Post-injury pain and behaviour: a control theory perspective

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Abstract

Injuries of various types occur commonly in the lives of humans and other animals, and lead to a pattern of persistent pain and recuperative behaviour that allows safe and effective recovery. Here, we propose a control-theoretic framework to explain the adaptive processes in the brain that drive physiological post-injury behaviour. We set out an evolutionary and ethological view on how animals respond to injury, illustrating how the behavioural state associated with persistent pain and recuperation may be just as important as phasic pain in ensuring survival. Adopting a normative approach, we suggest that the brain implements a continuous optimal inference of the current state of injury from diverse sensory and physiological signals. This drives the various effector control mechanisms of behavioural homeostasis, which span modulation of ongoing motivation and perception to drive rest and hyper-protective behaviours. However, an inherent

problem with this is that these protective behaviours may partially obscure information about whether injury has resolved. Such information-restriction may seed a tendency to aberrantly or persistently infer injury, and so promote transition to pathological chronic pain states.

Introduction

Injury is an inevitable consequence of life in a hazardous and competitive world, and animals' ubiquitous capability for tissue healing provides a passage to recovery that has been an essential feature of life across species throughout evolution[1]. However, animals are especially vulnerable during the recovery period, both because of the myriad of complex ways in which an injury might affect physiological and behavioural functions, and because external threats may be greater in the context of reduced functionality. In humans, one of the defining components of the injured state is pain, but pain is universally unpleasant and its role in helping to guide recovery remains unclear.

In health, acute phasic pain - for instance after touching a hot saucepan - provides a valuable and effective signal that informs of imminent harm, enabling us to rapidly respond to the cause of the threat, and learn from the experience to avoid it in the future[2]. But if a true injury is actually sustained - for instance you physically burn yourself - a different pattern of pain ensues. One aspect of this is a general amplification of evoked phasic pain around the injured region, which enhances protective behaviour and derives from a combination of peripheral and central sensitization[3]. Another aspect is a spontaneous background pain that persists at rest, and is typically associated with an ongoing sense of fatigue, lowered mood and anxiety[4]. The functional role of this background pain is less clear, and leads to a question as to whether persistent pain and its associated symptoms are part of an adaptive physiological response to an injury. If so, it should be possible to understand these symptoms in an evolutionary context and formalise their behavioural function.

In this Perspective, we set out the evolutionary framework for considering how animals across species respond to injury, and how such behaviours may improve adaptive fitness. We then show how this can be used to inform and constrain computational models of post-injury behavioural homeostasis, and formulate a control-theoretic approach for persistent pain. We argue that the very nature of adaptive control creates a fundamental problem for the system: that is, the behaviour used to protect against pain makes it difficult to know if an injury has resolved

(information restriction). From the control perspective, resolution of persistent pain and injury is equivalent to a finely tuned yet difficult inference problem, and maladaptive emotional and behavioural responses may lead to an inherent risk of augmentation and persistence into a chronic pain-like state.

Ecological and evolutionary perspectives.

Nociception is an evolutionary necessity, as important as the ability to identify sources of energy or food, and to reproduce[5-7]. Responses to injury vary enormously across the animal kingdom (**Supplemental FIG. 1a**). Sessile animals without nervous systems respond via molecular and cellular changes that prioritise tissue regeneration and repair, and these responses are highly conserved among all animals[8]. The molecular detectors for aversive control, for example, the transient receptor potential superfamily of receptors, have ancient homologues involved in thermal, mechanical and chemical sensation[9.10], evident in non-animal species from microbes to algae[11-15].

Over the course of evolution, injury is likely one of the earliest arising and most persistent features of an animal's sensory experience. Among extant animal species, there is abundant evidence that injuries of many kinds are common, arising from accidents and inanimate dangers, predator-prey interactions, parasites and infections, and within-species interactions and conflicts[16-19] (**Supplemental FIG. 1b**). The emergence of sensory neurons tuned to injury and noxious sensation (known as nociceptors) has occurred multiple times, with nociceptors described in nearly all extant animal phyla[20,21]. Even animals with very small nervous systems tend to dedicate neurons to the detection and response to injury[22]. This seemingly simple behaviour illustrates a basic control principle: sensors can detect environmental events and conditions before actual damage occurs, and use the signal to create a window of opportunity for evasive responses. This capacity for predictive control was extended early in brain evolution with development of the apparatus for associative learning (e.g. Pavlovian conditioning), which allows the sensed threat to be acted on as soon as it is predicted[23]. Homologues for the neural architectures and modulators involved in the sophisticated predictive aversive learning seen in mammals clearly exist in comparatively simple brains such as Drosophila[24].

Irrespective of nervous system size or complexity, effective avoidance of bodily damage relies on two core principles: accurate, reliable and early detection of potential harm, and eliciting the right

response in action. Depending on the context, optimal responses to the threat of injury might be offensive or defensive, and this complexity in selecting the optimal response to an acute nociceptive stimulus has led to a broad repertoire of highly context- and species-specific responses[25]. Meanwhile, larger brains also allow much more complicated *instrumental* behaviour - the ability to choose and reinforce actions supported by action-outcome learning, and through to cognitive architectures that allow an internal representation of the state of the external and internal environment[26]. Such an active sensing-action cycle is common and crucial for fitness and survival across animals.

Despite considerable sophistication in the capacity for avoidance, however, animals still frequently fail to avoid harm. Once an injury is incurred, the landscape of selection pressures acting on the brain shifts radically from circuits promoting injury-avoidance behaviour, onto those driving sustained recuperative, protective behaviour (**Supplemental FIG. 1c**). Importantly, failure to avoid injury comprises only a small proportion of the total fitness costs associated with injury. A major proportion of the cost is influenced by post-injury behavioural choices. In the post-injury phase, the adaptive value of long-lasting pain is apparent both as a potential means of driving recuperative behaviours during the healing period, and as a powerful enhancer of contextual memory of the painful event.

Given the frequency of injury occurrences and their obvious fitness costs, it is ultimately likely that behaviours that occur as a direct result of injuries are adaptive[7,27]. However, empirical tests of this pervasive hypothesis are uncommon, partly because the neural mechanisms driving these more complex behaviours are poorly understood in comparison to those driving immediate avoidance. What is clear is that in the aftermath of an injury, there is a dynamic transition from the acute defensive stage to a more prolonged recuperative stage, including whole-body behaviours such as rest, immobility, vigilance; and injury-directed behaviours such as wound guarding or grooming. This observation leads to the question regarding the role of persistent pain in driving recuperative behaviour. These complex behaviours are influenced by various homeostatic and autonomic systems, but evidence for the role of pain sensing to drive ecologically-relevant hypervigilance and recuperative behaviours can be found in studies of laboratory rodents [28], where provision of analgesic drugs acting directly on pain pathways restores normal behaviours [29-31]. Interestingly, only a few invertebrate animals – not surprisingly, those with the most complex brains such as decapod crustaceans and cephalopod molluscs - have been shown to engage in recuperative

and wound-directed behaviour, and is where evidence for vertebrate-like, persistent pain experience is strongest [32-35] (**BOX 1**).

One further important determinant of the nature and duration of recuperative behaviour is sociality, and whether the social environment facilitates extended recuperatory behaviours, which range from group protection of the injured member, to food provisioning, and to shared parental care. If we presume that persistent pain restricts the range of normal behaviour to those only that facilitate predator avoidance and wound healing, then recuperative behaviour (as hypothesised to be promoted by persistent pain) can only be adaptive in animals either whose physiology allows for extended periods of low nutrition, or whose social group can buffer the risks of starvation and isolation [27]. Thus, animals who have high energy demand or lack social groups to share resources, are less likely to benefit from extended recuperative behaviour. In an optimality model, it can be shown that animals should direct allocation of limited post-injury resources to combating an immediate survival threat and away from recuperation and maintenance, up until the cost of accumulated damage from neglecting recuperative and nutritive needs increases mortality[36]. It follows that animals under greater pressure to allocate resources to maintenance (such as those with high energy demands), must limit recuperative behavior to ensure survival. Sociality is one mechanism that provides an escape from this tradeoff, as it permits individuals to access resources provided by in-group members (food, shelter and co-operative wound-care, but also time spent scanning for predators and predator deterrent behaviors) without limiting recuperation. Social animals have evolved pain-signalling strategies, such as vocalisation and facial expression, to elicit help from their in-group members. However, these pain experiences are only adaptive when the sender and receiver both benefit from the sender's survival. Therefore, outward signals of pain in social animals are constrained by the risk of eavesdropping[37], which can be appreciated, somewhat paradoxically, by observing injury-feigning behaviour in birds ("the broken wing trick") that is highly effective at luring predators away from their chicks [38].

Overall, this ecology and evolutionary perspective illustrates the clear functional distinction in the roles of acute phasic vs. persistent pain, and promotes the idea that persistent pain may be as important in preserving the survival of injured animals as is acute phasic pain. Because the healing phase may vary in different species and vary from different types of injuries, this perspective also provides a framework for addressing the important question of whether our current clinical classification on acute vs. chronic pain fails to consider that persistent pain (which is typically considered pathological) can be a normal, adaptive and vitally important response to

injury that may be a necessary aspect of experience-dependent behavioural optimisation[39]. In other words, persistent pain arises as part of normal functioning of the pain system optimised over the course of evolution by natural selection, and is not necessarily an inherent pathological state. However, understanding the mechanism of persistent pain may help us comprehend how it may extend to be a pathological state in certain circumstances.

Formalising models of persistent pain

The temporal sequence of events transitioning from acute phasic nociception (associated with active defensive and rapid learning) to a tonic persistent injury state (associated with recuperative and protective behaviours) illustrates the fundamental ecological necessity of the pain system. The importance of this notion was highlighted by Wall[40], developed in the 'perceptual-defensive-recuperative' (PDR) model[41], and later adopted in the 'adaptive hypothesis' for injury-related behaviour[42]. In terms of adaptive control, evolutionary assumptions are key to constraining the space of solutions that brains adopt to achieve pain-associated behavioural functions[43,44]. Within this approach lies two conceptual dichotomies. The first is between normativity (the objective function of the behaviour or *why* animals behave in a certain way) and statistical optimality (how information is processed in a mathematically ideal way). The second is between computational and algorithmic levels of analysis, which distinguishes what problem the brain solves, from how it solves it[45].

By its very nature, acute phasic pain appeals to a notion of adaptive control, where the control signal is aimed to optimize a cost-to-go function. Once one assumes that nociceptive afferents deliver an at least partially reliable signal of impending tissue damage, then the brain can use this as a cost function, both in terms of driving immediate defensive responses and by shaping future responses through learning. In this context, evolution tunes both the nociceptive signal and the learning system [46,47]. This has been central to contemporary models of phasic pain processing, in which pain feeds into a control loop that comprises three core processes: stimulus or saliency detection, action selection, and action execution (**FIG. 1a**)[2]. This is operated in a hierarchy, interleaved with value learning and motor learning in the sensory-motor loop, supervised by top-down meta-learning that regulates the control process.

A key facet of applying this approach to the pain system is that it is exclusively concerned with the objective functions associated with pain, and does not directly concern itself with subjective phenomenology, which is of course a defining component of pain. And ultimately a fundamental

goal of pain neuroscience is to understand and find treatments for chronic pain as a subjective phenomenological state. However a computational approach to pain can be rationalised irrespective of whether this subjective phenomenology (qualia) of pain is a functional necessity or merely a by-product of computation (i.e. a cause or consequence of behaviour), as long as one assumes that qualia arise from neural mechanisms that themselves have a functional role in pain information processing[48].

A control systems approach to persistent pain and post-injury behaviour

To understand the core computations in a hierarchical control process as outlined in **FIG. 1a**, we can formulate persistent pain as an optimal control problem (**BOX 2).** Put simply, control theory aims to develop control strategies and apply control signals to achieve system optimality and stability. Let us consider a generic control diagram in the context for injury-state inference and action selection (**FIG. 1b**). The plant (dashed box) describes a continuous inference of the state of injury or recovery, which can be treated as a latent state $\mathbf{x}(t)$ of the system. The system receives sensory and physiological observations, $\mathbf{s}(t)$, makes inference on the latent state, and uses feedback to minimise prediction errors. The endogenous input $\mathbf{u}(t)$ is operated on the plant to achieve the "optimal control" of the perceived injury or pain, with the control process happening at multiple levels in the body and the brain. Meta-control, operated as a hierarchy to regulate the control process (**FIG. 1a**), can bias the control signal. One example of meta-control is the homeostatic priorities that finds a balance between exploration and risk-seeking behaviors. Central to the control system, the plant produces an action or behavioural output $\mathbf{y}(t)$, which may send an internal efference copy to predict, enhance or suppress the system nociceptive, autonomic, and endocrine signals in the feedback. A good example of this process has been demonstrated in a human self-reinforcing pain expectation experiment[49], showing that a subject's behavioural output (i.e., pain rating $\mathbf{y}(t)$) may be used to enhance the expected pain state $\mathbf{x}(t)$. The discrepancy between the predicted and actual sensory feedback can be used as an indirect measure of "perceived controllability", which is also related to the notion of 'surprisal' in active inference[50]. This perceived controllability may influence the control process (through meta-control or modifying the cost-rate function). Together, optimising $\mathbf{u}(t)$ and inferring $\mathbf{x}(t)$ based on a control approach provides a computational module for the hierarchical learning described in **FIG. 1a**.

This control perspective of injury and persistent pain leads to a series of central questions: i) How does the brain recognise and represent the state of injury; ii) What action or modulatory processes reflect the effector arm of such a control system; and iii) How the outcome of this control is sensed

and used to close the control loop. Despite growing effort of characterizing complex pain-related behaviours[51,52], relatively few experimental studies have explicitly probed physiological injury behaviours in humans. Because of the control-inference duality, the control-theoretic framework can shed light on understanding persistent pain and physiological injury behaviour.

Injury state representation. The brain has multiple modes of information relevant to the nature and extent of an injury that can be used to optimise injury inference. In addition to tonic nociceptor firing, patterns of non-nociceptor somatosensory afferent (e.g., haptic and mechanical sensation), autonomic afferents, immune signals, as well as other exteroceptive sensory information (e.g., seeing blood) convey discriminative information. Injury can be also inferred from changes in sensory feedback from actions and motor commands which may not be clear at rest, for example touch and probing behaviours to identify the presence or absence of peripheral sensitization, which occurs at least in part through brain-independent processes. It can also include sensing mechanical disability (e.g., joint instability) from exploratory actions to identify abnormalities in non-nociceptive feedback. Finally, other physiological signals, such as information arising from circulating inflammatory mediators and endocrine signals inform the brain about probable tissue insult[53,54]. In a Bayesian framework, therefore, an internal representation of self-injury should integrate and rationalise these multiple sources of information to infer the site, nature and severity of an injury, alongside prior information from existing beliefs.

This multimodal inference process expands the domain of inputs that are conventionally considered to have a core role in signalling injury beyond tonic nociceptor firing. This doesn't necessarily imply that tonic nociceptor firing is not normally required for perceiving injury, but it does imply that it could in some circumstances be insufficient in the absence of other concordant sensory information. In the proposed framework, these individual afferent sensory pathways sit beneath injury state representations in an inference hierarchy, so are inherently interpreted in the context of this higher-level representation. That is, a higher-level belief that the body is injured acts as a prior on the processing of the lower-level modalities**.** Such inferential hierarchies provide a mechanism for understanding various multisensory integration effects in pain perception[55,56].

Control output. The suite of effector mechanisms spans three distinct domains. First, widespread neuromodulatory influences (for example, through dopaminergic and serotonergic signalling) across a broad range of motivated behaviours can implement the adaptive changes required given the inferred state of injury[57]. Current normative computational models of reward and

motivation allow a clear prediction of how recuperative behaviour can be achieved given changes in homeostatic value function[58]. Specifically, this may involve modulation of reward learning in multiple ways: reducing reward sensitivity, increasing relief-seeking, reducing exploration and novelty seeking for non-injury relevant outcomes, increasing effort costs, and changing risk and ambiguity preferences in line with changed homeostatic priorities[59]. Additionally, explicitly protective behaviours can be facilitated through increased punishment sensitivity and increased punishment generalisation, as well as by enhancing innate defensive responses. Many of the global, non-regional responses are also seen in the context of inflammatory illness behaviours, which are also associated with fatigue, lowered mood, and increased anxiety, and now typically considered as adaptive responses in this context[60-62].

Second, endogenous modulation can tune pain sensitivity. In the acute phase, stress-related analgesia occurs, and reflects the reduction in pain that occurs in the context of an acute stressor or danger, and is assumed to facilitate evasive action by suppressing the potentially intrusive interference of motor pain responses[63,64]. Stress-induced analgesia is widespread among diverse animal clades with differing levels of neural complexity, suggesting deep evolutionary conservation [65,66] and strong ongoing selection pressure[67,68] on the behavioral outputs of stress-induced analgesia; most commonly, suppression of pain behavior in the context of acute predatory threat. However, once this has subsided, peripheral and central sensitization directly increase pain responsivity in the injury site, by increasing the sensitivity to pain (hyperalgesia) and expanding the type of stimuli that cause pain to non-nociceptors (allodynia) [69]. In mammals, this further drives protective action to specific injured body parts, which can elicit hyper-protective responses to further injury or increased hypersensitivity to phasic pain [70], and can change the sensory feedback to induce the reorganisation of a sensorimotor map [71]. This is associated with neural plasticity and supraspinal reorganisation[72,73]. For instance, the state of central sensitization leads to structured change in functional connectivity among dorsal horn neuronal populations[74]. In contrast, post-injury recovery is accompanied by supraspinal control of stepping and reorganisation of descending and propriospinal connections[75].

Third, injury states can direct the physiological responses appropriate to the specific nature of the injury, including autonomic, endocrine, and immune responses. These incorporate general stress responses, and may also include coordination of an injury-specific physiological response to regulate local tissue homeostasis[76].

Closed-loop control. A central part of control is to infer whether the injury has resolved, as opposed to persisted or worsened. However, inference may become difficult because behaviours that are associated with sensitising pain and avoiding further damage paradoxically restrict or degrade the information required to continually sense injury. For example, avoidant behaviours are negatively correlated with the information acquisition about what is being avoided - for instance continuing to not move an injured limb makes it difficult to know whether moving it still hurts. This is a form of exploration-exploitation dilemma: exploration involves accepting short-term risk of exacerbating one's pain in order to get information that allows one to better establish the current state or resolution of the injury; once this is determined, the information can be exploited, such as by returning to normality if the injury has been resolved[77]. Also, centrally mediated hyperalgesia and allodynia inherently amplify the signal that led to them in the first place; this can potentially obscure the presumed magnitude of the afferent nociceptive injury signal, making it difficult to know whether or not it is still required. In a control-theoretic account, to infer the state of peripheral injury, the brain needs to account for both top-down modulatory effects and bottom-up sensory information, as well as efference copy of its associated actions and its induced responses. This efference copy is incorporated into the inference process, whilst also considering that some responses are controlled by peripheral mechanisms, and some afferent signals may habituate over time. If the system operates optimally, then given any uncertainty in the posterior belief, the brain also needs to calculate the relative cost of incorrectly inferring injury resolution versus incorrectly inferring persistent injury. These costs also need to be calculated and incorporated into the controller. Hence in humans where recuperation costs may be relatively low, this will usually favour inferring persistent injury.

Meta-control. Meta-control reflects a higher layer of control that regulates the control process [78,79]. First, it may monitor and regulate control (**FIG. 1a**), and use the achieved controllability to optimise meta-parameters of control to improve performance. The perceived controllability may affect the meta-control, such as by modifying the cost-rate function to include an additional penalizing term. One example of meta-control is the homeostatic processes that seek balance between exploration and risk-seeking behaviours[80]. Second, it may also modify parameters according to factors outside of the control system, for instance threats of a different nature that might have some relevance, or other factors of homeostasis (for instance, sleep or energy homeostasis). Third, it may modulate the value function implicit within the control system: for example, the presence of conspecifics might increase the relative value of recuperation, given

the safety they confer. This higher-level of meta-control may also relate to subjective perceptions of controllability with direct clinical relevance[81].

Neural implementation

Hierarchical inference. In terms of functional anatomy, injury inference appeals to regions that receive multisensory afferents with the capability to integrate these signals to compute the likelihood of peripheral injury. The insula cortex is well positioned in the brain for its anatomical and functional connectivity to other areas along the afferent and efferent pain pathways (**FIG. 2a,b**), suggesting an active role in injury state inference similar to that proposed in other interoceptive and visceral states[82-84]. Specifically, the insula receives afferent signals from the range of interoceptive and exteroceptive sensory inputs that carry injury-relevant information[85,86]. This includes signals related to nociception, autonomic change, intercoceptive C-fibre input (thermal change, pleasant touch, and itch)[87], images of bodily injury[88,89], immune activation[90], and sensorimotor incongruence[91]. The insula also receives direct connections from the medial and lateral thalamic nuclei, brainstem autonomic sites (including vagal afferents), parabrachial and amygdala nuclei, and hypothalamus[92]. It can therefore integrate the convergent bodily information required for inference of injury, alongside other physiological states[93]. This also fits with the structural anatomy of the insula, which involves multiple topographic representations through dorsal granular regions (often viewed as a primary interoceptive cortex), projecting to distinct dysgranular 'stripes' and to anterior agranular regions that are associated with higher-level functions[94,95]. Nevertheless, other brain regions are also capable of supporting higher-level multimodal inference. For instance, the ventromedial prefrontal cortex (VMPFC) has been proposed for self-referential models of physical health[96], and the anterior cingulate cortex (ACC) also has a core integrative role that spans interoceptive, exteroceptive and motor domains in the context of pain[97,98]. These regions may therefore coordinate together to achieve integrative inference across a distributed pain network.

Second, a key part of injury inference relates to the recognition of new phasic (acute) pain, especially as a result of motor movement or external events. This appeals to exteroceptive inference in the sensorimotor control loop – in which the occurrence or magnitude of pain exceeds that is normally expected as a result of a particular stimulus or movement. This, alongside other exteroceptive information that comes from vision, plus higher-level information in the form of explicit and semantic knowledge, also needs to be integrated with interoceptive information to

conduct inference. Whilst the locus of higher-level injury representation is still unclear, we speculate that it is possible that it is encoded either in a localized region such as the anterior or mid-insula, or instead has a more distributed representation across the insula and ACC, as well as possibly including conceptual representations in regions such as the VMPFC, hippocampus, and linked with lower-level physiological representations in the hypothalamus. Such higher-order representations also relate to the concept of meta-control, which has not been well studied, but also thought to involve higher-order representations in the anterior insula, ACC, as well as ventromedial and dorsal prefrontal regions that are often associated with contingency knowledge, model-based decision-making, and subjective awareness[96].

More mechanistically, injury-state level probabilistic inference sits above lower-level inference in individual modalities, and can be implemented through local recurrent neural circuits (**FIG. 1c**)[99-101] and spike-timing synaptic plasticity[102-104]. Algorithmic implementation of inference in the brain has been broadly discussed[101,105]. This view also parallels neural architectures suggested to implement predictive coding within cortical layers[106] or between different cortical areas[107].

Efferent control. The multiplex nature of efferent control appeals to a broad network of regions implementing specific components of control. First, modulation of dorsal horn nociceptive neurons can be mediated by multiple opioidergic and monoaminergic descending pathways from the PAG and hypothalamus. These can implement descending facilitation, but also stress-related hypoalgesia when behaviourally required. These sites are likely controlled by a coordinated network, that includes the rostral anterior cingulate cortex (rACC), mid anterior cingulate cortex (mACC), VMPFC, and insula[92,108].

Next, modulation of physiological function, including regulation of sleep, appetite, arousal, endocrine and immunological tone is likely mediated by hypothalamic pathways[109-111]. For instance, hypothalamic dynorphin/KOR signalling modulates arousal, vigilance and sleep architecture in a mouse model of neuropathic injury[112]. And other hypothalamic neuropeptide systems such orexin are involved in co-regulation of pain and sleep[111,113]. Parabrachial-lateral hypothalamic circuits mediate bidirectional effects of energy homeostasis and pain[109,110], including appetite suppression during chronic pain[114]. Additionally, insula-hypothalamic circuits are implicated in integration and synchronisation of endocrine and immune activation during a range of stressors, including pain[115].

The modulation of motivational behaviour during chronic pain is closely associated with midbrain, frontostriatal and amygdala-centred circuits. These behaviours include seeking relief, revaluing, and learning changing reward priorities, and similarly enhancing punishment sensitivity, and risk preferences, which may have neuromodulatory effects on motivational and value learning systems (including dopamine and serotonin). For instance, tonic pain modulation of Pavlovian and instrumental reward and punishment valuation is apparent through the amygdala, cingulate and VMPFC responses in humans[116,117], and mesolimbic circuits are directly implicated in rodent models[59]. These circuits have also been involved in pathological chronification of pain in human patients[118]. More broadly, modulation of mesolimbic monoaminergic neuromodulatory pathways may also have the capacity to enhance learning and hence cortical reorganization across widespread regions[69].

Oscillatory Neurodynamics. The afferent and efferent pain pathways (**FIG. 2a,b**) fit with a proposed role as components of an injury-based control plant. One possible idea is that they may be synchronized by neural oscillations recruited locally and propagated between long-range neural circuits[119]. Traveling waves may provide a possible mechanism for integrating and transferring information across cortical and subcortical areas at different frequencies[120]. Theta (4-9 Hz) rhythms are also known to be associated with the saliency, arousal, and alert states in the cortex and hippocampus[121,122]. Human and animal studies have reported abnormal or augmented 8-10 Hz oscillations in both pain and injury states across many pain-associated areas (**FIG. 3a**), including the insula, somatosensory, anterior cingulate, prefrontal, posterior parietal cortices[123-127], and sensory thalamus[128]. The dynamics of somatosensory cortical theta oscillations may also represent the status of post-injury or pain state[129] (**FIG. 3b**). In healthy subjects, the pre-stimulus theta oscillations in the insula cortex modulate pain perception[130] (**FIG. 3c)**, whereas in chronic pain patients, post-stimulus theta oscillations are related to pain processing[124,131]. Time-dynamic pulse modulation of spinal cord simulation (SCS) in chronic pain-treated rats has shown reduced EEG theta power and spontaneous pain[132]. Further, modulation of theta power originated in the insula by a brain-computer interface (BCI) has shown that up-training theta activity leads to increased pain discrimination, whereas down-training theta activity has an opposite effect[133]. Recent human intracranial EEG recordings also showed that theta and beta oscillations are organized in the form of traveling waves along the anterior-posterior axis of the insula, suggesting frequency multiplexing used in insular information processing[134]. Put together, theta oscillations are a plausible mechanism by which an insula-centred hub coordinates activity with a broader

persistent pain network. In addition to theta oscillations, it is not impossible that propagating waves at other oscillatory frequencies, such as alpha (9-13 Hz), beta (13-30 Hz) and gamma (30-50 Hz) bands, carry complementary information across various degrees of injury-to-pain states[135-138] (**FIG. 3d**). Typically, higher frequency oscillations are confined to a small neuronal space or involve bottom-up processing, whereas very large networks are recruited during slow oscillations[119]. Our prediction is that low-frequency oscillations or traveling waves can efficiently transfer and mediate a large distributed persistent pain network.

Although the exact nature of cortical control of autonomic, endocrine and immune functions remains less well understood, the insula-cingulate network may have a core central modulatory role in detecting saliency, regulating brain network transition and facilitating rapid access to the motor system[139-141]. For instance, sympathetic and parasympathetic effects are evident from stimulations of posterior-to-anterior insular regions (respectively) in epilepsy patients[142], possibly through interactions with cingulate, amygdala and ventromedial hypothalamus[143].

Chronic pain transition: an information restriction model

There are multiple models and theories proposed to understand chronic pain, and these arise from different approaches founded on biological and psychosocial risk factors, neural plasticity and learning, and molecular and circuit-level dysfunction[144-146]. Drawing on insights from these, the computational approach espoused here leads to a novel perspective in which states causally associated with chronic pain may sometimes arise from an internal state wherein injury is incorrectly inferred (in contrast to instances whereby there are persistent peripheral drivers of ongoing pain, and in which injury is correctly inferred). Consequently, this internal state drives subjective persistent pain and its associated behaviours including hypersensitivity to pain, fatigue, low mood, sleep disturbance, and anxiety. This class of behaviours may be adaptive in the context of ongoing physiological injury, but can be considered maladaptive in the context of chronic pain. From a control perspective, maladaptivity may also relate to low perceived controllability.

The control-as-inference framework presented here illustrates a key route to chronification via information restriction (**FIG. 4a**). At the heart of the model is the assumption that pain in some instances of chronic pain exceeds the amount that would be predicted on the basis of the peripheral tissue injury and nociceptive input, a situation that could arise if an injury has resolved or reduced without the central brain control system (‘control plant’) recognizing this. This will occur

if the brain has incomplete or inaccurate information about the peripheral status of the injury, and the model illustrates several specific reasons why this might occur (**FIG. 4b**).

Maladaptive learning. First, increased avoidance responses will reduce the access to information about whether particular actions and movements continue to still cause increased pain. For instance, an injury might have been initially inferred from acute pain occurring when walking on a damaged joint, but avoiding walking means that the individual cannot access information about whether the acute pain is lessened or absent. Second, this problem will be exaggerated by the parallel motivational factors which change the experienced environment, including altered reward learning (reduced exposure to rewards and novelty), and increased punishment sensitivity and aversive generalization (negative exposure). This change in valuation makes the outcomes of situations and actions seem worse than they previously were. This type of information restriction has strong parallels with the classical fear avoidance and learning model[145,147-150], the maladaptive learning model[151-154], and psychosocial models of chronic pain[155].

Maladaptive model. The Bayesian control-theoretic approach assumes that the brain uses a generative model for the control processes, both central and peripheral, to modulate the incoming input. That is, descending facilitation, central sensitization, and peripheral sensitization increase incoming pain signals, and therefore amplify the acute pain signals that helped to infer injury in the first place. To avoid a self-potentiating loop, the Bayesian model implies that the control plant has an efference copy of these processes so they can be considered. But many of these facilitatory processes are complex and not directly controlled by the brain, and any modulation of the incoming signal has the capacity to add noise, and hence increase uncertainty[156-158]. Consequently, increased uncertainty may inherently bias inferring a state of persistent injury, because the relative cost of under-estimating injury is higher than that of over-estimating it. This mechanism draws on existing chronic pain models of spinal-brain interactions[143], and active inference[159,160].

Maladaptive integration. Lesions of the sensory system, spinothalamic system, autonomic system, nerve lesions, or amputation can lead to an obvious information loss. Because these lesions are likely to represent abnormalities that have not been encountered sufficiently often through evolution, the brain will not have an adaptive mechanism for factoring them in to internal models of the injury state, and so they will lead to persistent incongruent multisensory integration of information required to infer the absence or resolution of injury[161]. This persistent incongruent

state is strongly related existing models of sensorimotor reorganisation as a factor contributing to chronic pain[69].

***Maladaptive priors*.** Finally, incorrect or pessimistic beliefs and expectancies of persistent injury or reduced subjective controllability, including from other cognitive sources, will impact on higher-level meta-control and maintain injury representations[157]. This is because strongly held beliefs, in a Bayesian context, will downplay the importance of incoming afferent information, reducing the degree of potentially useful new information. This idea draws on models of chronic pain that highlight expectancy effects and the concept of chronic pain as a 'self-fulfilling prophecy' leading to persistence[49,162].

In summary, a control-theoretic model of physiological pain provides multiple routes to aberrant pain persistence, in which information restriction interferes with inference of return to health, leading to perpetuation of both pain and its accompanying suite of pain-related behaviours. Importantly, these predictions are experimentally testable, and indeed there is already experimental evidence that speaks to many components of them. There are several other novel predictions. For example: the model predicts that nociceptive input *per se* is not necessary for experiencing persistent pain, and it should be possible to generate illusions of pain by manipulating multisensory visual input and sensorimotor feedback loops to fool the brain into thinking there is an injury; testable using techniques like virtual reality. The model also predicts that motivational factors such as increased generalized punishment sensitivity should exist after injury, the magnitude of which generates risk of future transition likelihood to chronic pain; testable in longitudinal clinical studies. Finally, the neural model predicts that interfering with insula activity, for instance by transcranial ultrasound stimulation in humans, should reduce the set of generalized post-injury behaviours.

Importantly, a key feature of this model of chronic pain is that it highlights the potential of information-rich therapeutic strategies, such as cognitive and action-based approaches (including cognitive behavioural therapy and physiotherapy), and neurotechnologies designed to manipulate and augment information input to the brain (such as neurostimulation, neurofeedback and virtual reality).

Conclusion

Injury has been a prevalent problem throughout evolution, and the brain is likely to have evolved optimized survival strategies. In this Perspective, we have set out how this process can be formalized in information processing terms, with a particular focus on optimal control and inference of injury states. The dominant behavioural phenomenon associated with injury is pain, and our proposed framework distinguishes the acute protective and defensive role of phasic pain, with the recuperative role of tonic injury states associated with persistent pain. In a hierarchical model of injury, processing of afferent pain information sits beneath a higher latent injury representation, which exploits cross-modal interactions. Using this information, the brain can then direct control behaviours appropriate to injury, implemented within neural hierarchies across a network of hypothalamic, cortical and subcortical hubs. Importantly, the control-theoretic view illustrates a key vulnerability: because the control behaviours can make it harder to tell whether the injury has recovered – namely, they inherently restrict new information, there may be a susceptibility to incorrectly inferring persistence of injury, manifest clinically as transition to chronic pain.

BOX 1. Comparative studies reveal distinct ecological functions of acute and prolonged pain

Shared selection pressures have led to many conserved features of nociception and nociceptive plasticity among evolutionarily distant species. Nociceptors function at the molecular, cellular and sometimes circuit level with surprising similarity across clades, however, relatively few studies have attempted to identify how such similar cellular processes may drive similar injury-induced behaviors, and what function these behaviors may serve. Recent work in cephalopod molluscs (octopus, cuttlefish and squid) suggests that both acute and prolonged pain-like behaviours may have adaptive functions[163-165] (see **Box Figure**). Multiple studies of nociception and pain-like states in various cephalopod taxa now demonstrate many similarities between behavioral and neural responses to injury in cephalopods and those found in mammals[165-167]. Cephalopods have peripheral nociceptors that undergo intrinsic changes after injury to tissue they innervate, including acute reduction in activation threshold, increased firing rate and increased after discharge. Studies of acute post-injury behavior indicate that this primary nociceptive plasticity is necessary and sufficient to drive hypervigilance and hyper-reactivity to perceived threats, directing attention toward potential predators and investing energy into prolonged escape behaviors[163,164,168]. In some cephalopod taxa, short-term nociceptive plasticity also drives protective and wound-directed behaviors, similar in appearance and function to those seen in mammals and driven by complex (although still largely unexplored) central brain networks[34]. Likewise, long-lasting changes in behavior are driven by similar long-term or permanent changes to nociceptors, higher-order nociceptive or pain networks, and cognitive circuits in cephalopods as in mammals[163,164], promoting contextual memory and optimizing future behavioral choices. Spontaneous firing of nociceptors persists in cephalopods for multiple days after tissue injury, which may produce tonic or persistent pain experience[34]. Permanent changes to nociceptive networks in cephalopods after injury in early life appear to optimise response thresholds to tolerate persistent danger[165], suggesting an ecological role for these conserved patterns of long-lasting pain plasticity in mammals and humans.

BOX 2. Control theory and inference

Control theory deals with the control of dynamical systems, and aims to develop a model governing the application of system inputs to drive the system to a desired state (setpoint), while achieving control stability and optimality. One simple dynamical system is a continuous-time linear time-invariant (LTI) system for a *latent* state variable $\mathbf{x}(t) \in \mathfrak{R}^n$ and *observed* variable $\mathbf{y}(t) \in \mathfrak{R}^N$.

$$\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t)$$
$$\mathbf{y}(t) = \mathbf{C}\mathbf{x}(t) + \mathbf{D}\mathbf{u}(t)$$

where the eigenvalues of matrix $\mathbf{A} \in \mathfrak{R}^{n\times n}$ determine the response rates of associated modes as they are excited by the control signal $\mathbf{u}(t) \in \mathfrak{R}^{m}$; $\mathbf{B} \in \mathfrak{R}^{n\times m}$, $\mathbf{C} \in \mathfrak{R}^{N\times n}$ and $\mathbf{D} \in \mathfrak{R}^{N\times m}$ are weighting matrices. Without loss of generality, $\mathbf{x}(t)$ is assumed to be normalized around the desired state $\mathbf{x}^*(t)=0$. The LTI system is controllable if and only if it can be driven from any initial state to any desired final state in finite time[169]. The setpoint can be either constant or time-varying. There is a duality between control and estimation[170,171], and uncontrollability also implies unpredictability.

A control strategy can be categorized as feedforward and feedback control. While feedforward control "ballistic control") is simple, fast and energy efficient, feedback control can handle uncertainties of the system and change control signals via error feedback. Feedforward and feedback control can be combined to optimize performance. A feedforward control example is the autonomic nervous system (ANS) that regulates involuntary physiological processes such as heart rate, blood pressure and respiration, which is essential for maintaining homeostasis. In biological systems, homeostasis also depends on feedback control, including (additive-increase) positive feedback and (multiplicative-decrease) negative feedback. An example of such is synaptic plasticity[172].

Optimal control theory is naturally linked to reinforcement learning (RL): the control emphasizes cost minimization, whereas RL emphasizes reward maximization. In this setup, let $\mathbf{s} \in \mathfrak{R}^{n}$ denote the *observed* state, $\mathbf{a} \in \mathfrak{R}^{m}$ denotes the action to be optimized, and $L(\mathbf{s}, \mathbf{a})$ denotes a cost-rate function of state-action pair $(\mathbf{s}, \mathbf{a})$. The goal of optimal control is to find the policy for taking a dynamical system from one state to another in the presence of some constraints:

$$\text{control the system} \qquad \dot{\mathbf{s}}(t) = \boldsymbol{f}\big(\mathbf{s}(t), \mathbf{a}(t)\big)$$

$$\text{to minimize} \qquad \text{Cost}[\mathbf{a}] = \int_0^T L\big(\mathbf{s}(t), \mathbf{a}(t)\big)dt + \rho T$$

where $\boldsymbol{f}$ describes a known deterministic or stochastic dynamical system, $\mathbf{s}(0)$ and $\mathbf{s}(T)$ are fixed, and $\rho > 0$ is a constant penalizing the total duration T in computation. The cost-rate function can be modified to accommodate additional internal or external cost. For instance, the original cost function may reduce risk-aversion behaviors and lead to a sampling bias, so a penalizing term may help promote exploration or risk-seeking action. Another possibility is to find a balance between minimising short-term cost and maximizing long-term reward. The dynamical system, if stochastic, can be represented by a probabilistic graphical model; the search for the optimal policy is equivalent to an inference problem[173]. While control answers the question "which action leads to the optimum future", inference answers the question "which action is taken given the future is optimal". In a special case where $\mathbf{a}$ is a hidden discrete variable and $\mathbf{s}$ is an observed discrete variable, the inference or planning is given by a Welch-Baum algorithm for the hidden Markov model[174]. Generalizations of optimal control have been discussed elsewhere[175-177].

Figure legends

FIGURE 1. A control perspective for injury and pain.

a) Schematic diagram of hierarchical control loop for nociception, action selection and action execution, and meta-control. At the heart of this are two control loops: one for action selection, and one for action control. Sitting above this is a meta-control loop which monitors and modulates the 'lower' control loops. This illustrates the computational difference between pain and nociception: with nociception reflecting the sensory signal communicating afferent information, and pain representing the control signal that governs learning and response execution[2].

b) A general flowchart of closed-loop control for inferring the latent injured or pain state **x**(*t*). The system receives bottom-up input **s**(*t*), subject to an endogenous control input **u**(t), and produces a behavioral output. **y**(*t*). The behavioral output also produces feedback (such as an efference copy of action) to influence the bottom-up or top-down processes. The controllability of the plant (dashed box) induces two different outcomes: high level of controllability leads to adaptive emotional and behavioral responses, followed by pain recovery, whereas low perceived controllability leads to maladaptive emotional and behavioral responses which trigger chronic pain states.

c) An implementation view of Bayesian inference through a feedforward architecture, where neural firing rates representing belief distributions are encoded independently and summed toward an output. The generative model that produces a Bayesian prediction estimate from multisensory inputs through a nonlinear mapping $F(\bullet)$ can be implemented by a recurrent neural network of excitatory and inhibitory neurons[99-101].

FIGURE 2. Neural implementation and representations of injury and persistent pain.

a) Information flows and afferent (*left*) and efferent (*right*) pathways for insula-centered injury-state inference and effector control. At the heart of this is an insula-centered hierarchy with successively higher latent abstractions of the injury state. Afferent pathways feed various inputs to the hub, from subcortical and cortico-cortical projections; and efferent routes can implement different types of responses. This includes the multiple afferent pathways that ascend the spinal cord to various brainstem nuclei, such as the parabrachial, periaqueductal gray (PAG), dorsal respiratory group (DRG), locus coeruleus (LC) and others, forming the bidirectional brainstem-subcortical network[178,179].

b) Schematic illustration of an insula-hub perspective for injury state representations in more details, including the different types of sensory information important for inference. The anterior, mid, and posterior segments of the insula have distinct and complementary functional roles. Note that the injury state inference may be shared with broader cortical areas, including the ACC and VMPFC, which are omitted here.

FIGURE 3. Brain oscillations that encode post-injury or pain state.

a) Neuropathic patients showed augmented MEG theta/alpha power (8-10 Hz) in multiple brain regions (thalamus, posterior insula, and primary somatosensory cortex or S1) of the ascending nociceptive pathway compared to age-matched healthy control (adapted from REF[126], Wolter Kuwer Health, Inc).

b) Noxious stimuli generated a reversible shift in the S1 LFP theta-peak frequency from a formalin-induced mouse model of pain. The scatter plots illustrate the association between theta-peak frequency and theta-peak height, where each dot represents a sample computed from a 2-min moving temporal window. This shift in theta-peak frequency was observed during nociceptive phases but not during the baseline or recovery period and was inversely correlated with instantaneous pain intensity. This result suggest that dynamics of theta oscillations may represent the ongoing status of injury or pain state (adapted from REF[129], CC-BY-4.0).

c) Changes in pre-stimulus theta activity in the insula modulate human pain perception. *Left*: From EEG recordings of healthy subjects, time-frequency representations showed the difference between pain and non-pain trials averaged across two temporal electrodes (T7/TF7 vs T8/TF8). Solid outline indicates the significant pre-stimulus effect identified by permutation testing. EEG source localization revealed two generators at the bilateral insula cortex for the scalp theta power differences, especially at the contralateral insula site. *Right:* Comparison of brain topographies in relative power differences (dB) between pain and non-pain trials during the pre- and post-stimulus periods (adapted from REF[130], Society for Neuroscience).

d) LFP gamma oscillations (40-90 Hz) are enhanced in response to phasic pain. *Left:* Magnitude of gamma-band oscillations elicited by nociceptive stimuli in the contralateral left or right insula from insular LFP recordings of epileptic patients. The size of circles represents the magnitude of post-stimulus change in the gamma band magnitude (150-300 ms). *Right:* Comparison of time-frequency representation of the changes in oscillatory power (40-90 Hz) elicited by nociceptive, vibrotactile, auditory and visual stimuli at the insula (adapted from REF[135], Oxford University Press).

FIGURE 4. Information restriction model of chronic pain.

a) Illustration of pain through a timeline from injury through to recovery. The solid line reflects the normal, adaptive profile of pain; whereas the dashed line reflects the transition to chronic pain, mediated (at least partially, since there are other factors involved in chronic pain) by various mechanisms of information restriction.

b) Illustration of the four key mechanisms that seed information restriction, which effectively reduces the ability of the brain to recognize that an injury has resolved. This results in an internal model of a peripheral injury that is persistent, and which also continues to drive the physiological and behavioural responses appropriate to a state of true injury. We frame these mechanisms as 'maladaptive' to emphasize that the nature of the mechanism, when 'ill-tuned', leads to a sub-optimal outcome.

SUPPLEMENTAL FIGURE. Overview of injury-related behaviours.

a) A core classification of the different types of response to an injury, spanning recuperative, protective and physiological responses.

b) The spectrum of ecologically significant causes of injury that can occur, summarised across species, with different causes having different importance across species.

c) Timeline of how pain responses change following an injurious event, from immediate defensive behaviours through to recuperation and recovery.

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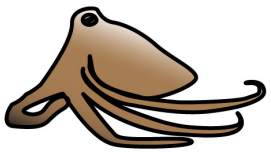
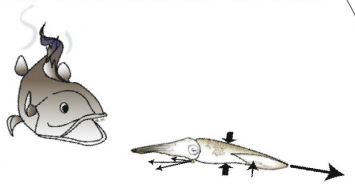
Activity-dependent plasticity sensitizes central pain circuits

Site-specific sensitization + central circuit plasticity



Wound grooming - lowers parastism and infection risk

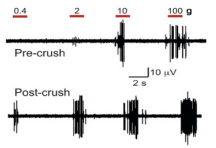
Peripheral plasticity drives central brain circuits



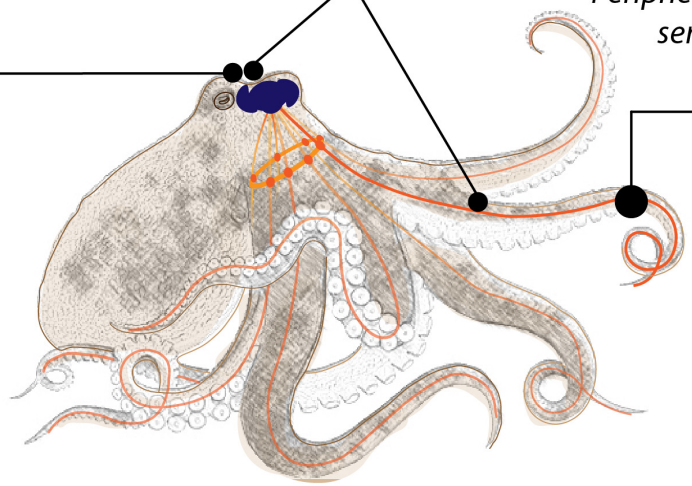
Visual hyper-responsiveness promotes escalated anti-predator behavior

Peripheral nociceptive sensitization

Allodynia

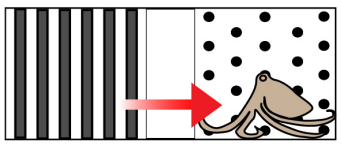


Hyperreflexia protects against further injury



Higher central processing

Changed affective state

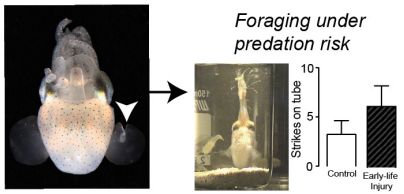


Conditioned place avoidance

Long-term contextual memory
Prediction and pre-emptive avoidance

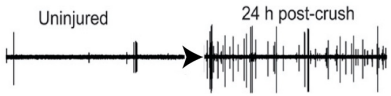
Global, permanent changes after injury in early life

Injury in early life permanently changes pain circuits

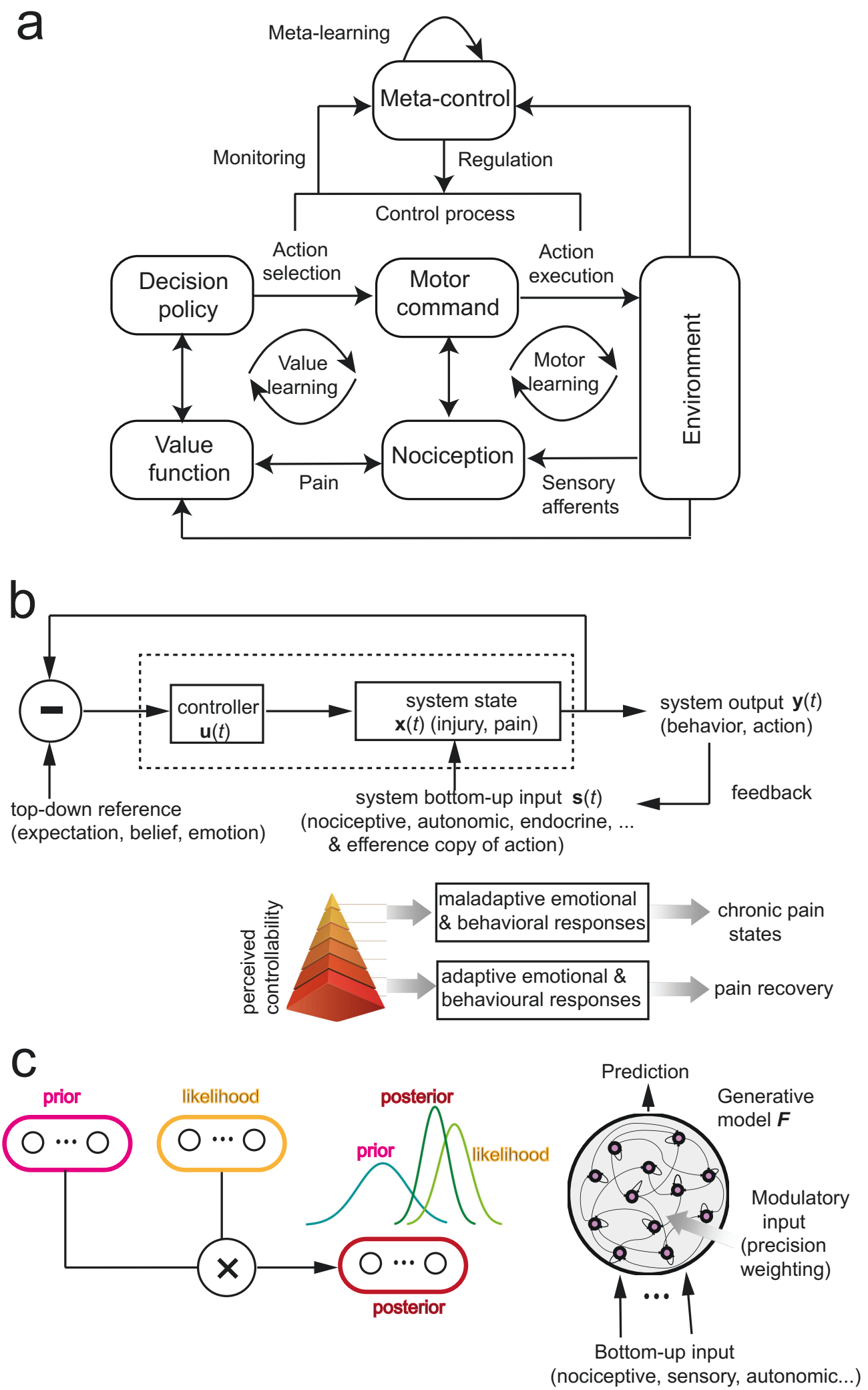


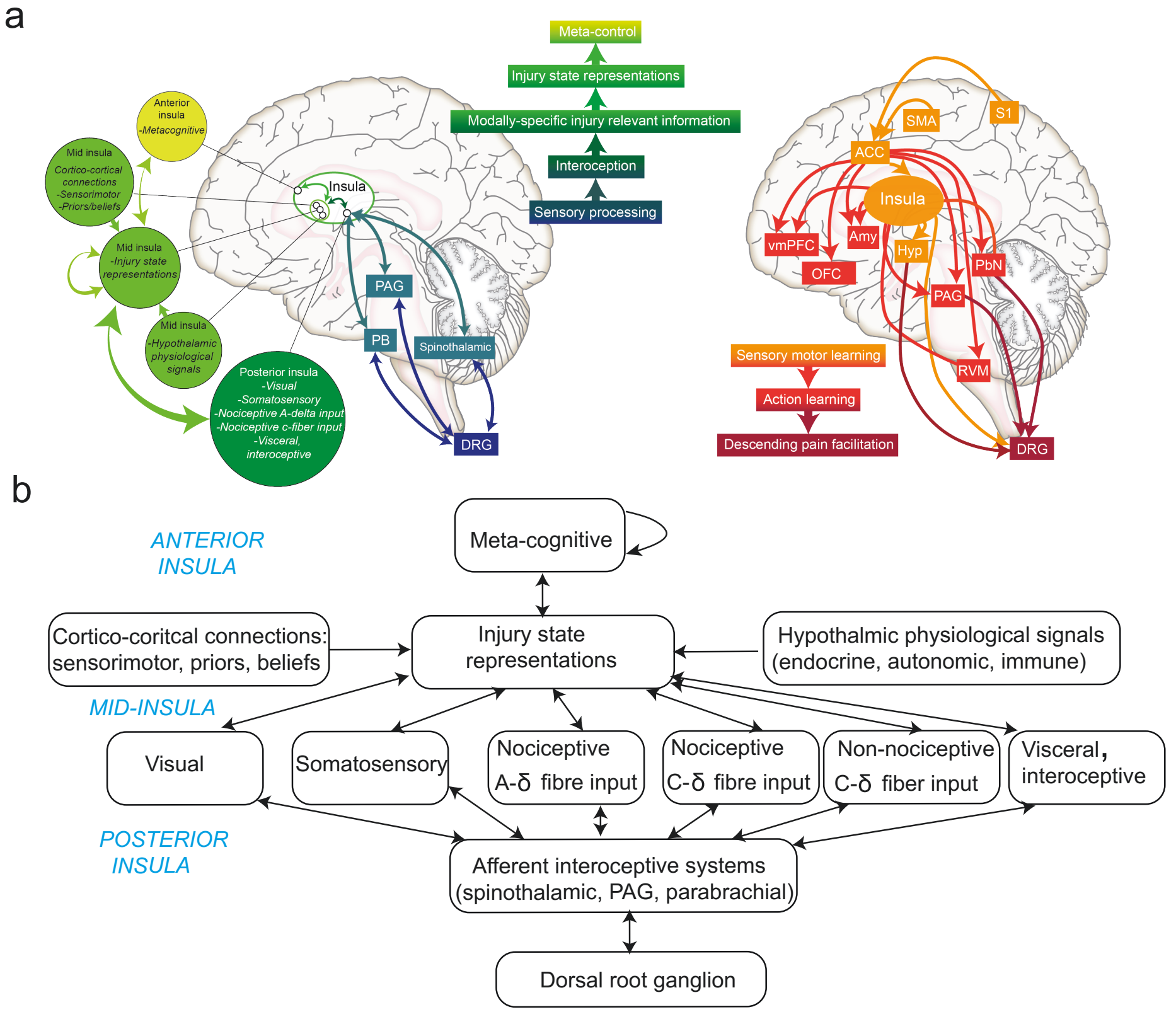
Sets baseline arousal and risk-tolerance appropriate to environment

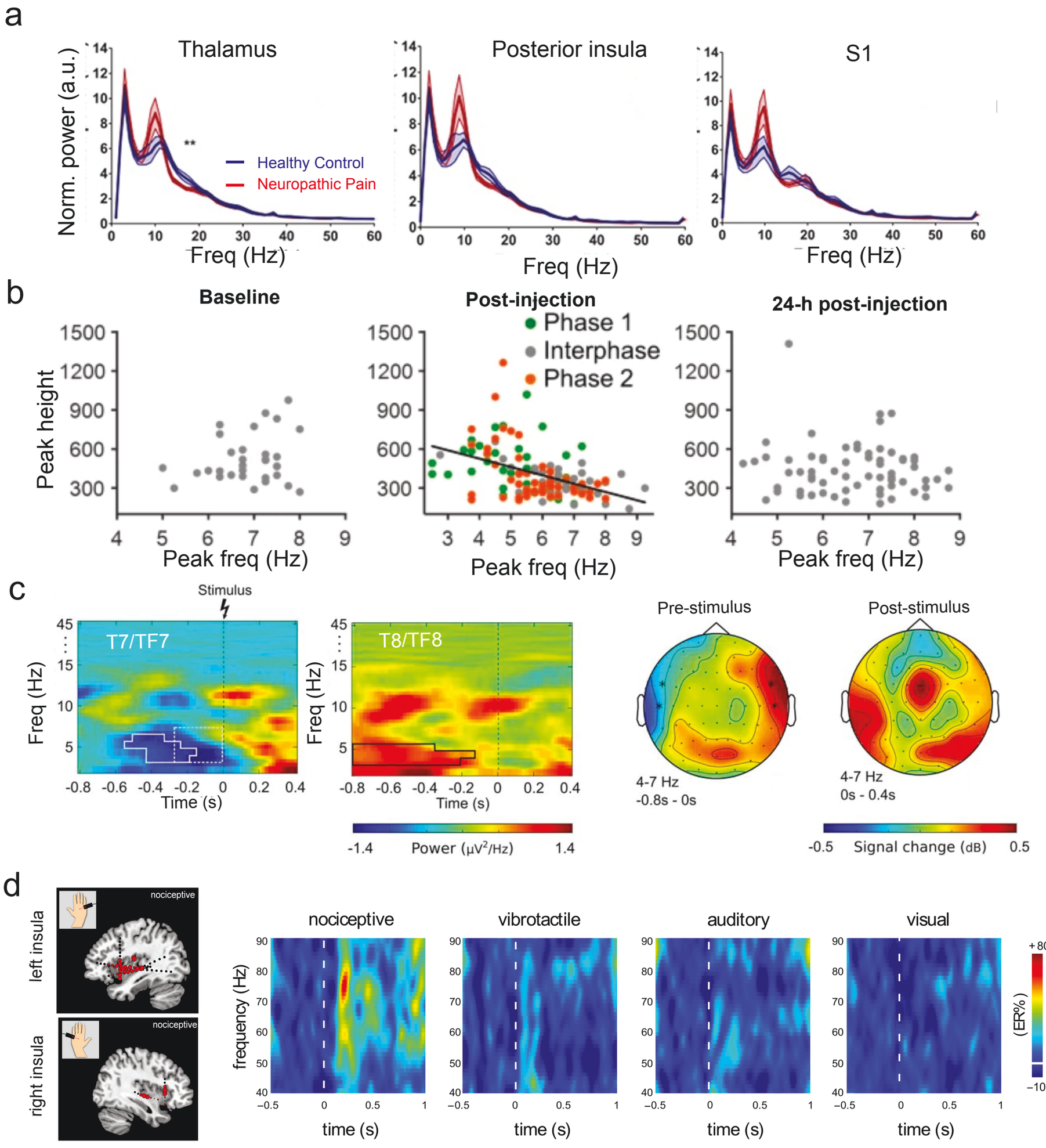
Long-term hyperexcitability and spontaneous activity



Compensates for denervation and protects regenerating tissues


a
Meta-learning
Meta-control
Monitoring
Regulation
Control process
Action selection
Action execution
Decision policy
Motor command
Environment
Value learning
Motor learning
Value function
Nociception
Pain
Sensory afferents
b
controller u(t)
system state x(t) (injury, pain)
system output y(t) (behavior, action)
feedback
top-down reference (expectation, belief, emotion)
system bottom-up input s(t) (nociceptive, autonomic, endocrine, ... & efference copy of action)
perceived controllability
maladaptive emotional & behavioral responses
chronic pain states
adaptive emotional & behavioural responses
pain recovery
c
prior
likelihood
posterior
prior
likelihood
posterior
Prediction
Generative model F
Modulatory input (precision weighting)
Bottom-up input (nociceptive, sensory, autonomic...)


a
Meta-control
Injury state representations
Modally-specific injury relevant information
Interoception
Sensory processing
Anterior insula
-Metacognitive
Mid insula
Cortico-cortical connections
-Sensorimotor
-Priors/beliefs
Mid insula
-Injury state representations
Mid insula
-Hypothalamic physiological signals
Posterior insula
-Visual
-Somatosensory
-Nociceptive A-delta input
-Nociceptive c-fiber input
-Visceral, interoceptive
Insula
PAG
PB
Spinothalamic
DRG
SMA
S1
ACC
Insula
Amy
vmPFC
Hyp
OFC
PbN
PAG
RVM
DRG
Sensory motor learning
Action learning
Descending pain facilitation
b
ANTERIOR INSULA
Meta-cognitive
Cortico-coritcal connections: sensorimotor, priors, beliefs
Injury state representations
Hypothalmic physiological signals (endocrine, autonomic, immune)
MID-INSULA
Visual
Somatosensory
Nociceptive A-δ fibre input
Nociceptive C-δ fibre input
Non-nociceptive C-δ fiber input
Visceral, interoceptive
POSTERIOR INSULA
Afferent interoceptive systems (spinothalamic, PAG, parabrachial)
Dorsal root ganglion


a
Thalamus
Posterior insula
S1
Norm. power (a.u.)
Freq (Hz)
Healthy Control
Neuropathic Pain
**
b
Baseline
Post-injection
24-h post-injection
Peak height
Peak freq (Hz)
Phase 1
Interphase
Phase 2
c
Stimulus
T7/TF7
T8/TF8
Freq (Hz)
Time (s)
Power (μV²/Hz)
Pre-stimulus
Post-stimulus
4-7 Hz
-0.8s - 0s
4-7 Hz
0s - 0.4s
Signal change (dB)
d
left insula
right insula
nociceptive
nociceptive
vibrotactile
auditory
visual
frequency (Hz)
time (s)
(ER%)

a

injury

information restriction

protective behaviours

Pain

recuperation

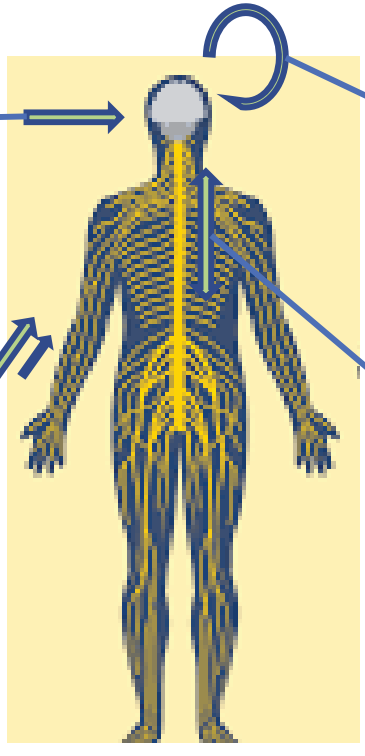
chronic pain

recovery

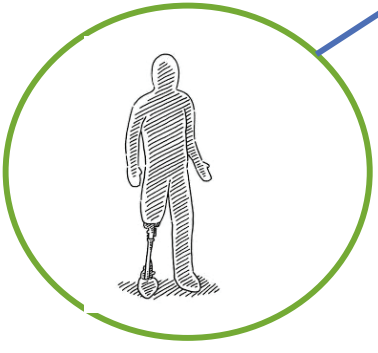
Time

b

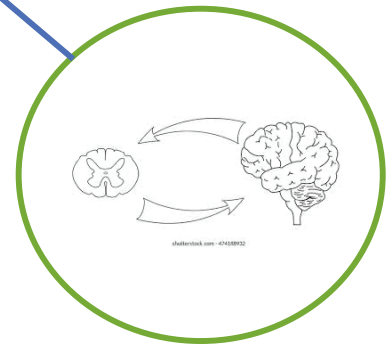
Maladaptive Learning:
Reduces experiential information acquistion



Maladaptive Priors:
Aberrant prior beliefs bias inference



Maladaptive Integration:
Irreconcilable incoming information flow



Maladaptive Model:
Incomplete generative model about afferent input

a

Injury and Pain Responses

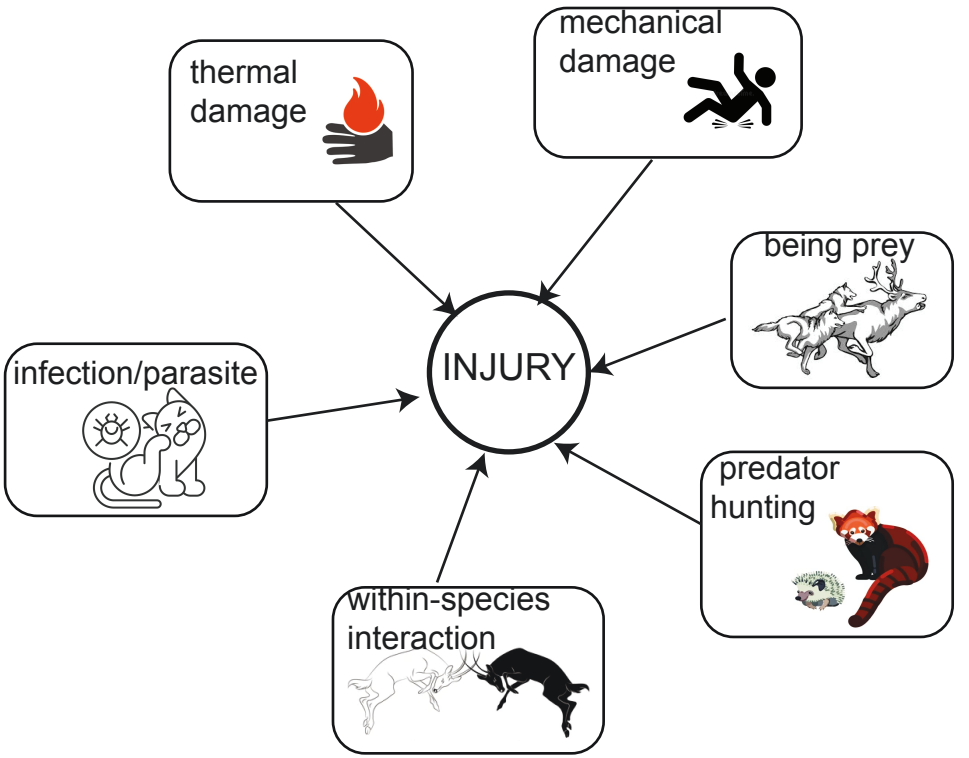
Recuperative behaviours
(wound tending, fatigue, anxiety
low mood)

Protetive behaviours
(pain sensitization,
allodynia, guarding,
defensive motor behaviors)

Physiological responses
(encodcrine, autonomic, immune modulation)

b

Causes of Injury



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