data. Taking into account feature overlap between the two classifications, both models can be implemented with 21 features from the claims database. This feature sparsity broadens our model's applicability because it lessens the risk of overfitting and may be applicable to insurance plans that support and track fewer treatments. Since several factors in the univariate analysis are highly predictive (**Figure 32; Figure 39**), it is likely that near-optimal accuracy can be achieved with even fewer features.

I found that predictors of hospitalization for IBD include prior hospitalizations, ED visits, new adalimumab prescriptions, and endoscopies of the small intestines. These factors all pointed to a more severe disease course, suggesting a higher risk of hospitalization in the future. If further validated, this model may be used as a proxy to assess disease course. In contrast, office visits and liver function tests correlated with a lower risk of hospitalization, perhaps indicating the importance of preventive care. Additionally, older age predicted a lower risk of hospitalization, most likely because IBD tends to have a milder disease course in older patients (Burisch and Munkholm 2013). I also found that predictors for the start of new biologics included the use of immunomodulators and IBD-related healthcare. The number of days that immunomodulators were used was a negative predictor of biologics use; this might indicate that more continuous immunomodulator usage is vital in preventing future hospitalizations.

Importantly, our hospitalization for IBD model demonstrated sufficient accuracy in the justification of an intervention on the behalf of the insurer's financial interests, if the efficacy of preventing a potential hospitalization for IBD exceeded 5%. I believe that this level of efficacy is achievable from available traditional and non-traditional treatments ranging from anti-inflammatories to mindfulness (Witte, Shivananda, and Lenn 2000; Braddock and Quinn 2004; Laake et al. 2005; Neilson et al. 2016).

The hospitalization rates reported in our data resembled those found in other analyses of different data sources, although biologics use in our population was higher, perhaps

due to the increasing availability and utilization of biologics in recent years (Herrinton et al. 2009; van Deen et al. 2014). The re-hospitalization rates reflected those reported in a cohort of UC patients with 24% 1-year rehospitalization rate (Golovics et al. 2015).

### 4.5.1 Topics interpretation

I used topic modeling, a novel mathematical approach, to identify patient subpopulations at higher risk for hospitalization. While topic modeling did not improve model accuracy by identifying different predictive features for each subpopulation, its value stemmed from its ability to pinpoint distinct subpopulations with differential risks for hospitalization.

Since the identified clusters improved prediction in both the development and validation sets, it is likely that the cluster modeling identified distinct patient groups with a differential risk of hospitalization for IBD and different treatment patterns. Given that it is not evident from a clinical perspective which types of patients were represented by each topic, these topics may represent the discovery of novel sub-populations in the juxtaposed context of clinical and insurance data. I hypothesized that multiple distinct patient groups fell within the same cluster because of overlapping features in their distinct treatments.

### 4.5.2 Limitations

#### *Alternative interventions*

I considered a narrow subset of patients, using no therapy or using steroids/5-ASA only, as eligible for intervention with biologics. Because I excluded the 34% of patients

already using immunomodulators or biologics, I were unable to investigate possible benefits of the two alternative interventions.

First, IBD may be managed with thiopurines as immunomodulators rather than biologics or steroids), which may be a cheaper alternative to biologics. Thiopurine therapy may reduce the risk of relapse from 66% to 39% in UC (41% efficacy); for CD, efficacy for maintaining remission is estimated at 17% (Talley et al. 2011b). Second, more rigorous therapeutic drug monitoring of thiopurines (Haines et al. 2011) or biologics (Amarasingham et al. 2014) may reduce hospitalizations with relatively low cost, compared with the expense of starting a new therapy altogether.

I excluded these alternatives because their efficacies in hospitalization prevention was less clear. I decided to construct our model with patients and interventions for whom I were most likely to obtain a treatment effect. In the future, as efficacies for these alternatives are studied further, our model may be adapted to these interventions.

***Social***

It is worth noting that this type of predictive modeling creates certain concerns with respect to volition. First, with regards to patient autonomy, concerns exist that adherence to model predictions will diminish considerations of patient preferences for treatment (Amarasingham et al. 2014). Second, their unmanaged application might diminish the influence of the physicians in managing outcome ambiguity in patient care (Sniderman, D'Agostino, and Pencina 2015). A delicate balance exists between the wishes of patients and physicians in patient care management. Our model did not

replace the paradigm but instead introduced a third component of algorithmic prediction. Hence, the significant benefit for patients and insurance companies may outweigh the concerns about both patient and physician volition.

### *Data*

Researchers debate about whether the use of events fewer than 10 per explanatory variable (EPV) can lead to issues, such as regression coefficients that are biased positively and negatively (van Smeden et al. 2016), overly narrow estimates of the sample variance of the regression coefficients, improper coverage in 90% confidence limits, and inflated Type I and Type II errors, among other problems (Peduzzi et al. 1996). Our training dataset on IBD hospitalization had 70.6 EPV, but because of the low incidence of hospitalization for IBD, this outcome had an EPV of only 3.39. This concern did not explain the high performance in the validation set but may imply instead that our model may be further improved with access to more data.

### *Applicability*

This data model may or may not apply to other insurance plans equally well. Treatment patterns may vary depending on the region (Hilsden et al. 2003a) and setting of care delivery (Hilsden et al. 2003b), so the results might not translate to other settings directly. In light of the equivalent predictive power between new and continuing patients of the insurance plan, however, I believe this model is independent of specific insurance plan coverage.

### 4.5.3 Further directions

Although I selected only two outcomes variables (hospitalization for IBD and biologics use) for predictive modeling, more predictive power existed in the dataset. Our data reflected medical management rather than medical outcomes of testing or treatment. Ideally, the predictions involved a generative model that incorporated underlying causes and measurements related to the biological underpinnings of the disease.

Prior work indicates the underlying epidemiology of IBD as a complex interaction of genetics (Chapman-Kiddell et al. 2010a), diet (Chapman-Kiddell et al. 2010b), pathogens (Ananthakrishnan 2015), season, and geography (Baumgart and Carding 2007). However, certain intermediate factors may indicate a poorer prognosis with higher risks for hospitalization and surgery. These include age at diagnosis, presence of perianal disease, need for steroids with first flare-up, presence of deep ulceration at colonoscopy, and presence of multiple antibodies to gastrointestinal luminal flora (Beaugerie et al. 2006; Allez et al. 2002; Dubinsky et al. 2006). By combining this biologically devoid claims data with medical information, I may be able to increase the predictive power of the signal detected in the data.

Our model warrants external validation to assess whether it has generalized insurance plans and treatment protocols. Future studies may use this model to develop the support and possibility of predictive and personalized patient care in IBD.

# Chapter V – General discussion

Since neuroscience began in earnest with Ramón y Cajal and Camillo Golgi studying the morphology and behavior of individual neurons (Ramón y Cajal 1959; Golgi 1906), the field developed technologies to record the activity and function of brain tissue containing large populations of neurons. As non-invasive neuroimaging technologies such as fMRI, fNIRS, and EEG became increasingly available and affordable, the quantity of data expanded rapidly (Gordon et al. 2005; MacKenzie-Graham et al. 2008). To understand increasingly complex and multi-dimensional data, we as a field have employed and improved the tools of mathematics, furthering the development of Random Field Theory (Adler 2010; Friston et al. 1994; Worsley et al. 1996), and contributing to an empirical underpinning for hyperparameter selection (Xie et al. 2016). My dissertation is the product of this relatively new but burgeoning intersection of neuroscience and advanced mathematics which aims to distinguish different diseases, mental states, and actions (Clark et al. 2014; Cohen et al. 2011; Schnyer, Clasen, and Gonzalez 2017). Here I discuss the broad relevance of my findings for the future of this field.

## 5.1 Contributions to pure and applied science

My dissertation juxtaposes neuroimaging and multivariate classification, often using the results of one aspect to inform the other. These could be labeled as “pure science” and “applied science,” respectively, as outlined in John Horgan’s (in)famous book *End of Science* (Horgan 2015). As Horgan defines the terms, pure science involves the pursuit of a fundamental understanding of the operational principles of the universe; for

example, the discovery of nuclear binding energy. In contrast, applied science uses knowledge for impact; for example, the use of nuclear binding energy to make an atomic bomb. In this context, my univariate and multivariate work contribute to both pure and applied neuroscience.

My empathy localizer included 105 subjects and was the largest study of its kind: identifying an "empathy network" of brain regions that are involved in someone's response to watching painful stimuli. I replicated previous findings, identified novel empathy-for-touch regions, and underscored the need for a more nuanced view of the dual-network hypothesis that affective and cognitive empathy regions overlap. The localization of the empathy and mentalizing networks informed my overarching goal: to diagnose the strength of affiliation towards one's ingroups. After excluding visual areas, my *a priori* model – synthesized from the networks identified in my univariate model – had a greater accuracy and AUC-ROC than did one of the gold standards: the Harvard-Oxford parcellation[1]. Both the *a priori* and Harvard-Oxford approaches use hypothesis-based neuroscience, relying on an average of related areas to inform and improve the classification. Whether due to a more accurate capture of contributing activity or better averaging of correlated noise, my result supports the principle of investing in pure science as a means of improving feature selection[2]. The converse is also true: backward modeling can contribute meaningfully to pure neuroscience.

[1] I did not test for the significance of this improvement, since that would force additional multiple comparisons corrections on other tests

[2] My application of neuroscience-informed feature optimization to the backward, decoding model is analogous to Jack Gallant's technique in decoding visual activation.

It is accepted by most that multivariate model weights cannot be interpreted individually (Haufe et al. 2014). To borrow an example from Haufe, imagine a two-feature model: one feature contains the signal of interest plus heartbeat, and the other feature contains the heartbeat only. One could classify the signal of interest perfectly using weights +1 and -1, respectively, even though the second feature lacks the signal of interest completely. Thus, in a multivariate model an individual weight could contain the signal of interest, or alternatively may be relevant because it contains correlated noise (which *should* be included to improve model performance). It is important to note that one *can* conclude from a model that the signal of interest does indeed exist in one or more of the features. One can then identify the statistically significant model features as possible areas for future study, despite the irrelevance of those features' magnitude and sign, because at least one of those features contains the signal of interest, necessarily.[3] The results of backward models may be incorporated with other evidence to inform future research. In this context, my findings in Chapter II's **Figure 18** suggest further investigation of the medial prefrontal cortex and right superior temporal sulcus as mechanisms for controlling the response of the empathy network.

### 5.2 Circumstantial utility

My dissertation concludes that the utility of machine learning is circumstantial, contributing to the long-standing debate about the cost-benefit tradeoff of machine learning on expensive datasets (Liu et al. 2001; Health Quality Ontario 2014; Tong et al.

[3] To be clear, these significant weights are not an exhaustive list of areas for further research; it is entirely possible for areas with signal to receive zero magnitude weights in sparsity-enforcing models.

2016). Below, I will discuss in which circumstances my findings recommend the employment of machine-learning.

### 5.2.1 Uncooperative patients

Using neuroimaging technologies to diagnose different mental states is surpassed in most cases by voluntary self-report. As an example from my own data, one of my machine learning models differentiates the *stab* versus *touch* conditions with 96% accuracy, using five minutes of fMRI data. It is no stretch of the imagination to believe a participant could report this difference verbally in a matter of seconds. Berkeley neuroscientist Jack Gallant used encoding and decoding machine learning models to reconstruction visualization from BOLD signals (Kay et al. 2008; Jack 2009). This groundbreaking work was astounding because it pushed the boundaries of just how accurately visual perception can be inferred from neuroimaging data. It was not, however, particularly impactful because it revealed anything the observer could not convey to us in less time and with far less expense.

This limitation evaporates when the participant is uncooperative. In Chapter II, I demonstrated that religious ingroup and outgroup affiliations can be distinguished correctly in a given participant with 70% accuracy. Critically, this classification requires neither good-faith nor effort from the participant. In fact, the task – watching labeled hands receive needle stabs or cotton-swab touches – is removed from the topic of interest: the differences between one's mental construct of ingroup and outgroup. DARPA funded this project for the broader goal of quantifying the biasing effect of narrative. In the future, it could perhaps be used to screen uncooperative insurgents or

personnel handling sensitive/dangerous information or equipment. Before this kind of critical deployment, the model would of course require further testing to determine whether participants that are informed of the test's true intention could modify their own neural responses, volitionally, to mentally parry the model.

Similarly, in chapter III I show that DTI normalized path length contributes significantly to distinguishing patients with AN from those with BDD. Imaging the anisotropy of water movement in axons in the brain requires nothing of the subject, and as far as we know, is unperturbed by participant mood or volition. In cases of clinical non-compliance and denial – which can be an issue for patients with eating disorders (Towell et al. 2001; Steiner, Mazer, and Litt 1990; Vitousek, Daly, and Heiser 1991) – neuroimaging may help distinguish cases of AN from BDD.

The ethical implications of quantifying a person's beliefs or diagnosing a person based on neural activation, without consent, are numerous and beyond the scope of this paper. Nonetheless, this manuscript contributes to the growing body of literature showing that such calculations are possible. Society must assess its legality.

### 5.2.2 Unsatisfactory forward models

At its core, a backward model such as machine learning reflects a gap in knowledge; it is a tool to overcome ignorance. Said another way, a fully-understood system uses a generative, forward model. Univariate examples of forward models include gravity and the standard GLM; Schrodinger's equation is a multivariate example. When a system is well understood, our knowledge sculpts the feature parameters and there is low or no

utility in applying backward models. In the data featured in this dissertation, however, there is sufficient ignorance regarding the outcomes' causal mechanisms that backwards modeling is fruitful. Thus, the collection of vast quantities of difficult-to-acquire data is justified to improve the overall accuracy of the dataset, even if and when many features of the dataset are not related fundamentally to the outcome in question.

In Chapter II, I review the literature on the correlation between ingroup/outgroup affiliations and the empathy and mentalizing networks. I find that there is significant evidence behind the dual networks hypothesis: the mental representation of ingroup and outgroups involves an interaction between empathy and mentalizing networks. Although there is some evidence to suggest that the mPFC inhibits the empathy network selectively (Christov-Moore et al. 2017), the exact nature of this interaction eludes the field of neuroscience currently, so my backwards model has predictive utility. It is worth noting that in the near future, the empathy-mentalizing circuit may be better understood such that a forward, generative model and a few electrodes over the frontal lobe are sufficient for generating predictions about ingroup and outgroup, supplanting the need for massively multivariate data acquisition.

In Chapter III, I discover that the maximum predictive power in distinguishing patients with AN from those with BDD is achieved through a multimodal model of psychometric and DTI data. The model has clinical potential precisely *because* the exact generative predictors of AN and BDD are unclear. As an example, there is no concrete evidence to explain why an interaction between BABS and normalized path length would distinguish

patients with AN from those with BDD (Figure 44). In this case, a plausible link may be discovered eventually, but until then, neuroimaging and machine learning can exploit possibly-causal links, while assuming correlation only.

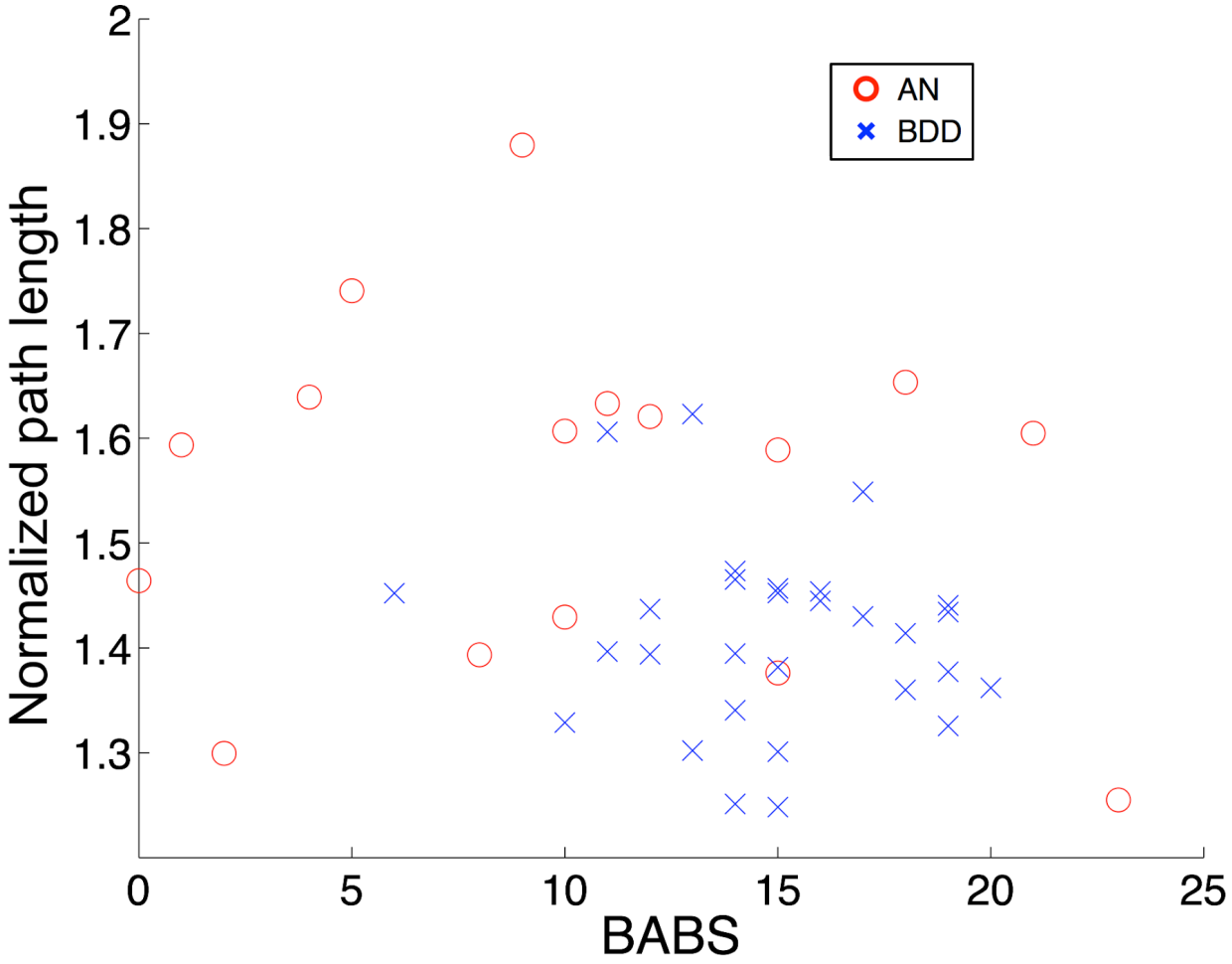



**Figure 44 - Scatter plot of normalized path length vs BABS for both patient groups.** Both normalized path length and BABS are significant features in the multivariate model. No strong empirical results explain their multivariate contribution in dividing patients with AN from those with BDD.

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This concept is perhaps most explicit in chapter IV, where I use insurance claims to predict outcomes for patients with IBD with regards to hospitalization and treatment with biologics. I found that the number of IBD-related insurance claims in a year was highly predictive of hospitalization, even though (presumably) no one believes that filing

insurance claims causes hospitalizations. In this case, multiple correlated, but clearly not causal, variables are more useful than what we believe to be the actual causative mechanisms. This reality justifies the considerable work of getting permission, aggregating, and cleaning a large insurance database.

As much as backward models may be perceived as a reflection of ignorance, they may also be considered stepping stones: tools which are useful because they deliver results in a not-fully-understood system. These backward models may be transient, phased out gradually for forward models as knowledge increases. As I allude to above, in the case of using electrodes to distinguish ingroups from outgroups, an equivalent forward multivariate model may require fewer features. Feature-reduction and overfitting are, by extension, products of incomplete knowledge. We penalize to compensate for them because we are on a somewhat-blind exploratory endeavor, trying to find an optimal extraction vector amongst a set of possibly-superfluous features.

### 5.3 Concluding remarks

Multivariate decoding models are most useful in problems that lack a well-understood forward model. In the multivariate context, weak univariate signals accumulate, so models can use interactions among features and correlated noise to improve prediction accuracy to a greater extent that can be done in univariate and generative models. Multivariate decoding models excel in fields with significant distance from what we as scientists might consider ‘truth’, as they can distill numerous possibly-non-causal features on the basis of performance alone. Although the individual features of the model are generally uninterpretable, distilled models may illuminate regions to target in

future study. Their contribution to neuroscience stems from their performance in the absence of a forward model, rather than explainability or direct contribution to our understanding of the universe.

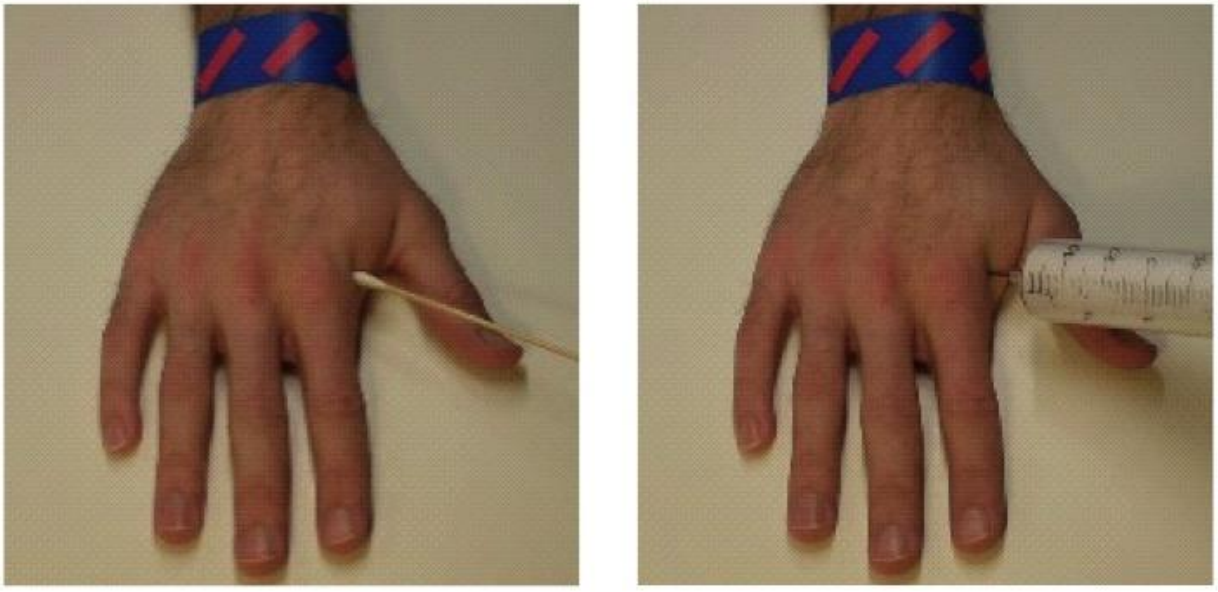
As classification performance improves, this field will reshape how we classify mental diseases and mental states in general. In the past, we lacked relevant, fine-grained neuroimaging data, so we made diagnoses from downstream outputs – patient behavior and self-report – rather than on any kind of neurological basis. For the sake of convenience and as a result of human mental processing limitations, the DSM clusters these symptomatologies into distinct diseases. With the introduction of high-resolution neuroimaging data and analyses, however, these clusters will be challenged and redefined. Imagine that my Chapter III classification of patients with AN versus BDD reached 98% accuracy. We would need to differentiate two hypotheses to explain the only 2% error: (1) there was noise and/or important features were missing from the data, or (2) the classifier is correct and the human diagnosis is not. Said another way, what is the basis of truth? What is the gold standard in the uncertain space of mental diseases? The NIMH recognized the problems with scalar labels and implemented the RDoC initiative (Kupfer and Regier 2011) to vectorize disease, but that is only part of what the near-perfect-classifier gedanken experiment reveals. The deep point here is not about the (obvious) benefit of using neural data to classify mental disease, nor about the efficacy of multi-dimensional disease labels. Instead, the essential lesson is that human notions of diseases are almost certainly limited by our mental processing power, and therefore inaccurate.

Given the computational limits of the human brain, optimally diagnosing the diseases of an organ with 100 trillion neural connections requires help. Just as the Sumerians invented writing (Glassner 2003; Sampson 1985) to offload the mental complexity of record-keeping, one can think of machine-learning on neuroimaging data as offloading the calculation and eventually, *refinement,* of mental diseases. Improved machine learning models will work circularly with our current understanding of diseases: we will use machine learning to build models for identifying the diseases we have already labeled, and then suggest revisions in our guidelines and diagnoses. Although it seems most relevant to the incomparably complex human brain, this approach applies to all intricate diseases. Just as we use an iPhone to schedule, we will use machine-learning to diagnose. We developed machine learning to diagnose disease, but this line of reasoning applies equally well to neurotypical states.

If one believes in macroscopic determinism – that any event approximated by classical mechanics has an antecedent described by the physical laws of the universe – then suboptimal technology and poor models are the only impediments to decoding brain signals into behavior with very high accuracy. Said another way, behavior is the result of biological processes exclusively and can in theory be highly predictable. As our understanding and technology improve, the decoding ability of machine learning will continue to approach perfection. This dissertation reflects a small contribution in that trajectory.

# Chapter VI - Appendix

## 6.1 Empathy



**Supplementary Figure S1 - needle and cotton swab stimuli**
An image from the *touch* and the *stab* condition. Each image is a single frame of a 60-frame (30 frames per second) video displayed to participants. The last frame lasted an additional 300ms, bringing the total length of each video to 2.3 seconds.

## 6.2 HBF

| Subject | MH | BABS | DTI | coherence | | Subject | MH | BABS | DTI | coherence |
|---|---|---|---|---|---|---|---|---|---|---|
| 1002_NW | X | | X | | | 1031_NW | X | X | X | X |
| 1003_NW | X | | X | | | 1032_NW | X | X | X | X |
| 1004_NW | X | | | | | 1034_NW | X | X | X | X |
| 1005_NW | X | | | | | 1035_NW | X | X | | X |
| 1006_NW | X | | X | X | | 1036_NW | X | X | X | X |
| 1008_NW | X | | X | | | 1039_NW | X | X | | X |
| 1012_NW | X | | X | | | 1041_NW | X | X | | X |
| 1013_NW | X | | X | X | | 1042_NW | X | X | | |
| 1014_NW | X | | X | X | | 1043_NW | X | X | | X |
| 1015_NW | X | | X | | | 2001_NW | X | X | | X |
| 1016_NW | X | | | | | 2002_NW | X | X | X | X |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1017_NW | X | X | X | X | | 2003_NW | X | X | | |
| 1018_NW | X | X | | | | 2004_NW | X | X | X | |
| 1019_NW | X | X | X | X | | 2005_NW | X | X | | |
| 1020_NW | X | X | X | X | | 2006_NW | X | X | | |
| 1021_NW | X | X | X | | | 2007_NW | X | X | X | |
| 1022_NW | X | X | X | X | | 2008_NW | X | X | | |
| 1023_NW | X | X | X | X | | 2009_NW | X | X | X | X |
| 1024_NW | X | X | X | X | | 2010_NW | X | X | X | X |
| 1025_NW | X | X | X | | | 2011_NW | X | X | X | X |
| 1026_NW | X | X | X | X | | 2012_NW | X | X | X | X |
| 1027_NW | X | X | X | X | | 2013_NW | X | X | X | |
| 1029_NW | X | X | X | X | | 2014_NW | X | X | X | |
| 1030_NW | X | X | X | X | | 2015_NW | X | X | X | X |

| **Subject** | **MH** | **BABS** | **DTI** | **coherence** | | **Subject** | **MH** | **BABS** | **DTI** | **coherence** |
|---|---|---|---|---|---|---|---|---|---|---|
| 2016_NW | X | X | | | | 2041_NW | X | X | X | X |
| 2017_NW | X | X | X | | | 2042_NW | X | X | | |
| 2018_NW | X | X | | X | | 2043_NW | | | | X |
| 2019_NW | X | X | | | | 2044_NW | X | X | | |
| 2020_NW | X | X | X | | | 3001_NW | X | | X | |
| 2021_NW | X | X | X | X | | 3002_NW | X | | | X |
| 2022_NW | X | X | | | | 3003_NW | X | | | X |
| 2023_NW | X | X | X | X | | 3005_NW | X | | | X |
| 2024_NW | X | X | X | | | 3006_NW | X | | | |
| 2025_NW | X | X | X | X | | 3007_NW | X | | X | X |
| 2026_NW | X | X | X | X | | 3008_NW | X | | | |
| 2027_NW | X | X | X | X | | 3009_NW | X | | X | X |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 2028_NW | X | X | X | | | 3010_NW | X | | X | |
| 2029_NW | X | X | X | | | 3011_NW | X | | X | X |
| 2030_NW | X | X | X | X | | 3012_NW | X | | | |
| 2031_NW | X | X | | | | 3013_NW | X | | X | |
| 2032_NW | X | X | | X | | 3014_NW | X | | X | |
| 2033_NW | X | X | X | X | | 3015_NW | X | | X | |
| 2034_NW | X | X | X | X | | 3016_NW | X | | X | |
| 2035_NW | X | X | X | | | 3017_NW | X | | X | X |
| 2036_NW | X | X | X | X | | 3018_NW | X | | X | |
| 2037_NW | X | X | X | X | | 3019_NW | X | | X | X |
| 2038_NW | X | X | | X | | 3020_NW | X | | X | X |
| 2039_NW | X | X | X | X | | 3021_NW | X | | | |
| 2040_NW | X | X | X | X | | 3022_NW | X | | X | X |

| **Subject** | **MH** | **BABS** | **DTI** | **coherence** |
|---|---|---|---|---|
| 3023_NW | X | | X | X |
| 3024_NW | X | | X | |
| 3025_NW | X | | X | X |
| 3026_NW | X | | | |
| 3027_NW | X | | X | X |
| 3028_NW | X | | | |
| 3029_NW | X | | X | X |
| 3030_NW | X | | X | X |
| 3031_NW | X | | X | X |
| 3032_NW | X | | X | X |
| 3033_NW | X | | | |
| 3034_NW | X | | X | X |

| | | | | |
|---|---|---|---|---|
| 3035_NW | X | | X | X |
| 3036_NW | X | | X | |
| 3037_NW | X | | X | X |
| 3038_NW | X | | X | X |
| 3039_NW | X | | X | X |
| 3040_NW | X | | | |
| 3041_NW | X | | X | X |
| 3042_NW | X | | X | |
| 3043_NW | X | | | |
| 3044_NW | X | | X | X |

**Supplementary Table S1 - available data among all participants.** Rows are subjects. X indicates data for a subject is present in a given modality indicated by the column.

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## 6.3 IBD

| # | Variable | Explanation | Mean | STD |
|---|---|---|---|---|
| 1 | Any use of IBD meds | Use of any IBD related medications (all the medications in variables #2-#43) | 0.88 | 0.33 |
| 2 | Days on rectal 5-ASA | Number of days rectal aminosalicylates used | 15.25 | 52.58 |
| 3 | Any rectal 5-ASA use | Rectal aminosalicylates used in this year: yes / no | 0.14 | 0.35 |
| 4 | Episodes on rectal 5-ASA | Number of times an episode of rectal aminosalicylates started | 0.17 | 0.52 |
| 5 | Days on oral 5-ASA | Number of days oral aminosalicylates used | 124.08 | 147.97 |
| 6 | Any oral 5-ASA use | Oral aminosalicylates used in this year: yes/ no | 0.53 | 0.50 |
| 7 | Episodes on oral 5-ASA | Number of times an episode of oral aminosalicylates started | 0.46 | 0.82 |
| 8 | Days on antibiotics | Number of days antibiotics used | 6.29 | 24.88 |
| 9 | Any antibiotics use | Antibiotics used in this year: yes/no | 0.23 | 0.42 |
| 10 | Episodes on antibiotics | Number of times an episode of antibiotics started | 0.30 | 0.67 |
| 11 | Days on budesonide | Number of days budesonide (local release steroid) used | 7.74 | 38.53 |
| 12 | Any budesonide use | Budesonide (local release steroid) used in this year: yes/no | 0.06 | 0.24 |
| 13 | Episodes on budesonide | Number of times an episode of budesonide (local release steroid) started | 0.08 | 0.37 |
| 14 | Days on rectal | Number of days rectal steroids used | 3.75 | 18.24 |

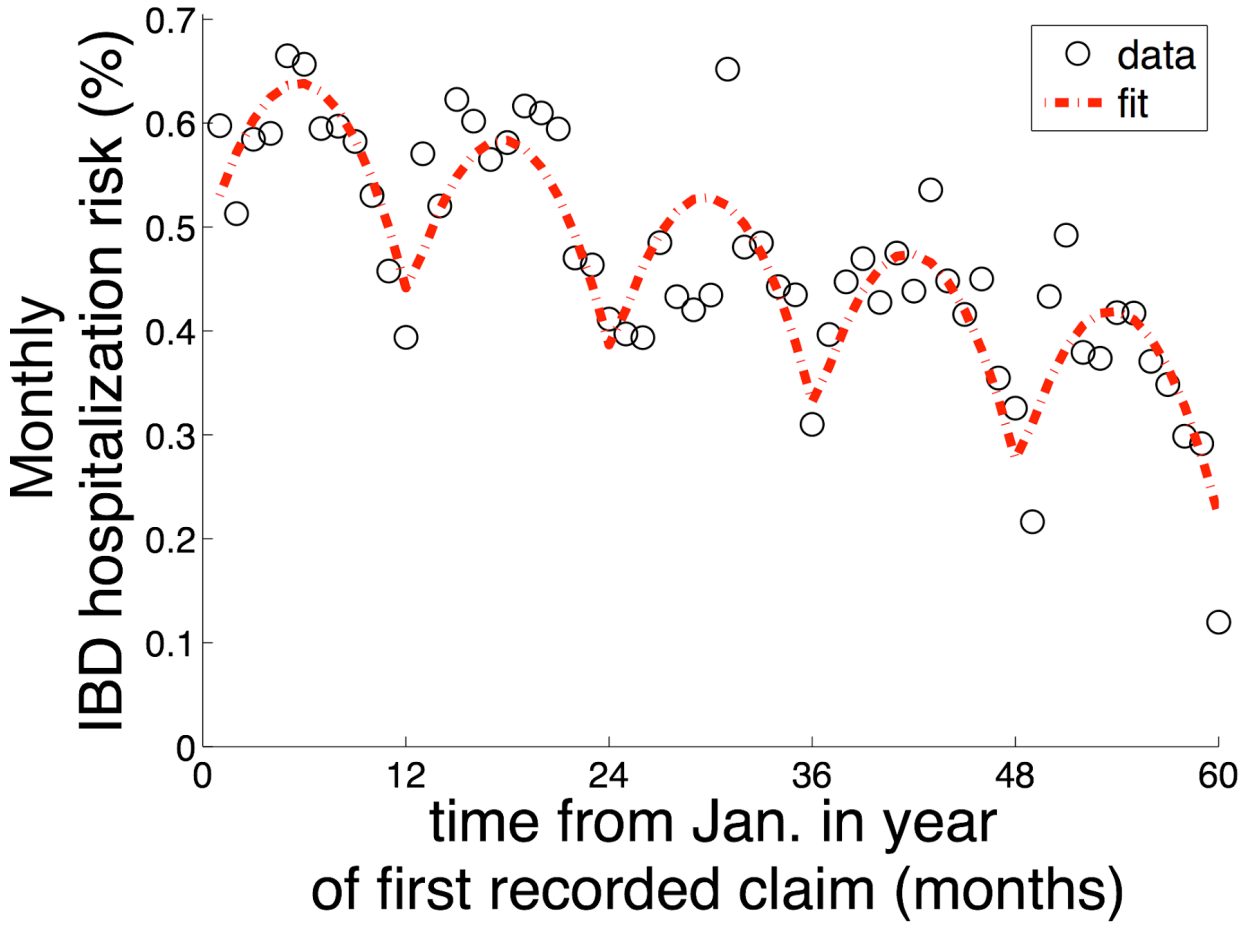
| | | | | |
|---|---|---|---|---|
| | steroids | | | |
| 15 | Any rectal steroid use | Rectal steroids used in this year: yes/no | 0.08 | 0.27 |
| 16 | Episodes on rectal steroids | Number of times an episode of rectal steroids started | 0.10 | 0.42 |
| 17 | Days on oral/IV steroids | Number of days systemic steroids used | 18.63 | 51.06 |
| 18 | Any use of oral/IV steroids | Systemic steroids used in this year: yes/no | 0.28 | 0.45 |
| 19 | Episodes on oral/IV steroids | Number of times an episode of systemic steroids started | 0.38 | 0.80 |
| 20 | Episodes of long-term steroid use | Number of times an episode of long term (>90 consecutive days) steroids started | 0.05 | 0.25 |
| 21 | Days on thiopurines | Number of days thiopurines used | 47.54 | 111.77 |
| 22 | Any thiopurine use | Thiopurines used in this year: yes/no | 0.19 | 0.39 |
| 23 | Episodes on thiopurines | Number of times an episode of thiopurines started | 0.13 | 0.47 |
| 24 | Days on MTX | Number of days methotrexate used | 6.34 | 41.04 |
| 25 | Any MTX use | Methotrexate used in this year: yes/no | 0.03 | 0.18 |
| 26 | Episodes on MTX | Number of times an episode of methotrexate started | 0.03 | 0.21 |
| 27 | Days on cyclosporine or tacrolimus | Number of days on cyclosporine or tacrolimus | 1.09 | 17.70 |
| 28 | Any use of cyclosporine or tacrolimus | Cyclosporine or tacrolimus used in this year: yes/no | 0.00 | 0.07 |
| 29 | Episodes on cyclosporine or tacrolimus | Number of times an episode of cyclosporine or tacrolimus was started | 0.00 | 0.08 |
| 30 | Days on ADA | Number of days adalimumab used | 16.92 | 69.70 |
| 31 | Any ADA use | Adalimumab used in this year: yes/no | 0.07 | 0.26 |
| 32 | Episodes on ADA | Number of times an episode of adalimumab started | 0.05 | 0.26 |
| 33 | Days on IFX | Number of days infliximab used | 31.03 | 92.95 |
| 34 | Any IFX use | Infliximab used in this year: yes/no | 0.12 | 0.32 |
| 35 | Episodes on IFX | Number of times an episode of infliximab started | 0.10 | 0.36 |
| 36 | Days on CTZ | Number of days certolizumab used | 3.18 | 31.14 |
| 37 | Any CTZ use | Certolizumab used in this year: yes/no | 0.01 | 0.12 |
| 38 | Episodes on CTZ | Number of times an episode of certolizumab started | 0.01 | 0.12 |
| 39 | Days on NAT | Number of days natalizumab used | 0.31 | 9.41 |
| 40 | Any NAT use | Natalizumab used in this year: yes/no | 0.00 | 0.03 |
| 41 | Episodes on NAT | Number of times an episode of natalizumab started | 0.00 | 0.03 |
| 42 | Episodes on biologics | Number of times an episode of biologics started. Variable #30-#41 are all biologics. This should be the sum of #32, #35, #38, and #41 | 0.16 | 0.47 |
| 43 | Any biologic use | Biologics used in this year: yes/no. Variable #30-#41 are all biologics. If any of those are >0 this | 0.19 | 0.39 |

| | | | | |
|---|---|---|---|---|
| | | should be 1. | | |
| 44 | IBD claims | Number of IBD claims | 5.99 | 8.53 |
| 45 | CD claims | Number of Crohn's disease claims | 3.35 | 7.96 |
| 46 | Any CD claims | Any Crohn's disease claims this year: yes/no | 0.50 | 0.50 |
| 47 | UC claims | Number of ulcerative colitis claims | 2.75 | 4.77 |
| 48 | Any UC claims | Any ulcerative colitis claims this year: yes/no | 0.63 | 0.48 |
| 49 | Office visits | Number of office visits | 8.08 | 7.64 |
| 50 | Any office visits | Any office visits this year: yes/no | 0.99 | 0.12 |
| 51 | IBD related office visits | Number of IBD related office visits | 2.35 | 2.77 |
| 52 | Any IBD related office visits | Any IBD related office visits this year: yes/no | 0.80 | 0.40 |
| 53 | IBD related office visits with GE | Number of IBD related office visits with a gastroenterologist | 1.21 | 1.78 |
| 54 | Any IBD related office visits with GE | Any IBD related office visits with a gastroenterologist this year: yes/no | 0.53 | 0.50 |
| 55 | IBD related office visits with UCLA GE | Number of IBD related office visits with a UCLA gastroenterologist | 0.02 | 0.13 |
| 56 | Any IBD related office visits with non-UCLA GE | Any IBD related office visits with a non-UCLA gastroenterologist this year: yes/no | 0.51 | 0.50 |
| 57 | Colonoscopies | Number of colonoscopies | 0.49 | 0.63 |
| 58 | Any colonoscopies | Any colonoscopies this year: yes/no | 0.44 | 0.50 |
| 59 | Upper endoscopies | Number of upper endoscopies | 0.15 | 0.40 |
| 60 | Any upper endoscopies | Any upper endoscopies this year: yes/no | 0.13 | 0.34 |
| 61 | Endoscopies of small intestines | Number of endoscopies of the small intestine | 0.02 | 0.20 |
| 62 | Any endoscopies of small intestines | Any endoscopies of the small intestine this year: yes/no | 0.02 | 0.14 |
| 63 | IBD surgeries | Number of IBD related surgeries | 0.06 | 0.35 |
| 64 | Any IBD surgeries | Any IBD related surgeries this year: yes/no | 0.04 | 0.20 |
| 65 | Acute IBD surgeries | Number of acute IBD related surgeries (this is a subset of IBD related surgeries) | 0.06 | 0.32 |
| 66 | Any acute IBD surgeries | Any acute IBD related surgeries (this is a subset of IBD related surgeries) this year: yes/no | 0.04 | 0.20 |
| 67 | CRP tests | Number of C-reactive protein tests | 0.73 | 1.55 |
| 68 | Any CRP tests | Any C-reactive protein tests this year: yes/no | 0.34 | 0.47 |
| 69 | ESR tests | Number of sedimentation rate tests | 0.91 | 1.73 |
| 70 | Any ESR tests | Any sedimentation rate tests this year: yes/no | 0.40 | 0.49 |
| 71 | Calprotectin tests | Number of stool calprotectin tests | 0.04 | 0.27 |
| 72 | Any calprotectin tests | Any stool calprotectin tests this year: yes/no | 0.03 | 0.17 |
| 73 | CBC tests | Number of complete blood counts | 2.68 | 3.60 |
| 74 | Any CBC tests | Any complete blood counts this year: yes/no | 0.83 | 0.37 |
| 75 | Liver enzyme tests | Number of liver enzyme tests | 2.31 | 2.94 |
| 76 | Any liver enzyme tests | Any liver enzyme tests this year: yes/no | 0.80 | 0.40 |
| 77 | Hepatitis B tests | Number of Hepatitis B tests | 0.12 | 0.41 |
| 78 | Hepatitis B vaccination | Hepatitis B vaccination this year: yes/no | 0.11 | 0.32 |

| | | | | |
|---|---|---|---|---|
| 79 | Abdominal X-rays | Number of X-rays | 0.23 | 0.86 |
| 80 | Any abdominal X-rays | Any X-rays this year: yes/no | 0.13 | 0.33 |
| 81 | Abdominal CT scans | Number of CT scans | 0.29 | 0.83 |
| 82 | Any abdominal CT scans | Any CT scans this year: yes/no | 0.19 | 0.40 |
| 83 | Abdominal MR scans | Number of MR scans | 0.06 | 0.29 |
| 84 | Any abdominal MR scans | Any MR scans this year: yes/no | 0.05 | 0.23 |
| 85 | Abdominal ultrasounds | Number of ultrasounds | 0.10 | 0.35 |
| 86 | Any abdominal ultrasounds | Any ultrasounds this year: yes/no | 0.09 | 0.28 |
| 87 | Bone loss assessment done | Bone loss assessment this year: yes/no | 0.07 | 0.25 |
| 88 | C. difficile tests | Number of Clostridium difficile stool tests | 0.16 | 0.51 |
| 89 | Any C. difficile tests | Any Clostridium difficile stool tests this year: yes/no | 0.12 | 0.32 |
| 90 | Tuberculosis tests | TB tested this year: yes/no | 0.09 | 0.28 |
| 91 | Influenza vaccination | Influenza vaccine this year: yes/no | 0.17 | 0.37 |
| 92 | Pneumococcal vaccination | Pneumococcal vaccine this year yes/no | 0.02 | 0.15 |
| 93 | Charlson comorbidity score | Charlson comorbidity score (higher score means more comorbidities) | 0.50 | 1.15 |
| 94 | Number of claims | Total number of claims | 73.79 | 89.59 |
| 95 | Days covered for prescriptions | Total number of days prescriptions were covered by plan | 364.15 | 8.02 |
| 96 | Hospitalizations | Number of hospitalizations | 0.27 | 0.82 |
| 97 | Any hospitalizations | Any hospitalizations this year: yes/no | 0.17 | 0.38 |
| 98 | Days in hospital | Total number of days hospitalized | 1.74 | 8.04 |
| 99 | IBD related hospitalizations | Number of IBD related hospitalizations | 0.10 | 0.42 |
| 100 | Any IBD related hospitalizations | Any IBD related hospitalizations this year: yes/no | 0.07 | 0.26 |
| 101 | Days in hospital for IBD | Total number of days hospitalized related to IBD | 0.76 | 4.53 |
| 102 | ED visits | Number of ED visits | 0.60 | 1.94 |
| 103 | Any ED visits | Any ED visits this year: yes/no | 0.27 | 0.44 |
| 104 | IBD related ED visits | Number of IBD related ED visits | 0.26 | 1.17 |
| 105 | Any IBD related ED visits | Any IBD related ED visits this year: yes/no | 0.14 | 0.34 |
| 106 | Age | Age | 42.02 | 13.94 |
| 107 | Moderate disease | Moderate disease this year: yes/no (based on a combination of number of relapses and long term steroid use) | 0.21 | 0.41 |
| 108 | Severe disease | Severe disease this year: yes/no (based on a combination of number of relapses and long term steroid use) | 0.15 | 0.36 |
| 109 | Relapses | Relapse rate (based on number of times | 0.60 | 1.03 |

| | | | | |
|---|---|---|---|---|
| | | systemic steroids and biologics are started and acute IBD related surgeries) | | |
| 110 | Years with Anthem | The number of years someone has been a continuous member of Anthem | 0.04 | 0.21 |

**Supplemental Table S2 - insurance claims data.** Both the training and validation data contained 110 features extracted from Anthem, California between 2011 and 2013.




**Supplementary Figure S2 - feature extraction.** Hospitalization risk is related to the time of year and length of time someone has been a continuous member of the insurance plan. The length of membership time is conflated with increased age.

## References


Abram, Samantha V., Krista M. Wisner, Rachael G. Grazioplene, Robert F. Krueger, Angus W. MacDonald, and Colin G. DeYoung. 2015. “Functional Coherence of Insula Networks Is Associated with Externalizing Behavior.” *Journal of Abnormal Psychology* 124 (4): 1079–91. doi:10.1037/abn0000078.

Adler, Robert J. 2010. *The Geometry of Random Fields*. SIAM. http://epubs.siam.org/doi/pdf/10.1137/1.9780898718980.bm.

Aggarwal, Charu C., Alexander Hinneburg, and Daniel A. Keim. 2001. “On the Surprising Behavior of Distance Metrics in High Dimensional Space.” In *Lecture Notes in Computer Science*, 420–34. doi:10.1007/3-540-44503-x_27.

Agüera, Zaida, Xandra Romero, Jon Arcelus, Isabel Sánchez, Nadine Riesco, Susana Jiménez-Murcia, Jana González-Gómez, et al. 2015. “Changes in Body Composition in Anorexia Nervosa: Predictors of Recovery and Treatment Outcome.” *PloS One* 10 (11): e0143012. doi:10.1371/journal.pone.0143012.

Allez, Matthieu, Marc Lemann, Joëlle Bonnet, Pierre Cattan, Raymond Jian, and Robert Modigliani. 2002. “Long Term Outcome of Patients with Active Crohn’s Disease Exhibiting Extensive and Deep Ulcerations at Colonoscopy.” *The American Journal of Gastroenterology* 97 (4): 947–53. doi:10.1111/j.1572-0241.2002.05614.x.

Allport, Gordon W., and J. Michael Ross. 1967. “Personal Religious Orientation and Prejudice.” *Journal of Personality and Social Psychology* 5 (4). American Psychological Association: 432. doi:10.1037/h0021212.

Altemeyer, Bob. 1981. *Right-Wing Authoritarianism*. University of Manitoba press.

Amarasingham, Ruben, Rachel E. Patzer, Marco Huesch, Nam Q. Nguyen, and Bin Xie. 2014. “Implementing Electronic Health Care Predictive Analytics: Considerations and Challenges.” *Health Affairs* 33 (7): 1148–54. doi:10.1377/hlthaff.2014.0352.

American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Pub. https://books.google.com/books?hl=en&lr=&id=-JivBAAAQBAJ&oi=fnd&pg=PT18&dq=Diagnostic+and+Statistical+Manual+of+Mental+Disorders+DSM-5+5th+Edn&ots=cdVT--MMsf&sig=tncDKvuTHPsRzyjaYYRx3M4vql0.

Ananthakrishnan, Ashwin N. 2015. “Epidemiology and Risk Factors for IBD.” *Nature Reviews. Gastroenterology & Hepatology* 12 (4): 205–17. doi:10.1038/nrgastro.2015.34.

Anderson, Ariana, Pamela K. Douglas, Wesley T. Kerr, Virginia S. Haynes, Alan L. Yuille, Jianwen Xie, Ying Nian Wu, Jesse A. Brown, and Mark S. Cohen. 2014. “Non-Negative Matrix Factorization of Multimodal MRI, fMRI and Phenotypic Data Reveals Differential Changes in Default Mode Subnetworks in ADHD.” *NeuroImage* 102 Pt 1 (November): 207–19. doi:10.1016/j.neuroimage.2013.12.015.

Andersson, Jesper L. R., Mark Jenkinson, and Stephen Smith. 2007. “Non-Linear Registration Aka Spatial Normalisation FMRIB Technical Report TR07JA2.” FMRIB Centre, Oxford.

Arienzo, Donatello, Alex Leow, Jesse A. Brown, Liang Zhan, Johnson Gadelkarim, Sarit Hovav, and Jamie D. Feusner. 2013. “Abnormal Brain Network Organization in Body Dysmorphic Disorder.” *Neuropsychopharmacology: Official Publication of the*

*American College of Neuropsychopharmacology* 38 (6): 1130–39. doi:10.1038/npp.2013.18.

Ashburner, John, and Karl J. Friston. 2005. “Unified Segmentation.” *NeuroImage* 26 (3): 839–51. doi:10.1016/j.neuroimage.2005.02.018.

Ashburner, John, and K. J. Friston. 1999. “Nonlinear Spatial Normalization Using Basis Functions.” *Human Brain Mapping* 7 (4): 254–66. https://www.ncbi.nlm.nih.gov/pubmed/10408769.

Ashburner, John, P. Neelin, D. L. Collins, A. Evans, and K. Friston. 1997. “Incorporating Prior Knowledge into Image Registration.” *NeuroImage* 6 (4): 344–52. doi:10.1006/nimg.1997.0299.

Asuncion, Arthur, Max Welling, Padhraic Smyth, and Yee Whye Teh. 2009. “On Smoothing and Inference for Topic Models.” In *Proceedings of the Twenty-Fifth Conference on Uncertainty in Artificial Intelligence*, 27–34. UAI ’09. Arlington, Virginia, United States: AUAI Press. http://dl.acm.org/citation.cfm?id=1795114.1795118.

Avenanti, Alessio, Domenica Bueti, Gaspare Galati, and Salvatore M. Aglioti. 2005. “Transcranial Magnetic Stimulation Highlights the Sensorimotor Side of Empathy for Pain.” *Nature Neuroscience* 8 (7): 955–60. doi:10.1038/nn1481.

Avenanti, Alessio, Ilaria Minio-Paluello, Ilaria Minio Paluello, Ilaria Bufalari, and Salvatore M. Aglioti. 2006. “Stimulus-Driven Modulation of Motor-Evoked Potentials during Observation of Others’ Pain.” *NeuroImage* 32 (1): 316–24. doi:10.1016/j.neuroimage.2006.03.010.

Azevedo, Ruben T., Emiliano Macaluso, Alessio Avenanti, Valerio Santangelo, Valentina Cazzato, and Salvatore Maria Aglioti. 2012. “Their Pain Is Not Our Pain: Brain and Autonomic Correlates of Empathic Resonance with the Pain of Same and Different Race Individuals.” *Human Brain Mapping* 34 (12): 3168–81. doi:10.1002/hbm.22133.

Baldi, P., P. Sadowski, and D. Whiteson. 2014. “Searching for Exotic Particles in High-Energy Physics with Deep Learning.” *Nature Communications* 5 (July): 4308. doi:10.1038/ncomms5308.

Barnett, Georgia, and Ruth E. Mann. 2013. “Empathy Deficits and Sexual Offending: A Model of Obstacles to Empathy.” *Aggression and Violent Behavior* 18 (2): 228–39. doi:10.1016/j.avb.2012.11.010.

Bates, David W., Suchi Saria, Lucila Ohno-Machado, Anand Shah, and Gabriel Escobar. 2014. “Big Data in Health Care: Using Analytics to Identify and Manage High-Risk and High-Cost Patients.” *Health Affairs* 33 (7): 1123–31. doi:10.1377/hlthaff.2014.0041.

Batson, C. Daniel. 2009. “These Things Called Empathy: Eight Related But Distinct Phenomona.” *The Social Neuroscience of Empathy*. Cambridge, Mass.: MIT Press. http://server2.docfoc.com/uploads/Z2015/12/19/OfieoZbKaY/07d63f7f5b092e160a131cb2f839dc59.pdf.

Batson, C. Daniel, J. Fultz, and P. A. Schoenrade. 1987. “Distress and Empathy: Two Qualitatively Distinct Vicarious Emotions with Different Motivational Consequences.” *Journal of Personality* 55 (1): 19–39. https://www.ncbi.nlm.nih.gov/pubmed/3572705.

Baumgart, Daniel C., and Simon R. Carding. 2007. “Inflammatory Bowel Disease: Cause and Immunobiology.” *The Lancet* 369 (9573): 1627–40. doi:10.1016/S0140-6736(07)60750-8.

bblah. 2007. “Non-Linear Optimisation FMRIB Technical Report TR07JA1.” FMRIB Centre, Oxford.

Beaugerie, Laurent, Philippe Seksik, Isabelle Nion-Larmurier, Jean-Pierre Gendre, and Jacques Cosnes. 2006. “Predictors of Crohn’s Disease.” *Gastroenterology* 130 (3): 650–56. doi:10.1053/j.gastro.2005.12.019.

Beck, Aaron T. 1979. *Cognitive Therapy of Depression*. Guilford Press. https://market.android.com/details?id=book-L09cRS0xWj0C.

Becker, H. 1931. “Some Forms of Sympathy: A Phenomenological Analysis.” *Journal of Abnormal and Social Psychology* 26 (1). American Psychological Association: 58. doi:10.1037/h0072609.

Beckmann, Christian F., and Stephen M. Smith. 2004. “Probabilistic Independent Component Analysis for Functional Magnetic Resonance Imaging.” *IEEE Transactions on Medical Imaging* 23 (2): 137–52. doi:10.1109/TMI.2003.822821.

Bellot, F., and Eugene E. Krause. 1988. “Taxicab Geometry: An Adventure in Non-Euclidean Geometry.” *The Mathematical Gazette* 72 (461): 255. doi:10.2307/3618288.

Bland, J. M. 2000. “Statistics Notes: The Odds Ratio.” *BMJ* 320 (7247): 1468–1468. doi:10.1136/bmj.320.7247.1468.

Blei, David M. 2012. “Probabilistic Topic Models.” *Communications of the ACM* 55 (4). New York, NY, USA: ACM: 77–84. doi:10.1145/2133806.2133826.

Blei, David M., Andrew Y. Ng, and Michael I. Jordan. 2003. “Latent Dirichlet Allocation.” *Journal of Machine Learning Research: JMLR* 3 (Jan): 993–1022. http://www.jmlr.org/papers/volume3/blei03a/blei03a.pdf.

Botvinick, Matthew, Amishi P. Jha, Lauren M. Bylsma, Sara A. Fabian, Patricia E. Solomon, and Kenneth M. Prkachin. 2005. “Viewing Facial Expressions of Pain Engages Cortical Areas Involved in the Direct Experience of Pain.” *NeuroImage* 25 (1): 312–19. doi:10.1016/j.neuroimage.2004.11.043.

Boyd, Stephen, Neal Parikh, and Eric Chu. 2011. *Distributed Optimization and Statistical Learning Via the Alternating Direction Method of Multipliers*. Now Publishers Inc. http://books.google.com/books/about/Distributed_Optimization_and_Statistical.html?hl=&id=8MjgLpJ0_4YC.

Braddock, Martin, and Anthony Quinn. 2004. “Targeting IL-1 in Inflammatory Disease: New Opportunities for Therapeutic Intervention.” *Nature Reviews. Drug Discovery* 3 (4): 330–39. doi:10.1038/nrd1342.

Bradley, Andrew P. 1997. “The Use of the Area under the ROC Curve in the Evaluation of Machine Learning Algorithms.” *Pattern Recognition* 30 (7): 1145–59. doi:10.1016/s0031-3203(96)00142-2.

Brainard, D. H. 1997. “The Psychophysics Toolbox.” *Spatial Vision* 10 (4). bbs.bioguider.com: 433–36. https://www.ncbi.nlm.nih.gov/pubmed/9176952.

Brown, Tiffany A., Lauren A. Holland, and Pamela K. Keel. 2013. “Comparing Operational Definitions of DSM-5 Anorexia Nervosa for Research Contexts.” *The International Journal of Eating Disorders* 47 (1): 76–84. doi:10.1002/eat.22184.

Bruneau, Emile G., Nir Jacoby, and Rebecca Saxe. 2015. “Empathic Control through Coordinated Interaction of Amygdala, Theory of Mind and Extended Pain Matrix Brain Regions.” *NeuroImage* 114: 105–19. doi:10.1016/j.neuroimage.2015.04.034.

Buccino, G., F. Binkofski, G. R. Fink, L. Fadiga, L. Fogassi, V. Gallese, R. J. Seitz, K. Zilles, G. Rizzolatti, and H-J Freund. 2001. “Action Observation Activates Premotor and Parietal Areas in a Somatotopic Manner: An fMRI Study.” *The European Journal of Neuroscience* 13 (2): 400–404. doi:10.1111/j.1460-9568.2001.01385.x.

Buchanan, B. G., S. L. Rossell, J. J. Maller, W. L. Toh, S. Brennan, and D. J. Castle. 2013. “Brain Connectivity in Body Dysmorphic Disorder Compared with Controls: A Diffusion Tensor Imaging Study.” *Psychological Medicine* 43 (12): 2513–21. doi:10.1017/S0033291713000421.

Bufalari, Ilaria, Taryn Aprile, Alessio Avenanti, Francesco Di Russo, and Salvatore Maria Aglioti. 2007. “Empathy for Pain and Touch in the Human Somatosensory Cortex.” *Cerebral Cortex* 17 (11): 2553–61. doi:10.1093/cercor/bhl161.

Bunce, Scott C., Meltem Izzetoglu, Kurtulus Izzetoglu, Banu Onaral, and Kambiz Pourrezaei. 2006. “Functional near-Infrared Spectroscopy.” *IEEE Engineering in Medicine and Biology Magazine: The Quarterly Magazine of the Engineering in Medicine & Biology Society* 25 (4): 54–62. https://www.ncbi.nlm.nih.gov/pubmed/16898659.

Burisch, Johan, and Pia Munkholm. 2013. “Inflammatory Bowel Disease Epidemiology.” *Current Opinion in Gastroenterology* 29 (4): 357–62. doi:10.1097/MOG.0b013e32836229fb.

Carr, Laurie, Marco Iacoboni, Marie-Charlotte Dubeau, John C. Mazziotta, and Gian Luigi Lenzi. 2003. “Neural Mechanisms of Empathy in Humans: A Relay from Neural Systems for Imitation to Limbic Areas.” *Proceedings of the National Academy of Sciences of the United States of America* 100 (9): 5497–5502. doi:10.1073/pnas.0935845100.

Caviness, V. S., Jr, J. Meyer, N. Makris, and D. N. Kennedy. 1996. “MRI-Based Topographic Parcellation of Human Neocortex: An Anatomically Specified Method with Estimate of Reliability.” *Journal of Cognitive Neuroscience* 8 (6): 566–87. doi:10.1162/jocn.1996.8.6.566.

Chapman-Kiddell, Christine A., Peter S. W. Davies, Lynda Gillen, and Graham L. Radford-Smith. 2010a. “Role of Diet in the Development of Inflammatory Bowel Disease.” *Inflammatory Bowel Diseases* 16 (1): 137–51. doi:10.1002/ibd.20968.

———. 2010b. “Role of Diet in the Development of Inflammatory Bowel Disease.” *Inflammatory Bowel Diseases* 16 (1): 137–51. doi:10.1002/ibd.20968.

Cheng, Yawei, Ching-Po Lin, Ho-Ling Liu, Yuan-Yu Hsu, Kun-Eng Lim, Daisy Hung, and Jean Decety. 2007. “Expertise Modulates the Perception of Pain in Others.” *Current Biology: CB* 17 (19): 1708–13. doi:10.1016/j.cub.2007.09.020.

Cheng, Yawei, Chia-Yen Yang, Ching-Po Lin, Po-Lei Lee, and Jean Decety. 2008. “The Perception of Pain in Others Suppresses Somatosensory Oscillations: A Magnetoencephalography Study.” *NeuroImage* 40 (4): 1833–40. doi:10.1016/j.neuroimage.2008.01.064.

Chong, Trevor T-J, Ross Cunnington, Mark A. Williams, Nancy Kanwisher, and Jason B. Mattingley. 2008. “fMRI Adaptation Reveals Mirror Neurons in Human Inferior

Parietal Cortex." *Current Biology: CB* 18 (20). Elsevier: 1576–80. doi:10.1016/j.cub.2008.08.068.

Christov-Moore, Leonardo, and Marco Iacoboni. 2016. "Self-Other Resonance, Its Control and Prosocial Inclinations: Brain--Behavior Relationships." *Human Brain Mapping*. Wiley Online Library. http://onlinelibrary.wiley.com/doi/10.1002/hbm.23119/pdf.

Christov-Moore, Leonardo, Taisei Sugiyama, Kristina Grigaityte, and Marco Iacoboni. 2017. "Increasing Generosity by Disrupting Prefrontal Cortex." *Social Neuroscience* 12 (2): 174–81. doi:10.1080/17470919.2016.1154105.

Cikara, Mina, Matthew M. Botvinick, and Susan T. Fiske. 2011. "Us versus Them: Social Identity Shapes Neural Responses to Intergroup Competition and Harm." *Psychological Science* 22 (3): 306–13. doi:10.1177/0956797610397667.

Ciresan, D., U. Meier, and J. Schmidhuber. 2012. "Multi-Column Deep Neural Networks for Image Classification." In *2012 IEEE Conference on Computer Vision and Pattern Recognition*. doi:10.1109/cvpr.2012.6248110.

Clark, Ian A., Katherine E. Niehaus, Eugene P. Duff, Martina C. Di Simplicio, Gari D. Clifford, Stephen M. Smith, Clare E. Mackay, Mark W. Woolrich, and Emily A. Holmes. 2014. "First Steps in Using Machine Learning on fMRI Data to Predict Intrusive Memories of Traumatic Film Footage." *Behaviour Research and Therapy* 62 (November): 37–46. doi:10.1016/j.brat.2014.07.010.

Cohen, Jessica R., Robert F. Asarnow, Fred W. Sabb, Robert M. Bilder, Susan Y. Bookheimer, Barbara J. Knowlton, and Russell A. Poldrack. 2011. "Decoding

Continuous Variables from Neuroimaging Data: Basic and Clinical Applications." *Frontiers in Neuroscience* 5 (June): 75. doi:10.3389/fnins.2011.00075.

Cohen, L., S. Dehaene, L. Naccache, and S. Lehéricy. 2000. "The Visual Word Form Area." *Brain: A Journal of Neurology*. Oxford Univ Press. http://brain.oxfordjournals.org/content/123/2/291.short.

Collignon, André, Frederik Maes, Dominique Delaere, Dirk Vandermeulen, Paul Suetens, and Guy Marchal. 1995. "Automated Multi-Modality Image Registration Based on Information Theory." In *Information Processing in Medical Imaging*, 3:263–74. https://mirc.uzleuven.be/download/public/MIC/publications/929/paper.pdf.

Contreras-Huerta, Luis Sebastian, Katharine S. Baker, Katherine J. Reynolds, Luisa Batalha, and Ross Cunnington. 2013. "Racial Bias in Neural Empathic Responses to Pain." *PloS One* 8 (12): e84001. doi:10.1371/journal.pone.0084001.

Coren, S., and P. L. Hewitt. 1998. "Is Anorexia Nervosa Associated with Elevated Rates of Suicide?" *American Journal of Public Health* 88 (8): 1206–7. https://www.ncbi.nlm.nih.gov/pubmed/9702149.

Cuff, Benjamin M. P., Sarah J. Brown, Laura Taylor, and Douglas J. Howat. 2016. "Empathy: A Review of the Concept." *Emotion Review: Journal of the International Society for Research on Emotion* 8 (2): 144–53. doi:10.1177/1754073914558466.

Culham, Jody C. 2006. "Functional Neuroimaging: Experimental Design and Analysis." *Handbook of Functional Neuroimaging of Cognition* 2. MIT Press Cambridge, MA: 53–82.

https://pdfs.semanticscholar.org/b195/6cc8944a14343e951a2c90fe5aba2e86c30c.pdf.

Davis, Jesse, and Mark Goadrich. 2006. “The Relationship Between Precision-Recall and ROC Curves.” In *Proceedings of the 23rd International Conference on Machine Learning*, 233–40. ICML ’06. New York, NY, USA: ACM. doi:10.1145/1143844.1143874.

Davis, Mark H. 1983. “Measuring Individual Differences in Empathy: Evidence for a Multidimensional Approach.” *Journal of Personality and Social Psychology* 44 (1): 113–26. http://doi.apa.org/journals/psp/44/1/113.pdf.

Dawkins, Richard. 2016. *The God Delusion*. Random House. http://philosophy.org.za/uploads_other/The_God_Delusion_(Selected).pdf.

Decety, Jean. 2010. “To What Extent Is the Experience of Empathy Mediated by Shared Neural Circuits?” *Emotion Review: Journal of the International Society for Research on Emotion* 2 (3): 204–7. doi:10.1177/1754073910361981.

Decety, Jean, Chenyi Chen, Carla Harenski, and Kent A. Kiehl. 2013. “An fMRI Study of Affective Perspective Taking in Individuals with Psychopathy: Imagining Another in Pain Does Not Evoke Empathy.” *Frontiers in Human Neuroscience* 7 (September). journal.frontiersin.org: 489. doi:10.3389/fnhum.2013.00489.

Decety, Jean, and John Grèzes. 1999. “Neural Mechanisms Subserving the Perception of Human Actions.” *Trends in Cognitive Sciences* 3 (5): 172–78. https://www.ncbi.nlm.nih.gov/pubmed/10322473.

Decety, Jean, and Claus Lamm. 2006. “Human Empathy through the Lens of Social Neuroscience.” *TheScientificWorldJournal* 6 (September). hindawi.com: 1146–63. doi:10.1100/tsw.2006.221.

Decety, Jean, Laurie R. Skelly, and Kent A. Kiehl. 2013. “Brain Response to Empathy-Eliciting Scenarios Involving Pain in Incarcerated Individuals with Psychopathy.” *JAMA Psychiatry* 70 (6). jamanetwork.com: 638–45. doi:10.1001/jamapsychiatry.2013.27.

Deen, Welmoed K. van, Martijn G. H. van Oijen, Kelly D. Myers, Adriana Centeno, William Howard, Jennifer M. Choi, Bennett E. Roth, et al. 2014. “A Nationwide 2010–2012 Analysis of U.S. Health Care Utilization in Inflammatory Bowel Diseases.” *Inflammatory Bowel Diseases* 20 (10): 1747–53. doi:10.1097/mib.0000000000000139.

Deen, Welmoed K. van, Arlen Spiro, A. Burak Ozbay, Martha Skup, Adriana Centeno, Natalie E. Duran, Precious N. Lacey, et al. 2017. “The Impact of Value-Based Healthcare for Inflammatory Bowel Diseases on Healthcare Utilization: A Pilot Study.” *European Journal of Gastroenterology & Hepatology* 29 (3): 331–37. doi:10.1097/MEG.0000000000000782.

Desikan, Rahul S., Florent Ségonne, Bruce Fischl, Brian T. Quinn, Bradford C. Dickerson, Deborah Blacker, Randy L. Buckner, et al. 2006. “An Automated Labeling System for Subdividing the Human Cerebral Cortex on MRI Scans into Gyral Based Regions of Interest.” *NeuroImage* 31 (3): 968–80. doi:10.1016/j.neuroimage.2006.01.021.

D'Haens, Geert, Filip Baert, Gert van Assche, Philip Caenepeel, Philippe Vergauwe, Hans Tuynman, Martine De Vos, et al. 2008. "Early Combined Immunosuppression or Conventional Management in Patients with Newly Diagnosed Crohn's Disease: An Open Randomised Trial." *The Lancet* 371 (9613): 660–67. doi:10.1016/S0140-6736(08)60304-9.

Dhar, Vasant. 2014. "Big Data and Predictive Analytics in Health Care." *Big Data* 2 (3): 113–16. doi:10.1089/big.2014.1525.

Didie, Elizabeth R., Tracy Kuniega-Pietrzak, and Katharine A. Phillips. 2010. "Body Image in Patients with Body Dysmorphic Disorder: Evaluations of and Investment in Appearance, Health/illness, and Fitness." *Body Image* 7 (1): 66–69. doi:10.1016/j.bodyim.2009.09.007.

Dixon, Philip M. 2002. "Bootstrap Resampling." *Encyclopedia of Environmetrics*. Wiley Online Library. http://onlinelibrary.wiley.com/doi/10.1002/9780470057339.vab028/full.

Donzé, Jacques, Drahomir Aujesky, Deborah Williams, and Jeffrey L. Schnipper. 2013. "Potentially Avoidable 30-Day Hospital Readmissions in Medical Patients." *JAMA Internal Medicine* 173 (8): 632. doi:10.1001/jamainternmed.2013.3023.

Dreiseitl, Stephan, and Lucila Ohno-Machado. 2002. "Logistic Regression and Artificial Neural Network Classification Models: A Methodology Review." *Journal of Biomedical Informatics* 35 (5-6): 352–59. https://www.ncbi.nlm.nih.gov/pubmed/12968784.

Dubinsky, Marla C., Ying-Chao Lin, Debra Dutridge, Yoana Picornell, Carol J. Landers, Sharmayne Farrior, Iwona Wrobel, et al. 2006. "Serum Immune Responses Predict

Rapid Disease Progression among Children with Crohn's Disease: Immune Responses Predict Disease Progression." *The American Journal of Gastroenterology* 101 (2): 360–67. doi:10.1111/j.1572-0241.2006.00456.x.

Dufresne, R. G., K. A. Phillips, C. C. Vittorio, and C. S. Wilkel. 2001. "A Screening Questionnaire for Body Dysmorphic Disorder in a Cosmetic Dermatologic Surgery Practice." *Dermatologic Surgery: Official Publication for American Society for Dermatologic Surgery [et Al.]* 27 (5): 457–62. https://www.ncbi.nlm.nih.gov/pubmed/11359494.

Eisenberg, N., and P. A. Miller. 1987. "The Relation of Empathy to Prosocial and Related Behaviors." *Psychological Bulletin* 101 (1): 91–119. https://www.ncbi.nlm.nih.gov/pubmed/3562705.

Eisen, J. L., K. A. Phillips, L. Baer, D. A. Beer, K. D. Atala, and S. A. Rasmussen. 1998. "The Brown Assessment of Beliefs Scale: Reliability and Validity." *The American Journal of Psychiatry* 155 (1): 102–8. doi:10.1176/ajp.155.1.102.

Eisler, Ivan, C. Dare, M. Hodes, G. Russell, E. Dodge, and D. Le Grange. 2000. "Family Therapy for Adolescent Anorexia Nervosa: The Results of a Controlled Comparison of Two Family Interventions." *Journal of Child Psychology and Psychiatry, and Allied Disciplines* 41 (6): 727–36. https://www.ncbi.nlm.nih.gov/pubmed/11039685.

Eisler, Ivan, Mima Simic, Gerald F. M. Russell, and Christopher Dare. 2007. "A Randomised Controlled Treatment Trial of Two Forms of Family Therapy in Adolescent Anorexia Nervosa: A Five-Year Follow-Up." *Journal of Child Psychology and Psychiatry, and Allied Disciplines* 48 (6): 552–60. doi:10.1111/j.1469-7610.2007.01726.x.

Ellis, P. L. 1982. “Empathy: A Factor in Antisocial Behavior.” *Journal of Abnormal Child Psychology* 10 (1): 123–34. https://www.ncbi.nlm.nih.gov/pubmed/7108052.

Fan, Rong-En, Kai-Wei Chang, Cho-Jui Hsieh, Xiang-Rui Wang, and Chih-Jen Lin. 2008. “LIBLINEAR: A Library for Large Linear Classification.” *Journal of Machine Learning Research: JMLR* 9 (Aug). jmlr.org: 1871–74. http://www.jmlr.org/papers/volume9/fan08a/fan08a.pdf.

Faravelli, C., S. Salvatori, F. Galassi, L. Aiazzi, C. Drei, and P. Cabras. 1997. “Epidemiology of Somatoform Disorders: A Community Survey in Florence.” *Social Psychiatry and Psychiatric Epidemiology* 32 (1): 24–29. https://www.ncbi.nlm.nih.gov/pubmed/9029984.

Fawcett, Tom. 2006/6. “An Introduction to ROC Analysis.” *Pattern Recognition Letters* 27 (8). Elsevier: 861–74. doi:10.1016/j.patrec.2005.10.010.

Feusner, Jamie Donald, Alexander Bystritsky, Gerhard Hellemann, and Susan Bookheimer. 2010. “Impaired Identity Recognition of Faces with Emotional Expressions in Body Dysmorphic Disorder.” *Psychiatry Research* 179 (3): 318–23. doi:10.1016/j.psychres.2009.01.016.

Fogassi, Leonardo, Pier Francesco Ferrari, Benno Gesierich, Stefano Rozzi, Fabian Chersi, and Giacomo Rizzolatti. 2005. “Parietal Lobe: From Action Organization to Intention Understanding.” *Science* 308 (5722). science.sciencemag.org: 662–67. doi:10.1126/science.1106138.

Ford, Alexander C., William J. Sandborn, Khurram J. Khan, Stephen B. Hanauer, Nicholas J. Talley, and Paul Moayyedi. 2011. “Efficacy of Biological Therapies in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis.” *The*

*American Journal of Gastroenterology* 106 (4): 644–59, quiz 660. doi:10.1038/ajg.2011.73.

Friston, K. J., P. Fletcher, O. Josephs, A. Holmes, M. D. Rugg, and R. Turner. 1998. "Event-Related fMRI: Characterizing Differential Responses." *NeuroImage* 7 (1): 30–40. doi:10.1006/nimg.1997.0306.

Friston, K. J., C. D. Frith, R. S. Frackowiak, and R. Turner. 1995. "Characterizing Dynamic Brain Responses with fMRI: A Multivariate Approach." *NeuroImage* 2 (2): 166–72. https://www.ncbi.nlm.nih.gov/pubmed/9343599.

Friston, K. J., A. P. Holmes, K. J. Worsley, J-P Poline, C. D. Frith, and R. S. J. Frackowiak. 1994. "Statistical Parametric Maps in Functional Imaging: A General Linear Approach." *Human Brain Mapping* 2 (4). Wiley Subscription Services, Inc., A Wiley Company: 189–210. doi:10.1002/hbm.460020402.

Friston, K. J., K. J. Worsley, R. S. Frackowiak, J. C. Mazziotta, and A. C. Evans. 1994. "Assessing the Significance of Focal Activations Using Their Spatial Extent." *Human Brain Mapping* 1 (3): 210–20. doi:10.1002/hbm.460010306.

Gadelkarim, Johnson J., Olusola Ajilore, Dan Schonfeld, Liang Zhan, Paul M. Thompson, Jamie D. Feusner, Anand Kumar, Lori L. Altshuler, and Alex D. Leow. 2014. "Investigating Brain Community Structure Abnormalities in Bipolar Disorder Using Path Length Associated Community Estimation." *Human Brain Mapping* 35 (5): 2253–64. doi:10.1002/hbm.22324.

Gallese, Vittorio, L. Fadiga, L. Fogassi, and G. Rizzolatti. 1996. "Action Recognition in the Premotor Cortex." *Brain: A Journal of Neurology* 119 ( Pt 2) (April): 593–609. https://www.ncbi.nlm.nih.gov/pubmed/8800951.

Gallese, Vittorio, Christian Keysers, and Giacomo Rizzolatti. 2004. “A Unifying View of the Basis of Social Cognition.” *Trends in Cognitive Sciences* 8 (9): 396–403. doi:10.1016/j.tics.2004.07.002.

Glassner, Jean-Jacques. 2003. *The Invention of Cuneiform: Writing in Sumer*. JHU Press. https://market.android.com/details?id=book-fhMTRcUm9WsC.

Gleason, Patrick P., G. Caleb Alexander, Catherine I. Starner, Stephen T. Ritter, Holly K. Van Houten, Brent W. Gunderson, and Nilay D. Shah. 2013. “Health Plan Utilization and Costs of Specialty Drugs within 4 Chronic Conditions.” *Journal of Managed Care Pharmacy: JMCP* 19 (7): 542–48. doi:10.18553/jmcp.2013.19.7.542.

Golgi, Camillo. 1906. “The Neuron Doctrine: Theory and Facts.” *Nobel Lecture* 1921. systems.neurosci.info: 190–217. http://www.systems.neurosci.info/Cortex/golginp.pdf.

Golovics, Petra A., Laszlo Lakatos, Michael D. Mandel, Barbara D. Lovasz, Zsuzsanna Vegh, Zsuzsanna Kurti, Istvan Szita, et al. 2015. “Does Hospitalization Predict the Disease Course in Ulcerative Colitis? Prevalence and Predictors of Hospitalization and Re-Hospitalization in Ulcerative Colitis in a Population-Based Inception Cohort (2000-2012).” *Journal of Gastrointestinal and Liver Diseases: JGLD* 24 (3): 287–92. doi:10.15403/jgld.2014.1121.243.pag.

Gordon, E., N. Cooper, C. Rennie, D. Hermens, and L. M. Williams. 2005. “Integrative Neuroscience: The Role of a Standardized Database.” *Clinical EEG and Neuroscience: Official Journal of the EEG and Clinical Neuroscience Society* 36 (2): 64–75. doi:10.1177/155005940503600205.

Grant, Jon E., Suck Won Kim, and Elke D. Eckert. 2002. “Body Dysmorphic Disorder in Patients with Anorexia Nervosa: Prevalence, Clinical Features, and Delusionality of Body Image.” *The International Journal of Eating Disorders* 32 (3): 291–300. doi:10.1002/eat.10091.

Grant, Jon E., and Katharine A. Phillips. 2004. “Is Anorexia Nervosa a Subtype of Body Dysmorphic Disorder? Probably Not, but Read On….” *Harvard Review of Psychiatry* 12 (2). Taylor & Francis: 123–26. doi:10.1080/10673220490447236.

Greck, Moritz de, Gang Wang, Xuedong Yang, Xiaoying Wang, Georg Northoff, and Shihui Han. 2012. “Neural Substrates Underlying Intentional Empathy.” *Social Cognitive and Affective Neuroscience* 7 (2): 135–44. doi:10.1093/scan/nsq093.

Greenberg, Jennifer L., Sarah Markowitz, Michael R. Petronko, Caitlin E. Taylor, Sabine Wilhelm, and G. Terence Wilson. 2010. “Cognitive-Behavioral Therapy for Adolescent Body Dysmorphic Disorder.” *Cognitive and Behavioral Practice* 17 (3): 248–58. doi:10.1016/j.cbpra.2010.02.002.

Grèzes, J., and J. Decety. 2001. “Functional Anatomy of Execution, Mental Simulation, Observation, and Verb Generation of Actions: A Meta-Analysis.” *Human Brain Mapping* 12 (1): 1–19. https://www.ncbi.nlm.nih.gov/pubmed/11198101.

Grocholewski, Anja, Sören Kliem, and Nina Heinrichs. 2012. “Selective Attention to Imagined Facial Ugliness Is Specific to Body Dysmorphic Disorder.” *Body Image* 9 (2): 261–69. doi:10.1016/j.bodyim.2012.01.002.

Grosbras, Marie-Hélène, and Tomás Paus. 2006. “Brain Networks Involved in Viewing Angry Hands or Faces.” *Cerebral Cortex* 16 (8): 1087–96. doi:10.1093/cercor/bhj050.

Guanglin Li, Guanglin Li, Aimee E. Schultz, and Todd A. Kuiken. 2010. “Quantifying Pattern Recognition—Based Myoelectric Control of Multifunctional Transradial Prostheses.” *IEEE Transactions on Neural Systems and Rehabilitation Engineering: A Publication of the IEEE Engineering in Medicine and Biology Society* 18 (2): 185–92. doi:10.1109/tnsre.2009.2039619.

Gunnarsson, Candace, Jie Chen, John A. Rizzo, Joseph A. Ladapo, Ahmad Naim, and Jennifer H. Lofland. 2011. “The Direct Healthcare Insurer and out-of-Pocket Expenditures of Psoriasis: Evidence from a United States National Survey.” *The Journal of Dermatological Treatment* 23 (4): 240–54. doi:10.3109/09546634.2010.550911.

Guo, Xiuyan, Li Zheng, Wei Zhang, Lei Zhu, Jianqi Li, Qianfeng Wang, Zoltan Dienes, and Zhiliang Yang. 2011. “Empathic Neural Responses to Others’ Pain Depend on Monetary Reward.” *Social Cognitive and Affective Neuroscience* 7 (5): 535–41. doi:10.1093/scan/nsr034.

Haines, Melissa L., Yousef Ajlouni, Peter M. Irving, Miles P. Sparrow, Rosemary Rose, Richard B. Gearry, and Peter R. Gibson. 2011. “Clinical Usefulness of Therapeutic Drug Monitoring of Thiopurines in Patients with Inadequately Controlled Inflammatory Bowel Disease.” *Inflammatory Bowel Diseases* 17 (6): 1301–7. doi:10.1002/ibd.21458.

Halmi, K., J. Mitchell, and S. Crow. 1999. “Fluoxetine vs. Cognitive Behavioral Therapy in Relapse Prevention for Anorexia Nervosa.” *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* 9: 373. doi:10.1016/s0924-977x(99)80592-6.

Hamilton, M. 1960. “A Rating Scale for Depression.” *Journal of Neurology, Neurosurgery, and Psychiatry* 23 (February): 56–62. doi:10.1136/jnnp.23.1.56.

———. 1969. “Diagnosis and Rating of Anxiety.” *The British Journal of Psychiatry: The Journal of Mental Science* 3 (special issue): 76–79.

Hanczar, Blaise, Jianping Hua, Chao Sima, John Weinstein, Michael Bittner, and Edward R. Dougherty. 2010. “Small-Sample Precision of ROC-Related Estimates.” *Bioinformatics* 26 (6): 822–30. doi:10.1093/bioinformatics/btq037.

Hand, David J. 2009. “Measuring Classifier Performance: A Coherent Alternative to the Area under the ROC Curve.” *Machine Learning* 77 (1). Springer US: 103–23. doi:10.1007/s10994-009-5119-5.

Hanley, J. A., and B. J. McNeil. 1983. “A Method of Comparing the Areas under Receiver Operating Characteristic Curves Derived from the Same Cases.” *Radiology* 148 (3): 839–43. doi:10.1148/radiology.148.3.6878708.

Hare, Robert D. 2003. *Manual for the Revised Psychopathy Checklist (2nd Ed.)*. Multi-Health Systems. https://philpapers.org/rec/HARMFT.

Hartmann, Andrea S., Jennifer L. Greenberg, and Sabine Wilhelm. 2013. “The Relationship between Anorexia Nervosa and Body Dysmorphic Disorder.” *Clinical Psychology Review* 33 (5): 675–85. doi:10.1016/j.cpr.2013.04.002.

Hatfield, Elaine, John T. Cacioppo, and Richard L. Rapson. 1994. “Emotional Contagion: Cambridge Studies in Emotion and Social Interaction.” *Cambridge, UK: Cambridge University Press. Errors-in-Variables Regression Model When the Variances of the Measurement Errors Vary between the Observations. Statistics in Medicine* 21: 1089–1101.

Hatfield, Elaine, Richard L. Rapson, and Yen-Chi L. Le. 2009. “Emotional Contagion and Empathy.” In *The Social Neuroscience of Empathy*. The MIT Press. doi:10.7551/mitpress/9780262012973.003.0003.

Haufe, Stefan, Frank Meinecke, Kai Görgen, Sven Dähne, John-Dylan Haynes, Benjamin Blankertz, and Felix Bießmann. 2014. “On the Interpretation of Weight Vectors of Linear Models in Multivariate Neuroimaging.” *NeuroImage* 87 (February): 96–110. doi:10.1016/j.neuroimage.2013.10.067.

Hayes, Dave J., Nir Lipsman, David Q. Chen, D. Blake Woodside, Karen D. Davis, Andres M. Lozano, and Mojgan Hodaie. 2015. “Subcallosal Cingulate Connectivity in Anorexia Nervosa Patients Differs From Healthy Controls: A Multi-Tensor Tractography Study.” *Brain Stimulation* 8 (4): 758–68. doi:10.1016/j.brs.2015.03.005.

Health Quality Ontario. 2014. “The Appropriate Use of Neuroimaging in the Diagnostic Work-up of Dementia: An Evidence-Based Analysis.” *Ontario Health Technology Assessment Series* 14 (1): 1–64. https://www.ncbi.nlm.nih.gov/pubmed/24592296.

Hein, Grit, Giorgia Silani, Kerstin Preuschoff, C. Daniel Batson, and Tania Singer. 2010. “Neural Responses to Ingroup and Outgroup Members’ Suffering Predict Individual Differences in Costly Helping.” *Neuron* 68 (1): 149–60. doi:10.1016/j.neuron.2010.09.003.

Hein, Grit, and Tania Singer. 2008. “I Feel How You Feel but Not Always: The Empathic Brain and Its Modulation.” *Current Opinion in Neurobiology* 18 (2): 153–58. doi:10.1016/j.conb.2008.07.012.

Henson, R. N. A., C. J. Price, M. D. Rugg, R. Turner, and K. J. Friston. 2002. “Detecting Latency Differences in Event-Related BOLD Responses: Application to Words versus Nonwords and Initial versus Repeated Face Presentations.” *NeuroImage* 15 (1): 83–97. doi:10.1006/nimg.2001.0940.

Herrinton, Lisa J., Liyan Liu, Bruce Fireman, James D. Lewis, James E. Allison, Nicole Flowers, Susan Hutfless, et al. 2009. “Time Trends in Therapies and Outcomes for Adult Inflammatory Bowel Disease, Northern California, 1998-2005.” *Gastroenterology* 137 (2): 502–11. doi:10.1053/j.gastro.2009.04.063.

Hilsden, Robert J., Marja J. Verhoef, Allan Best, and Gaia Pocobelli. 2003a. “A National Survey on the Patterns of Treatment of Inflammatory Bowel Disease in Canada.” *BMC Gastroenterology* 3 (June): 10. doi:10.1186/1471-230X-3-10.

———. 2003b. “A National Survey on the Patterns of Treatment of Inflammatory Bowel Disease in Canada.” *BMC Gastroenterology* 3 (June): 10. doi:10.1186/1471-230X-3-10.

Hippert, H. S., C. E. Pedreira, and R. C. Souza. 2001. “Neural Networks for Short-Term Load Forecasting: A Review and Evaluation.” *IEEE Transactions on Power Systems* 16 (1): 44–55. doi:10.1109/59.910780.

Hoek, Hans Wijbrand. 2006. “Incidence, Prevalence and Mortality of Anorexia Nervosa and Other Eating Disorders.” *Current Opinion in Psychiatry* 19 (4): 389–94. doi:10.1097/01.yco.0000228759.95237.78.

Hoek, Hans Wijbrand, and Daphne van Hoeken. 2003. “Review of the Prevalence and Incidence of Eating Disorders.” *The International Journal of Eating Disorders* 34 (4).

Wiley Subscription Services, Inc., A Wiley Company: 383–96. doi:10.1002/eat.10222.

Hoffman, Elizabeth R., Danielle A. Gagne, Laura M. Thornton, Kelly L. Klump, Harry Brandt, Steve Crawford, Manfred M. Fichter, et al. 2012. “Understanding the Association of Impulsivity, Obsessions, and Compulsions with Binge Eating and Purging Behaviours in Anorexia Nervosa.” *European Eating Disorders Review: The Journal of the Eating Disorders Association* 20 (3): e129–36. doi:10.1002/erv.2161.

Holbrook, Colin, Keise Izuma, Choi Deblieck, Daniel M. T. Fessler, and Marco Iacoboni. 2016. “Neuromodulation of Group Prejudice and Religious Belief.” *Social Cognitive and Affective Neuroscience* 11 (3): 387–94. doi:10.1093/scan/nsv107.

Hollander, E., D. Neville, M. Frenkel, S. Josephson, and M. R. Liebowitz. 1992. “Body Dysmorphic Disorder. Diagnostic Issues and Related Disorders.” *Psychosomatics* 33 (2): 156–65. doi:10.1016/S0033-3182(92)71991-4.

Holtkamp, K., K. Konrad, N. Kaiser, Y. Ploenes, N. Heussen, I. Grzella, and B. Herpertz-Dahlmann. 2005. “A Retrospective Study of SSRI Treatment in Adolescent Anorexia Nervosa: Insufficient Evidence for Efficacy.” *Journal of Psychiatric Research* 39 (3): 303–10. doi:10.1016/j.jpsychires.2004.08.001.

Homer, Mark L., Nathan P. Palmer, Kathe P. Fox, Joanne Armstrong, and Kenneth D. Mandl. 2017. “Predicting Falls in People Aged 65 Years and Older From Insurance Claims.” *The American Journal of Medicine*, January. doi:10.1016/j.amjmed.2017.01.003.

Hong, Liangjie, and Brian D. Davison. 2010. “Empirical Study of Topic Modeling in Twitter.” In *Proceedings of the First Workshop on Social Media Analytics*, 80–88. SOMA ’10. New York, NY, USA: ACM. doi:10.1145/1964858.1964870.

Horgan, John. 2015. *The End Of Science: Facing The Limits Of Knowledge In The Twilight Of The Scientific Age*. Basic Books. https://market.android.com/details?id=book-AQOCBgAAQBAJ.

Hrabosky, Joshua I., Thomas F. Cash, David Veale, Fugen Neziroglu, Elizabeth A. Soll, David M. Garner, Melissa Strachan-Kinser, Bette Bakke, Laura J. Clauss, and Katharine A. Phillips. 2009. “Multidimensional Body Image Comparisons among Patients with Eating Disorders, Body Dysmorphic Disorder, and Clinical Controls: A Multisite Study.” *Body Image* 6 (3): 155–63. doi:10.1016/j.bodyim.2009.03.001.

Hsieh, Cheng-Yang, Chih-Hung Chen, Chung-Yi Li, and Ming-Liang Lai. 2015. “Validating the Diagnosis of Acute Ischemic Stroke in a National Health Insurance Claims Database.” *Journal of the Formosan Medical Association = Taiwan Yi Zhi* 114 (3): 254–59. doi:10.1016/j.jfma.2013.09.009.

Huang, Sandy H., Paea LePendu, Srinivasan V. Iyer, Ming Tai-Seale, David Carrell, and Nigam H. Shah. 2014. “Toward Personalizing Treatment for Depression: Predicting Diagnosis and Severity.” *Journal of the American Medical Informatics Association: JAMIA* 21 (6): 1069–75. doi:10.1136/amiajnl-2014-002733.

Huang, Siyuan, and Shihui Han. 2014. “Shared Beliefs Enhance Shared Feelings: Religious/irreligious Identifications Modulate Empathic Neural Responses.” *Social Neuroscience* 9 (6): 639–49. doi:10.1080/17470919.2014.934396.

Iacoboni, Marco, Istvan Molnar-Szakacs, Vittorio Gallese, Giovanni Buccino, John C. Mazziotta, and Giacomo Rizzolatti. 2005. “Grasping the Intentions of Others with One’s Own Mirror Neuron System.” *PLoS Biology* 3 (3): e79. doi:10.1371/journal.pbio.0030079.

Iacoboni, Marco, R. P. Woods, M. Brass, H. Bekkering, J. C. Mazziotta, and G. Rizzolatti. 1999. “Cortical Mechanisms of Human Imitation.” *Science* 286 (5449): 2526–28. https://www.ncbi.nlm.nih.gov/pubmed/10617472.

Irani, Farzin, Steven M. Platek, Scott Bunce, Anthony C. Ruocco, and Douglas Chute. 2007. “Functional near Infrared Spectroscopy (fNIRS): An Emerging Neuroimaging Technology with Important Applications for the Study of Brain Disorders.” *The Clinical Neuropsychologist* 21 (1): 9–37. doi:10.1080/13854040600910018.

Iyer, R., David W. Hosmer, and Stanley Lemeshow. 1991. “Applied Logistic Regression.” *The Statistician: Journal of the Institute of Statisticians* 40 (4): 458. doi:10.2307/2348743.

Jack, Gallant. 2009. “Bayesian Reconstruction of Perceptual Experiences from Human Brain Activity.” *Frontiers in Systems Neuroscience* 3. doi:10.3389/conf.neuro.06.2009.03.225.

Jackson, Philip L., Eric Brunet, Andrew N. Meltzoff, and Jean Decety. 2006. “Empathy Examined through the Neural Mechanisms Involved in Imagining How I Feel versus How You Feel Pain.” *Neuropsychologia* 44 (5): 752–61. doi:10.1016/j.neuropsychologia.2005.07.015.

James, Karin H., and Laura Engelhardt. 2012. “The Effects of Handwriting Experience on Functional Brain Development in Pre-Literate Children.” *Trends in Neuroscience and Education* 1 (1): 32–42. doi:10.1016/j.tine.2012.08.001.

Jenkinson, Mark, Peter Bannister, Michael Brady, and Stephen M. Smith. 2002. “Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images.” *NeuroImage* 17 (2): 825–41. doi:10.1006/nimg.2002.1132.

Jenkinson, Mark, and Stephen M. Smith. 2001. “A Global Optimisation Method for Robust Affine Registration of Brain Images.” *Medical Image Analysis* 5 (2): 143–56. doi:10.1016/s1361-8415(01)00036-6.

Kang, Ben, So Yoon Choi, Hye Seung Kim, Kyunga Kim, Yoo Min Lee, and Yon Ho Choe. 2016. “Mucosal Healing in Paediatric Patients with Moderate-to-Severe Luminal Crohn’s Disease Under Combined Immunosuppression: Escalation versus Early Treatment.” *Journal of Crohn’s & Colitis* 10 (11): 1279–86. doi:10.1093/ecco-jcc/jjw086.

Kanjilal, P. P., and D. N. Banerjee. 1995. “On the Application of Orthogonal Transformation for the Design and Analysis of Feedforward Networks.” *IEEE Transactions on Neural Networks / a Publication of the IEEE Neural Networks Council* 6 (5): 1061–70. doi:10.1109/72.410351.

Kay, Kendrick N., Thomas Naselaris, Ryan J. Prenger, and Jack L. Gallant. 2008. “Identifying Natural Images from Human Brain Activity.” *Nature* 452 (7185): 352–55. doi:10.1038/nature06713.

Keel, Pamela K., David J. Dorer, Kamryn T. Eddy, Debra Franko, Dana L. Charatan, and David B. Herzog. 2003. “Predictors of Mortality in Eating Disorders.” *Archives of General Psychiatry* 60 (2): 179–83. https://www.ncbi.nlm.nih.gov/pubmed/12578435.

Keysers, Christian, Bruno Wicker, Valeria Gazzola, Jean-Luc Anton, Leonardo Fogassi, and Vittorio Gallese. 2004. “A Touching Sight: SII/PV Activation during the Observation and Experience of Touch.” *Neuron* 42 (2): 335–46. https://www.ncbi.nlm.nih.gov/pubmed/15091347.

Kittler, Jennifer E., William Menard, and Katharine A. Phillips. 2007. “Weight Concerns in Individuals with Body Dysmorphic Disorder.” *Eating Behaviors* 8 (1). Elsevier: 115–20. doi:10.1016/j.eatbeh.2006.02.006.

Kleiner, Mario, David Brainard, Denis Pelli, Allen Ingling, Richard Murray, Christopher Broussard, and Others. 2007. “What’s New in Psychtoolbox-3.” *Perception* 36 (14). Alezzo: 1. http://www.kyb.mpg.de/publications/attachments/ECVP2007-Kleiner-slides_5490[0].pdf.

Konstantakopoulos, George, Eleytheria Varsou, Dimitris Dikeos, Nikoleta Ioannidi, Fragiskos Gonidakis, George Papadimitriou, and Panagiotis Oulis. 2012. “Delusionality of Body Image Beliefs in Eating Disorders.” *Psychiatry Research* 200 (2-3): 482–88. doi:10.1016/j.psychres.2012.03.023.

Koran, Lorrin M., Elias Abujaoude, Michael D. Large, and Richard T. Serpe. 2008. “The Prevalence of Body Dysmorphic Disorder in the United States Adult Population.” *CNS Spectrums* 13 (4): 316–22. https://www.ncbi.nlm.nih.gov/pubmed/18408651.

Kupfer, David J., and Darrel A. Regier. 2011. “Neuroscience, Clinical Evidence, and the Future of Psychiatric Classification in DSM-5.” *The American Journal of Psychiatry* 168 (7): 672–74. doi:10.1176/appi.ajp.2011.11020219.

Kwong, K. K., J. W. Belliveau, D. A. Chesler, I. E. Goldberg, R. M. Weisskoff, B. P. Poncelet, D. N. Kennedy, B. E. Hoppel, M. S. Cohen, and R. Turner. 1992. “Dynamic Magnetic Resonance Imaging of Human Brain Activity during Primary Sensory Stimulation.” *Proceedings of the National Academy of Sciences of the United States of America* 89 (12): 5675–79. https://www.ncbi.nlm.nih.gov/pubmed/1608978.

Laake, K. O., A. Bjørneklett, G. Aamodt, L. Aabakken, M. Jacobsen, A. Bakka, and M. H. Vatn. 2005. “Outcome of Four Weeks’ Intervention with Probiotics on Symptoms and Endoscopic Appearance after Surgical Reconstruction with a J-Configurated Ileal-Pouch-Anal-Anastomosis in Ulcerative Colitis.” *Scandinavian Journal of Gastroenterology* 40 (1): 43–51. doi:10.1080/00365520410009339.

Lamm, Claus, C. D. Batson, and Jean Decety. 2007. “The Neural Substrate of Human Empathy: Effects of Perspective-Taking and Cognitive Appraisal.” *Journal of Cognitive Neuroscience* 19 (1): 42–58. doi:10.1162/jocn.2007.19.1.42.

Lamm, Claus, Jean Decety, and Tania Singer. 2011. “Meta-Analytic Evidence for Common and Distinct Neural Networks Associated with Directly Experienced Pain and Empathy for Pain.” *NeuroImage* 54 (3): 2492–2502. doi:10.1016/j.neuroimage.2010.10.014.

Lamm, Claus, Howard C. Nusbaum, Andrew N. Meltzoff, and Jean Decety. 2007. “What Are You Feeling? Using Functional Magnetic Resonance Imaging to Assess the

Modulation of Sensory and Affective Responses during Empathy for Pain." *PloS One* 2 (12): e1292. doi:10.1371/journal.pone.0001292.

Lawrence, E. J., P. Shaw, V. P. Giampietro, S. Surguladze, M. J. Brammer, and A. S. David. 2006. "The Role of 'Shared Representations' in Social Perception and Empathy: An fMRI Study." *NeuroImage* 29 (4): 1173–84. doi:10.1016/j.neuroimage.2005.09.001.

Lee, D. D., and H. S. Seung. 1999. "Learning the Parts of Objects by Non-Negative Matrix Factorization." *Nature* 401 (6755): 788–91. doi:10.1038/44565.

Leow, Alex, Olusola Ajilore, Liang Zhan, Donatello Arienzo, Johnson GadElkarim, Aifeng Zhang, Teena Moody, et al. 2013. "Impaired Inter-Hemispheric Integration in Bipolar Disorder Revealed with Brain Network Analyses." *Biological Psychiatry* 73 (2): 183–93. doi:10.1016/j.biopsych.2012.09.014.

Levine, Mark, Amy Prosser, David Evans, and Stephen Reicher. 2005. "Identity and Emergency Intervention: How Social Group Membership and Inclusiveness of Group Boundaries Shape Helping Behavior." *Personality & Social Psychology Bulletin* 31 (4): 443–53. doi:10.1177/0146167204271651.

Liu, Jun, Jianhui Chen, and Jieping Ye. 2009. "Large-Scale Sparse Logistic Regression." In *Proceedings of the 15th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining - KDD '09*. doi:10.1145/1557019.1557082.

Liu, T. T., L. R. Frank, E. C. Wong, and R. B. Buxton. 2001. "Detection Power, Estimation Efficiency, and Predictability in Event-Related fMRI." *NeuroImage* 13 (4): 759–73. doi:10.1006/nimg.2000.0728.

Li, Wei, T. M. Lai, C. Bohon, S. K. Loo, D. McCurdy, M. Strober, S. Bookheimer, and J. Feusner. 2015. “Anorexia Nervosa and Body Dysmorphic Disorder Are Associated with Abnormalities in Processing Visual Information.” *Psychological Medicine* 45 (10). Cambridge Univ Press: 2111–22. doi:10.1017/S0033291715000045.

Li, Wei, Tsz M. Lai, Sandra K. Loo, Michael Strober, Iman Mohammad-Rezazadeh, Sahib Khalsa, and Jamie Feusner. 2015. “Aberrant Early Visual Neural Activity and Brain-Behavior Relationships in Anorexia Nervosa and Body Dysmorphic Disorder.” *Frontiers in Human Neuroscience* 9 (June). ncbi.nlm.nih.gov: 301. doi:10.3389/fnhum.2015.00301.

Lobo, J. M., and A. Jiménez-Valverde. 2008. “AUC: A Misleading Measure of the Performance of Predictive Distribution Models.” *Global Ecology and*. Wiley Online Library. http://onlinelibrary.wiley.com/doi/10.1111/j.1466-8238.2007.00358.x/full.

Lock, James, W. Stewart Agras, Susan Bryson, and Helena C. Kraemer. 2005. “A Comparison of Short- and Long-Term Family Therapy for Adolescent Anorexia Nervosa.” *Journal of the American Academy of Child and Adolescent Psychiatry* 44 (7): 632–39. doi:10.1097/01.chi.0000161647.82775.0a.

MacKenzie-Graham, Allan J., Arash Payan, Ivo D. Dinov, John D. Van Horn, and Arthur W. Toga. 2008. “Neuroimaging Data Provenance Using the LONI Pipeline Workflow Environment.” In *Provenance and Annotation of Data and Processes*, 208–20. Springer, Berlin, Heidelberg. doi:10.1007/978-3-540-89965-5_22.

Madsen, Sarah K., Cara Bohon, and Jamie D. Feusner. 2013. “Visual Processing in Anorexia Nervosa and Body Dysmorphic Disorder: Similarities, Differences, and

Future Research Directions." *Journal of Psychiatric Research* 47 (10): 1483–91. doi:10.1016/j.jpsychires.2013.06.003.

Makris, Nikos, Jill M. Goldstein, David Kennedy, Steven M. Hodge, Verne S. Caviness, Stephen V. Faraone, Ming T. Tsuang, and Larry J. Seidman. 2006. "Decreased Volume of Left and Total Anterior Insular Lobule in Schizophrenia." *Schizophrenia Research* 83 (2-3): 155–71. doi:10.1016/j.schres.2005.11.020.

Marsh, Abigail A., Megan N. Kozak, Daniel M. Wegner, Marguerite E. Reid, Henry H. Yu, and R. J. R. Blair. 2010. "The Neural Substrates of Action Identification." *Social Cognitive and Affective Neuroscience* 5 (4): 392–403. doi:10.1093/scan/nsq004.

Mazure, C. M., K. A. Halmi, S. R. Sunday, S. J. Romano, and A. M. Einhorn. 1994. "The Yale-Brown-Cornell Eating Disorder Scale: Development, Use, Reliability and Validity." *Journal of Psychiatric Research* 28 (5): 425–45. https://www.ncbi.nlm.nih.gov/pubmed/7897615.

McCandliss, Bruce D., Laurent Cohen, and Stanislas Dehaene. 2003. "The Visual Word Form Area: Expertise for Reading in the Fusiform Gyrus." *Trends in Cognitive Sciences* 7 (7): 293–99. https://www.ncbi.nlm.nih.gov/pubmed/12860187.

Mehrabian, Albert. 1997. "Relations among Personality Scales of Aggression, Violence, and Empathy: Validational Evidence Bearing on the Risk of Eruptive Violence Scale." *Aggressive Behavior* 23 (6). Wiley Subscription Services, Inc., A Wiley Company: 433–45. doi:3.0.CO;2-H">10.1002/(SICI)1098-2337(1997)23:6<433::AID-AB3>3.0.CO;2-H.

Mehrabian, Albert, and N. Epstein. 1972. "A Measure of Emotional Empathy." *Journal of Personality* 40 (4): 525–43. https://www.ncbi.nlm.nih.gov/pubmed/4642390.

Merriam-Webster, and Inc. 1997. *Merriam-Webster's Geographical Dictionary*. Merriam-Webster. https://market.android.com/details?id=book-Co_VIPIJerIC.

Miller, P. A., and N. Eisenberg. 1988. "The Relation of Empathy to Aggressive and Externalizing/antisocial Behavior." *Psychological Bulletin* 103 (3): 324–44. https://www.ncbi.nlm.nih.gov/pubmed/3289071.

Mitchell, Jason P., Mahzarin R. Banaji, and C. Neil Macrae. 2005. "The Link between Social Cognition and Self-Referential Thought in the Medial Prefrontal Cortex." *Journal of Cognitive Neuroscience* 17 (8): 1306–15. doi:10.1162/0898929055002418.

Montalan, Benoît, Thierry Lelard, Olivier Godefroy, and Harold Mouras. 2012. "Behavioral Investigation of the Influence of Social Categorization on Empathy for Pain: A Minimal Group Paradigm Study." *Frontiers in Psychology* 3 (October). journal.frontiersin.org: 389. doi:10.3389/fpsyg.2012.00389.

Montgomery, S. A., and M. Asberg. 1979. "A New Depression Scale Designed to Be Sensitive to Change." *The British Journal of Psychiatry: The Journal of Mental Science* 134 (April): 382–89. https://www.ncbi.nlm.nih.gov/pubmed/444788.

Moody, T. D., M. A. Sasaki, C. Bohon, M. A. Strober, S. Y. Bookheimer, C. L. Sheen, and J. D. Feusner. 2015. "Functional Connectivity for Face Processing in Individuals with Body Dysmorphic Disorder and Anorexia Nervosa." *Psychological Medicine* 45 (16). Cambridge Univ Press: 3491–3503. doi:10.1017/S0033291715001397.

Morrison, India, and Paul E. Downing. 2007. “Organization of Felt and Seen Pain Responses in Anterior Cingulate Cortex.” *NeuroImage* 37 (2): 642–51. doi:10.1016/j.neuroimage.2007.03.079.

Morrison, India, Marius V. Peelen, and Paul E. Downing. 2007. “The Sight of Others’ Pain Modulates Motor Processing in Human Cingulate Cortex.” *Cerebral Cortex* 17 (9): 2214–22. doi:10.1093/cercor/bhl129.

Mugler, John P., and James R. Brookeman. 1990. “Three-Dimensional Magnetization-Prepared Rapid Gradient-Echo Imaging (3D MP RAGE).” *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine* 15 (1). Wiley Online Library: 152–57. http://onlinelibrary.wiley.com/doi/10.1002/mrm.1910150117/full.

Mulert, Christoph, Lorenz Jäger, Robert Schmitt, Patrick Bussfeld, Oliver Pogarell, Hans-Jürgen Möller, Georg Juckel, and Ulrich Hegerl. 2004. “Integration of fMRI and Simultaneous EEG: Towards a Comprehensive Understanding of Localization and Time-Course of Brain Activity in Target Detection.” *NeuroImage* 22 (1): 83–94. doi:10.1016/j.neuroimage.2003.10.051.

Nadler, Arie, Gal Harpaz-Gorodeisky, and Yael Ben-David. 2009. “Defensive Helping: Threat to Group Identity, Ingroup Identification, Status Stability, and Common Group Identity as Determinants of Intergroup Help-Giving.” *Journal of Personality and Social Psychology* 97 (5): 823–34. doi:10.1037/a0015968.

Neilson, Kate, Maria Ftanou, Kaveh Monshat, Mike Salzberg, Sally Bell, Michael A. Kamm, William Connell, et al. 2016. “A Controlled Study of a Group Mindfulness

Intervention for Individuals Living With Inflammatory Bowel Disease." *Inflammatory Bowel Diseases* 22 (3): 694–701. doi:10.1097/MIB.0000000000000629.

Newman, M. E. J. 2006. "Erratum: Scientific Collaboration Networks. II. Shortest Paths, Weighted Networks, and Centrality [Phys. Rev. E64, 016132 (2001)]." *Physical Review E* 73 (3). doi:10.1103/physreve.73.039906.

Neziroglu, Fugen, Dean McKay, John Todaro, and Jose A. Yaryura-Tobias. 1996. "Effect of Cognitive Behavior Therapy on Persons with Body Dysmorphic Disorder and Comorbid Axis II Diagnoses." *Behavior Therapy* 27 (1): 67–77. doi:10.1016/S0005-7894(96)80036-0.

Nomi, Jason S., Dag Scherfeld, Skara Friederichs, Ralf Schäfer, Matthias Franz, Hans-Jörg Wittsack, Nina P. Azari, John Missimer, and Rüdiger J. Seitz. 2008. "On the Neural Networks of Empathy: A Principal Component Analysis of an fMRI Study." *Behavioral and Brain Functions: BBF* 4 (September): 41. doi:10.1186/1744-9081-4-41.

Oden, Anders, and Hans Wedel. 1975. "Arguments for Fisher's Permutation Test." *Annals of Statistics* 3 (2). Institute of Mathematical Statistics: 518–20. http://www.jstor.org/stable/2958971.

Ogawa, S., T. M. Lee, A. R. Kay, and D. W. Tank. 1990. "Brain Magnetic Resonance Imaging with Contrast Dependent on Blood Oxygenation." *Proceedings of the National Academy of Sciences of the United States of America* 87 (24): 9868–72. https://www.ncbi.nlm.nih.gov/pubmed/2124706.

Otto, Michael W., Sabine Wilhelm, Lee S. Cohen, and Bernard L. Harlow. 2001. "Prevalence of Body Dysmorphic Disorder in a Community Sample of Women." *The*

*American Journal of Psychiatry* 158 (12): 2061–63. doi:10.1176/appi.ajp.158.12.2061.

Pallanti, S., L. Quercioli, G. Zaccara, A. B. Ramacciotti, and G. Arnetoli. 1998. “Eye Movement Abnormalities in Anorexia Nervosa.” *Psychiatry Research* 78 (1-2): 59–70. https://www.ncbi.nlm.nih.gov/pubmed/9579703.

Panaccione, Remo, and Subrata Ghosh. 2010. “Review: Optimal Use of Biologics in the Management of Crohn’s Disease.” *Therapeutic Advances in Gastroenterology* 3 (3): 179–89. doi:10.1177/1756283X09357579.

Parikh, Ravi B., Meetali Kakad, and David W. Bates. 2016. “Integrating Predictive Analytics Into High-Value Care: The Dawn of Precision Delivery.” *JAMA: The Journal of the American Medical Association* 315 (7): 651–52. doi:10.1001/jama.2015.19417.

Pavey, Louisa, Tobias Greitemeyer, and Paul Sparks. 2012. “‘I Help Because I Want To, Not Because You Tell Me To’ Empathy Increases Autonomously Motivated Helping.” *Personality & Social Psychology Bulletin* 38 (5). Sage Publications Sage CA: Los Angeles, CA: 681–89. http://journals.sagepub.com/doi/abs/10.1177/0146167211435940.

Peduzzi, P., J. Concato, E. Kemper, T. R. Holford, and A. R. Feinstein. 1996. “A Simulation Study of the Number of Events per Variable in Logistic Regression Analysis.” *Journal of Clinical Epidemiology* 49 (12): 1373–79. https://www.ncbi.nlm.nih.gov/pubmed/8970487.

Pellegrino, G. di, L. Fadiga, L. Fogassi, V. Gallese, and G. Rizzolatti. 1992. “Understanding Motor Events: A Neurophysiological Study.” *Experimental Brain*

*Research. Experimentelle Hirnforschung. Experimentation Cerebrale* 91 (1): 176–80. https://www.ncbi.nlm.nih.gov/pubmed/1301372.

Pelli, D. G. 1997. “The VideoToolbox Software for Visual Psychophysics: Transforming Numbers into Movies.” *Spatial Vision* 10 (4). booksandjournals.brillonline.com: 437–42. https://www.ncbi.nlm.nih.gov/pubmed/9176953.

Perry, Bruce D., and Maia Szalavitz. 2010. *Born for Love: Why Empathy Is Essential--and Endangered*. Harper Collins.

Petersen, S. E., P. T. Fox, A. Z. Snyder, and M. E. Raichle. 1990. “Activation of Extrastriate and Frontal Cortical Areas by Visual Words and Word-like Stimuli.” *Science* 249 (4972): 1041–44. https://www.ncbi.nlm.nih.gov/pubmed/2396097.

Pfeifer, Jennifer H., Marco Iacoboni, John C. Mazziotta, and Mirella Dapretto. 2008. “Mirroring Others’ Emotions Relates to Empathy and Interpersonal Competence in Children.” *NeuroImage* 39 (4): 2076–85. doi:10.1016/j.neuroimage.2007.10.032.

Pfuntner, Anne, Lauren M. Wier, and Claudia Steiner. 2013. “Costs for Hospital Stays in the United States, 2011: Statistical Brief #168.” In *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Rockville (MD): Agency for Healthcare Research and Quality (US). https://www.ncbi.nlm.nih.gov/pubmed/24455786.

Phillips, Katharine A. 2007. “Suicidality in Body Dysmorphic Disorder.” *Primary Psychiatry* 14 (12): 58–66. https://www.ncbi.nlm.nih.gov/pubmed/18449358.

Phillips, Katharine A., E. Hollander, S. A. Rasmussen, B. R. Aronowitz, C. DeCaria, and W. K. Goodman. 1997. “A Severity Rating Scale for Body Dysmorphic Disorder: Development, Reliability, and Validity of a Modified Version of the Yale-Brown

Obsessive Compulsive Scale." *Psychopharmacology Bulletin* 33 (1): 17–22. https://www.ncbi.nlm.nih.gov/pubmed/9133747.

Phillips, Katharine A., and Eric Hollander. 2008. "Treating Body Dysmorphic Disorder with Medication: Evidence, Misconceptions, and a Suggested Approach." *Body Image* 5 (1): 13–27. doi:10.1016/j.bodyim.2007.12.003.

Phillips, Katharine A., and William Menard. 2006. "Suicidality in Body Dysmorphic Disorder: A Prospective Study." *The American Journal of Psychiatry* 163 (7): 1280–82. doi:10.1176/appi.ajp.163.7.1280.

Phillips, Katharine A., Sabine Wilhelm, Lorrin M. Koran, Elizabeth R. Didie, Brian A. Fallon, Jamie Feusner, and Dan J. Stein. 2010. "Body Dysmorphic Disorder: Some Key Issues for DSM-V." *Depression and Anxiety* 27 (6): 573–91. doi:10.1002/da.20709.

Pietrini, F., G. Castellini, V. Ricca, C. Polito, A. Pupi, and C. Faravelli. 2011. "Functional Neuroimaging in Anorexia Nervosa: A Clinical Approach." *European Psychiatry: The Journal of the Association of European Psychiatrists* 26 (3): 176–82. doi:10.1016/j.eurpsy.2010.07.011.

Podolsky, D. K. 1991. "Inflammatory Bowel Disease (2)." *The New England Journal of Medicine* 325 (14): 1008–16. doi:10.1056/NEJM199110033251406.

Pompili, Maurizio, Iginia Mancinelli, Paolo Girardi, Amedeo Ruberto, and Roberto Tatarelli. 2004. "Suicide in Anorexia Nervosa: A Meta-Analysis." *The International Journal of Eating Disorders* 36 (1): 99–103. doi:10.1002/eat.20011.

Poppe, Andrew B., Krista Wisner, Gowtham Atluri, Kelvin O. Lim, Vipin Kumar, and Angus W. Macdonald 3rd. 2013. "Toward a Neurometric Foundation for

Probabilistic Independent Component Analysis of fMRI Data." *Cognitive, Affective & Behavioral Neuroscience* 13 (3): 641–59. doi:10.3758/s13415-013-0180-8.

Pruim, Raimon H. R., Maarten Mennes, Daan van Rooij, Alberto Llera, Jan K. Buitelaar, and Christian F. Beckmann. 2015. "ICA-AROMA: A Robust ICA-Based Strategy for Removing Motion Artifacts from fMRI Data." *NeuroImage* 112 (May): 267–77. doi:10.1016/j.neuroimage.2015.02.064.

Rabe-Jablonska Jolanta, J., and M. Sobow Tomasz. 2000. "The Links between Body Dysmorphic Disorder and Eating Disorders." *European Psychiatry: The Journal of the Association of European Psychiatrists* 15 (5): 302–5. https://www.ncbi.nlm.nih.gov/pubmed/10954874.

Rameson, Lian T., Sylvia A. Morelli, and Matthew D. Lieberman. 2012. "The Neural Correlates of Empathy: Experience, Automaticity, and Prosocial Behavior." *Journal of Cognitive Neuroscience* 24 (1): 235–45. doi:10.1162/jocn_a_00130.

Ramón y Cajal, Santiago. 1959. *Degeneration & Regeneration of the Nervous System*. Vol. 1. Hafner Pub. Co. https://books.google.com/books?hl=en&lr=&id=-mEvAQAAIAAJ&oi=fnd&pg=PR3&dq=ramon+y+cajal&ots=Ctw4M3M1mm&sig=uVUDVpSwtn0LWLSwAzwk2p_xRVk.

Rizzolatti, G., L. Fadiga, V. Gallese, and L. Fogassi. 1996. "Premotor Cortex and the Recognition of Motor Actions." *Brain Research. Cognitive Brain Research* 3 (2): 131–41. https://www.ncbi.nlm.nih.gov/pubmed/8713554.

Roweis, S. T., and L. K. Saul. 2000. "Nonlinear Dimensionality Reduction by Locally Linear Embedding." *Science* 290 (5500): 2323–26. doi:10.1126/science.290.5500.2323.

Ruffolo, Jessica S., Katharine A. Phillips, William Menard, Christina Fay, and Risa B. Weisberg. 2006a. “Comorbidity of Body Dysmorphic Disorder and Eating Disorders: Severity of Psychopathology and Body Image Disturbance.” *The International Journal of Eating Disorders* 39 (1): 11–19. doi:10.1002/eat.20219.

———. 2006b. “Comorbidity of Body Dysmorphic Disorder and Eating Disorders: Severity of Psychopathology and Body Image Disturbance.” *The International Journal of Eating Disorders* 39 (1): 11–19. doi:10.1002/eat.20219.

Ryali, Srikanth, Kaustubh Supekar, Daniel A. Abrams, and Vinod Menon. 2010. “Sparse Logistic Regression for Whole-Brain Classification of fMRI Data.” *NeuroImage* 51 (2): 752–64. doi:10.1016/j.neuroimage.2010.02.040.

Saarela, Miiamaaria V., Yevhen Hlushchuk, Amanda C. de C. Williams, Martin Schürmann, Eija Kalso, and Riitta Hari. 2007. “The Compassionate Brain: Humans Detect Intensity of Pain from Another’s Face.” *Cerebral Cortex* 17 (1): 230–37. doi:10.1093/cercor/bhj141.

Sampson, Geoffrey. 1985. *Writing Systems: A Linguistic Introduction*. Stanford University Press. https://market.android.com/details?id=book-tVcdNRvwoDkC.

Saxe, Rebecca. 2006. “Uniquely Human Social Cognition.” *Current Opinion in Neurobiology* 16 (2): 235–39. doi:10.1016/j.conb.2006.03.001.

Schmidhuber, Jürgen. 2015. “Deep Learning in Neural Networks: An Overview.” *Neural Networks: The Official Journal of the International Neural Network Society* 61 (January): 85–117. doi:10.1016/j.neunet.2014.09.003.

Schnyer, D. M., P. C. Clasen, and C. Gonzalez. 2017. “Evaluating the Diagnostic Utility of Applying a Machine Learning Algorithm to Diffusion Tensor MRI Measures in

Individuals with Major Depressive Disorder." *Psychiatry Research*. Elsevier. http://www.sciencedirect.com/science/article/pii/S0925492716302116.

Schreiber, Stefan, Mani Khaliq-Kareemi, Ian C. Lawrance, Ole Østergaard Thomsen, Stephen B. Hanauer, Juliet McColm, Ralph Bloomfield, William J. Sandborn, and PRECISE 2 Study Investigators. 2007. "Maintenance Therapy with Certolizumab Pegol for Crohn's Disease." *The New England Journal of Medicine* 357 (3): 239–50. doi:10.1056/NEJMoa062897.

Shamay-Tsoory, Simone G. 2011. "The Neural Bases for Empathy." *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry* 17 (1): 18–24. doi:10.1177/1073858410379268.

Shawe-Taylor, John, and Shiliang Sun. 2011. "A Review of Optimization Methodologies in Support Vector Machines." *Neurocomputing* 74 (17): 3609–18. doi:10.1016/j.neucom.2011.06.026.

Shayo, Moses, and Asaf Zussman. 2011. "Judicial Ingroup Bias in the Shadow of Terrorism *." *The Quarterly Journal of Economics* 126 (3): 1447–84. doi:10.1093/qje/qjr022.

Shirer, W. R., S. Ryali, E. Rykhlevskaia, V. Menon, and M. D. Greicius. 2012. "Decoding Subject-Driven Cognitive States with Whole-Brain Connectivity Patterns." *Cerebral Cortex* 22 (1): 158–65. doi:10.1093/cercor/bhr099.

Singer, Tania. 2004. "Empathy for Pain Involves the Affective but Not Sensory Components of Pain." *Science* 303 (5661): 1157–62. doi:10.1126/science.1093535.

Singer, Tania, and Claus Lamm. 2009. “The Social Neuroscience of Empathy.” *Annals of the New York Academy of Sciences* 1156 (March): 81–96. doi:10.1111/j.1749-6632.2009.04418.x.

Singer, Tania, Ben Seymour, John P. O’Doherty, Klaas E. Stephan, Raymond J. Dolan, and Chris D. Frith. 2006. “Empathic Neural Responses Are Modulated by the Perceived Fairness of Others.” *Nature* 439 (7075): 466–69. doi:10.1038/nature04271.

Smeden, Maarten van, Joris A. H. de Groot, Karel G. M. Moons, Gary S. Collins, Douglas G. Altman, Marinus J. C. Eijkemans, and Johannes B. Reitsma. 2016. “No Rationale for 1 Variable per 10 Events Criterion for Binary Logistic Regression Analysis.” *BMC Medical Research Methodology* 16 (1): 163. doi:10.1186/s12874-016-0267-3.

Smith, Stephen M. 2002. “Fast Robust Automated Brain Extraction.” *Human Brain Mapping* 17 (3): 143–55. doi:10.1002/hbm.10062.

Smith, Stephen M., Peter R. Bannister, Christian Beckmann, Mike Brady, Stuart Clare, David Flitney, Peter Hansen, et al. 2001. “FSL: New Tools for Functional and Structural Brain Image Analysis.” *NeuroImage* 13 (6): 249. doi:10.1016/s1053-8119(01)91592-7.

Sniderman, Allan D., Ralph B. D’Agostino Sr, and Michael J. Pencina. 2015. “The Role of Physicians in the Era of Predictive Analytics.” *JAMA: The Journal of the American Medical Association* 314 (1): 25. doi:10.1001/jama.2015.6177.

Sonnenberg, Amnon. 2007. “Similar Geographic Variations in Mortality from Peptic Ulcer and Inflammatory Bowel Disease.” *Inflammatory Bowel Diseases* 13 (6): 763–68. doi:10.1002/ibd.20111.

Sporns, O., D. Chialvo, M. Kaiser, and C. Hilgetag. 2004. “Organization, Development and Function of Complex Brain Networks.” *Trends in Cognitive Sciences* 8 (9): 418–25. doi:10.1016/j.tics.2004.07.008.

Steiner, H., C. Mazer, and I. F. Litt. 1990. “Compliance and Outcome in Anorexia Nervosa.” *The Western Journal of Medicine* 153 (2): 133–39. https://www.ncbi.nlm.nih.gov/pubmed/2219868.

Sullivan, P. F. 1995. “Mortality in Anorexia Nervosa.” *The American Journal of Psychiatry* 152 (7). search.proquest.com: 1073–74. doi:10.1176/ajp.152.7.1073.

Sunday, Suzanne R., and Katherine A. Halmi. 2003. “Energy Intake and Body Composition in Anorexia and Bulimia Nervosa.” *Physiology & Behavior* 78 (1): 11–17. https://www.ncbi.nlm.nih.gov/pubmed/12536005.

Suykens, J. A. K., J. Vandewalle, and B. De Moor. 2001. “Optimal Control by Least Squares Support Vector Machines.” *Neural Networks: The Official Journal of the International Neural Network Society* 14 (1): 23–35. doi:10.1016/s0893-6080(00)00077-0.

Swets, John A. 2014. *Signal Detection Theory and ROC Analysis in Psychology and Diagnostics: Collected Papers*. Psychology Press. https://market.android.com/details?id=book-IQrsAgAAQBAJ.

Talley, Nicholas J., Maria T. Abreu, Jean-Paul Achkar, Charles N. Bernstein, Marla C. Dubinsky, Stephen B. Hanauer, Sunanda V. Kane, William J. Sandborn, Thomas A.

Ullman, and Paul Moayyedi. 2011a. “An Evidence-Based Systematic Review on Medical Therapies for Inflammatory Bowel Disease.” *The American Journal of Gastroenterology* 106: S2–25. doi:10.1038/ajg.2011.58.

———. 2011b. “An Evidence-Based Systematic Review on Medical Therapies for Inflammatory Bowel Disease.” *The American Journal of Gastroenterology* 106: S2–25. doi:10.1038/ajg.2011.58.

Thevenaz, P., T. Blu, and M. Unser. 2000. “Interpolation Revisited [medical Images Application].” *IEEE Transactions on Medical Imaging* 19 (7): 739–58. doi:10.1109/42.875199.

Tong, Thaison, Praveen Thokala, Brian McMillan, Rob Ghosh, and John Brazier. 2016. “Cost Effectiveness of Using Cognitive Screening Tests for Detecting Dementia and Mild Cognitive Impairment in Primary Care.” *International Journal of Geriatric Psychiatry*, November. Wiley Online Library. doi:10.1002/gps.4626.

Towell, D. B., S. Woodford, S. Reid, B. Rooney, and A. Towell. 2001. “Compliance and Outcome in Treatment-Resistant Anorexia and Bulimia: A Retrospective Study.” *The British Journal of Clinical Psychology / the British Psychological Society* 40 (Pt 2): 189–95. https://www.ncbi.nlm.nih.gov/pubmed/11446240.

Turner, R. 2003. “Techniques for Imaging Neuroscience.” *British Medical Bulletin* 65 (1): 3–20. doi:10.1093/bmb/65.1.3.

Tzourio-Mazoyer, N., B. Landeau, D. Papathanassiou, F. Crivello, O. Etard, N. Delcroix, B. Mazoyer, and M. Joliot. 2002. “Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain.” *NeuroImage* 15 (1): 273–89. doi:10.1006/nimg.2001.0978.

Valeriani, Massimiliano, Viviana Betti, Domenica Le Pera, Liala De Armas, Roberto Miliucci, Domenico Restuccia, Alessio Avenanti, and Salvatore Maria Aglioti. 2008. “Seeing the Pain of Others While Being in Pain: A Laser-Evoked Potentials Study.” *NeuroImage* 40 (3): 1419–28. doi:10.1016/j.neuroimage.2007.12.056.

Valk, Mirthe E. van der, Marie-Josée J. Mangen, Mirjam Severs, Mike van der Have, Gerard Dijkstra, Ad A. van Bodegraven, Herma H. Fidder, et al. 2016. “Evolution of Costs of Inflammatory Bowel Disease over Two Years of Follow-Up.” *PloS One* 11 (4): e0142481. doi:10.1371/journal.pone.0142481.

Van Overwalle, Frank, and Kris Baetens. 2009. “Understanding Others’ Actions and Goals by Mirror and Mentalizing Systems: A Meta-Analysis.” *NeuroImage* 48 (3): 564–84. doi:10.1016/j.neuroimage.2009.06.009.

Veale, D. 2004. “Body Dysmorphic Disorder.” *Postgraduate Medical Journal* 80 (940). The Fellowship of Postgraduate Medicine: 67–71. doi:10.1136/pmj.2003.015289.

Villringer, A. 1997. “Non-Invasive Optical Spectroscopy and Imaging of Human Brain Function.” *Trends in Neurosciences* 20 (10): 435–42. doi:10.1016/s0166-2236(97)01132-6.

Vitousek, Kelly Bemis, Jennifer Daly, and Christopher Heiser. 1991. “Reconstructing the Internal World of the Eating-Disordered Individual: Overcoming Denial and Distortion in Self-Report.” *The International Journal of Eating Disorders* 10 (6). Wiley Subscription Services, Inc., A Wiley Company: 647–66. doi:3.0.CO;2-T">10.1002/1098-108X(199111)10:6<647::AID-EAT2260100604>3.0.CO;2-T.

Vogelaar, Lauran, Adriaan Van’t Spijker, and C. Janneke van der Woude. 2009. “The Impact of Biologics on Health-Related Quality of Life in Patients with Inflammatory

Bowel Disease." *Clinical and Experimental Gastroenterology* 2 (September): 101–9. https://www.ncbi.nlm.nih.gov/pubmed/21694833.

Voigtlaender, Paul, Patrick Doetsch, and Hermann Ney. 2016. "Handwriting Recognition with Large Multidimensional Long Short-Term Memory Recurrent Neural Networks." In *2016 15th International Conference on Frontiers in Handwriting Recognition (ICFHR)*. doi:10.1109/icfhr.2016.0052.

Völlm, Birgit A., Alexander N. W. Taylor, Paul Richardson, Rhiannon Corcoran, John Stirling, Shane McKie, John F. W. Deakin, and Rebecca Elliott. 2006. "Neuronal Correlates of Theory of Mind and Empathy: A Functional Magnetic Resonance Imaging Study in a Nonverbal Task." *NeuroImage* 29 (1): 90–98. doi:10.1016/j.neuroimage.2005.07.022.

Vul, Edward, Christine Harris, Piotr Winkielman, and Harold Pashler. 2009. "Puzzlingly High Correlations in fMRI Studies of Emotion, Personality, and Social Cognition." *Perspectives on Psychological Science: A Journal of the Association for Psychological Science* 4 (3): 274–90. doi:10.1111/j.1745-6924.2009.01125.x.

Vul, Edward, and Nancy Kanwisher. 2010. "Begging the Question: The Non-Independence Error in fMRI Data Analysis." *Foundational Issues for Human Brain Mapping*. MIT Press, Cambridge, Mass, 71–91. https://books.google.com/books?hl=en&lr=&id=Eh81vxxhtSAC&oi=fnd&pg=PA71&dq=vul+kanwisher+non+independence&ots=Fot9-_noHi&sig=XVZUsdqwg9lLTrREmlwcHj_EtF8.

Wall, D. P., J. Kosmicki, T. F. Deluca, E. Harstad, and V. A. Fusaro. 2012. “Use of Machine Learning to Shorten Observation-Based Screening and Diagnosis of Autism.” *Translational Psychiatry* 2 (April): e100. doi:10.1038/tp.2012.10.

Wang, Xiaogang, and Eric Grimson. 2008. “Spatial Latent Dirichlet Allocation.” In *Advances in Neural Information Processing Systems 20*, edited by J. C. Platt, D. Koller, Y. Singer, and S. T. Roweis, 1577–84. Curran Associates, Inc. http://papers.nips.cc/paper/3278-spatial-latent-dirichlet-allocation.pdf.

Wang, Xiaoming, Lili Liu, James Fackenthal, Shelly Cummings, Maggie Cook, Kisha Hope, Jonathan C. Silverstein, and Olufunmilayo I. Olopade. 2009. “Translational Integrity and Continuity: Personalized Biomedical Data Integration.” *Journal of Biomedical Informatics* 42 (1): 100–112. doi:10.1016/j.jbi.2008.08.002.

Wang, Yang, Payam Sabzmeydani, and Greg Mori. 2007. “Semi-Latent Dirichlet Allocation: A Hierarchical Model for Human Action Recognition.” In *Human Motion – Understanding, Modeling, Capture and Animation*, edited by Ahmed Elgammal, Bodo Rosenhahn, and Reinhard Klette, 240–54. Lecture Notes in Computer Science 4814. Springer Berlin Heidelberg. doi:10.1007/978-3-540-75703-0_17.

Weber, Griffin M., Kenneth D. Mandl, and Isaac S. Kohane. 2014. “Finding the Missing Link for Big Biomedical Data.” *JAMA: The Journal of the American Medical Association* 311 (24): 2479–80. doi:10.1001/jama.2014.4228.

Wells, W. M., 3rd, P. Viola, H. Atsumi, S. Nakajima, and R. Kikinis. 1996. “Multi-Modal Volume Registration by Maximization of Mutual Information.” *Medical Image Analysis* 1 (1): 35–51. https://www.ncbi.nlm.nih.gov/pubmed/9873920.

West, Douglas Brent. 2001. *Introduction to Graph Theory*. Pearson College Division. http://books.google.com/books/about/Introduction_to_Graph_Theory.html?hl=&id=TuvuAAAAMAAJ.

Westreich, Daniel, Justin Lessler, and Michele Jonsson Funk. 2010. “Propensity Score Estimation: Neural Networks, Support Vector Machines, Decision Trees (CART), and Meta-Classifiers as Alternatives to Logistic Regression.” *Journal of Clinical Epidemiology* 63 (8): 826–33. doi:10.1016/j.jclinepi.2009.11.020.

Wijk, Bernadette C. M. van, Cornelis J. Stam, and Andreas Daffertshofer. 2010. “Comparing Brain Networks of Different Size and Connectivity Density Using Graph Theory.” *PloS One* 5 (10): e13701. doi:10.1371/journal.pone.0013701.

Winkler, Anderson M., Gerard R. Ridgway, Matthew A. Webster, Stephen M. Smith, and Thomas E. Nichols. 2014. “Permutation Inference for the General Linear Model.” *NeuroImage* 92: 381–97. doi:10.1016/j.neuroimage.2014.01.060.

Wispé, Lauren. 1986. “The Distinction between Sympathy and Empathy: To Call Forth a Concept, a Word Is Needed.” *Journal of Personality and Social Psychology* 50 (2): 314–21. doi:10.1037//0022-3514.50.2.314.

Witte, J., S. Shivananda, and J. E. Lenn. 2000. “Disease Outcome in Inflammatory Bowel Disease: Mortality, Morbidity and Therapeutic Management of a 796-Person Inception Cohort in the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD).” *Scandinavian Journal of Gastroenterology* 35 (12): 1272–77. doi:10.1080/003655200453610.

Woodside, Blake D., and Randolf Staab. 2006. “Management of Psychiatric Comorbidity in Anorexia Nervosa and Bulimia Nervosa.” *CNS Drugs* 20 (8): 655–63. https://www.ncbi.nlm.nih.gov/pubmed/16863270.

Worsley, K. J., S. Marrett, P. Neelin, A. C. Vandal, K. J. Friston, and A. C. Evans. 1996. “A Unified Statistical Approach for Determining Significant Signals in Images of Cerebral Activation.” *Human Brain Mapping* 4 (1): 58–73. doi:3.0.CO;2-O">10.1002/(SICI)1097-0193(1996)4:1<58::AID-HBM4>3.0.CO;2-O.

Xie, Jianwen, Pamela K. Douglas, Ying Nian Wu, Arthur L. Brody, and Ariana E. Anderson. 2016. “Decoding the Encoding of Functional Brain Networks: An fMRI Classification Comparison of Non-Negative Matrix Factorization (NMF), Independent Component Analysis (ICA), and Sparse Coding Algorithms.” *Journal of Neuroscience Methods*. doi:10.1016/j.jneumeth.2017.03.008.

Xu, X., X. Zuo, X. Wang, and S. Han. 2009. “Do You Feel My Pain? Racial Group Membership Modulates Empathic Neural Responses.” *Journal of Neuroscience* 29 (26): 8525–29. doi:10.1523/jneurosci.2418-09.2009.

Yegnanarayana, B. 2009. *ARTIFICIAL NEURAL NETWORKS*. PHI Learning Pvt. Ltd. https://market.android.com/details?id=book-RTtvUVU_xL4C.

Yeo, Ai Cheo, Kate A. Smith, Robert J. Willis, and Malcolm Brooks. 2001. “Clustering Technique for Risk Classification and Prediction of Claim Costs in the Automobile Insurance Industry.” *Intelligent Systems in Accounting, Finance & Management* 10 (1). John Wiley & Sons, Ltd.: 39–50. doi:10.1002/isaf.196.

Yu, Lei, and Huan Liu. 2004. “Efficient Feature Selection via Analysis of Relevance and Redundancy.” *Journal of Machine Learning Research: JMLR* 5 (Oct): 1205–24. http://www.jmlr.org/papers/volume5/yu04a/yu04a.pdf.

Zaki, Jamil, Kevin N. Ochsner, and Kevin Ochsner. 2012. “The Neuroscience of Empathy: Progress, Pitfalls and Promise.” *Nature Neuroscience* 15 (5): 675–80. doi:10.1038/nn.3085.

Zand, Aria, Welmoed K. van Deen, Elizabeth K. Inserra, Laurin Hall, Ellen Kane, Adriana Centeno, Jennifer M. Choi, et al. 2015. “Presenteeism in Inflammatory Bowel Diseases: A Hidden Problem with Significant Economic Impact.” *Inflammatory Bowel Diseases* 21 (7): 1623–30. doi:10.1097/MIB.0000000000000399.

Zhang, A., A. Leow, L. Zhan, J. GadElkarim, T. Moody, S. Khalsa, M. Strober, and J. D. Feusner. 2016. “Brain Connectome Modularity in Weight-Restored Anorexia Nervosa and Body Dysmorphic Disorder.” *Psychological Medicine* 46 (13): 2785–97. doi:10.1017/S0033291716001458.

Zuo, Xi-Nian, Clare Kelly, Jonathan S. Adelstein, Donald F. Klein, F. Xavier Castellanos, and Michael P. Milham. 2010. “Reliable Intrinsic Connectivity Networks: Test-Retest Evaluation Using ICA and Dual Regression Approach.” *NeuroImage* 49 (3): 2163–77. doi:10.1016/j.neuroimage.2009.10.080.