Analysis Plan

I. Neuroimaging analysis

The steps of our neuroimaging analyses are listed in figure 1. Our main questions are focused on investigating brain mediators that mediate the relationship between cue to actual ratings; in order to address these questions, we first start out by modeling the signals and constructing parametric modulation maps. We plan to implement a less commonly used approach, discovery validation analysis, to model the BOLD signal (i.e., fixed-epoch model/variable-epoch model/flexible basis function model) and identify the best fitting model (**Analysis 1**). Using the identified HRF model, we will conduct a parametric modulation analysis and model the stimuli with parametric modulators, executed in four different versions (univariate/multivariate x domain-general/specific; **Analysis 2**). After constructing the parametric modulation maps, we now are able to investigate our central question of brain mediators that mediate the relationship between cue to actual ratings, where we use the parametric modulation maps as inputs for the two-path mediation analysis. The purpose of this two-path mediation analysis is to search for the two brain mediators that mediate the relationship between cue and actual rating (**Analysis 3.1**) Utilizing these found mediators, we will conduct a multi-path mediation analysis, which will identify the path between cue to expectation to actual stimulus experience to actual ratings (**Analysis 3.2**). Once the mediator brain maps are discovered, we plan to run a variance decomposition analysis, in order to identify how much variance is explained by the domain-general mediator map versus the domain-specific mediator map. The purpose is to identify the proportion of variance explained by domain-general vs. domain-specific processes (**Analysis 4**). Relatedly, we will also conduct a Bayesian model selection analysis to identify whether the voxels/patterns are better explained by the domain-general model or the domain-specific model (**Analysis 5**). Lastly, separate from the mediation analysis, we plan to analyze the stimulus epoch and classify them with pre-identified biomarkers (**Analysis 6**).

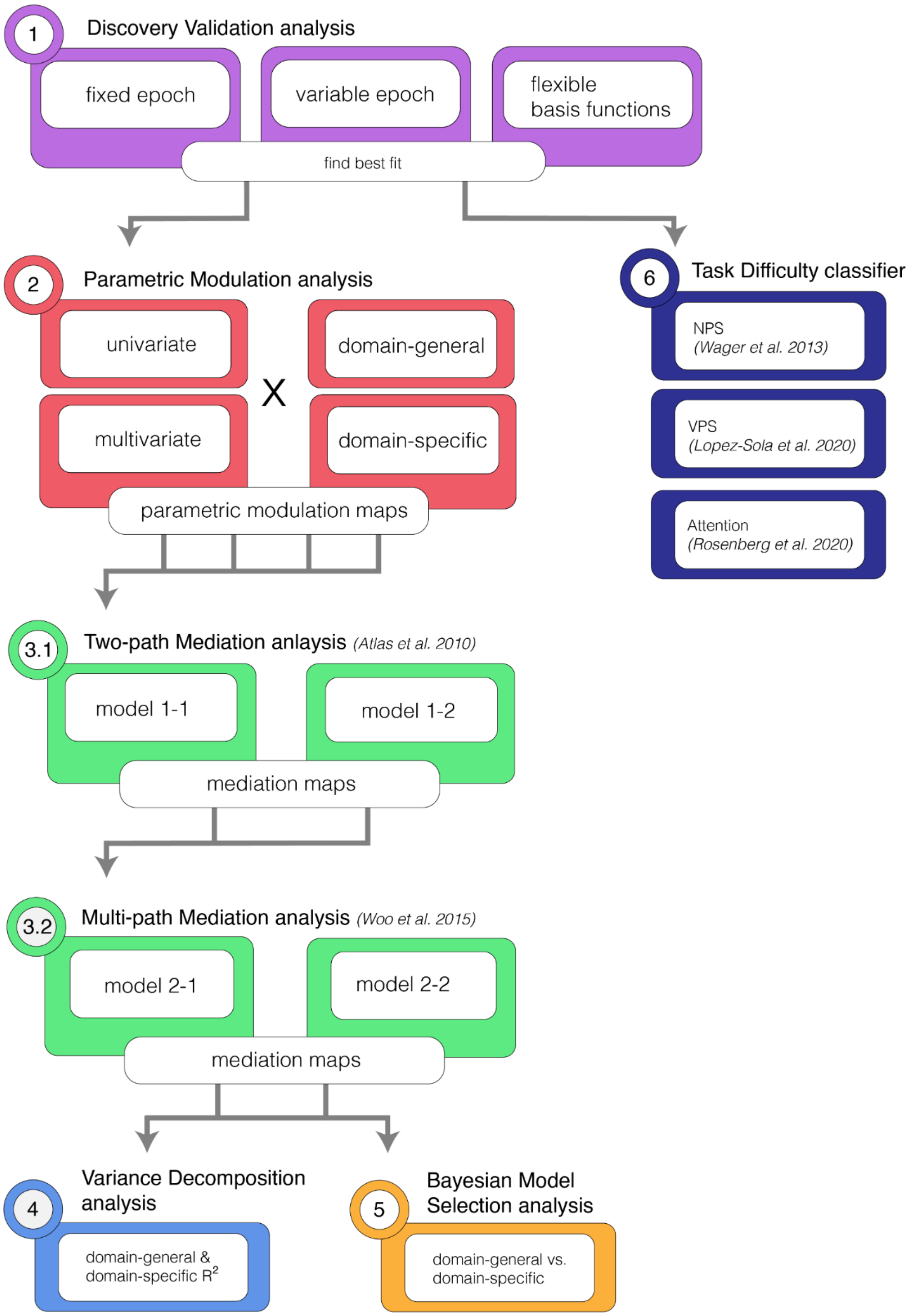


Fig 1. steps of neuroimaging analysis.

† **Regressor Glossary:** combinations of these regressors will be used for each model appropriately.

First-level regressors

- epoch of cue period (“**CUE**”)
  - Parametric modulator: cue [high=1; low=-1] (“**CUE_pm-cue”**)
  - Parametric modulator: expect rating (“**CUE_pm-expect”**)
- epoch of expect rating period (“**RATING_EXPECT**”)
- epoch of stimulus period (“**STIM**”)
  - Parametric modulator: cue [high=1; low=-1] (“**STIM_pm-cue”**)
  - Parametric modulator: actual rating (“**STIM_pm-actual”**)
  - Parametric modulator: expect rating (“**STIM_pm-expect”**)
  - Parametric modulator: stimulus intensity level (“**STIM_pm-taskdiff”**)
  - Parametric modulator: M2 mediator voxel-wise average (**“STIM_pm-M2”**)
- epoch of actual rating period (“**RATING_ACTUAL**”)

† As for the duration of the actual and expect rating regressor, we will use the reaction time of the rating response.

First level covariates

- Motion nuisance covariates (24 motion covariates)

2nd-level regressors

- mean-centered cue effect on actual ratings from behavioral analysis (19.1)
- mean-centered stimulus intensity effect from behavioral analysis (19.1)
- Revised Self-Monitoring scale
- Gender

1. **Neuroimaging** Discovery validation analysis

a) **Main question**: what is the best model for fitting the BOLD signal during the expectation phase and stimulus experience?
The canonical hemodynamic response function (HRF) makes several assumptions including that the time course of the evoked afferent signal is known and that this signal coincides throughout the brain. However, these are strong assumptions; the HRF can differ depending on different types of stimuli. Therefore, we will conduct three models of BOLD signal fitting and determine the best fit.

b) Method:

- Fixed epoch model
  - description: model the epoch using each onset time and the duration of the epoch. For example, when modeling a fixed CUE epoch, we would use the onset of the cue period and model the duration as the cue onset presentation time (1s).

- Variable epoch model
    - description: model the epoch from the beginning of the cue period until the end of the expect rating. For example, when modeling a variable CUE epoch, we would use the onset of the cue period, but model the duration of the cue AND expect rating phase, as the psychological process of expectations may extend beyond the cue epoch of 1s, up until the stimulus epoch. While the total duration of cue and expect rating differs due to jitters in between, the average duration would amount to 11s.
- Flexible basis function:
    - description: model the BOLD signal as a weighted combination of simple basis functions.

We plan to determine the winning model using bayes factors.

2. **Neuroimaging** Parametric modulation analysis

a) **main question:**
- Is CUE_pm-expect significant? — during the cue period, is there a univariate activation/multivariate pattern modulated as a function of expectation rating?
- Is STIM_pm-cue significant? — during the stimulus period, is there a difference in univariate activation/multivariate pattern for trials with higher cues?
- Is STIM_pm-actual significant? — during the stimulus period, is there a univariate activation/multivariate pattern modulated as a function of actual ratings?
- Is STIM_pm-expect significant? — during the stimulus period, is there a univariate activation/multivariate pattern that activates as a function of expectation ratings?
- Is STIM_pm-level significant? — during the stimulus period, is there a univariate activation/multivariate pattern that activates as a function of stimulus intensity?

b) **method**: types of parametric modulation analysis

Univariate vs. multivariate (number of dependent variables)
- For the univariate analyses, we estimate the parametric modulation maps via bootstrapping methods.
- For the multivariate analyses, we estimate the parametric modulation maps via stratified 10-fold cross validation.

Domain-general vs. domain-specific (domain)
- For the domain-general model, we include all trials from all three tasks.
- For the domain-specific model, we include task-specific trials from each task.

We will conduct 2 (number of dependent variables) x 2 (domains) parametric modulation analyses for the 5 aforementioned questions.

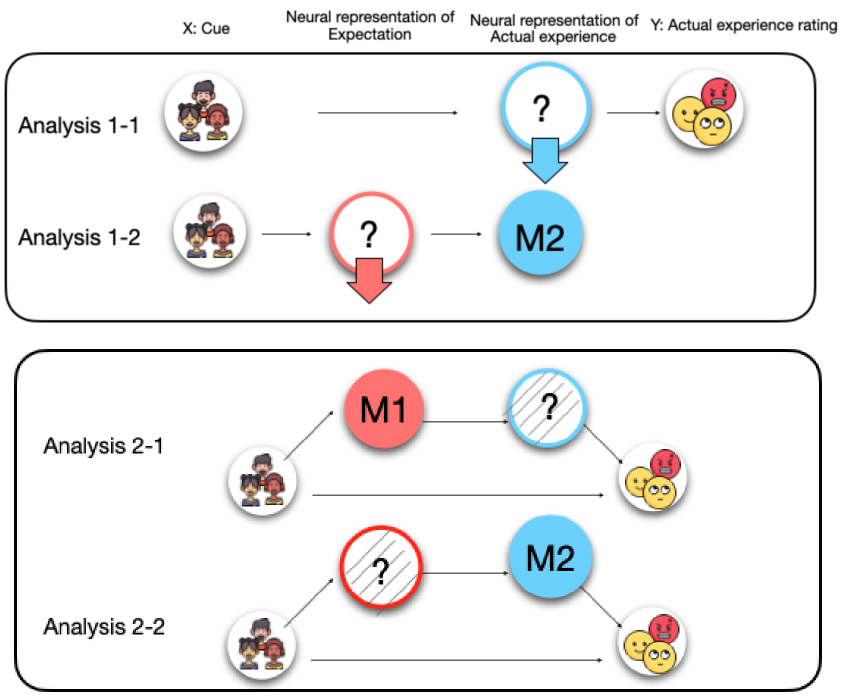
3. **Neuroimaging** Mediation analysis (two-path, then multi-path)

a) **main question:** Do expectations mediate actual experiences? (see 19.3.1)
- Is the stim period mediator significant? — which voxels/patterns significantly mediate the relationship between cue and actual rating?

- Is the cue period mediation significant? — which voxels/patterns mediate the relationship between cue and actual experience voxel/pattern?

b) **<u>method:</u> (two-path, then multi-path)**

We plan to identify the neural representation of a) expectations and b) experiences of pain, vicarious pain and cognitive effort, which mediate the relationship of cue and actual ratings. “Experience” refers to the stimulus period where participants are delivered pain/vicarious pain/cognitive stimuli; “actual ratings” refers to the subsequent ratings completed after each stimulus period, i.e. self reported “experience”. In order to conduct a multi-path analysis, a two-path mediation analysis is necessary to identify potential mediators. The figure illustrates the two-part analysis.



3.1. Two-path mediation analysis

First, We will conduct a two-path mediation analysis to identify the two neural representations via a whole brain search.

Analysis 1-1.

During the stimulus period, **i**s there a neural representation of actual experience that mediates the relationship between cue and actual ratings? We denote the identified neural representation of actual experience as “M2”.

Analysis 1-2.

Using the identified actual experience representation (M2) from analysis 1-1, we next explore the neural representation of expectancy effects.

Main question: During the cue period, is there a neural representation of expectation that mediates the relationship between cue and actual experience representation? We denote the identified neural representation of expectation as “M1”.

3.2. Multipath mediation analysis

With the identified representation of expectation (M1) and actual experience (M2), we conduct a multi-level multi-path mediation analysis (Woo et al., 2015).

Analysis 2-1.

Using the identified neural representation of expectations (M1) from analysis 1-2, we search for patterns that mediate cue to M1 and actual experience ratings. In other words, we fix cue, M1, and ratings, while searching for the neural representation of actual experiences.

Analysis 2-2.

Using the identified neural representation of actual experience (M2) from analysis 1-1, we search for patterns that mediate cue to M2 and actual experience ratings. In other words, we fix cue, M2, and ratings, while searching for the neural representation of expectations.

c) Types of mediation analysis

Univariate vs. multivariate (number of dependent variables)

- For the univariate analyses, we estimate the mediation maps via bootstrapping methods.
- For the multivariate analyses, we estimate the mediation maps via stratified 10-fold cross validation.

Domain-general vs. domain-specific (domain)

- For the domain-general model, we include all trials from all three tasks.
- For the domain-specific model, we include task-specific trials from each task.

We will conduct **2** (number of dependent variables) x **2** (domains) mediation analyses for model 1-1, 1-2, 2-1, and 2-2.

Appendix 1 for model 1-1. Example of a two-path mediation analysis for a univariate, domain-general analysis

- **Main question**: Which voxels mediate generalizable cue effects on actual experience? (i.e. searching for M2)
- **How is the mediation map defined?**
  - We multiply path a and path b maps, i.e. indirect effect ab (Mackinnon and Dwyer 1993), in order to derive the M2 map.

- ○ **Definition of path a**: parametric modulation map of stimulus period, modulated with cue (**"STIM_pm-cue")**
    - model regressors includes: 1) CUE, 2) RATING_EXPECT, 3) STIM, 3-1) **STIM_pm-cue**, 4) RATING_ACTUAL
  - ○ **Definition of path b**: parametric modulation map of stimulus period modulated with actual ratings ("**STIM_pm-actual**") controlling for cue (i.e., while turning off the orthogonalization in order to run a multiple regression;
    - model regressors include: 1) CUE, 2) RATING_EXPECT, 3) STIM, 3-1) STIM_pm-cue, 3-2) **STIM_pm-actual**, 4) RATING_ACTUAL
- **Resulting derivatives**: One domain-general M2 map (each M2 map will be averaged across voxels, so that we have one value per trial) These values will later be used as the outcome variable in model 1-2.

Appendix 2. Example of a two-path mediation analysis for a multivariate, domain-specific analysis (model 1-2)

- **Main question**: Which patterns mediate the effect of pain cue on actual pain brain pattern? (i.e. searching for M1)
- **How is the mediation map defined?**
  - ○ We multiply path a and path b maps, i.e. indirect effect ab (Mackinnon and Dwyer 1993), in order to derive the M1 map.
  - ○ **Definition of path a**: parametric modulation map of cue period, modulated with cue ("**CUE_pm-cue**")
    - model regressors include: 1) CUE, **1-1) CUE_pm-cue**, 2) RATING_EXPECT, 3) STIM, 4) RATING_ACTUAL
  - ○ **Definition of path b**: parametric modulation map of cue period, modulated with averaged voxel-wise value of M2 map
    - model regressors include: 1) CUE, 2) RATING_EXPECT, 3) STIM, 3-1) STIM_pm-cue, **3-2) STIM_pm-M2**, 4) RATING_ACTUAL
- **Resulting derivatives**: One pain-specific M1 map

4. **Neuroimaging** Variance decomposition analysis

a) **Main question:** In a given epoch, how much variance is explained by the domain-general vs. domain general maps?
b) **Method:** We plan to conduct a variance decomposition analysis (benchmarking the commonality analysis from Nimon *et al.*, 2008) with the domain-general and domain-specific mediation maps, uncovered from the multi-path mediation analysis (**Analysis 19.2.3.2**). We partition each participants' variance explained on actual ratings, which results in four components: 1) unique variance from domain-general model, 2)

unique variance from domain-specific model, 3) shared variance between domain-general and domain-specific model, 4) unexplained variance.

5. **Neuroimaging** bayesian model selection

a) **Main question:** Amongst the domain-general and domain-specific mediators, which is the winning model?
Using the domain-general and domain-specific mediator maps from the cue and stimulus period, we intend to identify the winning model that best explains expect and actual ratings.
b) **Method**: Bayesian model selection and exceedance probability for identifying the best models, i.e. domain-general vs. domain-specific.

6. **Neuroimaging** task difficulty classification

a) **Main question:** Do certain biomarkers predict task difficulty? Also, can biomarkers from a particular domain (e.g. pain classifier) predict task difficulty in a different task domain (e.g. trials from cognitive task)?
While the scope of the project focuses on expectations and modulations in experiences, we also plan to replicate prior findings on biomarkers on pain, vicarious, and cognitive stimuli. The plan is to use previously identified biomarkers and classify stimulus period trials from the three domains of pain, vicarious, and cognitive.
b) **Method:** Apply the following weight maps from each biomarker test classification accuracy
    - Pain biomarker (NPS; Wager et al. 2013)
    - Vicarious biomarker (VPS; Lopez-Sola et al. 2020)
    - Cognitive biomarker (Rosenberg et al. 2016)

II. Behavioral analysis

Regressor Glossary:

Outcome variable: actual rating and expect rating

Fixed-effect regressors

- Cue [high = 0.5; low = -0.5]
- Stimulus intensity linear: [high = 0.5; med = 0; low = -0.5]
- Stimulus intensity quadratic: [high = -0.33; med = 0.66; low = -0.33]

Random-effect regressors

- subjects

Main question:

- Is there a main effect of cue on expect rating — i.e. do cues modulate expectations?
- Is there a main effect of cue on actual rating — i.e. do cues modulate actual experiences?
- Is there a main effect of stimulus intensity on actual rating? — i.e. Is there a difference in actual ratings across the three levels of stimulus intensity?

Method: Hierarchical linear modeling