

Pain: a precision signal for reinforcement learning and control

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Abstract

Since noxious stimulation usually leads to the perception of pain, pain has traditionally been thought of as sensory nociception, but its variability and sensitivity to a broad array of cognitive and motivational factors have led to a common view that it is inherently imprecise and intangibly subjective. However the core function of pain is motivational - to direct both short and long-term behaviour away from harm. Here we illustrate that a reinforcement learning model of pain offers a mechanistic understanding of how the brain supports this, illustrating the underlying computational architecture of the pain system. Importantly, it provides an explanation as to why pain is tuned by multiple factors and necessarily supported by a distributed network of brain regions, and so recasts pain as a precise and objectifiable control signal.

Keywords

Pain and nociception, information theory, reinforcement learning, optimal control, active inference, avoidance learning, free energy, endogenous modulation, pregenual anterior cingulate cortex, computome.

Introduction

Despite the advent of brain imaging, a clear picture of how pain is processed in the brain has been much harder to unravel than anticipated, being beset by three problems. First, pain is associated with robust responses in multiple and diverse brain regions, most of which are not specific to pain (at least on a macroscopic scale), and so it has been hard to ‘pin down’ the pain system to any specific brain region. Second, pain is an inherently private percept, but an individual’s self-reports of pain can vary widely from moment-to-moment, and that it has remained unclear if this fluctuation represents irreducible noise and subjectivity, or a precise tuning of pain based on hidden factors. Third, pain is exquisitely sensitive to a broad range of emotional, environmental and cognitive factors - a phenomenon called endogenous modulation. Although this has led to an appreciation that pain is more than a simple read-out of nociceptive input, it has not led to any satisfactory unified explanation as to what pain really is. This has left the view that pain is simply a highly variable and malleable representation of assumed actual or potential tissue damage.

In this review, we propose a model of pain that centralises its role as a learning and control signal, and argue that this can solve these problems. We begin with a perspective of how theories of pain have evolved over recent decades, and how insights have emerged that have moved thinking beyond purely sensory accounts of pain. We then argue that current accounts still don’t fully capture how pain controls behaviour to minimise harm, which is its primary function. Importantly, although this is often achieved by immediate nocifensive responses, a substantial part of this comes from learning - allowing an animal to mitigate or avoid predictable harm long in to the future. The foundations of a learning account of pain are rooted in psychological models of animal learning, and we describe how these can be developed in computational terms to provide a mechanistic model of the architecture of the pain system. Critically, we argue that this requires pain to be shaped by a set of factors to optimise its role as a learning and control signal, and review evidence that suggests that a great deal of examples of endogenous control can be explained by this process. Finally, we briefly describe how the model offers potential insights into how pain might become chronic under certain conditions.

Background

There is a long history of theories and constructs that have attempted to capture the complex phenomenology of pain, but a number of models have played a particularly important role in evolving current concepts of pain. Against a historically dominant view that pain could be understood as a sensory system like any other, Melzack and Casey highlighted what they called the ‘man-in-the-brain’ problem that this seemed to create - the idea that the main function of the pain system was to inform some conscious module of the nature of a particular nociceptive stimulus. Instead, they proposed the **Tripartite model**, in which sensory-discriminative, affective-motivational, and cognitive-evaluative components are processed as part-independent, part-interacting pathways (Melzack, 1968). In this model, rather than the control of protective behaviour being merely downstream to sensory processing, they argued it was an intrinsic and fundamental part of pain experience, not least because pain was clearly sensitive to so many motivational and cognitive factors. A key substrate for modulation, namely descending pathways acting on dorsal horn neurons, had already been proposed in Gate Control theory (Melzack, Wall, et al., 1965). And in the brain, the model implied that different dimensions would involve multiple different cerebral loci - a premonition of the distributed pattern of cortical and subcortical pain responses that was later revealed by functional neuroimaging (Jones et al., 1991; Treede et al., 1999).

In light of the neurophysiological characterisation of many pain-specific receptors and ascending pathways, Craig subsequently proposed the **Homeostatic model**, in which sensory and motivational dimensions are inherently integrated as a single system, involving pain-specific lateral thalamocortical projections to insula cortex (A. Craig, 2003; A.D. Craig, 2002). Craig placed pain alongside other ‘interoceptive’ sensations such as temperature, itch and pleasant touch, as systems supporting bodily perception with intrinsic motivational value, with this value related to the core homeostatic drive to maintain the integrity of the body. This model proposed a hierarchical sensory processing stream from posterior to anterior regions of insula cortex, with this hierarchy explicitly tied to physiological and behavioural homeostasis. However, it was still largely unclear exactly how homeostatic behaviours were actually implemented, and why pain was modulated by so many factors.

The idea that as a motivational system, pain was directly modulated as a decision by the system itself was most clearly articulated in Fields' **Motivation-decision model** (Fields, 2006; Fields, 2018). The model proposed that pain was inhibited when overshadowed by more important reward- or escape-orientated goals, with descending control mediated by opioid pathways via the periaqueductal grey (PAG) and rostral ventral medulla (RVM) (Basbaum et al., 1984). The model also highlighted the fundamental role of pain in learning and the control of avoidance and escape, and this explicitly motivational perspective viewed pain as controlling not just immediate responses to limit tissue damage, but also long-term role harm minimisation through learned escape and avoidance (Johansen et al., 2001; Navratilova, Xie, et al., 2012). This re-conceived of pain as an inherently *predictive* system, not simply passively recording nociceptive inputs, in which the generation of pain predictions and expectations are central to the function of central pain circuits.

A central role for expectation and prediction also underlay the idea that pain involves a statistical (e.g. Bayesian) inference resulting from integration of prior expectancy and incoming nociceptive input (C.A. Brown et al., 2008; Seymour and Dolan, 2013; Morton et al., 2010; Anchisi et al., 2015; Tabor, Thacker, et al., 2017; Ongaro et al., 2019). More formally, Büchel proposed the **Predictive Coding model** (Büchel et al., 2014), involving a hierarchical processing stream from spinal cord to PAG, thalamus and posterior-to-anterior insula (Geuter et al., 2017; Grahl et al., 2018; Ozawa et al., 2017). In this context, expectations can be acquired through multiple means - through instructed information, learning (i.e. conditioning), and through observation (Wiech, 2016; Tabor, Thacker, et al., 2017), and suggested that descending control might be implementing top-down predictions and their uncertainties, to be integrated by ascending nociception information and prediction errors. In so doing, this provided an explanation of a set of instances of endogenous control, especially expectancy-based biases and placebo/nocebo responses.

However, inferential theories of pain processing leave open an account of how the motivational function of pain is directed. At an abstract level, concepts such as Friston's Free Energy Framework propose that sensation, motivation and action are intrinsically related by their drive to understand the causes of unexpected stimuli (Friston, 2010), and the notion of 'active inference' describes how actions can be conceived to ultimately reflect minimisation of future unexpected sensory instances of pain (Tabor and Burr, 2019). But understanding how the brain actually achieves this is much more complex (Pezzulo et al., 2015), and none of the existing models fully capture how the pain system successfully balances stimulus identification, information seeking, harm minimisation, and perhaps most critically, speed. Below, we outline a computational architecture of the pain system that may achieve this, based on a framework called Reinforcement Learning. In so doing, this casts light on the fundamental question of what the conscious perception of pain really reflects: an optimal inference of a real or presumed nociceptive stimulus, or an optimal control signal to minimise current and future nociceptive stimuli?

The Reinforcement Learning model.

Underlying the evolution of these concepts is the central idea that pain must be understood in the context of behavioural control to minimise current and future harm. Fundamental to this concept is *learning*: over-and-above the fact that pain elicits immediate defensive responses (withdrawal, orientation etc), it must also guide learning to optimise future responses. To illustrate this, consider a child touching a hot stove: although the immediate response limits the severity of any burn, the main benefit is through the sum of future instances when they don't touch stoves because they have a pain system. Therefore what has driven the evolution of the architecture of the pain system is its role as a learning signal to *prospectively* reduce harm. But understanding how the brain achieves this exposes a fundamental problem that any experience-based control system must solve - the credit assignment problem (Bellman, 2013).

The credit assignment problem.

Harm minimization is both a clearly definable and objectively measurable function, and is based on the ability to learn from trial-and-error interaction with the world. This allows actions that terminate (escape) or completely avoid pain, and has been well studied in humans and animal learning using Pavlovian (Classical) and instrumental (Operant) conditioning (Mackintosh, 1983). Most of these paradigms consider simple one-step escape or avoidance, in which pain is predicted by a single preceding cue which subsequently elicits an appropriate response. However, real-world learning often involves much longer sequences of events, which makes the problem of prediction

and avoidance more difficult. For instance, if a series of 5 actions leads to pain at the end, how do you know which of the 5 actions was the mistake (Fig 1a)? This problem is referred to as the credit assignment problem, which is well-known problem in engineering and control theory (Bellman, 2013).

The credit assignment problem can be solved using a class of learning rule from the field of Reinforcement Learning (RL) (Sutton et al., 1998). RL is effectively an extension of psychological learning models, such as the Rescorla-Wagner model (Rescorla, Wagner, et al., 1972). The Rescorla-Wagner model is usually applied to one-step learning, and uses a prediction error term - the difference between what was expected and observed - to update future predictions. But this doesn't work well if the outcome is far in to the future. RL models, on the other hand, don't need to wait for the outcome, and simply use the next available prediction (formalised as the *value*) as a proxy for the outcome. That is, they store a value term for each action and state, and compute the difference between values at each successive time-step, taking into account any reward/punishment experienced on the way (Sutton et al., 1998). Effectively, this allows pain predictions to be learned by looking at differences in predictions through time, which passes the prediction back to the earliest reliable predictor (Fig 1b). This error-based mechanism can be applied to passive predictions (learning state values), or active predictions (learning action values).

Fig 1c shows the basic architecture of RL control. By sensing the external environment, the organism's brain generates an internal representation of the current state (e.g. from visual information) and any salient outcomes (e.g. from nociception). This information is passed to 'agent' that decides what responses or actions to emit based on the current stored state and action values, and then updates these values based on the next state (Sutton et al., 1981). In this architecture, 'pain' is the internal reinforcement signal used for learning, and is distinct from the nociceptive sensing process (in the same way that reward is distinct from the sensory properties of a reinforcer (Singh et al., 2009)).

From its initial demonstration (Seymour, O'doherty, Dayan, et al., 2004), there is now substantial evidence that pain controls behaviour using an RL-based strategy, and that this involves a hierarchy of RL control processes. These are built on a basic system of innate responses that exists across species, and working together, coordination of these control processes provides a highly effective way of minimising future harm (Fig 2). Below, we outline the key aspects of each, and how they fit together to control pain behaviour.

Innate responses.

Nociceptive stimulation produces a broad and diverse set of complex motor, autonomic and behavioural defensive responses that are stimulus-specific, situation-specific, and species-specific (BOLLES, 1971; Fanselow and Lester, 1988). Innate responses are precise, sophisticated, and rapid - driving defensive activity within a few hundred milliseconds. They are also remarkably strong, overwhelming other ongoing behavioural activity (which as we explain later, has critical implications for the organisation of endogenous control mechanisms). These features are reflected in the corresponding neural substrates within a highly complex network of spinal and brainstem connections, including dorsal horn circuits governing motor responses, brainstem autonomic nuclei, and hypothalamic-PAG circuits driving basic behavioural programs (Fanselow, 1994; A. Craig et al., 1998).

Pavlovian learning.

Pavlovian learning allows innate responses to be activated in advance of a harmful stimulus - offering the chance to prepare for, reduce or even completely avoid it (Mackintosh, 1983; Bolles, 1972). Any sensory cue that reliably precedes pain can act as a predictor (a 'conditioned stimulus'), and it is known that acquisition of the response (the 'conditioned response') depends on prediction errors. Importantly, evidence suggests that the brain learns higher-order pain prediction errors - allowing the prediction to be transferred back in time to the earliest reliable predictor, in accordance with an RL solution to the credit assignment problem (Seymour, O'doherty, Dayan, et al., 2004). Pavlovian pain responses can be divided into two categories: pain specific responses, which tend to be well-timed motor responses thought to be mediated by cerebellar learning (e.g. leg flexion or eye-blink to foot or eyelid shock, respectively); and non-specific responses common to many aversive stimuli (such as withdrawal and autonomic arousal), which involve coordinated subcortical network including the amygdala, ventral putamen, ventral PAG, VTA and dorsal raphe (Groessl

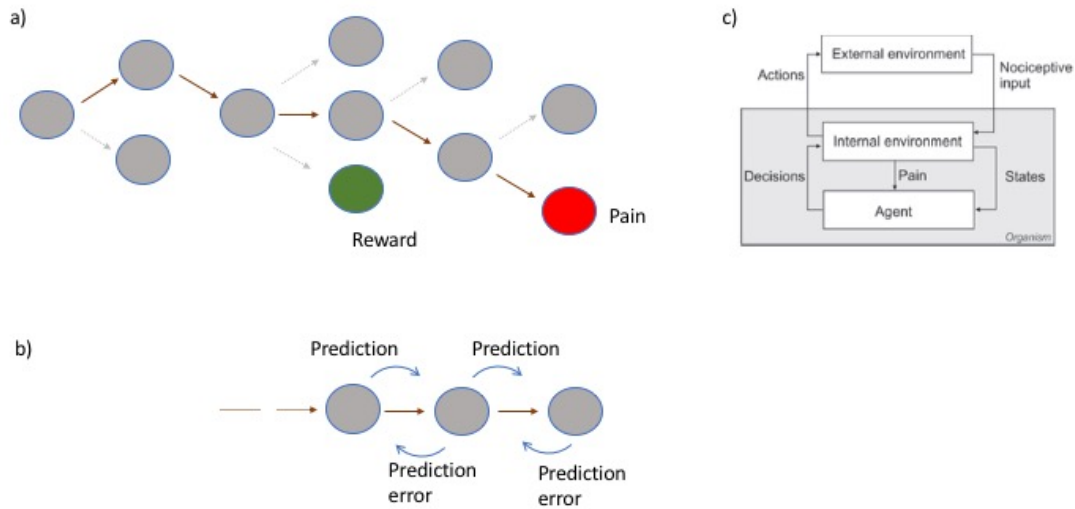


Figure 1: **The credit assignment problem and RL framework.** A) Reinforcement Learning (RL) provides an algorithmic framework for learning how to make optimal predictions and actions based on trial-and-error interaction with the world, in which salient outcomes (reward and punishment) can be sensed. In particular, it aims to solve the problem of correctly allocating predictive value to preceding states, in terms of the outcomes they eventually predict, when the transition through states of the world is either passive (not under the agents control, as in Pavlovian learning) or active (determined by the agent's actions, as in instrumental learning). B) This is achieved by using a prediction error term to update state or action values, which effectively transfer value predictions back in time to the earliest predictor. Here, the prediction error is equal to the difference between the current prediction, and the sum of the subsequent prediction plus any outcome experienced at this next state. C) The agent-environment interface illustrates the basic architecture comprising the agent (learns values, computes prediction errors and selects actions), the internal environment (which represents states and outcomes), and the external environment (which contains the sensed 'objects').

et al., 2018; Herry et al., 2014; Zhang, Mano, Ganesh, et al., 2016). These dissociable systems positively interact with each other (Betts et al., 1996; Pearce et al., 1981), and negatively interact with reward learning circuits (Seymour, O'doherty, Koltzenburg, et al., 2005; Konorski, 1948). Pavlovian predictions are sensitive to uncertainty, which enhances the learning rate, and controls autonomic responses such as skin conductance putatively through amygdala-dependent process (Li et al., 2011; Boll et al., 2013; Zhang, Mano, Ganesh, et al., 2016). Pavlovian values also *generalise* to perceptually and conceptually similar cues, allowing pain predictions to be made to novel stimuli in an efficient way (Onat et al., 2015; Dunsmoor, White, et al., 2011; Dunsmoor and Kroes, 2019; Koban, Kusko, et al., 2018).

Instrumental learning.

Whereas Pavlovian learning effectively deals with state-learning (that is, conditioned responses generally prepare for but don't fundamentally change the probability of pain), instrumental learning allows novel actions to be learned according to their outcomes, and so fundamentally influence the probability of their occurrence (Mackintosh, 1983). For pain, this involves escape (from persistent pain) and avoidance (of phasic pain). Current evidence suggests that the brain employs a parallel system in which action values for relief and pain are simultaneously learned and interact to guide choice (Seymour, Daw, et al., 2012; Eldar et al., 2016). Indeed there is a specific advantage to learning these two values separately: relief values can approximate the best-case scenario of future actions ('what to do'), and pain values can approximate the worst-case scenarios ('what not to do'), and the two values can in principle be integrated together to guide action (multi-attribute RL). Learning these two values separately in this way conserves information and allows for safer behaviour (Elfving et al., 2017).

Instrumental learning involves reciprocal interactions with the Pavlovian system. Pavlovian

values and prediction errors guide both the learning (e.g. two-factor theory (Maia, 2010; Moutoussis et al., 2008)) and expression (e.g. conditioned reinforcement, conditioned suppression, Pavlovian-instrumental transfer (Seymour, O’doherly, Koltzenburg, et al., 2005; Lawson et al., 2014; Talmi et al., 2008)) of instrumental actions. Neurobiologically, escape and avoidance are implemented in similar circuits to Pavlovian learning, and specifically involve posterior putamen and amygdala circuits (Menegas et al., 2018), with connections to ventromedial prefrontal regions encoding action values themselves (Seymour, Daw, et al., 2012; Roy et al., 2014). Generalisation of avoidance actions involves independent process for generalisation of pain-predictive (insula cortex) and relief (VMPFC) predictive action values (Norbury et al., 2018).

Cognitive learning.

In the systems described above, both Pavlovian and instrumental learning involve a process by which the brain learns a simple scalar value of a state or action, and use this value to guide responses and choices, respectively, in the absence of any internal model (‘model-free learning’). However, humans clearly have enormous capacity to build much more sophisticated representations of pain, events and contexts, and use them to guide deliberative behaviour. Under the umbrella term of cognitive learning or ‘model-based’ learning, these cognitive representations can encode specific states, actions and pain and formulate an internal model of the individual and their environment (Tolman, 1948; Dayan and Daw, 2008). Such an internal model can support explicit planning, evaluation (i.e. the ability to report a pain prediction or intensity judgment), instructed and observational learning, and episodic memory.

Computationally, by encoding an internal map of the world, cognitive learning can infer the presence of ‘hidden states’ and the structure of abstract rules, including the decision policies of other intelligent agents (Behrens et al., 2018). Accordingly, it provides a model-based mechanism that subsumes both Pavlovian and instrumental learning (Gershman et al., 2015). That is, cognitive processes are likely to be routinely involved in simple Pavlovian and instrumental tasks, allowing a more sophisticated representation of task structure than is possible than using simpler ‘model-free’ learning algorithms (Rescorla, 1988). Naturally, however, defining precisely what algorithms are used in cognitive learning is much more difficult to ascertain, simply due to the potential for complexity (Daw and Dayan, 2014). In the case of Pavlovian conditioning, however, Bayesian models can be shown to explain several aspects of learning difficult to explain using simpler RL algorithms (Courville et al., 2006). More generally, the notion of ‘model-free’ and ‘model-based’ control across state and action learning scenarios is embedded in a long literature of emotional and habitual behaviour, versus deliberative cognition (Daw, 2018). However, the reality may be more complex, and at least in the case of reward, there is evidence that the brain uses intermediate computational strategies that have features of both model-free and model-based learning (Momennejad et al., 2017).

Neurobiologically, cognitive learning and decision-making structures for pain are likely to include multiple regions of prefrontal cortex, including ventrolateral and dorsolateral PFC, anterior cingulate, and hippocampal regions (Atlas, Doll, et al., 2016; Olsson et al., 2007; Jeon et al., 2010; Carter et al., 2006; LeDoux et al., 2018; Qi et al., 2018). Importantly, there is evidently overlap in many brain regions identified in cognitive learning and simpler learning schemes, especially regions such as the amygdala and striatum (Madarasz et al., 2016; Koban, Jepma, et al., 2017).

Conscious pain perception and interactions between controllers

In the RL framework, the ‘pain’ signal acts as the primary teaching signal that drives the learning of values. This raises the question as to whether this reflects the conscious perception of pain, or exists as a distinct, subconscious entity. The multi-controller architecture does not necessarily mean that each controller uses precisely the same reinforcement signal, and because innate defense responses need to be rapid, they are inextricably linked to nociceptive input from the very earliest parts of the ascending pathway. However slower and computationally sophisticated sensory processing of nociceptive signals can be used by the higher cognitive controller, which is clearly directly associated with conscious processing (i.e. working memory, explicit reasoning, and planning). Furthermore, it must be the case that conscious pain can exert a direct effect on cognitive learning and control, because even if the conscious perception of pain emerged as some sort of epiphenomenon of neural processing, its perception would still lead to avoidance of this state in the future, given the choice.

For this reason, at the very least conscious pain must act as a control signal related to cognitive learning systems.

More broadly, cognitive processes are built atop a hierarchy that involves multiple facilitative interactions between layers. Although such an architecture seems complex, computationally it is highly efficient (Piccolo et al., 2018; J.H. Lee et al., 2019). For instance, exposure to an unexpected pain stimulus recruits the innate and Pavlovian systems first, to provide rapid, safe defense using evolutionarily learned information. This sets the 'action priors' upon which a cognitive system can evaluate the causes of pain based on building a model of what happened, allowing rapid learning and inference of optimal defensive responses. When these responses can lead to the reliable avoidance of pain, the basic (model-free) instrumental system takes over control, which provides computational efficiency and can help protect against unnecessary influence by random noise (Wang et al., 2018; Daw, Niv, et al., 2005). Overall, each system is optimal in a given situation, and as a whole the architecture balances speed and computational efficiency at one end, with computational sophistication at the other. The caveat, however, may be a necessary susceptibility to impulsiveness and compulsiveness, mostly due to the strength of innate and Pavlovian systems (Lloyd et al., 2018; Millner et al., 2017; Robbins et al., 2012).

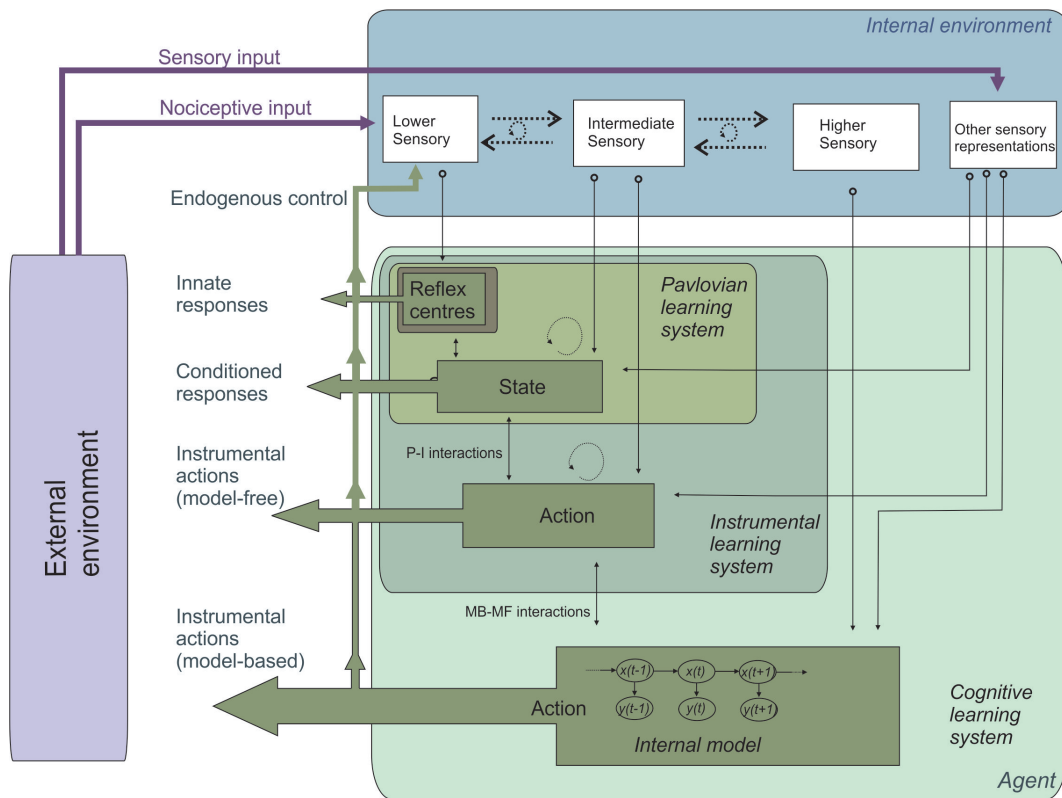


Figure 2: **The Reinforcement Learning model of pain.** This schematic details the computational architecture of the pain system. Basic brain representation(s) of pain receive ascending spinal nociceptive input, and are used to generate the internal reinforcement signal that is used for control. These feed into separate control systems which control behaviour in 1) an innate pain response system; 2) state-based, Pavlovian learning; 3) associative action-outcome learning ('model-free' habit learning), and 4) a cognitive ('model-based') action learning/planning system. Collectively, learning and responses/actions emerge through pavlovian-instrumental (P-I), and model-based-model-free interactions. Model simulation produces rapid, efficient harm avoidance, and outperforms single system models and conventional control systems for autonomous agents in terms of safe learning (Elfving et al., 2017). Endogenous control from these controllers reciprocally modulates the sensory pain pathway.

Endogenous control.

The RL framework shows how potential harm can be minimised through a nested hierarchy of controllers. This raises the question as to whether we should expect pain to be a fixed, stable signal that faithfully represents the nociceptive signal, or a flexible signal that adapts to the

current learning context. As we discuss below, the RL architecture indeed indicates that pain should be modulated by a number of factors if it is to operate optimally as a control signal.

Modulation by sensory inference.

The available evidence suggests that the RL control hierarchy has a corresponding sensory processing hierarchy, with crude spinal and brainstem nociceptive input feeding into lower controllers; and conscious pain feeding into higher controllers at the top (Fig 2). The function of sensory processing hierarchies is to allow the optimal estimate of the properties - such as the intensity - of the external stimulus (Seymour and Dolan, 2013; Büchel et al., 2014; Tabor, Thacker, et al., 2017). This estimate is ultimately an inference made based on prior experience and other relevant information, including simple predictive contingencies, multi-sensory integration, instructed knowledge, or observed knowledge. Based on the assumption that the incoming nociceptive input is inherently noisy, inference will improve the estimate of the true intensity. Computationally, sensory inference is typically proposed to approximate some sort of Bayesian inference (Colombo et al., 2012; Knill et al., 2004), and can in principle explain why pain perception is routinely biased towards prior knowledge (Colloca et al., 2006; Anchisi et al., 2015; Seymour and Dolan, 2013; Wiech, 2016; Atlas, Bolger, et al., 2010). And it is consistent with the observation that the magnitude of this bias depends on the certainty of the prior information (C.A. Brown et al., 2008; Yoshida et al., 2013). The inferred estimate may also be asymmetrically weighted by the cost of errors (i.e. under-estimating pain may be more costly than over-estimating (Rachman et al., 1991)). When errors do occur (for instance, when the discrepancy between prior and incoming nociceptive information reaches a threshold), then the information within the prior may need to be relearned, weakening its capability to bias future pain due to its increased uncertainty, but enhancing the way the information is used in the long-run (Angela et al., 2005; Hird et al., 2018). Although evidence suggests that in the case of pain, disconfirming sensory evidence may be relatively under-weighted (Jepma et al., 2018). Overall, however, modulation during perceptual processing creates a more accurate pain signal that is available to higher (cognitive) RL control.

Modulation by predictive value

A key feature of the RL model is that it deals with sequential stimuli - predicting outcomes both near and far in the future. This accommodates the fact that pain can both act as both a reinforcer (i.e. an outcome or an unconditioned stimulus, US), or a cue for other motivationally salient outcomes (a predictor, or conditioned stimulus, CS). That is, pain can predict it's own termination, explicit reward, or more pain (Gerber et al., 2014; Fields, 2018; Navratilova, Atcherley, et al., 2015) - indeed anything that improves or worsens homeostasis (Keramati et al., 2014). This means that the aversiveness of pain incorporates *two* quantities - its inherent (aversive) value as an outcome, and its value as a predictor. For instance in Pavlovian counter-conditioning, a subject might learn to predict a food reward following a pain stimulus: after training, the pain stimulus elicits no aversive response at all, only appetitive (positive) responses anticipating food (Erofëeva, n.d.). Here it is clear that the modulation of pain must be at an early level for defensive motor responses to be lost, but also that the pain stimulus continues to act as a discriminative stimulus despite being modulated, implying that at some level, modulation of pain must have a degree of selectivity to preserve discriminative information (Melzack, 1968).

Pain can also be a predictor for more pain, which will enhance its aversiveness, and raises the issue of how the duration to the next pain influences its aversive valuation. Evidence indicates that two processes are at work - temporal discounting and dread. Temporal discounting is a well-supported assumption in most RL models by which people discount future events as a function of distance into the future (Sutton et al., 1998; Frederick et al., 2002). But people also find the process of anticipating pain inherently aversive in its own right - a phenomenon called dread - which often causes them to choose sooner over distant pain (e.g. for a necessary dental procedure, people might want to 'get it out of the way' sooner so they don't need to worry about it) (Loewenstein, 1987; Berns et al., 2006). Hence the net behaviour is the combination of a dread function with a discount function, which leads to a 'n' shaped prospective function in which predictions of future pain has an intermediate peak aversive latency Story et al., 2013.

It is also possible for temporal patterns of pain to act as predictors. In a classic example, decreasing pain is felt as less aversive than increasing pain - the so-called 'peak-end' effect (Kahneman,

Wakker, et al., 1997; Kahneman, Fredrickson, et al., 1993). This implies that either temporal constructs can act as a cues for associative learning, or that people build a more sophisticated internal model (memory) of the episode to support prediction (Fiser et al., 2010).

Modulation by decision conflict

The RL model mediates a broad array of responses and actions, from autonomic and physiological responses, reflexive motor responses (e.g. limb withdrawal), innate behavioural programs (freeze, fight or flight), communicative responses (facial expression and vocalisations), and any type of instrumental motor action (such as pressing a keyboard in a pain experiment). Within this set, emission of some types of response can occur independently of others - for instance pressing a key will not interfere with a heart rate response or facial expression. But other types of response will: for instance, innate motor responses may well interfere with with instrumental actions which might be more important, such as escape from danger, or acquisition of a large reward that outweighs the magnitude of the pain (Maier et al., 1982; Fields, 2006; Fields, 2018; Dayan, Niv, et al., 2006). The problem the pain system has in managing this decision conflict is that because the innate responses are relatively hard-wired early in the ascending pain pathway, which is necessary to elicit rapid responses, the only way to suppress innate responses is to suppress nociceptive afferents when or soon after they enter the dorsal horn of the spinal cord. That is, it may not be feasible to selectively modulate innate responses without modulating ascending pain signals at the same time. This means that when instrumental decision circuits prioritise reward-seeking over pain avoidance or escape, or when active instrumental avoidance or escape involves actions different from innate avoidance or escape, then pain is endogenously reduced (Dum et al., 1984).

Decision conflict may also operate at the level of cognition, since pain inherently drives attention, learning and planning (Legrain et al., 2009; Van Damme et al., 2010). Thus in the face of a competing and more significant goal (i.e. escape, or large reward), pain may interfere with and disrupt more important cognitive processes (Eccleston et al., 1999). Just as it is the case that two physical actions may be incompatible, (such as simultaneously moving in two directions), two 'mental' actions may also be incompatible (such as planning to simultaneously move in two different directions) (T.I. Brown et al., 2016). Thus decision conflict may invoke endogenous control at both the level of action and cognition.

Modulation by informational value

The fact that attention and controllability reliably modulate pain (Eccleston et al., 1999; Wiech et al., 2006; Yoshida et al., 2013; Salomons, Nusslock, et al., 2014; Taylor et al., 2017; Salomons, Johnstone, et al., 2007; Bräscher et al., 2016), beyond that which can be explained by mechanisms above, suggests that factors intrinsic to learning and control specifically modulate pain. Although the goal of RL is to learn to minimise pain as an objective function, performance can be enhanced by intrinsically modulating pain according to it's informational value in learning. This is because prospective benefit of learning is not a fixed quantity, but varies according to how much there is to learn (uncertainty), how long there is to exploit learnable information (opportunity), and the capability to exploit it (controllability). In the case of reward, such intrinsic modulation of decision value is well-recognised (for instance in novelty-seeking and uncertainty-seeking), and helps solve the exploration-exploitation problem of trial-and-error learning (i.e. information sampling (Wilson et al., 2014; Wittmann et al., 2008)).

In the case of pain, therefore, the magnitude of a phasic pain stimulus should be enhanced if uncertainty, opportunity and controllability are high, because the marginal benefit of learning is higher. More precisely, the model predicts these factors should interact, because the benefit of learning is only manifest if the opportunity and controllability are both significant (Zhang, Yoshida, et al., 2018)(see Box 1). In the case of learning relief from tonic pain, the opposite effect should occur (i.e. background pain should be reduced if the benefit to learning about relief is high), because the object of learning is relief, not pain (and persistent pain exerts a tonic control effect on behaviour, as we discuss below). This appears to be the case - relief uncertainty reduces background tonic pain when relief uncertainty is high, when relief is controllable (Zhang, Mano, M. Lee, et al., 2018).

Across these demonstrations, uncertainty-based modulation reflects the mechanism underlying what is conventionally considered attention or salience (Eccleston et al., 1999). This spans attention that is driven by bottom-up processes learned through trial-and-error (i.e lots of errors equate

to high uncertainty), or top-down processes provided by external cues or instruction. In all cases, the effect is to enhance learning and guide choice in a way that benefits long-run prospects. Thus any relatively unexpected change in persistent or repetitive pain will have a modulatory effect: reductions in persistent nociceptive stimulation will cause an exaggerated reduction in pain perception, and increases in nociceptive stimulation an exaggerated increase in perceived pain. These effects are well-recognised in studies of relative valuation of pain (Winston et al., 2014; Vlaev et al., 2009), and offset hypoalgesia and onset hyperalgesia (Sprenger et al., 2018; Grill et al., 2002; Yelle et al., 2009).

Neural implementation of endogenous analgesia

The primary effector pathway for endogenous control (both hypo- and hyperalgesia) is known to involve descending control via the PAG to rostral ventral medulla, to the dorsal horn of the spinal cord (Heinricher et al., 2009). What has been harder to ascertain is which higher brain sites instruct this pathway, and where and how the amount of descending control is computed. One of the difficulties is that many classic paradigms of endogenous control may actually involve several distinct mechanisms, so it is difficult to relate computational mechanisms to specific neural loci without a considerable degree of uncertainty. For instance, placebo analgesia can involve all four of the above mechanisms. However, several cortical regions seem to play a key role, including regions of anterior cingulate cortex, dorsolateral prefrontal cortex and insula (Wiech, 2016; Tracey, 2010).

More specifically, the pregenual anterior cingulate cortex (pgACC) has emerged as the most consistently implicated cortical region in human endogenous control paradigms, including in placebo and expectancy hypoalgesia (Wager, Rilling, et al., 2004; Bingel, Lorenz, et al., 2006; Eippert et al., 2009), uncertainty-based analgesia (Zhang, Mano, M. Lee, et al., 2018; Zhang, Yoshida, et al., 2018), controllability (Salomons, Johnstone, et al., 2007; Salomons, Nusslock, et al., 2014), habituation (Bingel, Schoell, et al., 2007), stress-induced analgesia (Yilmaz et al., 2010) and even analgesia induced by motor cortex stimulation (Peyron et al., 2007). The pgACC is highly opioid-rich and sits within an anatomical network with connections to PAG and other subcortical regions involved in pain and learning, including amygdala, VMPFC, hippocampus, lateral OFC and PFC (Margulies et al., 2007; Vogt, 2005). These sites are central to pain and reward learning, and directly implicated in control by decision conflict (Fields, 2018), sensory inference (Büchel et al., 2014) and value learning (A. Craig, 2003; Seymour, O’doherly, Dayan, et al., 2004; Ploghaus et al., 1999). Furthermore, the pgACC is also implicated in both rodent models and human clinical cases of chronic pain (Qu et al., 2011; Segerdahl, Themistocleous, et al., 2018; Mano et al., 2018).

What has been less clear is the specificity of modulation of ascending pathways in the dorsal horn. An inherent paradox of endogenous control is that it risks degrading the information that pain carries as a predictive stimulus. Hence it is likely that at least some aspects of discriminative information must be selectively preserved in endogenous control in the ascending pathways (Box 1). Indeed psychologically, preservation of discriminative perception accompanying analgesia with opioids and cingulotomy is well-described (Melzack, 1968), and forms the basis of a conventional notion of dissociability of affective and discriminative pain processing in putative ‘medial and lateral pain systems’, respectively (Vogt and Sikes, 2000; Corder et al., 2019). Recent evidence indicates that this selectivity may be mediated by preferential control of C-fibres over A-delta fibres in the dorsal horn (Heinricher et al., 2009), which fits with the notion that the A-delta fibre pathways carry more refined discriminative information.

Translation to chronic pain

Tonic or persistent pain after injury serves several physiological functions. First, it has a direct effect on mood and cognition, encouraging rest and recuperation by reducing motivation to engage in non-essential reward-guided activity which is less important for homeostatic priorities. Second, it represents a state from which reduction or cessation of pain becomes a new motivational goal, hence frames relief as an objective function for appetitive reinforcement learning. Third, when accompanied by hyperalgesia and allodynia, it sensitises otherwise less or non-noxious stimuli to drive pain learning, which is clearly adaptive given that the area of injury may be more prone to further injury than normal.

This raises the question as to why physiologically persistent pain outlives its usefulness to become pathologically persistent pain in some individuals. Clearly chronic pain is heterogeneous, and many forms of chronic pain could simply reflect a normal brain response to increased nociceptive

input at peripheral or spinal levels. More commonly, however, it is likely that peripheral and central factors interact to generate the chronic pain state: persistent nociceptive signals are further amplified and maintained by aberrant brain processes.

The RL model of pain illustrates many specific computational mechanisms that could hypothetically contribute to this process. These could be perceptual: with persistent pain reflecting an inference of the state of injury, but subject to an excessive and irrefutable belief that this is the case biasing perceptual inference (a sort of 'self-fulfilling prophecy' (Jepma et al., 2018)). Or it could be motivational: such as excessive aversive valuation, elevated or asymmetrical aversive learning rates, over-generalisation, loss of any component of endogenous control, reduced extinction of movement-related fear, excessive dread, aberrant sequential learning and so on. This may have either a direct effect on pain perception, or an indirect effect: in the fear-avoidance model of musculoskeletal pain, excessive fear learning of movement leads to inactivity which itself causes increased tissue injury through secondary means (Vlaeyen et al., 2000).

From a computational perspective, therefore, it is likely that individual factors (i.e. the parameters of the RL model) act as individual risk factors for chronic pain, that subsequently interact to generate the chronic pain phenotype given appropriate external events (such as a precipitating tissue injury). This would define a 'computome' of chronic pain risk, and illustrates many ways in which some of the individual factors might be shared with co-incident psychiatric conditions, such as depression and anxiety (Fig 3). This framework also offers a computational framework to start to address some of the neurobiological differences seen in RL-linked circuits in chronic pain patients, including VMPFC and nucleus accumbens (Baliki, Petre, et al., 2012; Baliki, Geha, et al., 2010; Mano et al., 2018). However, given the complexity of the RL model (in terms of its architecture and large number of parameters), it strongly appeals to simulation methods to help predict how different factors might conspire together to generate chronic pain risk (Seymour and S.W. Lee, 2019).

Conclusions

Both theory and evidence point to view of pain as a precision signal that guides prospective behaviour to minimise harm through learning. The pain system has been shaped through evolution by the complexity and diversity of actual threats in the natural world, but in particular, it has faced four problems which have had a dominant impact on its architecture. First, how to learn about harm both near and far into the future (the credit assignment problem), which is solved by the predictive value learning system defined by reinforcement learning. Second, how to balance speed of response with processing sophistication (a type of speed-accuracy dilemma), which is solved by having a nested hierarchical architecture that spans rapid reflexes to internal models, and which interact through endogenous control. Third, how to balance information acquisition about threat with the concurrent need to avoid it (the information sampling dilemma), which is solved by endogenous fine tuning of pain to maximise its value as a learning signal. And fourth, how to suppress pain when needed, whilst not suppressing the information it carries, which is solved by having dissociable discriminative and affective subcomponents of pain. Overall, the reinforcement learning model of the pain system illustrates computationally how these solutions are implemented in the brain, and how this drives safe, efficient, rapid and effective pain behaviour.

The model also offers insight into the three broad issues in pain neuroscience raised in the introduction. From the perspective of the representation of pain in the brain (the 'pain matrix'), it is clear that pain is constructed not only from nociceptive input, but also from a set of cortical and subcortical components that compute the effective magnitude of pain as a control signal. That this implies that subjective pain will be best estimated from responses in multiple regions is consistent with general network/connectivity (Kucyi et al., 2015) and multivariate 'signatures' of pain (Wager, Atlas, et al., 2013; Woo et al., 2015; Marquand et al., 2010; Zunhammer et al., 2018), but goes beyond these by highlighting the importance of understanding exactly what each of the nodes in the pain network do (i.e. pain as a computational network). However, it is also consistent with cortical specificity models, because as long as endogenous modulation is primarily descending, there should still be a restricted cortical response that primarily reflects pain aversive intensity after modulation (for example in posterior insula or mid-anterior cingulate cortex (Segerdahl, Mezue, et al., 2015; Kragel et al., 2018; A.D. Craig and A. Craig, 2009)). In other words, although there is always most information available from a broad set of brain regions (involving processes are not individually unique to pain), it must also be the case that a unique and fundamental representations

of discriminative features and pain value are bound together to yield the unique subjective sense of pain. However key questions remain, and perhaps the most important is knowing where in the brain internal representations of pain used for cognitive planning and control are coded (i.e. where is the 'cognitive map' of pain?).

From the perspective of the subjectivity of pain, the RL model challenges the primacy of self-report. This is because at a fundamental level pain concerns control, and so control behaviour should serve as the ultimate measure of pain. Irrespective of the problems associated with self-report scales (Stewart et al., 2005), pain leads to a broad set of learning and control behaviours that can be objectively measured, and the conscious perception of pain merely serves these functions. This speaks to Melzack's and Casey's 'man-in-the-brain' problem - pain perception is merely a link (albeit it a critical one) in a self-organising control circuit, rather than a terminal node that informs an elusive higher controller. On this basis, the RL model's prediction is that all aspects of endogenous control should be reflected in subsequent choice behaviour, and this remains an important prediction for future studies (see Box 1).

Finally, the model yields a concept of pain as a signal that is tuned precisely to its function as a control signal. The concept that 'pain is modulated' presupposes that pain is a sensory nociceptive signal whose primary role is to retrospectively estimate of the objective intensity of a stimulus, and then needs to be tuned to support whatever behaviour is required at the time i.e. the view of modulation of pain as 'post-perceptual processing'. But as a prospective control signal pain behaves in precisely the way it needs, and hence should not be considered to be modulated at all. Although the factors that lead to the tuning of pain may be difficult to experimentally observe and objectify (such as complex social information about forthcoming pain), this doesn't mean that the brain doesn't estimate and represent these quantities in a precise manner. Ultimately, endogenous control illustrates how pain is constructed on a moment-by-moment basis based on an complex but objectively definable integration of broad sources of information.

Box 1: Key Predictions of the RL Model

- **Opposite effects of controllability and uncertainty on phasic and tonic pain.** The model proposes that uncertainty and controllability relate to a greater marginal benefit to learning, and phasic pain should be enhanced accordingly. However, in the case of tonic pain it is relief acts as the teaching signal, and ongoing pain acts has a direct suppressive effect on cognition, and so ongoing pain should be reduced to enhance relief learning. Existing support for this is mixed (Yoshida et al., 2013; C.A. Brown et al., 2008; Zaman et al., 2017; Bräscher et al., 2016; Wiech et al., 2006; Salomons, Johnstone, et al., 2007; Zhang, Mano, M. Lee, et al., 2018), partly because uncertainty is not always studied in the context of controllability, and increased controllability often results in reduced uncertainty, leaving this issue to be fully demonstrated.
- **Endogenous control should drive exploration** If a core function of endogenous control is to facilitate information acquisition, this should be reflected in choice, and manifest by a direct relationship between pain modulation and exploratory action. Furthermore, this should also be sensitive to the expected benefit of this information to future behaviour - i.e. greater opportunity to exploit information relates to greater endogenous control (cf. (Wilson et al., 2014)).
- **Pain discrimination is preserved during endogenous analgesia.** If pain can act as both a cue and an outcome, it is important that the capacity to discriminate pain remains unimpaired in the context of endogenous control. Although evidence suggests that descending modulatory pathways have a selective end-target in the dorsal horn (Heinricher et al., 2009), there is yet no behavioural evidence, for instance that fine discrimination (e.g. spatial or intensity) is preserved in endogenous analgesia.

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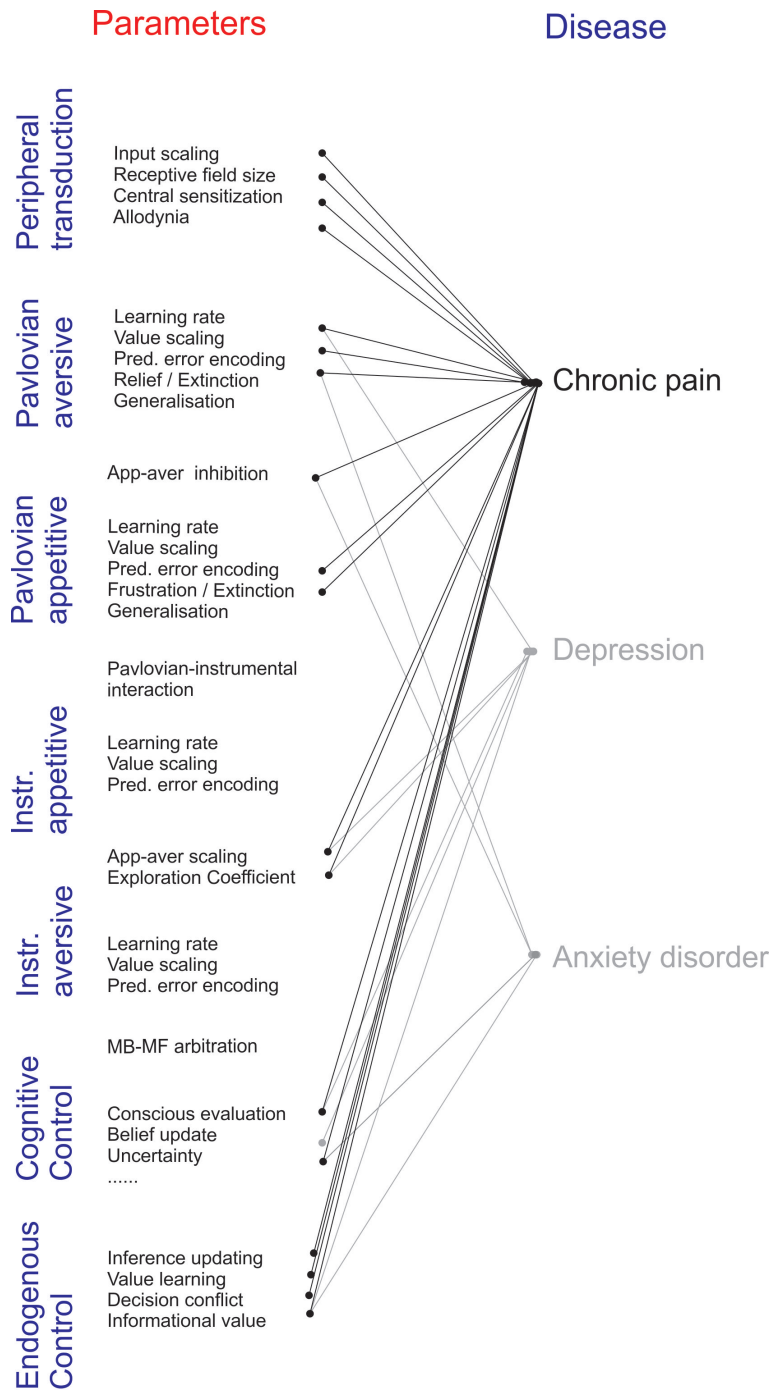


Figure 3: **The hypothetical chronic pain computome.** The RL model involves a large set of parameters that determine the way in which learning and decisions making operate within the control framework. Several of these have been proposed to be involved not only with chronic pain, but also other disorders associated with aversive learning, including anxiety and depression. The figure shows a schematic of how a series of hypothetical factors might operate together to create an overall risk for chronic pain, given an appropriate peripheral drive from an injury, and these factors might have different roles at different points in the pain chronification process. Importantly, the way these factors interact is determined by the complexity of the computational (RL) model which defines the information processing operations they govern, which means predicting how different combinations determine risk may require advanced simulation platforms (Seymour and S.W. Lee, 2019)