A Standardized Brain Image Repository for Big Data Approaches to Chronic Pain
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Executive Summary

The Pain and Interoception Imaging Network (PAIN) seeks to improve the understanding of the brain’s role in chronic disease, with a particular emphasis on chronic pain states. PAIN provides the infrastructure for storage of standardized resting state functional and structural brain imaging data and associated biological, physiological and behavioral metadata from multiple scanning sites, and provides tools to facilitate analysis of the resulting comprehensive data sets. Through these efforts, PAIN will facilitate new discoveries in brain endophenotypes and biomarkers of chronic pain states, and provide the basis for linking these brain signatures to complex genetic and biological data sets.

The Pain and Interoception Imaging Network (PAIN) Repository

With support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and as part of the Multidisciplinary Approaches to Pelvic Pain (MAPP) consortium, the UCLA Center for Neurobiology of Stress has pioneered the development of the first large repository of well characterized multimodal brain images from patients with various persistent pain disorders (including interstitial cystitis/painful bladder syndrome, irritable bowel syndrome, vulvodynia and fibromyalgia) (visit painrepository.org for details).

The MAPP Repository was developed in close collaboration with the Laboratory of Neuro Imaging (LONI) which has been the pioneer and world leader in building an extensive infrastructure to perform large multisite studies including an automated pipeline for acquiring, processing and analyzing imaging and patient data (see The PAIN Repository and the LONI Pipeline). The MAPP Repository has greatly benefited from the existing LONI infrastructure and expertise, both of which have been key elements of the most successful large multisite imaging initiatives including ADNI, fBIRN, ENIGMA and The Human Connectome Project (HCP). The PAIN Repository intends to continue this close interaction with LONI (loni.usc.edu).

The National Institute on Drug Abuse (NIDA) and the National Center for Complementary and Alternative Medicine (NCCAM) provided a 3 year grant to the UCLA Center in September 2013 to develop and pilot test the PAIN Repository. Fifteen participating sites in North America and in Europe have agreed to participate in this groundbreaking project which aims to collect and store standardized multimodal brain images of 1,000 well phenotyped subjects including standardized clinical, behavioral and genetic metadata. Following the LONI model, the PAIN Repository will use operational protocols, quality control and analysis pipelines, large data set analytic procedures and a governance structure to support ongoing and future large multisite studies in pain (Fig. 2). The PAIN Repository is in the process of expanding its member base further, both within the US and internationally, including data from patients with temporomandibular joint disorders, migraine, chronic pancreatitis and pediatric pain populations.

Figure 2. Coordination Processes in the PAIN Repository
How the PAIN Repository Differs from Other Brain Imaging Repository Initiatives

- **PAIN is specifically targeted towards discovery of mechanisms and biomarkers related to chronic pain and chronic pain treatment.**
- **PAIN is multimodal.** It contains three types of MRI scanning data for each subject, high quality structural information, DTI, and resting state functional imaging. Unlike site specific task related data, these three imaging modalities are obtainable with almost any high resolution scanner and are relatively context independent, provided standardized acquisition protocols.
- **Because of the known limitation of open access data bases without standardization, PAIN includes two imaging databases:**
  - **The PAIN Standardized Repository** is the primary PAIN Repository. It contains scans that have been collected using validated protocols (developed with other sites and different scanners) to allow for combined multisite analysis. It also contains a standardized set of clinical metadata for each subject that covers demographics, diagnoses, pain severity, comorbidity, cognitive and affective measures. Scans are assessed for quality and compatibility with the repository standards and each scan has a quality control record for use in analysis.
  - **The PAIN Archive Repository** is an open repository in which contributors can deposit any structural, DTI or resting state scans of pain patients or healthy controls which do not conform to the guidelines for scans in the supervised repository. Scans in the archive have minimal clinical information and can be very diverse in terms of scanning procedures. The Archive is seen as a resource to deposit and access data from already completed studies, older datasets or those with minimal subject data available. Interactions with existing open access repositories are planned.

Why Is There a Need for the PAIN Repository?

The majority of persistent pain syndromes as currently defined by subspecialty-specific symptom criteria share many clinical, epidemiological and some biological features. These similarities and the co-occurrence of several syndromes in the same patient are often referred to as "comorbidities" or "overlapping conditions." (Fig. 3)

Characterizing structural and resting state brain alterations in large datasets of well phenotyped patients has the potential to be able to classify patients suffering from persistent pain (regardless of their current symptom based classification) into biologically distinct subgroups, which may differ between male and female patients, which may extend across current symptom based definitions, and which may respond differentially to treatments. It will also allow for reliable examination of brain alterations associated with specific pain symptoms, mechanisms and co-morbidities.

Finally, by including data from pediatric populations with persistent pain conditions, it will make it possible to explore developmental aspects of chronic pain.

![Brain diagram](image)
The PAIN Repository and the LONI Pipeline

The PAIN Repository uses a collaborative website (painrepository.org) to coordinate data accrual, report quality assessments and discuss analysis and publication plans. Secure network protocols allow for easy data transfer to and from the repository. Extensive phenotyping of patients with chronic pain conditions, using clinical, behavioral, multimodal brain imaging and genetics approaches results in the generation of massive data sets of unprecedented complexity.

Efficient analytical tools are needed to extract information from these data sets, as are the means to link processing steps into comprehensive, end-to-end workflows. The LONI pipeline provides an open access extensive framework for interoperability of such resources by utilizing a graphical user interface to utilize processing modules and linking them into complex scientific workflows (Fig. 4). The Pipeline environment (pipeline.loni.usc.edu) is a distributed infrastructure model for mediating communications between different data resources, software tools and web-services. The Pipeline software architecture design is domain and hardware independent, which makes the environment useful in different computational disciplines and on diverse hardware structures.

Application of Brain Imaging to Biomarker/Endophenotype Discovery in Chronic Pain

The subjective chronic pain experience is not linearly related to interoceptive and nociceptive signals from the periphery, but is constructed by the brain from peripheral, and central (affective, attentional, memory) inputs. Chronic pain is therefore a highly variable experience between affected patients, and symptoms are often unreliable markers of underlying disease process.

Functional brain imaging studies using physical or psychological stimuli have relied on complex, time consuming and often single site-specific experimental paradigms. Due to these study requirements, and the associated expense and required local expertise; such studies have generally been employed in relatively small samples of subjects. However, recent advances in neuroimaging techniques and analytic strategies have generated tremendous interest in applying readouts from multimodal neuroimaging as candidate biomarkers for various CNS disorders, such as Alzheimer’s disease, depression, schizophrenia and chronic pain. These approaches include analysis of intrinsic brain oscillation and resting state networks, regional differences in brain morphometry (cortical thickness and grey matter volume) and alteration in white matter tract microstructure (diffusion tensor imaging, DTI). Analytical tools are now available to combine these imaging data to characterize the properties and alterations of large scale brain networks. (see Large Scale Connectivity and Complex Network Analyses)

Biomarkers based on these technologies are not only free from the limitations described for evoked response methods of current neuroimaging studies, but also are highly practical for use in large, multicenter studies, since they can easily be standardized. Data can be analyzed centrally in a standardized fashion and algorithms have been developed for combining data from multiple and different scanners.

As part of large international multicenter imaging studies (e.g. ADNI and fBIRN) such techniques have successfully been developed and used to collect and pool data obtained at different sites and with different scanners making it possible to obtain sufficient sample sizes to reliably determine brain alterations associated with individuals clinical, physiological and genetic data.
How Does PAIN Work?

**PAIN Standardized Repository.** Members of PAIN agree to contribute high quality structural, DTI and resting state scans which have been collected according to agreed upon and validated acquisition protocols, using the PAIN/LONI interface. They will also contribute a minimal set of standardized metadata based on validated questionnaires. In the future, as the repository grows, subgroups of members may develop their own disease specific set of metadata that they feel will increase the opportunities for disease specific analyses. Such future metadata may include disease specific questionnaires, or genetic, biological or physiological samples, including GWAS data, and gut microbiome related data.

The brain imaging data will undergo an initial quality control and contributors will be notified if scans do not meet the agreed upon acquisition parameters.

Any member who intends to analyze a data set in the Standardized Repository will be asked to coordinate their plan with other members of the repository, following a set of guidelines which have been developed based on the well established MAPP guidelines for joint publications (“Sociology of Pain”; for details, visit painrepository.org). These guidelines aim primarily to avoid duplication of planned analyses, and establish authorship prior to performing the analyses.

**PAIN Archive Repository.** Members can deposit any existing data sets that they are willing to share with other members for analyses. Contributors will be asked to provide a minimal data set including diagnosis, age and sex of subjects. In case a member plans to analyze such a data set which has been contributed by another member, he/she would contact the contributing party to obtain additional metadata if necessary. As different datasets in the archive is likely to have been acquired on different scanners with different acquisition parameters, and would not have accompanying compatible metadata, merging of data sets would be limited.

Who Can Use PAIN?

Any investigators who is willing to contribute structural, DTI and resting state data and a minimal set of clinical metadata, which have been acquired in a standardized way (for details, visit painrepository.org), can join PAIN and gain access to the PAIN Repository.

Currently, 15 members from North America and Europe are either members or have indicated their willingness to participate in the PAIN Standardized Repository (visit painrepository.org)

• Queen Mary University of London, UK
• Oxford University, Oxford, UK
• University of Leuven, Belgium
• University of Duisburg-Essen, Germany
• Radboud University, Nijmegen, Netherlands
• Linköping University, Linköping, Sweden
• Sahlgrenska University, Gothenburg, Sweden

• Northwestern University, Chicago, USA
• Harvard University, Boston, USA
• University of Michigan, Ann Arbor, USA
• Washington University, St. Louis, USA
• University of Maryland, Baltimore, USA
• Medical College of Wisconsin, Milwaukee, USA
• University of California, Los Angeles, USA
• McGill University, Montreal, Canada
What Types of Analyses Will PAIN Enable Members to Perform?

Members can take advantage of the PAIN repository by downloading raw data sets and performing their own analyses, or they can utilize the publically accessible LONI workflows to analyze their own or combined datasets.

Figure 5 shows a schematic of the current workflow used by the UCLA Center for Neurobiology Stress to generate brain signatures from multimodal data sets. After parcellation and integration, complex data sets can be displayed visually in the form of connectograms. Several quantitative approaches can be applied to these data sets as described in the following pages.
Identifying Brain Signatures from Multimodal Brain Imaging Data Sets

Brain imaging endophenotypes (brain “signatures”) derived from multimodal imaging studies and large scale network analyses provide a powerful and biologically relevant substrate to better examine the correlations between large scale biological, behavioral and clinical data sets with the brain in chronic pain conditions.

Correlating Clinical and Behavioral Data with Brain Signatures

In order to determine the functional implications of brain signatures, such as their relationship to pain severity and duration, it is necessary to correlate behavioral and clinical data sets with brain endophenotypes. For example, the correlation of alterations in saliency network properties with disease duration may suggest that the brain changes are secondary to nociceptive input to the brain.

Correlations between certain aspects of brain signatures with pain severity would suggest a role of the brain alterations in central pain amplification. Correlations between alterations of cortical modulation networks and cognitive measures (attention, prediction error, hypervigilance) would suggest a role of the observed brain signature alterations in these psychological constructs.

Figure 6. Schematic illustrating the endophenotype approach to studying complex symptom based disorders such as chronic pain. Brain networks are shaped during development as a consequence of genetic and epigenetic influences. Multiple brain endophenotypes interact to result in the clinical phenotype.
Large Scale Connectivity and Complex Network Analyses

Large scale connectivity and complex network analyses support the concept that symptoms or functional impairments are associated with disruption or abnormal integration of spatially distributed regions that comprise a large-scale network (i.e., abnormal topological organization of structural and functional brain networks).

Using graph theoretical methods brain networks can be characterized by metrics that describe local topological neighborhoods of individual nodes, global network communication and signaling, and local and global measures of centrality that permit quantification of each element to the network’s structural integrity and information flow. These network metrics have been useful in probing central changes in several clinical syndromes. Ultimately, compared to regional activity or structure, measures of network properties may prove to be more sensitive central biomarkers, endophenotypes and predictors of outcome.

Multivariate Pattern Analyses

Multivariate pattern analyses are applied to identify patterns in the brain that makes it possible to discriminate subjects with persistent pain from healthy control subjects, and possibly patients with different types of chronic pain (e.g. neuropathic pain from persistent pain) as well as predict treatment responders from non-responders and functionally link alterations in brain architecture (morphometric measures, volume, shape, cortical thickness) and resting state networks with measurable clinical and biological parameters enabling identification of distinct brain endophenotypes which characterize sub-populations of patients with different pathophysiology and treatment responses.

Ultimately, the goal of PAIN is to provide large scale data sets which can be used by members of the repository to develop accurate and sensitive classification algorithm based on biological markers (genetics, brain morphometry, resting state characteristics, network metrics, sympathetic and vagal measures) to inform treatment options for persistent pain disorders. Current algorithms include sparse PLS for regression, as well as discriminate analysis (sPLS, sPLS-DA) and random forest classification.
The Future

Identifying Biologically-Based Patient Subgroups Based on Endophenotype Clusters

Large well standardized brain and metadata data sets from patient groups with different persistent pain conditions will make it possible to identify commonalities and differences in brain signatures. For example, differences and commonalities between visceral and somatic pain conditions, between pain syndromes with and without somatic and psychiatric comorbidities, and between male and female patients can be investigated.

In addition, hypotheses can be tested about the existence of biologically based subgroups of patients which share clusters of brain endophenotypes, but are currently classified as distinct clinical syndromes based on symptom criteria. Such biologically based subgroups may respond to similar therapeutic strategies, even though they present with different pain symptoms. Finally, subgroups of patients may be identified.

Developmental Trajectories of Chronic Pain

Large well standardized brain and metadata sets from both pediatric and adult patient groups as planned for the PAIN repository will make it possible to identify early brain signatures which precede the adult brain phenotypes and which point to different brain network alterations. In addition, longitudinal data sets on the same patients will make it possible to identify moderators (predictors) of outcome.

Imaging Genomics

Attempts from candidate gene and genome wide association studies to identify strong associations of genetic factors with complex symptom based pain phenotypes have largely been disappointing. This disappointment has been one of the main justifications for the endophenotype approach to symptom based syndromes in pain and psychiatry. Advances in technology have made it possible to identify genomes, epigenomes and transcriptomes from chronic pain patients and link them to brain “signatures.”

A variety of such approaches has been proposed, ranging from associations of single or multiple SNPs with alterations in regional grey matter white matter tract microstructure to voxelwise gene-wide association studies to demonstrating associations of multi “omics” data sets with large scale network properties.

It is expected that in the future, the PAIN repository will make it possible for members to perform correlational analyses between large multimodal brain imaging data sets and multiomics data sets using advanced system biological analytical approaches.

Studying the Gut Microbiome Brain Axis

Rapidly growing evidence supports bidirectional interactions between the gut microbiome and the brain in neural development and in the modulation of adult brain function. Converging evidence from preclinical studies suggests a possible role of gut microbiota and their metabolites in modulating endogenous pain modulation systems, as well as stress and emotion regulation systems.

Based on these findings, it has been speculated that such interactions may also play a role in a number of brain diseases, including chronic pain and psychiatric and neurological conditions. PAIN members who are collecting gut microbiome data will be able to collaborate in determining possible correlations between microbiome related parameters (microbial ecology, microbiome related metabolites) and brain signatures related to chronic pain states.
Conclusions

Regardless of analytical approach, large standardized brain image repositories with linked metadatabases are essential to perform the majority of the analyses listed here. It is anticipated that the PAIN Repository, once fully populated, will provide unprecedented opportunities to study chronic pain disorders by providing insights into underlying mechanisms, interactions between the brain and peripheral systems, understanding developmental trajectories, identifying subgroups of patients who may differentially respond to therapies and characterize the effects of centrally acting drugs on brain networks in these disorders.

The sociology of the network will facilitate interdisciplinary interactions and provide a democratic structure for developing multi-authored high profile publications in the field of chronic pain.

How You Can Help

Current NIH funding to develop and beta test the PAIN repository is limited to 3 years and we will be working hard to obtain additional funding beyond this date. However, to assure the seamless transition into the maintenance phase of the repository and to make it possible to add additional non-imaging components (such as the gut microbiota) to the database, we are seeking philanthropic support. Should you be interested in providing such support, please contact Fornessa Randal, Oppenheimer Center for Neurobiology of Stress Administrator, at (310) 206-0192 or FRandal@mednet.ucla.edu.

References


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