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Intensive longitudinal brain imaging reveals personalized signatures of chronic pain

Tracking ongoing spontaneous pain in individuals with chronic pain is challenging. Using intensive longitudinal functional magnetic resonance imaging (fMRI) combined with continuous spontaneous pain ratings in two individuals with fibromyalgia, we trained personalized brain decoding models that could track moment-to-moment spontaneous pain fluctuations. Underscoring the need for precision approaches, neither decoding model generalized from one individual to the other.

The problem

Spontaneous pain is a hallmark of chronic pain, and occurs without an overt noxious stimulus and fluctuates over multiple time-scales within individuals[1]. Despite its central importance for clinical assessment and therapeutic development, capturing and tracking spontaneous pain remains challenging[2]. Clinical practice still relies on self-reports, which are essential but often influenced by contextual information and limited in their ability to provide useful information about underlying biological processes[2].

As chronic pain has increasingly been conceptualized as a disorder that involves central nervous system (CNS) processes, brain imaging — particularly fMRI — has emerged as a promising avenue for understanding the CNS processes that underlie spontaneous pain and for developing pain biomarkers[3]. However, most previous fMRI studies have assessed pain at only a few isolated time points[4,5], which neglects the dynamically fluctuating nature of spontaneous pain and thereby limits their clinical relevance for ongoing pain. Whether longitudinal fMRI sampling of individuals with chronic pain can capture the temporal dynamics needed to develop precise, person-specific brain markers of spontaneous pain remains unknown. Leveraging densely sampled fMRI data may allow for direct characterization of intraindividual variation in spontaneous pain while accounting for interindividual heterogeneity in its brain representations, and potentially enhance predictive power for clinical translation.

The solution

Over more than half a year, 2 individuals with fibromyalgia — a highly prevalent chronic pain disorder — underwent more than 20 fMRI sessions in which they continuously reported their spontaneous pain intensity (Fig. 1a). Using these longitudinal whole-brain fMRI and self-report data, we trained personalized machine-learning models to predict dynamic changes in spontaneous pain intensity based on time-varying functional connectivity patterns, estimated for each fMRI run using an edge timeseries method. This precision-mapping approach captured how spontaneous pain is instantiated in each individual's brain, rather than a common group-level representation.

Our decoding models accurately tracked spontaneous pain fluctuations within individuals. Predicted spontaneous pain ratings were substantially associated with self-reported pain intensity and reliably distinguished between self-reported states of high pain and low pain, across multiple temporal scales that ranged from minute-by-minute changes to run-level and session-level averages. Such prediction was not achievable with conventional fMRI data quantities (four to five sessions), and prediction accuracy increased with the amount of longitudinal data included in model training. Examination of the pain-predictive connectivity patterns of the two decoding models revealed pronounced individual differences in the brain regions that contributed most strongly to the spontaneous pain intensity prediction (Fig. 1b). Consistent with this, models trained on one individual with fibromyalgia failed to predict spontaneous pain intensity in the other, which demonstrates limited cross-individual generalizability and highlights the individualized nature of the brain representations of spontaneous pain.

The implications

Our precision-mapping approach demonstrated that intensive longitudinal sampling can be used to train models that track spontaneous pain fluctuations within individuals, which provides a way to identify personalized pain biomarkers that can supplement patients' self-reports and thus support a pluralistic approach to pain assessment. Furthermore, the individual-specific nature of these models supports the view of chronic pain as a uniquely individualized condition, which underscores the need for personalized approaches rather than developing one-size-fits-all models.

This study focused on a small number of individuals and a single chronic pain disorder, which may limit generalizability. Furthermore, because we did not include specificity testing, the decoding models may draw on brain processes that covary with pain rather than pain-specific ones. Finally, the intensive longitudinal sampling required may constrain feasibility and scalability in clinical settings.

Future studies should extend this approach to larger and more diverse patient populations to assess generalizability and identify potential subtypes. Incorporating specificity testing and developing more time-efficient data-collection strategies will be important next steps towards clinical translation. Together, these directions point towards a future in which chronic pain assessment is enriched by multiple complementary tools that integrate neural, behavioral and experiential information to better reflect the complexity of chronic pain.

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EXPERT OPINION

"The authors' approach moves away from the dominant strategies relying on large cross-sectional datasets to train and test pain prediction models intended to generalize across individuals. Instead, it takes the reverse approach, performing many recordings in a few patients to train and test individualized models. This is an innovative, timely and methodologically transparent approach that makes the study a landmark in the development of brain-based biomarkers of pain." **Markus Ploner, Technical University of Munich, Munich, Germany.**

FIGURE

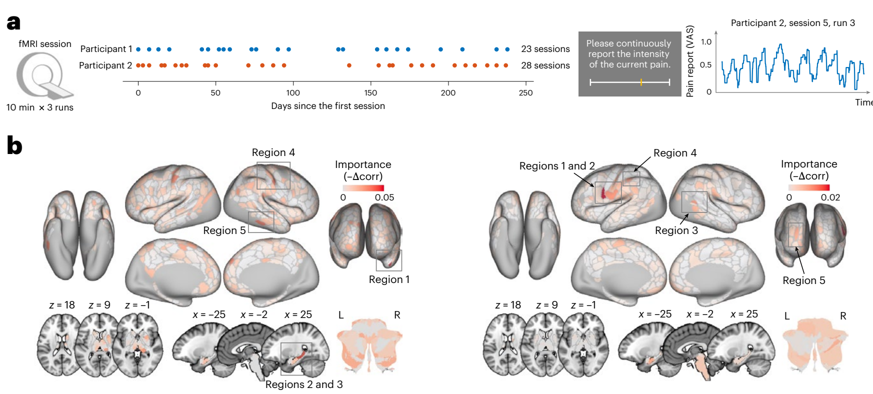

Fig. 1 | Precision brain imaging reveals personalized brain signatures of spontaneous pain. **a**, Two individuals with fibromyalgia underwent dense longitudinal fMRI sampling over more than a half year. Each fMRI session included three 10-min runs, during which the participants continuously reported spontaneous pain intensity using a visual analogue scale (VAS). Personalized decoding models were trained to predict pain intensity from time-varying fMRI connectivity patterns. **b**, Brain region-level contributions to prediction (feature importance) were quantified as the mean decrease in prediction–outcome correlation (−Δcorr) after permutation of all connections to each region. The top five brain regions with the highest feature importance showed no overlap between the two individuals, which highlights the individualized nature of spontaneous pain representations in the brain. © 2026, Lee, J.-J. et al.

BEHIND THE PAPER

One of the most important aspects of this project was data collection. Traveling from home to the laboratory and completing nearly 2 h of scanning across more than 20 sessions is a demanding commitment for anyone, and especially so for individuals living with fibromyalgia. The success of this study depended heavily on the participants' perseverance and willingness to engage in long-term research despite ongoing pain and fatigue. Their dedication made it possible to collect the dense longitudinal data required to pursue truly personalized analyses, and it fundamentally shaped what this project was able to achieve. **J.-J.L. & C.-W.W.**

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FROM THE EDITOR

"Lee et al. push the boundaries of pain research by showing that personalized neural decoding with longitudinal fMRI can transform how we understand and measure chronic pain. This work underscores the heterogeneity of chronic pain and the importance of individualized approaches." **Henrietta Howells, Senior Editor, *Nature Neuroscience*.**