# Separating within-subject and individual-difference predictions with multilevel MVPA

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## INTRODUCTION

Multivariate modeling of brain imaging data, or multivariate pattern analysis (MVPA), can capture useful brain representations of theoretical constructs and clinically meaningful outcomes. None of the methods which fall under this broad methodological umbrella take into account hierarchical structure in brain imaging data (e.g. subjects or imaging sites). Here we present the first multivariate pattern analysis technique which formally addresses this problem, multilevel principal component regression, and demonstrate its application capturing meaningful within subject variance and individual differences in two published datasets.

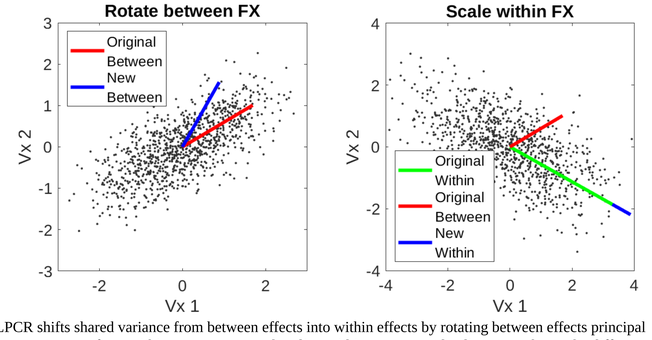
## METHODS

fMRI Study 1 – a study of ethnic differences in pain sensitivity
- N = 85 subjects, 1/3 Hispanic, 1/3 non-Hispanic white, 1/3 African American
- ~30 noxious thermal stimuli/subject, ~23 aversive auditory stimuli/subject
- Thermal stimulus: 47C, 48C, or 49C, short (8s), long (11s) or offset (2s at target T, 1s at 1C higher, 8s back at target T), to left volar forearm, rated for intensity
- Auditory Stimulus: 3 intensities of nails on chalkboard, or sounds of attacks, screaming or crying. 8s each, rated for intensity.

fMRI Study 2 –designed to test sensitivity and specificity of MVPA methods in distinguishing pain vs. warmth
- N = 32 subjects, ~45 pain stimuli/subject, ~45 nonpainful trials/subject
- Thermal stimulus: 44.3C, 45.3C, 46.3C, 47.3C, 48.3C, 49.3C x 7.5s to left volar forearm, rated for intensity

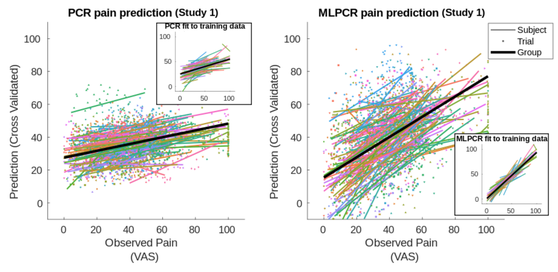
Multilevel MVPA – Multilevel Principal Component Regression (MLPCR)
- Input: "Beta series" GLM coefficient estimates
- Decompose outcome and beta coefficients into between and within maps using ANOVA principles
  - Between effects: average of within subject variance
  - Within effects: residual variance after subtracting out between effects
- Perform PCA separately on each variance component, retain a subset of components
- Orthogonalize between and within effects.
- Model outcome using between variance modeled as a fixed effect, and within variance modeled with random effects.
- Project fixed effect estimates (including "second level" group estimates of random effects) back to voxel space. Yields separate between/within maps.
- Voxel-wise sum of between and within patterns yields full MVPA result.
  $Pattern^{Total} = Pattern^{within} + Pattern^{between}$

Outcome measures
- 5-fold cross validation used to estimate prediction generalization performance



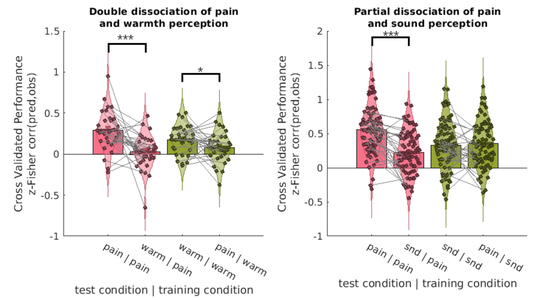

MLPCR shifts shared variance from between effects into within effects by rotating between effects principal components away from within components, and scaling within component loadings to make up the difference.

## 1 MLPCR separately models between and within effects for a predictive advantage



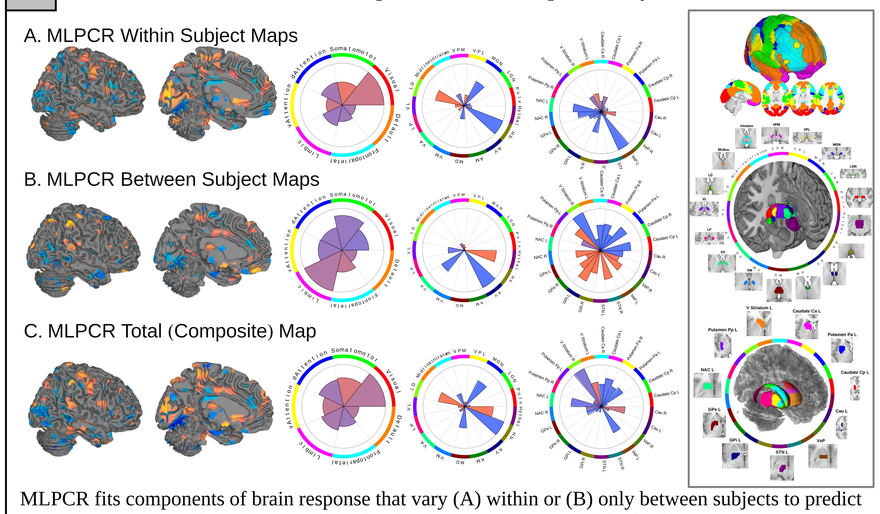

MLPCR (right) models between effects and random within effects for a unique advantage over other MVPA methods like PCR (left). Model fits to training data (inserts) show how multilevel modeling confers intrinsically greater capacity to capture between subject differences (tighter fit of slopes to mean slope), while 5-fold cross validated predictions show models fit within this framework generalize well to novel unseen data.

## 2 MLPCR is sensitive and specific to target outcomes



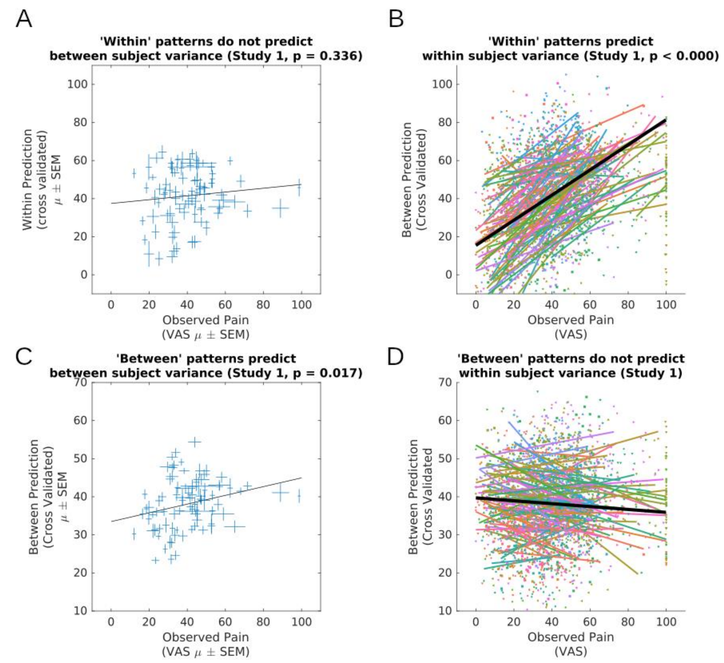

MLPCR viability is demonstrated by a double dissociation of pain from warmth (study 2) and a partial dissociation from sound (study 2). Models trained on pain predict pain better than warmth or sound (both $p < 0.001$, paired t-test), and those trained on warmth predict warmth better than pain ($p<0.05$). Points are within subject correlations.

## 3 Between and within effect maps facilitate interpretability in MLPCR




MLPCR fits components of brain response that vary (A) within or (B) only between subjects to predict a target outcome. Study 1 illustrates how this facilitates interpretation of a final pain predictive map (C): within subject predictive variance shows large sensory contributions (left circle plot, occupancy of cortical resting state network parcels indicated), while (B) shows that between subject predictive variance is largely limbic and shows highly specific recruitment of the basal ganglia (right circle plot; center circle shows how much of the pattern occupies each thalamic nucleus). Much of this is obscured in their composite (C). Voxel $p<0.05$ (bootstrap, n=1000 ). Insert: parcellations reference atlases.

## 4 A double dissociation of between and within subject predictions is possible using orthogonal elements of MLPCR models




Study 1 illustrates how separate components of composite MLPCR model predict either within subject variance or between subject outcome variance. (A) Within subject variance maps do not predict between subject variance in pain outcome, but do predict within subject pain variance (B). Conversely, between subject variance maps predict between subject variance in pain report (C), but do not predict within subject variance above and beyond an intercept term (D). SEM indicated in (A) and (C) by cross arm length.

## CONCLUSIONS

- Intermixing latent within and between subject factors obscures distinct underlying mechanisms (e.g. stimulus driven vs. predispositions).
- MLPCR retains the task specificity of traditional MVPA methods, but also adds sensitivity and specificity for latent factors related to either individual differences or within subject variation.
- Meaningful contributions of between and within subject factors can be measured (or predicted) at the level of the single stimulus event.
- This enables unique mechanisms to be more precisely measured and studied.

Matlab implementation available at
https://www.github.com/canlab/CanlabCore/CanlabCore/mlpcr

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