20 Deciphering Animal Pain

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1 Introduction: Pain by Analogy

In this paper we[1] assess the potential for research on nonhuman animals to address questions about the phenomenology of painful experiences. Nociception, the basic capacity for sensing noxious stimuli, is widespread in the animal kingdom. Even relatively primitive animals such as leeches and sea slugs possess nociceptors, neurons that are functionally specialized for sensing noxious stimuli (Walters 1996). Vertebrate spinal cords play a sophisticated role in processing and modulating nociceptive signals, providing direct control of some motor responses to noxious stimuli, and a basic capacity for Pavlovian and instrumental conditioning (Grau et al. 1990; Grau 2002). Higher brain systems provide additional layers of association, top-down control, and cognition. In humans, at least, these higher brain systems also give rise to the conscious experiences that are characteristic of pain. What can be said about the experiences of other animals who possess nervous systems that are similar but not identical to humans?

Much of our knowledge of the mechanisms underlying pain in humans is derived from research on nonhuman animals. Yet the extent to which animals (e.g., rats) provide a model of conscious pain experiences remains a matter of uncertainty among most pain researchers, and controversy among others. Experimenters who apply treatments such as capsaicin, heat, and electric shocks to rats frequently self-apply the stimuli to reassure themselves that the degree of pain that is caused is tolerable (e.g., Grau 2002). The supposition behind these self-tests is that the phenomenology of pain in rats is similar to the phenomenology of pain in humans. But this supposition is regarded by most as relatively insecure, founded only on broad analogies between the anatomy, physiology, and behavior of humans and other animals.

Analogical arguments are widely exploited in the animal welfare literature (see Allen 2004 for discussion). Anatomical similarities including the presence of nociceptors

connected to a central nervous system, physiological similarities including the existence of endogenous opioids, and behavioral similarities such as withdrawal, vocalization, and "nursing" responses to injury, have all been cited to support the view that many nonhuman animals suffer from pain and thus deserve moral consideration and legal protection. Some of the authors working in this area acknowledge that there is room for doubt about the force of the argument by analogy, but they apply the precautionary principle that it is better to err on the side of too much protection rather than too little. Other authors, however, place considerably more weight on the analogy argument, considering it to be firmly established scientifically that there are no significant differences between humans and many other animals in the capacity to feel pain. This conclusion is often bolstered by appeal to evolutionary continuity between the species.

Lists of shared features may be adequate to reassure those who are predisposed to accept the conclusion that there are no significant differences between pain experiences in humans and (at least some) other animals. But this approach is rather weak in the face of certain skeptical challenges that are commonly raised. Such challenges have at least two independent sources. Some skeptics are doctrinally convinced that conscious experiences of any sort are beyond the reach of empirical investigation. On this view, no scientific procedures can tell us about something that is (allegedly) essentially subjective and private. Other skeptics allow that empirical results are relevant, but they are convinced that there exist significant disanalogies between humans and other animals, which make it unlikely that the experiences of nonhuman animals are anything like the conscious experiences of humans. The capacity for speech and possession of "theory of mind" are two features of human cognition that are frequently presumed to mark a distinction between human consciousness and that of other animals (e.g., Carruthers 1996, 2000).

The standard analogy arguments that have been advanced by many philosophers are not sufficient to overcome either of these two variants of skepticism. This is because the providers of these lists of similarities generally do not provide any theoretical reasons for connecting them to attributions of conscious pain. Specialized nociceptors are found in such relatively primitive organisms as sea slugs and leeches, and as such do not provide strong grounds for attributing conscious pain to these organisms. Opioid systems are also widespread among animals. Many withdrawal responses, and even some forms of learning about noxious stimuli, can be accomplished by spinal cords without mediation by higher brain systems (Grau 2002). If items on the list do not individually entail conscious experience of pain, it is not clear why satisfying multiple criteria should add up to conscious experience. Analogy arguments are vulnera-

ble because for all the similarities between humans and other nonhuman animals, there are dissimilarities that can be used to deny the inference to conscious pain in nonhumans (cf. Nelkin 1986, p. 137). While human brains may be similar to animal brains at the level of gross anatomy and physiology, more fine-grained analysis reveals numerous differences. It is also open to critics to point out the many ways in which human behavior is not identical to the behavior of other animal species. Consequently, without an adequate framework for understanding the connection between the observed similarities and conscious pain, analogy arguments remain essentially weak.

In this paper we pursue the suggestion made by Allen (2004) that a functional understanding of pain in the context of learning would provide a framework for assessing comparisons of anatomy, physiology, and behavior. Fuchs's work (described below) on the sensory and emotional aspects of pain experiences in rats provides a context in which the functional roles of different components of the phenomenology of pain could be investigated with respect to anatomy (particularly the role of the anterior cingulate cortex), physiology (the effect of opioid substances), and behavior (avoidance of aversive contexts). While the development of such a framework may not ultimately convince either type of skeptic, it may help to preempt skeptical and antiskeptical arguments that are based on overly simplistic ideas about the functions of pain. Our aim is to chart a middle course between the excessively skeptical view that animal pain cannot be studied empirically and the overly credulous view that scientific investigation has already revealed that other animals (other mammals, at least) feel pain much as we do. We do not intend to show that rats experience pain consciously in this paper, but we do intend to outline an empirical research program that allows sophisticated comparisons to be drawn between the pain experiences of humans and those of other animals.

2 Functional Anatomy: The Role of the Anterior Cingulate Cortex

The link between pain and learning appears to go, at least in mammals, through the anterior cingulate cortex (ACC). Before going into detail about the role of the ACC in learning, it is useful to describe the phenomenological properties commonly associated with ACC activity in humans. The "classical" view of pain, as described elsewhere (Hardcastle 1997; Melzack and Casey 1968), generally holds that there are at least two key pathways involved in the experience of pain in humans. One pathway is responsible for the sensory or descriptive component of pain sensations (such as the intensity of the pain, the location of the pain, whether the pain is "sharp" or "dull," etc.),

and the other is responsible for the affective or motivational dimension of pain (i.e., how much one "minds" the pain or how unpleasant the pain is). Activity in the ACC is generally correlated with the latter of these two pathways and, in fact, research on the ACC has played a central role in establishing the existence of different pathways.

One of the earliest experimental indications that there may be multiple pathways involved in the processing of pain came from reports of patients who were administered morphine (Price et al. 1985). Patients who were given morphine while in pain stated that they still felt the pain but that it no longer bothered them. Interestingly, the subjects of cingulotomies (a procedure that ablates the ACC) reported the same thing (Foltz and White 1962; Gybels and Sweet 1989). These results seem to suggest a dissociation between sensations of pain and the unpleasantness that usually accompanies such sensations.

Several other recent discoveries have supported the dual pathway hypothesis. A study by Rainville et al. (1997) used hypnotic suggestion to increase or decrease the amount of unpleasantness subjects felt while holding their hands under 47°C water. Subjects rated the intensity of the pain sensation the same regardless of whether or not they underwent hypnotic suggestion, but their ratings of the unpleasantness of the sensation varied accordingly to the suggestion (i.e., they ranked pains as "more unpleasant" when given a suggestion that the pain would be more unpleasant, and "less unpleasant" when given the suggestion that it would be more unpleasant). Positron emission tomography conducted during the study revealed that the anterior cingulate cortex but not other areas (such as the somatosensory cortex) was increasingly active relative to "more unpleasant" rankings given by subjects and decreasingly active during "less unpleasant" rankings.

A later experiment by Rainville et al. (1999) used hypnotic suggestion to increase or decrease the intensity of the pain intensity in the same experimental setup. In this case, both the ACC and the somatosensory cortex were more active during suggestions of increased intensity and less active during suggestions of decreased intensity. This, according to Price (2002), suggests that there is a "direction of causation" that flows from the sensory qualities of pain to the perceived unpleasantness of the pain. Price accepts that there are dual pathways, but he rejects the view that consciously felt affect is processed in a parallel system that is entirely independent from the sensory processing stream. He favors a model in which the pain affect processing stream receives input from the pain sensation stream. Such a model allows for a dissociation between the affective and sensory aspects of pain, and Price provides evidence based on the psychophysical relationship between pain intensity and heat stimuli and the psychophysical relationship between pain unpleasantness and heat

stimuli. Both are positively accelerating power functions, but, according to Price, "pain unpleasantness ratings are less than those of pain sensation intensity ratings in response to 45–50°C temperatures" and consequently the exponents in the power functions must be different. The fact that pain sensation and pain unpleasantness bear different relationships to the pain-causing stimuli further supports the idea that there are at least two functionally distinct elements of the experience of pain.

If, as the evidence suggests, the ACC does play a central role in the experience of the unpleasantness of pain in humans, then it is clear that more detailed knowledge of the ACC will have important implications for both ethical and practical questions regarding the treatment of pain in humans. Likewise, because unpleasantness is such an important part of how humans conceptualize our own experience of pain, it also seems likely that ACC research on nonhuman animals could provide important information in relation to the question of whether animals consciously feel pain. However, as was indicated earlier, it is not enough to simply point out the presence or absence of the ACC in other animals as the deciding factor in an argument by analogy or disanalogy. It is important to place its function in an explanatory framework, and as such there are a couple more features of the ACC that are worth mentioning before moving on to a discussion of how animal research has and can aid our understanding of pain.

In addition to its role in the affective dimension of pain, recent research has suggested that the ACC plays a role in learning to avoid noxious stimuli. One of the ways this takes place is in the detection of errors. A study by Kiehl, Liddle, and Hopfinger (2000) found that the rostral region of the ACC, the same region that is active during pain, was activated during a task only after the subject made inappropriate responses and not when the subject made appropriate responses. (This connection to endogenous error signals is especially interesting in light of the suggestion by Allen and Bekoff [1997, ch. 8] that autonomous error correction could provide a significant source of evidence about animal consciousness.)

Eisenberger and Lieberman (2004) found that the dorsal ACC was active for subjects in situations of perceived social exclusion. And Carter et al. (1998) have shown that the conditions with strong competition between different response drives caused strong activation in the ACC. Though these results cover a wide range of situations, all of them involve circumstances in which the subject would potentially benefit by learning to avoid specific behaviors in the future. Thus, at least a large part of the function of the ACC appears to be critically linked with the ability of the organism to learn in various contexts.

Allen (2004) identifies learning as a key area for investigating the functions of conscious pain experiences. It is important, however, to realize that various forms of learning about noxious stimuli may take place in the spinal cord, with no implications for consciousness. Some kinds of learning, however, seem to be closely correlated to conscious awareness, for example, trace conditioning as opposed to delay conditioning (see Clark and Squire 1998) and to depend on higher brain mechanisms, for example, more sophisticated kinds of operant learning as opposed to simpler forms of instrumental learning (Grau 2000, 2002; Grau, Barstow, and Joynes 1998). It is these that are of most interest for our present purposes (see Allen 2004 for discussion).

While the ACC appears to be of considerable interest in understanding the connection of pain processing to higher cognitive functions, it is important not to place too much importance on any single chunk of neural tissue. Because the "classical" account pictures the pain system as having two tracks, comprised of a sensory-discriminative system that projects to somatosensory cortex and an affective-motivational system that projects to frontal lobes, some philosophers have been tempted to make bold claims about the functional isolation of these tracks in specific parts of the brain. Hardcastle, for example, writes: "The frontal lobe (and its connections) process our actual suffering" (1997, p. 391). But Coghill warns that while two subsystems of the classical account can be experimentally separated, "current views that sensory-discriminative and affective-motivational dimensions of pain are processed in parallel by distinct neural structures cannot account for a number of aspects of pain" (1999, p. 67). Coghill discusses brain-imaging studies that show that pain is processed by multiple regions in a highly distributed system, that there is no single brain region whose destruction completely abolishes the experience of pain, that sensory processing occurs in areas classically associated with affect, and affect itself is at least a three-layer process with the prefrontal cortex being mainly important for the latest stage of processing.

The ACC is thus just one part of a very complex system. Its particular interest to us lies in its functional significance for linking painful experiences in humans and other mammals to learning and motivation, but it is important to note that these functions may belong to other structures in nonmammalian animals with independently evolved neural architectures. In the remainder of this paper, however, we focus on organisms that do possess ACCs, namely rodents, and we seek to show how the investigation of functional connections between nociception, motivation, and learning in rodents has the potential to advance our understanding of the nature of painful experiences in nonhuman animals.

3 Testing the Functions of Pain

We are now in a position to discuss what research on certain nonhuman animals has taught us about pain. An examination of the literature reveals that the classical hypothesis of separate, interacting systems that process sensory-discriminative and emotional-motivational determinants of pain has not been rigorously examined in animals. A major factor for lack of direct testing is likely related to limitations in the commonly used behavioral testing methods in rodent models of nociception. For instance, following nerve injury, animals display changes in withdrawal behaviors in response to noxious stimulation that are thought to reflect clinical conditions of neuropathic pain. Quantification of these stimulus-evoked nociceptive behaviors is based almost exclusively on withdrawal thresholds—that is, measures of the strength or duration of the stimulus needed to provoke a response. A lowered threshold for responding (plotted graphically as a leftward shift in the stimulus–response function) following peripheral nerve injury or the induction of an inflammatory condition is thought to be the analogue for clinical symptoms of allodynia (displaced or inappropriate pain) and hyperalgesia (oversensitivity to pain). Treatments that have an antinociceptive effect are represented graphically as an attenuation of the leftward shift in the stimulus–response function. Manipulations (e.g., pharmacological) that fail to attenuate the leftward shift in the stimulus–response function are assumed to reflect a lack of antinociception. The withdrawal method has been useful for understanding certain aspects of the neural system and allowing for a fast initial screen for potentially useful analgesic compounds. Most of the studies that have examined supraspinal focal brain stimulation or microinjection of drugs into discrete nuclei have also utilized such measurements of reflexive behavioral response to acute noxious stimulation. Indeed, activation of various subcortical, brainstem, and spinal cord systems produce antinociception as revealed by an increase in the threshold or latency to respond to noxious stimulation (Basbaum and Fields 1978).

There is little doubt that the knowledge gained from behavioral testing based on withdrawal responses is of extreme importance. Nonetheless, the methodology has significant limitations (Fuchs 2000). First, recall that reflexive measures such as tail flick and leg withdrawal show the same response profiles in spinally transected rats as intact rats, and that various kinds of learning also take place in spinalized rats (Grau 2000, 2002; Grau, Barstow, and Joynes 1998). The absence of any connection to the brain in the spinalized condition indicates that any apparent hyper- or hypoalgesia need not reflect a change in conscious experience even in intact animals. Second, King

et al. (1996) showed that manipulations in rats (exposure to either heat or shock) that increased tail withdrawal latencies (apparent hypoalgesia) simultaneously lowered the latency to vocalize (apparent hyperalgesia). Thus, two different reflexive measures yield results that point in opposite directions if both are taken as simple measures of the intensity of experience. These results caution against simple reliance on reflexive measures when trying to determine the aversiveness of a stimulus experienced by an animal. Hence, analogical arguments about consciousness of pain in animals that are based on similarities between withdrawal behaviors or vocalizations elicited by noxious stimuli are also precarious. Specifically, the reflexive behavioral paradigms do not provide definitive information about the aversive and unpleasant qualities of a persistent pain condition (Fuchs 2000).

It has proven difficult to dissociate the affective-motivational and sensory-discriminative components of pain processing in rodents using reflexive behavioral measures alone. It becomes even more problematic when it is assumed that decreases in stimulus-evoked behavior, following manipulations to neural structures thought to be involved in emotional aspects of behavior, reflect changes in the affective-motivational dimension of pain processing (Fuchs and Melzack 1995; Donahue, LaGraize, and Fuchs 2001). This assumption has not been rigorously tested in animal models. To directly test the role of different neural substrates on the emotional aspect of nociceptive behavior, additional measures are needed.

Additional measures based on operant principles have been recently developed and are being used to evaluate the sensory and discriminative aspects separate from the motivational and affective components of pain, and to explore potential higher order brain processing in animals (Johansen, Fields, and Manning 2001; LaBuda and Fuchs 2000a; Vierck et al. 2002). One such approach is the use of operant techniques that measure escape and avoidance of animals (LaBuda and Fuchs 2000a; Mauderli, Acosta-Rua, and Vierck 2000; Yeomans, Cooper, and Vierck 1995). The assumption is that flexible exercise of choice between alternative behaviors to achieve escape or avoidance of a noxious stimulus is a clear indication that the stimulus's aversiveness is being registered at higher cognitive levels (see also Grau, Barstow, and Joynes 1998; Grau 2002). A behavioral test method based on this assumption has been recently reported (LaBuda and Fuchs 2000a). In this paradigm, the animals are allowed to "choose" where the mechanical stimulus is applied—an injured or uninjured region of the body. The basic paradigm requires the use of a chamber that is equally divided into a dark side and a light side. Under normal conditions, rats naturally prefer the dark area of the environment. During behavioral testing, a mechanical stimulus (476 mN von Frey monofilament—a flexible plastic wire used to simulate a pinprick of a fixed intensity)

is applied to an injured hindpaw when the animal is within the dark area or to the noninjured contralateral hindpaw when the animal is within the light area of the chamber. The amount of time that animals spend within the light side of the chamber is recorded. Control animals spend about 20 to 40 percent of the time in the light side of the chamber. However, the animals that have an injury demonstrate escape–avoidance behavior toward the dark side of the chamber and a shift in preference toward the light side of the chamber (see LaBuda and Fuchs 2000a for details of controls and quantitative results). The escape–avoidance behavior supports the notion that mechanical stimulation of the treated paw during a neuropathic or inflammatory pain condition is aversive and when given a choice, animals will perform purposeful behavior to minimize stimulation of the afflicted body region.

To further test the validity of the escape–avoidance test paradigm the effect of two commonly used analgesic agents, morphine and gabapentin have been tested (LaBuda and Fuchs 2000b). The rationale for these series of experiments is that analgesic compounds that decrease nociception should also decrease the aversive nature of stimulating an injured body region. Decreased mechanical sensitivity was measured using the traditional stimulus-evoked threshold method with von Frey monofilaments following nerve injury immediately prior to and then thirty minutes following the administration of different doses of morphine (1 mg/kg or 10 mg/kg) or gabapentin (30 mg/kg or 90 mg/kg). Compared to injured animal controls treated with the drug-delivery vehicle only, both morphine and gabapentin attenuated the enhanced response to mechanical stimuli in a dose-dependent manner (i.e., caused a leftward shift in the stimulus–response function). Of primary interest, however, is the additional finding that both morphine and gabapentin also attenuated the escape–avoidance behavior. Morphine (1 mg/kg) and gabapentin (30 mg/kg and 90 mg/kg) treated nerve-injured animals displayed less time in the light area of the chamber relative to vehicle-treated nerve-injured control animals. The findings indicate that analgesic compounds administered at a dose sufficient to decrease the sensory component of pain also decreased the affective component of the pain condition. In other words, the sensory experience was less intense, so the affective response was also reduced, in accordance with the "direction of causation" mentioned above.

Psychophysical evidence from humans indicates that morphine can selectively modulate the affective dimension of pain without altering the sensory aspect (Price et al. 1985). As we noted in the previous section, patients receiving morphine for pain control sometimes report that the pain is still present, but that it does not bother them as much. It is exactly this aspect of the experience that cannot be reliably measured with stimulus-evoked withdrawal tests but can be quantified using additional

behavioral test paradigms. When morphine is administered at a lower dose (0.5 mg/kg), there appears to be a selective attenuation of pain affect with no alteration in mechanical paw withdrawal threshold (LaGraize et al., submitted), a finding that is analogous to the clinical reports of morphine in patients with chronic pain conditions. Based on these results, it is concluded that manipulations that decrease hyperalgesia also attenuate escape–avoidance behavior. In other words, the behavioral test paradigm reveals that if the experimental condition is less "painful," then mechanical stimulation of the afflicted region is less aversive.

These behavioral paradigms can also reveal aspects of nociceptive processing that have not previously been accessible in animals. For example, the hypothesis that limbic system structures are involved in the aversiveness of stimulus-evoked pain has also been examined using this test paradigm. As indicated above, the anterior cingulate cortex (ACC) is a critical structure in processing pain in mammals, especially with regard to affect and motivation. This conclusion has been based on three primary lines of evidence. First, electrophysiological studies have revealed nociceptive neurons in the rat and rabbit ACC that have very large receptive fields, consistent with the notion that this region is involved in encoding intensity rather than spatial discrimination (Sikes and Vogt 1992). Second, as mentioned in our previous section, human imaging studies have correlated the unpleasantness of pain with ACC activation (Rainville et al. 1997; Tölle et al. 1999). Third, also mentioned above, cingulotomy provides significant pain relief in humans (Ballintine et al. 1967; Pillay and Hassenbusch 1992; Wong et al. 1997). The effectiveness of this procedure has been attributed to the interruption of the cingulate gyrus concerned with the emotional component of pain (Martinez et al. 1975). Indeed, patients with ACC lesions report that the intensity of their pain remains, but that it is less bothersome (Corkin and Hebben 1981).

The escape–avoidance paradigm has been used to determine if the same pattern of behavioral results could be obtained from the rat. It was predicted that lesions of the rat ACC would decrease the aversiveness of pain without altering the mechanical hyperalgesia. Indeed, results from Fuchs's lab confirm this hypothesis (LaGraize et al. 2004). First, bilateral ACC electrolytic lesions failed to reverse the decrease in mechanical withdrawal threshold following nerve injury. However, the ACC lesion caused a significant attenuation in the shift from the dark side of the test chamber relative to the control group which was not subject to nerve injury. These results are a reflection of the clinical reports of patients who indicate following ACC lesions the intensity of the pain remains, but that it is less bothersome. Although alternative explanations of the data have yet to be excluded (i.e., ACC lesions interrupt memory processes that are critical for the acquisition of the association), this finding provides preliminary

evidence to directly support the original proposition by Melzack and Casey (1968) that limbic system structures have different modulatory effects on sensory-discriminative and emotional-motivational dimensions of pain.

In summary, operant behavioral techniques can be used as a method to explore the complex nature of pain in rat models of nociception. Unlike traditional threshold measurement techniques, the general paradigm outlined above provides animals the opportunity to perform purposeful behavior to escape or avoid mechanical stimulation by a von Frey monofilament to the hyperalgesic body region. The assumption is that escape and avoidance behavior indicate that the aversiveness of the mechanical stimulus is playing a role in cognitive decision-making processes of the animal. This is analogous to a patient who might demonstrate guarding behavior and avoidance of environmental conditions that might exacerbate the severe discomfort associated with causalgia (a burning sensation along a peripheral nerve) or other clinical pain syndromes. Although the present approach is by all accounts not the only paradigm that can be used (i.e., Johansen, Fields, and Manning 2001; Mauderli, Acosta-Rua, and Vierck 2000), it is a very important initial step in developing operant behavioral test paradigms to unravel the complex processing of nociceptive information in supraspinal neural substrates.

4 Future Directions and Implications

The move from simple behavioral measures (stimulus–response) to more sophisticated operant behavioral techniques suggests additional methods for investigating the roles that different dimensions of painful experiences might play in higher order forms of learning. For example, we are interested in the question of whether long-term conditioning is differentially affected by blocking the sensory and affective components of pain processing. Does treatment with morphine affect the ability of rats to learn about noxious stimuli? Would treated rats fail to learn associations between contextual cues and noxious stimuli, or is sensory awareness sufficient? Would the effect vary for different types of pain conditions (i.e., is sensory awareness sufficient for acute conditions but not chronic conditions)? Additionally, if given the choice, would rats learn to self-administer sensory and affective pain relief differentially? A second topic of interest is motivational drives. Do animals experiencing food deprivation and pain simultaneously choose to eat, or does the pain drive supersede the hunger drive? Is their choice differentially affected by blocking sensory and affective components of pain processing? Furthermore, does loss of pain affect correlate with loss of affect in other behaviors (i.e., mating, predator–prey, and maternal behaviors)? Do losses of

pain affect versus sensory pain experience differentially modify these behaviors? The ability to investigate such questions opens the door to much more detailed analyses of the functions of these different aspects of painful experiences. It is also worth noting that the utility of these measures depends to a large degree on animals exercising choices in conditions where they are not in so much pain as to be rendered immobile or dysfunctional. While the deliberate infliction of pain on another organism is always a matter of moral concern, the experiments we propose generally involve a degree of pain that would be consistent with good overall welfare.

We began this paper with questions about the phenomenology of animal pain, to which we now return. We believe that animal pain studies are on the brink of some exciting advances that will make it possible to describe more precisely the roles played by different aspects of painful experiences. An understanding of how the unpleasantness of pain connects to the complex cognitive capacities of organisms would provide an explanatory framework that would allow behavioral evidence from a variety of species to be assessed. Of course, it is open to the more ideological kind of skeptic that we identified in the introduction to maintain that none of this tells us anything about the conscious nature of animal experiences, because all the anatomical, physiological, and behavioral evidence in the world is compatible with the complete absence of conscious experience. But this view applies just as much to our ability to investigate human experiences of pain as it does to nonhuman animals, and as such provides no special barrier to our understanding of animal pain. The other kind of skeptic we identified thinks that outstanding differences in higher cognitive abilities such as language processing or theory of mind abilities are the crucial elements for understanding the nature of conscious experience. They may be right, but no empirical method has been provided for testing the hypothesis that consciousness serves those functions. In contrast, the techniques we have described make it possible to test an alternative class of hypotheses linking the phenomenology of painful experiences to specific motivational and learning functions. By manipulating dimensions of the painful experience we stand to gain a more detailed view of the complex relationship between behavior, mechanism, and experience, which in turn strengthens the basis for analogical comparisons of animals and humans.

Both philosophers and scientists have, until now, tended to focus only on the most basic responses to painful stimuli, such as withdrawal and nursing behaviors. This has fostered some rather simplistic views about the functions of pain sensations (see Allen 2004 for criticism) that have, in turn, supported a polarized debate. On the one side are those who point to withdrawal and nursing behaviors in nonhuman animals as evidence that their pain systems are essentially no different from the human pain

system. On the other side are those who point out that these simple responses can be implemented with simple mechanisms that provide little confidence for the attribution of conscious experiences. If one limits oneself to these kinds of behaviors, it is indeed hard to think of empirical studies that would depolarize this debate, and philosophers, in particular, have an unfortunate tendency to think that if they can't imagine any relevant experiments to address a particular question, then there can't be any. With this paper we hope to have shown that there is much potential for investigating functional aspects of the experience of pain, providing, we hope, a fertile middle ground in which sophisticated comparisons of different species can grow.

Acknowledgments

We thank Murat Aydede, Verne Cox, Jim Grau, Gary Lucas, and Bill Timberlake for comments.

Notes

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References

Allen, C. 2004. "Animal Pain." *Noûs* 38: 617–643.

Allen, C., and M. Bekoff. 1997. *Species of Mind: The Philosophy and Biology of Cognitive Ethology*. Cambridge, Mass.: MIT Press.

Ballintine, H. T., W. L. Cassidy, N. B. Flanagan, and R. Marino. 1967. "Stereotaxic Anterior Cingulotomy for Neuropsychiatric Illness and Intractable Pain." *Journal of Neurosurgery* 26: 488–495.

Basbaum, A. I., and H. L. Fields. 1978. "Endogenous Pain Control Mechanisms: Review and Hypothesis." *Annals of Neurology* 4: 451–462.

Carruthers, P. 1996. *Language, Thought, and Consciousness*. Cambridge: Cambridge University Press.

———. 2000. *Phenomenal Consciousness*. Cambridge: Cambridge University Press.

Carter, C., T. Braver, D. Barch, M. Botvinick, D. Noll, and J. Cohen. 1998. "Anterior Cingulate Cortex, Error Detection, and the Online Monitoring of Performance." *Science* 280: 747–749.

Clark, R. E., and L. R. Squire. 1998. "Classical Conditioning and Brain Systems: The Role of Awareness." *Science* 280: 77–81.

Coghill, R. C. 1999. "Brain Mechanisms Supporting the Pain Experience." Pp. 67–76, in *Pain 1999—An Updated Review*, ed. M. Max. Seattle: IASP Press.

Corkin, S., and N. Hebben. 1981. "Subjective Estimates of Chronic Pain before and after Psychosurgery or Treatment in a Pain Unit." *Pain* 1 (suppl.): S150.

Donahue, R. R., S. C. LaGraize, and P. N. Fuchs. 2001. "Electrolytic Lesion of the Anterior Cingulate Cortex Decreases Inflammatory, but Not Neuropathic Nociceptive Behavior in Rats." *Brain Research* 897: 131138.

Eisenberger, N. I., and M. D. Lieberman. 2004. "Why Rejection Hurts: A Common Neural Alarm System for Physical and Social Pain." *Trends in Cognitive Sciences* 8: 294–300.

Foltz, E. L., and L. E. White. 1962. "Pain 'Relief' by Frontal Cingulotomy." *Journal of Neurosurgery* 19: 89–100.

Fuchs, P. N. 2000. "Beyond Reflexive Measures to Examine Higher Order Pain Processing in Rats." *Pain Research and Management* 5: 215–219.

Fuchs, P. N., and R. Melzack. 1995. "Analgesia Induced by Morphine Microinjection into the Lateral Hypothalamus of the Rat." *Experimental Neurology* 134: 277–280.

Grau, J. W. 2000. "Instrumental Conditioning." Pp. 767–769 in *The Corsini Encyclopedia of Psychology and Behavioral Science*, 3rd edition, ed. W. E. Craighead and Nemeroff, C. B. New York: John Wiley and Sons.

———. 2002. "Learning and Memory without a Brain." Pp. 77–88, in *The Cognitive Animal*. ed. M. Bekoff, C. Allen, and Burghardt, G. M. Cambridge, Mass.: MIT Press.

Grau, J. W., D. G. Barstow, and R. L. Joynes. 1998. "Instrumental Learning within the Spinal Cord: I. Behavioral Properties." *Behavioral Neuroscience* 112: 1366–1386.

Grau, J. W., J. A. Salinas, P. A. Illich, and M. W. Meagher. 1990. "Associative Learning and Memory for an Antinociceptive Response in the Spinalized Rat." *Behavioral Neuroscience* 104: 489–494.

Gybels, J. M., and W. H. Sweet. 1989. *Neurosurgical Treatment of Persistent Pain*. Basel: Karger.

Hardcastle, V. G. 1997. "When a Pain Is Not." *Journal of Philosophy* 94: 381–409.

Johansen, J. P., H. L. Fields, and B. H. Manning. 2001. "The Affective Component of Pain in Rodents: Direct Evidence for a Contribution of the Anterior Cingulate Cortex." *Proceedings of the National Academy of Sciences of the USA* 98: 8077–8082.

Kiehl, K. A., P. F. Liddle, and J. B. Hopfinger. 2000. "Error Processing and the Rostral Anterior Cingulate: an Event-Related fMRI Study." *Psychophysiology* 37: 216–223.

King, T. E., R. L. Joynes, M. W. Meagher, and J. W. Grau. 1996. "The Impact of Shock on Pain Reactivity II: Evidence for Enhanced Pain." *Journal of Experimental Psychology: Animal Behavior Processes* 22: 265–278.

LaBuda, C. J., and P. N. Fuchs. 2000a. "A Behavioral Test Paradigm to Measure the Aversive Quality of Inflammatory and Neuropathic Pain in Rats." *Experimental Neurology* 163: 490–494.

———. 2000b. "Morphine and Gabapentin Decrease Mechanical Hyperalgesia and Escape/Avoidance Behavior in a Rat Model of Neuropathic Pain." *Neuroscience Letters* 290: 137–140.

LaGraize, S. C., C. J. LaBuda, M. A. Rutledge, R. L. Jackson, and P. N. Fuchs. 2004. "Differential Effect of Anterior Cingulate Cortex Lesion on Mechanical Hyperalgesia and Escape/Avoidance Behavior in an Animal Model of Neuropathic Pain." *Experimental Neurology* 188: 139–148.

LaGraize, S. C., J. Borzan, Y. B. Peng, and P. N. Fuchs. Submitted. "Selective Regulation of Pain Affect Following Activation of the Opioid Anterior Cingulate Cortex System."

Martinez, S. N., C. Bertrand, P. Molina, and J. M. Perez-Colon. 1975. "Alteration of Pain Perception by Stereotaxic Lesions of Fronto-Thalamic Pathways." *Confinia Neurologica* 37: 113.

Mauderli, A. P., A. Acosta-Rua, and C. J. Vierck. 2000. "An Operant Assay of Thermal Pain Conscious, Unrestrained Rats." *Journal of Neuroscience Methods* 97: 19–29.

Melzack, R., and K. L. Casey. 1968. "Sensory, Motivational, and Central-Control Determinants of Pain." Pp. 423–443, in *The Skin Senses*, ed. D. R. Kenshalo. Springfield, Ill.: Charles C. Thomas.

Nelkin, N. 1986. "Pains and Pain Sensations." *Journal of Philosophy* 83: 129–147.

Pillay, P. K., and S. J. Hassenbusch. 1992. "Bilateral MRI-Guided Stereotactic Cingulotomy for Intractable Pain." *Stereotactic and Functional Neurosurgery* 59: 33–38.

Price, D. D. 2002. "Central Neural Mechanisms That Interrelate Sensory and Affective Dimensions of Pain." *Molecular Interventions* 2: 392–403.

Price, D. D., A. Von Der Gruen, J. Miller, A. Rafii, and C. A. Price. 1985. "Psychophysical Analysis of Morphine Analgesia." *Pain* 22: 261–269.

Rainville, P., B. Carrier, R. K. Hofbauer, M. C. Bushnell, and G. H. Duncan. 1999. "Dissociation of Sensory and Affective Dimensions of Pain Using Hypnotic Modulation." *Pain* 82: 159–171.

Rainville, P., G. H. Duncan, D. D. Price, B. Carrier, and M. C. Bushnell. 1997. "Pain Affect Encoded in Human Anterior Cingulate but Not Somatosensory Cortex." *Science* 277: 968–971.

Sikes, R. W., and B. A. Vogt. 1992. "Nociceptive Neurons in Area 24 of Rabbit Cingulate Cortex." *Journal of Neurophysiology* 68: 1720–1732.

Tölle, T. R., T. Kaufmann, T. Siessmeier, S. Lautenbacher, A. Berthele, F. Munz, W. Zieglgansberger, F. Willoch, M. Schwaiger, B. Conrad, and P. Bartenstein. 1999. "Region-Specific Encoding of Sensory and Affective Components of Pain in the Human Brain: A Positron Emission Tomography Correlation Analysis." *Annals of Neurology* 45: 40–47.

Vierck, C. J., A. Acosta-Rua, R. Nelligan, N. Tester, and A. Mauderli. 2002. "Low Dose Systemic Morphine Attenuates Operant Escape but Facilitates Innate Reflex Responses to Thermal Stimulation." *Journal of Pain* 3: 309–319.

Walters, E. T. 1996. "Comparative and Evolutionary Aspects of Nociceptor Function." Pp. 92–114, in *Neurobiology of Nociceptors*, ed. C. Belmonte and Cervero, F. New York: Oxford University Press.

Wong, E. T., S. Gunes, E. Gaughan, R. B. Patt, L. E. Ginsberg, S. J. Hassenbuch, and R. Payne. 1997. "Palliation of Intractable Cancer Pain by MRI-Guided Cingulotomy." *Clinical Journal of Pain* 13: 260–263.

Yeomans, D. C., B. Y. Cooper, and C. J. Vierck. 1995. "Comparisons of Dose-Dependent Effects of Systemic Morphine on Flexion Reflex Components and Operant Avoidance Responses of Awake Non-Human Primates." *Brain Research* 670: 297–302.