Published in final edited form as:

Pain. 2019 May ; 160(Suppl 1): S37–S48. doi:10.1097/j.pain.0000000000001529.

Deconstructing biomarkers for chronic pain: context and hypothesis dependent biomarker types in relation to chronic pain

Diane Reckziegel^{1,2}, Etienne Vachon-Preseu¹, Bogdan Petre¹, Thomas J. Schnitzer^{2,3,4}, Marwan Baliki¹, and A. Vania Apkarian^{1,2,4,5}

¹Department of Physiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.

²Center for Chronic Pain and Drug Abuse, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.

³Department of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois, USA.

⁴Department of Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

⁵Department of Anesthesia, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Abstract

This review covers advances in the field of developing biomarkers for chronic pain. It outlines the general principles of categorizing types of biomarkers driven by specific hypotheses regarding underlying mechanisms. Within this theoretical construct, example biomarkers are described and their properties expounded. We conclude that the field is advancing in important directions and the developed biomarkers have the potential of impacting both the science and the clinical practice regarding chronic pain.

Introduction

Chronic pain is a complicated multi-dimensional condition minimally characterized as continued suffering with pain long after the initial inciting injury/event subsides. Its temporal boundaries remain ill defined. Although the most common clinically used criterion defines chronic pain as pain persisting for more than 3–6 months, it remains unclear to what extent pains that recur, or flare, over months or years should be considered chronic conditions. The physical boundaries of the types of chronic pain also remain unclear. For example, is migraine that commonly occurs in combination with back pain a new comorbid condition? Or, is it simply the sum of two chronic pain conditions? There is unquestionable evidence now that both peripheral (and spinal cord) as well as supraspinal brain mechanisms are critical for understanding chronic pain [6; 20; 54; 59; 60; 64]. Still, a majority of studies in human conditions, and in animal models, have addressed underlying mechanisms by studying a single type of condition at a time, targeting either peripheral or central

mechanisms, and commonly confounding mechanisms of acute pain with that for chronic pain.

Work in our lab has concentrated primarily on musculoskeletal conditions, mainly on brain parameters that underlie chronic back pain and the transition from acute to chronic back pain [7]. However, we have also sought to look for similarities and differences between chronic back pain, chronic osteoarthritis pain, and complex regional pain syndrome. The current review outlines the progress made specifically regarding mechanisms and related biomarkers for musculoskeletal conditions, emphasizing complimentary insights from human and rodent model studies.

There is recent realization by the National Institutes of Health (NIH) and by the Federal Drug Administration (FDA) that chronic pain and opiate addiction are intricately related and that their combination has had a huge impact on disability, health care costs, and overdose deaths [17; 18; 63]. Perhaps first realized in the USA, there is now similar evidence accumulating worldwide. To combat these massive societal burdens, both NIH and FDA recently launched large initiatives towards the development of novel tools and therapies for combating chronic pain and for diminishing reliance on opiates for managing chronic pain. This effort has emphasized the urgent need for developing validated biomarkers, with the assumption that such biomarkers would in turn facilitate mechanistically driven development of novel therapies. Mechanisms and biomarkers are intricately interrelated and, in this sense, the ongoing work in our lab has been a 20-year search for brain biomarkers for chronic pain. The current review thus charts our viewpoint regarding biomarkers for chronic pain, emphasizing discoveries that point to potential paths for developing novel therapies for chronic pain.

Biomarkers for acute and chronic pain do not mix

Evidence continues to accumulate (both in humans and animal models) indicating that the brain in chronic pain undergoes large scale reorganization. Magnetic resonance spectroscopy shows brain metabolic changes across various regions and pain conditions [24; 25; 27–29]; structural studies indicate that grey matter density and shape change distinctly in different chronic pain conditions [5; 14; 26; 30; 56; 66] not just locally but also in the pattern of interrelationships across the whole neocortex in relation to the duration of persistence of chronic pain [13]; in addition functional connectivity between specific brain regions as well as globally seem to reflect the magnitude of chronic pain [8–12; 15; 22; 23; 38]. Thus, brain activity patterns and related biomarkers derived for pain states [65], or for responses to various medications [21], when studied in acute pain conditions cannot be generalized to chronic pain, and more likely need to be studied for each specific type of chronic pain. The latter leads to the conceptual dilemma that our research community faces, namely, that we still are not certain which chronic pain conditions, and to what extent, share mechanisms with each other.

We have shown a double dissociation between brain activity for thermal painful nociceptive stimuli in contrast to the ongoing fluctuations of pain experienced by individuals with chronic back pain [9]. Intensity of thermal painful stimuli are encoded in the same brain

region in chronic back pain and healthy control subjects. This region (anterior insula) does not reflect perceived fluctuations of chronic back pain, while the brain region (medial prefrontal cortex, mPFC) where magnitude of chronic back pain is reflected does not encode acute thermal stimuli.

Perhaps the best-known brain-derived presumed biomarker for acute pain is the whole-brain multi-voxel pattern generated by Wager and colleagues, labeled neurological pain signature (NPS), [65]. NPS was built from brain blood-oxygen-level dependent responses to thermal stimuli increasing in intensity and giving rise to reports of increased magnitudes of perceived pain. NPS does distinguish between noxious painful stimuli and other emotional states, and generalizes to noxious stimulus response data collected in many different labs [69]. Thus, NPS seems associated with nociceptive signal in the brain, although its specificity remains unclear. Importantly, encoding of noxious stimuli in fibromyalgia cannot be captured by NPS [37]. Instead it needs to be partitioned into its positive and negative components, demonstrating that even the cortical expanse for representation of nociception is disrupted in chronic pain patients, although the NPS-positive component does reflect intensity of noxious stimuli [37].

As an extension of these nociceptive representation studies regarding drug development-related brain targets, a study pooled data across various drug treatments for analgesic efficacy across populations of healthy subjects, patients and for various analgesics. The study demonstrated that, combining machine learning techniques, one could identify reliable associations between drug-related activity modulations and drug efficacy (pharmacodynamics) for acute noxious stimuli, which can then be used to assess new data [21]. Importantly, the authors themselves raise the issue that the method may only be successful for acute stimuli and for single dose drug effects. Thus, it is unlikely that the approach would generalize to chronic pain treatment studies where long-duration repeated administration of therapies is necessary and where one expects that even the same drug treatment may give rise to distinct brain signatures in different chronic pain conditions. Given that we formulate chronic pain as a state of the brain being addicted to nociceptive inputs [7], a simple analogy from the addiction field is informative. There is extensive evidence that brain activity for, as an example, a single bout of alcohol ingestion in healthy subjects has little similarity to brain activity for alcohol ingestion in addicted subjects.

As an actual case example, we take that of ketamine, whose full pharmacokinetic-pharmacodynamic (PKPD) modeling has been performed in both healthy subjects for acute noxious stimuli [53], as well as in chronic complex regional pain syndrome patients [19]. Ketamine is an N-methyl-D-aspartate (NMDA) antagonist and at subanesthetic doses it is a potent analgesic in both acute and chronic pain. Population PKPD modeling details will not be discussed here; only the results in acute and chronic pain cases will be contrasted. Over a 2-hour ketamine infusion, blood levels of the drug and reported analgesia were tightly inter-related for acute painful stimuli, and pain levels returned to baseline in close relationship with clearance of ketamine post-cessation of infusion [53]. In contrast, in a study of a 100-hour ketamine infusion in chronic complex regional pain syndrome patients with 12-weeks of follow-up, model results indicated that relief of neuropathic pain was approximately 50-times lower than that observed for relief of acute noxious pain. Moreover, plasma

concentration of ketamine dropped within hours while its analgesic effect persisted for weeks. And finally, the modeling provided an objective subdivision of participants into subgroups: two types of non-responders and another two types of responders. Thus, overall ketamine analgesia effects are far more complex in the chronic pain condition than in acute pain, and the results in one condition cannot be extrapolated from the other (for more details and other examples see [40; 67]).

Hypothesis-dependent biomarkers for chronic pain

A recent task force evaluated the state of knowledge regarding biomarkers for pain, specifically examining three domains: 1) quantitative sensory testing (QST), 2) skin biopsy, and 3) brain imaging [55]. The review concludes that all three modalities have potential applicability as diagnostic, prognostic, predictive, and pharmacodynamic biomarkers. Yet, they all require further evidence prior to being accepted as valid and reliable biomarkers and to qualify by regulatory agencies for use in clinical trials. Here we want to expand on this opinion emphasizing that such biomarkers will remain inadequate unless they are considered within the construct of mechanistic hypotheses. Moreover, we want to emphasize that hypothesis-driven and validated biomarkers are now available primarily for brain imaging. We surmise that such biomarkers will be accepted as valid and reliable by regulatory agencies only after they demonstrate utility in novel drug development. Figure 1 illustrates the general concept of different stages of chronic pain. The classic (peripheralist) viewpoint has been that all four stages illustrated are controlled and determined by nociceptive afferent properties and their influence on spinal cord circuitry (central sensitization). Within this construct, QST becomes the primary method with which one seeks biomarkers for chronic pain [4]. Additionally, skin biopsies, searching for anatomical evidence that would complement or confirm QST data, assumes that the underlying hypothesis is that anatomy of skin innervation defines and identifies chronic pain states. We presume that, although this approach may yield evidence of some correlates to chronic pain, these at best will be poor associations, mainly because these approaches suffer from a confusion of categories [1; 2; 4]. If one is pursuing biomarkers for pain, be it acute or chronic, peripheral tissue properties are the wrong source of information. The latter may provide information regarding abnormal or heightened nociceptive inputs to the nervous system, but cannot capture conscious subjective pain states that vary in time, context, and are continuously modulated based on recent experiences and acquired memories.

Our position is simple. We posit that: 1) Pain is a subjective conscious perception that is distinct from nociception. It requires brain activity, thus the main search for biomarkers must be an enquiry of underlying brain processes. 2) As similar injuries are commonly observed to only result in chronic pain in a small minority of subjects, and also in most of such conditions the actual injury seems to provide little explanatory value, we assume that the bulk of the risk for chronic pain is based on brain properties, as a consequence of a lifetime accumulation of experiences (nurture) as well as genetic determinants (nature). 3) Even in chronic pain conditions where there may be a blatant nociceptive drive, persistence of pain may itself be sufficient to carve a new brain state with distinct interaction rules between nociceptive activity and the brain interpretation of this activity as pain. Therefore, our lab has been searching for brain biomarkers contributing to the distinct stages of chronic pain.

Here we briefly review parts of these studies specifically from the viewpoint of biomarker development, and within the framework of the stages of chronic pain outlined in Figure 1. This research can be briefly summarized regarding processes controlling these four stages: 1) Limbic-emotional circuitry define predispositions; 2) Emotional-learning mechanisms underlie and control the transitional stage (3), which is a consequence of the interaction between predispositions and injury-related nociceptive inputs to the nervous system. Moreover, maintenance or chronic pain (4) is a new brain state, with distinct anatomical and functional properties (see [7] for more details). Figure 2 establishes the types of biomarkers that one would associate with each of the four stages of chronic pain. Within this construct, properties of each kind of biomarker can be defined.

Properties of prognostic biomarkers (predispositions):

- Pre-existing risks that should remain constant and not change past the transition phase and even in the chronic pain state
- Predictive of the future transition to chronic pain or to remission, therefore, causally linked to underlying mechanisms
- Independent of variations of chronic pain perception
- Validated, pre-existing and stable
- Reveal underlying mechanisms
- Unique signature for predicting chronic pain; should not differ much between different types of chronic pain

Properties of nociceptive biomarkers (injury-related):

- Peripheral or central injuries that enhance nociceptive signaling
- May be transient, episodic, or persistent
- Peripheral QST, skin biopsies, stress indicators, lifestyle may also contribute

Properties of preventive biomarkers (transition-related):

- Reflect consequences of the interaction between predispositions and injury
- Critical phase where mechanisms determine who persists and who recovers
- Underlying mechanisms are prime targets for developing prevention therapies

Properties of diagnostic biomarkers (maintenance-related):

- Emergent in time, therefore should be a consequence of transitioning into the maintenance stage of chronic pain; should also be reversible with appropriate therapeutic treatment
- Should track variations in chronic pain perception
- Generalize across types of chronic pain or be specific to a given type of chronic pain

- Validated and stable as long as the chronic pain persists
- Differentiate between chronic pain and other negative mood states

Disruption of information sharing as a diagnostic biomarker

An example of a diagnostic brain biomarker that seems common across musculoskeletal chronic pain conditions and that also generalizes across species is related to global disruption of functional connectivity within the neocortex, which here we refer to as information sharing. What follows is a brief review of its properties and the extent to which it fulfills the requirements listed above as a candidate prognostic biomarker. In data obtained from a series of studies in people with chronic pain, global information disruption was calculated from brain functional magnetic resonance imaging data. For each subject and every neocortical location, the extent of information sharing with the rest of the brain was derived, labeled degree, which is defined as the number of brain locations with which activity fluctuations within a given region covaries (correlates at a fixed threshold). The whole-brain degree map then represents the spatial pattern of information sharing (which brain locations dominate information sharing). Such maps can be derived for healthy subjects, and also for chronic back pain, complex regional pain syndrome, and chronic knee osteoarthritis patients. Voxel-wise comparison of a single subject to a group of healthy subjects can then be used to derive global deviation from normal degree maps, characterized by rank order disruption index (k_D), the slope of deviation of each subject relative to the healthy control mean. It could be demonstrated that group average, and individual subject k_D , significantly deviated from zero, in all three patient populations (figure 3A) [38]. Moreover, the extent of deviation was proportional to individual subjects' reported magnitude of chronic pain [38]. Importantly, k_D was shown to be present everywhere in the brain of chronic pain patients, as random subsamples of voxels replicated k_D [38]. Acute thermal stimuli did not induce disruption of information sharing ($k_D = 0$) [38]. In subacute back pain patients, k_D emerged slowly in time only in patients where back pain persisted for about one year. The same relationship was also observed in neuropathic injured rats in contrast to sham injury, where BOLD was measured under anesthesia and k_D emerged at later times after peripheral injury (figure 3B) [38]. To validate the results, k_D was computed in a new sample of chronic back pain and chronic osteoarthritis pain patients, and used to derive individual subject chronic pain intensity, resulting in a strong correlation between predicted and reported pain (figure 3C). For more details see [38]. It should be noted that localized degree map disruptions could also be identified specifically for each chronic pain condition. Thus, localized information disruption is present in these patients in parallel to global information disruption. It remains unclear whether persistent negative moods (anxiety or depression) may give rise to similar global information disruptions. We surmise that most likely they would induce specific localized information disruption, but these remain to be established.

In order to test the sensitivity of global information disruption with therapy, here we explore potential changes in this measure following opioid withdrawal. To this end, we examined global and local functional reorganization associated with an acute opioid withdrawal (24 hours) in one patient who was on long-term opioid therapy for several years. The patient was

scanned before (visit 1), and at 24 hours after (visit 2) abstinence of opioid medication. Withdrawal of opioid was associated with increased spontaneous pain from 7 to 9 (on a 0 to 10 numeric rating scale). We observed rank order disruption of a magnitude closely corresponding to that in chronic back pain patients, which was further exacerbated with medication abstinence (figure 4A). To investigate local nodal degree changes following opioid withdrawal, we identified the top 1% of voxels showing either increased or decreased functional connectivity between the two scans. Opioid withdrawal increased nodal degree in bilateral primary and secondary sensory regions and anterior cingulate cortex, and decreased nodal degree in frontal regions and amygdala (figure 4B). These are encouraging results as they show global network reorganization with opioid withdrawal, but they are not placebo controlled and remain to be studied in a larger cohort. Taken together, these results are consistent and suitable for k_D to be considered a validated diagnostic marker for musculoskeletal chronic pain, that may be useful even in assessing efficacy of therapies for chronic pain.

Grey matter reorganization as a diagnostic biomarker

The Apkarian lab has pioneered the concept that chronic pain is associated with brain anatomical reorganization, especially grey matter density changes [5]. The concept has now been replicated in hundreds of studies, in many pain conditions, and meta-analyses show the impact of pain on the anatomy of diverse brain circuitry [14; 56]. In a longitudinal study, we have shown that such changes emerge in time, only in the patients who are transitioning to chronic pain, and that the regional grey matter density shifts are related to functional disruption in proportion to the magnitude of experienced pain [12]. Moreover, there is evidence that when chronic pain is properly treated and is diminished, at least some of the cortical reorganization reverses towards normal [52]. These results seem to generalize to rodent models of chronic pain where, following neuropathic injury, in time, cortical regional grey matter decreases emerge [51]. Similar to functional disruption, grey matter reorganization also shows both regional and global changes [13], where the global reorganization impacts on the grey matter density as a function of distance within the neocortex (figure 5A, B). While global functional disruption is tightly linked to chronic pain intensity (above), anatomical global reorganization (average covariance change across the whole neocortex) reflects the duration of persistence of chronic pain (figure 5C). Thus, cortical grey matter reorganization has the necessary characteristics to be considered a diagnostic biomarker for chronic pain. Yet, the bulk of studies in the topic have been done in small groups of subjects, remain mainly exploratory in nature, and validation of findings are lacking. Much larger population-based studies are needed, and here we are concerned with whether subtle differences in brain imaging acquisition parameters among centers may disrupt the small anatomical changes observed. We also do not know the similarity of observed changes to ones expected to be seen in negative mood conditions.

Prognostic biomarkers

Prognostic biomarkers are of great interest as they unravel causal mechanistic insights regarding brain circuitry that controls transition to chronic pain. As the bulk of research in chronic pain is performed in cross-sectional contrasts, such studies tend to confound

between prognostic and diagnostic measures and thus mix causes with consequences of chronic pain. Our longitudinal study in which we tracked subacute back pain patients (SBP) through transition to either recovery (SBPr) or persistence (SBPp) remains the only human study of this kind and has yielded a long list of parameters that are predictive, at time of entry into the study, in differentiating between SBPp and SBPr one year later. Importantly the study was designed such that all SBP subjects entering the study met a minimum baseline ongoing pain intensity for a minimal duration. Thus, patients who a year later were classified as SBPp or SBPr started with equivalent initial back pain intensities and thus also generally matched for qualitative pain properties and level of depression (figure 6A, B).

The main predictive outcome that we could identify was the mPFC-NAc functional connectivity [12]. Subsequent animal model studies indicated that optogenetic [34] and chemogenetic [48] manipulations of this circuitry can modulate neuropathic pain-like behavior in rodents as well. Involvement of this circuitry in chronic pain in turn suggests that chronic pain may be viewed as the brain becoming addicted to nociception (figure 6C). We further expound below on the properties of mPFC-NAc in the human longitudinal study to demonstrate that it meets the necessary properties to be considered a prognostic biomarker.

In this longitudinal study, the functional connectivity of mPFC-NAc, identified at baseline when group mean pain levels were similar, differentiated SBPp and SBPr groups, one year prior to their clinical differentiation as persistent and recovering. This difference remained constant at four different time points over the year (figure 7A), and accurately differentiated between the groups, which could be replicated in a new cohort (figure 7B). Given that these results are consistent with rodent evidence that the same circuit causally controls neuropathic pain-like behaviors, it can be concluded that properties of this circuit are a mechanistically important prognostic biomarker, at least for CBP. It remains unclear whether this circuit is also prognostic of transition to chronic pain in other pain conditions, although the results suggest that this biomarker is independent of negative mood states [12]. Very similar properties have been observed for mesolimbic white matter distortions, where regional fractional anisotropy (FA) differences predict SBPp and SBPr groupings one year later [39]. In addition, we have also observed that hippocampal and amygdala volumes, as well as mesolimbic brain functional connectivity, and white matter structural connectivity also are predictive of future SBPp and SBPr groupings in the future [62].

Nociceptive biomarkers

Tissue integrity assessments and related quantitative sensory testing have been extensively studied as potential diagnostic and/or prognostic biomarkers for chronic pain, with the hypothesis that such processes are necessary and sufficient for understanding chronic pain. Here we have argued that studying such parameters with no consideration of their interaction with predisposing factors would not seriously advance the field. Unfortunately, brain biomarkers and injury-related biomarkers have not been integrated with each other, and thus overall the influence of one over the other remains to be uncovered.

Preventive biomarkers

We hypothesize that the transitional stage is a critical and malleable phase in developing chronic pain. Brain, especially learning and memory circuitry that are embedded within the limbic brain and that are controlled by emotional states and emotional memories, and perhaps peripheral changes, determine and can carve new neocortical circuits as well as new spinal cord circuits. Thus, control mechanisms and related biomarkers of the transition state can be used to abrogate the transition and thus rescue patients from a lifetime of suffering with chronic pain. As the temporal boundaries of the transition state remain unclear, and clinically this window is often not even available (within the health care system, patients are seen in acute pain or in chronic pain, but rarely in the transition phase), we have little knowledge regarding the underlying processes. Potentially this window is readily available in animal model studies but traditionally little attention has been paid to the notion of a transitional state, especially in studies of spinal cord circuitry and peripheral afferent inputs. Yet at least in the mesolimbic circuitry, there is evidence of time-dependent changes in brain morphology, receptor expression, adult hippocampal neurogenesis, and excitability of various circuits and cell types [3; 16; 31; 34; 36; 42; 44; 45; 47–50; 68], all of which may be considered targets with potential utility in preventing transition to chronic pain. These complex changes and their interactions also highlight the important concept of the florid large-scale changes that brain circuitry undergoes in the transitional phase between acute and chronic pain. Which of these events are critical and which are secondary consequences remain to be determined to properly implement prevention therapies.

Concluding remarks

Here we charted a roadmap for biomarker development within a hypothesis-driven construct of mechanisms underlying chronic pain. The topic is still larger, and other domains that may in fact provide additional critical biomarker information have not been covered. Importantly, we have avoided discussing genetic factors and electroencephalographic (EEG) biomarkers, as well as bloodborne cytokine and chemokines. The genetics of chronic pain remains a confusing topic, as many of the early gene associations have not been replicated in larger studies [43]. Yet, undoubtedly genetic and epigenetic variations play a critical role especially in prognostic biomarkers, and their influence needs to be uncovered. Given the need of large samples, one worries about proper phenotyping, and the heterogeneity, of patient populations being studied. Perhaps a simpler approach would be to explore the genetic influence of biomarkers derived from brain neuroimaging analyses. To our knowledge no EEG biomarkers have been identified for chronic pain [46], although important efforts in this direction are underway [32; 33; 35; 41]. Implementing EEG technology is becoming less costly and its analysis is getting automated; thus, it could be readily used in a routine clinical setting if its utility can be demonstrated.

The current review emphasizes a rationale and context-dependent roadmap, and illustrates the state-of-the-art, in the topic of biomarkers for chronic pain. The candidate biomarkers illustrated are important steps forward, and they are currently being tested in new clinical trials as to their validity and usefulness in studying novel therapies. Although not covered here, we have used a similar approach to develop prognostic biomarkers for placebo

response in the clinical setting [57; 58; 61]. It remains imperative that we and others demonstrate that such markers, in fact, lead to more efficient, mechanism-driven, novel discoveries for treating the pain patient. Only such successes will change the clinical and research course of the field.

Acknowledgements

The authors acknowledge support by National Institute of Dental and Craniofacial Research (DE022746), National Center for Complementary and Integrative Health (AT007987) and National Institute on Drug Abuse (DA044121).

References

- [1]. Apkarian AV. Definitions of nociception, pain, and chronic pain with implications regarding science and society. *Neuroscience letters* 2018.
- [2]. Apkarian AV. Nociception, Pain, Consciousness, and Society: A Plea for Constrained Use of Pain-related Terminologies. *The journal of pain : official journal of the American Pain Society* 2018;19(11):1253–1255. [PubMed: 29890297]
- [3]. Apkarian AV, Mutso AA, Centeno MV, Kan L, Wu M, Levinstein M, Banisadr G, Gobeske KT, Miller RJ, Radulovic J, Hen R, Kessler JA. Role of adult hippocampal neurogenesis in persistent pain. *Pain* 2016;157(2):418–428. [PubMed: 26313405]
- [4]. Apkarian AV, Reckziegel D. Peripheral and central viewpoints of chronic pain, and translational implications. *Neuroscience letters* 2018 In press.
- [5]. Apkarian AV, Sosa Y, Sonty S, Levy RE, Harden RN, Parrish TB, Gitelman DR. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 2004;24:10410–10415. [PubMed: 15548656]
- [6]. Arendt-Nielsen L, Graven-Nielsen T. Translational musculoskeletal pain research. *Best practice & research Clinical rheumatology* 2011;25(2):209–226. [PubMed: 22094197]
- [7]. Baliki MN, Apkarian AV. Nociception, Pain, Negative Moods, and Behavior Selection. *Neuron* 2015;87(3):474–491. [PubMed: 26247858]
- [8]. Baliki MN, Baria AT, Apkarian AV. The cortical rhythms of chronic back pain. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2011;31(39):13981–13990. [PubMed: 21957259]
- [9]. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, Apkarian AV. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *J Neurosci* 2006;26(47):12165–12173. [PubMed: 17122041]
- [10]. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J Neurosci* 2008;28(6):1398–1403. [PubMed: 18256259]
- [11]. Baliki MN, Mansour AR, Baria AT, Apkarian AV. Functional Reorganization of the Default Mode Network across Chronic Pain Conditions. *PloS one* 2014;9(9):e106133. [PubMed: 25180885]
- [12]. Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature neuroscience* 2012;15(8):1117–1119. [PubMed: 22751038]
- [13]. Baliki MN, Schnitzer TJ, Bauer WR, Apkarian AV. Brain morphological signatures for chronic pain. *PloS one* 2011;6(10):e26010. [PubMed: 22022493]
- [14]. Cauda F, Palermo S, Costa T, Torta R, Duca S, Vercelli U, Geminiani G, Torta DM. Gray matter alterations in chronic pain: A network-oriented meta-analytic approach. *NeuroImage Clinical* 2014;4:676–686. [PubMed: 24936419]
- [15]. Cecchi GA, Huang L, Hashmi JA, Baliki M, Centeno MV, Rish I, Apkarian AV. Predictive dynamics of human pain perception. *PLoS computational biology* 2012;8(10):e1002719. [PubMed: 23133342]

- [16]. Chang PC, Pollema-Mays SL, Centeno MV, Prociassi D, Contini M, Baria AT, Martina M, Apkarian AV. Role of nucleus accumbens in neuropathic pain: linked multi-scale evidence in the rat transitioning to neuropathic pain. *Pain* 2014;155(6):1128–1139. [PubMed: 24607959]
- [17]. Collins FS, Anderson JM, Austin CP, Battey JF, Birnbaum LS, Briggs JP, Clayton JA, Cuthbert B, Eisinger RW, Fauci AS, Gallin JI, Gibbons GH, Glass RI, Gottesman MM, Gray PA, Green ED, Greider FB, Hodes R, Hudson KL, Humphreys B, Katz SI, Koob GF, Koroshetz WJ, Lauer MS, Lorsch JR, Lowy DR, McGowan JJ, Murray DM, Nakamura R, Norris A, Perez-Stable EJ, Pettigrew RI, Riley WT, Rodgers GP, Sieving PA, Somerman MJ, Spong CY, Tabak LA, Volkow ND, Wilder EL. Basic science: Bedrock of progress. *Science* 2016;351(6280):1405.
- [18]. Collins FS, Koroshetz WJ, Volkow ND. Helping to End Addiction Over the Long-term: The Research Plan for the NIH HEAL Initiative. *Jama* 2018;320(2):129–130. [PubMed: 29896636]
- [19]. Dahan A, Olofsen E, Sigtermans M, Noppers I, Niesters M, Aarts L, Bauer M, Sarton E. Population pharmacokinetic-pharmacodynamic modeling of ketamine-induced pain relief of chronic pain. *Eur J Pain* 2011;15(3):258–267. [PubMed: 20638877]
- [20]. Davis KD, Flor H, Greely HT, Iannetti GD, Mackey S, Ploner M, Pustilnik A, Tracey I, Treede RD, Wager TD. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. *Nat Rev Neurol* 2017;13(10):624–638. [PubMed: 28884750]
- [21]. Duff EP, Vennart W, Wise RG, Howard MA, Harris RE, Lee M, Wartolowska K, Wanigasekera V, Wilson FJ, Whitlock M, Tracey I, Woolrich MW, Smith SM. Learning to identify CNS drug action and efficacy using multistudy fMRI data. *Science translational medicine* 2015;7(274):274ra216.
- [22]. Farmer MA, Baliki MN, Apkarian AV. A dynamic network perspective of chronic pain. *Neuroscience letters* 2012;520(2):197–203. [PubMed: 22579823]
- [23]. Farmer MA, Chanda ML, Parks EL, Baliki MN, Apkarian AV, Schaeffer AJ. Brain functional and anatomical changes in chronic prostatitis/chronic pelvic pain syndrome. *The Journal of urology* 2011;186(1):117–124. [PubMed: 21571326]
- [24]. Grachev ID, Fredrickson BE, Apkarian AV. Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. *Pain* 2000;89(1):7–18. [PubMed: 11113288]
- [25]. Grachev ID, Fredrickson BE, Apkarian AV. Brain chemistry reflects dual states of pain and anxiety in chronic low back pain. *J Neural Transm* 2002;109(10):1309–1334. [PubMed: 12373563]
- [26]. Gwilym SE, Fillipini N, Douaud G, Carr AJ, Tracey I. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty; a longitudinal voxel-based-morphometric study. *Arthritis and rheumatism* 2010;62(10), 2930–2940. [PubMed: 20518076]
- [27]. Harfeldt K, Alexander L, Lam J, Mansson S, Westergren H, Svensson P, Sundgren PC, Alstergren P. Spectroscopic differences in posterior insula in patients with chronic temporomandibular pain. *Scand J Pain* 2018;18(3):351–361. [PubMed: 29794260]
- [28]. Harper DE, Ichesco E, Schrepf A, Halvorson M, Puiu T, Clauw DJ, Harris RE, Harte SE, Network MR. Relationships between brain metabolite levels, functional connectivity, and negative mood in urologic chronic pelvic pain syndrome patients compared to controls: A MAPP research network study. *NeuroImage Clinical* 2018;17:570–578. [PubMed: 29201643]
- [29]. Harris RE, Clauw DJ. Imaging central neurochemical alterations in chronic pain with proton magnetic resonance spectroscopy. *Neuroscience letters* 2012;520(2):192–196. [PubMed: 22445845]
- [30]. Kim JH, Suh SI, Seol HY, Oh K, Seo WK, Yu SW, Park KW, Koh SB. Regional grey matter changes in patients with migraine: a voxel-based morphometry study. *Cephalalgia* 2008;28(6): 598–604. [PubMed: 18422725]
- [31]. Kiritoshi T, Neugebauer V. Pathway-Specific Alterations of Cortico-Amygdala Transmission in an Arthritis Pain Model. *ACS Chem Neurosci* 2018;9(9):2252–2261. [PubMed: 29630339]
- [32]. Koyama S, LeBlanc BW, Smith KA, Roach C, Levitt J, Edhi MM, Michishita M, Komatsu T, Mashita O, Tanikawa A, Yoshikawa S, Saab CY. An Electroencephalography Bioassay for Preclinical Testing of Analgesic Efficacy. *Scientific reports* 2018;8(1):16402. [PubMed: 30401974]

- [33]. Koyama S, Xia J, Leblanc BW, Gu JW, Saab CY. Sub-paresthesia spinal cord stimulation reverses thermal hyperalgesia and modulates low frequency EEG in a rat model of neuropathic pain. *Scientific reports* 2018;8(1):7181. [PubMed: 29740068]
- [34]. Lee M, Manders TR, Eberle SE, Su C, D'Amour J, Yang R, Lin HY, Deisseroth K, Froemke RC, Wang J. Activation of corticostriatal circuitry relieves chronic neuropathic pain. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2015;35(13):5247–5259. [PubMed: 25834050]
- [35]. Levitt J, Nitenson A, Koyama S, Heijmans L, Curry J, Ross JT, Kamerling S, Saab CY. Automated detection of electroencephalography artifacts in human, rodent and canine subjects using machine learning. *Journal of neuroscience methods* 2018;307:53–59. [PubMed: 29944891]
- [36]. Li XY, Ko HG, Chen T, Descalzi G, Koga K, Wang H, Kim SS, Shang Y, Kwak C, Park SW, Shim J, Lee K, Collingridge GL, Kaang BK, Zhuo M. Alleviating neuropathic pain hypersensitivity by inhibiting PKMzeta in the anterior cingulate cortex. *Science* 2010;330(6009):1400–1404. [PubMed: 21127255]
- [37]. Lopez-Sola M, Woo CW, Pujol J, Deus J, Harrison BJ, Monfort J, Wager TD. Towards a neurophysiological signature for fibromyalgia. *Pain* 2017;158(1):34–47. [PubMed: 27583567]
- [38]. Mansour A, Baria AT, Tetreault P, Vachon-Presseau E, Chang PC, Huang L, Apkarian AV, Baliki MN. Global disruption of degree rank order: a hallmark of chronic pain. *Scientific reports* 2016;6:34853. [PubMed: 27725689]
- [39]. Mansour AR, Baliki MN, Huang L, Torbey S, Herrmann KM, Schnitzer TJ, Apkarian AV. Brain white matter structural properties predict transition to chronic pain. *Pain* 2013;154(10):2160–2168. [PubMed: 24040975]
- [40]. Martini C, Olofsen E, Yassen A, Aarts L, Dahan A. Pharmacokinetic-pharmacodynamic modeling in acute and chronic pain: an overview of the recent literature. *Expert Rev Clin Pharmacol* 2011;4(6):719–728. [PubMed: 22111858]
- [41]. May ES, Nickel MM, Ta Dinh S, Tiemann L, Heitmann H, Voth I, Tolle TR, Gross J, Ploner M. Prefrontal gamma oscillations reflect ongoing pain intensity in chronic back pain patients. *Human brain mapping* 2019;40(1):293–305. [PubMed: 30260531]
- [42]. Metz AE, Yau HJ, Centeno MV, Apkarian AV, Martina M. Morphological and functional reorganization of rat medial prefrontal cortex in neuropathic pain. *Proceedings of the National Academy of Sciences of the United States of America* 2009;106(7):2423–2428. [PubMed: 19171885]
- [43]. Mogil JS. Pain genetics: past, present and future. *Trends in genetics* 2012;28(6):258–266. [PubMed: 22464640]
- [44]. Mutso AA, Radzicki D, Baliki MN, Huang L, Banisadr G, Centeno MV, Radulovic J, Martina M, Miller RJ, Apkarian AV. Abnormalities in hippocampal functioning with persistent pain. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2012;32(17):5747–5756. [PubMed: 22539837]
- [45]. Neugebauer V, Li W, Bird GC, Bhawe G, Gereau RW. Synaptic plasticity in the amygdala in a model of arthritic pain: differential roles of metabotropic glutamate receptors 1 and 5. *J Neurosci* 2003;23(1):52–63. [PubMed: 12514201]
- [46]. Ploner M, May ES. Electroencephalography and magnetoencephalography in pain research-current state and future perspectives. *Pain* 2018;159(2):206–211. [PubMed: 29944612]
- [47]. Pollema-Mays SL, Centeno MV, Chang Z, Apkarian AV, Martina M. Reduced DeltaFosB expression in the rat nucleus accumbens has causal role in the neuropathic pain phenotype. *Neuroscience letters* 2018.
- [48]. Ren W, Centeno MV, Berger S, Wu Y, Na X, Liu X, Kondapalli J, Apkarian AV, Martina M, Surmeier DJ. The indirect pathway of the nucleus accumbens shell amplifies neuropathic pain. *Nature neuroscience* 2016;19(2):220–222. [PubMed: 26691834]
- [49]. Ren WJ, Liu Y, Zhou LJ, Li W, Zhong Y, Pang RP, Xin WJ, Wei XH, Wang J, Zhu HQ, Wu CY, Qin ZH, Liu G, Liu XG. Peripheral Nerve Injury Leads to Working Memory Deficits and Dysfunction of the Hippocampus by Upregulation of TNF-alpha in Rodents. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2011;36(5):979–992. [PubMed: 21289602]

- [50]. Schwartz N, Temkin P, Jurado S, Lim BK, Heifets BD, Polepalli JS, Malenka RC. Chronic pain. Decreased motivation during chronic pain requires long-term depression in the nucleus accumbens. *Science* 2014;345(6196):535–542. [PubMed: 25082697]
- [51]. Seminowicz DA, Laferriere AL, Millicamps M, Yu JS, Coderre TJ, Bushnell MC. MRI structural brain changes associated with sensory and emotional function in a rat model of long-term neuropathic pain. *NeuroImage* 2009;47(3):1007–1014. [PubMed: 19497372]
- [52]. Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2011;31(20):7540–7550. [PubMed: 21593339]
- [53]. Sigtermans M, Dahan A, Mooren R, Bauer M, Kest B, Sarton E, Olofsen E. S(+)-ketamine effect on experimental pain and cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. *Anesthesiology* 2009;111(4):892–903. [PubMed: 19741495]
- [54]. Smith SM, Dworkin RH, Turk DC, Baron R, Polydefkis M, Tracey I, Borsook D, Edwards RR, Harris RE, Wager TD, Arendt-Nielsen L, Burke LB, Carr DB, Chappell A, Farrar JT, Freeman R, Gilron I, Goli V, Haeussler J, Jensen T, Katz NP, Kent J, Kopecky EA, Lee DA, Maixner W, Markman JD, McArthur JC, McDermott MP, Parvathani L, Raja SN, Rappaport BA, Rice AS, Rowbotham MC, Tobias JK, Wasan AD, Witter J. The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. *The journal of pain : official journal of the American Pain Society* 2017.
- [55]. Smith SM, Dworkin RH, Turk DC, Baron R, Polydefkis M, Tracey I, Borsook D, Edwards RR, Harris RE, Wager TD, Arendt-Nielsen L, Burke LB, Carr DB, Chappell A, Farrar JT, Freeman R, Gilron I, Goli V, Haeussler J, Jensen T, Katz NP, Kent J, Kopecky EA, Lee DA, Maixner W, Markman JD, McArthur JC, McDermott MP, Parvathani L, Raja SN, Rappaport BA, Rice ASC, Rowbotham MC, Tobias JK, Wasan AD, Witter J. The Potential Role of Sensory Testing, Skin Biopsy, and Functional Brain Imaging as Biomarkers in Chronic Pain Clinical Trials: IMMPACT Considerations. *The journal of pain : official journal of the American Pain Society* 2017;18(7):757–777. [PubMed: 28254585]
- [56]. Tatu K, Costa T, Nani A, Diano M, Quarta DG, Duca S, Apkarian AV, Fox PT, Cauda F. How do morphological alterations caused by chronic pain distribute across the brain? A meta-analytic co-alteration study. *NeuroImage Clinical* 2018;18:15–30. [PubMed: 30023166]
- [57]. Tetreault P, Baliki MN, Baria AT, Bauer WR, Schnitzer TJ, Apkarian AV. Inferring distinct mechanisms in the absence of subjective differences: Placebo and centrally acting analgesic underlie unique brain adaptations. *Human brain mapping* 2018;39(5):2210–2223. [PubMed: 29417694]
- [58]. Tetreault P, Mansour A, Vachon-Pressseau E, Schnitzer TJ, Apkarian AV, Baliki MN. Brain Connectivity Predicts Placebo Response across Chronic Pain Clinical Trials. *PLoS biology* 2016;14(10):e1002570. [PubMed: 27788130]
- [59]. Tracey I Can neuroimaging studies identify pain endophenotypes in humans? *Nat Rev Neurol* 2011;7(3):173–181. [PubMed: 21304481]
- [60]. Tsuda M, Inoue K, Salter MW. Neuropathic pain and spinal microglia: a big problem from molecules in “small” glia. *Trends Neurosci* 2005;28(2):101–107. [PubMed: 15667933]
- [61]. Vachon-Pressseau E, Berger SE, Abdullah TB, Huang L, Cecchi GA, Griffith JW, Schnitzer TJ, Apkarian AV. Brain and psychological determinants of placebo pill response in chronic pain patients. *Nature communications* 2018;9(1):3397.
- [62]. Vachon-Pressseau E, Tetreault P, Petre B, Huang L, Berger SE, Torbey S, Baria AT, Mansour AR, Hashmi JA, Griffith JW, Comasco E, Schnitzer TJ, Baliki MN, Apkarian AV. Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain* 2016;139(7), 1958–1970 [PubMed: 27190016]
- [63]. Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain--Misconceptions and Mitigation Strategies. *The New England journal of medicine* 2016;374(13):1253–1263. [PubMed: 27028915]
- [64]. von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron* 2012;73(4):638–652. [PubMed: 22365541]

- [65]. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. *The New England journal of medicine* 2013;368(15):1388–1397. [PubMed: 23574118]
- [66]. Yamasue H, Kasai K, Iwanami A, Ohtani T, Yamada H, Abe O, Kuroki N, Fukuda R, Tochigi M, Furukawa S, Sadamatsu M, Sasaki T, Aoki S, Ohtomo K, Asukai N, Kato N. Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. *ProcNatl AcadSciUS A* 2003;100(15):9039–9043.
- [67]. Yassen A, Passier P, Furuichi Y, Dahan A. Translational PK-PD modeling in pain. *J Pharmacokinet Pharmacodyn* 2013;40(3):401–418. [PubMed: 23197248]
- [68]. Zhang Z, Gadotti VM, Chen L, Souza IA, Stemkowski PL, Zamponi GW. Role of Prelimbic GABAergic Circuits in Sensory and Emotional Aspects of Neuropathic Pain. *Cell reports* 2015;12(5):752–759. [PubMed: 26212331]
- [69]. Zunhammer M, Bingel U, Wager TD, Placebo Imaging C. Placebo Effects on the Neurologic Pain Signature: A Meta-analysis of Individual Participant Functional Magnetic Resonance Imaging Data. *JAMA Neurol* 2018;75(11):1321–1330. [PubMed: 30073258]

Figure 1: Distinct stages that comprise chronic pain.

We have proposed in [7] that chronic pain, in similarity to other chronic conditions, should comprise of 4 distinct stages: 1. Predisposition; 2. Injury or inciting events; 3. Transitional phase, where the system shifts away from an acute state to a chronic condition (persistence of pain), or alternatively, reverts to a pain-free state (recovery); and 4. Maintenance, which is the chronic, long-term, persistence of pain condition, where the system is far less malleable and hard to reverse. Image adapted from [4].

Relevant biomarkers:

Figure 2: Distinct stages of chronic pain define specific biomarker types associated with respective mechanisms.

1. Predisposing factors for chronic pain should define prognostic biomarkers. As such biomarkers define future risk for developing chronic pain they are deemed to be embedded in causal mechanisms that control transition to chronic pain. 2. We presume that QST and skin biopsy measures would best capture the enhanced nociceptive drive associated with the inciting event. These signals may be transient, recurrent, or persistent, depending on the type of chronic pain. In all cases, their interaction with prognostic biomarkers is critical to development of chronic pain. 3. The transitional state is most likely the most unstable state of the processes underlying chronic pain. Thus, understanding its mechanisms and associated biomarkers should lead to processes that control transition to recovery or to persistence, and thus is the best candidate for identification of biomarkers for prevention of transition to chronic pain. 4. Maintenance or chronic pain state should be associated with diagnostic biomarkers, which may be either defining large categories of chronic pain, such as musculoskeletal, or specific to a condition such as chronic back pain. Image adapted from [4].

Figure 3: Global disruption of functional information sharing as a diagnostic biomarker for chronic pain.

A. Human data: Top row: Group average voxel-wise shift in functional information sharing relative to off-site group of healthy subjects, in CBP, CRPS, OA, and within site healthy controls. The shift of the slope away from zero defines the extent of disruption. Inserts are individual patient slopes, k_D s. Second row: Individual patient k_D values reflect magnitude of back pain at the time of brain scan. In all three musculoskeletal chronic pain groups information disruption is proportional to pain magnitude. **B. Rat neuropathic pain model:**

Rats received either spared nerve injury (SNI) or sham surgery. Resting state blood oxygenation level dependent scans were done at 5 and 28 days after surgery. Left panel: SNI, but not sham, animals exhibit tactile allodynia at 5 and 28 days after injury. Right panels: At 5 days after injury there is no evidence of information disruption, while at 28 days SNI neocortex exhibits group and individual animal k_D shifts (which were correlated to tactile allodynia). **C. Validation in new patient sample:** In new cohorts of CBP and OA patients, individual k_D measures were used to predict perceived pain. Observed and predicted pain measures were strongly correlated. Figure adapted from [38]. CBP, chronic back pain; OA, chronic osteoarthritis pain; CRPS, complex regional pain syndrome.

Figure 4: Modulation of global information disruption by drug treatment, in a single patient with a single dose.

A. Degree rank order shift with opioid withdrawal. Scatter plots depict the individual patient k_D compared to an off-site healthy control group before (Visit 1) and 24 hours (Visit 2) after skipping opioid medication dose. **B. Localized connectivity changes with opioid withdrawal.** Distribution of nodal degree differences (visit 2 – visit 1). Red and blue represents the top 1% of nodes that showed increased and decreased connectivity following drug withdrawal, respectively. Brain slices depict the spatial localization of the top 1% nodes that presented functional differences. These results indicate that skipping a single opioid dose further exacerbates information sharing disruption, which was accompanied with increased magnitude of chronic pain.

Figure 5: Global reorganization of grey matter density as a diagnostic biomarker for chronic musculoskeletal chronic pain.

A. Correlation matrices show extent of similarity for grey matter density across Brodmann areas (80 regions of interest, 40 left brain and 40 right brain). It is visually apparent that similarity is disrupted to different extents in the three chronic pain conditions, relative to the healthy subjects. **B.** Correlation matrix values plotted as a function of distance between pairs of regions. In healthy subjects there is an inverse distance to similarity relationship. This pattern is disrupted to different extents in the chronic pain patients. **C.** Extent of overall whole-brain reorganization of grey matter density relative to healthy controls, (Δd), tightly reflects duration of pain experienced in individual patients, with a distinct time-curve for each type of musculoskeletal chronic pain. CBP, chronic back pain; CRPS, chronic regional pain syndrome; OA, chronic osteoarthritis pain; a.u., arbitrary units. Figure adapted from [13].

Figure 6: Longitudinally tracking subacute back pain patients disambiguates between prognostic and diagnostic biomarkers.

A. Predisposition biomarkers are psychological, and brain structural and functional characteristics that predict who in the future persists or recovers from back pain. **B.** All SBP entering into the study started at the same back pain intensity, half of them persisted at the same back pain one year later (SBPp, becoming CBP), the rest rapidly decreased in back pain intensity and continued to further recover from back pain (SBPr). **C.** A single measure, functional connectivity between two regions (extent of information sharing between medial

prefrontal cortex and nucleus accumbens) predicted future groupings of SBPp and SBPr. Subsequent (upper green arrow) showed that optogenetic stimulation of either the mPFC or the NAc reversed tactile allodynia in neuropathic mice [34]. Also, chemogenetic studies showed that upregulation or downregulation of NAc shell dopamine D2 receptor medium spiny neurons can control tactile allodynia in neuropathic rodents [48]. Question marks indicate other regions within the mesocorticolimbic circuitry where we have initial evidence that chemogenetic manipulations result in controlling neuropathic pain-like behaviors. Thus, human and rodent evidence shows causal relationship of mPFC-NAc circuitry controlling chronic pain. As this circuit has repeatedly been associated with addictive behaviors for rewarding stimuli or drugs, we conclude that the results imply that chronic pain may be viewed as the brain becoming addicted to nociception. CBP, chronic back pain; SBP, subacute back pain; mPFC, medial prefrontal cortex; NAc, nucleus accumbens.

Figure 7: Prefrontal-accumbens functional connectivity is a validated prognostic biomarker for transition to chronic pain.

A. Mean mPFC-NAc functional connectivity at time 0 is higher in SBP who are classified as SBPp one year later, relative to SBPr. This result is based on a whole-brain contrast and post-hoc contrast, thus it is a biased result. mPFC-NAc connectivity at visits 2, 3, and 4 were derived based on coordinates identified in visit 1. These results closely replicate the group difference seen at visit 1, are an unbiased replication, showing the constancy of the result despite back pain intensity shifting away in the two groups (figure 6B). **B.** Left: Receiver operator curves (ROC), using visit 1 data, indicate accuracy (D-values) in differentiating SBPp and SBPr at different time points in the future. Right: In a new sample of SBP, visit 1 mPFC-NAc functional connectivity predicts the SBPp and SBPr groupings 1 year later at about the same accuracy as in the original groups. SBP, subacute back pain; mPFC, medial prefrontal cortex; NAc, nucleus accumbens. Figure adapted from [12].

Figure 8, Table 1,

lists 10 biomarkers that we have identified in the longitudinal study of SBP transitioning to CBP. The block diagram (left) shows the result of path analysis within the limbic brain anatomical and functional circuits, which explains 60% of the variance for risk for chronic pain, independently from initial intensity of back pain (presumably reflecting initial nociceptive drive), adapted from [62]. Our general machine learning approach used a Naïve Bayes classification scheme (right), illustrated for a 2-parameter model using FA and hippocampus volume. The contour map reflects the probability of developing chronic pain, with all SBP participants depicted on the map. Within this general construct, an optimal multi-factor model can be constructed and tested in future clinical trials as to its validity, stability, and generalizability. SBP, subacute back pain; FA, fractional anisotropy; Hipp, hippocampus; Vol, volume.