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The Neurobehavioral Nature of Fishes and the Question of Awareness and Pain

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ABSTRACT: This review examines the neurobehavioral nature of fishes and addresses the question of whether fishes are capable of experiencing pain and suffering. The detrimental effects of anthropomorphic thinking and the importance of an evolutionary perspective for understanding the neurobehavioral differences between fishes and humans are discussed. The differences in central nervous system structure that underlie basic neurobehavioral differences between fishes and humans are described. The literature on the neural basis of consciousness and of pain is reviewed, showing that: (1) behavioral responses to noxious stimuli are separate from the psychological experience of pain, (2) awareness of pain in humans depends on functions of specific regions of cerebral cortex, and (3) fishes lack these essential brain regions or any functional equivalent, making it untenable that they can experience pain. Because the experience of fear, similar to pain, depends on cerebral cortical structures that are absent from fish brains, it is concluded that awareness of fear is impossible for fishes. Although it is implausible that fishes can experience pain or emotions, they display robust, nonconscious, neuroendocrine, and physiological stress responses to noxious stimuli. Thus, avoidance of potentially injurious stress responses is an important issue in considerations about the welfare of fishes.

KEY WORDS: pain, nociception, stress, awareness, anthropomorphism.

I. INTRODUCTION

In recent years, commercial and sport fishing have been challenged increasingly on grounds of humaneness. These challenges have appeared in the research literature (Verheijen and Flight, 1997) and in the arena of public opinion (American Fisheries Society Position Statement, 1999). A principal underlying assumption of the scientific and nonscientific challenges is that fishes are capable of suffering from pain in a manner similar to that experienced by humans (Bateson, 1992; Gregory, 1999; Verheijen and Flight, 1997). A similar assumption is evident in federal regulations pertaining to the use of fishes in research, in that these regulations apply to all live vertebrate animals (National Institutes of Health, 1985; National Research Council,

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1996). An examination of the validity of this assumption from a scientific perspective is clearly needed.

Advances in neuroscience research during recent decades have greatly improved our understanding of the neurological basis of pain as well as the neurobiological nature of fishes. The objective of this article is to utilize this knowledge to examine the neurobehavioral nature of fishes and to specifically address the question of whether fishes are capable of experiencing pain and suffering. In order to achieve this objective, the article addresses the following issues and concepts:

1. Anthropomorphic thinking undermines our understanding of other species.
2. An evolutionary perspective is essential to understanding the neurobehavioral differences between fishes and humans.
3. Neurobehavioral differences between fishes and humans result from known differences in central nervous system structure.
4. Behavioral responses to noxious stimuli are separate from the psychological experience of pain, such that behavioral responses to these stimuli can occur in the absence of pain experience.
5. Awareness of pain in humans depends on specific regions of the cerebral cortex. Fishes lack these brain regions and thus lack the neural requirements necessary for pain experience.
6. Previous assertions that fishes can experience pain will be critiqued.
7. Conscious experience of fear, similar to pain, is a neurological impossibility for fishes.
8. Fishes display robust but nonconscious, neuroendocrine, and physiological stress responses to noxious stimuli. Potentially injurious stress responses, as opposed to pain or emotional distress, are the proper matter of concern in considerations about the welfare of fishes.

II. ANTHROPOCENTRISM HINDERS UNDERSTANDING OF OTHER SPECIES

A critical guiding principle for understanding the nature of vertebrates with differing evolutionary histories such as fishes and mammals is to view them from the perspective of their respective evolutionary paths. The evolutionary radiation of modern fishes unfolded, to a great extent, separately from that of mammals (Long, 1995). Consequently, comparative neuroanatomical studies have revealed that the mammalian brain has many embellishments and expansions that are not present or present only in more elemental form in fishes (Butler and Hodos, 1996; Nieuwenhuys *et al.*, 1998a). These developments of the mammalian, especially the human brain, have engendered neurobehavioral and psychological capacities that are not present in fishes. Thus, human capacities such as language and consciousness with self-awareness have resulted from later, very separate evolutionary development of this uniquely complex and enlarged brain (Deacon, 1992a; 1992bc; Donald, 1991;

Lieberman, 1992; Macphail, 1998; Preuss, 2000; Raichle, 2000). The existence of these complex capacities in humans is not a justification for presuming the existence of similar capacities in species that had very different evolutionary histories leading to very different neurobehavioral adaptations. Recognition of this basic difference in evolutionary histories is essential to a valid understanding of the neurobehavioral differences between ourselves and other vertebrates. This evolutionary perspective is critical because of the widespread anthropomorphic tendency of humans to view other vertebrates as having mental states similar to our own. So, in observing the actions of other organisms where the actions appear to resemble our own, often it is assumed that these non-human organisms have intentions and experiences similar to ours. This human tendency to attribute mental states to others is called "theory of mind" and is probably the basis for our tendency to feel empathy toward other people. Theory of mind is thought to have evolved as a device for increasing our accuracy in predicting the behavior of other humans (Bogdan, 2000; Macphail, 1998). If we anthropomorphically apply the human theory of mind to other organisms, however, we are increasingly likely to be mistaken as the neuropsychological differences between ourselves and another organisms increases. Most scientists familiar with higher nervous system functions would not attribute human mental states and experiences to an earthworm or an ameba. However, the matter is more troublesome when we are observing the behavior of other vertebrates, especially mammals, where we are often inclined to interpret their behavior to represent the occurrence of human-like mental states (Kennedy, 1992). This problem seems especially great in cases where pain-like behavior is involved.

An additional basic problem with anthropomorphism is that the behavior and underlying brain systems of vertebrates are highly diverse and for many species highly distinctive. Consequently, there are many vertebrate neurobehavioral systems and refinements that have no counterpart in humans. Examples would be electroreception and signaling by electric fish or echolocation in bats, dolphins, and some birds. Likewise, many human behaviors and their underlying brain systems are profoundly unique. Human uniqueness is evident in our capacity to learn and create languages spontaneously, our great behavioral diversity, our capability for long-term planning, our creativity, including art, science, and the existence of religious beliefs. The massive expansion of the human cerebral cortex appears to be at the heart of this uniqueness. Given the extreme distinctiveness of humans in so many respects, it is highly inappropriate and misleading to use human nature as the basis for generalizing to other, decidedly different, species. This matter is no different from using the physiological mechanisms underlying respiratory or water/ion-balance functions of fishes as an unqualified basis for inferring the mechanisms for breathing or water/ion balance in mammals.

The quandary of the private nature of personal experience has a practical, empirical solution. This solution lies in one of the most well-established principles of neuroscience: that neurobehavioral function, including sensory perception and psychological experience, are based on specific, identifiable properties of nervous system structure. This principle is most obvious for sensory and motor function. Sensory regions of the cerebral cortex show pronounced species differences in macroscopic and microscopic structure (and associated physiological properties) that are responsible for species differences in sensory function. For example, echolocating bats have highly specialized regions of auditory cortex for processing

echoes received from self-generated vocalizations. Such cortical regions are absent in the brains of mammals without echolocation capability (Suga and Kanwal, 1995). In a similar vein, the motor cortex of humans has an enlarged region devoted to the control of the fingers and thumb. This degree of functional expansion is not present in species having forepaws rather than hands, opposable thumbs, and the associated manual dexterity of humans (Allman, 1999; Kandel *et al.*, 2000). Even though the neurostructural basis for some of the novel human dimensions of nervous system function, such as language or long-term planning, have not been delineated to the same degree as many aspects of sensory and motor function, the basic structural substrates of these capabilities are well known (Kolb and Whishaw, 1995). The important point for the purpose this discussion is that an examination of the nervous system, especially brain structural organization, provides powerful insights into the nature of an organism, including its capabilities and limits.

III. THE FUNCTIONAL PLANS AND CAPABILITIES OF NERVOUS SYSTEMS ARE BEST UNDERSTOOD FROM THE PERSPECTIVE OF THEIR EVOLUTIONARY DEVELOPMENT

The vertebrate nervous system evolved interdependently with the vertebrate body plan. Throughout this process, certain features of the vertebrate nervous system have been perpetuated, although the evolutionary process has mainly resulted in progressively more complex brains. Some of the most profound evolutionary changes in early vertebrates, such as the acquisition of jaws, appear rather simple on the surface. However, such evolutionary changes necessitated corresponding neural adaptations that led to far-ranging neurobehavioral diversification in foods and feeding styles that allowed exploitation of more diverse physical environments (Allman, 1999; Long, 1995; Radinsky, 1987). As organisms made the transition from a purely aquatic existence to a terrestrial one, new neurological and behavioral adaptations allowed exploitation of different modes of life. There have been many major additions and refinements, especially in the mammalian central nervous system, in response to natural selection for niches very different from those occupied by fishes. Examples are special adaptations for controlling the limbs for terrestrial locomotion and grasping, the function of body hair as a tactile sensory system, neuroendocrine adaptations for lactation and autonomic nervous system control of sweat glands for thermoregulation. The great demands of mammalian endothermy were supported by the evolution of the energy-conserving, forebrain-controlled, quiet sleep state, which occurs in its most well-developed and highly differentiated form in mammals (Karmanova, 1982; Nicolau *et al.*, 2000). Thus, there have been changes in neural and behavioral complexity during vertebrate evolution in which the nervous system, with its stable genetic foundation has undergone great modification, elaboration, and diversification.

The presence of an obvious neural structure-function association between differing modes of vertebrate existence has a corollary principle: common functional problems tend to have common solutions, whereas special functional problems tend to have more specialized, neurostructurally conspicuous solutions. For example, the

neural control of breathing is mediated by evoutionarily conserved neural systems in the lower brainstem of all vertebrates, in spite of the differences in the of manner of breathing that exists between fishes, mammals, and other vertebrates (Wullimann, 1998; Kandel *et al.*, 2000). Similarly, the neural systems controlling locomotor movements are present in the spinal cords of fishes and mammals, alike, in spite of the great differences in the specifics and complexity of locomotion in these taxa (Grillner *et al.*, 1998; Kandel *et al.*, 2000; Rose *et al.*, 2000). In the case of brainstem structure, there is a stable genetic foundation, exemplified by hox genes (Allman, 1999; Kandel *et al.*, 2000), that has fostered the evolutionary solution of common problems by progressive modification of conserved, preexisting neural mechanisms. In contrast, a novel functional capability of a species or related group of species typically has a neurostructural solution that is not shared with other species. This is seen in the mammary glands of mammals, where the milk letdown reflex is controlled by a specialized sensory, neuroendocrine, neuromuscular, and glandular system that is not present in non-mammals even though it is derived from characteristics, such as the neurohypophyseal hormone oxytocin, that had a precursor in the brains of ancestral vertebrates (Moore, 1992).

IV. THE CAPACITY FOR CONSCIOUSNESS DEPENDS ON FUNCTIONS OF THE NEOCORTEX, A BRAIN STRUCTURE UNIQUE TO MAMMALS

The question of whether non-human animals, particularly fishes, are consciously aware of experiences is an issue central to this review, for the simple reason that consciousness is a prerequisite to the experience of pain and its distressing emotional aspect. Without consciousness, there is no awareness of pain, which is why anesthetics are used to prevent pain during surgery. It is of interest to note that anesthetic dosages that obtund awareness of pain do not necessarily prevent motor reactions to surgery, a reason that myoneural blocking agents are used as adjuncts to anesthetics (Taylor, 1990). These points, that pain experience depends on conscious awareness and that awareness of pain and bodily responses to injury are separate phenomena, are pursued at greater length subsequently.

An answer to the question of consciousness in non-humans can be found in the differences in brain structure across species. Although vertebrates have a common mode of nervous system organization, there are great differences across vertebrate taxa in the structure and complexity of the brain (Butler and Hodos, 1996; Nieuwenhuys *et al.*, 1998a). A principal difference between mammalian brains and those of other vertebrates is the expansion and complexity of the mammalian cerebral hemispheres (Nieuwenhuys *et al.*, 1998a; Preuss, 2000; van Dongen, 1998). Cerebral hemisphere size and complexity has reached its greatest extreme in mammals, with the development of neocortex, a six-layered type of cortex present only in mammals (Allman, 1999; Preuss, 2000; Voogd *et al.*, 1998). Even among mammals there is a wide range of cerebral hemisphere development, with primates tending to have substantially more neocortex relative to their body size than most other mammals (van Dongen, 1998; Voogd *et al.*, 1998). Humans have the greatest degree of cerebral hemisphere development in two major respects: relatively more total neocortex for our body weight and more differentiation

of neocortex structural subtypes (Mountcastle, 1998; Preuss, 2000). The latter fact is especially evident in the large, specialized cortical regions that mediate our distinctive, species-specific capacities for language, long-term planning, and abstract thinking (Donald, 1991; Kolb and Whishaw, 1995; Preuss, 2000).

Extensive evidence demonstrates that our capacity for conscious awareness of our experiences and of our own existence depends on the functions of this expansive, specialized neocortex. This evidence has come from diverse sources such as clinical neuropsychology (Kolb and Whishaw, 1995), neurology (Young *et al.*, 1998; Laureys *et al.*, 1999, 2000a-c), neurosurgery (Kihlstrom *et al.*, 1999), functional brain imaging (Dolan, 2000; Laureys *et al.*, 1999, 2000a-c), electrophysiology (Libet, 1999) and cognitive neuroscience (Güzeldere *et al.*, 2000; Merikle and Daneman, 2000; Preuss, 2000). A strong case has been made that it is mainly those cortical regions that have achieved such massive expansion in humans that are most centrally involved in the production of consciousness (Edelman and Tononi, 2000; Laureys *et al.*, 1999, 2000a-c).

Although consciousness has multiple dimensions and diverse definitions, use of the term here refers to two principal manifestations of consciousness that exist in humans (Damasio, 1999; Edelman and Tononi, 2000; Macphail, 1998): (1) "primary consciousness" (also known as "core consciousness" or "feeling consciousness") and (2) "higher-order consciousness" (also called "extended consciousness" or "self-awareness"). Primary consciousness refers to the moment-to-moment awareness of sensory experiences and some internal states, such as emotions. Higher-order consciousness includes awareness of one's self as an entity that exists separately from other entities; it has an autobiographical dimension, including a memory of past life events; an awareness of facts, such as one's language vocabulary; and a capacity for planning and anticipation of the future. Most discussions about the possible existence of conscious awareness in non-human mammals have been concerned with primary consciousness, although strongly divided opinions and debate exist regarding the presence of self-awareness in great apes (Macphail, 1998). The evidence that the neocortex is critical for conscious awareness applies to both types of consciousness. Evidence showing that neocortex is the foundation for consciousness also has led to an equally important conclusion: that we are unaware of the perpetual neural activity that is confined to subcortical regions of the central nervous system, including cerebral regions beneath the neocortex as well as the brainstem and spinal cord (Dolan, 2000; Güzeldere *et al.*, 2000; Jouvet, 1969; Kihlstrom *et al.*, 1999; Treede *et al.*, 1999).

Although consciousness has been notoriously difficult to define, it is quite possible to identify its presence or absence by objective indicators. This is particularly true for the indicators of consciousness assessed in clinical neurology, a point of special importance because clinical neurology has been a major source of information concerning the neural bases of consciousness. From the clinical perspective, primary consciousness is defined by: (1) sustained awareness of the environment in a way that is appropriate and meaningful, (2) ability to immediately follow commands to perform novel actions, and (3) exhibiting verbal or nonverbal communication indicating awareness of the ongoing interaction (Collins, 1997; Young *et al.*, 1998). Thus, reflexive or other stereotyped responses to sensory stimuli are excluded by this definition. Primary consciousness appears to depend greatly on the functional integrity of several cortical regions of the cerebral hemispheres especially the "association areas" of the frontal, temporal, and parietal lobes (Laureys *et al.*, 1999, 2000a-c). Primary consciousness also

requires the operation of subcortical support systems such as the brainstem reticular formation and the thalamus that enable a working condition of the cortex. However, in the absence of cortical operations, activity limited to these subcortical systems cannot generate consciousness (Kandel *et al.,* 2000; Laureys *et al*., 1999, 2000a; Young *et al.,* 1998). Wakefulness is not evidence of consciousness because it can exist in situations where consciousness is absent (Laureys *et al*., 2000a-c). Dysfunction of the more lateral or posterior cortical regions does not eliminate primary consciousness unless this dysfunction is very anatomically extensive (Young *et al.,* 1998).

Higher-order consciousness depends on the concurrent presence of primary consciousness and its cortical substrate, but the additional complexities of this consciousness require functioning of additional cortical regions. For example, long-term, insightful planning of behavior requires broad regions of the "prefrontal" cortex. Likewise, awareness of one's own bodily integrity requires activity of extensive regions of parietal lobe cortex (Kolb and Whishaw, 1995). In general, higher-order consciousness appears to depend on fairly broad integrity of the neocortex. Widespread degenerative changes in neocortex such as those accompanying Alzheimer's disease, or multiple infarcts due to repeated strokes, can cause a loss of higher-order consciousness and result in dementia, while the basic functions of primary consciousness remain (Kandel *et al*., 2000; Kolb and Whishaw, 1995).

The reasons why neocortex is critical for consciousness have not been resolved fully, but the matter is under active investigation. It is becoming clear that the existence of consciousness requires widely distributed brain activity that is simultaneously diverse, temporally coordinated, and of high informational complexity (Edelman and Tononi, 1999; Iacoboni, 2000; Koch and Crick, 1999; 2000; Libet, 1999). Human neocortex satisfies these functional criteria because of its unique structural features: (1) exceptionally high interconnectivity within the neocortex and between the cortex and thalamus and (2) enough mass and local functional diversification to permit regionally specialized, differentiated activity patterns (Edelman and Tononi, 1999). These structural and functional features are not present in subcortical regions of the brain, which is probably the main reason that activity confined to subcortical brain systems can't support consciousness. Diverse, converging lines of evidence have shown that consciousness is a product of an activated state in a broad, distributed expanse of neocortex. Most critical are regions of "association" or homotypical cortex (Laureys *et al*., 1999, 2000a-c; Mountcastle, 1998), which are not specialized for sensory or motor function and which comprise the vast majority of human neocortex. In fact, activity confined to regions of sensory (heterotypical) cortex is inadequate for consciousness (Koch and Crick, 2000; Lamme and Roelfsema, 2000; Laureys *et al*., 2000a,b; Libet, 1997; Rees *et al*., 2000).

V. FISHES HAVE A NEUROBEHAVIORAL NATURE, DIFFERENT IN MANY WAYS FROM MAMMALS, THAT IS CLOSELY TIED TO PHYLOGENETIC DEVELOPMENT OF THEIR CENTRAL NERVOUS SYSTEMS

Fishes are the most ancient type of vertebrate for which fossil evidence is available, dating from the jawless ostracoderms about 500 million years ago (Radinsky, 1987;

Long, 1995). Jawed fishes appear in the fossil record more than 400 million years ago. The brain development of the early ostracoderms was extremely simple (Janvier, 1993), resembling that found in modern jawless fishes such as lampreys and hagfish. Nonetheless, the basic pattern of vertebrate brain organization was evident in ostracoderms, which were probably capable of only a very limited behavioral repertoire. Subsequently, fishes have developed into the most diverse vertebrate radiation, comprising more than 25,000 extant species of jawless, cartilaginous, and bony taxa, presenting extreme variety in anatomical, physiological, and behavioral adaptations (Helfman *et al.*, 1997). It is critical to recognize that the vertebrate line that gave rise to mammals diverged from the line that led to extant fishes in the Devonian era, roughly 400 million years ago. The first mammals did not appear until the Triassic, about 200 million years later. Especially important is the fact that teleosts, the most numerous of modern fishes, did not emerge until the Jurassic, long after the advent of mammals. This point further emphasizes the evolutionary separateness of fishes and mammals.

The complexity of fish behavior and associated sensory and motor function varies greatly, with agnathans such as lampreys having more rudimentary or restricted capacities and teleosts being more advanced, with corresponding neural specializations. References pertaining to the following description of behavior can be found in reviews by Davis and Northcutt (1983), Evans (1998), Helfman *et al.* (1997) and Nieuwenhuys *et al.* (1998a).

Sensory capacities of fishes show wide differences in degree of development. Some species, such as salmonids, have color vision and high acuity, whereas benthic species are typically more limited in their response to photic stimuli due to adaptations for life under low light of more limited spectral properties. Chemosensory properties show extreme variations (Sorensen and Caprio, 1998). Some species, such as silurid catfish, have taste receptors across their entire body surface rather than just the oral cavity. Likewise, the structure and function of the olfactory system shows great diversity across species. Feeding behavior is extremely diverse and specialized in the sensory modalities used to locate food and in the oral motor specializations employed in food capture or ingestion. Some of the most distinctive sensorimotor specialists are gymnotid and mormyrid teleosts, electric fish that generate and detect pulsed electrical currents to communicate with their conspecifics and to locate objects in their environment. Reproductive behavior is highly diverse. Most species display little or no parental care, whereas some exhibit active protection of young, as in mouth brooding cichlids or defense of nest sites by male fathead minnows. Social displays in mating can entail elaborate courtship and in some cases, as in sex-changing wrasses, a bisexual behavioral capability.

Fishes are clearly capable of associative learning, that is learning a relationship between sensory stimuli or between a stimulus and a behavioral response. Examples of these types of learning in fish include Pavlovian conditioning of visceral responses such as heart rate and respiration, migration guided by olfactory imprinting, and approach or avoidance conditioning. Although most behavior of fishes is not dependent greatly on learning, it is clear that learning and experience are often necessary for the complete development of species-typical behaviors. A critical point concerning the associative learning shown by fishes is that this form of learning, also known as implicit learning, is a virtually universal capability of vertebrate and invertebrate animals, including those lacking brains (Macphail, 1998). Furthermore,

implicit learning occurs without conscious awareness, even in humans (Kolb and Whishaw, 1995; Macphail, 1998), so the presence of this type of learning in fishes does not constitute a capacity for awareness.

Unlike the subsequent course of mammalian emergence, the evolution of fishes placed them in a niche where neurobehavioral processes that could be mediated by a brain comprised mainly of brainstem structures and relatively small cerebral hemispheres was adequate for their fitness needs. Fishes, being a highly diverse taxon, have extreme variations in brain structure, especially at the brainstem level (Nieuwenhuys *et al.*, 1998b; Butler and Hodos, 1996). It is important to emphasize that fish brains can have highly complex, unique adaptations due to their diverse evolutionary paths. Consequently, these brains are not merely simpler versions of mammalian (or amphibian or reptilian) brains (Nieuwenhuys *et al.*, 1998b; Butler and Hodos, 1996; Wulliman, 1998).

In spite of the diversity and complexity among species, the behaviors of fishes are nonetheless highly stereotyped and invariant for a given species. Such stereotyped species-typical behaviors, however, are not simple or merely reflexive. Species-typical behaviors in vertebrates are known to be controlled by motor patterning mechanisms that are far more complex than reflexes (Ewert, 1987; Fentress, 1987). The basic behaviors involved in reproduction, feeding and drinking, escape or defense, and reactions to noxious stimuli, are controlled by motor patterning mechanisms that are located mainly in the brainstem and spinal cord of mammals (Berntson and Micco, 1976; Rose, 1990) and nonmammalian vertebrates alike (Ewert, 1987; Rose, 2000).

In fishes, the degree to which most aspects of neurobehavioral function are controlled by the brainstem and spinal cord is extreme, as shown by experiments in which the cerebral hemispheres have been removed from diverse species of fishes, leaving only the brainstem and spinal cord intact (Overmier and Hollis, 1983). The behavior of these fishes is strikingly preserved. They still find and consume food, show basic capabilities for sensory discrimination (except for the loss of the sense of smell, which is processed entirely in the forebrain) and many aspects of social behavior, including schooling, spawning, and intraspecies aggression. Although there are some species differences, courtship, nest building, and parental care often persist after forebrain removal. Most of the forms of learning of which fishes are capable are intact in the absence of the forebrain, although avoidance learning seems to be much more difficult for fish with the cerebral hemispheres removed (Overmier and Papini, 1986). This difficulty with avoidance learning is not due to reduced responsiveness to noxious stimuli because the reflexive and locomotor, including escape, responses to such stimuli by fish without cerebral hemispheres appear to be quite normal. The general conclusion that emerges from many studies is that the basic patterns of fish behavior are controlled by lower brain structures, mainly the brainstem and spinal cord. The cerebral hemispheres serve mainly to "modulate" behavior, that is, to regulate its intensity or frequency and to refine its expression (Overmier and Hollis, 1983). Thus, the neurobehavioral evolution of fishes has resulted in a highly diversified array of species in which the essentials of neurobehavioral function are mediated mainly by neural systems below the cerebral hemispheres.

Two other lines of evidence demonstrate that the brainstem rather than the forebrain is the dominant level of processing and neurobehavioral control. First, the

cerebral hemispheres of fishes tend to be smaller, in comparison with the brainstem, than in mammals (Nieuwenhuys *et al.,* 1998a). This is important because size of a brain region is typically related to its functional significance. Second, extreme behavioral specialization in fishes is associated with expanded brainstem as opposed to cerebral hemisphere development (Figure 1). For example, electric rays have an enormously developed electromotor lobe on the dorsal medulla. Neurons in this lobe innervate the electric organ in the pectoral disc, which the rays use for defense as well as for stunning prey. In some rays, this lobe alone comprises 60% of the total brain weight (Nieuwenhuys *et al.*, 1998b). Similarly, chemosensory behavioral specialization is associated with large lobes on the dorsal medulla that process sensory input from taste receptors (Nieuwenhuys *et al.*, 1998a; Sorensen and Caprio, 1998). The cerebral levels of this sensory pathway for taste are much smaller than the brainstem level, constituting what is known as a diminishing system (Nieuwenhuys *et al.*, 1998b). In contrast to these extremely specialized fish species, are many species regarded as more generalized, such as hexanchiform sharks and dipnoans, which have slender, elongated brainstems, without any enlarged subsystems (Nieuwenhuys *et al.*, 1998a). In comparison with the prominence of the brainstem, the cerebral hemispheres of fishes are comparatively small, even diminutive, especially if the purely olfactory regions of the cerebrum are excluded (Figure 1). There are, however, rather great variations between the agnathans, chondrichthyans, and osteichthyans in the degree of cerebral hemisphere development, with relative size and differentiation of the cerebrum tending to increase somewhat across these three groups, respectively (Nieuwenhuys *et al.*, 1998a).

VI. THE MAMMALIAN RADIATION IS ASSOCIATED WITH CEREBRAL HEMISPHERE EXPANSION AND GREATER CEREBRAL HEMISPHERE DOMINANCE OVER NEUROBEHAVIORAL FUNCTION

Mammalian evolution, similar to that of fishes, has exhibited increasing diversification and complexity. Unlike the brainstem-based specializations in fishes, however, behaviorally specialized mammals have conspicuously developed cortical regions. Neural systems that are enlarged at the cerebral hemisphere level, such as the complex visual cortex of the owl monkey (Allman, 1999), are known as expanding systems and are characteristic of mammals (Nieuwenhuys *et al.*, 1998b). Of particular significance in mammals is the development of a unique, six-layered type of cerebral cortex called neocortex. The development and expansion of this cortex has embellished sensory processing and motor control greatly. In addition, as discussed earlier, the massively expanded neocortex in humans appears to be the foundation of our consciousness.

Mammals, similar to fishes, are highly diversified. They include specialists as well as generalists, with considerable neurological diversity at the level of the cerebral hemispheres. Humans represent an extreme case of cerebral hemisphere and neocortical expansion. The volume of the human cerebral cortex is 3.2 times larger than that of a chimpanzee of similar body weight, whereas the size of the lower brainstem is nearly the same in the two species (Deacon, 1992a; Kolb and

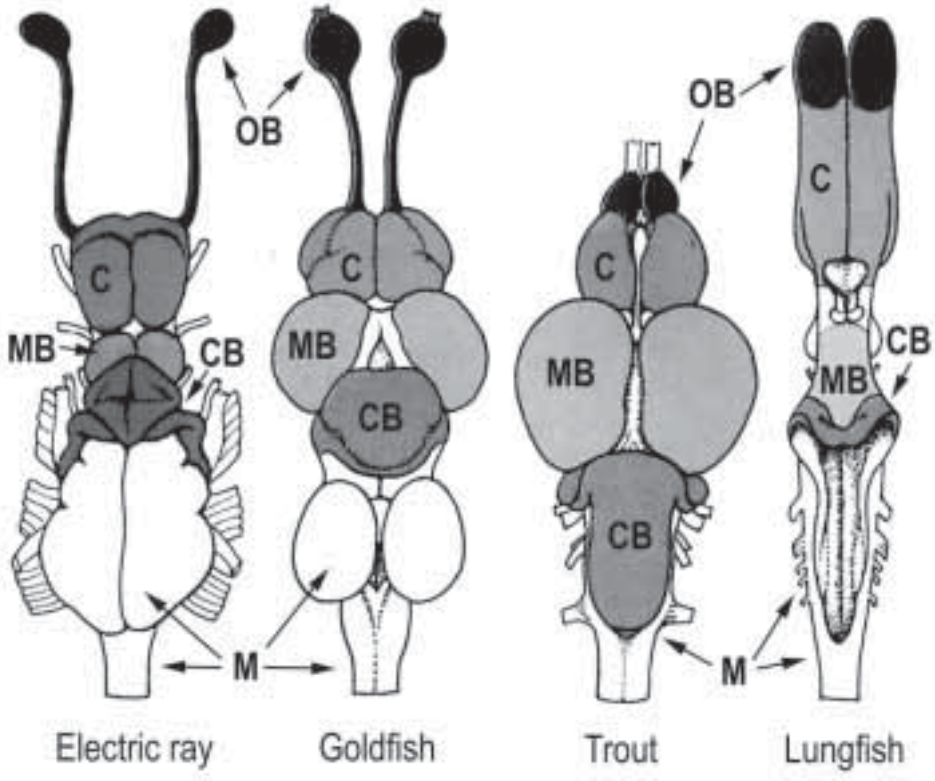

FIGURE 1. Comparison of brain structure in four fish species. These dorsal views show the basic similarity of brain structural organization in diverse types of fishes, yet certain striking differences related to function are clearly apparent. Structural specializations are most pronounced in the brainstem, which consists of the medulla, cerebellum and midbrain. The electric ray (*Raja clavata*) has a large electromotor nucleus on the dorsal surface of the medulla (shown by the upper arrow pointing to the medulla). The goldfish (*Carassius auratus*) has a large vagal lobe (upper arrow pointing to the medulla) due to its extensively developed chemosensory system for taste. The rainbow trout (*Oncorhynchus mykiss*) has a relatively large optic tectum of the midbrain due to its visual specialization. The South American lungfish (*Neoceradotus forsteri*), regarded as an unspecialized species, has a slender brain lacking structural exaggerations. Redrawn from Nieuwenhuys *et al.,* 1998a. Abbreviations: C — cerebral hemisphere; CB — cerebellum; M — medulla; MB — midbrain (the optic tectum is the only midbrain structure visible in this dorsal view); OB — olfactory bulb.

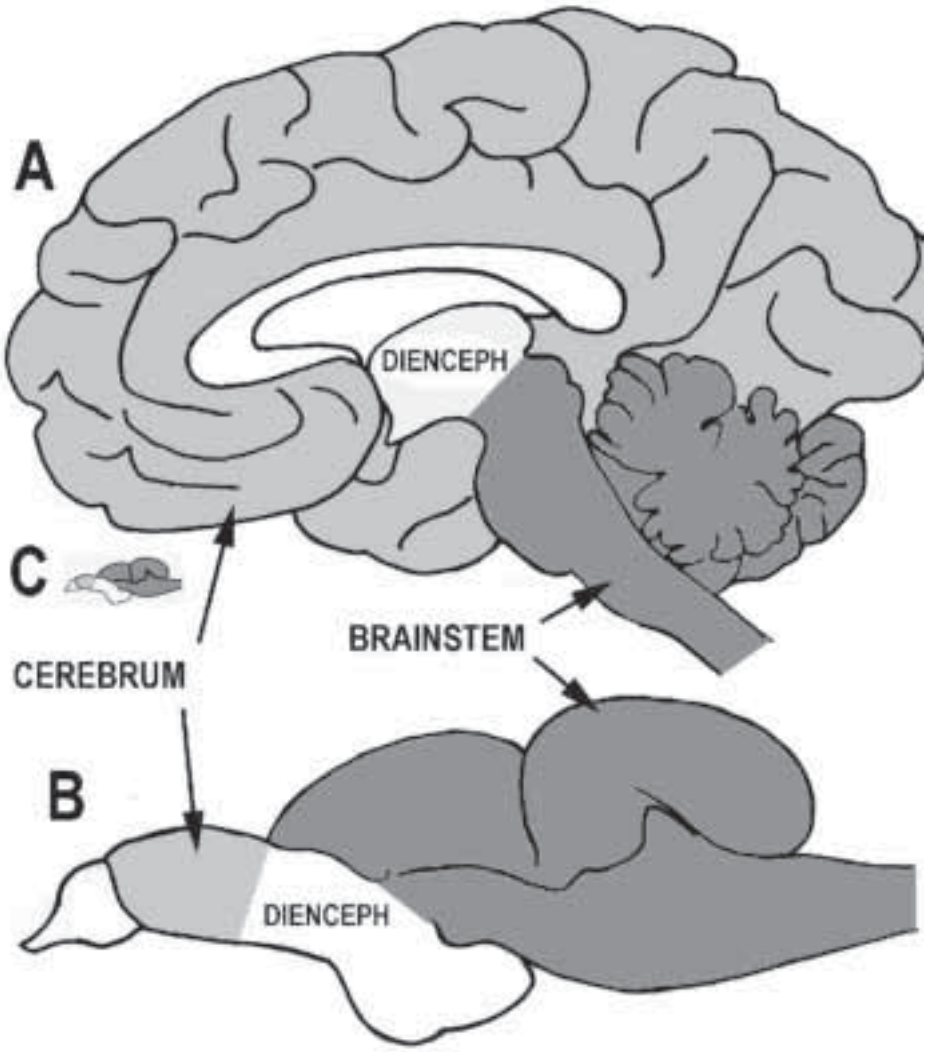

FIGURE 2. Comparison of human brain with a trout brain. (A) Diagram of a midline view of a human brain. The cerebral hemisphere, comprised mostly of neocortex, is light gray and the brainstem is dark gray. The diencephalon (DIENCEPH) consists of the thalamus (dorsal half), which is connected with the cortex of the cerebral hemispheres and the hypothalamus (ventral half), which is connected mainly to subcortical structures. (B) Diagram of a side view of a rainbow trout brain. The cerebral hemisphere is very small relative to the size of the brainstem. The diencephalon of the trout is mostly hypothalamus. The white structure at the left of the cerebral hemisphere is the olfactory bulb. (C) Brain of a 30-cm rainbow trout shown at the same scale as the human brain diagram.

Whishaw, 1995). This massive neocortical expansion has resulted in several transformations of the human brain that are qualitative rather than just quantitative. These transformations include a large prefrontal cortical region that mediates long-term planning and language-specialized regions of the frontal, temporal, and parietal lobes. The expansion of the cerebral hemispheres has also allowed lateralized functions of the two cerebral hemispheres, such that the left hemisphere has a predominant role in language and the right hemisphere in visual-spatial processing, both of which are manifestations of higher-order consciousness (Kolb and Whishaw, 1995).

The expansion of the cerebral hemispheres in mammals has resulted in a greater dependency on this brain level, especially in humans. Cerebral cortex destruction leaves a human in a persistent vegetative state in which all conscious awareness is abolished (Figure 3). Sleep-wake cycles and reactions to noxious stimuli persist in such cases due to mediation of these processes by lower levels of the central nervous system (Jouvet, 1969; Young *et al.,* 1998). Although many of the more stereotyped behaviors of humans and other mammals are generated by brainstem and spinal systems, these behaviors are still very dependent on support by the cerebral hemispheres for effective functioning (Berntson and Micco, 1976; Grill and Norgren, 1978; Huston and Borbely, 1974). Non-primate mammals are capable of a greater range of functional behavior after the destruction of the cerebral hemispheres. These animals exhibit locomotion, postural orientation, elements of mating behavior, and fully developed behavioral reactions to noxious stimuli (Berntson and Micco, 1976; Rose, 1990; Rose and Flynn, 1993). However, unlike fish with similar brain damage, these behaviors are not really functional and such mammals cannot survive without supportive care, including assisted feeding. Thus, the brainstem-spinal system in mammals contains the neural circuitry for basic, stereotyped behavioral programs, as it does in nonmammalian vertebrates such as fishes, but mammals have greater dependence on the cerebral hemispheres for functionally effective behaviors.

VII. THE SIGNIFICANCE OF NEOCORTICAL EVOLUTION – THE QUESTION OF CONSCIOUS AWARENESS.

As stated previously, the neural substrates necessary for consciousness are becoming more clearly defined. Although consciousness cannot be explained in detail, we know when it is present or absent and we know what parts of the human brain are required to have it. In contrast to the diverse and extensive evidence that consciousness depends on neocortical functioning, some writers, most notably Donald Griffin (1976, 1992), have argued for the existence of conscious awareness in diverse, nonmammalian vertebrates and invertebrates. A major problem with this proposal is that it has been made without consideration of its feasibility. Specifically, the nervous systems of invertebrates not only lack any type of cortex, but they also are organized in fundamentally different ways, usually with far fewer neurons than a mammalian brain. Likewise, the cerebral hemispheres of fishes have a more rudimentary structure that differs substantially from the structure of mammalian neocortex. A simple type of three-layered, "general cortex" is present in the cerebral hemispheres of reptiles, but true neocortex, with its greatly enriched information

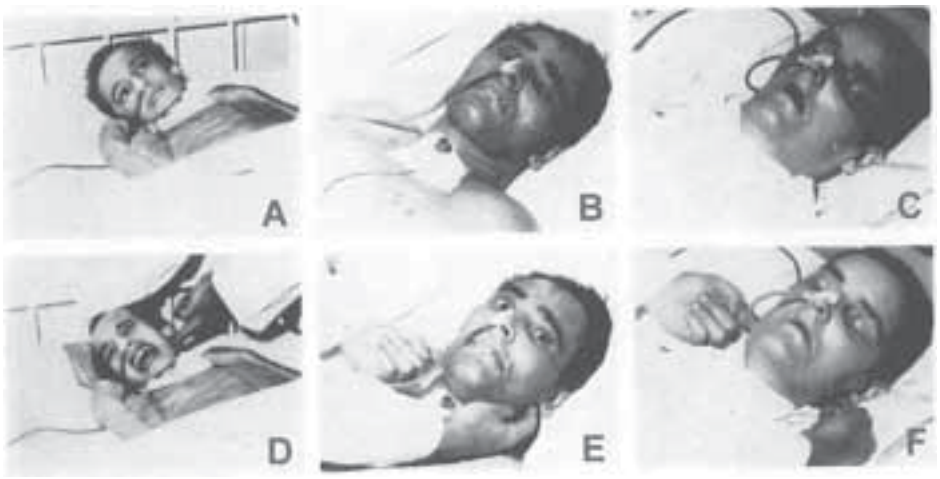

FIGURE 3. Behavioral responses to noxious stimuli in people with decortication syndrome and unconsciousness. A — A decorticate individual with wakefulness but no consciousness. Noxious stimulation consisting of pressure on the mastoid processes of the skull (D) evokes a facial grimace and cry, similar in appearance to those likely to occur in a normal, conscious individual. Such decorticate individuals may also push at the hands of the examiner. B — A decorticate, unconscious individual who is not spontaneously awake but shows waking and a facial display (E) during noxious stimulation. C — An individual with brainstem damage who is unconscious and shows no waking or facial display during noxious stimulation (F). These individuals are still capable of spinally mediated withdrawal responses to noxious stimulation of a limb (Jouvet, 1969). (Reprinted with the author's permission.)

processing capacity is found only in mammals (Nieuwenhuys, 1998a; Northcutt and Kaas, 1995).

Whereas the qualitative differences in cortical structure and function are quite pronounced between reptiles and the simplest mammals, these differences are overshadowed by the large differences in neocortical structure and function found between orders of mammals. The proportion of the mammalian brain that is neocortex varies greatly. Insectivores such as hedgehogs, which are thought to resemble the early mammals, have fairly small amounts of neocortex. Simians have 45.5 times more neocortex for a given body size than primitive insectivores and humans have 145 times more neocortex than the most primitive mammals (Stephan and Andy, 1964). This enlargement of human neocortex is accompanied by greater cortical structural differentiation and functional diversification (Mountcastle, 1998).

The fact that all forms of human consciousness require neocortical functioning leads to two possible conclusions: (1) non-mammals simply cannot have consciousness, even primary consciousness, because they lack the known neural requirement for it, or (2) these organisms are able to generate consciousness by a different neurological process. This issue is examined below in several ways.

Because it is known that neocortex is necessary for consciousness in humans, it might also be assumed that other animals with neocortex, that is all mammals, should have some form of consciousness as well. In practice, there is a wide range of beliefs or working assumptions about this matter among neuroscientists. Macphail (1998) has argued that evidence from behavior warrants the conclusion that non-human mammals cannot have consciousness of any type. In contrast, some neuroscientists routinely use primates to investigate the cortical neural mechanisms

underlying primary consciousness (Edelman and Tononi, 2000; Koch and Crick, 1999, 2000). While many neuroscientists seem to assume the existence of primary consciousness in at least some mammals, particularly primates, extended consciousness is generally considered a uniquely human capacity (Donald, 1991; Edelman and Tononi, 2000).

A critical point in this analysis is the fact that a large part of the activity occurring in our brain is unavailable to our conscious awareness (Dolan, 2000; Edelman and Tononi, 2000; Koch and Crick, 2000; Libet, 1999; Merikel and Daneman, 2000). This is true of some types of cortical activity and is true for all brainstem and spinal cord activity. We are unaware of activity confined to primary sensory cortex (Koch and Crick, 2000; Lamme and Roelfsma, 2000; Laureys *et al.*, 2000c; Libet, 1999; Rees *et al.*, 2000). We also have no conscious contact with the massive numbers of neurons in our cerebellum, despite the fact that these neurons are intensely active, controlling many aspects of movement and posture. Likewise, we are unaware of the activity of neurons in our hypothalamus, whose firing regulates our heart rate, blood pressure, and neuroendocrine function. Thus, for organisms such as fishes, which have no neocortex at all, it seems entirely logical that none of their brain activity could be consciously experienced. Although computer analogies with brain function are often misleading, a simple example may help to communicate this argument. Consciousness functions as a monitor that gives us awareness of some but not all operations that are occurring in our brain. In our consciousness, most of the activity in the spinal cord, brainstem, and some parts of the cortex is not displayed on the monitor of our consciousness, so we are unaware of it despite its effective functioning. In animals without the consciousness monitor provided by the neocortex, brain and spinal cord activity function effectively, as they do in our subcortical systems, without any means for reaching awareness or any need for it, just as programs do in a computer with the monitor off.

VIII. THE NEUROPSYCHOLOGICAL BASIS OF PAIN IN HUMANS

A. PAIN IS A PSYCHOLOGICAL EXPERIENCE THAT IS SEPARATE FROM BEHAVIORAL REACTIONS TO INJURIOUS STIMULI

Extensive empirical research on the human pain experience has provided a definition of pain formulated by the International Association for the Study of Pain (Wall, 1999): (1) pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage; (2) pain is always subjective; (3) pain is sometimes reported in the absence of tissue damage and the definition of pain should avoid tying pain to an external eliciting stimulus. One of the most critical concepts about pain is the distinction between nociception and pain. As Wall (1999) emphasized, nociception, which is "…activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state." The points critical to understanding differences between fishes and humans with respect to pain are that: (1) pain is both a sensory and emotional experience (that requires conscious awareness) and (2) nociception

does not result in pain unless the neural activity associated with it reaches consciousness.

A commonplace experience helps to illustrate the distinction between nociception and pain in humans. When a dentist injects a local anesthetic to block conduction in part of the trigeminal nerve, surgery on a tooth still excites nociceptive receptors that normally trigger pain. However, the nerve block, being administered between the site of surgery and the nerve's connection with the brain, prevents this activity from reaching the brain. Thus, there is no behavioral reaction to the nociceptive stimulus and no pain. Another informative example is that of a spinal injury that transects the cord in a human. A noxious stimulus applied to a limb below the level of the spinal transection excites nociceptive sensory receptors and nociceptive pathways within the spinal cord. This nociceptive activity at the spinal level produces a limb withdrawal response, but because nociceptive pathways are interrupted between the spinal cord and the neocortex, no pain is felt.

B. NOCICEPTIVE REACTIONS IN ANIMALS

The distinction between nociception and pain is critical to the question of whether fishes can experience pain because nociception-based behaviors are commonly confused with the pain experience. The capacity to react to injurious or threatening stimuli is a universal characteristic of animal life. Thus, the presence of reactions to injurious stimuli in unicellular forms that have no nervous systems and in primitive invertebrates that have no brains demonstrates that reactivity to noxious stimulation, per se, can occur in the absence of awareness of such stimuli (Dewsbury and Rethlingshafer, 1973; Bullock *et al.*, 1977). In all vertebrates, including humans, reactions to injurious stimuli are generated by neural systems in the spinal cord and brainstem. Vertebrates generally have more complex nervous systems than invertebrates and, unlike most invertebrates, they have a clearly developed brain. This brain receives information from the spinal cord and cranial nerves about noxious stimuli that contact the body surface and head, respectively. Working together with the spinal cord, the brain generates responses that cause the organism to "escape" or "avoid" these stimuli. These responses are produced by innate neural programs and include withdrawal of the stimulated body part, struggling, locomotion, and in some animals vocalizations. All of these responses are generated by lower levels of the central nervous system: the brainstem and spinal cord. This is known because animals with the cerebral hemispheres removed leaving the brainstem and spinal cord intact are fully capable of exhibiting the typical "pain-like" behavioral reactions to injurious stimuli (Berntson and Micco, 1976). As explained below, this same functional scheme for generation of nociceptive responses applies to humans.

C. A SYNOPSIS OF THE NEUROLOGICAL BASIS OF PAIN IN HUMANS

The following is a brief summary of what is known about the neural basis of pain in humans. Primary literature references for this account are available in a recent review of this subject by Price (1999) and a more comprehensive volume by Wall

and Melzack (1994). The human pain experience, as explained previously, is a psychological process of the brain, separate from the behavioral responses to nociceptive stimuli. It is a complex, multifaceted experience with at least three, intertwined dimensions (Price, 1999; Melzack and Fuchs, 1999): (1) a sensory-informational component that conveys the locus of noxious stimulation, its physical features, and its intensity; (2) an emotional dimension that constitutes the suffering and unpleasantness of the experience; and (3) a cognitive-evaluative component involving attention, previous experience and the perceived threat to the individual. All of these facets of the pain experience are predicated on concurrent consciousness for their existence; an unconscious person would experience none of these aspects of pain.

Noxious stimuli activate sensory receptors called free nerve endings (Figure 4). These receptors consist of two varieties, a type that responds specifically to injurious stimuli (nociceptors) and a type that responds to other somatic stimuli, but especially to intense noxious stimuli with greatest firing rates (polymodal nociceptors). It should be emphasized that it is incorrect to characterize nociceptors as "pain receptors" because activation of these receptors initiates only nociceptive neural activity, which, by itself, is inadequate for producing the psychological experience of pain. Activity is transmitted to the spinal cord from free nerve endings by two types of nerve fibers, small-diameter myelinated axons and small-diameter unmyelinated axons. A similar system exists for nociception involving the face and mouth through the trigeminal nerve and its brainstem connections. The myelinated axons are principally responsible for eliciting "first pain", such as that from a pinprick, which is rapidly experienced, of short duration, well localized and not especially unpleasant. The unmyelinated axons are responsible for eliciting "second pain", which is slowly experienced, poorly localized, long-lasting and very unpleasant. Both types of axons synapse in the dorsal gray matter of the spinal cord, where subsequent processing of their input signals occurs in diverse types of neurons. Spinal cord neurons send axons to the brain, mainly through the ventrolateral spinal tract. This pathway is also called the spinothalamic tract because many of its component axons travel all the way to the thalamus in the brain before synapsing. Of additional importance, however, is a complex network of neurons in the reticular formation of the brainstem that also receives connections from the spinothalamic tract. This reticular network processes nociceptive information and transmits it to diverse subcortical brain structures, including parts of the thalamus. In addition, this brainstem reticular network generates innate behavioral responses to nociceptive stimuli. Our fundamental behavioral reactions to noxious stimuli, including vocalization, facial grimacing, and withdrawal, are mediated by subcortical brain and spinal systems (Jouvet, 1969; Kandel *et al.*, 2000; Laureys *et al.*, 1999, 2000a,b; Young *et al.,* 1998). Activation of these responses by noxious stimuli can occur without consciousness in people with extensive cortical damage (Figure 3) and in humans born without cerebral hemispheres (Kolb and Whishaw, 1996; Steiner, 1987). Thus, the behavioral displays related to noxious stimuli or emotion in humans, as in other animals, are stereotyped, automatic behavioral programs controlled by lower levels of the central nervous system, and these responses can be evoked without any corresponding awareness of noxious stimuli. Limb withdrawal and leg locomotor responses, of course, are produced directly at the spinal cord level.

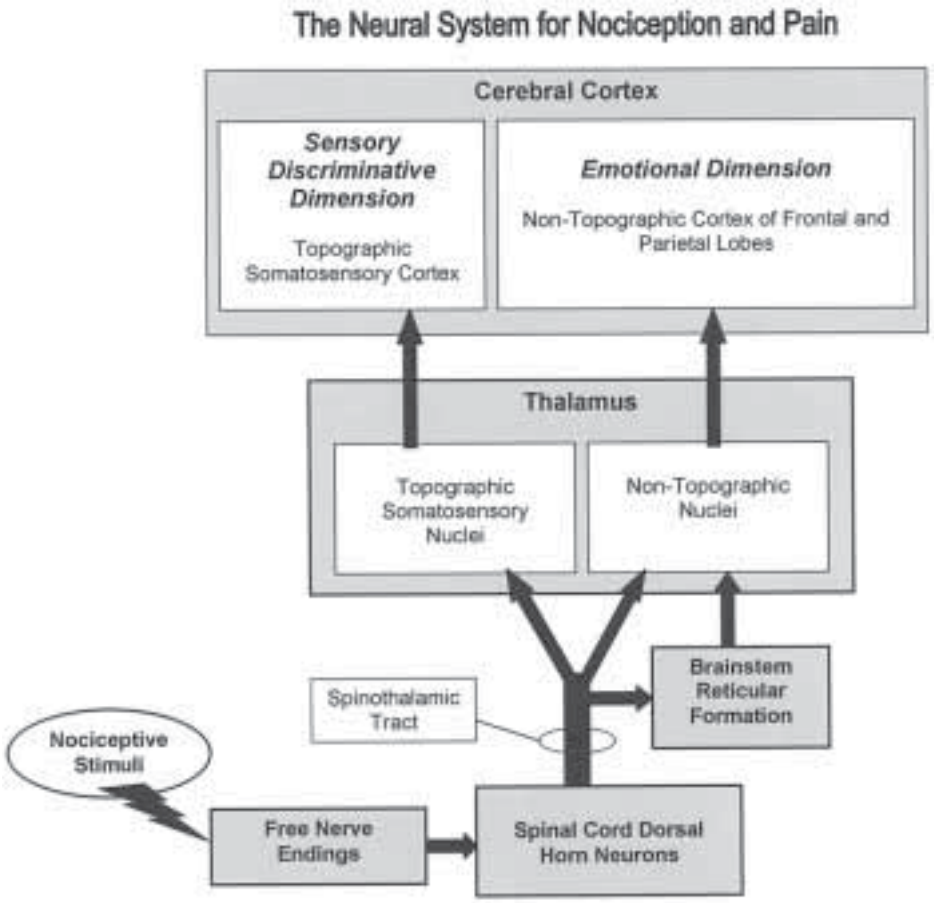

FIGURE 4. The ascending neural system for nociception and pain in humans. Nociceptive stimuli activate free nerve endings in body tissues. This activity is conducted the dorsal spinal gray matter (dorsal horn) through small-diameter unmyelinated and small-diameter myelinated nerve fibers. Spinal neurons project to the brain, through the spinothalamic tract, to two somewhat separate systems. One system encodes locations of stimuli on the body (topographic organization) and provides a sensory-discriminative dimension to pain at the somatic sensory cortical level. In this system, the spinothalamic tract connects directly to topographic somatosensory nuclei of the thalamus, which project to the topographic, primary somatosensory cortex. Another system receives projections from the spinothalamic tract at two levels, one division going directly to non-topographic nuclei in the thalamus and another connecting with neurons of the brainstem reticular formation. Some of the latter neurons project to nontopographic thalamic nuclei. Nociception-related activity from the nontopographic thalamic nuclei is projected to diverse nontopographic regions of the cortex, principally in the frontal lobes. Activity in these cortical regions is responsible for the emotional unpleasantness (suffering) dimension of pain. For greater clarity, the descending components that regulate ascending nociceptive activity have not been included in this diagram. (See the text for additional explanation.)

The direct spinothalamic tract terminates, in large measure, in a somatotopically organized region of the thalamus that processes diverse types of body sense information and projects to the primary somatic sensory cortex. This primary cortex also is organized somatotopically for analyzing locations of body stimuli. A separate part of the spinothalamic tract, as well as nociceptive signals transmitted through the brainstem reticular network, converge on nontopographically organized nuclei of the thalamus. These thalamic nuclei project to multiple cortical regions, mainly in the frontal and parietal lobes. Thus, there are two major routes through which nociceptive activity reaches the cortex: one that preserves spatial information about the stimulus and another that influences a much wider cortical territory, but does not encode spatial information.

Several caveats are required in this highly simplified presentation. First, the multiple ascending nociceptive pathways that generate pain experience at the cortical level work in concert. Consequently, there is no specific structure that can be designated a "pain pathway", "pain nucleus" or "cortical pain zone". Second, there is a "gate control" system in the dorsal gray matter of the spinal cord that actively suppresses the transmission of nociceptive activity to the brain. In addition, there is a system descending from the brainstem that contains opioid neuropeptides and suppresses the upward flow of nociceptive activity. Thus, there are spinal and brainstem systems that can powerfully attenuate the transmission of nociceptive information to the higher levels of the brain, and, ultimately, the cortical level of pain perception.

Probably the greatest advance in our knowledge about pain in recent years is understanding the role of the cortex. This information is of particular importance to a consideration of whether fishes can experience pain. A variety of evidence shows that diverse frontal and parietal lobe cortical regions are involved in generating the conscious experience of pain (Figure 5). The sensory properties of nociceptive stimuli, including location, stimulus characteristics (burning, crushing, piercing) and spatial extent, are signaled by activity in the somatotopically organized somatosensory cortex area of the parietal lobe. In contrast, pain intensity is signaled by activity in more widespread areas of the frontal and parietal lobes, involving all of the regions that are implicated in cortical processing of pain. The emotional unpleasantness of pain is processed predominantly by frontal lobe cortex, including the anterior cingulate gyrus, the insula, and prefrontal cortex. In brain imaging studies based on magnetic resonance imaging and positron emission tomography, the former two structures have shown activity specifically associated with the perceived unpleasantness of pain (Coghill and Duncan, 1999; Ploghaus *et al.*, 1999; Rainville *et al.*, 1997; Xu *et al.*, 1997). The anterior cingulate gyrus is thought to be especially important for processing the emotional unpleasantness of pain. It is a unique type of five-layered cortex, known as mesocortex, nearly identical in structure with neocortex and specific to mammals, but also having unique structural features in great apes and humans (Nimchinsky *et al.*, 1997). For simplification of this discussion, cingulate cortex will be included in references to neocortex.

Independent confirmation of the importance of frontal lobe structures for the perception of the unpleasantness of pain comes from a long history of neurosurgical procedures. Many people have undergone a destruction of a portion of the anterior cingulate gyrus to alleviate severe, chronic pain (Bouckoms, 1994; Cosgrove and Rausch, 1998; Tasker, 1994). Persons receiving such surgery report that the pain is

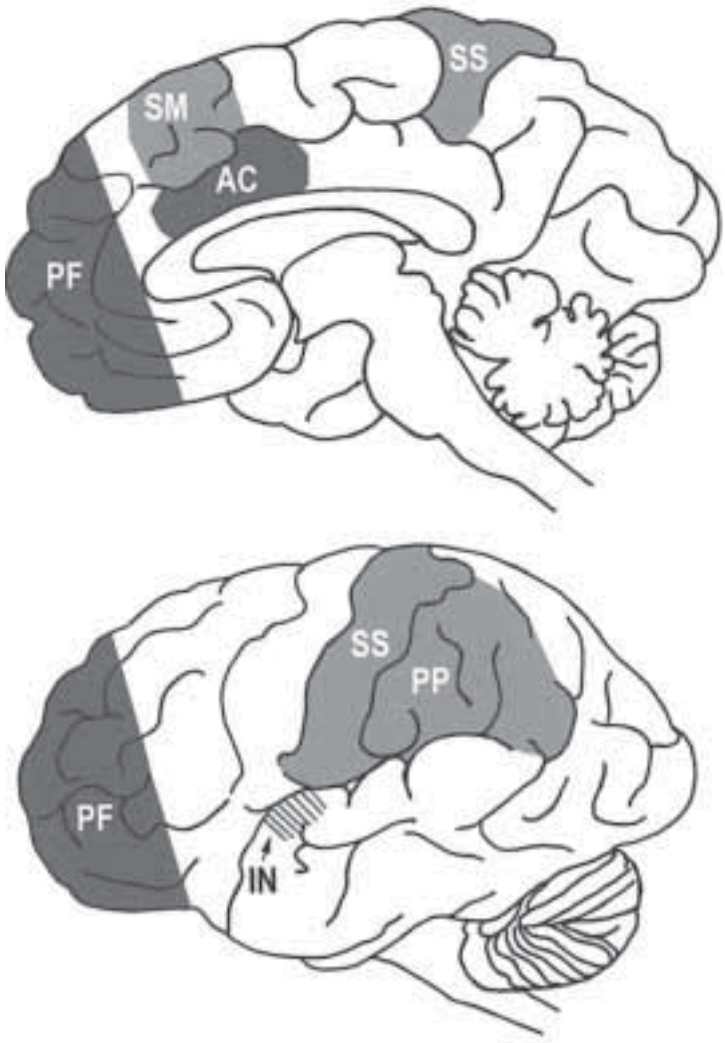

FIGURE 5. Cortical regions involved in the human pain experience. These regions have been identified by magnetic resonance imaging, positron emission tomography, neurosurgical procedures, neurological case studies, and electrophysiological recording (Price, 1999; Treede *et al.*, 1999). AC — anterior cingulate gyrus; IN — anterior insula, a frontal cortical region covered by the temporal lobe; PF — prefrontal cortex; SM — supplemental motor cortex; SS — primary somatic sensory cortex of the postcentral gyrus and the small, adjacent second somatic sensory area (not labeled). PP — posterior parietal cortex. SS is critical for the sensory-discriminative dimension of pain. The intensity dimension of pain is perceived by activation of multiple regions, including AC, IN, PP, SM, and SS. Low-intensity stimuli activate cortex of the contralateral hemisphere, while more intense stimuli activate these cortical regions in both hemispheres. The cognitive-evaluative component of pain, involving attention to the pain, perception of a threat to the individual and conscious initiation of strategies for dealing with the pain depends on AC, PF, and SM.

still present (the sensory-informational aspect of the pain), but it is no longer unpleasant or distressing (the emotional suffering aspect of the pain). A similar effect on pain experience was found to accompany prefrontal lobotomies (Bouckoms, 1994). After such prefrontal cortex damage, the tendency to perceive pain as unpleasant and something that is a cause for concern is greatly diminished. The effects of these neurosurgical procedures are one line of evidence showing that the cognitive-evaluative components of pain (attention to the pain, perceived threat to the individual, and conscious generation of strategies for dealing with the pain), are based on frontal lobe structures, especially the prefrontal cortex and anterior cingulate gyrus. There may be other cortical regions and processes that are important for the totality of the pain experience. The most important point here is that the absolute dependence of pain experience on neocortical functions is now well established (Price, 1999; Treede *et al.*, 1999).

It is also revealing to note that the cortical regions responsible for the experience of pain are essentially the same as the regions most vital for consciousness. Functional imaging studies of people in a persistent vegetative state due to massive cortical dysfunction (Laureys *et al.*, 1999, 2000a,b) showed that unconsciousness resulted from a loss of brain activity in widespread cortical regions, but most specifically the frontal lobe, especially the cingulate gyrus, and parietal lobe cortex. In these unconscious individuals, nociceptive stimulation caused strong activation of the brainstem and thalamus, and in some cases the primary somatic sensory cortex. However, in the absence of more widespread cortical function, this nociceptive stimulation did not generate consciously perceived pain. Recall, as explained earlier, that individuals in this functionally decorticate condition can still make organized motor responses to nociceptive stimuli and appear to be wakeful (Figure 3). Thus, intense nociceptive activation of subcortical structures, and even limited cortical regions, is inadequate for conscious awareness of pain.

IX. THE QUESTION OF PAIN AND DISTRESS IN FISHES

A principal cause for assumptions that fishes feel pain is an anthropocentric interpretation of reactions by a fish to stimuli that probably would cause pain in a human. There is no scientifically valid evidence in support of this assumption. Compared with mammals, however, fishes have received much less investigation of nociceptive function. Nevertheless, neuroanatomical, neurophysiological, and behavioral findings from studies of elasmobranchs lead to serious doubt that sharks or rays have an adequate neural system even for nociception. First, none of several elasmobranch species that have been studied had many unmyelinated sensory axons in nerves entering the spinal cord (Coggeshall *et al.*, 1978; Snow *et al.*, 1993). This is critical because unmyelinated nerve fibers are the predominant type responsible for signaling the occurrence of nociceptive stimuli and tissue injury (Price, 1999; Wall, 1999). Humans and other mammals have more unmyelinated than myelinated spinal sensory nerve fibers and humans with greatly reduced numbers of unmyelinated spinal nerve fibers have insensivity to pain (Willis, 1985). Second, the first layer in the spinal dorsal gray matter, a region where nociception-signaling sensory fibers normally synapse, was not present in any of four species of sharks and rays investigated (Cameron *et al.*, 1990). Third, a neurophysiological study in a stingray

revealed an absence of typical nociceptive sensory neurons innervating body tissues (Leonard, 1985). Lastly, observations of sharks have documented that severe lacerations and wounds did not interfere with feeding behavior (Snow *et al.*, 1993). Collectively, these observations with diverse species lead to the conclusion that elasmobranchs lack the neural structures for processing nociceptive information, much less sensing pain.

A lack of nociceptive responsiveness may constitute something of an advantage to elasmobranchs feeding on otherwise noxious prey. For example, individual specimens of the great hammerhead, *Sphyrna mokarran*, which preys on stingrays, have been found with numerous (as many as 96) stingray barbs embedded in the mouth, throat, and tongue (Helfman *et al.,* 1997). Another important point is that sharks and rays, as well as other fishes, react with "escape" responses to being caught by hook and line angling in spite of their apparent deficiency in detecting nociceptive stimuli. This fact suggests, as has been concluded from some observations of teleosts (Gregory, 1999), that interference with their free movement is a major factor creating flight responses rather than noxious stimulation from a hook. Of course, diverse taxa of fishes eat prey having spines, sharp fin rays, or thorny exoskeletons. It would seem adaptive for such fishes to have somewhat low nociceptive reactivity, especially in the oral cavity. It would also seem logical for there to be sufficient reactivity to prevent excessive trauma to the predator, although this logic does not appear to apply well to elasmobranchs.

Neuroanatomical and neurophysiological studies of nociceptive sensory nerve fibers similar to those in sharks and rays apparently have not been done in teleost fishes. However, anatomical studies have identified free nerve endings in the skin tissues of teleosts (Whitear, 1971). As explained above, free nerve endings are sensory receptors that transduce diverse types of somatic stimuli, including nociceptive ones. Although it remains to be demonstrated that in teleosts these receptors actually respond differentially to nociceptive stimuli, their presence suggests that bony fishes, unlike elasmobranchs, may have receptors for detection of nociceptive stimuli.

In spite of the differences between elasmobranchs and teleosts in peripheral nerve and spinal gray matter components of nociceptive processing, neuroanatomical studies have shown that the fundamental spinal and brainstem pathways for somatic sensory transmission are present in both elasmobranchs (Ebbeson and Hodde, 1981) and teleosts (Oka *et al.*, 1986; Wulliman, 1998). These pathways constitute a dorsal spinal tract that terminates in the lower brainstem and a lateral spinal pathway that terminates at multiple brainstem levels (Oka *et al.,* 1986). There is remarkable variation among teleost species in the exact structures and levels of brainstem termination of the ascending lateral spinal pathway (Wulliman, 1998). Unlike the somewhat clearer interpretations that can be made from studies of unmyelinated, peripheral sensory fibers, the function of these spinal cord-brainstem pathways is less clear from purely anatomical data. To generalize from mammals, the lateral ascending spinal pathway in fishes, comparable to the spinothalamic tract of mammals, would convey diverse somatic sensory information, but would also be the pathway with ascending connections of most importance for nociception (Wall, 1999; Price, 1999). One interpretation stemming from these neuroanatomical data is that the basic spinal cord and brainstem structures that process nociceptive stimuli by mammals are present (albeit with more variation) in fishes. This interpretation

must be qualified by the fact that the same spinal-brainstem pathway is present in sharks, which probably lack a capacity for nociception. Thus, the anatomical presence of an ascending lateral spinal-brainstem system is not evidence for a nociceptive function as opposed to purely mechanosensory function. Of course, for conscious pain experience, as opposed to just nociception, a large amount of neocortex appears to be required. As discussed below, there is no such structure in brains of fishes.

Functional evidence of nociception in fishes comes from studies in which fish were trained with an electric shock stimulus in either Pavlovian "fear" conditioning or instrumental avoidance conditioning paradigms (Davis and Klinger, 1994; Overmier and Hollis, 1983). In such studies, an electric shock of sufficient intensity to cause behavioral reactions can be used to produce behavioral avoidance responses or classically conditioned responses such as changes in branchial movements. It should be reiterated that these conditioning tasks are examples of implicit learning, which, as stated earlier, occurs without conscious awareness. Whether an electrical shock delivered to a fish immersed in water has the same nociceptive properties as an electric shock applied to the skin of humans is unknown. However, findings showing that morphine can reduce reactivity to electric shocks in goldfish, and that opiate antagonists such as naloxone reduce the effects of morphine (Ehrensing *et al*. 1982), tend to support the notion that electric shocks given to a fish activate some type of nociceptive process. However, as explained elsewhere, the nociceptive reactions of a fish to electric shocks do not, by themselves, demonstrate "pain" experience, which requires conscious awareness. Furthermore, opiates, such as morphine, are known to produce their antinociceptive effects by acting at subcortical brainstem and spinal cord sites (Price, 1999). Thus, opiate effects on nociceptive processing are not evidence of a capacity for consciously perceived pain. There is also a major problem in referring to these classic conditioning paradigms with fish as "fear" conditioning. As explained below, awareness of emotions, such as fear, is in a similar neuropsychological category as awareness of pain; it requires participation of cortical brain systems that fishes do not have.

A. IS THERE A NON-NEOCORTICAL MECHANISM FOR GENERATING CONSCIOUSNESS IN FISHES?

Neocortex, the essential brain level for conscious awareness of pain, does not exist in the brains of fishes. However, it might be argued that conscious awareness of experiences exists in fishes through some mechanism other than the neocortically based consciousness of humans (Verheijen and Flight, 1997).

As mentioned previously, the idea that organisms having simpler nervous systems, including invertebrates as well as vertebrates, are capable of some degree of conscious awareness has been advanced on behavioral grounds (Griffin, 1976; 1992; Rollin, 1998). Others have criticized the evidence for this proposition and made compelling arguments that there is nothing about the capabilities of most, if not all non-humans, that demonstrates the capacity for consciousness (Blumberg and Wasserman, 1995; Donald, 1991; Kennedy, 1992; Macphail, 1998). More pertinent to the present discussion is the critical issue of mechanistic feasibility. Conjectures that a different, nonneocortical mechanism for consciousness might exist, are contra-

dicted by extensive neurobiological evidence. As explained earlier, the neural processes mediating conscious awareness appear to be highly complex, requiring large, structurally differentiated neocortical regions with great numbers of exactly interconnected neurons (Tononi and Edelman, 1998). What is more, the type of neocortex most essential to consciousness, the nonsensory association cortex, comprises the vast majority of human cerebral cortex, but it is a very small proportion of the neocortex in most mammals (Mountcastle, 1998; Deacon, 1992a). Consequently, conscious experience resembling that of humans would be extremely improbable for the great majority of mammals. Even great apes, having substantially less nonsensory association neocortex than humans (Deacon, 1992a), would be unlikely candidates for human-like higher-order consciousness, as their behavioral characteristics, such as inability to acquire true language use, indicate (Donald, 1991; Macphail, 1998).

As the foregoing presentation has explained, the brains of fishes are profoundly lacking in both the quantitative and qualitative structural features required for the generation of consciousness as we understand it. Furthermore, fish brains are understood well enough to make it highly implausible that there are alternate, functionally uncommitted systems that could meet the requirements for generation of consciousness, namely, exceptionally high interconnectivity within the cortex and between the cortex and thalamus, and enough nonsensory cortical mass and local functional diversification to permit regionally specialized, differentiated activity patterns (Edelman and Tononi, 1999). In addition, despite the great differences between fishes and humans at the level of the cerebral cortex, the organization of the brainstem and subcortical cerebrum has much fundamental similarity (Wullimann, 1998). This similarity stems, of course, from a shared vertebrate genotype. Consequently, many shared neurobiological problems in mammals and other vertebrates tend to have conserved, common neurobiological solutions. Several examples illustrate this point. Locomotor patterns are generated by the spinal cord and brainstem in fishes and mammals alike (Grillner *et al.*, 1998; Rose *et al.*, 2000). Neuroendocrine control issues from the hypothalamus to the pituitary in all vertebrates (Butler and Hodos, 1996). Identical neurochemicals, such as monoamines, are produced by neurons in corresponding vertebrate brainstem locations, and these neurochemical systems appear to serve similar, shared functions across species (Butler and Hodos, 1996; Nieuwenhuys *et al.*, 1998a).

Conspicuous exceptions to such vertebrate neural continuities occur in cases where an organism, through a separate evolutionary path, has acquired something fundamentally new, such as language in humans. Even here, the new neural mechanism was probably founded on an expansion of less specialized cortical regions already present in primate ancestors (Preuss, 2000). These specialized human cortical regions, through genetic change, took on previously impossible functions. Furthermore, as inferred above, nothing about the behavior of a fish requires a capacity for conscious awareness for its explanation (Kennedy, 1992; Macphail, 1998). In contrast to the predictable, species-typical behavior of fishes, the immense diversity of human solutions to problems of existence through novel, mentally contrived strategies, is unparalleled by any other form of life. The full range of this behavioral diversity and flexibility depends on the capacity for consciousness afforded by the human neocortex (Kolb and Whishaw, 1995; Donald, 1991).

Another computer analogy is instructive here. Those of us who used desktop computers throughout their development during recent decades have seen greatly increased capabilities of these devices emerge with absolute dependence on changes in hardware and software. It is inconceivable that one could run Windows™, read and write to compact disks, and search the Internet, all at high speed and in high-resolution color, with a 1982 desktop computer that had minimal memory, no hard disk drive, and a monochrome monitor. The massive additional neurological hardware and software of the human cerebral cortex is necessary for the conscious dimension of our existence, including pain experience. However, as in fishes, our brainstem-spinal systems are adequate for generation of overt reactions. To propose that fishes have conscious awareness of pain with vastly simpler cerebral hemispheres amounts to saying that the operations performed by the modern computer could also be done by the 1982 model without additional hardware and software.

Thus, fishes have nervous systems that mediate effective escape and avoidance responses to noxious stimuli, but, these responses must occur without a concurrent, human-like awareness of pain, suffering or distress, which depend on separately evolved neocortex. Even among mammals there is an enormous range of cerebral cortex complexity. It seems likely that the character of pain, when it exists, would differ between mammalian species, a point that has been made previously by pain investigators (Melzack and Dennis, 1980; Bermond, 1997). Bermond has critiqued claims that non-human species can experience pain and suffering and argued that because conscious awareness of pain depends on extensively developed frontal lobe neocortex, few (if any) mammals besides humans possess an adequate cortical substrate for pain experience.

X. THE REACTIONS OF FISHES TO NOCICEPTIVE STIMULI ARE SIMILAR TO THEIR REACTIONS TO PREDATORS AND OTHER NON-NOCICEPTIVE STIMULI

Humans are acquainted with behavioral responses of fishes through our attempts to capture them. For example, when a fish is hooked by an angler, it typically responds with rapid swimming behavior that appears to be a flight response. Human observers sometimes interpret this flight response to be a reaction to pain, as if the fish was capable of the same kind of pain experienced as a human. From the foregoing explanation, it should be clear that the fish's behavior results largely from brainstem and spinal patterns of activity that are elicited by being hooked. However, the flight responses of a hooked fish are essentially the same as responses of a fish that is being pursued by a visible predator or a fish that has been startled by a vibration in the water. These visual and vibratory stimuli would not activate nociceptive types of sensory neurons. Consequently, the flight responses of fishes are actually evoked by many types of stimuli, including those that do not activate nociceptive neural systems. Recall, that elasmobranchs make vigorous "flight" responses to being hooked in spite of being ill-equipped to process nociceptive stimuli. Thus, the escape responses of a fish cannot be taken to represent a specific response to nociception. Instead, they represent protective responses to a wide

range of stimuli associated with predators or other threats, to which a fish responds with innate behavior programs and possibly nonconscious, implicit learning.

It might be proposed that the fish's responses to being hooked or pursued by a predator are indications of a fear response. This proposal leads to the same type of analysis that was applied to the psychological experience of pain. There is a close parallel between current neuroscientific understanding of pain as well as emotions like fear: the experience of fear is also a conscious psychological phenomenon that, similar to pain, requires an adequate neocortical system to be felt. Emotional reactions, like nociceptive responses, are generated by subcortical brain systems. The principal brain region that generates fear reactions is the amygdala, a subcortical structure deep in the temporal lobe (Kolb and Whishaw, 1996; LeDoux, 1996; Price, 1998; Strauss *et al.*, 1982). However, there is no experienced dimension to such emotional responses unless they become registered at the neocortical level that supports consciousness (Dolan, 2000; LeDoux, 1996; Öhman *et al.*, 2000). This understanding of the neurology of emotion has been succinctly expressed by Joseph LeDoux (1996):

> Emotional feelings result when we become consciously aware that an emotion system of the brain is active..Emotions evolved not as conscious feelings… but as brain states and bodily responses. The brain states and bodily responses are the fundamental facts of an emotion, and the conscious feelings are the frills that have added icing to the emotional cake.

Fishes and other animals without the extensive nonsensory association neocortex that is required to support consciousness may be capable of certain basic behaviors and physiological reactions that fit the functional definition of emotional responses. However, these responses, like nociceptive responses, occur without a felt, experiential dimension. The brain systems known to be necessary for the experience of fear or other emotional experiences are not present in fishes.

XI. PREVIOUS STATEMENTS CONCERNING THE ABILITY OF FISHES TO EXPERIENCE PAIN

There have been diametrically opposed statements made concerning the capacity of fishes to experience pain, with writers disputing this capacity (LaChat,1996; Macphail, 1998) and others asserting it, for example, Bateson (1992) Gregory (1999), Stoskopf (1993, 1994); Verheijen and Flight (1993, 1997). The arguments presented in support of the belief that fishes are capable of feeling pain appear to take three forms: (1) that behavioral reactivity to presumed noxious stimuli is evidence of pain perception; (2) that learning by fishes to avoid noxious stimuli or to develop Pavlovian conditioned responses to these stimuli is evidence of pain experience; and (3) that the same or equivalent neural structures and neurochemicals mediating pain in humans are present in fishes. The following presentation will show that none of these arguments is valid.

The first argument, equating behavioral reactivity with pain experience, obviously fails to distinguish nociception or nociceptive responses from pain experience. This misinterpretation, fueled by anthropomorphic thinking, is rampant in the

culture at large and much of the scientific community. However, as this article has explained at length, the separateness of nociception and nociceptive behaviors from the psychological experience of pain is a well-established principle in the scientific literature. What apparently is not understood by those who advance this argument is that the neural mechanisms generating nociceptive behaviors operate at lower levels of the nervous system and run their course regardless of whether there is a higher level where the conscious experience of pain is produced. Because the higher brain level responsible for awareness of the sensory and emotional dimensions of pain does not exist in fish brains, all of their neurobehavioral reactivity to noxious stimuli is nociception and not pain. In addition, the preceding section made the point that the responses of fishes to nonnociceptive and nociceptive stimuli may be very much alike. This point further illustrates the fact that an anthropomorphic, face value interpretation of responses of fishes to noxious stimuli is invalid. The notion of sentience is sometimes used by proponents of the argument that fishes can experience pain. This word is used to mean that reactivity denotes conscious awareness of stimuli (Fox, 1986). Thus, the word's broad application to simple and complex organisms, alike, conveys an unsubstantiated attribution of a higher-order neuropsychological capacity. Of course, the notion of sentience also fails to distinguish nociception from pain. This archaic word is very misleading, with invalid connotations that are granted without critical appraisal. It has little place in scientific discourse.

The second argument assumes that the presence of learning signifies a capacity for conscious awareness of the noxious stimuli used to reinforce that learning. As has been explained, instrumental and Pavlovian conditioning are forms of associative, implicit learning that occur in fishes and diverse other vertebrates and invertebrates. As cases of implicit learning, they operate without awareness (Macphail, 1998) and constitute no evidence of awareness of pain or any other experience. Evidence of learning to avoid noxious stimuli has been presented as an argument that the behavior of the fish is more than a reflexive response (Verheijen and Flight, 1997). While this is true, many complex, nonreflexive behaviors are done without consciousness, even in humans (Macphail, 1998), so the presence of complex behaviors in response to nociceptive stimuli is not evidence of awareness of pain. The term "fear" conditioning has also been used to suggest that a conscious awareness of fear is involved in the learning process (Davis and Klinger, 1994). In fact, "fear" conditioning paradigms are always examples of implicit learning and no awareness of "fear" is necessary for their occurrence (Dolan, 2000).

The third argument takes various forms. In one form it is stated that fishes have spinal cord and brainstem pathways similar to those that transmit "pain" in humans or other mammals. It is also stated that fishes have many of the same neurotransmitters and neuromodulators, such as endogenous opioid neuropeptides, that are present in mammalian spinal and brainstem nociception systems (Gregory, 1999; Stoskopf, 1994). The conclusion drawn from this evidence is that fishes must be capable of experiencing pain. It is evident that the spinal cord and brainstem of fishes do have similar neuroanatomical components, such as ascending spinoreticular/spinothalamic pathways, that are utilized for processing nociceptive information (Nieuwenhuys *et al.*, 1998a; Wulliman, 1998). To the extent that a fish or any other animal can react to nociceptive stimuli, there must be a neural system meditating such reactions. However, in the absence of an adequate neural substrate for

generating consciousness and awareness of the pain experience such as an extensive fronto-parietal neocortical system, the behaviors evoked by nociceptive stimuli are performed without conscious awareness. The effectiveness of analgesics such as morphine for reducing behavioral responses of fish to noxious stimuli has also been given as an argument for a capacity for pain experience (Gregory, 1999; Stoskopf, 1994). Of course, as has been discussed already, opiates act on lower levels of the nervous system to reduce nociceptive responsiveness, so opiate effects constitute no evidence of a capacity for pain experience. The presence of endogenous opioids in fish and the behavioral effectiveness of opiate analgesics does suggest that these endogenous opioids might attenuate nociception in fishes as they do in mammals. Having said this, one must again point to the case of elasmobranchs, where the capacity for nociception is doubtful. In these fishes some of the typical components of the nociceptive system are present, such as the ascending lateral spinal pathway and the peptides substance P and enkephalin in the spinal gray matter (Snow *et al.,* 1993). These neuropeptides are thought to be a critical facilitator and attenuator, respectively, of nociceptive neural transmission. Neuropeptides tend to serve multiple functions, however, such as promoting vasodilation and healing (Strand, 1999), and it would appear that these peptides must be serving nonnociceptive functions in elasmobranchs (Ritchie and Leonard, 1983).

Another variation on the argument of neurostructural similarity is the claim that forebrain structures believed to be important for pain experience in humans have homologies in fishes (Verheijen and Flight, 1997). This assertion misrepresents what is known about fish forebrain structure. The relationship between cerebral hemisphere structures of fishes and those of mammals has been debated throughout the history of comparative neuroanatomy (Nieuwenhuys *et al.*, 1998a). Compared with mammals, the cerebral hemispheres of fishes are very poorly differentiated, making it extremely difficult to define structural subdivisions with confidence, much less show that these subdivisions correspond to specific regions of a mammal's brain. Two classes of structures are at issue here: limbic structures and neocortex. Limbic structures are a collection of subcortical nuclear and cerebral cortical structures that are believed to have a role in generation of emotion and a variety of life-sustaining behaviors, including reproduction, aggression and defense, feeding, and drinking. Because of the limited structural differentiation of fish cerebral hemispheres, determining if specific limbic system components such as the amygdala are present, has long been unresolved. It now seems agreed among neuroscientists that some mammalian limbic structures such as the septal region and the amygdala have homologous structures in fish brains. The presence of structural homologies, however, cannot be taken as evidence that the emotional reactivity and pain experience of humans and fishes is similar. First, it must be emphasized that homology only means that a structure is believed to have been present in a common ancestor of fishes and mammals (Butler and Hodos, 1996). No functional equivalency is established by neuroanatomical homology. In fact, functional equivalency of such structures is impossible because the amygdala in fishes lacks the diverse structural subdivisions and specific connections, such as frontal lobe neocortex, that are critical to the functions the human amygdala. In addition, increasing evidence shows that activity in the amygdala is not consciously perceived unless this activity also registers in the neocortex (e.g., Dolan, 2000). So, even if a functionally equivalent amygdala were present in a fish brain (which it is not), the absence of a neocortical mechanism

for consciousness would prevent it from generating "fear" or any other consciously experienced emotion.

In contrast to previous assertions (Verheijen and Flight, 1997), a specific role for of the amygdala in pain is not established (Price, 1999). More pertinent to this discussion is the cingulate gyrus. As previously discussed, this structure appears to be critical for the emotional aversiveness of pain, but differing from most other limbic structures it is identifiable only in mammals, probably because its structure depended on the evolution of neocortex.

The structural homology argument has also been extended to neocortex. It has been denied that "cortex" is a recent evolutionary acquisition that ought to distinguish fishes from humans (Verheijen and Flight, 1997). This argument is another straw man, because neocortex is the only type of cortex in question and its absence in fishes is an undisputed neuroanatomical fact (Allman, 1998; Butler and Hodos; 1996; Northcutt and Kaas, 1995; Nieuwenhuys *et al.*, 1998b). It has also been implied that dependence of a particular type of avoidance learning in a fish on the telencephalon (e.g., cerebral hemispheres) proves that fishes are aware of nociceptive stimuli (Gregory, 1999). This interpretation is invalid, of course, because avoidance conditioning occurs unconsciously and is not evidence of awareness of pain or any other experience.

There is also a more general argument assuming that pain is poorly understood, and facts critical to answering the question of pain experience in fishes are either unknown or unknowable. Given this view, it is assumed that the best course is to err on the side of believing that fishes can experience pain (Stoskopf, 1994, 1993). It should be evident clearly from the foregoing presentation that pain and its neurological basis have been under intense and productive investigation for decades and the resultant body of empirical data have clear implications for the question of pain in fishes. The issue of greatest concern is whether fishes can experience pain and suffering in a way that resembles our experience, that is, do fishes have a capacity to suffer that meaningfully approximates the psychological impact of pain-induced suffering in humans? A large and diverse array of empirical evidence addressing this issue has been presented. This evidence identifies, with a high degree of certainty, the neurological requirements that are essential for the conscious experiences of pain and suffering. These requirements consist of an extensive system of functionally differentiated neocortical structures that underlie both consciousness and the psychological dimensions of pain experience. There is no similar system in fish brains, nothing with the structural or functional capability of neocortex, much less human neocortex. This fact must be appreciated in light of one of the most well-substantiated principles of neuroscience: that functions of nervous systems, including psychological functions, depend on specific structural features of these nervous systems.

A related argument is that a fish can not be asked if it feels pain; therefore, it is unknowable if it does or not. The fact that an indirect approach is needed to answer the question of pain experience by fishes is neither ground for suspending judgment or an unusual circumstance in science. The clinical identification of brain death provides an instructive illustration. The structural and functional conditions required for a living, viable brain are known. If diverse tests reveal that these conditions do not exist, the diagnosis of brain death, with its momentous implications, is made (Young *et al.*, 1998). Although it's impossible to talk to the victim to make a determination of brain death, there is a high degree of certainty about the diagnosis.

XII. FISHES RESPOND TO NOXIOUS STIMULI WITH STRESS RESPONSES

Regardless of the probable absence of the psychological experience of pain or fear in fishes, these organisms are still neurologically well designed to react to injurious or threatening stimuli with defensive responses. The vertebrate nervous system has exquisite features for mediating predator-avoidance and escape from threatening stimuli, as well as compensatory physiological and neuroendocrine stress responses. These defensive responses have well-documented health and well-being implications for fishes (Iwama *et al.*, 1997). It is at this level of function that concerns about reactivity to nociceptive and other stress-inducing stimuli should be addressed.

As mentioned above, one salient vertebrate neurological common denominator is the neuroendocrine system, which includes the subdivision that mediates the stress response (Sumpter, 1997). In humans and fishes alike, neural activity evoked by noxious stimuli enter the brain from diverse sensory pathways and ultimately activate hypothalamic neurons that initiate neuroendocrine and physiological stress responses. In fishes, stressful stimuli evoke a suite of immediate responses, including hormonal events, such as cortisol and catecholamine release, as well as various behavioral responses (Schreck *et al.*, 1997). In humans, as explained above, there is no awareness of purely subcortical brain events. Thus, the subcortical processes that control our endocrine and physiological stress responses occur unconsciously. Also, we may or may not be consciously aware of the provocative environmental events that constitute the stressors, because some emotionally provocative types of stimuli are processed subcortically without our awareness (Dolan, 2000; LeDoux, 1996; Öhman *et al.*, 2000). In many cases, of course, we are aware of pain-provoking or emotionally distressing events that cause endocrine stress responses because these events generate adequate cortical activity for conscious awareness. However, the foregoing argument supports the conclusion that stress responses in fishes, such as behavioral reactions to noxious stimuli, are produced without conscious awareness of the eliciting stimuli, even though such stimuli might trigger behavioral avoidance or physiological stress responses. Thus, fishes would undergo stress without emotional distress.

Nonetheless, endocrine stress responses, especially sustained or repeated ones, can undermine the health and well being of fishes (Iwama *et al.*, 1997). In addition, when fishes are used in research, their physical well-being is of great importance for the collection of sound scientific information. Considerations of the welfare of fishes in research, or other contexts such as aquaculture, should focus on reducing exposure of fishes to conditions that provoke stress or undermine their physical well-being rather than on concerns about human-like psychological emotional distress, of which fishes are neurologically incapable.

SUMMARY AND CONCLUSIONS

There are widely disparate beliefs concerning whether fishes can experience pain and suffering. These beliefs influence policies governing the diverse uses of fishes. Given these differences in understanding and opinion, the extensive contemporary knowledge on the neural basis of pain and the neurobehavioral nature of fishes has

been reviewed to provide the first detailed analysis of whether fishes can experience pain and suffering. The human predilection for anthropomorphic interpretations of the behavior of non-humans tends to undermine this type of inquiry. Human-centered perspectives on fishes are inappropriate because the evolutionary histories of fishes and mammals have been separate for about 400 million years, and the appearance of the brain structures that are the basis for human-like experience is quite recent. A consequence of this long evolutionary separation is that the brainstem is the most conserved and similar brain feature in fishes and humans, whereas the massive expansion of the cerebral hemispheres and development of neocortex in humans, and other mammals, sets these species substantially apart from fishes.

The neurological basis of human consciousness is becoming increasingly well understood and is known to depend on functions of the neocortex. All forms of consciousness in humans depend specifically on the presence of expansive regions of "association" cortex, regions that are the most developed in humans. Neural activity confined to subcortical brain regions such as the brainstem is inaccessible to consciousness.

The behavior of fish species is highly diverse and often complex, but it is also stereotyped and species typical. Nonetheless, fishes, similar to all vertebrates and diverse invertebrates, are capable of associative, implicit learning, a type of learning that occurs without conscious awareness. The great majority of nonolfactory behaviors shown by fishes, including responses to noxious stimuli, can be performed after removal of the cerebral hemispheres. Thus, the evolution of fishes has resulted in a mode of adaptation that is served by neurobehavioral processes controlled largely by the brainstem and spinal cord. This stands in contrast with the great dependency of mammalian behavior, especially that of humans, on the cerebral hemispheres.

Whether the neocortex of non-human mammals can support a rudimentary type of consciousness is not entirely clear. While some argue that only humans are capable of consciousness, others propose that some rudimentary form of consciousness exists in nonmammalian vertebrates, even invertebrates. The latter claim has been made without the rigor of a mechanistic analysis. The need for such a mechanistic analysis is a critical issue because increasing evidence shows consciousness to depend on extensive regions of higher-order, functionally unique, nonsensory neocortex. The neocortex of most mammals is predominantly sensory cortex and non-mammals have no neocortex or any equivalent neural system.

In humans, pain is a psychological experience with a sensory-informational dimension and a dimension of emotional unpleasantness or suffering. These components of pain are experienced only in a conscious individual and depend on processes involving the somatic sensory regions of the neocortex (sensory dimension) and extensive nonsensory cortical regions of the frontal and parietal lobes (emotional dimension). In distinction to the neocortically based conscious experience of pain, all of the neural processing of noxious stimuli by peripheral nerves, the spinal cord, the brainstem, and other subcortical regions of the brain, occurs without conscious awareness. This subcortical processing is designated "nociception" to distinguish it from the conscious awareness of pain. In all vertebrates, including humans, innate responses to nociceptive stimuli, such as limb withdrawal, facial displays, and vocalizations are generated by neural systems in subcortical levels of the nervous system, mainly the spinal cord and brainstem. Understanding that the

display of behavioral responses to nociceptive stimuli does not, by itself, imply conscious awareness of pain is vital for a valid conceptualization of the neural basis of pain. For example, humans that are completely unconscious due to massive damage of the cerebral cortex can still show facial, vocal, and limb responses to nociceptive stimuli even though the experience of pain is impossible. Fishes with the cerebral hemispheres removed exhibit essentially normal responses to noxious stimuli.

Nociceptive reactions to noxious stimuli are a universal characteristic of animal life, even in simple invertebrates that have no brains, a fact demonstrating that reactivity to noxious stimuli does not imply conscious awareness. The nociceptive processes of fishes have received much less study than those of mammals, but it is clear that there are major differences as well as some similarities between fishes and mammals in neural systems that might mediate nociception. Sharks and rays show a conspicuous absence of the essential peripheral nerve and spinal cellular components of nociception, which may explain their relative behavioral unresponsiveness to injury. Teleosts have peripheral nerve, spinal, and brainstem structures more similar to those mediating nociception in mammals. However, the brain level of most importance for the conscious awareness of pain in humans, an extensive frontal and parietal lobe neocortex, is completely absent in fishes. The cerebral hemispheres of fishes have only a more simple type of cortex that lacks the structural complexity, massive interconnectivity, and spatial extent of neocortex, the cortex necessary for pain experience. There is no alternate neural system that could provide another, functionally comparable, mechanism for pain experience in fishes. The same conclusion applies to emotions such as fear. The neural structures known to be important for conscious emotional experiences, which include extensive neocortical regions such as those involved in pain, are not present in fishes, aside from very rudimentary homologues, which could not mediate conscious emotional experiences.

It is a well-established principle in neuroscience that neural functions depend on specific neural structures. Furthermore, the form of those structures, to a great extent, dictates the properties of the functions they subserve. If the specific structures mediating human pain experience, or very similar structures, are not present in an organism's brain, a reasonably close approximation of the pain experience can not be present. If some form of pain awareness were possible in the brain of a fish, which diverse evidence shows is highly improbable, its properties would necessarily be so different as to not be comparable to human-like experiences of pain and suffering.

Claims for and against the possibility that fishes can experience pain have been published, but none have considered the full range of evidence presented in the present review. Arguments that fishes are capable of experiencing pain and suffering have mainly taken three forms. First, behavioral reactivity to injurious or presumed noxious stimuli has been taken as prima facie evidence of conscious pain experience. Obviously, this interpretation confuses nociceptive behavioral responses, which are mediated by subcortical, and, hence, nonconscious levels of the nervous system, with subjective, conscious experiences that depend on neocortical brain regions that fishes do not have. Second, it has been asserted that learning by a fish to avoid noxious stimuli or to develop Pavlovian conditioned responses to these stimuli is evidence of pain experience. This interpretation fails to acknowledge that these types of implicit learning occur unconsciously and, thus, constitute no

evidence of awareness of pain. Third, it has been claimed that the same or equivalent neural structures as those known to mediate pain in humans are present in fishes. This assertion is clearly invalid for elasmobranchs and is only partly correct for teleosts. The latter species have peripheral nerve, spinal, and brainstem components for nociception similar to those present in mammals. However, the essential neural components for pain experience, extensive frontal and parietal neocortical regions, are not present in fishes. It has been claimed by some that the fish cerebrum has a cortex equivalent to neocortex, but this claim is strongly contradicted by extensive empirical evidence. In addition, the presence of "pain-related" endogenous opioid neuropeptides, or of analgesic actions of opiate drugs in fishes, is not evidence of pain experience because the actions of these compounds are principally at lower, subcortical levels of nociceptive processing.

The fundamental neural requirements for pain and suffering are now known. Fishes lack the most important of these required neural structures, and they have no alternative neural systems for producing the pain experience. Therefore, the reactions of fishes to noxious stimuli are nociceptive and without conscious awareness of pain. The evidence supporting this conclusion is extensive and diverse, thus permitting a high degree of confidence in its correctness. In view of the weight of the evidence presented here, any future proposal for the existence of pain awareness in fishes, or neurologically comparable vertebrates, should provide a compelling empirical basis to justify its consideration. Such a proposal must address the mechanistic plausibility of any hypothesized alternate neural basis for pain experience. The proposal must also show that some aspect of the response of fishes to nociceptive stimuli requires pain awareness, rather than just nociception, for its explanation.

Although it is concluded from the foregoing analysis that the experiences of pain and emotional distress are not within the capacity of fishes, this conclusion in no way devalues fishes or diminishes our responsibility for respectful and responsible stewardship of them. Fishes constitute a highly evolved, diverse, and complex life form whose history on the Earth vastly eclipses the brief existence of humans. Our diverse uses of fishes have ancient historical precedents and modern justifications, but our increasingly deleterious impacts on fishes at the population and ecological levels require us to use our best scientific knowledge and understanding to foster their health and viability.

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