



CHAPTER 2

Using Neuroimaging to Understand Pain: Pattern Recognition and the Path from Brain Mapping to Mechanisms

Tor D. Wager

The brain is the proximal generator of pain. Certainly, many kinds of pain start in the body, in the skin, muscles, or bones; but without a brain none of them become experiences. They do not lead to avoidance, inspire fear, or cause any worry or suffering whatsoever.

To understand pain, we need to understand its brain mechanisms—the central brain processes that represent noxious events in the body and the actual or potential harm they imply. In many forms of pathological pain, the brain is functioning normally, responding appropriately to bodily insult. If a peripheral cause can be identified and removed, the problem may be solved. Too often, however, what starts with an initially healthy brain response to peripheral injury can become pathological. Neurons in the spinal cord and brain may sensitize. Central representations of pain may trigger avoidance, disuse, and ultimately isolation and depression. Innocuous events may become reminders of pain, and pain may take on special significance in the central nervous system, dominating attention, memory, and internal thought. We need better models of how these processes work at the brain level.

Researchers have been using neuroimaging techniques—fMRI and PET—to study the brain mechanisms of pain for over 20 years, since the first seminal publications in 1991 [34, 58]. We have moved rapidly from the first groundbreaking, exploratory studies to a mature literature that has yielded reliable procedures and findings on acute and chronic pain, including functional responses to pain [2, 14] and structural changes that accompany chronic pain [42, 55]. We now have the potential to take a “quantum leap” forward, but we have not done so yet. What is that quantum leap? It is the translation from basic findings to having useful brain markers that can help diagnose pain in individuals, determine the *neurophysiological type* of pain, and understand its mechanisms and connections with other brain systems (e.g., those that mediate fear, avoidance, and depression). This chapter is about some of the things we must consider as we prepare to make the jump.

The central thesis of this chapter is that we are now ready to make the transition from brain mapping, the dominant approach for the first 20 years of neuroimaging, to the *brain biomarker* approach, the use of brain patterns as markers for functional outcomes (e.g., pain and performance under pain). I first describe the brain biomarker approach and how it is supported by a new class of algorithms, *machine learning* or *statistical learning*, that are now in widespread use in research and commercial applications across fields [1, 28]. Then, I describe the criteria for developing brain biomarkers that can be applied and used in research and clinical settings, and some of the potential applications. I will argue that the ultimate goal of the biomarker approach

is to identify brain representations of pain and other outcomes. Importantly, not all applications of machine learning are equally viable as biomarkers, but building systematically on carefully developed biomarkers could transform the way pain is understood, assessed, and treated.

BRAIN BIOMARKERS

The potential applications and markets for an understanding of how the brain generates and regulates pain are substantial [8, 25]. Both optimists and skeptics are waiting for breakthrough applications of neuroimaging techniques in clinical and commercial use. But, with few exceptions, those applications have not appeared in the first 20 years of neuroimaging. As one recent, authoritative review put it: “Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?” [37].

One simple answer is that we have not really tried to develop neuroimaging-based clinical tests. The vast majority of the thousands of human neuroimaging studies, including early neuroimaging studies of pain, have not attempted to do anything that could lead to a clinical test based on measures of human brain activity. These studies have focused on *brain mapping*—an endeavour that seeks to identify which brain regions respond to events in a particular psychological or stimulus category (e.g., painful events, remembered items, or attended objects). The outcome of these studies is a statistical map of brain responses, and these maps have taught us much about the brain. For example, the human insula, cingulate, and thalamus respond to multiple kinds of noxious events, and are hyperactivated in at least some forms of hyperalgesia [14]. A characteristic feature of brain maps is that they subject each region or “voxel” to an independent analysis, seeking to explain its activity level over time as a function of psychological and physical states. Another characteristic is that the outcome is a “yes/no” answer at each voxel—a test of whether there is a statistically nonzero response to the psychological event being mapped.

This is a worthy, and even critical, scientific goal. However, a translational approach requires something qualitatively different: the use of measured brain activity across multiple systems to (a) predict both performance and long-term functional outcomes, and (b) test effects of cognitive, behavioural, or pharmacological interventions (Fig. 2-1). This approach is tantamount to first developing *brain biomarkers* of outcomes of clinical or translational interest, and then using those brain biomarkers to provide mechanistic information on how potential treatments work [9, 10].

The brain biomarker approach inverts the traditional analysis. Instead of treating brain activity in a “voxel” as the outcome, the outcome is the function to be explained or predicted (e.g., pain intensity, pain duration, cognitive performance, or other affective symptoms). All brain information available, including measured activity in multiple regions within and across brain areas, is used to predict the outcome. Brain data can be combined across types of imaging (e.g., functional and structural imaging) or with other measures (traditional clinical assessments, blood biomarkers) to refine the predictions; the limits depend on the application, for example, which measures will be available for test cases.

CONTRASTING THE BIOMARKER APPROACH WITH STANDARD BRAIN MAPPING

In brain mapping as practiced over the last 20 years, efforts are not generally made to (a) evaluate how large and meaningful reported effects are using unbiased techniques and (b) perform exact replications. These shortcomings have had major repercussions for the translation of scientific findings into clinical and commercial settings.

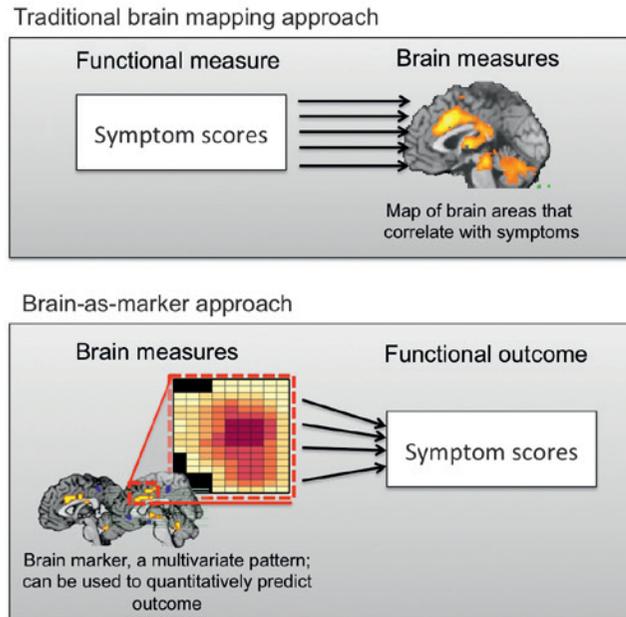


FIGURE 2-1 Traditional and emerging approaches to neuroimaging analysis. Top: A traditional approach with limited potential for translation. Every brain “voxel” or region is treated as a separate outcome, and the goal is to explain brain responses with symptoms and tasks. Bottom: The “brain biomarker” approach, in which machine learning algorithms are used to identify patterns of brain activity that closely predict symptoms or other functional outcomes.

In the area of drug discovery, this has led to failed attempts by pharmaceutical companies to replicate basic research findings and develop them commercially, at great expense to the companies and, ultimately, the public [7, 25, 32]. These failures have caused pharmaceutical companies to dramatically scale back mental health research in some cases. As Dr. Thomas Insel writes, “Despite high prevalence and unmet medical need, major pharmaceutical companies are de-emphasising or exiting psychiatry, thus removing significant capacity from efforts to discover new medicines” [31].

Translational approaches require a very different strategy. Rather than cataloguing statistically significant differences [37], brain markers must be identified that are *strongly predictive* of diagnostic categories or functional outcomes. The diagnostic value of these markers must be assessed across individuals, samples, settings, and research groups. Markers must be *optimized* so that they are maximally diagnostic and robust, including markers that integrate multiple brain measures and systems.

Brain Markers and Effect Sizes

Traditional brain mapping approaches focus on hypothesis testing and correction for multiple comparisons, to reduce false-positive brain findings. However, they are not suitable for testing how *large* the effects are. This point was the core of a heated debate about effect sizes in neuroimaging studies several years ago, which received widespread media coverage and debate in journal editorial offices and funding agencies [62]. Essentially, in neuroimaging as in any other domain, if one performs many tests, the ones that pass the threshold for statistical significance and reporting will tend to include error that favours a significant finding—the “winner’s curse.” In meta-analysis, the same problem is called the “file drawer problem”—if one runs 100 studies on a phenomenon with no effect, on average 5 of them

will be “significant” at $P < 0.05$. If the 5 studies are the only ones published and the 95 null findings go in the proverbial file drawer, then it will appear as though the effect is reliable. Brain maps routinely consist of between 50,000 and 200,000 tests, and the significant findings appear to have much larger effect sizes (correlations with symptoms, t - or Z -values for effects) than they actually have. Correcting for multiple comparisons limits the reporting of false-positive findings, but it makes the effect-size problem *worse*: By raising the bar for statistical significance, the degree to which significant findings capitalize on chance is increased [65].

Why should we care about effect sizes? Traditional scientific findings are based on hypothesis testing, and effect sizes have hardly been considered. But if one cares about which effects are meaningfully large and where interventions might make a difference, effect sizes are of paramount importance. They are directly related to the ability to classify (or diagnose) cases and accurately predict future outcomes. Large effects (not small ones) are likely to be replicable, important, and useful. Of the thousands of potential causes and correlates of complex clinical conditions, those with large effects deserve particular follow-up study and can inform interventions and policy.

The brain biomarker approach circumvents the effect-size estimation obstacle. The primary analysis metric is an effect size: the error in predicting the outcome in new test cases (e.g., new individuals). The important consideration is whether the estimate of the effect size is valid, and what test cases it applies to. Useful predictions about pain will typically be about new individuals: How much pain (or what type of pain) an individual is feeling, based on their brain state. If a model is developed that relates brain activity maps to one type of pain, and then predictions are made about a new type of pain, or a different group of individuals from a different demographic, the effect size may shrink. The goal is to estimate predictive accuracy across different samples and test conditions, to determine the *breakdown point* or the boundary conditions for the predictive test.

Brain Markers and Replicability

There is an increasing recognition of the need for replication of results across laboratories [33, 47]. This is true across multiple fields that deal with complex data, including both neuroimaging [15] and genetics [22], and in other fields as well [54].

In traditional brain mapping analyses, findings are aggregated and replications “counted” at the level of gross anatomical regions. For example, if two studies show that a distraction modulates activity in the rostral dorsal anterior cingulate (rdACC), then the pair will be counted as a replicated effect by many scientists. This is not unreasonable, as this region is usually circumscribed within one functional zone or “parcel,” and is treated as a homogenous region [61]. However, the rdACC contains hundreds of voxels, and there is a question about how close is “close enough” for two brain findings to be considered replicates. In addition, there is ample room for studies that activate different sets of voxels to be considered as replications. These findings would not replicate if a predefined set of voxels were used, and this flexibility introduces an additional level of uncertainty. Although it is commonplace to think of activation patterns that are nearby or overlapping, but not identical, as similar, one must remember that activity in the rdACC and other brain regions at this scale is not a pure measure, and reflects potentially hundreds of distinct processes.

In the brain biomarker framework, there is an explicit emphasis on using precisely defined brain patterns in new individuals and samples. Testing a brain marker on a new

sample constitutes an exact replication of the marker at the level of the brain pattern. And, indeed, the precise brain pattern—including which voxels (or connections) are “active” and exactly how strongly they activate in relation to the outcome—must be specified in advance in order to test generalization to new individuals and samples. By holding the brain pattern constant, the brain biomarker approach is naturally suited to replications, and to assessing how variation in the sample, procedures, conditions tested, or other factors affects the size of brain–outcome relationships.

MACHINE LEARNING: A KEY TO DEVELOPING USEFUL BIOMARKERS

An important trend in the neuroimaging literature is the use of “statistical learning” or “machine learning” algorithms to identify distributed patterns of fMRI activity within and across regions [30, 45]. Machine learning is a broad class of algorithms designed to predict outcomes from multivariate datasets. Techniques encompass “supervised learning” techniques designed to predict outcomes of interest, including regression (for predicting continuous outcomes) and classification (for categorical outcomes), and “unsupervised learning” techniques for identifying clusters and dimensional components in datasets. They also include nonlinear and adaptive techniques such as reinforcement learning. Applied to brain data, the machine learning approach is closely aligned with “multi-voxel pattern analysis” (MVPA), the practice of identifying activity *patterns* across voxels and using them to classify or “decode” stimulus conditions [29].

MVPA techniques do not necessarily involve machine learning, but machine learning provides the most powerful ways of identifying patterns of brain activity that have specific profiles of psychological responsivity. Not all machine learning analyses are suitable for the brain biomarker approach: Machine learning is a class of algorithms, and models estimated using machine learning techniques and their outputs can be more or less interpretable, and thus more or less useful for neuroscientific discovery and measurement. However, machine learning algorithms share several features that make them particularly suited for the brain biomarker approach.

Quantitative Diagnostic Assessment

Although the family of machine learning techniques is broad, several specific principles are particularly germane to the brain biomarker approach. First is the notion of quantitative diagnostic testing—evaluating the diagnostic properties of a defined brain marker. This can be captured fairly well by the sensitivity and specificity of the marker in predicting the outcome, from which can be derived the positive and negative predictive values of the brain pattern when applied as a test of the outcome. The positive predictive value is the probability of an outcome (e.g., pain above a specified threshold) when the brain pattern is present (e.g., expression of the brain pattern above a specified threshold). These values are easily interpretable and meaningful in clinical applications. They are not unique to machine learning, and are routinely applied to all kinds of diagnostic tests, but they are of particular interest in machine learning analyses because of the emphasis on prediction; in machine learning, sensitivity and negative predictive value are called “recall” and “precision,” and “precision–recall curves” are typically reported. Neither the brain activity nor the outcome

need be treated as a categorical measure, however, and continuous measures of prediction error can also be quantified.

Generalization and Application to Individual Persons

Second is the idea of cross-validation [23], a procedure in which a model is developed (“training”) on a subset of the data, and tested on a “holdout” dataset. The assignment of training and test data is done multiple times, often so that each observation (e.g., each individual participant) is part of the test set exactly once. These training–test splits are called “folds,” and the model is reestimated on the training data for each fold and applied to the test data from that fold. Performed correctly, cross-validation can provide reasonably unbiased estimates of the accuracy in generalization to the test data.

However, cross-validation can yield optimistically biased estimates if (a) the observations are not truly independent, creating dependence between the errors in training and testing datasets, or (b) cross-validated analyses are repeated on the same dataset many times, with different combinations of data processing or algorithmic choices. The first problem can occur in the presence of any unmeasured confound, for example, slow changes in the sample, scanner, or experimenters with the passage of time. The second can occur whenever researchers seek to optimize accuracy and pick the best among a series of models. For this reason, it is often advantageous to (a) stratify the training–testing assignment on potential confounds and (b) reserve a final holdout set for testing only after all analyses are completed and the “final” model is selected.

Hyper-Resolution

Another powerful idea is that patterns derived from machine learning can circumvent some of the limitations in spatial resolution of fMRI, because patterns can be sensitive to the local structure of functional columns and differential functional organization across microvascular beds [17, 38]. Pattern information about functional topography is often preserved at a mesoscopic level, and is detectable even when the voxels sampled are larger than the columns themselves [17, 35, 36, 57]. In addition, mesoscopic organization is often preserved across individuals, permitting accurate inferences about individuals based on normative group-level data [48, 51, 52, 64]. This means that distributed local patterns of activity can be sensitive to the differential distribution of different types of neurons across a brain region. Thus, whereas any one voxel in a region such as the anterior cingulate may not be highly diagnostic of pain [60, 66], a particular local pattern across voxels within the anterior cingulate may be diagnostic [64].

USING MACHINE LEARNING TO SUPPORT THE BRAIN BIOMARKER APPROACH: CHARACTERISTICS OF A USEFUL BRAIN-BASED BIOMARKER

Machine learning, MVPA, and the brain biomarker approach are all conceptually distinct, and the vast majority of machine learning and MVPA fMRI studies are not suitable for use as biomarkers. Rather, neuroimaging-based biomarkers should conform to a particular set of standards [10]. What is at stake is whether a particular brain marker robustly and specifically reflects the core features that cause an outcome (e.g., that cause pain), or reflects

noise or superfluous brain processes. The stronger the evidence for these characteristics, the more useful and trustworthy the marker:

1. **Prospectively defined pattern:** The pattern of activity, connectivity, etc. must be *precisely* defined a priori. A priori definition of regions or networks of interest is common in the literature, but their definition is flexible depending on which prior studies or atlases are used. Activation in brain maps is yet more flexible; two studies may activate a region (e.g., the amygdala or dorsal posterior insula) and yet activate nonoverlapping voxels and uncorrelated patterns across voxels. The most useful markers will specify precisely which voxels (or connections) are used within and across brain regions, and the *specific relative activity levels* across voxels. The dangerous potential for capitalizing on chance by testing multiple algorithms, brain features or patterns, and samples and picking the best ones can hardly be overstated.
2. **Diagnostic for individual people (sensitive and specific):** The stronger a pattern separates patient/control groups or predicts other continuous outcomes like pain, the more likely it is to be useful as a diagnostic or prognostic aid. In addition, strongly diagnostic markers are more likely to represent core brain features linked to outcomes. Diagnosticity can be captured by (at a minimum) two values: sensitivity and specificity. In a pain context, sensitivity relates to the effect size of brain responses to pain or, in probabilistic terms, the probability of observing a response in the brain marker above threshold given pain, $P(\text{brain marker} \mid \text{pain})$. Specificity relates to the probability of observing a response given conditions other than pain, $1 - P(\text{brain marker} \mid \text{no pain})$. Specificity must be evaluated relative to specific alternatives to pain (warmth, negative emotion, other salient cues, or events), and very few studies have attempted to address specificity [64]. Specificity is particularly important because current thinking about brain networks emphasizes the generality of brain responses in the “pain matrix” or pain-processing regions [20, 46, 66], though it is likely that machine learning-derived patterns can be much more specific to pain than regional activation [64].
3. **Interpretable:** Brain markers that reflect core brain features of outcomes are likely to be interpretable, in the sense that they (a) can be evaluated by human scientists and (b) conform to predictions based on other sources of data, including studies in non-human animals, lesion studies, human and nonhuman electrophysiology, and other neuroscience methods. For example, an interpretable acute pain biomarker should include activity in dorsal posterior insula and SII, stimulation of which evokes pain in humans [43], as well as other regions known to be important from the vast literature on pain across species. Some machine-learning-based markers that have fared well in prediction—even winning competitions for predictive accuracy—are not interpretable, and appear to capture activity in the ventricles or other brain structures not known to be related to the phenomena they are predicting [24, 56]. In some cases, they appear to be related to confounding variables—for example, a recent competition-winning pattern that “diagnosed” attention-deficit hyperactivity disorder versus control subjects appeared to track head motion, rather than psychological elements of the disorder [24].
4. **Transfer across laboratories, scanners, and populations:** Useful brain markers must be demonstrably diagnostic across multiple laboratories, populations, and scanners. Markers that appear to be diagnostic in one sample from one geographical location may not be diagnostic in other samples. Markers that are robust and

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that represent core features of the outcome being measured should transfer across laboratories and populations. In addition, they must be able to be shared and applied prospectively and still yield good results. The imperative of testing on datasets independent from those used to identify the marker has, in part, led to multisite efforts to prospectively share neuroimaging data (e.g., http://fcon_1000.projects.nitrc.org/indi/IndiPro.html). Of course, like any assay, a particular brain marker may not perform well in some populations and with some scanning and data processing procedures. These variations must be quantified, so that markers are applied under conditions where good sensitivity and specificity can be expected.

5. **Transfer across conditions:** The sensitivity and specificity of a brain marker must be evaluated relative to the conditions under which it is tested. For a brain marker to be specific to acute pain, it must be sensitive to multiple types of acute pain (e.g., pain evoked by pressure, heat, cold, chemical signals, and inflammation). Of course, if no single brain system tracks all these kinds of pain, there may not be any single marker that tracks pain across these conditions. There may not be any common representation of “pain” across all types, but there may be multiple representations of acute pain, inflammatory pain, chronic neuropathic pain, etc. Alternatively, the systems that represent heat pain and mechanical pain may be different, implying that there is no single representation of “acute pain.” Thus, the pattern of conditions a marker transfers versus does not transfer to can help inform us about how the brain is organized and what the neurophysiological types of pain are.

Thus, the brain biomarker approach is a *specific use* of MVPA and machine learning techniques, and putative markers must be evaluated in terms of these (and related) functional characteristics. The process of demonstrating and testing markers across samples, scanners, populations, and task/condition variants (e.g., types of pain) requires substantially more effort than single studies that simply establish an effect or phenomenon [10, 50].

Seen in this light, most examples of machine-learning-based studies in the literature are not suitable for person-level prediction at all. In particular, “searchlight” MVPA approaches [39]—involving search for multivariate predictors of an outcome across many local patterns—are not suitable. They do provide measures of accuracy, but these measures are biased for the same reasons that whole-brain effect-size maps are biased: They capitalize on chance by searching across many variables and picking the “winners.” To be used as markers, predictive regions from a searchlight analysis must be tested on a *completely new set of individuals*, with *no additional model selection or retraining*. Searchlight analyses are useful for identifying and studying what information is represented in different brain regions, but not for use as markers unless searchlights are combined into a single, predictive model and then validated for that purpose.

STATE OF THE FIELD: APPLICATIONS OF MACHINE LEARNING TO DEVELOPING BRAIN MARKERS FOR CLINICALLY RELEVANT OUTCOMES

As neuroimaging is increasingly used in clinical and translational studies, there is increasing focus on the diagnostic value of brain patterns for clinical conditions [6, 11, 18, 21, 67] and treatment responses [19, 44]. To provide diagnostic value, studies like these are

beginning to use the brain biomarker approach, combined with various MVPA and machine learning methods, to develop brain markers useful in measuring endogenous brain responses linked to outcomes of clinical, psychological, and behavioural interest. These efforts are in the early stages, and the criteria above have seldom been systematically applied. However, these studies show great promise for increasingly systematic application and testing across laboratories.

To date, several studies have focused on using machine learning techniques to identify patterns within an individual person that predict the intensity or incidence of acute pain for that person [11, 12, 16, 41]. Other studies have used EEG [49] to make predictions, which is promising because the technology is less expensive and deployable on a large scale. These studies do not use prospectively designed patterns and make predictions about individuals, so they do not meet criteria 1 and 2 above, but they are important stepping stones towards biomarker development.

Additional studies have shown that it is possible to predict acute pain *without training data on an individual person*, based on a normative model [13, 64]. This is variously referred to as “between-person classification/prediction” or “generalization to out-of-sample individuals,” and fulfils criterion 1 above. Such models can be applied prospectively to data from individual persons, without knowledge of the “ground truth” about pain for that individual. Such approaches are required if the brain biomarker approach is to be used to augment tests for pain and other psychological phenomena (e.g., emotional responses).

In a recent study, Wager et al. [64] attempted to address the other criteria above systematically, and in so doing identify a biomarker for acute pain. We identified a pattern based on a sample ($N = 20$) that was composed mainly of patterns of activity within pain-responsive regions (Fig. 2-2). Linear machine learning techniques were used to stabilize the pattern and increase interpretability (criterion 3), which is evidenced by the fact that

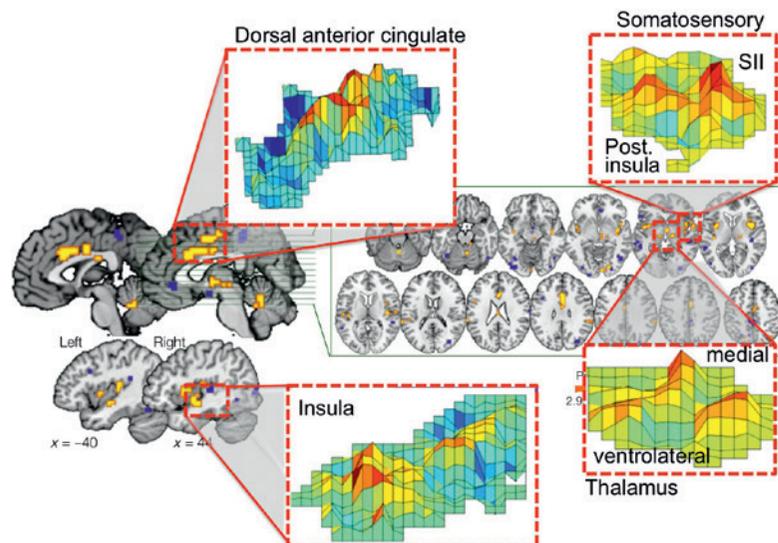


FIGURE 2-2 An example of neuroimaging-based biomarker pattern [64]. This pattern across voxels, including multiple pain-related brain regions, serves as a marker that can be tested in individual persons. The integrated activity across the pattern provides a continuous readout of predicted acute pain intensity. This readout is compared with a threshold to determine whether a condition elicits this pain-related brain pattern or not, and predict which of two conditions is more painful.

increases in predicted pain intensity were driven by increases in activity in multiple “known” pain-related regions. We tested its performance on three additional, independent samples, one from a different scanner (with a different field strength and manufacturer) running different acquisition sequences (criterion 4). In these test samples, we validated that the model has over 90% sensitivity and specificity at the individual person level for discriminating acute pain from nonpainful warmth, pain anticipation, pain judgment, and romantic rejection-related stimuli that otherwise activate very similar brain patterns as acute pain. The rejection condition was negative, arousing, and salient, and activated portions of the dorsal posterior insula and SII that are otherwise quite pain specific [40], providing a strong test case for the pain biomarker.

Applications to clinical samples have, thus far, typically used between-person classification to identify whether a patient has a clinical diagnosis or is a healthy control based on brain activity. For example, functional activity in the nucleus accumbens after pain [5] and brain structural measures related to grey-matter density [59] have been used to classify low back pain patients versus controls. Patient–control separation based on brain measures has also been reported in schizophrenia [21], Alzheimer disease [18], and depression [67]. These studies meet criterion 1, and in some cases are strongly diagnostic of patient versus control status, though their specificity relative to other disorders or confusable controls has not been tested (criterion 2). However, apart from tests in Alzheimer disease—which have benefitted from multisite consortium support and are now used in clinical trials—they have yet been tested for generalizability across samples, populations, and test conditions (criteria 4 and 5). An additional limitation is that the candidate markers vary in interpretability (criterion 3); and, critically, a marker trained to identify patients versus controls can capitalize on *any* differences between the groups, including those that are irrelevant to the core features of the disorder (e.g., how patients understand task instructions or attend to visual stimuli or move their heads). Therefore, patient versus control classification is a starting point, but not an end point, for biomarker development.

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Models that can be applied prospectively are predictive ones that can be used to guess patient status or predict recovery before outcome data become available. These models are particularly promising and important for early identification of risk and intervention. For example, Apkarian’s group has used functional connectivity in medial frontal–striatal circuits to predict whether patients will recover from back pain or transition to chronic pain [6, 26]. Machine learning techniques have also been used to predict treatment recovery in depression [53] and social anxiety [19]. This is one of the most promising applications of the brain biomarker approach, as it could be used to (a) identify high-risk individuals who will benefit from intensive treatment; (b) permit early intervention, before disease processes have caused irreparable damage; and (c) predict who will respond best to a particular treatment. Other work has sought to predict who will respond to placebo treatments [27, 63], which could be clinically useful for (a) identifying placebo responders, (b) assessing how placebo and drug responses are related (they may be independent or interact [3, 4]), and (c) screening or controlling for placebo responses in clinical trials.

Machine learning approaches, when used in particular ways, are also particularly suited to *person stratification*—one of the great translational needs described earlier. Approaches such as *collaborative filtering* attempt to identify subgroups of individuals and make predictions specific to that individual’s group. These approaches are widely used in commercial “big data” applications, and are just beginning to be applied to neuroimaging data; however, such approaches have not yet been widely applied in clinical settings.

SUMMARY AND POTENTIAL APPLICATIONS

Neuroimaging-based biomarkers for pain can be developed, and they have many uses. They could serve to augment pain measurement as part of multimodal assessments, and could be used in clinical trials for multiple purposes [8]. They could help screen drugs for brain penetrance and pharmacodynamic properties in early-stage (Phase 1) trials, demonstrate efficacy in affecting objective, pain-related outcomes in Phase 2 and 3 trials, and separate drug responses from placebo responses based on physiological outcomes in Phase 3 trials, increasing the efficacy of trials and understanding of the mechanisms of drug action in the brain. They can also be used for early identification of risk factors, and thus cost-effective early treatment. They can potentially be used to identify subgroups of healthy individuals and patients with different neurophysiological “types” (sources) of pain, who may respond to different treatments. And, perhaps most importantly, they can provide an increased understanding of the neurophysiological components, or “ingredients,” of pain, and an understanding of how these vary across types of pain, disorders, contexts, and treatments. A biomarker that is predictive of pain or diagnostic of patient status is a first step, an entry point into the assessment of the brain *representations* that constitute the ingredients of pain at the brain level. And understanding pain’s representational basis is the key to developing ways of thinking about and treating pain that are beyond our current vision. It is also the key to comparing representations across species and better understanding how mechanisms discovered and studied in animals apply to humans.

However, developing translationally useful biomarkers requires more rigorous evidence than most scientific studies of brain function [10]. Precise markers must be identified and used prospectively, and they must be diagnostic in individual persons. We must characterize what precisely they are diagnostic of (a specific type of pain? Negative affect? Arousal? Salience?), in different populations and relative to multiple potentially confusable alternative states (emotion, apprehension, distress without the *pain*). Obtaining rigorous evidence requires testing of multiple studies across multiple laboratories as well as the establishment of imaging practices and quality controls so that results can be widely used and trusted. If we embrace this goal and work together, then real advances in the understanding, prevention, and treatment of pain in humans and across species are possible.

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Query Log

Title: Apkarian

Chapter: 2

Query Nos.	Query	Remarks
AQ1	Please confirm whether the expansion introduced for the acronym ADHD in the sentence "In some cases, they ..." is correct.	yes, confirmed
AQ2	Please clarify whether you meant "not yet" here.	yes, "not yet"
AQ3	Please confirm whether the edits made to ref. 4 are correct.	ok
AQ4	Please confirm whether the edits made to ref. 59 are appropriate.	ok