



Pain: an unpleasant topic

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Abstract

This essay is an attempt to clarify the construct of unpleasantness in the context of the psychophysics of pain. The first critical point is that one aspect of unpleasantness is tightly coupled to stimulus intensity and is therefore a sensory discrimination. Pain has this quality, but so do other somatic sensations such as itch and dysesthesias that are not recognized as painful by most people. A corollary of this is that pain must have a quality other than unpleasantness that allows it to be unequivocally identified. I use the term algosity for that quality. In addition to stimulus bound (primary) unpleasantness, there is an unpleasant experience that reflects a higher level process which has a highly variable relationship to stimulus intensity and is largely determined by memories and contextual features. I have termed this experience secondary unpleasantness. I suggest that the sensory-discriminative/affective-motivational dichotomy has outlived its usefulness and is currently more of an impediment than a guide to neurobiological explanations of pain. In order to increase our understanding of pain we need psychophysical tools designed specifically to differentiate primary unpleasantness from both algosity and secondary unpleasantness. These tools can then be used to determine the neural mechanisms of pain. © 1999 International Association for the Study of Pain. Published by Elsevier Science B.V.

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To consider only the sensory features of pain, and ignore its motivational and affective properties, is to look at only part of the problem, and not even the most important part at that (Melzack and Casey, 1968).

1. Introduction

Over the past three decades neuroscientists have exploited powerful new tools to expand our understanding of brain function at the cellular, molecular and systems level. These advances challenge pain researchers to refine the questions they ask. Nowhere is this challenge more salient than for the issue of the affective dimension of pain. In this essay I will attempt to clarify what I believe to be areas of confusion about the relation of pain sensation and affect.

For the ancient Greeks, pain was grouped with the emotions or appetites, not with sensation. They considered pain to be the opposite of pleasure (Marshall, 1894; Keele, 1957; Livingston, 1998). This view of pain as pure emotion went into decline in the late 19th century with the development of quantitative psychophysical methods to study sensation. About that time the focus of pain studies began to shift from anecdotal questioning of people in pain to

controlled delivery of near-threshold stimuli to normal subjects. In the mid- to late 20th century, with the explosive growth of modern neuroscience and of tools to analyze the neural mechanisms of sensation, the view of pain as an emotion faded further (see Melzack and Casey, 1968). The position that has come to dominate current thinking is that pain is first and foremost a sensation, best studied using the well-established methods of psychophysics and sensory physiology. The fly in the ointment is that because pain is characteristically unpleasant, while other sensations are affectively neutral, the concept of sensation doesn't seem to encompass the experience of pain (Price, 1988). Another problem is that there are unpleasant somatic sensations that are not pain. Whether it is sensation or emotion, the challenge is to conceptualize unpleasantness in a way that will lead to a better understanding of the neural mechanisms of pain.

In contrast to other sensory modalities such as vision and hearing, pain is, by definition, unpleasant at threshold. This unpleasantness is the subjective correlate of a drive to escape and avoid externally imposed tissue-damaging stimuli or, in the case of deep tissue injury or disease, to immobilize the damaged body part. In clinical settings, it is the unpleasantness of a somatic sensation that correlates with its significance to the patient. Noxious stimulation produces arousal, orientation, escape or immobilization

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and help-seeking. Each of these is a behavior that reflects a motivational demand. This motivational demand explains the power of noxious stimuli to shape our behavior and thought. The striking passivity and indifference of patients with frontal lobotomies (see below) informs us that negative affect is a characteristic response to ongoing tissue damage. In psychophysical studies *unpleasantness* is a construct that has been used to measure this 'affective motivational' component of pain (Price, 1988; Rainville et al., 1992). Unfortunately, the assumptions underlying this construct are hazy and the relationship of unpleasantness to pain is currently unresolved.

For me, the question of the relationship between pain and unpleasantness arose, as have many interesting issues, in the clinic. My routine clinical examination of pain patients includes gently stimulating their skin with moving strands of cotton wool. In skin regions distant from the site of their pain, such stimuli usually elicit sensations that are neither pleasant nor unpleasant. As the stimulus is applied closer to the area of pain and the patients are queried about the sensation, their report generally depends on the nature of the question. If I ask them whether the stimulus evokes pain, they usually say, 'no it isn't painful'. On the other hand if I specifically ask whether the sensation elicited is pleasant, unpleasant or neutral, they say, 'definitely unpleasant'. Moreover, there is a sharp and often reproducible boundary between the skin regions where the sensation produced by this stimulus is affectively neutral and the region where the perception is distinctly unpleasant.

Despite the clinical importance of unpleasantness, experimental psychophysics has focused on other aspects of the pain sensation. Typically, stimuli of graded intensity are applied, usually to the skin, and subjects are asked to report pain intensity. Robust, reproducible response curves can be generated using visual analog scales (Price and Harkins, 1987; Price, 1988). These psychophysical curves provide the defining characteristic of the pain sensory system. Electrophysiological (and microstimulation) studies of the component neurons of somatosensory pathways demonstrate that certain neurons, or populations of neurons have response properties suggesting that their activity can; one, *encode* a nociceptive signal and, two, *elicit* sensations recognizable as pain. From a purely esthetic standpoint, this psychophysically based approach to the neurobiology of pain has been phenomenally successful. The experiments are elegant, satisfying and conclusive. They have identified candidate neurons for nociceptive transmission in peripheral nerve, dorsal horn, ventrobasal thalamus and somatosensory cortex (see below, and Willis and Coggeshall, 1991; Wall and Melzack, 1994). The success of this psychophysical approach demonstrates what can be achieved when the goal is clearly stated, in this case to determine the neural mechanisms underlying pain sensation. On the other hand, it is reasonable to question whether the story generated by these elegant experiments has great generality. Although it is premature to minimize the biological or clinical signifi-

cance of this vast body of knowledge, I would argue that the dimension that is usually studied in psychophysical experiments using near-threshold cutaneous stimuli and asking only for reports of pain intensity reflects a highly specialized somatosensory function. To the extent that unpleasantness is neglected, such studies have limited relevance to clinical pain. Broadening of our view of which psychophysical parameters are relevant to nociception is necessary for better understanding of the relationship between stimulus, sensation and emotion.

1.1. Unpleasant somatic sensations that are not pain: the need for a new word

According to the official IASP definition, pain is an 'unpleasant sensory and emotional experience *associated with actual or potential tissue damage*, or described in terms of such damage'. By this official definition, it isn't clear whether the unpleasant sensation reported by my nerve injury patients is pain, and, in fact they often say it isn't pain. Although there has been tissue damage, in that their nerve is injured, the words such patients use to describe the sensation do not correspond to stimuli associated with actual or potential tissue damage. This contrasts to the reported experience of patients with pains resulting from common tissue damaging insults. Such patients use words like 'burning', 'cutting' or 'stabbing' that evoke images of tissue being damaged. On the other hand, patients with nerve injury often report sensations that are unfamiliar and they use words that don't suggest threat or damage. Is their sensation pain even if they are uncomfortable using that word to describe it? Should we try to shoehorn their experience into categories that we have contrived? It seems to me that despite (or perhaps because of) our greater 'knowledge' we are more confused than the patients. The depth of our confusion is illustrated by our tortured terminology. For example, we can tell the patient (and each other) that what they are feeling is *allodynia*. The official IASP definition of allodynia is, 'Pain due to a stimulus which does not normally provoke pain.' (see Merskey and Bogduk, 1994 p. 210). A rough translation of allodynia is 'other pain'. But how can allodynia be pain if it isn't associated with actual or potential tissue damage and isn't described in terms of such damage? If the sensation has an electrical or crawling quality but no burning, stabbing or aching, it doesn't meet the strict definition of the word pain and therefore shouldn't be called allodynia, even if it is unpleasant. Luckily, all is not lost, we still have the term *dysesthesia*, which applies to an unpleasant sensation that doesn't require tissue damage and needn't be described in terms evocative of tissue damage.

Is dysesthesia pain or a different class of unpleasant sensation? Since this is a question about labeling a subjective experience, the key issue is not the type of *stimulus* but whether the experience differs in *quality* from sensations that we readily recognize as pain. For example, the fact that a 42°C thermal stimulus, which is normally innocuous,

elicits burning pain on sunburned skin doesn't make the sensation any less painful nor is it experienced as unfamiliar. The sensation is technically allodynia, but everyone would call it pain. The sensation is likely produced by activity in the same primary afferents and central pathways as that produced by a 46°C stimulus in non-sensitized skin. In this case we are using two terms to describe an experience likely produced by identical central mechanisms. In contrast, one of my patients with nerve injury described the sensation of lightly stroking her skin as 'Like someone scratching a chalkboard with their fingernail.' Extremely unpleasant but unlike most experiences we call pains and certainly not described in terms associated with tissue damage (i.e. not IASP pain). Although dysesthesia is a useful label for such an *unfamiliar* unpleasant somatic sensation, the important point is that the patient, who has never heard the term dysesthesia, is pretty clear that what she feels is an unpleasant sensation but *not pain*.

1.2. Algosity

I think that what such patients are telling us is that there is some quality that allows them to identify some somatic sensations as pain and that the sensation they are currently experiencing *doesn't have that quality*. Whatever we want to call that quality, it is in the same psychophysical category as cold, warmth, itch, and tickle, each of which is a distinct (and probably primary) quality of somatic sensation. Itch is a particularly relevant example of a common somatic sensation that is usually experienced as unpleasant but not painful. Because it has a distinct and familiar quality that has a universally agreed upon name we don't need to call it dysesthesia.

Clearly, pain is only *one of several different unpleasant somatic sensations*. Because there are several types of unpleasant sensations that are not pain we need a term for the psychophysical property of an unpleasant somatic sensation that allows us to identify it as pain. The most obvious name for this quality would be painfulness. However, this term comes with baggage because its root, pain, refers to a sensation that includes this quality plus unpleasantness. After much soul searching and despite my aversion to neologisms (especially those that mix Greek and Latin stems) I suggest that we use the term *algosity* to refer to this quality (it sounds better to me than the etymologically pure *algosmos* or *dolorosity*). Thus itch would have unpleasantness with zero algosity. Dysesthesia might have high unpleasantness but low algosity. Pain, by definition, has both algosity and unpleasantness. Throughout this article I will use the term *algosity* in this sense. As will become more clear later in this essay, the use of this term allows us to avoid the conceptual trap that results from the current fashion of dividing pain into sensory-discriminative and affective-motivational components.

Because pain is not the only unpleasant somatosensory experience, the psychophysics and underlying neural

mechanisms of unpleasantness and algosity can and should be studied separately. Although different terminology is currently used (sensory-discriminative for algosity and affective-motivational for unpleasantness), I believe that leading scientists doing the psychophysics of pain have implicitly recognized this point (Gracely et al., 1978; Price, 1988; Rainville et al., 1992). Recognizing unpleasantness and algosity as the two defining qualities of pain could lead to a paradigm shift in the way we think about and analyze the central circuits that mediate these two somatosensory experiences. Instead of the current approach which asks one question, 'What neural mechanisms underlie the sensation of pain?', we might ask a series of more specific questions such as: 'What sensations are produced when primary afferent nociceptors are activated?' or 'What neural mechanisms underlie the quality of unpleasantness?' or 'Does the unpleasantness associated with activation of A β low threshold mechanoreceptors have a different central mechanism from that associated with activation of unmyelinated polymodal nociceptors?' Such questions would facilitate progress in understanding thalamocortical mechanisms of nociception. This approach could lead to greater understanding of the unpleasant sensations that characteristically occur following peripheral and central nervous system injury.

1.3. Is unpleasantness a primary sensory quality, an emotional reaction to pain sensation or both?

The modern emphasis on what is currently called the sensory-discriminative aspect of pain has two major causes. First, unpleasantness has many non-somatosensory causes and, second, even when it has a somatic origin it is highly susceptible to influence by contextual factors that are unrelated to the properties of the somatic stimulus. For example, one could imagine that, even if the receptors activated were identical, the sensation of being touched lightly by a spider visibly crawling on your arm would be less pleasant than that elicited by a cotton swab applied to the same area. The fact that the unpleasantness of a somatic sensation can be either tightly coupled to the somatic stimulus, or primarily context bound has contributed to the uncertainty about whether unpleasantness is sensation or emotion. At some level, perhaps, a vague appreciation of this uncertainty has led many excellent scientists to conclude that the study of unpleasantness is outside the realm of respectable sensory physiology. In this case, the quest for respectability has led us to ignore a vital aspect of pain.

The impact of context upon somatosensory unpleasantness is potentially very large. Because of this and by analogy with 'emotional reactions' to the meaning of a context (e.g. the presence of threat or loss), some have justifiably taken the position that the 'affective-motivational' aspect of pain (unpleasantness) is a response to the 'sensory-discriminative' component of pain. For example, Price states (Price, 1988 p. 5),

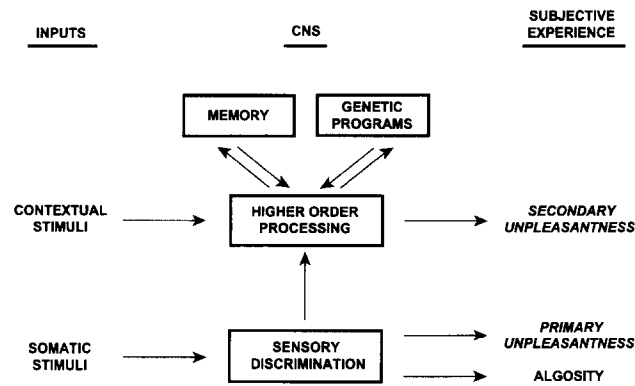


Fig. 1. Flow diagram for CNS activity related to algosity and unpleasantness.

'The affective dimension of pain is *based on* experienced meanings and is thereby intimately related to the cognitive-evaluative dimension of pain. These meanings are directed toward the painful sensations, the context in which they occur, and the implications for impending harm to the self.' (italics mine)

This view of nociceptive processing is similar to that developed for other sensory 'pathways'. For example, one view of visual experience is that perceptions result from the action of interconnected hierarchically organized relays which 'extract' meaningful signals (e.g. house, cat) from an array of inputs transmitted by earlier stages of the pathway such as retinal ganglion cells (center/surround receptive fields) and primary visual cortex (oriented edges) (e.g. (DeYoe et al., 1994; Shepherd, 1994). According to this view, convergent processing by 'higher order' visual relays (in visual association and limbic cortex) leads to more abstract and more 'meaningful' perceptions, (e.g. from oriented edges to faces, moving objects).

To the extent that the unpleasantness of pain represents a *response* to a *sensory discrimination* such a hierarchical model is undoubtedly correct. I will define this aspect of pain as *secondary unpleasantness*. Thus part of what people currently call the affective-motivational component of pain does represent a 'higher order' computation, produced by serial processing of inputs from 'lower order' sensory-discriminative pathways and requiring information in addition to what is provided by the noxious stimulus (e.g. memories, context cues) (see Fig. 1). On the other hand, while this hierarchical view has merit, it is incomplete and has, to a certain extent obscured the idea of unpleasantness as a sensory discrimination. Furthermore, the idea that pain is a sensation that produces a response experienced as unpleasant obscures a rather fundamental concept, i.e. that there are two sensory dimensions of pain: unpleasantness and algosity (Fig. 1). In fact, as demonstrated convincingly by Price and Harkin (Price and Harkins, 1987) using visual analog scales, the mathematical relationship of reported unpleasantness to cutaneous thermal stimulus intensity is a power function that is similar to that for 'pain intensity'

(algosity?). To the extent that unpleasantness is tightly coupled to the stimulus I will call it *primary unpleasantness* to distinguish it from secondary unpleasantness as defined above (Price's affective dimension of pain).

Rainville and colleagues (Rainville et al., 1992) have recently demonstrated that while both pain intensity and unpleasantness are tightly coupled to stimulus intensity across different stimulus types, tonic stimuli (ischemic exercise and cold pressor) are reported as more unpleasant at any given level of pain intensity. Thus primary unpleasantness, while tightly coupled to stimulus intensity is not invariably coupled to perceived pain intensity. The tight coupling to stimulus intensity (and location) supports the notion that primary unpleasantness is just as much a sensory discrimination as 'pain intensity'. Its variable relation to perceived pain intensity suggests that the neural circuits that mediate primary unpleasantness are at least partially separate from those involved in what is currently called pain intensity (algosity?). It seems reasonable to conclude that primary unpleasantness is a sensory dimension of pain that can be distinguished from its other primary dimension (algosity, or what is currently rated as 'pain intensity' in most studies using VAS intensity scales).

1.4. Sensory-discriminative and affective-motivational aspects of pain: confusing simplicity

The division of pain by Melzack and Casey (Melzack and Casey, 1968) into sensory-discriminative and affective-motivational components has had a profound and lasting impact on pain research. This idea is so widely accepted as established fact and is such a central tenet of pain research that most people are unaware that it is only an hypothesis and, moreover, one that has never been seriously tested. Although at first glance the dichotomy between these two aspects of pain seems obvious, on close examination its ambiguities become apparent. Recognizing these ambiguities is essential in order to avoid the logical and semantic labyrinth that obscures our understanding of primary unpleasantness. First of all the terminology is ambiguous because it mixes behavioral, psychophysical and neurobiological concepts. The confusion is most obvious when considering the affective-motivational component of pain. For the behaviorist, *motivation* refers to a drive state that is inferred by observing an animal's behavior. From this perspective, it is not necessary, nor even helpful to consider a subjective state. On the other hand, *affect* is a psychophysical construct that specifically refers to a subjective emotional state and ultimately depends upon introspection and verbal report for validation. Since affect and motivation might be viewed as different aspects of an identical neural process it is reasonable to bundle the two different concepts for purposes of designing animal experiments to uncover their underlying mechanism. On the other hand, it is difficult to see how this bundle can be clearly differentiated from and compared to a sensory-discriminative process. The term

sensory-discriminative is also ambiguous but in a different way than affective-motivational. Thus, sensation and discrimination can refer either to psychophysical, i.e. subjective, phenomena, to observable behaviors or to the objectively measurable electrophysiological processes that are proposed to generate them. To avoid the ambiguity, it is essential, when using these terms to specify the sense in which they are being used. Unfortunately, this is rarely done.

If we restrict our discourse to psychophysical constructs, in this case affect (unpleasantness) and sensation (algesity) we mitigate the semantic ambiguity but are lead to an experimental dead end. The problem is that the psychophysical constructs of affect and sensation have no necessary one-to-one correlation with specific neural processes. There is no reason, for example, why unpleasantness can't be *both* an affective experience *and* a sensory discrimination. To illustrate this problem, in Melzack and Casey's original formulation, the medial affective-motivational systems (brainstem reticular formation, medial thalamus and limbic system) were proposed to function as a central intensity monitor while the sensory-discriminative pathways (the neospinothalamic tract) processed information about spatial, temporal and magnitude properties of the stimulus. On reflection the proposed distinction between the function of these two pathways breaks down. Just because the subjective experience of unpleasantness is associated with an urge to escape doesn't mean it isn't a sensory discrimination. In fact, whatever the subjective or behavioral consequence (affective experience, reflex withdrawal, or the localization of a stimulus), at the level of neural mechanisms the analysis of stimulus intensity is by definition a sensory discrimination.

The unnecessary confusion caused by the artificial separation of sensation and affect has been a roadblock to understanding. For example, in discussing the fact that nociceptive specific lamina I neurons project directly to supraspinal sites traditionally linked to affect and that neurons in those regions can perform exceptionally fine intensity discriminations, Rainville and colleagues (Rainville et al., 1992) state, 'As an explanation for these seemingly conflicting findings, we have recently proposed that a neuron's ability to *discriminate* noxious stimulus intensity should not be considered solely a *sensory-discriminative* function.' (italics are mine). They go on to state, 'Thus although sensory-discriminative and affective aspects of pain may be linguistically and conceptually separable, it is doubtful that completely independent pathways are responsible for processing these two aspects of pain sensation.' One way out of this confusion is to accept my suggestion that both unpleasantness and algesity are primary somatosensory qualities that represent two distinct intensity-based sensory discriminations. The attempt to pigeonhole unpleasantness as either sensation or affect is misguided because it is both. The more productive strategy is to correlate regional brain activity with unpleasantness or algesity while manipulating

stimulus parameters and contextual features, an approach that has just gotten under way (Rainville et al., 1997). Primary unpleasantness and algesity are two distinct stimulus-bound qualities of pain. At the level of neural mechanisms they represent sensory discriminations carried out by supraspinal circuits that are partly separate and parallel. In addition, there is a response to the sensory discrimination, i.e. a serial upstream computation based on both analysis of the somatosensory stimulus, the 'internal state' of the organism and external context features (secondary unpleasantness). Thus unpleasantness is generated by neural mechanisms that have both a parallel (primary) and series (secondary) relationship to those mediating algesity (Fig. 1).

1.5. Central nervous system pathways for unpleasantness

Enormous progress has been made in understanding nociceptive primary afferents and second order dorsal horn neurons. Activation of primary afferent nociceptors activates a subset of dorsal horn neurons which includes projection cells. These projecting dorsal horn neurons can mediate both algesity and primary unpleasantness. Different types of noxious stimulus (heat, cold, pinch, pin prick) will activate distinct spatiotemporal patterns of activity in somatosensory pathways which in turn determine the quality of the sensation. It is important to point out however, that we don't know whether subsets of dorsal horn neurons with different supraspinal projection targets contribute differentially to algesity versus unpleasantness. The finding of Rainville and colleagues that different stimulus types and locations produce variable ratios of unpleasantness and algesity magnitude (Rainville et al., 1992) supports the concept that different (but possibly overlapping) circuits mediate these two primary dimensions of pain.

The major supraspinal targets of dorsal horn nociceptive neurons include the medullary and pontine reticular formation, the midbrain parabrachial nucleus and periaqueductal gray and the thalamus and hypothalamus (Mehler et al., 1960; Cliffer et al., 1991; Craig and Dostrovsky, 1997). Although minor, there are also direct projections from dorsal horn to amygdala, basal forebrain and neocortex (Cliffer et al., 1991).

It is difficult to establish homologous thalamic nuclei in different species, however, there is general agreement that at least four distinct regions relay nociceptive input from dorsal horn to cortex (see Fig. 2). The most extensively studied area is the ventrobasal complex (VB), which includes the ventroposterolateral (VPL) and ventroposteromedial (VPM) nuclei. This region receives input from low threshold mechanoreceptive primary afferents via the dorsal column nuclei. Nociceptive input reaches VB via neurons in dorsal horn laminae IV and V. Immediately subjacent to VPM is the ventroposterior inferior nucleus (VPI) which receives input predominantly from lamina I (Apkarian and Hodge, 1989; Ralston and Ralston, 1992). Caudal to VPI is a

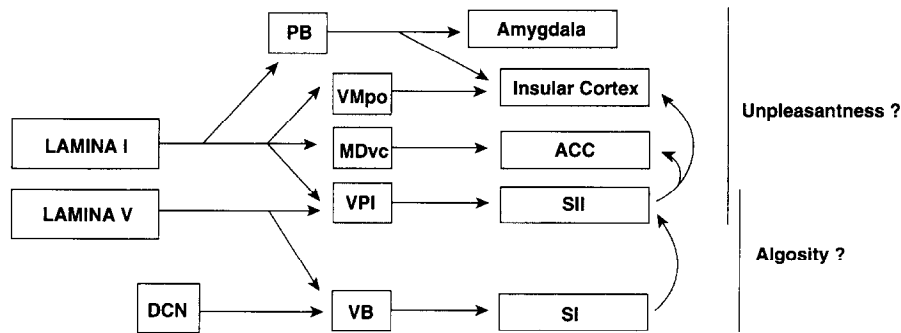


Fig. 2. Nociceptive inputs to dorsal horn laminae I and V have overlapping but distinct supraspinal projection targets; these include the brainstem parabrachial (PB) and, possibly, the dorsal column (DCN) nuclei, and, in the thalamus, the ventromedial part of the posterior nucleus (VMpo), the ventrocaudal Mediodorsal nucleus (MDvc), the ventroposterior inferior nucleus (VPI) and the ventrobasal complex (VB). These nuclei, in turn project to somatosensory and limbic forebrain structures as shown. ACC, anterior cingulate cortex; SI and SII, primary and secondary somatosensory cortex respectively.

third area that lies posteromedial to VB in rat and ventrocaudal to VB in primate. In rodent this area includes the posterior thalamic/posterior intralaminar region (PoT/PIL) (Shi and Davis, 1999) while in primate it is the posterior part of ventromedial nucleus (VMpo) (Craig and Dostrovsky, 1997). There is evidence that a homologous region exists in human thalamus (Vcpc) (Lenz et al., 1993; Craig et al., 1994; Craig and Dostrovsky, 1997). A fourth area is the medial/intralaminar region (including the centralis lateralis (CL), parafascicularis (Pf) nuclei and, in primate, the adjacent caudoventral mediodorsal nucleus (MDvc).

The VB and VPI project to primary (S1) and secondary (S2) somatosensory cortex (SSC), respectively, (Fig. 2). Anatomical information on the medial thalamic pathways is less extensive. Both the PoT/PIL in rodents and VMpo in primates receive direct nociceptive input from dorsal horn (Cliffer et al., 1991; Craig et al., 1994) and project to the dysgranular insular cortex (dIC) (Friedman and Murray, 1986; Barnett et al., 1995). It is potentially important that the dIC (which is apparently homologous to the anterior insula in primate and human) also receives direct input from the parabrachial nucleus (which has a large lamina I input) and the adjacent SII cortex (Friedman and Murray, 1986; Shi and Cassell, 1998). In primate, noxious input is relayed via MDvc to the anterior cingulate cortex (ACC) (Craig and Dostrovsky, 1997). In rat, rabbit and cat, there is evidence that neurons in the medial/intralaminar group relay noxious input to ACC (Vogt et al., 1981; Berendse and Groenewegen, 1991; Sikes and Vogt, 1992; Kuroda et al., 1995).

In summary, there are at least four distinct cortical regions (S1, S2, ACC and dIC) that receive nociceptive input from dorsal horn via distinct thalamic relay nuclei. The contribution of each of these parallel thalamocortical projection pathways to primary unpleasantness and algosity is unknown. Whereas SSC has been investigated extensively in animals, interest in the ACC and dIC regions grew markedly in the early 1990's when human functional imaging studies revealed that they are strongly activated by noxious stimuli (Talbot et al., 1991; Casey et al., 1994;

Coghill et al., 1994). Because the ACC and dIC have major direct connections to limbic system structures they are obvious candidates to mediate (or contribute significantly to) unpleasantness.

1.5.1. The anterior cingulate cortex (ACC)

Nociceptive neurons have been recorded in area 24 of ACC. In rat and rabbit ACC neurons have very large, often whole body receptive fields consistent with a role in intensity rather than spatial discrimination (Sikes and Vogt, 1992; Yamamura et al., 1996). In the rat, injection of formalin into the hindpaw produces significant bilateral increases in c-fos immunoreactivity in the ACC (Liu et al., 1998). Consistent with a parallel rather than series relationship between SSC and ACC, the nociceptive responses of ACC neurons depend upon inputs from medial thalamic nuclei, but not other cortical regions (Sikes and Vogt, 1992). Furthermore, ACC neurons are excited by electrical stimulation of medial thalamic sites responsive to noxious stimulation (Hsu and Shyu, 1997). Neurons recorded in ACC of awake primates respond both to threshold noxious stimuli and to innocuous cues that predict a noxious stimulus (Koyama et al., 1998). Consistent with a role in the aversive aspect of pain, lesions of rodent ACC reduce avoidance conditioning when noxious somatic stimuli are used as unconditioned stimuli (Gabriel et al., 1991).

Human functional imaging studies explicitly implicate the ACC in unpleasantness (Devinsky et al., 1995; Rainville et al., 1997). First, there is a significant correlation of pain unpleasantness with ACC activation. Second, when stimulus intensity is held constant and hypnotic suggestion used to increase or decrease subjective unpleasantness, positively correlated changes in regional cerebral blood flow are observed in ACC, but there is no change in primary SSC (Rainville et al., 1997). Clinical observations also support the concept that the ACC is essential for unpleasantness. Surgical destruction of ACC has been reported to provide significant relief of intractable cancer and severe nonmalignant chronic pain in some patients (see Foltz and White, 1968; Hurt and Ballantyne, 1974; Devinsky et al., 1995).

Patients with ACC lesions reportedly describe the intensity of their pain as unchanged but say that it is less bothersome. No systematic psychophysical studies have been carried out to determine whether, for example, VAS scales of unpleasantness and/or 'pain' intensity are differentially altered in such patients. Functional imaging studies designed to distinguish the contribution of ACC to primary versus secondary unpleasantness could be of great value in guiding animal research.

1.5.2. Dysgranular Insular Cortex

Although the anatomical and human functional imaging studies implicate the anterior (dysgranular) insula in nociception, other supportive data is scanty. In rodents, there is evidence indicating that dIC contributes to taste, visceral sensation and autonomic control (Cechetti and Saper, 1987; Ruggiero et al., 1987). A recent electrophysiological study in anesthetized rats demonstrated that over 40% of neurons in a restricted region of dIC respond to noxious tail pinch (Hanamori et al., 1998). Many of the same neurons respond to visceral, baroreceptor and osmotic stimuli. Other evidence consistent with a contribution of dIC to nociception is that herpes simplex virus injected into mouse tooth pulp is transported via the parabrachial nucleus to dIC (Barnett et al., 1995). None of these studies bear on the issue of whether dIC contributes differentially to unpleasantness or algosity.

1.5.3. Somatosensory cortex

The contribution of SSC to unpleasantness is unclear. Most SSC neurons respond maximally to innocuous stimulation but there are nociceptive subpopulations in rat and primate SSC. Many nociceptive SSC neurons, even in SI, have very large receptive fields, while others are topographically organized and have spatially restricted receptive fields (e.g. Kenshalo and Isensee, 1983; Lamour et al., 1983). Lesions of SSC in primates impair their ability to detect, discriminate and localize noxious stimuli (Kenshalo and Willis, 1991). In cats, bilateral SI lesions increase escape latency but not threshold, whereas both latency and threshold are increased by bilateral SII lesions (Berkley and Parmer, 1974). Because of the possibility of motor or attentional impairment, these results are difficult to interpret. If, as suggested by human functional imaging studies, the cortical areas that mediate unpleasantness include limbic frontal cortex (ACC) but not SSC, lesions of SSC should be less effective than those of ACC in reducing the aversiveness of noxious stimuli. A recent case report suggests that this is indeed the case. Ploner et al. used a laser to deliver thermal stimuli to a 57 year old man with a right sided post-central gyrus stroke that damaged most of SI (Ploner et al., 1999). When a left sided stimulus significantly above normal pain threshold on the right hand was delivered to his left hand, the patient reported a poorly localized unpleasant sensation. Significantly, the patient denied that the sensation was painful. In fact, when asked to pick terms that might describe

his sensation from a list that included 'hot', 'burning', and 'pain', the patient chose none. Although replication of these findings is essential, they are consistent with the idea that the anatomical pathways mediating algosity and unpleasantness are parallel and at least partially independent.

A serial connection may also contribute to unpleasantness. Thus, SI and SII are interconnected and SII projects strongly to the dIC and thus could serve as a relay for input contributing to unpleasantness. Future functional imaging studies should directly address this issue by comparing the psychophysics and regional brain activity using different noxious stimuli in the same subjects. A more detailed circuit analysis of unpleasantness will present a serious challenge since there is no accepted behavioral correlate in animals for unpleasantness and it would be particularly difficult to separate animal equivalents to primary and secondary unpleasantness.

2. Summary

In this essay, I have attempted to clarify the construct of unpleasantness in the context of the psychophysics of pain. The most important point is that primary unpleasantness reflects a somatic sensory discrimination. Pain has this quality, but so do other somatic sensations such as itch and dysesthesias that are not recognized as painful by most people. A corollary of this is that pain must have a quality other than unpleasantness that allows a person to identify it unequivocally. I suggest the term algosity for this quality since it comes without the semantic baggage of common usage. In addition to stimulus bound (primary) unpleasantness, there is a higher level process to which contextual features contribute powerfully resulting in an emotional experience that I have termed secondary unpleasantness. I suggest that the sensory-discriminative/affective-motivational dichotomy has outlived its usefulness and is currently an impediment to neurobiological explanations of pain. In order to increase our understanding we need psychophysical tools designed specifically to differentiate primary unpleasantness from both algosity and secondary unpleasantness. Such tools could be used in the design of functional imaging studies that in turn could guide animal studies. However, because unpleasantness is a purely psychophysical concept the problem of designing an animal model of primary unpleasantness is daunting. Until that problem is solved any neural explanation of unpleasantness will remain largely speculative. The following statements encapsulate the major points of this essay:

- Pains are a subset of unpleasant somatic sensations. I propose the term algosity to refer to that quality of an unpleasant somatic sensation that allows it to be identified as pain.
- Unpleasantness and algosity are both sensory discriminations. This component of unpleasantness is termed primary unpleasantness.

- The magnitude of primary unpleasantness can be dissociated from that of 'pain' intensity (i.e. algosity magnitude). This suggests at least a partial separation of the circuits mediating primary unpleasantness and algosity.
- There is a component of unpleasantness related primarily to cognitive-evaluative factors. This component, termed secondary unpleasantness, represents higher order neural processing.
- It is premature at this point to identify specific supraspinal structures as necessary and sufficient for either algosity or primary unpleasantness. However, there is evidence that activity in postero-medial thalamus and anterior cingulate gyrus neurons contributes significantly to unpleasantness.
- Unpleasantness is a psychophysical construct of greater biological generality and clinical significance than algosity.

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