TITLE

Predictive mechanisms linking brain opioids to chronic pain vulnerability and resilience.

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ABSTRACT

Chronic pain is a major global healthcare problem that is currently inadequately treated. In addition, the current use of opioids for treatment has reached far beyond the paucity of evidence for long-term benefits relative to risks. Benefit-risk models for opioid and non-opioid treatments would benefit from a rational, mechanism-based understanding of neuroplastic and neurochemical contributions to chronic pain. Here we evaluate the findings and limitations of representative research investigating brain neuroplasticity and neurochemistry in chronic pain. In sum, the mechanisms of pain-related neuroplasticity in the brain remain poorly understood because neuroimaging studies have been largely descriptive. We argue that definition is needed of optimal (pain resilient) and suboptimal (pain vulnerable) functioning of the endogenous opioid system in order to identify neurochemical contributions to aberrant neuroplasticity in chronic pain. We outline the potential benefits of computational approaches that utilise evolutionary and statistical optimality principles, illustrating this approach with mechanistic hypotheses on opioid function. In particular, we discuss the role of predictive mechanisms in perceptual and associative plasticity and evidence for their modulation by endogenous opioids. Future research should attempt to utilise formal computational models to provide evidence for the clinical validity of this approach, thereby providing a rational basis for future treatment and ideally prevention.

ABBREVIATIONS

CS: Conditioned Stimulus

EO: Endogenous Opioid

fMRI: functional Magnetic Resonance Imaging

OR: Opioid Receptor

PAG: Periaqueductal Grey

PC: Predictive Coding

RL: Reinforcement Learning

US: Unconditioned Stimulus

INTRODUCTION: THE CHALLENGE OF CHRONIC PAIN

Chronic pain is a major global health problem that is difficult to manage, on account of a number of factors: its high prevalence in the population, comorbidity (for example, with mental ill-health) a high degree of heterogeneity (in symptoms and causal mechanisms), and treatments that are largely poorly targeted to underlying mechanisms.

Prevalence and comorbidity: The prevalence of chronic pain varies from 19% to 50% depending on the survey methods used and definitions of severity (Croft et al., 2010), with arthritis as the most common diagnosis. Increased prevalence and disproportionate disability has been reported in the elderly (Gunzelmann et al., 2002; Eriksen et al., 2003; Mottram et al., 2008), with 62% prevalence in those over 75 in the UK (Fayaz et al., 2016). One of the challenges we face is comorbidity with mental health problems. Chronic pain is consistently linked with an increased risk of depression (Breivik et al., 2013). The comorbidity of pain and depression is associated with a greater burden to the individual and society than either condition alone (Mossey and Gallagher, 2004). There has long been debate as to whether depression is a cause or consequence of chronic pain, but it is widely accepted that the presence of one will at least exacerbate the other (Bair et al., 2003). This raises the question as to whether the overlap between chronic pain and depression reflects a true or artificial comorbidity, i.e. whether there are shared biological vulnerability factors.

Heterogeneity: Heterogeneity poses a serious challenge for research, because it introduces uncontrolled sources of variance, making it difficult to understand causal processes, and limits generalisation of results. How we select patients for research (e.g. according to symptoms criteria) has a bearing on generalisability. We highlight two related types of heterogeneity (Figure 1) which do not have a straightforward relationship. Due to *symptom heterogeneity,* many patients with chronic pain, particularly those diagnosed with arthritis, have a combination of recurrent acute pain and chronic ongoing pain. Indeed, in osteoarthritis there is a generally poor relationship between the severity of joint damage and chronic pain (Jordan et al., 1997; Wood et al., 2008). Even in rheumatoid arthritis, widespread pain unrelated to joint pathology is common (Lee and Weinblatt, 2001; Andersson et al., 2013). It can be argued that this is fundamentally due to *mechanistic heterogeneity*. Chronic pain is increasingly regarded as reflecting a spectrum of mechanisms including nociceptive, neuropathic, and central. For example, chronic ongoing pain in arthritis suggests neuropathic elements (Thakur et al., 2014). Chronic pain conditions in which there is very little evidence

of nociceptive or neuropathic elements, such as atypical facial pain and chronic widespread pain (or fibromyalgia) have recently been termed "nociplastic" pain (from "nociceptive plasticity") to reflect change in function of nociceptive pathways, probably in the central nervous system (Kosek et al., 2016).

Inadequate management: In a European survey, 40% of chronic pain patients reported that their treatment was inadequate (Pain Proposal, 2010). For elderly people in particular, there is a more limited range of pain therapies available because of immobility issues, a lack of efficacy of pain killers (e.g. paracetamol (Roberts et al. 2015)) and/or increased side-effects from pain killers including non-steroidal analgesics and opiates (Shaheed et al., 2016). In the United States, rates of misuse, abuse and addiction to opioids (three use patterns contributing to the so-called "opioid epidemic") are concerning, with misuse estimated to range from 21-29% and addiction from 8-12% (Vowles et al., 2015). This is despite only clinically-unimportant short-term effects on pain and function for guideline-recommended doses in chronic low back pain (Shaheed et al., 2016) and a complete lack of evidence for long-term benefits with concomitant dose-escalating serious risks (Chou et al., 2015). Decision-making for long-term use is currently complex and requires individual benefit-risk assessment vs. the relative benefits of non-opioid therapies, a judgement that is currently not evidence-based (Chou et al., 2015). Generally, patients report a substantial preference for non-drug therapies (Breivik et al., 2006). Surgical therapies for specific pathologies (e.g. brain stimulation (Cruccu et al., 2007)) are limited in usefulness by eligibility, while other orthopaedic procedures are no better than placebo or exercise (Moseley et al., 2002; Kise et al., 2016). Therapies focused on training the brain to deal with pain better, such as cognitive-behavioural therapy (Williams et al., 2012; Kong et al., 2016), hypnosis and neuro-feedback, provide low to moderate effects sizes but potentially long-term benefits and so further research is needed (Jensen et al., 2014).

There is an urgent need to broaden the choice of safe therapies based on an understanding of the brain's own powerful mechanisms of pain relief and resilience. There is also a need for effective predictive models of benefits and risks of different (e.g. opioid) therapies. In this review, we focus on the potential role of the opioid receptor (OR) system in neuroplasticity underlying pain vulnerability and resilience, and outline how future computational models have the potential to identify sub-optimal opioid function and improve patient stratification for treatment.

NEUROPLASTICITY AND OPIOID FUNCTION IN CHRONIC PAIN

BRAIN ORGANISATION IN CHRONIC PAIN

Neuroplasticity (a change in the neuronal response after repeated experience and use), is a fundamental property of the whole brain (Feldman, 2009) observed in all sensory systems (Seitz and Dinse, 2007). Chronic pain is associated with profound changes in brain structure and function reflecting neuroplasticity in midbrain, thalamus and widespread regions of the cerebral cortex (see Table 1 for example studies). A number of different types of experience-dependent neuroplasticity occurring in chronic pain have been observed; for example, changes in somatosensory cortices in Complex Regional Pain Syndrome and back pain (Table 1, and reviewed in detail elsewhere (Di Pietro et al., 2013; Kuner and Flor, 2016; Kuttikat et al., 2016)), changes in connectivity within the "default-mode network" (DMN) and connectivity of the DMN with descending modulatory regions (Table 1, especially Baliki et al., 2014; Kucyi et al., 2014) and changes in the midbrain theorised to relate to the balance of inhibition and facilitation in nociceptive processing in fibromyalgia (Lee et al., 2011; Fallon et al., 2013). However, understanding of cellular and molecular mechanisms contributing to central sensitisation in musculoskeletal pain conditions is largely limited to the spine (reviewed in (Thakur et al., 2014)). Despite a wealth of observational evidence, we have a very limited understanding of whether and how brain neuroplasticity might contribute to chronic pain symptoms and what vulnerability factors underlie this.

While most types of pain, whether acute or chronic, tend to activate the same network of brain regions (Apkarian et al., 2005), there is evidence that acute experimental pain and clinical pain produce subtle differences in extent and amount of activation. For example, in patients with arthritis, clinical pain results in greater activity within prefrontal, cingulate and insula cortices, amygdala and putamen compared to intensity-matched experimental acute pain (Kulkarni et al., 2007). However, interpretation of these findings is complicated by the fact that many differences in pain processing are likely to be due to differences in psychological comorbidities. In patients with fibromyalgia, depression is associated with increased experimental pain responses in the amygdala and insula cortex compared to those without depression (Giesecke et al., 2005). More extensive differences, including greater prefrontal and parietal responses (Gracely et al., 2004) have been associated with high levels of pain catastrophising in chronic pain patients. More promisingly, functional magnetic resonance imaging (fMRI) studies of natural fluctuations in back pain have demonstrated

activations of medial prefrontal cortices that appear to be quite specific to coding chronic pain intensity (Baliki et al., 2006, 2011). Still, the mechanisms underlying these observations are unknown.

BRAIN REORGANISATION AFFECTING OPIOIDERGIC FUNCTION

Neurochemical differences in chronic pain have been well reviewed (Tracey and Mantyh, 2007; Morton and Jones, 2016) and include changes in dopaminergic, opioid and GABA receptor systems. Evidence is consistent with the endogenous opioid (EO) system being activated mainly within the medial pain system during chronic pain including arthritic and neuropathic pain (Table 1). In chronic pain, observations of neuroplasticity within the network of brain regions mediating opioid-dependent analgesia point to the possibility of altered output properties of descending controls conferring states of pain vulnerability (Table 1). These might either reflect increased occupation by EOs or a fall-out of ORs. In relation to post-stroke pain, we favour the latter interpretation as naloxone failed to alter the pain in our study (Jones et al., 2004) and this would also explain the requirement for higher doses of synthetic opiates in this type of pain (Rowbotham et al., 2003).

Given the anatomical overlap between brain regions binding exogenous opioids and those undergoing neuroplasticity in chronic pain, an important consideration is whether opioid treatment for chronic pain is one potential driver of observed neuroplasticity. Evidence supporting this thesis is limited to studies of long-term opiate users showing deficits in certain cognition functions, namely fear-learning (Basden et al., 2016), prospective memory (Terrett et al., 2014) and episodic foresight (imagining the future) (Terrett et al., 2017), known to involve medial prefrontal interactions with basal ganglia (Peira et al., 2016) that undergo neuroplasticity in chronic pain (Baliki et al., 2014). While cause and effect (between opioid use and cognitive deficits) cannot be established from these studies, observations of changes in opioidergic and dopaminergic circuits and regions predicting chronic pain in the striatum (Baliki et al., 2012), point to the possibility that reinforcement-related changes in both brain plasticity and behaviour in relation to opioid use and misuse may overlap with some of the observations of chronic pain neuroplasticity. In relation to this it has been hypothesised that changes in motivational learning may be a vulnerability factor for chronic pain (Mansour et al., 2014).

Pain vulnerability resulting from neuroplasticity in the opioid system could be countered by physiologically enhancing pain resilience. One possibility is to inhibit the breakdown of endogenous opioids with inhibitors of natural enkephalinases in the brain (Le et al., 2003).

Another possibility is increasing OR density through yet-to-be-discovered mechanisms. Indeed, our recent study of patients with arthritis (Brown et al., 2015) suggest that variability in OR density is a natural aspect of endogenous pain regulation. In particular, patients with greater recent clinical pain had greater OR binding (consistent with greater OR density) in the striatum, thalamus, insula and periaqueductal grey (PAG). Evidence for this being a possible mechanism of pain resilience is that binding in the striatum (caudate nucleus) was also correlated positively with acute pain threshold in both patients with arthritis and normal pain-free volunteers. The mechanism by which this occurs is not clear but one possibility is that delta OR agonism (as a result of EO release in response to pain) upregulates mu-ORs in humans as it has been shown to in animals (Wang et al., 1999; Cahill et al., 2001; Morinville et al., 2003).

Cognitive or lifestyle interventions may be able to enhance EO mechanisms; for example, exercise in normal volunteers enhances activity of the EO system in prefrontal, cingulate and insula cortices (Boecker et al., 2008), but with unknown effects on OR density. However, the rational use of such interventions for the purposes of enhancing opioid-dependent pain resilience is limited by a current lack of mechanistic understanding of the function of the EO system in the brain.

INVESTIGATING PAIN AND OPIOID MECHANISMS WITH NEUROIMAGING

Understanding the role of neuroplasticity and opioid function in chronic pain vulnerability requires a mechanistic understanding of pain processing in the brain. Until the mid-20th century, pain perception was thought to be a direct reflection of the afferent processes of nociception - pain processing in the brain was considered unidirectional and passively received by a single brain centre (Melzack and Wall, 1965). However, after the introduction of the 'pain matrix' theory (Melzack and Wall, 1965), the concept of pain evolved towards active, multidirectional and multicentre cognitive information processing. More recently, the concept of pain-specific cognitive and emotional networks has been replaced with a view of shared brain functions involved with processing pain as well as other motivationally salient stimuli (Legrain et al., 2011), although it seems likely that pain is likely to be a construct of a specific pattern of activity within this network (Wager et al., 2013). Furthermore, cognitive and emotional processing takes an active role in the endogenous modulation of pain (see Table 1). Observations such as these contribute towards our understanding of mechanistic heterogeneity

in chronic pain, particularly with regard to understanding individual differences in the efficacy of endogenous pain control, a common factor thought to affect many types of chronic pain (Staud, 2012).

BOX 1: CHALLENGES IN UNDERSTANDING THE MECHANISMS OF PAIN VULNERABILITY AND RESILIENCE

Research question: Investigating a biological mechanism requires asking the right research question. Neuroimaging studies have been largely descriptive, i.e. seeking to answer the question of *what* the brain (including the opioid system) does in response to (or in prediction of) acute and chronic pain, and cognitive and affective modulation of pain. Such descriptions provide useful data for classification, prediction, and for the generation of hypotheses and models, but are unable to test hypotheses to answer *why* and *how*; for example, why and how does neuroplasticity in opioidergic brain regions contribute to chronic pain? In other words, we currently lack a comprehensive *process theory* for the functional role of the opioid system in pain perception and chronic pain vulnerability. Research questions seeking to identify such a theory would help to integrate descriptive research findings and provide greater utility in inform us about what treatments may be appropriate under certain contexts.

Sample selection: Research normally seeks to answer questions in specific populations, involving the selection of recruitment criteria to sample the right patients. Most commonly, selection relies on diagnostic categories and symptom profiles. However, such categories lack predictive clinical validity (e.g. in predicting the outcome of certain treatments), because diagnostic heterogeneity does not currently map on to mechanistic heterogeneity. This means that we cannot distinguish whether descriptive observations of brain abnormalities in a patient group defined by diagnostic category (e.g. osteoarthritis) are due to a unique biological pathology, a psychological comorbidity (that nonetheless has more complex biological substrates), or a difference in cognitive strategy or emotional response to the experiment, for example patient anxiety at being in an MRI scanner.

Design and methodology: While appropriate research design largely follows from the research question and sample, some general considerations are outlined here. Methodological challenges arise from a number of factors including arranging for the subject to be in an appropriate pain state, practical or technological limitations in measuring the target physiological processes, limitations in the number of variables/factors that can be investigated within a single study, and a lack of standardisation of how neuroimaging data are acquired, making it difficult (but not impossible) to compare and combine data across sites and studies. More longitudinal studies are also required to establish which brain responses are associative and which causal in relation to pain vulnerability. Future work will benefit from efforts to standardise and share neuroimaging data, enabling larger-scale and more highly powered research, necessary for longitudinal research and some of the more complex designs (Table 1).

However, the majority of neuroimaging studies of cognitive and emotional influences on pain have been conducted using experimental pain stimuli in healthy people (Table 1). Furthermore, studies are generally descriptive rather than providing evidence of mechanisms underlying cognitive and emotional influences on pain. Hence, whilst functional brain imaging has made a major contribution to our understanding of pain physiology and pathophysiology over the past few decades, we are still barely scratching the surface of understanding the fundamental mechanisms underlying chronic pain vulnerability.

We identify three main challenges (Box 1): identifying the correct research question, selecting the appropriate participant samples for study, and designing/implementing the appropriate experimental methodology (e.g. Table 1). Here we focus on the first challenge: identifying the right research question. *Descriptive* approaches (asking "what" questions) frequently do not provide insight into the causal mechanistic processes that explain observations. By contrast, *normative* approaches are explicit about the hypothesised function of a system, for example, considering what problem is being solved or goal of the system and how this might be optimally achieved (Niv, 2009), thereby providing a basis for understanding and identifying sub-optimal function. Normative approaches commonly refer to the evolutionary principle that the purpose of organisms is to provide optimal or near-optimal adaption to the (physical and social) environment (Kacelnik, 1997). In this regard, the function of the brain can be thought of as optimising perception and behaviour through *learning processes*. This provides the ability to generate and direct test computationally explicit hypotheses about the function of brain systems (Niv, 2009), including neurotransmitters such as opioids, in terms of how they optimise perception and behaviour through learning.

Evolutionary pressures have hard-wired brain systems towards adaptation through processes that maximise reward (e.g. food, mating opportunities, money, knowledge) and minimise punishment (e.g. pain, hunger, social rejection). These processes can sometimes be related, such that failure to acquire reward is punishing (Tom et al., 2007), and avoiding a punishment or relieving pain is rewarding (Navratilova and Porreca, 2014). In this case, there is a cooperative opposition in the pain and reward systems (Leknes and Tracey, 2008), which has been linked to activity in the striatum consistent with dopamine signalling during associative learning tasks (Seymour et al., 2005, also see Box 2). Likewise, maximising longer-term rewards may require suppressing short-term pain, for example when reaching limits of physical endurance during exercise in which the long-term goal is greater physical fitness. In

this case, opioidergic activity in the striatum may be important suggested by endorphin release during exercise (Boecker et al., 2008). These reward-pain motivational interactions have been conceptualised by Fields (2006) according to a motivation-decision model, in which neural decision-making is based on the predicted homeostatic value to the organism of each option. Current reinforcement learning (RL) models (see Box 2) require theoretical advances to account for how the value of certain actions can be approximated when rewards depend on the long-term consequences of those actions (Gershman and Daw, 2017). These more advanced RL models are likely to enable a more complete understanding of the cooperation between dopaminergic and opioidergic signalling in the basal ganglia.

In parallel, the specific function of endogenous opioids in the brain requires further elaboration. Evidence summarised in Figure 2 challenges the assumption that opioids only mediate antinociceptive responses, suggesting rather that opioids modulate nociception bi-directionally via the basal ganglia and insula, converging on a common midbrain descending pathway. An alternative hypothesis of opioid function is called for to account for these considerations. A promising candidate that we will explore in the following sections (see also Figure 2) is that the opioid system within the basal ganglia and midbrain functions to optimise *predictions* about pain, consistent with striatal functions in learning predictions of reward value and that of the amygdala and anterior insula in learning predictions of aversive value. Testing this hypothesis will require models of the explicit neural computations involved.

BOX 2: COMPUTATIONAL MODELS OF LEARNING AND PERCEPTION

Computational neuroscience uses normative principles to understand explicit mechanisms of brain function. A common approach, inspired from David Marr's influential work (Marr, 1982), is to (1) define the computational optimisation problem (i.e. identify the problem the brain is trying to solve and its underlying principles), (2) identify a range of potential process models / algorithms (i.e. what representations and operations are required in the brain to solve the problem), and (3) constrain the repertoire of process models with reference to biological observations (i.e. how do neurons carry out the algorithm to achieve the computational goal?). A successful example is that of reinforcement learning (RL). Originally popularised by Rescorla and Wagner (Rescorla and Wagner, 1972), RL models formalise how associative learning occurs. The *optimisation* problem, maximising future reward, is solved by learning the value of environmental cues according to an *algorithm* in which organisms are "surprised" (generate a *prediction error*) when events violate expectations. Prediction errors have been equated to the motivational salience of environmental cues that provide information about rewards (Berridge, 2007). Critically, empirical evidence supports RL models in that both reward and aversive prediction errors are closely related to phasic activation of the ventral striatum consistent with dopaminergic signalling (O'Doherty et al., 2003; Seymour et al., 2004).

While RL provides a compelling model of reward and aversive learning, it does not provide a model for pain-related neuroplasticity in sensory pain networks. An important consideration is that in order to optimally learn and adapt to the environment, the brain needs to make perceptual decisions (e.g. "Is this painful or not?"; "Is this situation dangerous?") as well as behavioural decisions (e.g. avoidance or approach). This leads to the question of how the brain deals with the uncertainty, a major topic of research in the neurosciences (for a review, see Bach and Dolan, 2012). Sources of uncertainty in sensory perception include neuronal noise and incomplete/ambiguous information, meaning that there are many possible states of the world that could give rise to any one sensory input (Friston, 2003). This leads naturally to the idea that perception is a process of unconscious, statistical inference (the "Bayesian brain" hypothesis), which to be optimal requires that the brain represents sensory information in the form of probability distributions (with variance indicating uncertainty) (Friston, 2003). However, there is debate as to whether the brain can actually perform such computations due to the problem of *bounded rationality* which recognises cognitive processing capacity limitations available to the brain (Gershman et al., 2015). Recent computational theories of perceptual inference borrow theoretic principles from statistical physics and information theory to solve this problem by assuming that the optimality principle the brain uses for sensory perception is to minimise free-energy, or the upper bound on the surprise (entropy) of the sensory states it experiences (Friston et al., 2006). This principle converts intractable Bayesian inference into a neuronally computable optimisation problem.

BAYESIAN MODELS OF PAIN NEUROPLASTICITY

Computational neuroscience has provided normative models for how the brain might optimise perception and behaviour (Box 2), with many approaches converging on the view that the brain applies statistical inference to sensory inputs in order to resolve uncertainty. How this is implemented in the brain is an active topic of research. A leading framework is that of predictive coding (PC), which provides a biologically plausible scheme based on simple rules of synaptic plasticity (Hebbian learning) (Bogacz, 2015). PC models assume that learned knowledge (implicit or explicit) about the world is represented hierarchically as a set of 'priors', which capture the statistical regularities of brain activity (reflecting environmental regularities) at lower levels to resolve sensory uncertainty.

Predictive coding provides an attractive framework to account for the modulation of pain by learning processes such as those underlying placebo and nocebo effects (Büchel et al., 2014) commonly attributed to the endogenous opioid system. We and others (Edwards et al., 2012; Kuttikat et al., 2016) have also suggested that PC is an appealing approach to understand functional and potentially subsequent structural plasticity occurring in chronic pain. According to the Bayesian optimality principle, pain experience would depend on the extent of the mismatch between the learnt predictions and current sensory inputs, but also on their relative 'precision' weights, reflecting the uncertainty of the representation. Precision weights are thought to be learnt over a lifetime (Bogacz, 2015), thus providing stable or slowly changing traits. This may be particularly important in chronic pain conditions associated with psychological trauma in childhood and early adulthood (Gupta et al., 2007). However, to date, there has been no investigation of whether the PC framework provides an explanation for neuroplastic changes in chronic pain.

Our experimental observations in healthy individuals and chronic pain patients have, however, provided some general support for a Bayesian account of pain vulnerability. If the brain uses a Bayesian updating scheme for pain perception, at least three phenomena would need to occur: firstly, that the brain predicts nociceptive inputs; secondly, that the brain models the uncertainty (inverse precision) of those predictions; thirdly, that greater precision (certainty) in predictions more greatly biases pain perception in the direction of those predictions. Our and others research measuring anticipatory brain responses has indeed discovered that neural processes prior to the experience of pain predict the subsequent nociceptive input and serve as the basis for the modulation of pain perception by expectations

(Brown et al., 2008a, 2008b; Atlas et al., 2010). Furthermore, we have shown that subjective confidence (as a metacognitive representation of Bayesian precision (Meyniel et al., 2015)) in predictions is related to the extent to which expectations influence pain perception and is related to activity in the anterior insula cortex (Brown et al., 2008b), a region through which expectancy effects are mediated (Atlas et al., 2010). While this research does not directly test a Bayesian model or a predictive coding scheme for pain perception, it does point to the importance of predictive processes in acute pain and is consistent with Bayesian optimality principles. Furthermore, predictive processing appear to have relevance to chronic pain: In patients with fibromyalgia, the anterior and posterior insula are over-active when anticipating pain, while anticipatory posterior insula activity predicts pain symptoms in patients with fibromyalgia as well as those with osteoarthritis (Brown et al., 2014).

However, despite recent interest in the Bayesian and predictive coding framework for acute pain, knowledge is currently limited on how these principles pertain to the situation of chronic pain. Very little work has been done in computational modelling of chronic pain symptoms and behaviour. Such models may provide the ability to test the recent hypothesis (derived from descriptive longitudinal studies of chronic pain neuroplasticity (Mansour et al., 2014)) that the value and saliency of both nociceptive and rewarding stimuli are altered in those vulnerable to chronic pain. In important first step in this direction will be to test for the *construct validity* of predictive coding models in chronic pain, i.e. do they effectively account for individual variability, and variability over time, in pain-related neuroplasticity in the brain? In addition, the validity of *generative* computational models (such as predictive coding) would rest on their ability to account for how symptoms can arise from underlying hidden mechanisms. A second step required is *clinical validation*, for example do such models have predictive validity for future pain symptoms and/or treatment outcomes? If so, once other hurdles (such as test-retest reliability of different models) have been overcome, the clinical potential is substantial. By inferring mechanisms rather than relying on symptom profiles, the approach may finally achieve the lofty ambition of mechanism-based stratification for treatment.

OPIOID FUNCTION IN PAIN VULNERABILITY AND RESILIENCE

We argue the need to better understand the precise *function* in the brain of the opioid system in a normative sense. This will provide a definition of optimal and suboptimal functioning to

facilitate diagnosis and treatment. A view of the brain's predictive mechanisms provide insights into the role of the EO system in chronic pain vulnerability and resilience.

EOs have been intensively studied for their role in the modulation of nociception. Many nociceptive forebrain areas are rich in ORs (mu, delta and kappa) and modulated by EOs, including the frontal cortices, anterior cingulate and midcingulate cortices, the thalamus, striatum, insula, hypothalamus and central nucleus of the amygdala. Opiate drugs and EOs act on ORs in these regions to produce analgesia (Jones et al., 1991; Petrovic et al., 2002; Zubieta et al., 2005; Eippert et al., 2009). However, evidence suggests that the actions of EOs is partly to mediate or reinforce neural predictions. For example, placebo analgesia, thought to be mediated by conscious or unconscious (e.g. conditioned) expectations (Watson et al., 2012), is opioid-mediated (Benedetti et al., 2005). Furthermore, behavioural and neuroimaging studies show that the analgesic effect of synthetic opiates during experimental pain is blocked by negative suggestion (Bingel et al., 2011). This highlights a potentially important interaction between opioids and predictive mechanisms in the brain.

Further evidence from Pavlovian fear conditioning experiments suggests that endogenous opioids may specifically optimise predictions about pain to promote associative learning. In rodents, when a neutral conditioned stimulus (CS) was repeatedly paired with an unconditioned stimulus (US, a painful shock) and over time came to predict that shock, endogenous opioids were released resulting in analgesia (Fanselow and Baackes, 1982). The effect was blocked with opioid antagonism (e.g. naloxone), which in addition facilitated learning of the CS-US pairing, in rats (Bolles and Fanselow, 1982; McNally et al., 2004) and humans (Eippert et al., 2008). However, a series of experiments (McNally et al., 2004) involving blocking designs discovered that opioid enhancement of fear learning is not due to a greater US (i.e. increased pain) from opioid antagonism, but rather results from a specific increase in the prediction error learning signal (the discrepancy between the US and CS). Further observations were that over the course of fear conditioning, the CS increasingly resulted in EO signalling in the ventrolateral PAG, which acted to limit further fear learning (McNally and Cole, 2006). In addition, EO signals act to not only limit fear learning, but also fear extinction (McNally, 2009). These observations are consistent with OR activity encoding the *prediction* (i.e. the CS) rather than the painful outcome (i.e. the US), as the latter would result in the opposite to the observed extinction learning behaviour (McNally, 2009). In other words, EOs appear to be important for learning the prediction, i.e. the transfer of information from the US to the prior CS over time. Buchel et al., in discussing predictive mechanisms of

placebo (Büchel et al., 2014), speculate that opioidergic signalling specifically represents the *precision* of predictions, consistent with Bayesian updating scheme for pain perception. However, whether there is a pain vulnerability mechanism involving altered opioid signalling during the encoding or expression of predictions of pain is a hypothesis that remains to be tested.

CONCLUSIONS

The brain is best considered as an active participant in shaping the sensory-perceptual and cognitive/emotional aspects of pain. In chronic pain, observations of neuroplasticity within the network of brain regions mediating opioid-dependent analgesia may confer states of pain vulnerability, but the meanings of such observations have proved challenging to interpret in light of the potential for a range of influences on these regions such as from nociceptive inputs, cognitive and behavioural strategies, and long-term use of opiate analgesics. Computational models that use normative optimality principles may help to make sense of pain-related pathophysiology in individuals with chronic pain. Evidence currently supports (but does not explicitly test) the hypothesis that endogenous opioids function to optimise predictions about pain to serve adaptive perception and behaviour. Further research is required to test whether opioids directly modulate prediction per se or act on the precision of predictions according to a Bayesian updating scheme. Identification of these mechanisms, requiring psychopharmacology experiments in combination with computational modelling, will serve to provide a definition of sub-optimal opioid system functioning and a rational basis for chronic pain prevention and treatment.

AUTHOR CONTRIBUTIONS
AKPJ and CAB drafted, revised and approved of the final version of this manuscript, and are accountable for the accuracy and integrity of all aspects of the work.

NOMENCLATURE OF TARGETS AND LIGANDS
Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander et al., 2015).

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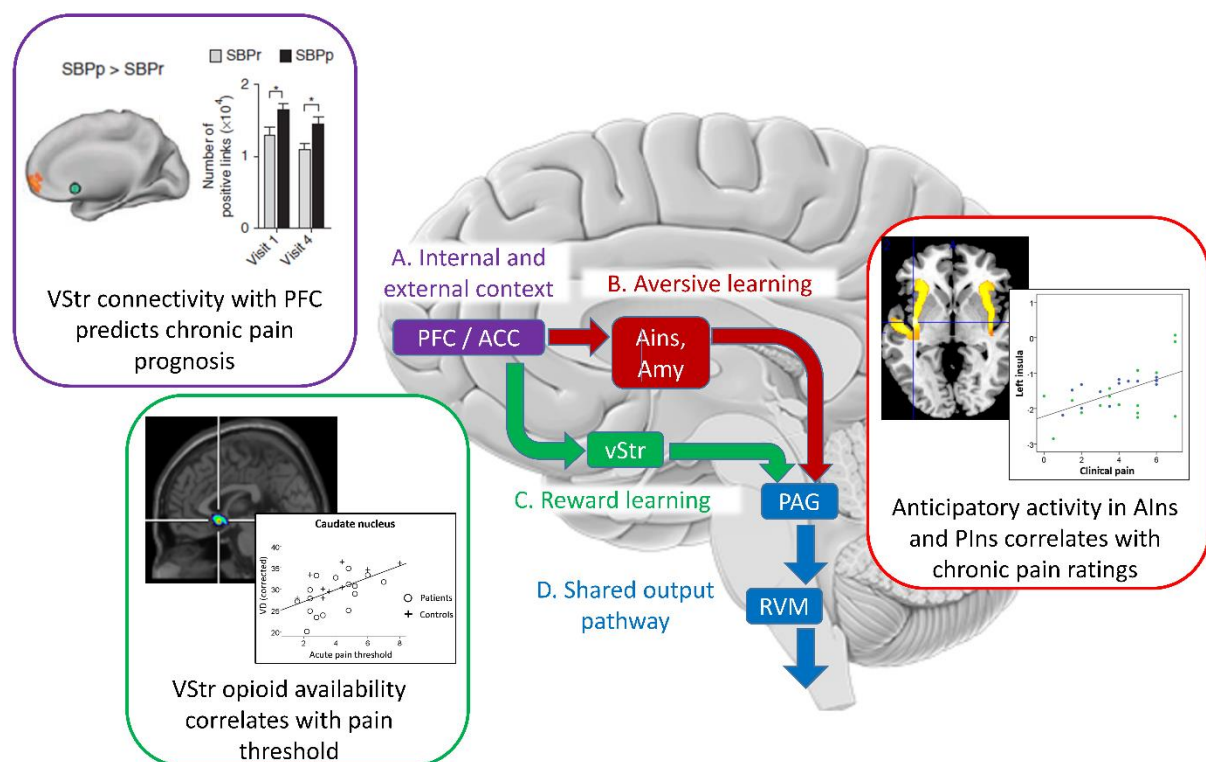
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FIGURE 1
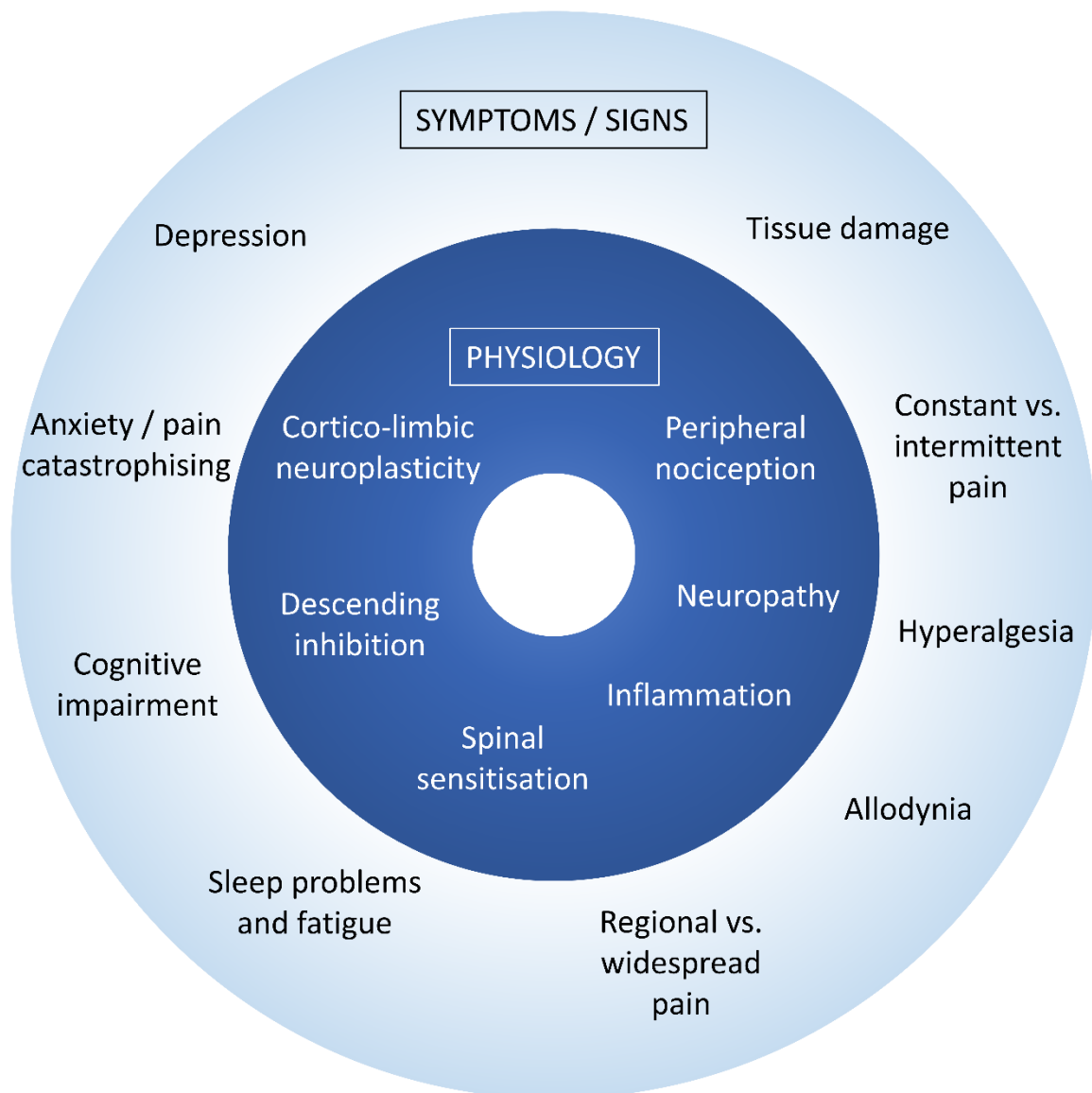
Two types of clinical heterogeneity. Due to *symptom heterogeneity,* many patients with chronic pain have a combination of recurrent acute pain and chronic ongoing pain, variable evidence of tissue damage and differences in cognitive and mood symptoms. The underlying *mechanistic heterogeneity* reflects variability in nociceptive, inflammatory, neuropathic, and central mechanisms.

FIGURE 2

VStr connectivity with PFC predicts chronic pain prognosis

VStr opioid availability correlates with pain threshold

A. Internal and external context

B. Aversive learning

C. Reward learning

D. Shared output pathway

Anticipatory activity in AIns and PIns correlates with chronic pain ratings

Opioidergic modulation of motivational learning processes play a role in the contextual modulation of pain. For illustrative purposes, the schematic simplifies the main opioid-mediated top-down pathways involved in the modulation of nociception by internal (e.g. beliefs, mood, distress) and external (e.g. placebo treatment) context. Further bottom-up and recurrent pathways exist but are not illustrated for clarity and were recently reviewed elsewhere (Büchel et al., 2014; Navratilova and Porreca, 2014).

A) Many cortical systems potentially mediate phenomena such as placebo hypoalgesia (Büchel et al., 2014), but all likely originate within the prefrontal cortex and it's interactions with the perigenual ACC as evidenced by their activation during anticipation of pain and prediction of placebo analgesia (Wager et al., 2004, 2011). This regions, through interactions with limbic areas, provide contextual cognitive information critical to the learning of reward and aversive value information (reviewed in Navratilova and Porreca, 2014). This is consistent with observations of abnormal vStr activity being a potential vulnerability factor in chronic pain (Purple inset, Baliki et al., 2012). SBPp: Subacute back pain, persistent. SBPr: Subacute back pain recovered.

B) AIns-Amyg form a circuit required for fear learning (Critchley et al., 2002) that shows opioid release during placebo analgesia (Zubieta et al., 2005). While anterior

insula is deactivated during placebo analgesia (Price et al., 2008), it mediates the effects of negative expectations on increased pain (Brown et al., 2008b; Atlas et al., 2010) and shows abnormal anticipatory processing in patients with chronic pain (Red inset, Brown et al., 2014).

C) A role for opioiderigic activity in vStr in setting nociceptive sensitivity/salience is evidenced by bidirectional modulation of vStr attenuating or enhancing nociception (Gear and Levine, 2011) which depends on upstream ACC opioid circuits (Navratilova et al., 2015). Consistent with this, pain thresholds in chronic pain patients correlate with opioid receptor availability in vStr (Green inset, Brown et al., 2015) presenting a potential vulnerability/resilience factor.

D) The cortical and subcortical projections all converge onto the PAG-RVM-spinal cord system which either inhibits or facilitates nociception (Fields, 2004).

TABLE 1:

Research methodologies and example results in the neuroimaging of pain.

Pain induction method	Within-subject comparisons	Between-subject/group comparisons	Mixed comparisons
1. Experimental pain induction	Modulation of pain processing by: Cognitive distraction (e.g. Bantick et al., 2002). Expectation (e.g. Lorenz et al., 2005; Brown et al., 2008a; Atlas et al., 2010) Hypnotic analgesia (e.g. Rainville et al., 1999; Huber et al., 2013) Placebo treatments (e.g. Wager et al., 2004; Watson et al., 2009). Mindfulness meditation (e.g. Brown and Jones, 2010; Zeidan et al., 2011). Endogenous opioid function (Zubieta et al., 2001; Sprenger et al., 2006).	Cerebral pain processing affected by individual differences in pain catastrophising (e.g. Gracely et al., 2004; Michael and Burns, 2004; Brown et al., 2014; Loggia et al., 2015), fear and anxiety (e.g. Ochsner et al., 2006) and altered sleep (Petrov et al., 2015).	Studies are needed to investigate the moderator effects of between-subjects characteristics (e.g. pain catastrophising) on within-subject contextual modulation of pain (e.g. attention, expectation and placebo effects).
2. Chronic pain presence / absence or induction / suppression	Reductions opioid receptor binding within the medial pain system in patients with post-stroke pain (Jones et al., 1999)	Reduced opioid receptor binding in fibromyalgia vs. controls (Harris et al., 2007), post-stroke pain vs	Future research could investigate (1) interactions between psychological factors (e.g. pain catastrophising) and

	and arthritic pain (Jones et al., 1994). Fluctuations in chronic low back pain correlating with functional connectivity of medial prefrontal cortex with other brain regions (Baliki et al., 2011).	controls (Willoch et al., 2004) and central vs peripheral neuropathic pain (Maarrawi et al., 2007). Changes in resting-state functional networks between chronic pain conditions and controls (Baliki et al., 2014; Kucyi et al., 2014; Fallon et al., 2016)	changes in opioid receptor binding in response to chronic pain, (2) how patients with different patterns of network connectivity in the brain differ in endogenous opioid system functioning.
3. Chronic pain *vs.* acute pain	Greater processing in the medial pain system for chronic arthritic vs. acute pain (Kulkarni et al., 2007; Parks et al., 2011).	N/A – requires within-subject comparisons	Future studies could investigate whether differential medial pain system activity in chronic vs. acute pain is related to levels of psychological distress.
4. Chronic pain natural history or treatment response	Structural brain changes from of arthroplasty in osteoarthritis (Gwilym et al., 2010). Differences in brain function and structure in subacute vs. chronic pain	N/A – requires within-subject comparisons	Identifying patient subgroups with different prospective outcomes from baseline brain structure/function (e.g. Baliki et al., 2012).

	stages of low back pain (e.g. Baliki et al., 2012). Changes in somatosensory cortical reorganisation with recovery in patients with Complex Regional Pain Syndrome (Maihöfner et al., 2004). Changes in prefrontal cortex structure or function with cognitive-behavioural therapy (e.g. Seminowicz et al., 2013; Čeko et al., 2015) or mindfulness meditation (e.g. Brown and Jones, 2013).		Studies are required to identify predictors of response to difference treatments, e.g. cognitive-behavioural therapy, analgesics, physical therapies.

Footnote: Studies can be broadly categorised into (1) those that use a standardised acute or tonic pain stimulus to understand different aspects of pain processing, (2) studies where patients are scanned in different clinical pain states, (3) where responses are compared between standardised experimental pain and clinical pain, (4) longitudinal observations of changes in pain processing according to naturalistic changes or treatment-related changes. Furthermore, in each case, studies can make within-subject, between subject or mixed comparisons. Examples are provided of studies within each category where possible. Studies further down and/or to the right side of the table generally require greater sophistication and resources, and are therefore less common, but provide greater mechanistic insights into chronic pain vulnerability.