Effects of Expectations on Negative Affect, Perceived Cognitive Effort, and Pain

NCT05425563

Study IRB Protocol

January 20, 2022

TITLE: Individualized spatial topology in functional neuroimaging

PRINCIPAL INVESTIGATORS (MPI):

Name: Tor Wager
Address: Psychological and Brain Sciences, HB 6207, Dartmouth College, Hanover, NH 03755
Telephone: 303-398-1069
Email**: tor.d.wager@dartmouth.edu**

Name: Martin Lindquist
Address: 615 N. Wolfe Street, Room E3634, Baltimore, MD 21205
Telephone: 410-614-5107; 410-955-0958
Email: **mlindquist@jhu.edu**

I. OBJECTIVES

Here we aim to develop a new functional alignment method for fMRI that both improves inter-subject alignment and allows for topological inference. We will apply the methods to create a library of population-level reference spaces for task states and behaviors drawn from multiple psychological domains, and compare multivariate predictive models developed on data referenced to anatomical vs. functional reference spaces. This endeavor has two benefits critical to the field. First, it will greatly **enhance the accuracy of machine learning-based models** of psychological states and behaviors. Second, it will provide a way to **analyze inter-task and inter-individual differences in the spatial topology** of brain activation, providing statistical inferences about the location and shape of activated regions. Like existing methods, the approach aligns individual functional maps to a common set of *functional* population-level reference spaces. However, we align single-participant activation images based on **topological properties rather than representational reference space**.

We will develop topological models purpose-designed for fMRI activation and inter-subject functional alignment, and develop methods and software for topological inference. We will develop and compare two approaches. First, our research team has successfully developed explicit models of spatial topology in structural data, based on the use of the nonlinear large deformation diffeomorphic metric mapping (LDDMM) algorithm, which allows shape variation to be uniquely encoded by a deformation field normal to the outline of the template. This algorithm is specifically designed to accomodate deformations while retaining the topology of the object (i.e., structure preserving). Our models have inspired other anatomical diffeomorphic toolboxes, such as SPM's 'DARTEL' anatomical registration tool [88]. We propose to **extend the LDDMM algorithm to allow for functional alignment**. Local differences in the amount of transformation needed for different regions will be studied and compared across experimental tasks. LDMM provides us with geometric information regarding the spatial transformations required to align a functional activation image to the population-level functional reference. This information will be used for analyzing the population variability of brain anatomy and functional activation maps, through the Jacobian determinant of the deformation field.

In a second, alternative approach, we will construct spatial models of the relative misalignment of the individual-subject functional images with respect to a latent activation template map based on the use of 3D **Gaussian processes** [89, 90], which models activation (or other variables) with Gaussian functions whose parameters vary continuously over time or space. The fully Bayesian formulation of the model will enable inference on the latent surface via posterior samples. Importantly, these two models will allow us to test several types of hypotheses fundamental to the

endeavor of brain mapping and cognitive neuroscience: (a) Is the extent of activation in a task confined to the boundaries of an anatomical region, or does it extend into neighboring regions? (b) Is activation for one task located in a significantly different location to activation for another task? (c) Do two tasks activate the same region, but with significantly different activation topology (i.e., shape), suggesting activation of different subregions or local circuits? (d) Do individuals vary in the location and/or pattern of local activation in a task, and how much of the observed differences are reliable individual differences vs. noise? (e) Is local activation best characterized by a single activation location with spread/blurring, or multiple, distinct local activation peaks? These tests formalize many of the concepts brain mapping researchers want to test in order to understand brain structure-to-function mapping. They also formalize inferences about the utility of multi-voxel pattern maps that are currently assumed—in particular, that the local topological pattern is reliable and carries more information than the voxelwise activation magnitudes.

Here, we will test and validate the methods in an experiment (n = 150) that includes naturalistic narrative experiences (movies) and tasks from three functional domains (pain, emotion, and cognition). These tasks are designed to elicit specific brain responses, which will be utilized to construct a more sophisticated functional alignment for specific brain activation.

II. BACKGROUND AND SIGNIFICANCE

Neuroimaging is poised to take a substantial leap forward in understanding the neurophysiological underpinnings of human behavior. This is due in part to the combination of (a) improved analytic techniques, including machine learning and related pattern-recognition algorithms [1-8] and (b) improved data quality, particularly the increasing spatial resolution of functional Magnetic Resonance Imaging (fMRI) data [9-11]. These advances permit researchers to develop brain models of the functional representations underlying behavior, performance, clinical status and prognosis, and other outcomes. Most such models take the form of multivariate patterns of brain activity and connectivity (e.g., Preliminary Data in **Figure 1**). If such 'signatures' are generalizable across individuals, i.e., they predict outcomes in new, out-of-sample participants, they constitute population-level models—also called 'signatures', 'neuromarkers', or biomarkers in the literature—that can be shared and rigorously tested across laboratories [12-19].

Such models have multiple advantages. They constitute research products that can advance the cumulative science of brain function by testing their *generalizability*, *sensitivity*, and *specificity* for particular behaviors, mental events, and other outcomes across a widening circle of laboratories and conditions [6]. Because they make strong, quantitative predictions about outcomes, they can be falsified (in the Popperian sense [20]), refined, and improved. In addition, distributed models are suited for capturing information represented in distributed neural population codes, which recent studies show are critical for many aspects of cognition and behavior [21-27]. Because they can capture pattern information [28-30] within and across regions at multiple spatial scales, they have yielded signatures that predict stimulus conditions and experiences like pain and emotion with large effect sizes, which can increase statistical power in fMRI studies by an order of magnitude [31, 32] (e.g., d = 3.3 in **Figure 1** vs. average d = ~0.5 for single voxels [33]). We view the development of population-level models of clinically relevant outcomes as a critical step towards both understanding the functional anatomy of brain disorders and developing brain-based measures useful in translational contexts [6]. We also view such models as critical for understanding the brain representations underlying basic cognitive and emotional processes.

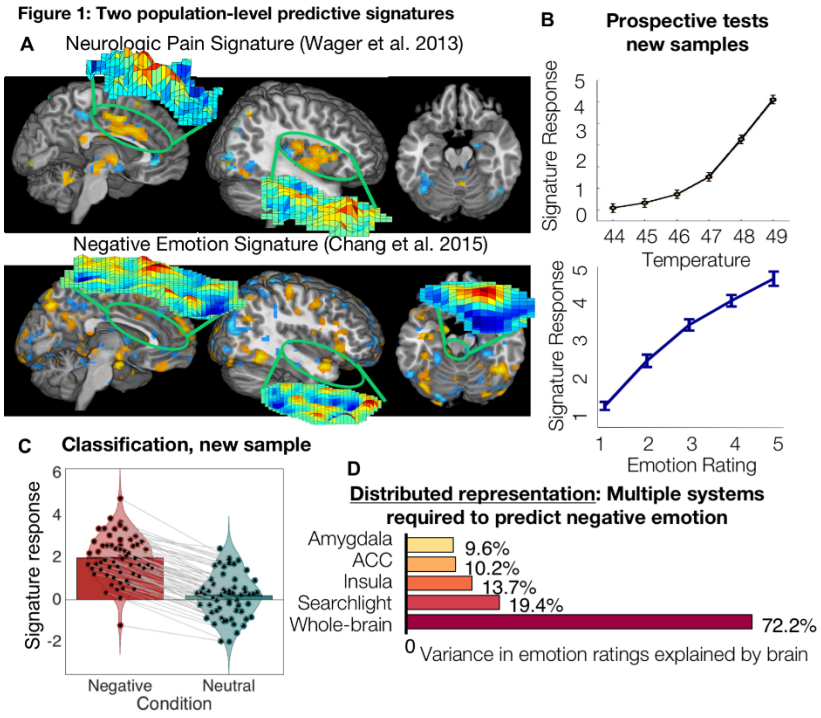


Figure 1. **Two population-level predictive models**. A) *Top*: Signature predicting pain intensity elicited by painful heat. *Bottom*: Signature predicting intensity of negative emotion elicited by aversive images. Both involve areas associated with "negative affect," including dorsal anterior cingulate, insula, and amygdala. However, the patterns of activity that are predictive within these regions are different (spatial r = 0.04). B) Prospective application of the two signatures to independent data from new samples. The Pattern Response (y-axis) is calculated as the dot product of the signature with input images from out-of-sample participants, yielding a single weighted average response. *Top*: Pain signature responses predict increases in pain across levels of painful, but not non-painful, heat (x-axis) and closely track reported pain (not shown). *Bottom*: Emotion signature responses track increases in reported negative emotion. C) The emotion signature classifies negative from neutral pictures in an independent sample (N = 60), with a large effect size (Cohen's d = 3.3). Each line connecting a pair of dots represents a participant. D) Variance explained in emotion ratings by patterns within individual regions and the whole-brain signature. ACC is the dorsal anterior cingulate, and searchlight is the (optimistically biased) highest single region across the brain. The superior performance of the whole-brain signature indicates that multiple regions are required to accurately predict emotion from brain activity.

Promising advances towards population-level models have been made for many categories of clinical conditions (for reviews, see [6, 15, 34]), and such models have been used to successfully predict task states and/or performance on non-clinical and pre-clinical outcomes [35-38]. However, much work remains, as most models have not been truly tested prospectively on independent cohorts of participants; in a recent review of nearly 500 papers using population-level machine learning-based models, predictive accuracy was tested on independent cohorts in only 9% of cases [6]. Accuracy for those models averaged around ~80% for patient vs. control discrimination (chance ~50%), arguably not high enough to be useful in translational settings. Our collaborative group (PI Lindquist and Co-I Wager's labs) has been actively involved in developing such population-level models [38-45] (**Figure 1**), and accordingly, we have focused on testing prospectively in new samples and evaluating generalizability across scanners, task variants, ethnic/racial groups, and cultures. In sum, population-level multivariate brain models offer an exciting way to make and test strong, quantitative predictions about clinical and basic outcomes, and thereby understand the brain representations involved. But we clearly need ways of improving

the models' performance. Here, we identify **two fundamental obstacles** impeding progress in the field, namely the problem of **individual variation in functional brain anatomy** and the **lack of formal statistical spatial inference** in fMRI analysis, which motivate the new methods we propose.

I. The problem of inter-subject variability in functional anatomy. Current standard practice is to use nonlinear transformations to warp individual participants' anatomical data to an average, anatomically based 3D reference space (e.g., "Montreal Neurologic Institute" (MNI) space). Those transformations are then applied to functional data. Though individual-subject, whole-brain fMRI data can now be collected at a resolution of 2 mm^3 'voxels' or smaller, once functional maps are combined across individuals to construct a population-level model, the effective resolution is dramatically lower. This is largely due to inter-subject variability in the location and distribution of functional regions relative to anatomical landmarks (**Figure 2**).

Large inter-individual differences in both brain anatomy and functional localization after anatomical alignment [46-63] are a major limitation in conducting group analyses and population-level inference. For example, primary visual cortex (V1) can vary in size by as much as 2-fold across different subjects' brains [53] and in location relative to other anatomical landmarks [47], as can sulcal locations [56]. In some cases, inter-individual differences can be accounted for by nonlinear warping into a common anatomical reference space, but in other cases they cannot. For example, the cingulate sulcus is structurally dimorphic [60]—a substantial minority of individuals possesses a double cingulate sulcus—precluding anatomical alignment using current methods. In addition, considerable variability in functional localization persists even after anatomical alignment [47, 49, 62, 63]. For example, the location of visual motion-sensitive area MT can vary by more than 2 cm. The location and extent of lateral occipital cortex (LOC; [50]) and fusiform face area (FFA; [46, 51]) are also highly variable across individuals and located in different places relative to anatomical sulcal landmarks (see **Figure 2**). Accordingly, functional connectivity is also variable across individuals even after anatomical alignment, with the greatest variability in areas showing significant expansion in humans relative to monkeys [52]. Such

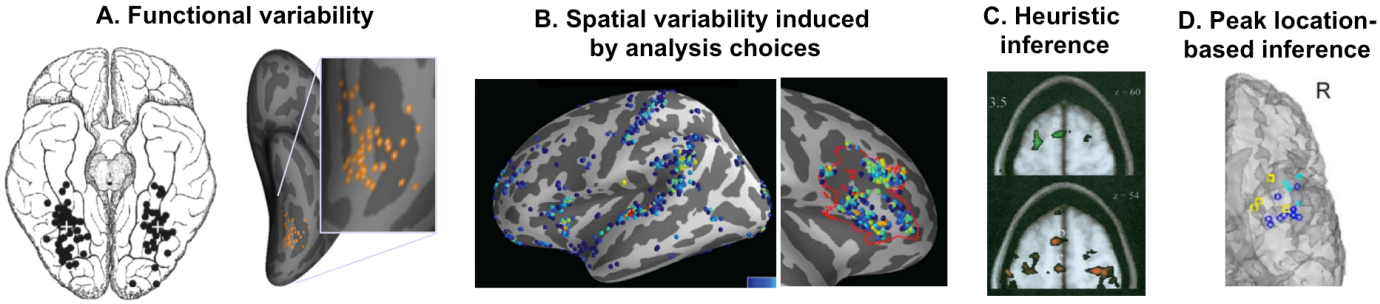


Figure 2. Functional variability and problems with heuristic spatial inference in fMRI. Substantial variability in activation locations is caused by both (1) inter-subject variability in functional localization and (2) inherent instability and sensitivity to analyis choices in peak location estimation. **A) Left:** Variability in face-specific regions assessed with intracranial EEG in 93 patients (Allison et al. 1999). **Right**: inter-individual variability in peak word-selective areas in fMRI. **B)** Peak activation locations in group analyses vary widely across different preprocessing and analysis choices. Carp (2012) analyzed nearly 7,000 combinations of basic analysis choices; hotter colors reflect more frequent peak activation locations across different combinations. **C)** Formal spatial models are necessary to infer activation locations, but these are not provided in major packages. The standard method for making spatial inferences about activation location and shape has been heuristic, informal judgments. This is problematic. For example, in a classic task switching study, Rushworth et al. (2002) write, "…the visual switching results [green] are slightly more medial and dorsal than those showing the response switching results [red], reflecting the more dorsal and medial position of the visual switching activation." But the replicability of this spatial difference over samples is not assessed, and no confidence levels or P-values for this inference are estimated. **D)** A valid, but rudimentary, way of making spatial inferences is to extract peak locations across participants or studies for different task types, and compare those locations. A meta-analysis by Wager et al. (2004) found that peak locations of switching among object attributes (yellow, similar to "visual switching") in the lateral prefrontal cortex are medial, anterior, and dorsal to other switch types, whereas rule switching peaks were located ventral and anterior to other switch types. This confirms the Rushworth interpretation with explicit spatial statistics for the lateral prefrontal cortex, but not in the medial prefrontal cortex.

variability dramatically decreases the spatial resolution and precision of population-level brain mapping, as features will not be properly aligned for subsequent statistical analysis.

Recent approaches have sought to circumvent this problem by mapping individual brains into a *functional* population-level reference space rather than an anatomically based brain space. The first such model is the 'hyperalignment' procedure [64], Here brain activity patterns corresponding to stimuli and other cognitive events are represented as vectors in a neural **representational space** spanned by the voxels in a local neighborhood. Hyperalignment rotates each participant's local voxel-wise activity patterns through multivariate voxel space using a Procrustes transformation to align the representational geometry across subjects. Mathematically, this is similar to Canonical Correlation Analysis (CCA). A number of refinements of hyperalignment have recently appeared, including: kernel hyperalignment [65] which performs nonlinear hyperalignment in an embedding space; regularized hyperalignment [66] which uses a ridge CCA formulation; the two-phase joint SVD-Hyperalignment algorithm [67], where singular value decomposition (SVD) provides a lower dimensional feature space where hyperalignment is applied; the shared response model [67] which casts the model in a probabilistic framework; and searchlight hyperalignment [68] which allows for whole-brain coverage. Other methods have been developed that align subjects based on inter-subject correlations in time-series data during movie viewing. One method is functional time series alignment (FTSA) [69], which matches voxels across subjects using a 2D 'rubber sheet' warping and maximizing inter-subject correlations across voxels [70]. Another is functional connectivity alignment (FCA) [71], which matches voxels to a functional reference by minimizing the Frobenius norm of the difference between a subject's connectivity matrix and a reference matrix with a shape-preserving penalty function. Both methods use warping and penalization strategies specific to the cortex, so it is unclear how easily they can be adapted to include subcortical regions.

This body of work shows great promise for allowing participants to vary in their functional activation patterns [64], but suffers from several shortcomings. First, hyperalignment requires subjects to watch a long film (up to 2 hours) to align subjects into a common representational space, and functional connectivity-based methods require substantial resting state data. Second, the choice of reference data (movie or rest) influences which types of functional patterns can be appropriately aligned. For example movie reference data works well for audio-visual representations but not prefrontal and limbic networks. Functional connectivity-based measures work better for limbic cortex, but are expected to perform more poorly on object and semantic representations. Neither type of method has been tested on subcortical representations, or on clinically relevant functions such as pain and emotion. Third, these methods do not include an explicit spatial model able to make inferences on the location or extent of activation, though a few recent studies have taken steps in this direction [72]. Indeed, hyperalignment is designed to preserve inter-item similarity at the cost of topology.

II. The lack of formal statistical spatial inference in fMRI analysis. Topological models that explicitly model the shape and extent of fMRI activation are a crucial advance for the field, but examples are rare in the literature (cf. [73-78]). Such models are needed to make inferences about where brain activation is located, or if two subjects/tasks activate significantly different locations. Major packages (e.g., SPM, FSL, AFNI) provide no way of making such inferences. While standard voxel-wise brain mapping give the illusion that activation is being localized, they only test the magnitude of activation in a given location, providing maps of locations above a threshold (**Figure 2**). They do not provide inferences about where spatial boundaries of activation lie, or whether two tasks activate significantly different locations. This has caused substantial confusion in the field. Likewise, the use of cluster extent thresholding doesn't provide spatial inferences. They simply test the null hypothesis that the extent of activation is larger than expected by chance [79]. This permits one to conclude there is signal somewhere in the region deemed active, but provides no information about spatial boundaries of activation [80]; in fact, they produce invalid results when used to infer the boundaries of spatial extent [80]. Finally, most packages use *ad hoc* algorithms for finding peak activation locations, which are routinely used to define regions of interest and conduct meta-analyses. But these algorithms provide no inference about variability in those locations. Peak locations are unstable and vary widely across individuals [71], studies [81-83], and analysis methods [84] (**Figure 2**). Likewise, they provide no inference

about whether there is a single or multiple distinct, local peaks. The lack of spatial inferences is a major impediment to progress in the field.

III. PRELIMINARY STUDIES

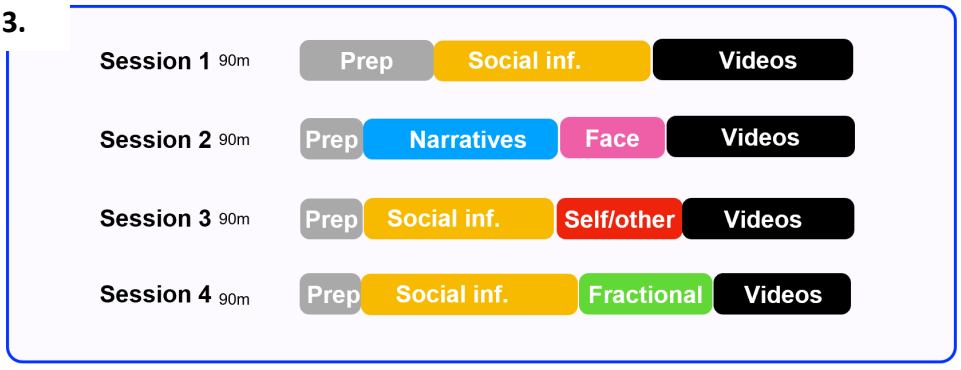
Over the past 5 years, our team[47-52] and others[53-58] have pioneered a new paradigm for studying the brain, grounded in building models of how brain regions and systems work together to create cognitive and affective states. Such models make quantitative, testable predictions about mental states that can be validated or falsified. The approach is grounded in three pillars: **(i)** the use of multivariate pattern-recognition techniques to develop brain models predictive of mental states; **(ii)** assessment and optimization of the models' diagnostic value; and **(iii)** a program of initially broad exploration followed by increasingly rigorous assessment of generalizability across samples, research contexts and populations[59]. We have generated several preliminary findings (see Figure 1) that we hope to extend through this proposal by improving methods for aligning spatial topology in neuroimaging.

IV. RESEARCH STUDY DESIGN

N=150 participants will be recruited as outlined in the "ABOUT THE SUBJECTS" section in this protocol). Considering that a possible dropout rate for behavioral studies is around 20%, and that we need at least 100 participants' data to gain sufficient power, we need 150 participants. Based on our previous experience we expect data collection to last for approximately 18 months.

The experiment has the following 4 separate fMRI sessions (see figure 3), each at least one day apart, taking place at the Dartmouth College Brain Imaging Center fMRI scanner in Moore Hall, Hanover, NH. Below is an outline of the sessions and tasks; for a detailed description of each session and tasks, see Procedures section.

Figure 3.



This study will consist of 4 separate fMRI sessions. The sessions will include a period of time before the scan in which participants will become familiar with the tasks.

Prior to Sessions (1 hour)

1. Participants will be given a link to access surveys that will be filled out prior to coming in for their first session.

Session 1 procedures (~2.75 hours):

1. Prior to scanning (1.25 hours)
    a. MRI screening form
    b. Bartoshuk scale practice
    c. Pain familiarization and site selection
    d. Practice tasks
        i. Social influence task explanation and familiarization
        ii. Video ratings explanation and familiarization, and practice ratings
    e. Preparation for fMRI scan

2. fMRI tasks (1.5 hours)
    a. Social influence task
    b. Video compilation task
    c. Structural scan
    d. Diffusion Tensor Imaging (DTI) scan

Session 2 procedures (~2.75 hours):

1. Prior to scanning (1.25 hours)
    a. MRI screening form
    b. Instructions and practice tasks
    c. Preparation for fMRI scan

2. fMRItasks: narrative task, face task, and video compilation task (1.5 hours)

Session 3 procedures (~3.25 hours):

1. Prior to scanning (1.75 hours)
    a. Instructions and practice tasks: learning and attribution phases of learning task, and self/other task familiarization and practice
    b. Preparation for fMRI scanning

2. fMRI tasks: social influence task, self/other task, and video compilation task (1.5 hours)

Session 4 procedures (~3 hours):

1. Prior to scanning (1.25 hours)
    a. Practice tasks: fractional factorial tasks familiarization and practice
    b. Preparation for fMRI scanning

2. fMRI task: social influence task, fractional factorial task, and video compilation task (1.5 hours)

3. Debriefing and payment: After completing the tasks, participants will be payed based on the hourly rate. Then, they will be offered a debriefing form (Attachment 2), which will provide the lab and PI contact information. (0.25 hours)

Pain Stimuli: During tasks that will involve heat pain, participants will receive standardized thermal stimuli (Medoc Pathways, Medoc, Inc.) on the outer surface of the right and left calf/arm. Pain stimulation will be administered in accordance with the process outlined in the pain screening protocol (Protocol # 31999, Attachment "stimulation_guidelines"). Pain ratings are made on a semi-circular scale after each trial using an MR-compatible trackball (5 sec, Current Designs, Inc.).

Physiological measurements: Throughout the study we will passively record a number of physiological variables: (a) non-invasive electrodes will be placed on the left foot, in order to measure skin conductance, and (b) a photoplethysmogram will be placed on the big toe of the right foot, in order to measure heart rate/pulse. These recordings will be entirely passive and non-invasive and will not require any additional effort on the part of the participants (except for having sensors attached to one's left foot and right big toe for physiological recording). The devices used to record the physiological data are MRI-compatible and will be recorded using the BioPac Acquisition system and the Siemens Physiological Monitor system. There are no known health risks involved in collecting this data.

Data Analysis Plan:

Video Compilations: During the scanning sessions, participants will answer questions after each video regarding the content of the video (see Attachment 3). We will code semantic concepts using categories from Huth et al. (2016) and extract other features and codes (e.g., appearance of faces, expressions, social interactions in videos).

Pain: Primary outcomes are effect sizes for (a) brain-based decoding of pain vs. other tasks; (b) brain-based prediction of trial-by-trial pain reports. In addition to nominal stimulus intensity levels, there is substantial endogenous variation in pain reports due to expectations, sequence effects, and endogenous variation in attention, which will be modeled in our trial-by-trial predictive analyses.

Cognitive Tasks
The primary outcomes for the tasks are as follows:

1. Social influence task: personal pain ratings, vicarious pain ratings (estimating the degree of pain the other person is experiencing), cognitive difficulty rating
2. Narratives task: judgments regarding how the participant feels and/or what they believe is going to happen next
3. Face task: judgments regarding the age, sex, and emotional intensity of the expressions
4. Fractional Factorial tasks: 1) Memory task: episodic retrieval ("Do you remember this item"), 2) Attention task: "Indicate target location", 3) Theory of mind task: judgments on stories, 4) Why and how task: judge human faces based on set of questions

Power assessment. The sample size (n = 150) was chosen to power the study at 80% power for voxel-wise analyses with whole-brain family-wise error rate correction ($p < 0.05$ corrected), for moderate effect sizes of Cohen's $d = 0.5$ or larger. Recent estimates for voxel-wise effects in fMRI studies average around $d = 0.5$ [179]. Our proposed sample size of n = 150 provides 80% to detect moderate effects of $d = 0.5$, and over 95% power to detect "large" effects of $d = 0.8$. We will test for sex differences in exploratory analyses, with 80% power to detect very large effects ($d = 1.1$). This power calculation is appropriate for making inferences on voxel-wise contributions to multivariate predictive models, i.e., to identify brain regions with stable predictive weights when *training* models. When *testing* multivariate predictive models on new individuals, different calculations apply. First, effect sizes can be substantially larger, and second, multiple

comparisons correction is not required as information is integrated into a single measure. Estimated effect sizes for the Neurologic Pain Signature response tested on data from the Colorado 3T scanner (n = 23) were *d* = 2.12 for a 2-degree difference in painful heat. In our other prior work, the effect size when testing our high vs. low negative emotion signature was *d* = 4.7 [149], and testing our vicarious pain signature (also on the Colorado scanner) was *d* = 3.9, all in out-of-sample participants. For *testing*, our proposed sample sizes are powered to detect much smaller effects: With n = 150, we have 80% power to detect small effects (*d* >= 0.26) at p < .05 two-tailed, and sex differences in predictive accuracy for effects of d >= 0.52. If effect sizes for multivariate models are as large as in our previous work (d = 2.0 and above), we will be able to make accurate inferences about individuals. Thus, our proposed sample sizes are appropriate for identifying regions that contribute consistently to multivariate predictive models across individuals, and testing those predictions with high power.

fMRI acquisition and preprocessing. Images will be acquired on a Siemens Trio (3T) MRI scanner the Dartmouth Brain Imaging Center. We will collect a T1-weighted anatomical image, scout EPI images, and functional images. High-resolution T1-weighted anatomical scans will serve as a reference for localizing functional activity. Head movement will be minimized by padding and soft restraint as is standard for the Dartmouth Brain Imaging Center. We expect a maximum of 1 mm displacement / 1.5° rotation within-run is achievable in ~95% of participants[152]. State-of-the art image preprocessing techniques (SPM12; Wellcome Department of Cognitive Neurology, UCL), use procedures detailed in our published work[153-159].

Total participation time for the entire study will be approximately 12.75 hours. Duration of the session is dependent on the tasks before, during, and after the scan.

Name of procedure/instrument/tool	Purpose (i.e., what data is being collected?)
Consent form (Attachment 4)	Information pertaining to the study in order to inform the participant of the procedures
Pre-Session Surveys, Online (Attachment 5)	The following measures will be used to assess personality, mod, Perceptual/Affective Bias, and Cognitive Control
a) Jessor demographics	Measures Demograpics
b) Multidimensional Assessment of Interoceptive Awareness	Measures interoception
c) PROMIS-57 Profile v2.1	Measures physical function, anxiety, depression, and pain
d) Canlab Pain Survey (Pain Symptoms)	Records any pain disorders or sensitivies
e) Life Orientation Test Revised (LOT-R)	Trail levels of optimism and pessimism
f) Positive and Negative Affect Scale	Trail levels of positive and negative affect
g) Fear of Pain (FOP)	Measures fear and anxiety associated with pain

h) **Behavioral Inhibition/Behavioral Activation (BIS/BAS)**	Trait levels of approach and avoidance behavior
i) **The "Big 5" Inventory Brief Version**	Survey designed to measure various personality traits
j) **Ego-Resiliency Scale (ER89)**	Ability to respond adaptively and resourcefully to new situations
k) **Adverse Childhood Experience (ACE) Questionnaire**	Measures childhood trauma (if any)
l) **Marlow-Crowne Social Desirability Scale 13-Item Short Form**	Measures social desirability
m) **Interpersonal Reactivity Index**	Measures thought and feelings in a variety situations
n) **Phenx Alcohol Lifetime Use**	Degree of lifetime use of alcohol
o) **Phenx Alcohol Age of First Use**	Age of first alcohol use
p) **Phenx Alcohol 30Day Quantity and Frequency**	Quantity and frequency of alcohol use
q) **Phenx Substances Lifetime Use**	Degree of lifetime substance use
r) **Phenx Substance Age of First Use**	Age of first substance use
s) **Phenx Substance 30Day Frequency**	Frequency of substance use
t) **Phenx Cigarette Smoking Status Adult**	Status of cigarette smoking
u) **Phenx Tobacco Age of Initiation of Use Adolescence**	Age of tobacco initiation
v) **Phenx 3Tobacco 30Day Frequency**	Frequency of tobacco use
w) **Self-Report Psychopathy Scale**	Identification of psychopathic traits and behaviors
x) **Balanced Inventory of Desirable Responding (BIDR) Short-Form**	Measure of socially desirable responding
y) **20-Items Prosopagnosia Index**	Measure of face recognition abilities
z) **Tendency to Conform**	Measure of social conformity
aa) **Therapeutic Reactance**	Measure of psychological reactance
bb) **Revised Self-Monitoring**	Measure of sensitivity to expressive behavior and ability to monitor self-representation
cc) **Concern for Appropriateness**	Measure of tendency to conform
In-Session Behavioral Tasks/Surveys	**The Following tasks or assessments will be conducted during the in-person sessions**

a) **MRI Safety Screening Form (Attachment 6)**	Used to confirm fMRI eligibility
b) **Visual Semicircular Analog Scale (Bartoshuk Scale practice and use; see Attachment 7)**	Scale used to submit ratings regarding questions pertinent to each task (e.g., pain ratings)
c) **Pain Familiarization**	Familiarizing the participants with the range of thermal temperatures
fMRI Cogntiive Tasks	**Brief Description of Tasks (for examples see Attachment 7)**
a) **Social Influence Task**	Effect of social infuelnce on one's own ratings across a variety of domains
b) **Video Compilation**	Videos for functional alignment; questions regarding current feelings (e.g., happy, sad, afraid)
c) **Narrative Task**	Narratives that vary in emotional content; judgments about how they feel and/or what they think will happen next
d) **Face Identification Task**	Brief videos of facial expressions; judgments about age, sex, and emotional intensity of facial expressions
e) **Self/other Task**	Neurological differences in types of social judgments; judgments made about the target character
f) **Fractional Factorial**	Four different tasks
a. **Theory of Mind Task**	True of false questions
b. **Why/how Task**	Yes or no questions
c. **Posner Task**	Identify which direction a target was presented
d. **Memory Task**	Memorize items, indicate whether they previously saw the items
Other	
Biopac Systems	Utilized for physiological measurements: Heart rate and skin conductance
Pain Medication Assessment	Administered each session to determine if participants have utilized pain medication within 12 hours of their visit
Menstruation Questionnaire	Administered once to assess menstruation

V. FUNDING

National Institute of Health, Spatial Topology Grant, Principle Investigator: Tor Wager
National Institute of Health, Placebo Effects Grant, Principle Investigator: Tor Wager

VI. ABOUT THE SUBJECTS

All participants will be recruited and screened prior to consent. We will primarily recruit individuals aged 18-55 years who have no reported substance abuse within the last six months, are capable of performing experimental tasks (e.g., are able to read), are fluent or native speakers of English, and have no current or recent history of pathological pain or reported neurological disorders. Individuals who are left-hand dominant only will not be eligible; eligible participants must be right-handed or ambidextrous. Participants less than 18 years old will be excluded because of population vulnerability issues. Participants over 55 years of age will be excluded based on a diminished sensitivity to pain and changes in brain structure that require special studies of older populations, which is outside the scope of this study. Participants with current psychiatric or major neurological diagnoses will be eligible to participate because we want to account for broader individual differences and maintain a population that is neurodiverse. Only patients who are competent and have the cognitive ability to provide informed consent will be allowed to participate. For full capacity, participants must be able to: (a) make choices, (b) understand the given information, (c) appreciate its content, and (d) rationally process the information (Amer, 2013; Gupta & Kharawala, 2012; Grisso & Appelbaum, 1998). At the first study visit, the research staff will review the study procedures with the participant and verify that the participant displays sufficient understanding of the study as well as its risks and benefits. At each study visit, the participant will be asked if they would like to continue their participation and will then be asked to re-sign the consent form, accordingly.

In addition, participants who have currently or recently suffered from chronic pain will be excluded, as they are unlikely to successfully complete a pain study and provide informative results. Chronic pain status will be initially assessed via self-report and verified by additional screening questions. We will also exclude people who cannot tolerate the maximum level of thermal pain stimuli (for thermal stimuli: 50 °C).

Participants who have any contraindication to magnetic resonance scanning (e.g., metal in body, claustrophobia, pregnant) will be also excluded. These exclusions are specific to MRI and are consistent with most studies involving MRI. Potential participants will be screened for the presence of any of these exclusion criteria prior to participating in this MRI study.

Subject Population(s)	Number to be enrolled in each group
fMRI experiment participants	150

VII. VULNERABLE POPULATIONS

We will not exclude anyone based on class or income so there is a possibility that economically disadvantaged individuals will be enrolled in this study, but no other vulnerable populations will be included, and recruitment will not target vulnerable populations.

VIII. RECRUITMENT METHODS

Recruiting will take place through community flyers, university mailing lists, newspaper ads, social media platforms (e.g. Facebook ads), online bulletin boards such as craigslist, and via word-of-mouth. Data collected over the Internet will be kept confidential and made available only to the Screening Coordinators. We may also refer to approved recruitment procedures from CPHS 31999.

IX. COMPENSATION

Laboratory participants will be compensated $400 at the conclusion of the four sessions, including a $150 bonus for completing the study (all four sessions). Subjects who discontinue participation will be paid a prorated rate for the time of participation based on the $250 rate. Specifically, we will offer participants $57-64 for each completed session, and a prorated rate for partially completed sessions ($25/hour of scanning, $10/hour of online/behavioral testing, and $7.25/hour of behavioral setup).

Undergraduates at Dartmouth College may opt to receive compensation via SONA T-points. Eligible students will receive 1 T-point/hour of scan participation and they will receive monetary compensation for every hour of behavioral participation ($10/hour of online/behavioral testing and $7.25/hour of behavioral setup). Subjects who discontinue participation will be given prorated compensation based on their time. Participants who select this compensation method will also be eligible for the same monetary completion bonus.

Additionally, participants may receive up to $20 based on their performance in the fractional task. This compensation will be issued to participants with the overall study compensation, after debriefing.

All participants who have completed the study will be contacted via email and asked to complete a brief online survey to provide additional demographic data necessary for grant reporting requirements. As a retention incentive, participants who previously completed the study will be offered $15 in compensation for providing this data. Active participants will be issued the demographic survey during their participation. Additional compensation will not be offered to active participants because the effort required to complete the survey is minimal and retention is not a motivating concern.

We may offer eligible participants the opportunity to be scheduled as a backup participant. Backup participants will participate in the experiment (and be compensated at the regular compensation rate) if our originally scheduled participant unexpectedly can't be present. Otherwise, the session will proceed with the originally scheduled participant and the backup participant will be compensated for their time (i.e., $20 payable via check, cash, or gift card for each backup session). Our study will collect and store information necessary to pay participants via a secure database such as REDCap.

X. INFORMED CONSENT

We will obtain a general consent following the process outlined in the pain screening protocol (Attachment 1: Protocol # 31999), which involves a screening form. After filling out the screening form, and passing our laboratory's eligibility, potential participants will be contacted by an experimenter and sent a link to an experiment-specific electronic copy of the consent form via RedCap e-Consent. The consent form will provide information regarding the fact that the study involves: 1) viewing video clips that vary in emotional content and listening to narratives from storytellers; 2) experiencing thermal stimuli that are painful but tolerable, according to their individual sensitivity; and 3) engaging in several cognitive tasks. The participant will read and electronically sign the consent form. The signed copy will be saved to the RedCap project's File Repository, as well as on a password protected computer accessible only by study team members. Once participants have signed the electronic consent form, they will be sent a link to complete the required online surveys (Attachment 5). Upon arrival for their first session,

participants will be asked if they have any questions or would like any clarification on any of the items included in the consent form. The participant's voluntary participation is stressed in that they are informed, both verbally and in writing, that they can discontinue the study at any time. Subjects who discontinue participation will be paid a prorated rate for the time of participation based on the hourly rate established for the study. Participants will be given the option to receive a paper copy of the signed consent form.

XI. PROCEDURES

Each eligible participant will be assigned two IDs prior to data collection:

1. REDCap generated ID
2. BIDS random ID

Identifying information from REDCap may be used by a single member of the research staff to verify eligibility and confirm completion of surveys and other study requirements. Once a participant is determined eligible, this research staff member will assign the BIDS IDs to the participant and will maintain a restricted-access spreadsheet that links the REDCap ID and BIDS ID. Additional members of the research staff will be permitted to access deidentified data only.

Prior to their first session, participants will be sent a link in order to complete a series of pre-session surveys at home and online (Attachment 5). Completion of the surveys will take roughly one and a half hours. We are administering these surveys, along with the others, in order to study the basis of emotion in a novel way. The relationship between emotions, drug use, and early life experiences are crucial to capture, because they may be important moderators of emotion-related activity in our sample and they also serve as outcomes of interest for population models that we are going to develop.

Each session will begin with the initial preparation that is required to conduct the MRI.

Preparation for each scan: after having signed the consent form via RedCap e-Consent at home, and completing our facility's MRI screening form, and prior to going into the MRI scanner, the MRI technologist on duty will ask participants to remove all jewelry and metal objects from their pockets. Participants will be required to change into scrubs to prevent any possible risk from metallic objects or decorations in their clothing.

In an MRI scan the subject lies down on a table and is placed into a long donut-shaped magnet. A specially designed coil will be placed around the head to provide better images (as is done with standard clinical examinations). As the MRI scan is performed, the participant will hear loud rapping and knocking noises that are normal for an MRI scan. Participants will be provided with earbuds that block out some of the noise from the MRI scanner; they will also have access to a squeeze ball that they can squeeze in order to get the attention of the MRI technologist and stop the scan. MRIs will be conducted according to the policies and procedures of the Dartmouth College Brain Imaging Center, 6207 Moore Hall, Hanover, New Hampshire.

Below is a detailed explanation for each session. The term paradigm is used to refer to the design of a task during the fMRI session. For a comprehensive explanation of cognitive tasks, questions being asked during the tasks, and examples, see Attachment 7.

Session 1:

Upon arrival participants will complete our facilities MRI safety screening form (Attachment 6). Next, they will practice using the Bartoshuk scale, which they will use in the scanner to make pain ratings. Next, participants will be familiarized with the range of temperatures used during the tasks. Finally, participants will be familiarized with the session specific tasks (the social influence task and the video questions/ratings).

This session begins with a structural scan and a DTI scan. Next, participants will complete the first part of the social influence task. The aim of this task is to investigate the effect of social influence on one's own rating across a variety of domains, including affective and cognitive experiences. Therefore, we will incorporate three conditions where participants experience the following – 1) personal pain, 2) vicarious pain, and 3) a cognitive condition -- in order to assess whether other people's opinions of these experiences can affect one's experience across a number of cognitive and affective settings.

The sequence of one trial is as follows (see figure 4): participants will see a fixation cross (fixation), followed by rating bars that indicate other people's opinions (cue), thus instigating social influence. Then they will be prompted to rate their own expectations for this upcoming experience (expectation). Next, participants will go through the three conditions, 1) personal pain (heat pain for three to four seconds), 2) vicarious pain (three- to four-second video clips of patients with shoulder pain), and 3) a cognitive condition (participants will perform a cognitively demanding "mental rotation" task while responding quickly to instructions. Participants are required to mentally rotate two 3D objects and indicate whether they are the same or different). Lastly, participants will rate their experience. For personal pain they will rate how painful the experience was; for vicarious pain they will rate how much pain it seemed that the patient was in; and for the cognitive conditions the participant will rate how difficult the task was. In total, the task will be from 30-40 minutes.

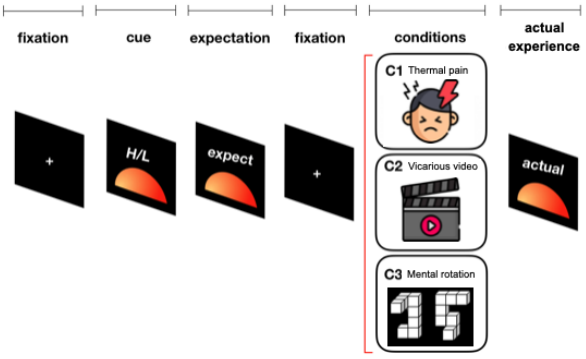


Figure 4. Social influence task experimental design.

During the last segment of the first session, participants will watch a compilation of short to medium length videos and will be asked a series of questions regarding the videos.

Session 2:

Upon arrival, participants will complete forms and receive task instructions and/or complete practices.

The first segment of session two will be an fMRI paradigm, in which participants will listen to brief narratives (3 to 5 sentences each) describing situations that vary in emotional content. Each narrative will be presented in two segments. Between the two sections, participants will make judgments about how they feel and/or what they think is going to happen next. Four runs of scanning lasting approximately 8 minutes will be completed, with different narratives presented in each run.

The next task will be the face identification fMRI paradigm, in which participants will be presented with brief videos of computer-generated facial expressions. Following each video, participants will make judgments about the age, sex, and emotional intensity of the expressions. Three runs of scanning lasting approximately 5 minutes will be completed, with different videos presented in each run.

During the last segment of the first session, participants will watch a compilation of short to medium length videos and will be asked a series of questions regarding the videos.

Session 3:

Upon arrival participants will be familiarized with the session specific tasks (social influence and self/other task).

Participants will complete the second part of the social influence task, as described above.

The next task is a self/other task, which is designed to investigate the neurological differences in related types of social judgements and to develop a neurological biomarker for self-referential processing. Participants will view a series of 5-10 second video clips portraying a character (target) from longer videos with which the participants are already familiar. After each video clip, participants will be asked to make one of three types of judgements about the target: 1.) a judgement of how similar the target is to themselves 2.) a judgement of how much they like the target or 3.) a judgement about what the target is thinking or feeling.

During the last segment of the first session, participants will watch a compilation of short to medium length videos and will be asked a series of questions regarding the videos.

Session 4:

Upon arrival, participants will complete forms and receive task instructions and/or complete practices.

The first segment of session four will be the third run of the social influence task, as described above.

The next segment of session four will be a fractional design with four different tasks.
Task one will be a theory of mind task. The aim of this task is to investigate the ability to think about others mental states. Participants will read stories and answer true or false questions. There will be two types of stories: 1) stories describing false beliefs ("belief") and 2) stories describing outdated, i.e. false photographs and maps ("Photo"). Both sets of stories require participants to represent false content; the critical difference is in the type of false content represented (i.e., a

belief versus a photograph/map). Stories were followed by a true/false question that referred either to the situation in reality or to the false representation. We use the false belief task localizer task from Dodell-Feder and colleagues (2010).

Task two will be a social why/how task. The aim of the task is to identify human brain regions associated with answering why and how questions about human behavior. Participants will be prompted with a question, followed by pretested photographs of naturalistic human behaviors. After observing the image, participants are to determine “Yes/No” to answer the prompted question.

The questions used in the Yes/No Why/How Task will be used to manipulate and measure attention to “why” versus “how” for actions and expressions. All questions began with the string “Is the person”. The questions used in the task is presented in the table below. The task is the replicate the findings from Spunt and Adolphs, therefore, we use the exact same task design that is shared by the authors.

Task three will be a Posner task. The aim of this task is to investigate visual search facilitation with visual cues. Participants will be asked to look for a target and identify which direction it was presented, left or right, as fast as they can. In addition to the target, cues will be presented to facilitate the visual search process. Cues will be in the form of colored squares, which will indicate the location of the upcoming targets. We hypothesize that congruent trials will help visual search where people will be faster at identifying the target. This study will be a replicate of the Posner cueing task (1984).

Task four will be a memory task; specifically, an episodic memory retrieval task. Participants will view a number of black-and-white drawings. They will be asked to memorize the items ("encode"). Afterwards, they will be shown a number of drawings - some will have been presented during the "encode" stage, some will be novel drawings. Participants will determine whether they saw the item before or not. Responses will be collected with a button press.

Task incentive Participants will receive extra payment based on their task performance, in order to incentivize their behavior. Payment will range from $0-$20.

After the scan participants will be taken to a behavioral testing room where they will complete the recall memory task. Next, they will be debriefed and compensated for their participation.

Session #	Procedures/Tools	Location	How much time the visit will take
Session 1	• Task practice and preparation for MRI scanning • fMRI scanning • Scheduling next visit	-Moore Hall -Dartmouth Brain Imaging Center	2.75 hours

Session 2	• Preparation for fMRI scanning • fMRI task • Scheduling next visit	-Moore Hall -Dartmouth Brain Imaging Center	2.75 hours
Session 3	• Task practice and preparation for fMRI scanning • fMRI task • Scheduling next visit (10 min)	-Moore Hall -Dartmouth Brain Imaging Center	3.25 hours
Session 4	• Preparation for fMRI scanning • fMRI task • Debriefing and payment	-Moore Hall -Dartmouth Brain Imaging Center	3 hours

XII. SPECIMEN MANAGEMENT

N/A

XIII. DATA MANAGEMENT

Data Security Risk = Level 2

Strict standards of confidentiality are maintained for each experiment and any follow-up procedures. MRI data and questionnaire data will be electronically stored and analyzed using ID codes. If the data are published subjects will remain anonymous in all publications. Data will be stored indefinitely and will not be shared with other investigators without explicit permission from the Dartmouth College IRB.

Basic identifying information (name, address, phone number/email address) is collected from every research participant for the purpose of research logistics (schedule visits, etc.) and mailing of the radiological review letter, as appropriate.

MRI data will be stored according to standard DBIC data management procedures. MRI images will be housed on a Dartmouth server.

It is now common practice in MRI research to store de-identified data and use them for future research. It is increasingly common for NIH-funded studies to require public sharing of de-identified data in a public NIH-sponsored or researcher-maintained data repository, as they are a valuable resource for large-scale scientific efforts. Our analysis plan includes sharing and reuse of de-identified data after the end of the study period. Upon the completion of the data and sharing of de-identified data, codes linking participants' data to identifying information will

be removed and potential features (e.g., facial information) will be removed from structural MRI scans, so that the data shared/reused are anonymized.

XIV. WITHDRAWAL OF PARTICIPANTS

Participants will be ruled ineligible for further participation if pain thresholds fall outside a safe range and/or scientifically useful range. Participants who are ruled ineligible for subsequent studies will be compensated for their time at the normal rate but will not be further contacted or invited to participate in subsequent study opportunities.

Participants may withdraw voluntarily from a study at any time. Participants may either withdraw from a particular experimental session, or request that they be removed entirely from the laboratory subject pool. In the latter case, all of the participant's partial or full data will be destroyed immediately.

XV. RISKS TO PARTICIPANTS

1) Burn due to thermode malfunction: There is a very slight risk to the participant in case of thermode malfunction. Thousands of participants are tested using this equipment (Pathway system, Medoc, Inc.) annually throughout the U.S., usually without adverse events. However, several reported cases of thermode malfunction have occurred in the past 5 years (four cases, to our knowledge), which have resulted in minor 1st or 2nd degree burns. The manufacturer (Medoc, Inc.) has responded to these reports by building in enhanced hardware safety mechanisms; thus, we do not anticipate a substantial risk. The PI's lab has conducted experiments on approximately 400 subjects at Columbia University and over 400 at UC-Boulder with no adverse events. Although it is not possible to precisely determine the probability of a burn, we estimate based on our prior experience that it is considerably below 1%. We also note that the vast majority of potential burns that could potentially result from equipment malfunction would consist of minor blistering that would heal naturally without any treatment within several days.

2) Safety concerns in MR environment:

- The magnetic field of the MR environment has the potential to cause burns or bodily injury if ferrous metal objects are implanted in the body, or if personal articles containing ferrous material are brought into the environment.
- The risk of MRI to pregnant women and fetuses is currently unknown.
- The MRI may cause discomfort due to scanner noise.
- There may be some discomfort from lying still and in one position for a long time
- Peripheral nerve stimulation (PNS/tingling). At sufficient exposure levels, peripheral nerve stimulation is perceptible as "tingling" or "tapping" sensations. PNS symptoms will usually subside shortly after the scan is completed.
- Subjects may experience nervousness and/or claustrophobia during the MRI. While generally safe, it is not known whether an MRI would harm a fetus.
- There is a risk that the image will reveal an observation concerning an individual research participant that has potential clinical importance but is beyond the aims of this protocol. In the event of the confirmation of a significant anomaly in a participant's brain image, this information will likely be distressing to the participant.
- Participants will be screened for the possibility of being or becoming pregnant during the online pain screening (Protocol 10-0243) prior to participation.

3) Psychological discomfort: Studies involving administration of pain by definition require the induction of psychological discomfort, so this is an unavoidable risk of participation. However, as described above, the level of pain administered is calibrated to always be within participants' tolerable level, and participants are informed prior to each session involving pain that they are free to discontinue the experiment (e.g., removing the thermode) at any time should they wish.

As the emotional stimuli (audio narratives, and movie) may evoke emotional reactions, participants may experience some emotional distress. Participants will be informed about these possible reactions upfront and can quit the study at any point by just discontinuing the study. We predict a low probability, magnitude, and duration of psychological discomfort to emotional stimuli.

4) Cognitive task risks: There are no known risks for completing the various cognitive tasks. If any issues arise, participants are free to discontinue the task at any time.

There are no known less risky alternatives to the use of any of the procedures proposed in these experiments that would provide comparable scientific information.

XVI. MANAGEMENT OF RISKS

1) Burn due to thermode malfunction: Pain stimulation will always occur within well-tested and verified parameters (Protocol # 31999, Attachment "stimulation_guidelines"). The equipment used is widely available and includes several built in safety mechanisms including an auto-shutoff as well as maximum temperature restrictions. Additionally, participants are given an emergency shut-off button that they can press at any time and instantly stops heat delivery. The equipment is regularly maintained and tested by our trained personnel. All personnel who use the equipment are trained on equipment procedures.

2) Safety concerns in MR environment: This protocol will be performed using an MR scanner employing pulse sequences and hardware that have been approved by the FDA for human clinical use. The field strength is 3 Tesla and all relevant operating characteristics (RF power deposition, rate of change of the field gradients, coil design) fall within the limits of FDA guidelines for NMR exposure. Participants will be carefully screened to exclude those who may have metal in or on their bodies that cannot be removed (e g., bullets, metal filings, body piercings, etc.). MR Facility rules strictly forbid staff from entering the magnet room carrying metal objects. The risk of claustrophobia is minimized by screening subjects for self-reported claustrophobia and making sure the subject is lying comfortably with head and neck supported and providing ear protection with headphones, a mirror to see out, a button to signal distress, and an intercom. Scan time will be kept to a minimum. If they are unsure about whether or not they may be pregnant, female participants will be given the opportunity to complete a urine pregnancy test immediately before the scanning period, and those with a positive result will not be scanned. With regard to PNS, participants are given a squeeze ball to use in case of an emergency. They are informed that if they experience PNS related sensations or are otherwise uncomfortable, they can alert the MRI technologist via the squeeze ball and the technologist will stop the scan immediately.

3) Incidental findings: MRI data collection performed at the Dartmouth Brain Imaging Center (DBIC) is not optimized for use as a diagnostic medical tool. However, in the event of incidental findings, DBIC administration will be contracted due to their established protocols to handle such circumstances.

4) Psychological discomfort: Participants are clearly informed of this risk prior to participation during the instruction period, and the ability to tolerate heat pain is explicitly listed as one of the first screening questions. There is virtually no possibility of long-term psychological distress or unanticipated psychological discomfort that exceeds the proximal response to pain, as the amount of pain delivered is comparable to or less than that experienced in many day-to-day situations (e.g., holding a hot cup of coffee). However, they will be encouraged to inform the experimenter if they are uncomfortable with the nature of the stimuli. There is no evidence for long-term psychological distress or discomfort associated with viewing emotional videos, listening to audio narratives, or completing the cognitive tasks. If participants experience any lasting negative effects related to the emotional content of this study, they will be encouraged to contact the Principal Investigator, Dr. Tor Wager, at tor.d.wager@dartmouth.edu. He will discuss options for counseling referrals and provide a referral. The cost of any follow-up counseling, should any be required, would be borne by the participants and/or their insurance provider. The participant will be informed that neither the study team nor any of its individual members will be responsible for follow-up treatment.

XVII. POTENTIAL BENEFITS

There is no direct benefit to the subject from this screening protocol save for the knowledge that their participation may help scientists understand the psychological and neural mechanisms involved in pain processing and self-regulation of brain activity.

XVIII. PROVISIONS TO MONITOR THE DATA FOR THE SAFETY OF PARTICIPANTS

In the event that a medical professional determines that tissue damage occurred due to study procedures, the study will be put on hold until the cause of the issue is determined, the IRB will immediately be notified via email, and a formal report will be filed with the IRB by one of the study co-investigators.
The MRI technologists are not trained to identify potentially significant clinical anomalies in the brain images. Should the MRI technologist notice something he or she believes to be a potential anomaly in a brain image, he or she will follow the procedure noted in section XVI to ensure appropriate radiological review. The participant will be contacted if the radiologist recommends a scan to determine the clinical significance of any anomaly. Additional action will be taken to ensure the subject's personal safety as per recommendations made for that specific subject.

The research coordinator will conduct monthly reviews of the safety information for this protocol to determine if any changes need to be made.

XIX. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Observations or data collection will occur in a private laboratory setting. We do not anticipate any issues for each participant's ability to interact with researchers and provide information about themselves.

XX. MEDICAL CARE AND COMPENSATION FOR INJURY

In the event that a participant has experienced a burn, they will be directed to rinse the affected location under cool water for several minutes, and to seek independent medical attention if symptoms persist after a day or two. If there is any unexpected medical issue, we will call 911. No on-site medical care will be provided, and no compensation is available in the event of research-related injury. This is clearly explained on the informed consent sheet participants must agree to before they may participate in any study involving pain

XXI. COST TO PARTICIPANTS

Participants who travel to the research site with their own vehicle will not be compensated for gas or wear and tear. However, we will reimburse participants for, or cover, all other expenses associated with participation, such as parking. Participants who must travel a long way to reach the research site (> 30 minutes each way) will be compensated for travel time at the normal rate, to a maximum of 2 hours for a round trip.

XXII. DRUG ADMINISTRATION

N/A

XXIII. INVESTIGATIONAL DEVICES

N/A

XXIV. COLLABORATIVE STUDIES

All laboratory procedures will be performed at the Dartmouth College Brain Imaging Center in Hanover, NH. An IAA will be in place with John's Hopkins University (JHU) ceding IRB review to Dartmouth. Only de-identified data will be sent to JHU as per the coded agreement form. The oversight plan for PI Tor Wager can be found in attachment "PI_Oversight_Plan_Att10."

XXV. SHARING OF RESULTS WITH PARTICIPANTS

There are no plans to share the results of this study with participants as a standard procedure. Participants or any other individuals who inquire about the results of the study at a later date will be informed of any publications that have resulted from the study.

Participants may be given a copy of their structural brain scan on CD, if they choose to receive a copy. They will be required to sign an Image Release Form if they take a copy of their brain scan (see attached), to ensure they understand that the scan was not collected for medical purposes.