Evaluating the Potential for Brain-based Classification of Chronic Pain

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Introduction

Past attempts to develop brain-based biomarkers of chronic pain have shown promise using machine learning (73-91% accuracy)[1] However, many biomarker studies are hindered by small datasets (n=~100), limiting the validation and generalization of the markers[2]. **Here, we aim to train a brain-based biomarker in a large cohort (UKBiobank: n = 37,781) able to distinguish pain-free controls from individuals reporting various chronic pain phenotypes.**

Methods

Data:

- A total of 37,781 individuals (Healthy Controls=24,341, Chronic Pain=13,440, 54% F) were obtained from the UKBB

Magnetic Resonance imaging:

- White matter tract diffusivity, structural T1 imaging, and rsfMRI data were concatenated across all subjects (**Fig. 1a**) to derive a feature space of multi-modal brain metrics for machine learning.
- Two features variants were used in the analysis: 1) raw (confound-unadjusted) features 2) features with confounds (age, sex, and head motion) regressed out.
- Machine learning models were trained on the resulting features to distinguish subjects reporting various chronic pain phenotypes (**Fig. 1b**) from pain-free.

Machine Learning Pipeline:

- The dataset was divided into a train set (70%) and a validation set (30%) and nested cross validation implemented to tune, train, and validate a logistic regression model. Results are reported using ROC-AUC score.
- Normalized odds—ratios were computed across 5 psychosocial health dimensions and each chronic pain phenotype.

Statistical Analyses:

- Partial correlations controlling for age, sex, and head motion were computed between cortical thickness subcortical volume, and resting state functional connectivity and number of chronic pain sites.
- Results are reported using brain maps corrected for false discovery rate (Benjamini-Hochberg method)

Results

Figure 1. Model Variables

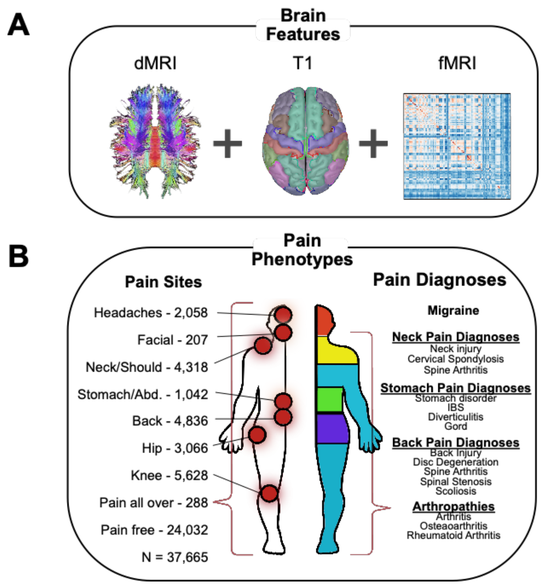


Figure 2. Machine Learning Analysis

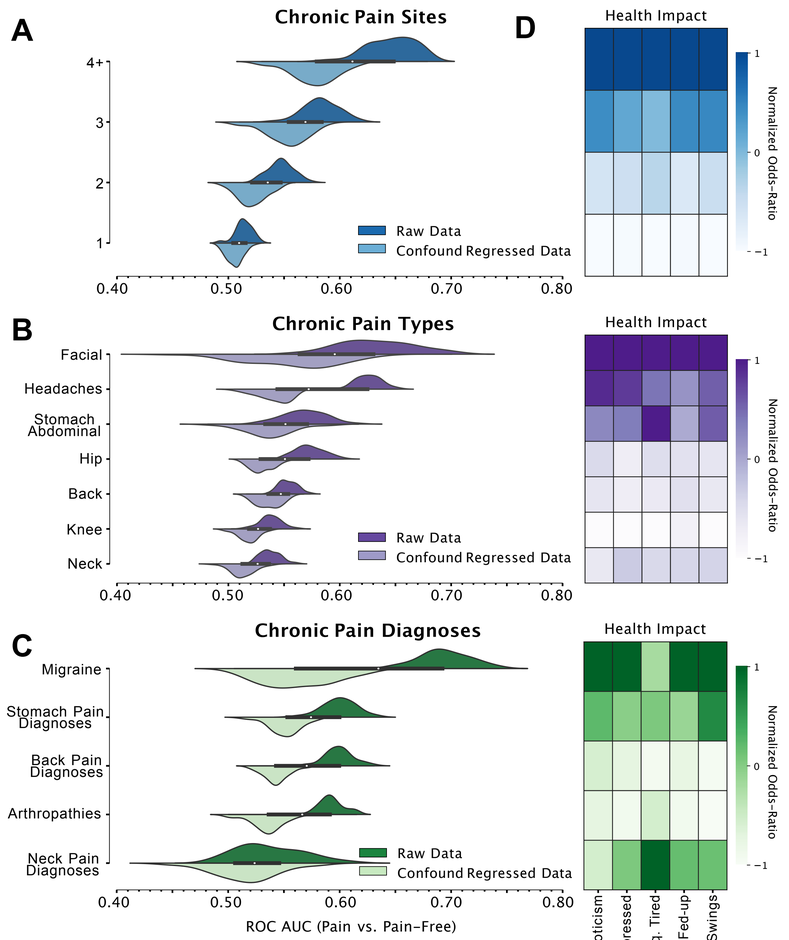
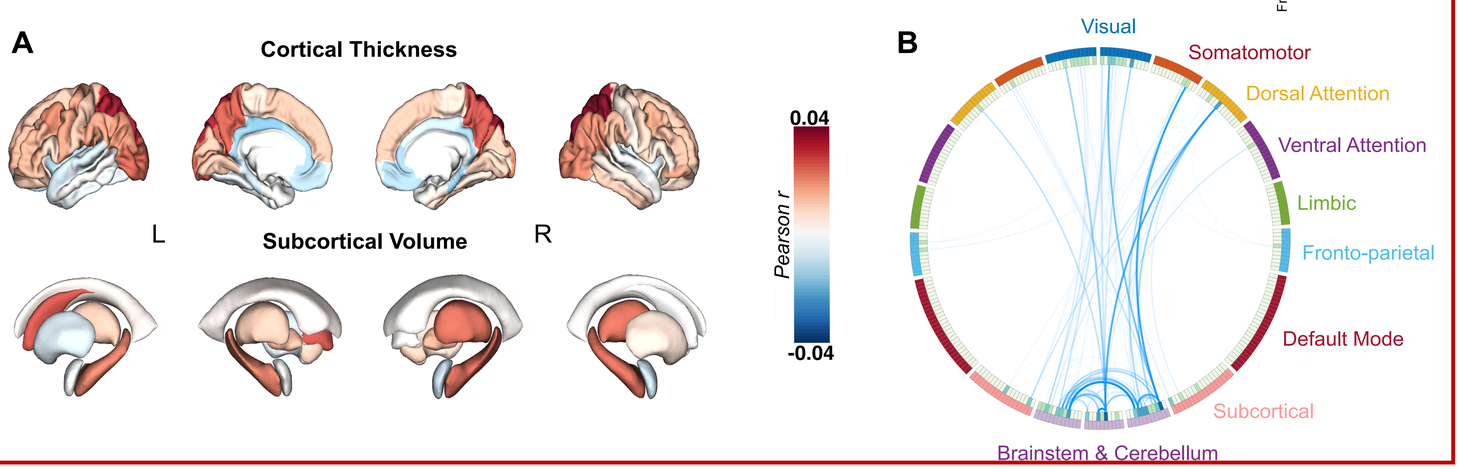


Fig. 1 ***(top).*** **Brain features and pain phenotypes used in analysis. A.** Measures derived from multi-modal brain imaging used in analyses. **B.** Pain phenotypes used as target variables for machine learning analysis including site of pain, number of pain sites, and pain diagnosis.

Fig. 2 ***(right).*** **Validation performances (ROC-AUC) from discriminating subjects reporting various pain phenotypes from pain-free controls based on multi-modal brain data and odds-ratios between psychosocial health variables and pain phenotypes. A.** Discrimination performance improves as models are trained on subjects with increasing numbers of pain sites. **B.** Performance associated with subjects reporting non-musculoskeletal pain types (i.e., pain of the face, head, or stomach/abd.). **C.** Performance associated with subjects reporting non-musculoskeletal pain diagnoses (i.e., migraine). **D.** Discrimination performance associated with the odds of expressing a worsened psychosocial health impact across all pain categories.

Fig. 3 ***(bottom).*** **Partial correlation statistics between structural and functional brain imaging metrics and number of chronic pain sites, controlling for age, sex, and head motion. A.** Association with cortical thickness and subcortical volume. **B.** Top 5% significant correlations of resting state functional connectivity edges.

Figure 3. Univariate Analyses



Discussion

1) Multivariate pattern classification applied to multi-modal brain data reveal that ***chronic pain is most neurologically predictable where it is most psychosocially burdensome, at the cost of increased confounding***.
2) Robust brain-wide statistical differences exist in chronic pain at a population level. We observed increased cortical thickness in the parietal lobules, increased subcortical volume in the putamen and caudate, and reduced connectivity in the brain stem and cerebellum associated with increased spreading of chronic pain.
3) Future studies should consider the cognitive, affective, and physical elements associated with a pain state in order to progress toward development of an objective neuroimaging biomarker of chronic pain.

References

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