THE CUTANEOUS BORDERS OF INTEROCEPTION: ACTIVE AND SOCIAL INFERENCE OF PAIN AND PLEASURE ON THE SKIN

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Abstract

Pain and pleasant touch have been recently classified as interoceptive modalities. This reclassification lies at the heart of long-standing debates questioning whether these modalities should be defined as sensations on their basis of neurophysiological specificity at the periphery or as homeostatic emotions on the basis of top-down convergence and modulation at the spinal and brain levels. Here, we outline the literature on the peripheral and central neurophysiology of pain and pleasant touch. We next recast this literature within a recent Bayesian predictive coding framework, namely active inference. This recasting puts forward a unifying model of bottom-up and top-down determinants of pain and pleasant touch and the role of social factors in modulating the salience of peripheral signals reaching the brain.

Key words: pain, pleasant touch, nociceptors, C-Tactile afferents, active inference, allostasis, homeostasis

1. Introduction

Humans are capable of conscious feelings that concern the state of the body, such as pain, itch, muscular and visceral sensations, hunger, thirst, sexual desire and air need. The classification of such feelings and particularly their relation to the more classical sensory systems for vision, audition and touch, as well as to emotions such as anger and happiness has been a matter of ongoing debate.. Unlike sight, smell and hearing that have dedicated sensory organs, there are no dedicated bodily organs for position and movement sense, pain and many other modalities. Instead, developments in physics, anatomy, and physiology since the 19th century have given rise to a wide interest in mapping and classifying the senses with reference to criteria such as the nature of the stimulus, the nature, anatomy and location of receptors across body parts, the pathways to and the representation of the signal at the central nervous system (CNS), as well as the quality of the experience. This interest led to a number of classifications of the senses; for example, in exteroceptive (their receptive field "lies freely open to the numberless vicissitudes and agencies of the environment" Sherrington, 1910, p. 132), interoceptive (sensory receptors located within the body and primarily in the viscera) and proprioceptive sensations (receptors in muscles, tendons, and joints detecting position and movement of the body). Since this influential classification (see Ceunen, Vlaeyen, & Van Diest, 2016 for a review), exteroceptive and proprioceptive systems have received far more attention than interoceptive modalities. However, as this volume exemplifies, this has changed in the two last decades. On the one hand, theories and studies in affective neuroscience (e.g. Damasio, 2010) have brought to the foreground William James's older idea that interoceptive sensations may lie at the heart of our emotions and self-awareness. On the other hand, progress in anatomy and physiology have urged certain researchers (e.g. Craig, 2002) to propose alternative classifications of the senses

that include a more encompassing definition of interoception, as the sense of the physiological condition of the entire body, not just the viscera.

Bud Craig's proposal relies in synthesizing findings regarding the functional anatomy of a lamina I spinothalamocortical pathway that is portrayed as the long-missing afferent complement of the efferent autonomic nervous system, underling distinct, conscious, affective bodily feelings such as cool, warm, itch, first (pricking) pain, second (burning) pain, pleasant or sensual touch, muscle burn, joint ache, visceral fullness, flush, nausea, cramps, hunger, thirst, and visceral taste (Craig, 2002). Specifically, he proposes that the primate brain has evolved a direct sensory pathway to the thalamus that provides a modality-specific representation of various individual aspects of the physiological condition of the body (interoception re-defined; Craig 2002, 2003a). This pathway is thought to originate in lamina I of the spinal dorsal horn and in the nucleus of the solitary tract in the caudal medulla and to represent the afferent inputs from sympathetic (somatic) and parasympathetic nerves, respectively, and to terminate with a posterior-to-anterior somatotopic organization in a specific thalamic structure (the posterior and basal parts of the ventral medial nucleus, Craig 2002). He has further proposed that the functional role of this pathway is to represent the sensory aspects of homeostatic emotions (Craig 2003a, 2008) and their accompanying motivations (represented in anterior cingulate cortex) that serve to maintain the body in a relative stability despite ongoing internal and external changes (e.g. variabilities in metabolic energy levels and the availability of food). This proposal brings the concept of interoception in a tight relation to the notion of homeostasis (Cannon, 1929, see also Chapter Y in present volume by Bentson, Giannaros &Tsakiris, and Chapter X by Corcoran & Jakob Hohwy), so that interoception is the sensory representation of the physiological condition of the whole body allowing homeostatic, and ultimately 'allostatic' control (i.e., self-

initiated temporary change in homeostatic imperatives to prepare for a predicted external change). In other words, interoceptive signals provide information regarding current homeostatic levels (e.g. reduced glucose levels in the blood), which are used as motivations to steer action (e.g. ingest food to restore glucose levels). This definition of interoception, which subsumes cutaneous pain, itch and pleasant touch, differs greatly from the classic association of these modalities with exteroception and particularly discriminatory touch. Moreover, in addition to this 'spinal pathway', there are also other proposed interoceptive pathways (Critchley & Harrison, 2013), and more broad proposals regarding the role of higher order processing in interoception (Ceunen et al., 2016).

We will here focus on pleasant touch and cutaneous pain, which are two interoceptive (Craig, 2003a, 2003b) sub-modalities of touch that have contrasting affective qualities (pleasantness/unpleasantness) and social meanings (care/harm). Although the source of the skin stimulation lies outside the body and the resulting sensations can be used to gain information about how, where and by what one is touched, we also assume that these modalities are of fundamental homeostatic importance, signalling physiological safety (i.e. the pleasantness of touch signifies a homeostatically safe environment in is contact with the body) or threat (i.e. pain signifies the reverse) to the organism and leading to certain behavioural and physiological reactions of homeostatic and allostatic significance. In the present chapter, we first briefly outline the current literature on the peripheral and central neurophysiology of unpleasant, cutaneous pain and affective, pleasant touch. Subsequently, we make use of recent neurocomputational theories of perception and action, as applied to both exteroceptive and interoceptive modalities, to put forward a unifying model of how bottom-up and top-down signals can be integrated to give rise to these modalities. We speculate that the understanding of

these modalities within the Bayesian predictive coding framework of ‘active inference’ (Friston, 2010) offers a unique opportunity to unify various insights into a common framework that emphasizes particularly: 1) the deep interdependence between bottom-up and top-down mechanisms in any modality; 2) the deep interdependence of perception and action in any modality; 3) the special role of these modalities in homeostatic and allostatic control; 4) the particular relevance of social developmental factors in determining the salience of interoceptive modalities such as pain and pleasant touch.

2. The Peripheral and Central Neurophysiology of Cutaneous Pain and Pleasant Touch

Surrogate animal models and human studies have revealed that nociceptors are distinctive afferent units rather than the extremes of a single class of receptors with a continuum of features (reviewed by Marks, Raja, Campbell, & Meyer, 2006). While low-threshold, mechanoreceptive or thermoreceptive afferent neurons cannot discriminate reliably between noxious and non-noxious (innocuous) stimulation, nociceptors can (Bessou, Burgess, Perl, & Taylor, 1971). These two classes of fibers also differ in their termination patterns in the spinal cord (Sugiura, Lee, & Perl, 1986), their membrane constituents (Caterina, Schumacher, Tominaga, & Rosen, 1997) andproperties, including their action potential shape (Ritter & Mendell, 1992). . Broadly, nociceptors can be divided into two types: A- (most in the Aδ- range) and C-fibers, which are mediated by myelinated fast (5-30 m/s) and unmyelinated slow (0.4-1.4m/s) conductive axons (Dubin & Patapoutian, 2010), corresponding to initial fast-onset pain (sharp pain sensation) and slow second pain (pervasive burning pain sensation), respectively. Nociceptors, particularly in musculoskeletal tissue, have been mostly thought to be electrically ‘silent’, transmitting all or none action potentials only when excited and thus give rise to pain (Marks et al., 2006).

Different pathways on how the nociceptor is conveyed to the CNS have been suggested, including different spinal neural features and their functional role. First, it is thought that an afferent volley is produced upon activation of the nociceptor. The nociceptive volley travels along the periphery and enters the dorsal horn of the spinal cord (Brooks & Tracey, 2005) and mostly terminates in laminae I where they synapse with relay neurons and local interneurons important for signal modification (see Dubin & Patapoutian, 2010 for the specific role of laminae I, IV, V in relation to A- and C- fibres). Via spinal ascending pathways, the relay neurons project to the thalamus and brainstem, which in turn project to large distributed brain networks (Dubin & Patapoutian, 2010). However, a different type of multimodal spinal neurons located deeper in the dorsal horn, namely the wide dynamic (WDR) neurons, has also been implicated in nociceptive and pain-related mechanisms (Perl, 2007).

More generally, peripheral neurophysiological specificity does not seem to lead to a direct relation between nociception and conscious pain perception. While the activation of nociceptors and nociceptive pathways can lead to pain (Marks et al., 2006), it is also known that nociceptors can be active in the absence of pain perception and pain can occur without known nociceptive activity. Indeed, there have been observations of a lack of reported pain by soldiers during battle, despite severe injuries, as well as experimental evidence suggesting that pain perception varies with psychological state and context (Head & Holmes, 1911; Gaughan & Gracely, 1989). In fact, since the proposal of the influential ‘gate control theory’ (inhibition of nociceptive excitatory signalling at the level of the spinal cord), and more recent insights regarding the heightened sensitivity of afferent signals at the same level, known as ‘central sensitization’, it is widely accepted that although much pain is a consequence of stimulation of

peripheral nociceptors, the CNS plays a major role in the processing of noxious sensations (Melzack & Wall, 1967).

Furthermore, more potent neuroscientific methods in recent decades have provided corroborating evidence for the role of the brain in pain (Rainville et al., 1997; Ploghaus et al., 1999; Ploner et al., 1999). For example, novel cortical stimulation studies have qualified Penfield's inability to detect 'pain cortical areas'; Mazzola, Isnard, Peyron, & Mauguiere, 2011). Moreover, functional neuroimaging studies indicate that noxious stimulation involves large distributed brain networks (Brooks & Tracey, 2005; Talbot et al., 1991). The so-called 'pain matrix' has been subdivided into a medial and lateral pain system, based on their respective projection sites from the thalamic structures to the cortex. The lateral pain system involves the S1 and secondary somatosensory cortex (S2) and is thought to play a role in the sensory-discriminative aspect of pain (i.e., where is the stimulus and how intense it is), whereas the medial pain system, including areas such as the AAC, the insula and the amygdala, is thought to be involved in the affective-cognitive aspect of pain. However, the insular cortex may play a role in facilitating the integration of information between the lateral and medial pain systems (Brooks & Tracey, 2005) and some studies suggest that the functional role of these areas may not be pain-specific but rather relating to the processing of all sensory salient-events (see Legrain, Iannetti, Plaghki, & Mouraux, 2011). Nevertheless, it is assumed that a top-down descending circuitry modulates ascending nociceptive information and consequently, influence pain perception. Hence, scientific and health organisations such as the International Association for the Study of Pain stress the difference between nociception and pain. However, debates regarding the bottom up versus the top-down contributions to pain and its corresponding definition remain. Similar debates surround the study of pleasant touch..

Recent research suggests that slow conducting unmyelinated (non-nociceptive) afferent CT fibres mediate the affective, pleasant component of touch. These C fiber tactile afferents were first identified in a cat in 1939 by showing low spike heights using the skin-nerve preparation technique (Zotterman, 1939). More recently, low threshold mechanosensitive C fibres (C-LTMs; detected by cutaneous sensory neurons, i.e., C low threshold mechanoreceptors, C-LTMRs) have been found in the hairy skin of rodents and primates (Bessou et al., 1971). C-LTMs are now acknowledged to also exist in human skin, termed as CT afferents (Vallbo et al., 1999). CTs have different characteristics than myelinated fast conducting Aβ-fibres associated with discriminative touch, including their conduction axon velocity (0.6-1.3 m/s) and skin location (i.e., found in hairy but not glabrous skin).

Microneurography studies have shown that CTs are highly sensitive mechanoreceptors responding to stimuli that are clearly innocuous and their firing rate seems to be distinct from myelinated afferents, reflecting an inverted U-shaped relationship between the stroking velocity and mean firing rate with the most vigorous responses being at 1-10 cm/s (Loken, Wessberg, Morrison, McGlone, & Olausson, 2009). Moreover, subjective responses of perceived pleasantness in response to stroking also showed an inverted U-shape relationship, with the highest pleasantness responses found at 1-10 cm/s stroking velocities (Loken, et al., 2009), indicating that CT afferents may carry a positive hedonic quality. Furthermore, CTs are also temperature sensitive (i.e., preferentially discharged ≈ 32°C, the typical skin temperature; Ackerley et al., 2014). However, one main difficulty in our understanding of selective CT stimulation is related to the fact that to date, we cannot stimulate CT fibres without stimulating Aβ-fibres in healthy subjects. Nevertheless, insights have been provided from patients with sensory neuropathy, as these patients are thought to lack Aβ afferents while their CTs afferents

remain intact (Olausson et al., 2002, 2008). Research has shown that CT stimulation in these patients activates the insula (i.e., the preferential cortical target for CT afferents; see more below), but not somatosensory regions associated with the sensory discriminative processing of touch (Olausson et al., 2002). Moreover, these patients were able to detect, although poorly, slow brushing on the forearm (where CTs are abundant; Olausson et al., 2008). Given the sensory discriminative properties associated with Aβ-fibres and the lack thereof in these patients, it is possible to presume that CT afferents may follow a separate neurophysiological route than Aβ mediated discriminative touch (Olausson et al., 2008).

Unfortunately, our knowledge on how CTs peripheral information reaches spinal, brainstem and cortical areas in humans remains scarce. Yet, meaningful insights regarding the spinal processing of CTs have been obtained from animal studies. Mice studies suggest that C-LTMS enter the laminae II of the dorsal horn; with axons arborizing in lamina I, where they would synapse with secondary afferent neurons (reviewed by McGlone et al., 2014). Secondary afferent neurons then project to higher centres such as the insula via spinal pathways (Andrew, 2010). Furthermore, as with pain, there could be different classes of spinal neurons responsive to gentle touch, including WDR neurons (Andrew, 2010). Finally, yet controversially, recent findings using mice genetic tools indicate the dorsal horn as the key initial focus for integration of Aβ and C-LTMRs (Abraira & Ginty, 2013). Together, these lines of work suggest that there may be different pathways through which CT peripheral information is conveyed to higher centres, although these pathways may likely vary across species.

Similar to pain, neuroimaging research has shown that gentle stroking activates the posterior superior temporal sulcus, medial prefrontal cortex, orbitofrontal cortex (OFC) and ACC, which are typically implicated in the cognitive-affective aspects of pleasant touch (Gordon

et al., 2011). Further, while investigating the cortical areas that represent pleasant touch, painful touch and neutral touch, studies have also found increased activity in the OFC in response to pleasant and painful touch, highlighting the role of the OFC on the affective aspects of the touch. In contrast, the somatosensory cortex was less activated by pleasant and painful touch, relative to neutral touch (Rolls et al., 2003; see also Gordon et al., 2011; Olausson et al., 2002). These studies suggest that CT-based touch may not be involved in the discriminative aspects of touch. Importantly, slow gentle touch on CT skin has also been shown to preferentially activate the insula (Olausson et al., 2002; Gordon et al., 2011), although the insula also plays a critical role in integrating sensory-discriminative and affective-cognitive aspects of the touch (McCabe et al., 2008; Rolls, 2010).

3. An Integration: The Predictive, Active and Social Components of Pain and Pleasant Touch

The history of the study of pain, and more recently of pleasant touch can be said to be steeped in the debates between bottom-up, neurophysiological specificity at the periphery versus top-down convergence and gating at the spinal and brain levels. In this section, we make use of a Bayesian, predictive coding framework, namely the Free Energy Principle, also referred to as 'active inference' (Friston, 2010) to put forward a unifying model of how bottom-up and top-down signals can be integrated to give rise to affective, pleasant touch and unpleasant, cutaneous pain.

3.1. Action-perception Loops and the Control of Physiological States

Recent neurocomputational theories of perception and action assume that the brain is an organ that learns and self-improves a generative model of the organism and its environment based on sensory signals and action (Friston, 2010). A basic tenet of such accounts is that

perception is an active process, whereby top-down mechanisms are activated to make predictions about the upcoming bottom-up sensory signals. Thus, perception is an inferential process, whose aim is to minimize prediction errors or the difference between top-down hypotheses about the most likely causes of sensations (termed 'empirical prior beliefs') and current sensations. Recurrent message passing among several levels of the sensorimotor hierarchy allows the suppression of (small, or irrelevant) prediction errors by priors, or the adjustment of (empirical) prior expectations by (large or highly salient) prediction errors. Furthermore, the relative influence of predictions versus prediction errors across several layers in this hierarchical organization is determined by the weighting (precision) of predictions versus prediction errors at each level. Precision can be regarded as a measure of signal-to-noise ratio or confidence, or mathematically, as the inverse variance, uncertainty or reliability of a signal (Feldman & Friston, 2010; Friston et al., 2012). Uncertainty is thought of as encoded mainly by neuromodulations of synaptic gain (such as dopamine and acetylcholine) that encode the precision of random fluctuations about predicted states, i.e. the context in which sensory data is encountered (Quattrocki & Friston, 2014). For example, cholinergic or dopaminergic neuromodulatory mechanisms can optimise the attentional gain of populations encoding prediction errors, so that greater attention is allocated to certain salient events in the environment influencing the relative weighting or importance of prediction errors.

Importantly, prediction errors can also be minimized through action. At the simplest control loop level, peripheral reflexes are engaged to suppress proprioceptive prediction errors (Feldman & Friston, 2010), generated by comparing primary afferents from receptors in muscles, tendons, and joints with proprioceptive predictions regarding body position that descend to alpha motor neurons in the spinal cord and cranial nerve nuclei. Thus, action is driven by such

predictions rather than descending motor commands. Ultimately action is seen as a prediction-driven tendency to re-sample the world to generate more sensory evidence for one's predictions (active inference). Importantly, the organism could solve a discrepancy between prediction and error (e.g., unexpected noxious stimulation) by either changing its predictions (effectively convincing oneself that one is not in pain) or by generating protecting action (moving to avoid the noxious source of the prediction error). Both of these can be adaptive depending on the magnitude, as well as the context of the noxious stimulation and hence, their relation needs to be optimized by weighting in each case. This framework emphasizes the tight interconnection of perception and action as well as the fundamental integration of bottom-up and top-down factors in all perceptual and active inference.

Recently several proposals have applied this framework to interoception (Paulus & Stein, 2006; Barrett & Simmons, 2015; Gu et al., 2013; Pezzulo et al., 2015; Seth, 2013; Seth, Suzuki, & Critchley, 2011), and by extension to the concepts of 'homeostatic' and 'allostatic' control (see also Chapter X by Corcoran & Hohwy). 'Homeostasis' (Cannon, 1929) refers to the maintenance of a relative stability in one's physiological states despite ongoing internal and external changes. 'Allostasis' refer to the idea that physiological changes need to be anticipated by adaptive changes and choices across different spatial and temporal scales, e.g. adjusting one's metabolic needs in certain environments where foraging is dangerous (Sterling & Eyer, 1988). In predictive coding frameworks, both homeostatic and allostatic control can be cast formally as active inference (e.g. Pezzulo et al., 2015; Stephan et al., 2016). Homeostatic control enslaves reflexes to produce corrective actions that fulfill beliefs about bodily states, and allostatic control entails changing homeostatic beliefs under guidance by higher predictive models about future perturbations of bodily states.

Moreover, as in the case of exteroceptive perception and action, the balance between homeostatic and allostatic regulation rests upon the precision (i.e. weighting) placed in deeper expectations about the organism and its environment. For example, during conditions of bodily threat or psychological stress, such as pain sharp object approaching one's face, noxious signals on one's body may induce low-level proprioceptive predictions that mobilize withdrawal movements away from the source of the stimulation. However, high-precision, predictions at higher-level of the neurocognitive hierarchy may indicate that the source of the noxious stimulation is actually our dentist, then predictions of tooth pain can be fulfilled without engaging, low-level motor reflexes and instead engage allostatic changes in the form of updated beliefs about the 'safety' and tolerance (i.e. attenuated pain) of nociceptive signals in this context, in order to ensure future pain-free and healthy teeth.

3.2. Active, Interoceptive Inference and Feelings on the Skin

Despite the above proposals of interoceptive predictive coding, there is currently no direct evidence for the proposal that interoceptive predictions, prediction errors and their relation rest on a common neurocomputational framework (for a first step, see Kleckner et al., 2017). There are however ample circumstantial findings in the pain and pleasant touch literature that can be cast in this light and importantly, the framework can allow some specific predictions regarding the nature of pain and pleasant touch, and their modulation by cognitive and social factors, that we will focus on here.

First, this framework suggests that peripheral signals, such as nociceptive and CT tactile channels, do not cause homeostatic perceptions or emotions (e.g. pain or the affectivity of touch), or vice versa. Instead, there is a circular and multi-layered causality, where on one end of the neural hierarchy, neuronally encoded predictions about bodily states, including in this case states

of the skin, engage autonomic, somatic and motor reflexes in a top-down fashion. On the other end of the hierarchy, specialised skin organs and their spinal cord circuitry carry interoceptive signals in a bottom-up way that informs and updates predictions at the levels above. These aspects can be linked to the cognitive and sensory aspects of pain, respectively. Moreover, the affective component of pain or touch can be seen as an attribute of the weighting (precision, see above) of any representation that generates predictions and prediction errors about the physiological state of the skin (see also Ainley et al., 2016; Fotopoulou, 2013). In other terms, the subjective feelings of pain or pleasant touch can be linked to the neuromodulatory weighting of the corresponding sensory prediction errors in relation to more higher order predictions regarding these sensory states. Typically, the optimisation of precision is linked with the function of neuromodulators in the brain (see Section 3.1. Action-perception Loops and the Control of Physiological States) but similar processes of synaptic gain modulation have long been described in the spinal cord, particularly in the context of pain (see Section 2. The Peripheral and Central Neurophysiology of Cutaneous Pain and Pleasant Touch). We have previously proposed that in interoceptive modalities, optimizing the precision of internal body signals can be seen as optimising *interoceptive sensitivity and related feelings* in perceptual inference (see also Ainley et al., 2016; Fotopoulou, 2013). We propose here that concepts such as 'precision' and its reverse, uncertainty, relate to the affective, conscious components of pain and pleasant touch. The intensity of painful or pleasurable aspects of touch can be thus understood as our sensitivity to such tactile, interoceptive signals in a given context (e.g. a measurement of our subjective pain threshold in the lab) and our corresponding behavioural tendency to approach the world to gather more information (uncertainty) or to avoid resampling (the certainty of pain and pleasant touch).

This view can offer a new integration of previous theories of pain and hence potentially also pleasant touch, as we specify below.

Specifically, classic theories may view cutaneous pain and the affectivity of touch as signals of danger or safety to the organism, respectively, starting in the periphery and reaching consciousness if a 'threshold' is surpassed at the spinal cord level, allowing the the brain to 'read' them as pain or pleasure. For example, this threshold may be equated to the "gate control theory" (Melzack & Wall, 1967), or more modern "central sensitization" theories, where the gain of the spinal cord nociceptive synapse is amplified and hence 'travels up' the hierarchy to elicit conscious pain (Woolf & Salter, 2000). On the contrary, more 'active', alternative theories of pain suggest that acute pain is not a warning signal but rather is the failure of the 'aversion' machinery (nociceptor activity) designed to operate unconsciously in order to avoid harm and ultimately also conscious pain (Baliki & Apkarian, 2016). In such accounts, most nociceptive activity is designed to remain 'subconscious' and protect the organism from harm without necessarily eliciting conscious pain. Conscious pain instead only emerges when subconscious pain is converted to conscious pain in subcortical areas in the brain. In such accounts, it is conscious pain that has the capacity to modulate spinal nociceptive sensitivity and thus actively determine "gate control" and/or "central sensitization" spinal nociceptive processes, mediated through descending pathways (Vera-Portocarrero et al., 2006).

From the point of view of active inference models, these are not competing but supplementary views. Allostatic control is an extension of homeostatic control and they both work to minimise prediction errors. Thus, these two perspectives can be integrated in the following way, illustrated here with specific reference to cutaneous pain and pleasant touch. For homeostatic control purposes, the organism entails (in an embodied manner) a set of inherited

prior expectations of the state of the skin. Any stimulation of the skin that deviates from the range of such predicted states generates a prediction error. This prediction error is corrected in simple, unconscious loops, by reflexive motor or autonomic reactions that fulfil the initial beliefs about the state of the skin. If however these 'homeostatic corrections' fail (i.e. the prediction error persists), then the prediction error travels up the hierarchy to generate posterior beliefs (updated predictions) at the above hierarchical level. These updated beliefs act as priors towards future positive or negative events, thus attempting to anticipate and avoid danger, or anticipate and approach pleasure, before these occur (allostasis). Specifically, more complex, generative, predictive models of the organism's needs are able to better predict stimuli at the levels below and at different time-scales and hence 'suppress' any future, anticipated prediction errors at the level below by guiding autonomic function and action more effectively and under the control of higher-order predictive models. Please note that these homeostatic and allostatic control operations are understood to be processes of unconscious inference for the most part, so conscious feelings of skin pain and pleasure are not necessary for such processes. This conclusion however raises the question of why should we have conscious feelings such as pain and pleasure, if we can predict and control our sensations unconsciously? We speculatively propose that it is important that the organism registers the core feelings that relate to the specificity of innate, homeostatic needs (in this case safe or dangerous contact on the skin), so that the cognitive resources available for scanning the world and the body for novelty and salience are always constrained by, and in competition with, the high precision of our innate expectations. In other terms, conscious pain and pleasant touch are there to ensure that we do not habitually update, or ignore our predictions about what is safe versus dangerous for the skin.

Interestingly, although these two modalities, pain and unpleasant touch appear opposite in hedonic content and behaviour tendencies towards their particular sensory stimulus (i.e. avoidance versus approach), from the point of view of the certainty-uncertainty axis described here, they are of similar characteristics. The greater the pain, or the felt pleasure of touch, the more one's attention and behavior is captured in the experience and the less one is likely to engage in active, exploration of new sensations. Instead, the organism's resources are focused on controlling or, escaping pain, and enjoying or, prolonging the feelings of pleasant touch. This view goes against the intuitive, long-standing view of core affective consciousness, pain and pleasure, as monitoring hedonic quality. Instead, the core quality of affective consciousness is a kind of certainty-uncertainty, or disambiguation principle (Fotopoulou, 2013). Pain and pleasant touch therefore are a measure of how important is for a given organism, in a given context, to be 'certain' about what was predicted versus what occurred.

This view of the conscious feelings of pain and pleasant touch, tallies with long-standing insights regarding the dissociation between sensory and affective aspects of pain and more recently pleasant touch, as well as with the fact that the physiology of nociception has a well-known specificity at the periphery which is not mirrored at the brain (see Section 2. The Peripheral and Central Neurophysiology of Cutaneous Pain and Pleasant Touch). The unique feeling qualities of painful or pleasant touch may be associated with the CNS's capacity for synaptic gain modulation and large-scale integration of information arising from the body and the world in different timescales. This is consistent with the fact that no one area or network in the brain has been reliably associated with the conscious perception of pain (Baliki & Apkarian, 2015). Instead, the various networks that have been associated with pain and its modulation, and with pleasant touch and its modulation, are not only common to these two modalities, but seem

relevant to the processing of the salience of any sensory modality (Legrain et al., 2011). Indeed, several recent neuroimaging studies have included such areas and their observed functional connectivity in various hypothesized "salience networks" (Legrain et al., 2011; Medford & Critchley, 2010; Wiech et al., 2010). For instance, predictive signals from such a "salience network" process and integrate information about the significance of an impending noxious stimulus and determine whether or not such a stimulus will be consciously perceived as painful (Wiech et al., 2010).

More generally, a plethora of neuroimaging studies have shown that cognitive, affective and social factors modulate our perception of cutaneous pain, with emerging evidence also making a case for these factors modulating the pleasantness of CT-optimal touch. For example, expectations may help an individual to adjust sensory, cognitive and motor systems in order to optimally process the noxious stimuli in terms of neural and behavioural responses (Wiech, Ploner, & Tracey, 2008; see also Villemure & Brushnell, 2002 for review). Most consistently with the present proposal, expectations in which there is a high level of certainty regarding the stimulus may activate descending control systems to attenuate pain, whereas in contrast, uncertainty may increase pain (Ploghaus et al., 2003).

Although there is less evidence on the neural mechanisms underlying the cognitive and social factors that modulate pleasant CT-optimal touch, studies suggest that a person's beliefs about the stimulus (McCabe et al., 2008) or the person (Ellingsen et al., 2015) providing pleasant touch influences the perceived pleasantness of the touch. We use the example of the social modulation of pain below to unpack and better illustrate these ideas.

3.3. The Mentalisation of Nociception and CT Stimulation: Homeostatic and Allostatic Control by Proxy

The long observed fact that conscious pain is modulated by social context has received experimental support in recent years (see Krahé et al., 2013 for review). In the last decade, similar observations have also been made regarding the modulation of pleasant touch by social context. In this section, we will apply the above insights from the active inference framework to propose some mechanisms by which this social modulation takes place. This application has the advantage that it can provide a mechanistic, unified account of the relation between bottom-up (e.g., neurophysiological) and top-down (e.g., psychosocial) influences on homeostasis and allostasis. Existing biopsychosocial models of pain offer similar insights but the current model has the advantage of offering direct links between these different bottom-up and top-down determinants of pain and pleasant touch, instead of treating them as merely additive variables.

Specifically, we propose that the perception of the social environment of pain or pleasant touch can affect inferential processes about the perception of these modalities, as well as related active tendencies, by influencing the certainty or precision of an individual's predictions about an impending stimulus vs. the certainty or precision of related prediction errors. As aforementioned, top-down predictions do not represent just the content of lower level representations but also predict their context, defined in mathematical terminology as the *precision* of a probability distribution (inverse variance or uncertainty). For example, the allocation of attention toward specific events can optimize their salience and ultimately influence the relative weighting or importance of prediction errors against predictions. This kind of top-down prediction in sensory cortices is thought to be mediated by cholinergic neuromodulatory mechanisms that optimise the attentional gain of populations encoding prediction errors (Feldman & Friston, 2010), as well as by dopamine in fronto-striatal circuits (Fiorillo, Tobler, & Schultz, 2003) and by neuropeptides such as oxytocin in social contexts (Quatrokki & Friston,

2014). In interoception, precision may relate to attention to signals from the body or interoceptive sensitivity (Ainley et al., 2016; Fotopoulou, 2013) and may be modulated by several contextual factors. Therefore, factors such as active social support or empathy may modulate pain or pleasant touch by changing the precision of top-down predictions about nociception or CT stimulation. In such social contexts, individuals have learned to anticipate social support and thus the optimization of the weight allocated to bottom-up signals versus top-down predictions maybe different than in conditions of experiencing similar stimuli alone, or in hostile environments. For example, in previous studies we have shown that the administration of intranasal oxytocin versus placebo, or the provision of high versus low empathy, or social support may modulate the subjective, behavioural and neural responses to noxious stimulation (Hurter, Paloyelis, Williams, & Fotopoulou, 2014; Krahé et al., 2015; Paloyelis et al., 2016). More generally, based on a systematic review of the experimental pain literature (Krahé et al., 2013), we have concluded that precision modulation by interpersonal interactions takes several forms, including two main categories: (a) social signals about the safety or threat and thus the salience of the impending stimulus itself, and (b) social signals about the threat or safety and thus the salience of the environment in which the stimulus occurs. In turn, the perception and interpretation of such interpersonal variables themselves may in turn depend on (a) their own salience, as well as (b) an individual's prior beliefs about interpersonal relating and associated behaviours (see below for further details).

This notion of social modulation as precision modulation is compatible with previous theories such as the social baseline theory, which proposes that the presence of other people helps individuals to conserve metabolically costly somatic and neural resources through the social regulation of emotion (Beckes & Coan, 2011; see also Decety & Fotopoulou, 2014).

Integrating such notions within a predictive coding model has the advantage of placing them in a wider and neurobiologically plausible framework and hence integrating findings across many fields, as well as generating novel hypotheses, as we outline below.

3.3.1. Developmental considerations: The social origins of interoceptive inference. The active inference framework we propose allows us to observe that the social modulation of pain and pleasant touch is not a simple 'add-on' in our understanding of such modalities. Rather, it appears that interpersonal interactions are necessary in shaping all interoceptive modalities from the onset. This claim is supported by several observations (presented in detail elsewhere, Fotopoulou & Tsakiris, 2017), the most important of which we outline below. Namely, in early infancy, when the human motor system is not yet developed, interoceptive function and homeostasis are wholly dependent on embodied interactions with other bodies. Action and perception do not mature at the same time. As human infants are born without a fully matured motor system, and hence they cannot regulate their own homeostasis unaided, the actions of their caregivers necessarily determine how they come to update their beliefs by active inference and ultimately how they experience all their sensations and particularly those requiring purposeful actions. For example, young infants cannot position, balance, feed, thermoregulate or protect themselves from accidentally cutting or burning their skin (beyond some reflexive avoidance movements). Thus, in the case of these interoceptive modalities, *no available movement on the part of the infant alone can change certain key neurophysiological states relating to homeostasis and allostasis*. As such, the young infant cannot use action to collect evidence about the causes of interoceptive experience to test its interoceptive predictions against the world.

Instead, infants use autonomic and motor reflexes in response to unpredicted physiological states (e.g. crying when hypothalamic function detect that glucose level are not

within the predicted viable range) to elicit caregivers' actions that can change the infant's physiological state (for example by feeding it) until the homeostatic needs are met (i.e. glucose levels are within the predicted range). Thus, updating interoceptive predictions in infants (close the action-perception loop) includes multisensory signals regarding the reaction of caregivers to infants' initial autonomic and proprioceptive predictions; a process we have termed as the 'mentalization' of physiological states elsewhere; Fotopoulou & Tsakiris, 2017). In other words, the origins of interoceptive active inference are always by necessity social, and thus core subjective feelings such as hunger and satiation, pain and relief, cold or warmth have actually social origins.

3.3.2. Adult predictions about the role of others in pain and pleasant touch. The above conclusions about the social origins of interoceptive feelings such as pain and pleasant touch are also consistent with the literature on the relation between these modalities and social attachment (see also Panksepp, 1998). As we aforementioned, pain and pleasant touch may be modulated by social factors. In turn, the perception and interpretation of social variables themselves may depend on individual prior beliefs, or generative models about interpersonal relating and associated behaviours. One influential way of conceptualizing prior beliefs about relating to others is attachment theory. Attachment theory posits that from early in life, attachment partners can serve as a 'secure base' from which the infant explores the world (Bowlby, 1969). If a secure attachment bond is formed over repeated instances of responsive caregiving, the 'secure base' signals safety to the infant, while insecure bonds lead to more ambivalent or even threatening signals from others. These bonds lead to the formation of attachment styles, which remain relatively stable into adulthood.

Individual differences in attachment style have been linked directly with the perception of

pain and related reactions (e.g. Hurter et al., 2014; Meredith, Ownsworth & Strong, 2008; Sambo et al., 2010). Moreover, in the clinical pain literature, insecure attachment has been proposed as a vulnerability factor for developing chronic pain (Meredith et al., 2008), supporting its importance as a pain-relevant prior. In a series of pain studies by our lab, we have shown that differences in attachment style influence the effects of interpersonal variables on subjective, behavioural, physiological and neural responses to pain. For example, social contextual factors and individual differences in attachment style determine the amount of subjective report, facial expressions, heart-rate, skin conductance and neural responses people show in response to experimental pain (Sambo et al., 2010; Hurter et al., 2014; Krahe et al., 2015; 2016).

. Using laser-evoked potentials (LEPs) we further found that active, social support can reduce both subjective and neural pain-related outcomes (Krahe et al., 2016; von Mohr et al., upublished data). However, contrary to other neuroimaging studies on passive forms of social support between couples (e.g., Coan et al., 2006; Eisenberger et al., 2011), our neural effects indicate that the effects of active support by one' romantic partner may begin at earlier stages of cortical nociceptive processing, as reflected by changes in the N1 local peak amplitude. The N1 component is thought to reflect pre-perceptual sensory response (outside of conscious awareness), with activation in the operculoinsular and primary somatosensory cortex (Garcia-Larrea et al., 2003; Valentini et al., 2012). Given that LEPs have been recently proposed to detect environmental threat to the body in response to sensory salient events (Legrain, Iannetti, Plaghki, & Mouraux, 2011), we speculate that affective touch by one's romantic partner seems to reduce the sensory salience of impending noxious stimulation.

Similar findings have been reported in relation to the perception of pleasantness and attachment style in response to CT-optimal touch (Krahé et al., unplublished data). Nevertheless,

the field of pleasant touch is still at its infancy and further neuroscientific studies are needed in both humans and other animals before firm conclusions can be drawn about the social nature of this modality.

4. Summary and Conclusions

Cutaneous pain and pleasant touch have been recently classified by some researchers as interoceptive modalities, even if their stimulation site lies outside the body. This reclassification is basis a more encompassing definition of interoception itself, as the sense of the physiological condition of the entire body, not just the viscera. However, this reclassification lies at the heart of long-standing debates regarding the nature of such modalities and particularly the question of whether they should be defined as sensations on their basis of their bottom-up, neurophysiological specificity at the periphery or as homeostatic emotions on the basis of top-down convergence and modulation at the spinal and brain levels. In the present chapter, we speculatively recast this current state of knowledge within a recent, Bayesian predictive coding framework of brain function, namely the active inference model., This framework suggests that peripheral signals, such as nociceptive and CT tactile channels, do not cause homeostatic perceptions or emotions (e.g. pain or pleasant touch), or vice versa. Instead, there is a circular and multi-layered causality, where on one end of the neural hierarchy, neuronally encoded predictions about bodily states, including in this case states of the skin, engage autonomic, somatic and motor reflexes in a top-down fashion. On the other end of the hierarchy, specialised skin organs and their spinal cord circuity carry interoceptive signals in a bottom-up way that informs and updates predictions at the levels above. These aspects can be linked to the cognitive and sensory aspects of pain, respectively. The affective component of pleasant or painful touch is a third component of this circular causality. Such affects are an attribute of the optimisation of

the weighting (precision) of any representation that generates predictions and prediction errors about the physiological state of the skin (see also Ainley et al., 2016; Fotopoulou, 2013). This weighting is further not only determined by such specialised modalities and pathways but also necessarily contextualized by concurrent proprioceptive signals, as well as by concurrent exteroceptive cues about the body itself and about the physical, material and social environment currently and across different time-scales (for allostatic control purposes). The painful or pleasurable aspects of touch can be thus understood as our sensitivity to bottom-up signals in given interoceptive, exteroceptive, cognitive, social and time contexts and our corresponding behavioural and anticipatory tendencies.

These assumptions have received some empirical support in adult studies from our lab, as well as many other labs, that show that 'on-line' social factors such as active social support or empathy, as well as 'off-line' predictions about the availability of social help (e.g. individual differences in attachment style), may modulate pain or pleasant touch by changing the precision of top-down predictions versus prediction errors from nociception or CT stimulation. Finally, such claims are supported by the developmental observation that in early infancy, when the human motor system is not yet developed, interoceptive function and homeostasis are dependent on embodied interactions with other bodies. It is the adult's actions that will generate changes in interoceptive states and hence ultimately close the action-perception loop. Thus, the origins of interoceptive active inference are always, by necessity social, and core subjective feelings, such as hunger and satiation, pain and relief, cold or warmth, have actually social origins.

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