

Helmut Segner

Fish  
Nociception and pain  
A biological perspective



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## Contents

Preface	7
1. Introduction	9
2. Nociception and pain perception in man	14
2.1 Nociception: peripheral sensing of noxious stimuli	16
2.2 Processing of nociceptive information at the spinal cord level	19
2.3 The human brain: from nociception to pain	20
3. Nociception and pain perception in fish	31
3.1 Nociception	32
3.2 Pain perception: neuroanatomical evidence	35
3.2.1 The fish brain	35
3.2.2 Neuroanatomical correlates of pain perception	38
3.3 Pain perception: neurophysiological evidence	47
3.4 Pain perception: behavioural evidence	50
3.4.1 Fish cognition	50
3.4.2 Behavioural responses of fish to noxious stimuli	59
4. Consciousness in fish	67
5. Conclusions	76
Acknowledgements	79
References	80

## Preface

In spring 2010, the Federal Ethics Committee on Non-Human Biotechnology (ECNH; Eidgenössische Ethikkommission für die Biotechnologie im Ausserhumanbereich, EKAH) commissioned two studies on pain perception and consciousness in fish. Both studies were intended to critically review the recent literature on cognitive abilities of fish and their capability to feel pain. These questions can be approached both from a biological perspective and from a philosophical perspective, as the issues of consciousness and cognition are not only a matter of biological facts – which fall within the competence of life sciences – but also a matter of notions and terms, which are within the competence of philosophy. Therefore, two studies were done in parallel, with one report written by a biologist (Helmut Segner), and one written by a philosopher (Markus Wild).

The two reports can be read independently of each other; however, they are complementary in many aspects. While, for instance, Markus Wild's report touches only shortly on the neurological basis of pain perception in man and fish, Helmut Segner's report places great emphasis on this aspect. In contrast, while Segner's report provides little detail on the terminology and notion of consciousness, Wild presents a systematic and in-depth discussion of this aspect.

We investigated the same topic from different perspectives. Despite our differences in background, methodological approach, focus, argumentation and assessments, we converge and agree in the two major results of our studies: First, we are both convinced that a new picture of the cognitive capabilities of fish has been emerging over recent years. Fish should no longer be considered simple-minded, inflexible “reflex machines”, but there is increasing awareness of their surprisingly complex cognitive competences. This picture is developing only now, and we are still in an early

phase of discovering the minds of fish and their fascinating cognitive adaptations to the challenges of their diverse habitats. Second, we both believe that at least certain fish species, such as rainbow trout, salmon, perch, goldfish and zebrafish, possess the capacity to perceive pain. While the biologist has some minor reservations because of a few as-yet unanswered questions, the philosopher is more confident. Both, however, agree and are strongly convinced that the information and knowledge that is available from recent research convincingly argues in favour of the existence of pain perception in fish, and it is now up to those who oppose this opinion to provide the evidence for rejecting this conclusion.

We are grateful to the ECNH for initiating this work, in particular for the decision to commission both a biological and a philosophical study. We gratefully acknowledge the support received from the members of the ECNH and their willingness to take part in stimulating and helpful discussions on the topics of cognition, pain perception and consciousness in fish.

We hope that these two reports will be of value for researchers and experts as well as for those who are professionally engaged with fish. We further hope that these reports will help to acquaint the interested public with this new perception of fish, and will provide a basis for ethical, political and legal discussions on the question of pain perception and welfare of fish.

Bern and Zeglingen, July 2012

Helmut Segner, Markus Wild

## 1. Introduction

The word pain commonly refers to a constellation of sensory, emotional and conscious experiences, often connected with discomfort and stress. The International Association for the Study of Pain (IASP) defines pain as an “unpleasant, sensory and emotional experience associated with actual or potential tissue damage”. It is important to note that according to this definition, pain is not merely a sensory but also an emotional, subjective event. Indeed, in contrast to the more objective nature of other senses, pain is a highly individual and subjective experience (Dubin and Patapoutian 2010). The perception of pain involves discriminative-sensory and emotional-affective components, and as such it bears attributes both of a sensation (detection, signalling and recognizing stimuli) and of an emotion (Millan 1999, Perl 2007).

Pain can be provoked by noxious stimuli, for instance, by chemical and physical injuries of the body surface or by pathologies of internal tissues. Pain is not the result of a single event but of a series of events. It starts with sensing of noxious stimuli in peripheral tissues (nociception), the transmission of the nociceptive signal to the brain, nociceptive processing in distinct areas of the brain, and, finally, the conversion of the nociceptive information into pain perception. Importantly, activity induced in the nociceptors and nociceptive pathways by a noxious stimulus is not yet pain. For instance, a behavioural response of an animal to a noxious stimulus such as the withdrawal response does not necessarily implicate that the animal consciously perceives this stimulus as pain, but it may simply represent a non-conscious reflexive response. It is only the interpretation of the nociceptive signal in the brain under the influence of emotional and cognitive factors which turns nociception into pain.

Responses of organisms to pain include immediate reflexive behaviours such as withdrawal reactions or vocalizing, but also high-

er level responses such as avoidance learning. The translation of nociceptive signals into the experience of pain depends on a variety of factors, for instance, pain perception can be curtailed by stress, it can be exacerbated by anticipation, or already existing tissue damage can exaggerate the pain perception of additional noxious stimuli (hyperalgesia). There is a strong psychological component in pain perception, as evident, for instance, from the ability of placebo treatment to reduce pain (Wager et al. 2004), or from the fact that empathy for a person experiencing pain can induce pain sensations in the observer (Singer et al. 2004).

Our perception of pain is strongly driven by our own experience, and the question arises what pain actually means when we transfer this term to animals. The pain experienced by an animal will be qualitatively different to the pain sensation we experience. As pointed out by Rose (2007), most people would consider the use of the term “love” for describing the emotional situation of mating animals to be inappropriate – similarly, what we experience as pain is not the same what an animal experiences when it is exposed to a noxious stimulus. This does not implicate that an animal is not able to feel pain, but it highlights that we must exercise some caution when using the term “pain” for animals. Along this line of thinking, the present text, when referring to animal pain, does not stick to the definitions of human pain as given by the IASP, which is focused on the quality of human pain experience. When we talk of pain in fish, we deal with a qualitatively different form of pain experience, probably a more “primitive” (in an evolutionary sense) or “simple” form of pain (“einfacher Schmerz” in the study of Wild 2012). For this understanding of pain, the definition as suggested by Molleny (1997) may be more appropriate than the human-focused IASP definition:

*“Animal pain is an aversive, sensory experience representing awareness by the animal of damage or threat to the integrity of tissues. It changes the animal’s physiology and behaviour to reduce or avoid the damage, to reduce the likelihood of its recurrence, and to promote recovery.”*

How can we know if an animal “feels” pain, how can we assess their subjective experiences when exposed to noxious stimuli (Bateson 1991)? In humans, assessment of pain experience often

relies on verbal report of the individuals exposed to noxious stimuli, and this qualitative experience is then connected to quantifiable measurement parameters such as neuroimaging signals. To assess the capability of non-human animals for pain experience, as verbal record is not possible, research strongly relies on a comparative approach, that is we evaluate similarities and continuities between structures and functions which are involved in pain perception in man to the corresponding structures and functions in animals. This includes analogies and/or homologies of neuroanatomy, neurophysiology, and behavioural responses to painful stimuli. The interpretation of such data, however, can be equivocal; intuitively, it may still work for species being closely related to man such as primates, but it is getting increasingly difficult for evolutionary more distant species such as fish. Much of the controversial debate on the existence of pain perception in animals relates to this difficulty (Bateson 1991).

The difficulties in assessing pain and understanding its nature are also reflected in the historical perspectives of pain (Brooks and Tracey 2005, Perl 2007). Aristotle (384–322 BC) classified pain as an emotion and this remained the dominating opinion for a long time. Originally, Galen (AD 130–201), and later Avicenna (AD 980–1037) and Descartes (AD 1596–1650), placed pain into the sphere of sensation, but a controversial discussion remained if pain is indeed an independent sensation with its own sense organs and pathways (specificity theory), or if pain sensation is the result of an intense activation of other sensory systems (intensity, pattern and gate theories) (cf. Perl 2007). One important argument why pain was considered to be not a specific sensation on its own was the fact that it can be induced by different types of stimuli (mechanical, physical and chemical), a feature that is different to other senses and apparently argues against the existence of specific “pain receptors”. In the course of the 20th century, however, an increasing number of anatomical studies provided evidence for the existence of a distinct class of afferent nerve fibres that selectively respond to tissue injury, irrespective if the tissue injury is caused by a chemical, physical or mechanical factor (Sherrington 1906, Burgess and Perl 1967). Subsequent electrophysiological studies showed that activity in these afferent fibers correlates with pain behaviour and pain experience

(e.g. Konietzny et al. 1981, Ochoa and Torebjörk 1983), thereby providing strong evidence that they act as “nociceptors”.

Not only was the existence of nociceptors controversially discussed, but also the question where in the brain the pain sensation is generated. For a long time, it was believed that pain is the product of thalamic processes, discounting a contribution of the cerebral cortex (cf. Perl 2007). This view was based on the conception of the thalamus as a site of emotion processing. Also, studies showing that no change of pain sensation occurred in patients with cortex lesions argued against a role of the cortex in pain perception. Only late in the 20th century, it was recognized that pain processing and perception strongly involve cortical regions. The current view, which has evolved over recent years, is that pain sensation does not result from the activity of a single brain region but is generated by the integrated action of a “pain matrix”, which consists of a dispersed network of cortical as well as sub-cortical brain regions (see chapter 2.3.1).

A critical issue in the discussion on the existence of pain perception in non-human animals is the question if animals are conscious organisms. In man, pain is defined as conscious, subjective experience. It was long believed that only man, but not animals, are conscious – an opinion which goes back to Descartes – and, in this line of thinking, animals are not capable of experiencing pain. Attitudes and perceptions towards animals, however, have changed, and the view of man as unique has been abandoned. It is now widely accepted that at least those animals which are closely related to us, such as primates in particular or mammals in general, are sentient, that is they possess positive and negative emotions. Particularly for sympathetic animals like cats or dogs, we readily believe that they suffer from injury and are able to experience some form of pain. The situation is different, however, if it comes to cold and slimy animals like fish; here, we are more reluctant to accept the idea that experience emotive states and are able to feel pain.

The present work aims to critically review the available biological evidence for or against nociception and pain perception in fish. Research over the last 10 to 20 years has created important new insights into the capability of fish to experience pain. For instance, one outcome of recent research with fish is the demonstration that

they possess nociceptors – a fact that has been proven only during the last decade. What is controversially discussed until to date is the question, if fish are able for pain perception: while one group of scientists argues that fish can not feel pain since they lack certain neuroanatomical structures which in humans are associated with pain perception (Rose 2002, Arlinghaus et al. 2007), other scientists claim that the neuroanatomical and physiological capacities of fish are sufficient to perceive at least some primitive form of pain (Oidtmann and Hoffmann 2001, Braithwaite 2010, Cottee 2012).

The following text will start with a very short overview on nociception and pain perception in man in order to provide some baseline information. The main part of this work will deal the question what the existing knowledge on fish neuroanatomy, neurophysiology and behaviour tells us on their capability to perceive pain and to act as conscious, sentient organisms. The discussion will be restricted to nociception and pain perception in bony fish (teleosts or, more specifically, actinopterygians), but will not include the more ancient fish groups, Agnatha and Chondrichthyes, because the available data base for these groups is too limited. Even among the 20,000 to 30,000 known teleostean species, information on nociception and pain processing is available for a negligibly small number of species only. Findings obtained from these few fish species probably represent principal properties of nociception and pain perception in actinopterygian fish in general, still one must be cautious in generalization and cross-species extrapolation.

## 2. Nociception and pain perception in man

Pain perception in man is a sensation that results from three major steps (Figure 1):

- peripheral nociception, that is the sensing of noxious stimuli in peripheral organs such as skin, viscera, etc.,
- processing of nociceptive information at the spinal cord level, and transmission to the brain,
- processing of the nociceptive information in the brain.

It is this processing of nociceptive message in the brain that turns the nociceptive signal into the sensation we perceive as “pain”. Pain arises from the integration of a sensory-discriminative component, which records intensity, location, and modality of the noxious stimuli, with an affective-cognitive component, which associates the nociceptive input with cognitive properties (e.g., attention, memory) and with emotional properties (e.g., fear, unpleasantness) (Millan 1999, Peyron et al. 2000). As formulated by Tracey (2005), pain is “an interpretation of the nociceptive input influenced by memories, emotional, pathological and cognitive factors”.

Perceiving pain leads to behavioural pain expression and (protective) responses. These reactions are governed both by automatic processes (unintentional/reflexive, for instance, screaming, vocaling, withdrawal reflex) and controlled processes (intentional/purposive, for instance, sequences of instrumental motor activity) (Craig et al. 2010). Neuro-anatomically, these reactions are anchored in the brainstem (e.g., reticular area, globus pallosa), in subcortical regions such as thalamus, as well as in the cortex (Rose 2002, Braz et al. 2005).

In the following, the three steps leading from nociception to pain perception will be discussed with respect to man. This is intended to provide a basis for discussing nociception and pain per-

ception in fish. The discussion will focus on acute pain, neglecting other aspects of pain such as chronic pain or the modulation of pain experience by psychological factors, for instance, individual attitudes and beliefs.

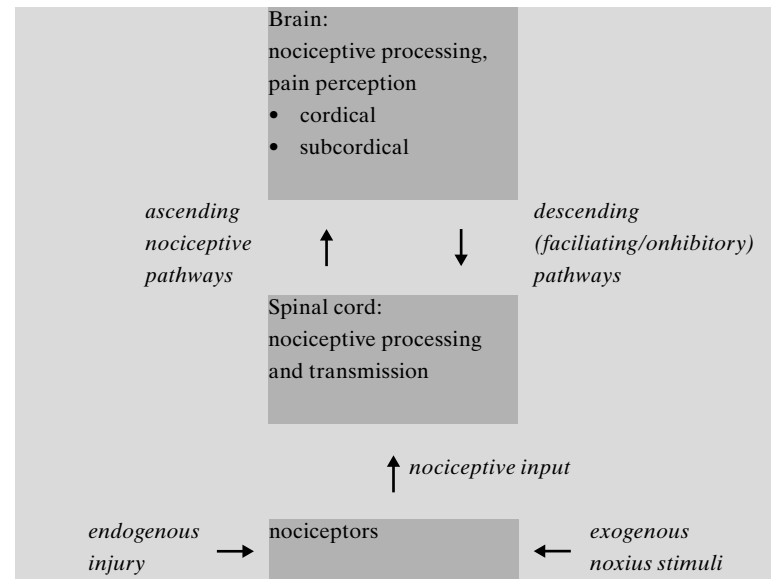


Figure 1: Schematic overview of key elements in pain perception: peripheral nociception, spinal cord processing and transmission, and brain processing



## 2.1 Nociception: peripheral sensing of noxious stimuli

Both animals and plants have developed sensors to detect changes of the internal as well as external environment, as this is crucial to respond adaptively to the changes, and to survive, grow and reproduce under variable conditions of life. One particular sensing process is nociception, which is the ability to detect damaging or potentially damaging (“noxious”) stimuli. The word is derived from the Latin *nocere* meaning “to hurt/harm”. It refers to the neural process of sensing, encoding and processing noxious stimuli. Importantly, nociception is not yet pain sensation.

The receptors which detect noxious stimuli are called nociceptors. They are sensory afferent fibers which are sensitive to noxious stimuli. In the definition of the International Association for the Study of Pain (IASP), nociceptors are “receptors preferentially sensitive to noxious stimuli or to stimuli which would become noxious if prolonged”. The existence of functional nociceptors in man was demonstrated relatively late, more precisely, in the 1960s (Burgess and Pearl 1967). Their detection gave support to the theory that pain is an independent sensation with its own sensors, a view that is in contrast to the intensity theory, which postulates that nociception is a matter of intensity and arises from intense activation of receptors that serve other sensations (cf. Perl 2007).

Nociceptors are stimulated by chemical, physical and mechanical stimuli. They are characterized by the following properties:

- *threshold*: nociceptors usually show a high threshold in responding to stimuli. This is in contrast to other sensors, but biologically it makes sense because otherwise even faint stimuli would be perceived to be noxious. For instance, while weak tactile (mechanical) stimulation of our skin is perceived as positive, only strong mechanical pressures will be perceived as painful;
- *modality*: the majority of (cutaneous) nociceptors, in contrast to most other sensors, are polymodal, i. e. do not detect just one type of stimulus, either chemical, physical or mechanical, but can detect all three;
- *conduction velocity*: nociceptors differ in the velocity by which they transmit the nociceptive signal (see below).

Nociceptors are best studied in the skin (and the subsequent description refers mainly to skin nociceptors) but they occur also in viscera, muscles, periost etc. Nociceptors of the Nervus trigeminus are responsible for nociception from face and teeth. Cutaneous nociceptors are pseudounipolar cells, with the cell body located in the dorsal root ganglion or in the trigeminal ganglion, from where they send a peripheral axon to innervate the skin, and a central axon to synapse to second-order neurons in the spinal cord or in

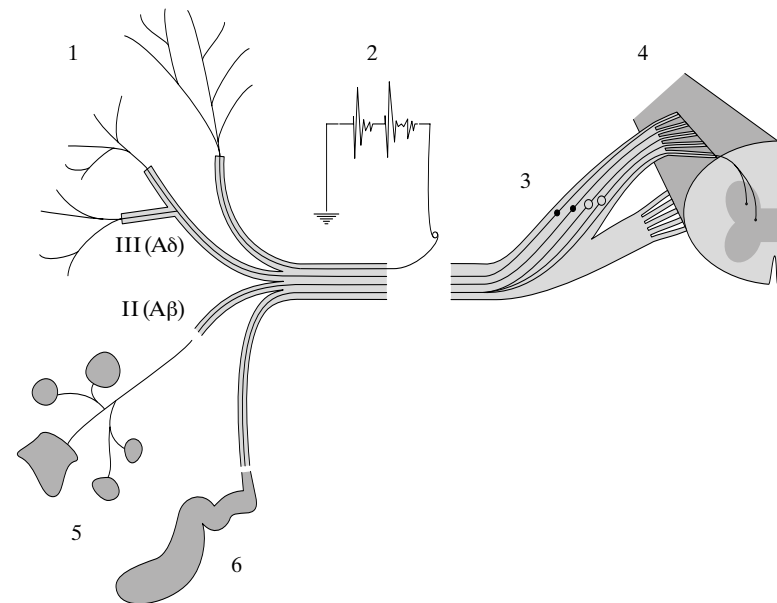


Figure 2: Different forms of sensory terminals and different fibre types of cutaneous nociceptors.

(Modified from Messlinger, 1997)

1. non-corporcular endings
2. registration of action potential
3. spinal ganglion
4. dorsal horn
5. Ruffini corpuscles
6. Paccini corpuscle

II A $\beta$ , III A $\delta$ , Abbreviations designate different fiber types (see text)

the trigeminal subnucleus caudalis (Dubin and Patapoutian 2010). The peripheral axons branch into free un-encapsulated nerve endings (Figure 1) that innervate distinct regions in skin and epidermis. They can be arranged in non-corporcular or corporcular endings. It is at these free nerve endings where the transduction of noxious stimuli into an electrical signal takes place. The transduction occurs through depolarizing of the peripheral membrane, a process that involves a range of ion channelling receptor molecules (Basbaum et al. 2009, Belmonte et al. 2009, Dubin and Patapoutian 2010). An example is provided by the TRPV1 receptor (capsaicin receptor) which transduces noxious chemical stimuli (capsaicin, contained in chilli pepper) – but also noxious heat stimuli – into an action potential of the nociceptor membrane. Another well-studied example of how a noxious stimulus is transduced into an action potential is provided by the thermally gated  $\text{Na}^+ \text{K}^+$  channels (Dubin and Patapoutian 2010).

Once stimulated, nociceptors transmit the action potential along the axon in the direction of the spinal cord. Transmission velocity correlates directly to the diameter of the axons and whether or not they are myelinated. The so-called C-fibers, which constitute the majority of cutaneous nociceptive afferents, are unmyelinated axons of small diameter ( $\leq 1\mu\text{m}$ ), which are bundled in fascicles ensheathed by non-myelinating Schwann cells. These axons support conduction velocities of 0.4 to 1.5 m/s. In contrast, A-fibre nociceptors (mostly A $\delta$ ) are myelinated, thicker ( $2\mu\text{m}$ ) axons with conduction velocities of 5 to 30 m/s. The A $\delta$ -fibers are responsible for the initial fast-onset pain, while the C-fibres are responsible for the deep, longer-lasting pain (St. John Smith and Lewin 2009, Dubin and Patapoutian 2010). The intensity of the noxious stimulus is encoded in the train – not in the amplitude – of the impulses. Nociceptors can undergo sensitization, what means that their threshold can change after the initial stimulation (Witt and Griffin 1962). This process is considered to be at least partly responsible for increased pain sensitivity of injured tissue (primary hyperalgesia).

The ability to detect damaging environmental forces is a very common, evolutionary conserved sensory trait of animal species (St. John Smith and Lewin 2009). Given the fundamental role nociception plays to protect animals from harmful impacts, the

evolutionary early development of nociceptive systems is hardly surprising (Braithwaite 2010). Already bacteria show behavioural responses to mechanical stimuli. Although as unicellular organisms they cannot possess nociceptors, they possess mechanosensitive ion channels, similar to those in the terminal endings of nociceptors. In the animal kingdom, the first appearance of nervous systems occurs within the phyla Cnidaria and Ctenophora. Although they show a still fairly simple organization, they are already able of sensing electrical and mechanical stimuli. True nociceptors, finally, develop within the Bilateria, and here they were found in all groups studied to date (St. John Smith and Lewin 2009).

## 2.2 Processing of nociceptive information at the spinal cord level

Nociceptive primary afferents from the skin, i.e. the small diameter C-fibers and the medium diameter A $\delta$ -fibers terminate primarily in the superficial laminae (I and II) of the dorsal horn of the spinal cord (Millan 2002, Todd 2010). There is evidence that peptidergic nociceptors, which express neuropeptides, target primarily projection neurons and interneurons of lamina I, while non-peptidergic nociceptors terminate primarily in lamina II. Collaterals of the primary afferents terminate in deeper layers (laminae V/VI). Also visceral nociceptors convey their information to the outer layers of the dorsal horn, while nociceptive information from face and teeth is transmitted through the branches of the Nervus trigeminus. In the dorsal horn, the primary afferents stimulate numerous ascending projection neurons which relay the information to the brain. The principal neurotransmitter of the primary afferents is glutamate, what implicates that primary afferents have an excitatory effect on their postsynaptic targets.

The ascending neurons project to several brainstem and cortical regions, many of them being interconnected and thus receiving also indirect nociceptive inputs (see below). The main relay site of nociceptive information in the brain is the thalamus (Millan 1999, Todd 2010). Neuroanatomy and organisation of ascending projection pathways in mammals are highly complex, as the axons originate from several laminae of the dorsal horn, and involve diverse axon types and neurotransmitters (for details see Millan

1999). The most prominent ascending projection which transmits nociceptive information from the dorsal horn to the brain is the contralateral tractus spinothalamicus.

Importantly, the spinal dorsal horn is not simply a relay station, but has a strong filtering and modulating effect on nociceptive transmission (Millan 2002, Todd 2010). This is due to the activity of neuronal circuits in the dorsal horn: the primary afferents are not only connected to the ascending neurons, but they have cross-connections with inhibitory and excitatory interneurons in the laminae. In addition, descending pathways from the brain – mainly serotonergic, noradrenergic and GABA (gamma-aminobutyric acid)-ergic axons – exert inhibitory as well as facilitating effects on nociceptive transmission in the spinal cord. As a result, the intensity of the nociceptive input can be strongly modulated at the spinal cord level (Millan 2002, Tracey and Mantyh 2007).

### 2.3 The human brain: from nociception to pain

Understanding of pain perception and its neural correlates depends to a large extent on the methodological possibilities available to study the relevant processes in the brain. Here, significant progress has been achieved since the advent of (non-invasive) neuroimaging techniques. These methodological approaches enabled to relate neural activity changes to subjective pain experience of humans (Brooks and Tracey 2005).

Importantly, according to current understanding of pain perception, pain does not result from the activity of a single, particular part of the brain, but arises from the concerted activation of several brain regions (“pain matrix”– see below). Brain regions that have been reported to be involved in pain processing in man include cortical, subcortical and brainstem regions (Millan 1999, Price 2000, Braz et al. 2006, Baumgärtner 2010).

In the following, a very brief overview of brain anatomy will be given in order to introduce anatomical terms related to nociceptive and pain processing in the brain (see also Kardong 2006, and Figure 3). Based on anatomical, functional and ontogenetic criteria, the vertebrate brain can be subdivided into the following parts (from anterior to posterior):

1. Prosencephalon (forebrain)
  - Telencephalon (Cerebrum), with
    - Tractus olfactorii/olfactory bulbs
    - Cerebral hemispheres/cortical region
    - Corpus striatum, pallidum
    - Hippocampus
    - Ventricles 1 and 2
  - Diencephalon, with
    - Thalamus
    - Hypothalamus
    - Pineal gland
    - Ventricle 3
2. Mesencephalon (midbrain)
  - Mesencephalon, with
    - Optical lobe
    - Cranial nerves III and IV
3. Rhombencephalon (hindbrain)
  - Metencephalon, with
    - Cerebellum
    - Pons
    - Periaqueductal gray
    - Ventricle 4
  - Myelencephalon, with
    - Medulla oblongata
    - Reticular system (Formatio reticularis)
    - Cranial nerves V–XII

The telencephalon includes a subcortical and a cortical part, which builds from a pair of expanded lobes or cerebral hemispheres. Left and right hemispheres of the cerebrum are connected via commissures, with the corpus callosum being one of the more prominent commissures. The outer layer of grey and white matter covering the telencephalic hemispheres is called pallium. In basal vertebrates such as fish, the pallium forms a relatively simple three-layered structure. In higher vertebrates, it develops into the cerebral cortex with an increasingly complex structure. The evolutionary youngest development is the so-called neocortex of mammals, which is made up of six layers (I to VI). The neocortex is part of the overall cerebral cortex, along with the evolutionary older

archi- and palaeocortex. In humans, the neocortex is involved in higher functions such as sensory perception (including pain), generation of purposive motor commands, spatial reasoning, conscious thought and language. The neocortex is folded to accommodate its increasing volume. The folds are called gyri, and the grooves in between are designated as sulci. The cortex is anatomically subdivided into frontal, temporal, parietal and occipital lobes, and it contains many subregions with distinct functions, e.g., the cingulate cortex which is located close to the corpus callosum, or the primary somatosensory cortex in the frontal lobe.

The diencephalon includes (i) the ventral hypothalamus, with a number of neurosecretory functions and intimate relationship to the hypophysis or pituitary gland, (ii) the dorsal epithalamus, with the pineal gland which secretes melatonin, and (iii), the thalamus, which basically represents the lateral walls of the diencephalon. The diencephalon also houses the chiasma opticum.

The metencephalon contains as a prominent structure the cerebellum. This brain part is important for equilibrium, and it processes information pertaining to touch, vision, hearing, proprioception and motor information from higher centres. The cerebellum modifies, refines and monitors motor activity, but it does not initiate it. An important pathway of information exchange between cortex and cerebellum is the pons. Often, the midbrain structures cerebellum and pons, together with the medulla, are designated as brainstem; the brainstem connects the cerebellum with the spinal cord, and it controls autonomic functions of the peripheral nervous system.

The myelencephalon contains the nuclei of a number of cranial nerves, and the medulla oblongata, which operates primarily at the reflex level. Information arriving via ascendent projections is partly processed in the medulla, and, vice versa, efferent output to adjust visceral or reflexive motor activity is initiated here.

A brain component that is frequently mentioned in the context of pain perception is the limbic system. It is not an anatomically discrete region but represents a functional association between several cortical and subcortical centers. There is no generally accepted definition which brain structures constitute the limbic system but most frequently the following structures are included: insular and cingulate cortex, thalamus, hypothalamus, hippocampus, amygdala-

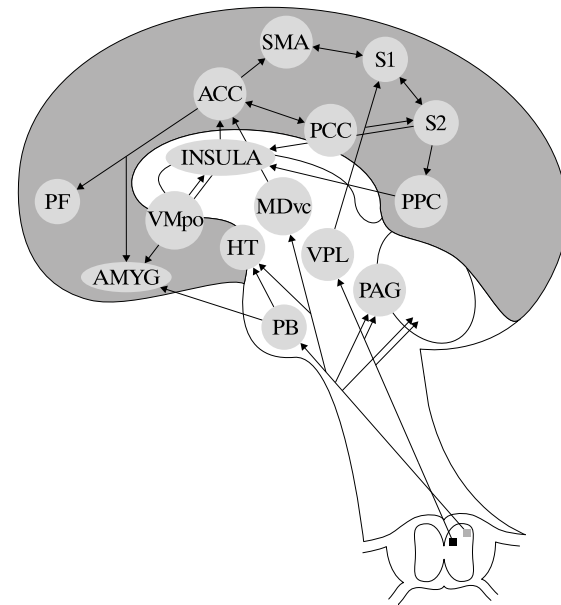


Figure 3: Schematic of ascending pathways, subcortical structures, and cerebral cortical structures involved in pain perception. (Modified from Price, 2000)

PAG periaqueductal gray, PB parabrachial nucleus of the dorsolateral pons, VMpo ventromedial part of the posterior nuclear complex of the thalamus, MDvc ventrocaudal part of the medial dorsal nucleus of the thalamus, VPL ventroposterior lateral nucleus of the thalamus, ACC anterior cingulate cortex, PCC posterior cingulate cortex, HT hypothalamus, S1 and S2 primary and secondary somatosensory cortical areas, PPC posterior parietal complex, SMA supplementary motor area, AMYG amygdala, PF prefrontal cortex.

la and certain brainstem regions (Pessoa 2008). The limbic system is considered to be important for emotion and affect. For instance, the hypothalamus is connected to the autonomic nervous system and thereby influences emotions, the amygdala is active in generation of fear and aggression, or the cingulate gyrus is active during emotive states.

Nociceptive processing and pain perception involve cortical, subcortical and brain stem regions. Meta-analyses of results from neuroimaging studies identified those human brain regions that are most frequently active during acute pain experience (Peyron et al. 2000, Bingel et al. 2002, Apkarian et al. 2005): primary and secondary somatosensory cortices (SI and SII), insular cortex, anterior cingulate cortex, prefrontal cortex, thalamus, basal ganglia, cerebellum, amygdala, and hippocampus (see also Figure 3). Exactly these regions are also sensitive to pharmacologically induced analgesia, what again supports their functional role in nociceptive processing and pain perception (cf. Tracey and Mantyh 2007). Importantly, the aforementioned list of brain regions is not restricted to the cortex, but includes subcortical areas, thalamus, hypothalamus, reticular formation of brain stem, ventrolateral medulla, lateral parabrachial area, amygdala, caudate medulla, periaqueductal grey matter, and pallidus/putamen. All these regions are targeted by ascending nociceptive pathways from the spinal cord (Millan 1999, Braz et al. 2006, Baumgärtner 2010). The subcortical, nociception-processing regions provide both direct and indirect input to the following cortical regions: somatosensory cortices (SI and SII), the insular cortex, the anterior cingulate cortex, and the prefrontal cortex (Millan 1999, Tracey and Mantyh 2007, Baumgärtner 2010). The cortical regions do not only display a complex pattern of connections among themselves but they possess intensive reciprocal connections to subcortical regions and thalamus. Thus, the various brain regions being active in a situation of pain perception are intensively interconnected.

At the cortical level, the somatosensory regions SI and SII participate in the sensory-discriminative aspects of pain thereby enabling to locate noxious stimuli – a property that is required for immediate defense and withdrawal behaviour (May 2007). Two cortical regions that are associated with pain affect are anterior insular cortex and anterior cingulate cortex (Price 2000, Weston

2012). It is well documented that individuals experiencing emotional feelings show activity in these two cortical areas, and individuals experiencing pain also display activity in the insular and cingulate cortices suggesting that nociceptive and affective information get connected in these regions (Vogt 2005, Craig 2009). The two cortical areas are also part of the limbic system, which generally shows an intimate connection with the pain matrix, as all parts of the limbic system – which is central for emotion and affective states – also participate in pain matrix (Peyron et al. 2000, Price 2000). Finally, both cingulate cortex and insular cortex are involved in imagined pain experience and in empathic pain, i.e. pain arising from observing another person receiving pain stimuli (Singer et al. 2004, Wager et al. 2004, May 2007).

The main relay station for the reception and processing of nociceptive information en route to the cortex is the thalamus. It interlinks with cortical and limbic structures and is involved in both the sensory-discriminative and affective-cognitive dimensions of pain (Millan 1999). Nociceptive neurons of the contralateral spinothalamic tract ascend to specific medial nuclei of the thalamus, which then project to limbic cortical areas such as insular cortex, anterior cingulate cortex (Price 2000). Other ascending projections target somatosensory relay nuclei of the thalamus from where the information is transmitted to somatosensory cortices. Many ascending projections terminate in brain regions belonging to the limbic system (e.g., amygdala, hypothalamus) but they also target brain regions such as globus pallidus which are involved in regulating motor function (Braz et al. 2006). While the former (limbic) connection contributes to emotional component of pain, the latter connection contributes to the stereotypic motor behaviours that are usually evoked by noxious stimuli.

The brainstem regions are actively involved in processing and modulating nociceptive information. For instance, the brainstem is active in gating nociceptive signals to the cortex and it functions in descending inhibition from the brain to the dorsal horn (Tracey and Mantyh 2007). Additionally, the brain stem possesses a high density of opioid receptors which can further shape nociceptive signalling. This capacity to modulate nociceptive information both in the cortical direction and in the spinal cord direction points to the important role of the brainstem in affecting pain experience. For instance, the periaqueductal grey is central for generation of

hyperalgesia (Tracey 2005). Also, it is at the level of the brainstem where nociceptive information can be integrated with arousal or autonomic processes, thereby linking nociception with overall homeostatic regulation in the organism.

The large distributed network of interconnected cortical, sub-cortical and brainstem regions that is accessed during nociceptive processing is commonly referred to as pain circuit or “pain matrix” (Figures 3 and 4). The existence of this matrix highlights that pain perception is not a matter of one specific brain region or brain part, but arises from a concerted network activity. Based on neuroanatomical, neurophysiological, pharmacological and neuroimaging data, the pain matrix is often subdivided into a lateral and medial pain systems, with both systems containing brainstem, subcortical as well as cortical components (Schnakers and Zasler 2007, Tracey and Mantyh 2007). The literature is not always consistent regarding what regions are to be included in the two systems, but generally the lateral pain system is considered to consist of the lateral thalamus, primary and secondary somatosensory cortex (SI and SII), parietal operculum and insula, while the medial system includes the medial thalamus, anterior cingulate cortex, prefrontal cortex, amygdala, hippocampus, hypothalamus, nucleus accumbens, and periaqueductal grey matter (i. e. mainly components of the “limbic system” that are known to be connected to affect). In addition, there exist connections of both systems to motor-related brain regions such as primary motor cortex, striatum and cerebellum, as they are also part of the pain matrix (Peyron et al. 2000).

It has been proposed that the lateral and medial pain systems have distinctive roles in producing pain perception: Activation of the lateral pain system is thought to be related to the sensory-discriminative aspects of pain, while the medial system is believed to participate primarily in the emotional-cognitive aspects (Peyron et al. 2000, Price 2000). Already at the thalamic level, a subdivision into a sensory and emotional-cognitive part appears to be realized, as specific thalamic nuclei are interconnected with the lateral system and other nuclei with the medial system (Millan 1999, Perl 2007). Those thalamic nuclei which belong to the medial system are known to play a role in affective and motivational reactions, while those of the lateral system are involved in somatosensory functions.

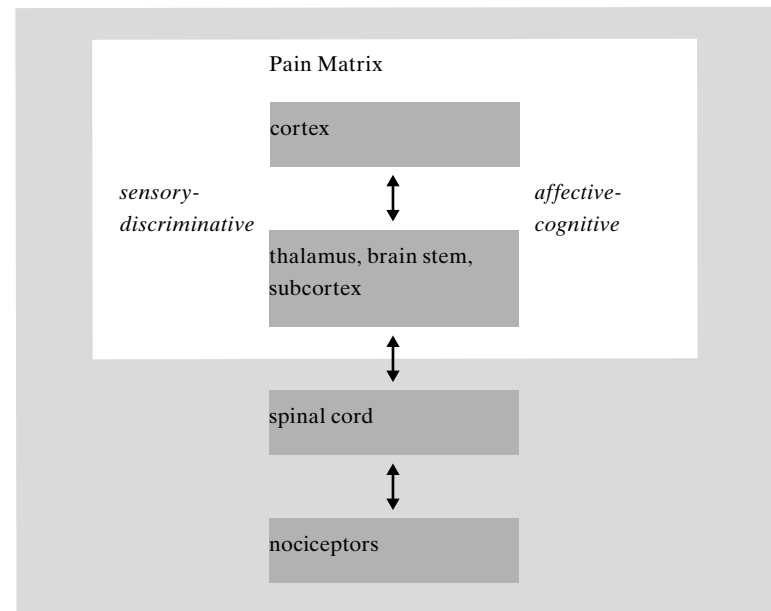


Figure 4: Sensory, affective and cognitive processing of nociceptive input in the brain results in pain sensation

The – at least partly artificial – distinction is an attempt to discriminate between those elements of pain perception which respond primarily to stimulus intensity, from those parts which reflect primarily the emotional side (“unpleasantness”) of the pain sensation. Support for the concept of an at least partial division of pain sensation into perceptions of different quality comes from clinical observations which show that selective lesions on the anterior cingulate cortex alleviate the affective component of pain, while lesions to SI/SII cortical regions affect the discriminative component of pain

(Foltz and White 1962, Ploner et al. 1999). Also neuron tracing and human brain imaging observations show neuronal connections and activity patterns that are consistent with discriminative and affective reactions in the lateral and medial systems, respectively. In addition to spatial differentiation, also temporal distinction exists, as brain processing of nociceptive signals can occur both in parallel and in series (Price 2000).

The description above provides information which brain regions are involved in processing of nociceptive information, but it does not yet inform on their functions in generating the pain sensation. The different brain structures contribute to different dimensions of pain experience, although this does not mean that one region has one singular function, but the individual regions are integrated in complex ways into the pain circuits. Also, while for some brain areas, for instance, for the periaqueductal gray matter, their function in pain perception is reasonably well understood, for other regions such as nucleus accumbens, we are only beginning to unravel their function in pain perception. The role of individual brain regions in pain processing may be not uniform but heterogeneous, and the association between nociceptive signals and affective or cognitive informations can be complex. For instance, the anterior cingulate cortex possesses subregions which mediate different aspects of pain: fear-avoidance in the median cingulate cortex, unpleasantness in a more anterior subregion, and skeletomotor orientation in posterior subregions (Vogt 2005, Pessoa 2008). In the anterior and mid regions, there exists overlap of the pain-activated sites with sites activated by emotion. In contrast, the posterior subregion, although showing a robust activation by nociceptive input shows no activation by emotional states; probably this subregion evokes skeletomotor body orientation to the noxious stimulus without affective content (Vogt 2005).

Notwithstanding the complexity of the pain matrix in the human brain, two common features are evident:

- the different functional pain components – sensory, affective, cognitive – cannot be seen as separate entities, but they are intimately interlinked (Pessoa 2008, Craig 2009). For instance, the insular cortex is viewed as a relay station for sensory input into the limbic system and pain processing therein, and it conveys cognitive aspects of pain such as learning and memory (Pessoa

2008). Neurons in the cingulate cortex stimulated by nociceptive inputs are not able to recognize where in the body a noxious stimulus is located, but the insular cortex receives this information indirectly via SI and SII somatosensory cortices, as well as via a loop going from SI and SII over subcortical amygdala and hippocampus back to cingulate cortex (Price 2000, Vogt 2005). Similarly, cognitive and emotional processes are interlinked, as cognition can trigger affective feelings, and affect can influence cognitive processes (Duncan and Barrett 2007). For instance, prefrontal and parietal cortices are considered to have a central role in cognition but they also function in processing affective information. As put by Pessoa (2008):

*“the affective processing of a stimulus is not independent of cognitive factors such as attention: on the one hand, an item’s affective significance appears to guide attention and enhance the processing of emotion-laden information, on the other hand, goal-directed attention and task context influence the neural fate of affectively significant items.”*

Earlier, it has been argued that emotion, pain and cognitive control are functionally segregated in distinct regions of the brain or different subregions of a given brain area, however, recent observations encourage a fundamentally different view. The current understanding is that negative affect, pain, and cognitive control activate overlapping regions of the brain (Shackman et al. 2011).

- pain perception is not a matter of a single brain structure, e.g. the neocortex, but results from the integrated activity of the pain matrix which includes a broad array of brain regions from neocortex, subcortex, and brainstem. For instance, for the cingulate cortex, anatomical studies reveal that the anterior subdivision of the midcingulate cortex constitutes a hub where on the one hand pain/affect information can be linked to motor centres for expressing affect and executing goal-directed behaviour, and, on the other hand, substantial reciprocal connections exist with subcortical regions involved in affect and pain. Importantly, information is not only flowing from brainstem and subcortical regions to the cortex, but also the reverse direction, and many

pathways are ultimately converging on the same subcortical and limbic structures that are directly accessed by ascending spinal pathways (Price 2000). The few examples may illustrate that the generation of pain is anything else than a linear translation of a nociceptive signal into pain sensation, but results from a complex crosstalk between different regions in cortex, subcortex and brainstem. There is general agreement that the extent to which a pain stimulus is experienced as an affective or emotive state depends upon parallel and serial activities in different areas of the pain matrix (Tracey 2005). Nociceptive input is rapidly conveyed to multiple brain regions that collectively, as a circuit, are capable of processing the input. The fact that pain perception is an integrated brain activity is undisputed, only the relative importance of specific regions or pathways is subject of ongoing discussions. For instance, while Pessoa and Adolphs (2010, 2011) emphasize the importance of cortical activities, de Gelder et al. (2011) point to the essential role of subcortical regions. Both groups, however, do not claim that pain perception takes place either in cortex or subcortex, but they emphasize the idea of the pain matrix.

### 3. Nociception and pain perception in fish

When studying pain in animals, a principal obstacle is that we have no direct access to their subjective experience and feelings. While we still can record the sensing of environmental stimuli, the feelings and emotions possibly associated with the sensing the stimuli have to be deduced from the presence and/or response of operational indicators of the emotional states. Typically, parameters which connect in an identifiable and defined way with pain perception in man are used as operational indicators, and these indicators are then studied in animals in order to infer from their presence or absence on the capability of pain perception in the animal under study (Bateson 1991, Rose 2007, Cottee 2012). Rose (2007) provides an illustrative example of this approach:

*“Stress in man is characterized by an elevation of plasma cortisol levels. Thus, stress may be operationally defined as ‘elevation of plasma cortisol levels’. If an animal in a stressful situation shows an increase of plasma cortisol levels, we infer that this animal experiences stress, in reference to what we know from man. In the case of cortisol and stress, it is easy to accept that ‘cortisol’ is a valid operational indicator of ‘stress’; however, it is much more problematic to identify a valid operational indicator for complex cognitive properties and emotive states such as ‘feeling of pain.’”*

The problem may be exemplified by the controversial discussion on the role of the neocortex for an animal’s capability to sense pain. In man, the neocortex is of central importance for conscious pain perception. Therefore, presence or absence of the neocortex may be taken as indicator for the capability of pain perception in an animal.

Following this line of thinking, only mammals would be able to experience pain. Indeed, the fact that fish lack a neocortex (see



below) has been interpreted by several authors that fish are not capable of pain experience (Rose 2002, Arlinghaus et al. 2007). However, how valid is the indicator parameter “neocortex”? As discussed above, pain perception in man is not exclusively associated with the neocortex, but involves also other brain areas such as subcortical and brain stem regions, which have homologous regions in the fish brain. In addition, the absence of a neocortex structure is *per se* not sufficient to conclude on the absence of neocortex-associated functions, as non-mammalian species may possess functional analogues executing these functions. A striking example are birds, which have no neocortex, but use a brain region called “Wulst” to perform functions that are neocortex-based in mammals. This example may illustrate the uncertainties concerning the validity of the operational indicators used to assess “pain perception” in non-human animals in general and in fish in particular.

In the following, we will focus on those structural and functional parameters that have been and are used to assess the capability of fish for pain sensation: neuroanatomical, neurophysiological, and behavioural parameters. The discussion will start with the question if fish possess the capability for nociception, as this is the essential prerequisite for any form of pain perception. Although the question may appear trivial, unequivocal evidence for the existence of nociception in teleost fish has been provided only rather recently. The next chapters will discuss:

- if there exists evidence for neuroanatomical basis of pain perception in fish,
- if there exists evidence for a neurophysiological basis of pain perception in fish,
- if there exists evidence from behavioural studies that fish are able to experience pain.

### 3.1 Nociception

Neuroanatomically, pain perception in humans involves both peripheral nociceptors for sensing noxious stimuli –, and central neural structures – for the conversion of nociceptive signals into a consciously perceived emotive state. The latter process has its

basis in the integrated activity of a dedicated system in the brain, the pain matrix. When evaluating the ability of fish to feel pain, the question arises if fish possess similar neuroanatomical equipment for nociception and pain perception. More specifically, the questions are:

- do fish possess nociceptors?
- do fish possess central nervous structures and functions that are able to convert nociceptive information into pain sensation?

Here, we will discuss the available evidence for the existence of nociceptors in teleost fish. Until the early 2000s, there was no comprehensive information available whether teleost fish possess nociceptors. There have been a few reports in the 1970s describing free nerve endings resembling nociceptors in the skin of fish (Whitaker 1971) but there was no functional data to support the interpretation that the observed structures do function as nociceptors. The first functional evidence for the presence of nociceptors in fish skin was provided by the studies of Sneddon (2002) and Sneddon et al. (2003a, b). The authors performed an anatomical and neurophysiological analysis of the trigeminal nerve in the head of rainbow trout, *Oncorhynchus mykiss*. Electron microscopical examination of the three branches of the trigeminal nerve revealed the presence of A $\beta$ , A $\delta$  and C-fibre types, i. e. the same fiber types known from mammalian nociceptors (see above). Interestingly, trout as a representative of bony fish had both myelinated and unmyelinated nerve fibers while the latter fibre type is absent in elasmobranch fish (St. John and Lewin 2009). The C-fibres comprised only 4 % of the total fibres, what is a considerably smaller percentage than in man (about 50 %); the biological significance of this difference is not clear (Sneddon 2002). In addition to the anatomical studies, Sneddon and co-workers also performed electrophysiological analyses. They applied three types of noxious stimuli: pressure, heat and chemical irritant (acetic acid). The noxious stimuli were able to trigger electrical firing of the trigeminal nociceptors, indicating that the fibers with a nociceptor-like morphology do indeed function as nociceptors (Sneddon 2002, Sneddon et al. 2003a, b, Sneddon 2004). Various types of nociceptors were observed: mechano-thermal nociceptors, mechanochemical nociceptors, polymodal

nociceptors as well as slow and fast adapting mechanical receptors (Sneddon et al. 2003a, Ashley et al. 2007). All receptor types except mechanothermal receptors showed an increase in peak firing frequency with increased strength of stimulation, with evidence of response saturation at higher intensities (Ashley et al. 2007). The mechanical thresholds were higher in the polymodal than in the mechanical receptors, but generally they were very low compared to the thresholds of mechanoreceptors in the skin of mammals. Sneddon (2003a) speculated that this is a compensatory feature to the more easily damageable nature of fish skin. Thermal nociceptors of trout showed a threshold that was about 10°C lower than the thermal threshold of mammalian thermal nociceptors, and none of the tested receptors gave any response to water temperatures below 7°C, indicating an absence of cold receptors (Ashley et al. 2007). Both properties might be explained by the poikilothermic physiology of fish. Overall, the results from this series of studies provide good evidence for the presence of nociception in teleostean fish, and that the properties of the nociceptors are adapted to the specific biological properties of fish. This conclusion agrees with the conclusion from the EFSA Report (2009) which says that “there is good scientific evidence that fish possess the sensory equipment for detecting potentially painful stimuli”.

In mammals, the next step after peripheral nociception is the processing of the nociceptive signals at the spinal cord level (see above). Fish, in general, show an organization of major spinal pathways that is similar to mammals, including spino-thalamic, spino-mesencephalic, spino-reticular and spino-limbic tracts (Chandross et al. 2004a). This similarity suggests that spinal tracts of fish function in carrying nociceptive signals to the brain, although to date actual experimental confirmation of this assumption is not available. What, however, has been shown is the presence of neuronal activities in the brain of fish after cutaneous noxious stimulation (Dunlop and Lamig 2005), indicating that peripheral nociceptive signals reach the brain. This observation provides indirect evidence for the functioning of the spinal cord of fish in nociceptive transmission.

### 3.2 Pain perception: neuroanatomical evidence

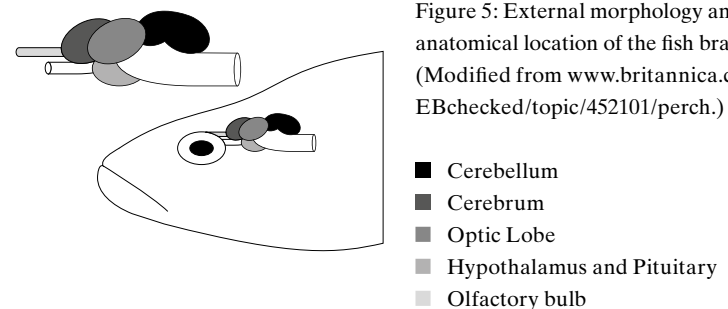
#### 3.2.1 The fish brain

The brain anatomy of teleostean fish is rather diverse, reflecting their diverse habitats and modes of life (Butler and Hodos 1996, Kotschal et al. 1998, Nieuwenhuys et al. 1998, Wulliman 1998). As emphasized by Rose (2002):

*“Fish brains are not merely simpler versions of mammalian or amphibian or reptilian brains, but they can have highly diverse, unique adaptations due to their diverse evolutionary paths.”*

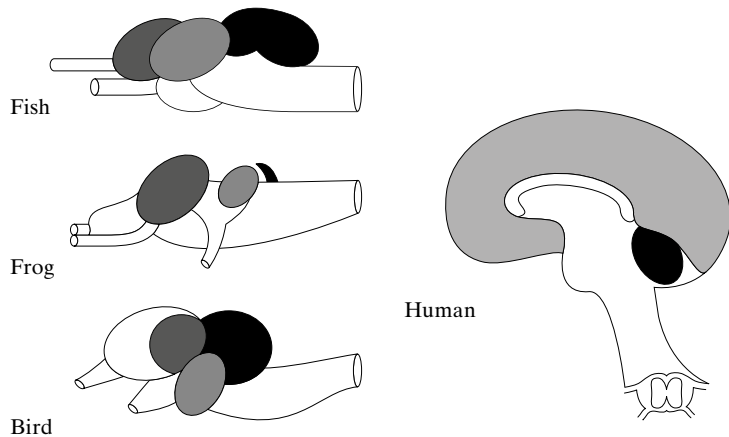
For instance, electro-sensing mormyrid fish have a specific structure, the valvula, for the central processing of electric stimuli.

Independent of species variations, however, the fish brain comprises the principal elements of the vertebrate brain, as also found in human brain (see above): telencephalon (with the olfactory lobe), diencephalon, mesencephalon (with the optic tectum), metencephalon (with the cerebellum), and myelencephalon (Figure 5). The teleost telencephalon receives input from the olfactory bulbs, but there are large areas of the pallium which are not devoted to olfactory input and are involved in other functions (see below). The telencephalon shows many reciprocal connections with the other parts of the brain. Advanced teleost fish like the percids tend to enlarge the midbrain and develop a prominent optic tectum in order to process the sensory information from the visual system as well as from the lateral line system, which provides the fish



with detailed information on its three-dimensional environment. The hindbrain contains a prominent reticular formation including giant Müller and Mauthner cells for very rapid avoidance and escape behaviours. The size of fish brains relative to body size is much smaller than it is the case for human brain (Huntingford et al. 2006).

A prominent difference between mammalian and fish brains exists with respect to the forebrain, particularly the telencephalon or cerebrum (Figure 6). The difference is expressed both with

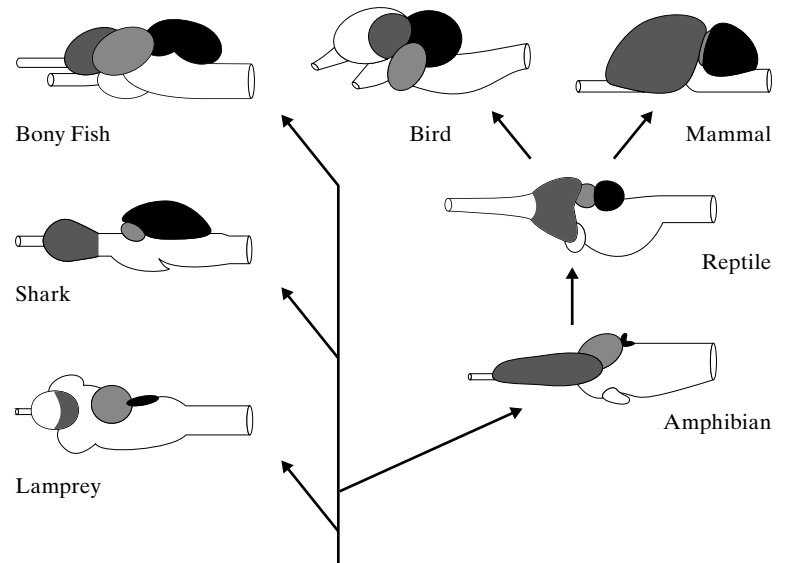


- Cerebellum
- Cerebrum
- Optic Lobe
- Neocortex

Figure 6: Comparison of brain anatomy across vertebrate classes. While the fish brain is dominated by telencephalum/cerebrum, optic lobe and cerebellum, the human brain is dominated by the neocortex. (Modified from [www.solarnavigator.net/human-brain.htm](http://www.solarnavigator.net/human-brain.htm))

respect to the overall size of the forebrain and with respect to its surface layer, the pallium or cortex.

Generally, brain evolution within vertebrates must not be seen as a linear development, from the most simple brains in fish to the most advanced brains in mammals. Instead, brain evolution within vertebrates has taken divergent routes, with one route moving towards bony fish, one towards birds and one towards mammals (Figure 7).



- Cerebellum
- Cerebrum
- Optic Tectum

Figure 7: Routes of brain development within the class of vertebrates, illustrated for forebrain, cerebrum, cerebellum, and optic tectum. (Modified from Kardong, 2006)

### 3.2.2 Neuroanatomical correlates of pain perception

Pain perception in man has its neural correlate in the pain matrix which comprises brain stem, thalamus, subcortical as well as neocortical areas. While the neocortex is absent in teleost fish, the brainstem regions and the thalamus are present. The situation is less clear with respect to the subcortical components of the pain matrix which have their origin in the telencephalon such as amygdala and hippocampus. Earlier theories on the evolution of the cerebrum in vertebrates held that new regions gradually emerged out of pre-existing regions (Kardong 2006). Along this line, the neocortex was understood as a “neostructure” which evolutionary developed from a pallial archistructure. Meanwhile, a revised view of cerebral evolution in vertebrates is established which understands the evolution of the vertebrate forebrain not as a stepwise, linear process, but as a divergent differentiation from a common ancestral anatomy. That basal structure of the vertebrate cerebrum comprises a pallium with medial, dorsal and lateral divisions, and a subpallium with striatum, septum and pallidum (Northcutt 1995, Kardong 2006, Medina and Abellan 2009). In teleosts, the pallium (but not the subpallium) becomes everted and swings outward involving re-arrangement of pallial areas (Northcutt 2008), while in all other vertebrates, it becomes inverted, with the medial pallium and septum rolling inward and the lateral and dorsal walls inverting outward (Figure 8). Compared to the brains of the other vertebrates, the fish pallium, therefore, can be considered to be inside-out.

Among the tetrapods, the pallial (cortical) regions undergo diverse evolutionary developments, which involve not only an increase in size but also a thickening and differentiation into layers. In reptiles, the lateral pallium gets hypertrophied and develops into the dorsal ventricular ridge which dominates the cerebral hemispheres. In birds, this dorsal ventricular ridge expands further and forms the so called Wulst, a region that has a high capacity for processing of visual information. In mammals, it is the dorsal pallium that experiences a tremendous evolution and gives rise to the neocortex. The medial pallium, together with parts of the lateral pallium forms the hippocampus of tetrapods. The subpallium contributes to basal ganglia, caudate nucleus, putamen and amygdala of tetrapods.

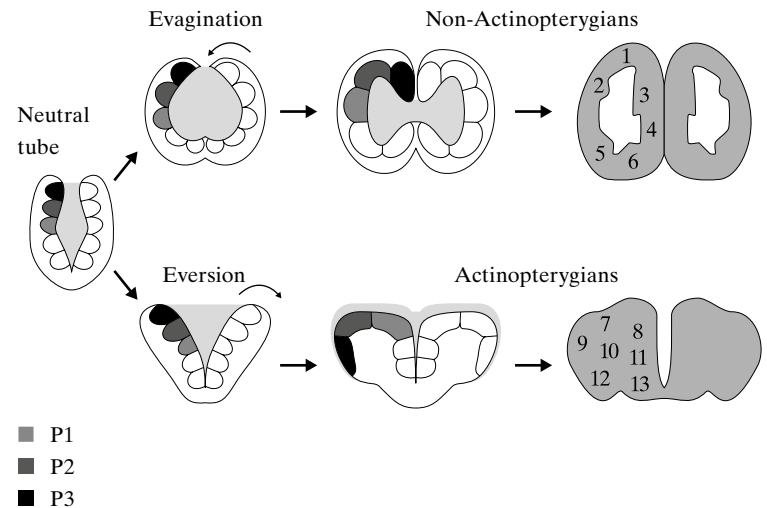


Figure 8: Development of the pallium in actinopterygian vertebrates (fin-rayed fish, including teleosts) and in non-actinopterygian vertebrates (including tetrapods). In teleosts, the pallium (but not the subpallium) becomes everted and swings outward involving rearrangement of pallial areas (Northcutt 2008), while in the other vertebrates, it becomes inverted, with the medial pallium and septum rolling inward and the lateral and dorsal walls inverting outward. These differences complicate the recognition of homologies. P1, P2, and P3 correspond to the three main subdivisions of the pallium. (Modified from Broglio et al., 2003)

1. Dorsal pallium
2. Lateral pallium
3. Medial pallium
4. Septum
5. Striatum
6. Accumbens
7. Area dorsalis telencephali pars dorsalis
8. Area dorsalis telencephali pars medialis
9. Area dorsalis telencephali lateralis pars dorsalis
10. Area dorsalis telencephali pars centralis
11. Area ventralis telencephali pars dorsalis
12. Area dorsalis telencephali lateralis pars ventralis
13. Area ventralis telencephali pars ventralis

For teleost fish, given the everse instead of inverse development of the pallial regions (see above), the neuroanatomical and developmental evaluation of homologies of pallium and subpallium to the cerebral brain regions of tetrapod vertebrates is complicated (Moreno and Gonzalez 2007, Northcutt 2008). Instead, a more promising approach may be to compare functional analogies between the fish and mammalian cerebrum. While originally it was thought that the primary role of the teleostean cerebrum is the processing of olfactory input, it is now clear that the function of the teleost cerebrum goes clearly beyond that aspect. The teleost cerebrum has developed into a highly differentiated structure being essential for the processing of diverse sensory information and possibly also affective information. Research over the last decade has demonstrated remarkable cognitive, learning and memory capabilities of fish, and it is the cerebrum which appears to be the major neural correlate to these capabilities (cf. Chandroo et al. 2004a, Braithwaite 2010): pallial and sub-pallial regions of the teleost cerebrum show neural connections to other brain areas which resemble those in higher vertebrates (Butler and Hodar 1996, Nieuwenhuys et al. 1998), they are involved in processing of somatosensory, gustatory, visual, acoustic and other sensory modalities, they mediate complex behaviours and integrative functions such as avoidance learning, spatial learning, general arousal and social behaviour, and they are central for motivation and emotional learning as well as memory. The lateral pallium, for instance, is crucial for spatial learning, while the medial pallium is essential for emotional learning and related processes, such as avoidance learning (Portavella et al. 2004, Broglio et al. 2005, Vargas et al. 2009). Fish with lateral pallium lesions show severe and permanent deficits in identifying a familiar place, in finding and implementing new routes or in memorizing known routes (Rodriguez et al. 2002, Broglio et al. 2010, Duran et al. 2010). Spatial learning results in increased activity of the lateral pallium and removal of this brain region significantly impairs spatial learning capability (Rodriguez et al. 2002). Surgical removal of other pallial areas remained without effect on spatial learning and memory of fish (Broglio et al. 2010). Lesions in the medial pallium have an effect on emotional learning of fish. For instance, both Broglio et al. (2005) and Portavella et al. (2002) observed that medial lesion impaired acquisition

and retention of conditioned avoidance response in learning experiments. These observations suggest that lateral and medial pallium have similar involvements in emotional and spatial learning as do hippocampus and amygdala of tetrapods. The tetrapod amygdala, in particular, is known to play a major role in fear and fear responses (LeDoux 1996), and in fact, lesions to teleost medial and lateral pallium disrupt fear-related behaviour (Broglio et al. 2005, Cottee 2012). Observations as exemplified above suggest homology of lateral, medial and dorsal pallium of fish to the subcortical regions, hippocampus and amygdala, of tetrapods (Broglio et al. 2005, Braithwaite and Boulcott 2007, Vargas et al. 2009). It also has been proposed that the dorsal pallium is homologous to the mammalian (neo)cortex, for instance, due to the nerve connections with other brain areas which are similar to tetrapods (Echtemer and Saidel 1981), or because of homologies in genetic markers between dorsal pallium and mammalian neocortex (Wullimann and Müller 2004). Overall, however, the available evidence on a neocortex homologue in fish remains weak.

With respect to pain perception, the absence of a neocortex in fish has given rise to a controversial discussion on the capability of fish to feel pain. Based on this lack of higher cortical centres in the fish brain it has been argued that they may not be able to experience pain. This has been formulated by Rose (2002) in his influential article on pain perception of fish. Rose (2002, 2007) argues as follows:

*“Pain perception is a conscious experience, and since consciousness is located – at least partly (see below) – in the neocortex, animals without neocortex do not possess pain perception. This implicates that fish, as they have no neocortex, are not capable of pain perception.”*

While this line of arguing is consistent in itself, the critical question is if pain perception depends indeed that exclusively on the neocortex as claimed by Rose (2002) and others. Two alternative scenarios might be possible:

- could a (simple) pain perception arise from the activity of non-neocortical elements of the pain matrix, such as subcortical

regions, thalamus, brain stem? Could it be that the integrated action of these regions are sufficient to generate a “simple” pain sensation? Is the fact that pain perception in man is not an exclusive function of the cortex, but arises from the integrated activity of the pain matrix involving neocortical as well as non-neocortical regions supportive to such an interpretation? This leads also to the question on the evolution of pain perception: Has pain evolved only with the advent of the neocortex, with zero perception before presence of the neocortex, but full pain perception once the neocortex has evolved? Or was there a more gradual evolution of pain-related emotions and sensations, starting as a simple pain experience mediated by phylogenetically older brain regions?

- the neocortex is a particular evolutionary feature of the mammalian vertebrates. Other vertebrate classes have taken different routes of brain evolution. Could it be that those vertebrate classes which possess no neocortex utilize other brain areas for functions which in mammals are executed by the neocortex (Chandross et al. 2004a, Huntingford et al. 2006, EFSA 2009)?

The generation of pain sensation in the human brain involves a complex pain matrix, which comprises not only cortical areas but also subcortical and brainstem regions, or, as formulated by Craig (2009):

*“The anterior cingulate cortex certainly does not operate autonomously.”*

While Rose does not negate this fact, his view is that the subcortical areas alone, in the absence of the higher integrative system such as the neocortex, are not able to generate pain sensation. According to Rose (2002), brainstem and subcortical regions may be able to modulate perceptive processes in the cortex, but they cannot perform the perceptive process alone, without cortex. Rose (2002) supports his view from observations on humans with cerebral cortex destruction or congenital cortex deficits. These persons are believed to be in a vegetative state in which all conscious awareness of environmental stimuli is abolished. Importantly, these persons still show behavioural responses to pain such as withdrawal reac-

tion or facial expressions. Since they have no neocortex function, Rose (2002) considers these responses as reflexive, stereotyped behaviours. However, this interpretation is partly in conflict to findings from patients with frontal lobotomy or cingulotomy. Until the 1950s, this surgery was sometimes done with patients who suffered from chronic pain or depression. Indeed, removal of the frontal cortex or the cingulate cortex was able to remove chronic pain and depression, under retainment of the general intelligence of the patients. However, they lost emotional depth and feeling (Hurt and Ballantine 1974). The patients retained normal pain reflexes, they were aware of the pain, but they did not experience the emotional feeling of pain, the reaction was entirely in the present, and they seemed to have lost fear of the pain (Freeman and Watts 1950). Obviously, removing the frontal cortex does not completely eliminate pain perception but eliminates certain qualities of pain perception. This interpretation is supported by the findings of Schnakers and Zasler (2007). These authors measured neuronal activities in patients with no functional cortex. Upon nociceptive stimulation, neural activities in the subcortical regions of decorticate patients were not zero, but there were still rudimentary activities on-going. Patients with a minimally functional neocortex showed brain activation patterns which were similar to brain activation patterns of control subjects. Schnakers and Zasler (2007) interpret these observations not as indication that pain perception is impossible without neocortex, as claimed by Rose (2002), but their conclusion is that full pain perception depends on the interaction between cortical and subcortical regions. Also Duncan and Barrett (2007) emphasize that pain perception in man involves the integrated activity of multiple regions from neocortex, subcortex and brainstem, and that pain perception, similar to many complex experiences, may emerge from the flow and integration of information among several brain areas rather than from activation of one specific part of the brain. This agrees well with common understanding in the recent literature is that there is no single brain area which can be designated specifically to be responsible for pain perception, but that this property is widely distributed in the brain, and arises from the interplay between the various regions.

What does the importance of interactions between brain areas for pain perception mean with respect to pain perception in animal

brains without neocortex? Is pain sensation completely abolished in species without neocortex, or is there a simple pain sensation, mediated by the non-neocortical elements of the pain matrix? As discussed above (Freeman and Watts 1950, Hurt and Ballantyne 1974, Schnakers and Zasler 2007), patients with a non-functional cortex appear to have not zero pain perception – as claimed by Rose (2002) –, but they seem to have a limited pain perception, apparently experiencing pain in a different quality of pain compared to patients with functional cortex. Further evidence for subcortical pain perception comes, for instance, from studies on children suffering hydranencephaly: Despite total or near-total absence of the neocortex, these children possess discriminative awareness of environmental stimuli, and they respond to noxious stimulation not in a merely reflexive but in purposeful way (Shewmon et al. 1999, Schnakers and Zasler 2007). Vegetative state patients generate only an incomplete brain activation pattern upon nociceptive stimulation; however, it remains unclear if this means absent or incomplete pain perception (Schnakers and Zasler 2007). In this context, it is an interesting observation that loss of pain perception caused by brain lesions occurs only if the lesion is located in the thalamus, not in the cerebral cortex (what gave rise to the earlier belief that pain is the product of a thalamic mechanism; Perl 2007).

Another important question is to what extent findings on the role of cortex and subcortex in pain perception of man can be extrapolated to pain perception of fish. The human brain has evolved as a functional unit involving both neocortical and non-neocortical components. Taking the neocortex out of this evolutionary shaped unit will necessarily result in a loss of function, as the system is designed to function as a whole, and not in separate parts (this may be an explanation why surgical lesions to specific brain areas often failed to relieve pain). The situation is different with avian or piscine brains, which have evolved cognitive and affective capacities in the absence of the neocortex. They may perform similar functions – albeit in a different quality – with alternative brain areas. Rose (2002) has addressed this argument and rejected it on the following grounds:

*“Fish brains are understood well enough to make it highly implausible that there are alternate, functionally uncommitted systems.”*

It is indeed plausible that the fish brain has no alternate region which could substitute for the human cortex, but this is not the question; the question is whether fish possess brain areas that are capable of linking a nociceptive signal with affect and cognition, thereby moving it beyond a merely reflexive, stereotypic level. In this context, Cottee (2012) provides an illustrative example:

*“Imagine if you will be a fish stating to humans: ‘I have fins. If I am missing my fins, I can no longer swim. Fins are therefore essential for swimming. Humans do not possess fins. Therefore, humans cannot swim.’”*

Of course, man is not able of the elegant and efficient swimming like fish, but man is still able of some simple form of swimming, even in the absence of the functional correlate for fish swimming, i. e. fins. The bias in this simple example is immediately evident, and although it cannot be directly extrapolated to the cortex/pain issue, it is still worthy to think over potential flaws in that discussion.

How cautious one has to be in concluding from the presence or absence of specific neuroanatomical structures on the presence or absence of neural functions is exemplified by the recent change of our understanding of the functional properties of bird brains. Several bird species display behaviour reminiscent of the sophisticated levels of cognition and higher levels of consciousness which are usually associated with mammals, including the ability to fashion tools and to learn vocal sequences (Butler and Cotterill 2006). At the same time, however, birds and mammals show a marked dissimilarity in the dorsal pallium regions of the brain. While both birds and mammals possess a hippocampus originating from the lateral and medial pallium, the remaining, largest part of the pallium forms the neocortex in mammals and the so-called “Wulst” in birds. The significant difference of brain structure between the two taxa implicates that the two vertebrate classes apparently achieve similar cognitive and perceptive capabilities despite clear differences in neuroanatomy. Many functions, for which in mammals the neural substrate is the neocortex, are mediated by the Wulst in birds (Medina and Reiner 2000, EFSA 2009). Recent research has revolutionized the understanding of the avian brain neuro-

anatomy and the homologies to the mammalian brain (Jarvis et al. 2005), and the lesson learned from this development is that we need to be very cautious in extrapolating from brain structures and associated functions in man to other vertebrates. Apparently, the same function can be served by different brain structures in different vertebrate groups (EFSA 2009). As outlined by Butler and Cotterill (2006), similarity of neural features of two vertebrate groups is not primarily a matter of similarity in brain structure, but of similarity in neural circuits (Butler and Cotterill 2006).

This brings us back to the question on the affective-cognitive capabilities of the fish brain. In chapter 3.4, several examples of emotional and cognitive learning in fish will be provided. Fish are able to perform a number of functions which in the human brain are processed – at least partly – in the neocortex. Bshary et al. (2002) provide examples of cognitive phenomena of fish, particularly in their social and environmental relationships, which in mammals are considered to be functions of the neocortex. As fish never evolved a neocortex, obviously other brain regions must execute these cognitive functions. Like the mammalian cortex, the fish pallium appears to have a highly developed capability for processing of sensory information: it is intensively interconnected with other brain areas such as mesencephalon and dienecehalon (Rink and Wullimann 2004), it is active after noxious stimulation (Dunlop and Laming 2005), and it contains structures which appear to be homologous to the mammalian amygdala and hippocampus (Portavella et al. 2002, 2004). Fish also possess a hypothalamus which is involved in functions such as sensual and social behaviour, and it integrates signals originating from those telencephalic regions which have been implicated in fear responses (Chandroo et al. 2004a). All this is not to say that fish have the same cognitive capabilities as primates, but both the behavioural and the neuro-anatomical observations point to continuities in brain functions and of neural correlates of emotive and mental states throughout vertebrate evolution, rather than drawing a sharp line between pre- and post-neocortex vertebrates. Another example of evolutionary continuity in the development of the cognitive vertebrate brain is indicated from the manifestation of cerebral lateralization through all vertebrate classes (Vallortigara 2000). There is now an increasing body of data from studies in humans and animals that point to

continuity of cognitive and emotion processing and its evolutionary role in shaping adaptive behaviour (Tamietto and de Gelder 2010).

The principal question underlying them of the discussion above is the question how animals assign biological value to a stimulus: Animals are able to decide which stimuli are “good” and which ones are “bad”, they are able to learn on this, to approach the good ones and avoid the bad ones, keep memory on them, etc. These processes depend on specific neural correlates. The discussion above indicates that different animal taxa may use different neuroanatomical structures for one and the same task. Even for mammals, where pain sensation is based on neural circuits between subcortical and neocortical regions, it is not yet fully understood how the neocortex interprets subcortical input, and how much circuitry between the various areas is needed to feel pain. Therefore, an equation “no neocortex=no pain perception” may be too simplified and may not adequately reflect the complex processes through which nociceptive signals are converted into perceived pain in the vertebrate brain.

### 3.3 Pain perception: neurophysiological evidence

The previous chapter discussed evidence for or against pain perception in fish as derived from neuroanatomical features. This chapter will discuss available information on physiological properties of the fish brain which may shed light on the capability of fish for pain perception.

Neuroimaging and electrophysiological studies have been intensively applied in studies with mammals to reveal changes in the functional state of brain after nociceptive stimulation. This type of studies showed, for instance, increased neuronal activity in areas such as anterior cingulate cortex when human volunteers were subjected to unpleasant noxious stimuli like tonic cold (Kwan et al. 2000). Comparable studies with fish are very rare to absent, probably not only because of technical difficulties but also because of difficulties in interpretation. If, for instance, an electrophysiological response is observed in a specific brain area of the fish, how can be proved that this does not represent nociception but pain perception? As pointed out by Rose (2007), the



demonstration of physiological responses in certain brain areas in response to noxious stimuli is no evidence of pain, but may simply represent nociceptive responses. Dunlop and Laming (2005) subjected trout and goldfish to mechanoreceptive and nociceptive stimuli, and recorded electrophysiological responses in the brain. Activity was found not only in brainstem and spinal cord regions (which are considered to be the key players in reflexive responses to nociceptive stimuli – see Rose 2002), but also in the forebrain, i.e. that brain region where higher cognitive centres are located. Also Nordgreen et al. (2007) found that electric stimulation of the tail of Atlantic salmon, *Salmo salar*, led to neuronal activity in the telencephalon. Similarly, Reilly et al. (2008) who studied gene expression in different brain areas of fish exposed to nociceptive stimuli observed gene induction responses in the telencephalon. These findings suggest that the neural response of fish to painful stimuli is not confined to the lower brain centres of mid- and hind-brain, but extends to the telencephalon. Since the telencephalon is central to learning and memory, nociceptive processing in this part of the brain may indicate – but is not yet a prove! – that the neurophysiological response of fish to nociceptive signals goes beyond a simple reflexive response but may process the external stimuli at a cognitive and emotional level (Nordgreen et al. 2007). A promising next step has been taken by Nordgreen et al. (2007) who treated salmon with electric stimuli of different intensities, which they considered as putatively non-noxious (low intensity) and putatively noxious (high intensity). The two treatments evoked significantly different electric potentials in the telencephalon. While this finding indicates that salmon distinguish between the putatively noxious and putatively non-noxious stimuli, it remains unclear what this difference means with respect to pain perception.

The fish brain possesses neurotransmitters, which in man are involved in emotional states including pain, for instance, dopamine. Dopamine has important functions in motivation and reward behaviour. Interestingly, administration of dopaminergic agonists like amphetamine evokes reward behaviour not only in mammals but also in fish (Chandroo et al. 2004a), possibly indicating some capability of fish to experience emotions. Also substance P, which in mammals is involved in pain mediation as well as in reward processes, affects the reward behaviour of fish (Mattioli et al. 1995).

Much emphasis in studying neurophysiological aspects of the nociception and pain in fish was given to the question if fish possess an endogenous analgesia system. Vertebrates can endogenously control transmission of nociceptive signals and reduce pain sensation by means of opiod peptides, enkephalins and the corresponding opiod receptors. In man, neurons using opiod peptides as neurotransmitters are located, for instance, in ascending and descending projections of the spinal cord and in the brain stem (Millan 1999); and relatively high concentrations of opiod receptors are found in the higher association centres as well as in components of the limbic system including the amygdala (Zubietta et al. 2001). There exists good evidence that fish, like other vertebrates, possess opiod receptors, endogenous opioids and enkephalins. First evidence for the presence of endogenous opioids and opiod receptors became available in the late 1980s (Vallarino 1985, Rosenblum and Callard 1988, McDonald and Dores 1991). Meanwhile it is well established that fish possess all four main opiod receptor types (delta, kappa, mu and NOP) found in vertebrates (Weber 2011), that the protein structure of piscine opiod receptors is very similar to that of mammalian opiod receptors, and that the distribution of endogenous opioids and enkephalins in the fish brain is similar to that in mammalian brains (EFSA 2009). Importantly, expression of opiod receptors in the fish brain is not confined to brainstem, but, comparable to mammals, they are also found in the telencephalon of fish, i.e. they can potentially interfere with higher level processing of sensory and affective information (Gonzalez-Nunez and Rodriguez 2009). Behavioural studies revealed that the opiod system in fish indeed has an analgesic function, since administration of analgesic substances such as morphine or opiate antagonists such as naloxone to fish results in reduced behavioural response to painful stimuli (Ehrensing and Michell 1982, Chervova 1997, Sneddon 2003a, b, Nordgreen et al. 2009, Mettam et al. 2011). Molecular, biochemical and pharmacological properties of fish opiod receptors are fundamentally similar to their mammalian counterparts. Consequently, fish species like zebrafish are meanwhile used as model organisms to study opiod activity and to develop new analgesic and psychoactive drugs for man (Gonzalez-Nunez and Rodriguez 2009). Again, however, the presence of opiod system in fish is not yet sufficient to conclude on the presence of pain

perception in fish. This system may simply serve to suppress nociceptive responses, although one may wonder if this would require an apparently elaborated analgesic system.

Similarities between fish and mammals extend beyond analgesia. Fish species such as zebrafish are also used as model to investigate the hedonic effects of addictive drugs as well as the mechanisms of dependence from opiate drugs (Darland and Dowling 2001, Guo 2004, Lau et al. 2006, Ninkovic and Bally-Cuif 2006). Darland and Dowling (2001) demonstrated a genetic basis for the response of zebrafish to cocaine. They showed that zebrafish exhibit strong or weak cocaine-induced conditioned place preference behaviour depending on their genetic make-up of the fish. These differences in cocaine sensitivity of behavioural preferences were associated with differences in stress sensitivity and novelty response, two parameters which in rats are associated with the dopamine system, reward behaviour and amphetamine self-administration. Selective advantages of the ability to decide for pleasure and to avoid pain are obvious, and observations like the aforementioned ones raise the question on how gradually or abruptly this ability developed during vertebrate evolution.

### 3.4 Pain perception: behavioural evidence

#### 3.4.1 Fish cognition

After having discussed neuroanatomical and neurophysiological evidence for or against the capability of fish to perceive pain, this chapter will address the evidence available from behavioural studies. Animals can respond behaviourally to environmental signals in a rather inflexible, stereotypic way, or in a flexible way, what can increase the adaptive value of the response. To be able to respond in a flexible way, the animal needs advanced capabilities to process the information, memorize it, connect it with other information and/or with emotion, and to deduce logical decisions from these cognitive processes. Behavioural studies can provide insight into the mental states of animals, that is their capability to process information input and to annotate it emotionally (Bateson 1991, Rose 2002, Chandroo 2004a, b, Broom 2007, Cottee 2012). The

area of behavioural research which deals with animal minds is also designated as cognitive ethology (Bekoff 2007, Wild 2012). Intimately related to the study of animal mental states is the question of animal consciousness, however, this aspect will be discussed in a separate chapter.

Concerning cognitive capabilities of fish, conventional wisdom portrays fish as simple-minded, instinct-driven organisms with “a three-second-memory” (Laland et al. 2003, Salas et al. 2006, Braithwaite 2010), showing mainly reflexive behaviour and little cognitive capabilities (basically a behaviouristic idea – see also Wild 2012). Recent research has challenged this view and has demonstrated profound capabilities of fish for cognitive processes, for instance, fish are able to create mental representations of their social interactions and their environment (e. g., Bshary et al. 2002, Sloman et al. 2006). To cite Laland et al. (2003):

*“Gone (or at least obsolete) is the image of fish as drudging and dim-witted pea brains, driven largely by instinct, with what little behavioural flexibility they possess being severely hampered by an infamous three-second-memory.”*

It is undisputed that fish are able of simple forms of learning such as associative learning. This represents the classical “Pawlow” conditioning and operant learning, i. e. any form of learning in which a response becomes associated – via reward or punishment – with a stimulus. This form of learning represents reflexive behaviour which does not require higher cognitive capabilities. Accordingly, associative learning is already present in animals with relatively simple nervous systems such as the mollusc *Aplysia* (Lorenzetti et al. 2006). Thus, the presence of associative learning does not yet indicate the presence of higher cognitive capabilities in fish. However, fish execute cognitive learning processes that go clearly beyond associative learning (Bshary et al. 2002, Laland et al. 2003, Warburton 2003, Braithwaite 2006). The evolutionary advantage of differentiated cognitive capabilities is that they enable animals to make decisions and to be able to respond to new situations in a flexible rather than in a stereotypic way (Kotrschal and Taborsky 2010). Fish can recognize spatial patterns and complex temporal sequences, they memorize experiences, they display highly devel-

oped social behaviours, and they are able to learn from experiences in order to adapt their behaviour to new situations. Nowadays, fish – particularly species like zebrafish which offer the possibility of genetic screens in conjunction with behavioural studies – are promoted as models for neurobehavioural research in mammals, due to their many behavioural and cognitive similarities to rodents (Egan et al. 2009, Sison and Gerlai 2010, Stewart et al. 2010, Wong et al. 2010, Gaikwad et al. 2011).

As pointed out by Bshary et al. (2002), cognition is the basis for flexible behavioural responses of organisms to both social and environmental information. Many fish species, like many mammalian species, live in stable social groups of varying size and sex composition, and defend their territories or take care for their offspring, what requires highly developed cognitive capabilities for dealing with social information (Bshary et al. 2002). For instance, individual recognition, usually based on optical cues, does exist in such groups (Griffiths 2003). Also for fish species living in shoals, individual recognition has been demonstrated (Bshary et al. 2002). In addition to individually knowing their mates, fish can also monitor their social status and track social relationships among third parties (Griffiths 2003, Laland et al. 2003). These cognitive capabilities are the basis for more complex social behaviours (Braithwaite 2006). Social learning and traditive behaviour are widespread among mammalian species, but they also exist in fish. This includes, for instance, learning on the location of spawning sites, learning by observation on what to eat and what to avoid, or the learning of anti-predator behaviour by tutors (Bshary et al. 2002, Brown and Laland 2003). Fish can gather information about relationships of other group members and integrate this information into their behaviour (Brown and Laland 2003). In fact, fish are able to develop mental representations or “maps” on social information. A cognitive or mental map is defined as a memory representation of social or environmental information. The ability to form mental maps is a key element for the cognitive capabilities of animals, as the mental maps provide the basis for decision making and planning, i. e. for non-stereotypic, but flexible, “intelligent” behaviour. One example to illustrate this may be provided by the study of Dugatkin and Goding (1992) on the influence of social factors on mate choice: These authors

performed experiments in which a female guppy received the opportunity to choose between two males. Subsequently, a second female was introduced and the first one could observe the male preference of the second female. When now the first female was allowed to choose again among the two males, it changed the initial mate choice and copied the preference of the second female. Obviously, the social relationships in the experimental group were represented in the mind of the first female (“mental map”) and influenced its decision making.

Also very complex forms of social learning such as co-operative hunting, which is considered a hallmark of hominid evolution, have been reported for fish. There exist a number of examples of co-operative intraspecific hunting in fish (Strübin et al. 2011). For instance, mackerels hunt in groups for their prey (Hobson 1974). Co-operative interspecific hunting has been described by Bshary et al. (2002) in a study on giant moray eels, *Gymnothorax javanicus*, and red sea coral grouper, *Plectropomus pessuliferus*. Both species hunt in coral reefs. When prey fish of the grouper hide in caves of the corals, which are not accessible to the grouper but to the eel, the grouper informs the moray eel on this situation. To this end, the grouper uses a special signalling behaviour, which obviously is understood by the eel, because the eel then approaches the prey in the cave, while the grouper is waiting outside the cave to catch the escaping prey fish. The advantage for the eel is that it also can feed on the prey. In this example, the grouper solicits the eel to hunt together, with the two species playing different roles during hunting. In this sense, the co-operative hunting is not an opportunistic one (occurring by chance), but an intentional one (one species motivates the other one to join the hunting).

In addition to cognitive capabilities for processing social information, fish possess well-developed cognitive capabilities to behaviourally deal with their environment and with environmental changes. An example is provided by their capability of learning and encoding spatial information on their environment into spatial maps. For a long time, fish orientation, for instance during migration, was understood as a primarily genetically fixed behaviour. However, as the physical environment can change, it is advantageous to be more flexible and to possess the capability to learn and process spatial information. In fact, fish can memorize

information about their environment and can encode mental maps on the spatial relationships between multiple cues, landmarks or sensory features. This enables the subject to locate an object or its own position (Salas et al. 2006). Fish often rely on more than one source of spatial information such as visual landmarks, olfactory landmarks and information from water movement or sun-compass orientation (Odling-Smee and Braithwaite 2003). An illustrative experiment to demonstrate the capability of fish of encoding spatial maps was performed by Burt de Perrera (2004a) using the Mexican cavefish, *Asytanax fasciatus*. This species is blind but recognizes physical structures in its environment via changes in the flow field around its body. Detection of the flow field occurs by means of the neuromasts in the lateral line system. Cavefish swim faster when faced with unfamiliar landmarks in their environment, but they eventually get familiar with the spatial conditions of the environment and then reduce swimming speed. When cavefish, after having been habituated to a given spatial environment, are then confronted with a change in this spatial arrangement, they increase swimming velocity (Burt de Perera 2004a). This behaviour indicates that the fish memorized the original spatial environment and was able to recognize its alteration. Apparently, the fish compared the environment they actually perceived with an internal representation of the environment they had learnt. The capability to encode spatial maps has been shown for a number of other fish species as well, for instance, coral reef fish such as butterfly fish memorize the paths connecting their feeding patches with their home area. When landmarks along this path are displaced, the fish stop swimming and search for the missing landmark (Reese 1989).

The capability to encode spatial maps includes also the capability to remember the spatial and temporal order of landmarks in the environment. This has been proven by Burt de Perera (2004b) who trained Mexican cavefish to habituate to an environment with a distinct arrangement of landmarks. Swimming speed of the fish decreased with increasing habituation and familiarity with the spatial map. Then the spatial sequence of the landmarks was switched and the fish responded to this by increased swimming velocity, indicating that the fish had memorized the original order of landmarks and recognized the change in the spatial order.

Fish show flexibility of their environmental behaviour. Again, spatial orientation may serve as example. Young children, when disoriented, use geometric cues for spatial re-orientation, however, they fail to re-orient by non-geometric information such as differently coloured walls (cf. Sovrano et al. 2002). The same has been reported for adult individuals of rats and several other mammalian species. Adult men, in contrast, are more flexible and make use of combinations of geometric and non-geometric information for spatial orientation. Sovrano et al. (2002) studied the capability of fish to combine different sources of information in spatial orientation. To this end, a spatial orientation test was done with the fish species, *Xenotoca eiseni*, in which either only geometric or a combination of geometric and non-geometric landmarks were available. The fish were able to use both sources of information for their orientation in space, i.e. they showed flexibility in their behaviour as human adults do.

An interesting aspect of the capability of fish to cognitively deal with environmental information is the learning of numbers. The ability to count objects or to discriminate among sets with different numbers of items is relevant in many environmental contexts, and, accordingly, this ability has been demonstrated in a wide variety of vertebrate species and classes. Non-human primates, proverbial human infants and human adults possess the ability to spontaneously represent numbers in their minds, usually by means of a small number system that supports the precise representation of individual objects up to numbers of 3 or 4 units, while larger numbers are represented as an approximate magnitude system. Fish appear to have a similar numerical capacity; they can learn to precisely discriminate small quantities and to estimate quantities larger than 4 units (Dadda et al. 2009, Agrillo et al. 2009, 2010). As observed in human and non-human primates, the numerical system of fish appears to have virtually no upper limit while the numerical ratio has a clear effect on the performance.

Studies on foraging behaviour demonstrate the cognitive capabilities of fish for integrating social and environmental information. Fish use associative learning for finding food, for instance, they can easily learn to associate a stimulus (e.g., a visual cue) with food reward (Warburton 2003). Beyond classical conditioning, fish are also able of active anticipation of unconditioned

stimuli. For example, golden shiners, *Notemigonus chrysoleucas*, were trained to expect food at midday at a specific site in their tank. After a short training period, they displayed active food anticipatory behaviour, i. e. towards midday they spent more and more time at the specific feeding site (Reebs 2000). Fish are also able for probability matching, i. e. if offered several feeding sources; they chose the one with the higher likelihood of food reward. They remember feeding patch profitabilities, what enables them to spend longer time in patches with higher prey densities (Warburton 2003). Social information is actively used by fish to modify their feeding behaviour and to cooperate in the search for food (Milinski et al. 1990). For instance, Laland and Williams (1997) have shown that guppies learn the way to hidden food sources by observing knowledgeable conspecifics. More generally, socially transmitted information in fish shoals facilitates the acquisition of dietary preferences or the finding of food sources (Brown and Laland 2003). Fish employ social information also for strategic decisions in their foraging behaviour, as demonstrated by, e.g., Dugatkin and Wilson (1992): Individual bluegill sunfish, *Lepomis macrochirus*, remembered the feeding success with individual conspecifics, and used this information to prefer or avoid those associates for joint food search.

Cognitive functions of fish can be modified by stress, in the same ways it is the case in man. This may be illustrated on the example of the interplay between stress and memory. For humans it is well established that stress affects cognitive functions and can impair learning and memory. This is paralleled in fish, as shown, e.g., by Gaikwad et al. (2011): Zebrafish were trained in an aquatic plus-maze for 14 days using food as reward. Prior to the final testing, the fish were acutely stressed by either one of two ecologically relevant stressors, which were exposure to a predator fish species or exposure to an alarm pheromone. Acute stress markedly impaired spatial memory as well as cued memory of zebrafish in the plus maze test, i.e. the affective state associated with the stress situation impaired the cognitive performance of the individual. This observation with fish corresponds fully with results from plus maze studies with mammals.

The most important message from the behavioural studies with respect to the question of pain perception is that the cognitive

capabilities of fish go clearly beyond the level of reflexive, invariant or associative learning, but they have higher cognitive capabilities such as recognition and memory of individuals, recognition of co-operators, observational and social learning, cultural transmission, and, importantly, logical deductions. An example to the latter point is provided by the study of Grosenick et al. (2007). These authors used a cichlid species, *Astatotilapia burtoni*, which regularly fights over territories. A male fish – the observer – was placed in a central aquarium surrounded by five other tanks containing five males – A, B, C, D, E – of similar size. When transferring, e.g., male A into aquarium of male B, the fish started to fight, and the observer fish could see which individual wins the fight. In this way, the observer fish could learn that, e.g. fish A is stronger than fish B, and fish B is stronger than fish C. In a next step, the observer fish was confronted in a choice test with fish A and C. In this situation, the observer fish decided to spend more time in fighting the weaker fish, i.e. fish C. Apparently, the observer fish memorized the identity of the different individuals, linked this with information on their previous fighting performance, and then made a logical deduction which individual to attack in order to optimize its own chance to win. To tell that fish C is subordinate to fish A, the observer fish must be able to form a mental map of the hierarchies between individuals A, B and C, i.e. it memorized that A defeated B, and B defeated C, and from this it made the logical deduction that A should be stronger than C. This cognitive process is designated as transitive inference. Animals which are known to have the capability of transitive inference include some bird species such as crows, and mammals such as rodents and primates. In man, the ability of transitive inference develops around the age of four years, but is not present in younger children. The observation of Grosenick et al. (2007) suggests that at least certain fish species have the capability for a complex cognitive process such as transitive inference.

Another example of fish making logical deductions may be provided by the study of Hollis et al. (2004). These authors used male blue gouramis, *Trichogaster trichopterus*, which form dominance hierarchies. Dominant and subordinate individuals, who knew each other, were separated and individually trained to associate a light signal with feeding. The fish expressed the learning by ap-

proaching the aquarium site where the food was dropped as soon as the light was switched on, actually already before the food was there (anticipatory behaviour – see above). After this training, dominant and subordinate fish were combined in pairs and the light-feeding experiment was repeated. In this situation, only the dominant individuals showed the learned feeding response while the subordinates did not; they stayed away from the feeding site and adopted a submissive posture. Obviously, the subordinate fish knew that the light signal announced the arrival of food, but they also knew that they will suffer aggression from the dominants if approaching the feeding site. They combined these two types of information and made a logical decision to ignore the light signal and to stay away from the food in order to avoid aggression by the dominant fish.

Taken together, the few examples discussed above provide clear evidence that fish possess substantial cognitive capabilities which in many aspects parallel those of mammals. This is the case despite the absence of the neocortex, what brings us back to the question of the neural basis of cognitive capabilities in fish. In mammals, high order cognitive attributes such as spatial memories and maps, which require complex associational processing, take place in hippocampus and neocortex. Fish perform complex spatial tasks in a way comparable to mammals, although their neuroanatomy is different to mammals: while they have a hippocampus homologue (the – dorsal – pallium of the fish brain is considered to be homologous to the tetrapod hippocampus – see above), they lack a neocortex. Apparently, fish use brain structures other than the neocortex to perform cognitive functions which in mammals are at least partly based in the neocortex. As formulated by Bshary et al. (2002):

*“Fish as a taxon have found solutions to almost all the problems that supposedly led to the evolution of a large neocortex and cognitive skills in primates.”*

### 3.4.2 Behavioural responses to noxious stimuli

The research discussed above provides strong evidence that fish possess explicit cognitive capabilities. This is one important pre-requisite to be able to convert nociceptive information into pain (Grandin and Deesing 2003). However, it does not automatically imply that pain perception indeed takes place. Therefore, here we will discuss the existing knowledge on the behavioural responses of fish to noxious stimuli, and if these responses are indicative of perception of the stimuli as pain.

Fish exposed to (acute) noxious stimuli show a number of physiological responses such as increased ventilation activity, what can be explained as cortisol/catecholamine-mediated stress response, as well as behavioural responses such as escape response (Sneddon et al. 2003a, b, Newby and Stevens 2008, Reilly et al. 2008). Fish can also learn to avoid noxious stimuli, as shown, for instance, in the study of Dunlop et al. (2006): In this experiment, goldfish and rainbow trout received electric shocks in certain areas of their aquaria, i.e. they were trained to associate a spatial area in a tank with noxious stimulation. Both species learned to avoid that area. Obviously, they were able to connect the nociceptive information with spatial information to develop spatially cued avoidance behaviour (Dunlop et al. 2006). Protective reactions to noxious stimuli such as an escape response are a universal characteristic to animal life, and do not require a complex nervous systems or higher cognitive capabilities. These reactions can occur in the absence of awareness of the noxious stimuli, but may be mediated by neural systems in spinal cord/brainstem regions (Rose 2002). Also avoidance learning of noxious stimuli is not necessarily indicative of higher cognitive processing, but, as pointed out by Rose (2009), may represent non-conscious procedural learning.

Behavioural responses can be taken as indicators of pain perception only if it is possible to demonstrate that they are different to behavioural responses nociception alone might trigger (Dunlop et al. 2006, Braithwaite 2010). This requires sophisticated experimental design and careful interpretation of the results. Even then, however, the interpretation of the behavioural responses is difficult and can lead to conflicting conclusions. An example from mammals on a behavioural response which is indicative of pain perception rather than nociception is pain guarding, that is protecting, for instance, an

injured leg by avoiding putting weight on it, or going off feed because of abdominal injury (Grandin and Deesing 2003). Such an approach has been selected by Sneddon et al. (2003a) to obtain insight into the capability of trout for pain perception. These authors gave rainbow trout injections of painful agents (acetic acid, bee venom) into their lips. The hypothesis tested was that if the fish would experience the injected solutions as painful, they would try to pain-guard their lips and stop feeding. In fact, fish injected with either bee venom or acetic acid into the lips stopped feeding for 170 minutes. This was in contrast to trout that were injected with a neutral agent (saline); those animals stopped feeding for only 80 instead of 170 minutes. Reduced interest in food has been observed also in fish with peritonitis, a disease that causes severe and chronic visceral pain in man (Bjorge et al. 2011). Also in mammals, suppression of food intake is a typical behaviour associated with pain experience. Sneddon et al. (2003a, b) interpreted the suppressed feeding activity of rainbow trout injected with acetic acid or bee venom into their lip to represent a pain-guarding response, i.e. the fish aims to protect the injured part of the body in order to avoid the pain sensation. To this end, the fish prioritized the aversive stimulus – pain – over the positive stimulus – food intake –, and decided between the two motivational states. This would argue against a purely reflexive response; instead it would point to the involvement of cognitive processes and pain perception. This interpretation, however, was challenged by Rose (2007). His criticism did not target the validity of the connection between reduced food intake and pain, but the validity of the experimental findings, in particular the fact that Sneddon et al. (2003a) injected rather large volumes of irritants, and that the effect of the treatment was rather small (bee venom/acetic-acid injected fish resumed feeding with a less than 2-hour-delay compared to saline-injected fish). According to Rose (2007), the comparatively rapid re-initiation of feeding relative to vehicle-injected control fish is inconsistent with the assumption that the fish were suffering from pain:

*“When it is considered that the acid and venome injections would presumably have produced a large-scale and sustained nociceptor activation, it is remarkable that the injections had so little effect. Rather than proving a capacity for pain, these results suggest resilience to oral trauma by the trout.”*

Another challenge to the findings of Sneddon et al. (2003a, b) comes from the report of Newby and Stevens (2008), who did not observe a suppressive effect of acetic acid injection on the feeding response of trout – however, it remains open how comparable the experimental conditions of the two studies actually were.

To further elaborate the nature of the behavioural response of trout to noxious stimuli, Sneddon et al. (2003b) investigated if attention of fish might be affected by the presence of noxious stimuli. Attention to novelty requires the animal to focus on a single aspect while neglecting the other ones. This behaviour represents a complex, higher order cognitive process. As known from man, pain is well able to distract attention. To test how noxious stimuli affect attention in fish, Sneddon et al. (2003b) confronted rainbow trout, after injection with either saline vehicle or acetic acid solution, with a novel object in their aquarium, and then observed how the fish responded to it. When confronted with a new object in their environment, trout initially dare to come close to it, apparently being afraid of the unknown object. In the experiment, trout that were given the saline injection showed the typical daring behaviour towards the new object. In contrast, trout given the acetic acid injection showed no such behaviour and moved close to the new object. The authors interpreted these results to show that the attention of the fish to the novelty of the object was impaired by the presence of the noxious stimulus, comparable to the attention behaviour of mammals under pain. Sneddon et al. (2003b) hypothesized that if the distracted attention of trout in the experiment was pain-based, then pain relief should restore the normal behavioural response – comparable to the response of man under analgesic treatment: while pain distracts our attentional awareness, pain relief by analgesic drugs can restore it. To test their hypothesis, Sneddon et al. (2003b) administered morphine to acetic acid-injected trout, and indeed, after the analgesic treatment the acetic acid-injected trout showed the same behavioural response towards the novel object as fish from the control group. The authors concluded that the behavioural responses observed in their study are beyond reflexive (i.e. nociceptive) behaviour but would indicate that the fish were cognitively aware and experienced the aversive consequences of the acetic acid treatment. Rose (2007) does not agree with this interpretation; according to his view, which refers

to findings with sleep-walking man (Plazzi et al. 2005, Ebrahim 2006), complex behaviour – such as distraction of attention – can be executed without awareness of relevant stimuli. Also Chandroo et al. (2004b) are critical towards the conclusion of Sneddon et al. (2003b); they argue that the labelling of the attention behaviour as “complex, higher order cognitive process” is simply based on value judgement but not underpinned by functional insight into the nature of the cognitive processing.

The influence of analgesic drugs on the behavioural response of fish to noxious stimuli has been repeatedly used as argument that the response of fish to a noxious stimulus represents pain perception (Sneddon 2003a, Nordgreen et al. 2009, Braithwaite 2010). As described above, fish possess opioid receptors in their brain, and, thus, they are sensitive to analgesic drugs. Fish show altered behavioural responses to noxious stimuli after treatment with compounds such as morphine or lidocain (Sneddon et al. 2003 a, b, Mettam et al. 2011). However, since opioid receptors occur both in brainstem and higher brain areas, an analgesic effect on pain/nociceptive behaviour is not sufficient as argument for the presence of pain perception in fish, since the analgesic effect may be mediated via modulation of nociceptive signalling in brainstem regions (Rose 2002, 2007). A clear signalling of pain perception would be if the animal is actively seeking pain relief by accessing opiates. This type of studies has been done with rodents, but not (yet) with fish.

Another indication that a behavioural reaction to noxious stimuli represents pain perception rather than nociception comes from the flexibility of the response. Avoidance learning (see above) is usually interpreted as associative learning, which requires no higher cognitive capabilities. However, avoidance learning is not always invariable but can show flexibility and incorporate conceptual information so that the fish match their response according to the environmental situation. For instance, Dunlop et al. (2006), in their study of the spatially cued avoidance learning of trout found that the learning process could be modified by the presence of conspecifics. The authors used a classical choice experiment to further explore the flexibility of the behavioural response. The experiment built on the postulate that, due to shoaling behaviour, fish will prefer to stay close to a conspecific, what represents a

“pleasure” stimulus to the animal. In the experiment, the fish had to make a choice between the “pleasure” stimulus – staying close to a conspecific –, and the aversive pain stimulus – a mild electric shock. The hypothesis was that the fish will change their avoidance behaviour in the vicinity of a conspecific. The results showed that the behavioural response to the electric shock was indeed changed by the presence of a conspecific. This trade-off between the willingness to remain in the vicinity of the conspecific and receiving a mild electric shock was in expectation with the hypothesis. Apparently, the fish made a cost/benefit analysis, and changed their pain avoidance behaviour according to differing circumstances. The flexibility of fish pain behaviour “suggests that pain responses are not just confined to lower brain reflex actions, to some degree, involve perception” (Dunlop et al. 2006).

Fish learn to avoid aversive stimuli by linking them with stimuli which per se are not aversive. This was shown, for instance, in a study by Zerboglio and Royalty (1983) who trained goldfish to learn the relationship between neutral signals and an aversive event (electric shock). For the training, not only matching signals but also oddity signals were used. The fish were well able to learn matching and oddity discrimination in order to avoid being shocked. A similar study was performed by Portavella et al. (2004): In this experiment, goldfish received an aversive stimulus (mild electric shock) in a particular area of their tank when an optical signal (green light) was switched on for several seconds. The fish quickly learned to avoid that particular area of their tank when the optic signal was presented. The conditioned avoidance response was retained after the training period. The biochemical basis of the conditioning process was enlightened by Xu et al. (2007) in a study with zebrafish: the authors could show that treatment of zebrafish with antagonists of the N-methyl-D-aspartate receptor impairs the avoidance learning. This observation agrees well with findings from other vertebrates, where also the N-methyl-D-aspartate receptor is involved in conditional learning.

In the experimental arrangements as chosen in the studies of Zerboglio and Royalty (1983) and Portavella et al. (2004), a previously neutral signal – e. g., green light – becomes a conditioned aversive stimulus by pairing it with an aversive event (e. g., electric shock). Importantly, it is not the stimulus that changes – green light



remains green light – but the perception of the stimulus by the animal – a neutral signal like green light gets an aversive meaning (Cottee 2012). One may call this response a fear reaction. Fear is a negative, aversive emotion induced by a perceived threat which motivates the animal to avoid the threat or to move away from it. Neuroanatomically, the amygdala is the major site of fear processing (Killcross et al. 1997). Learned avoidance responses of fish to painful stimuli have been repeatedly interpreted as fear behaviour. Although some authors consider the use of terms like “fear” for fish to represent anthropomorphism, there exists strong evidence for the existence of fear behaviour in fish (Yue et al. 2004, Nordgreen et al. 2009). This is not surprising as fear is probably an evolutionary old adaptation to avoid dangerous situations (Dawkins 2000). In addition, fish possess the neuroanatomical substrate for fear processing, as parts of the pallium are homologous to the tetrapod amygdala (see above). Fear is different from pain, but both conditions can cause suffering (conscious perception of unpleasant external and internal stimuli) of animals (Chandroo et al. 2004, Huntingford et al. 2006). Investigating fear in fish can teach us lessons on pain perception in fish: First, fear – like pain – represents an unpleasant mental state, and a capability of fish to feel fear implicates the capability for sentience to feel pain (notwithstanding the fact that the neuroanatomical and neurophysiological correlates of fear and pain are different). Second, fear responses – similar as pain responses – can be learned through Pavlovian conditioning, but they can also involve higher cognitive processes. For instance, Cantalupo et al. (1998) reported that mosquitofish which has been exposed repeatedly to a simulated predator in a specific spatial area of the aquarium developed an anticipatory fear response, that is the fish crossed the critical spatial area using rapid zig-zag swimming, even if the predator was not present. Apparently, the fish remembered the previous threatful situation and attempted to avoid or escape a possible predator attack by the specific swimming behaviour. Such an anticipatory behaviour points to higher order cognitive processes rather than reflexive responses. Finally, fear and pain are closely interconnected, as exposure of fish to noxious stimuli modulates affective states such as fear or anxiety (Sneddon et al. 2003b, Chandroo et al. 2004a, Yue et al. 2004, Egan et al. 2009).

How do the findings from studies on the behavioural reaction of fish to noxious stimuli connect to the existing knowledge on functional brain neuroanatomy of fish? Rose (2002, 2007) has been arguing that the neural basis of the response of fish to noxious stimuli is based at the levels of brainstem and spinal cord. Spatial information, however, is encoded in the telencephalic pallium (Broglio et al. 2003, 2005). In addition, the fish telencephalon contains neurons which get activated under noxious stimulation (Dunlop and Laming 2006). Finally, there exists evidence that the telencephalon is involved in avoidance learning (Overmier and Papini 1986, Onishi 1997) and contains the emotional system critical for fear conditioning (Portavella et al. 2004). All these data suggest that processing of nociceptive input in the fish brain involves processes beyond the brainstem in the telencephalon, what argues against a purely reflexive reaction requiring only lower brain centres such as spinal cord and brain stem.

Strong disagreement with the conclusions above comes from Rose (2002, 2007). According to this author, the brain receives nociceptive information from the spinal cord and cranial nerves. Working together with the spinal cord, the brain generates responses which cause the organism to escape or to avoid the noxious stimuli. These responses are produced by innate neural programs and include reactions such as withdrawal of the stimulated body part or locomotion. All of these responses are generated by lower levels of the central nervous system, mainly brain stem and spinal cord, while the cerebral hemispheres would serve mainly to “modulate” behaviour. However, Rose (2007) does not refer to studies like those of Broglio et al. (2003, 2005) or Portavella et al. (2004) which postulate a stronger involvement of the forebrain into behavioural responses of fish, so that is not possible to judge if Rose considers the arguments of those authors to be conclusive. Likewise, Rose (2002, 2007) argues that behaviour of fish is inconsistent with the assumption of pain perception. Unfortunately, the literature on fish behaviour and cognition is somewhat weakly represented in the work of Rose (2002, 2007), what makes it difficult to weigh his arguments against the evidence provided by the studies discussed above. Rose (2007) claims that interpretations of behavioural experiments often suffer from “anthropomorphism” and that we tend to humanize animal behaviours – a criticism, which is correct, at

least to a certain extent. Still, we need to find ways how to deal with and interpret different levels of complexity in animal behaviour. The approach of Rose to distinguish only two levels – conscious (implicating pain perception) and non-conscious (implicating nociception) (see next chapter) – may be too simplistic to reflect gradual evolutionary developments in way how vertebrates deal with nociceptive signals. It is clear that we must exercise some caution when we interpret animal behaviour in terms of pain (Braithwaite and Boulcott 2007). However, at least several of the behavioural studies discussed above suggest that behavioural responses of fish to noxious stimuli are not merely a reflexive response but involve higher order cognitive processes and probably pain perception. Overall, the available information from behavioural studies strongly argues for the presence of some form of pain perception in fish.

#### 4. Consciousness in fish

It is the conscious perception of noxious stimuli that turns a nociceptive signal into the experience we designate as pain. Thus, consciousness is an intrinsic component of pain perception in man. Accordingly, the IASP definition of pain explicitly refers to pain as “conscious experience”. Given the central role of consciousness in pain perception, the question is if fish are conscious organisms. This question has taken a prominent role in the discussion on pain experience of fish. The overall direction of this discussion is well reflected by Rose (2002) who argues that “in order to prove that a fish feels pain, it is necessary to show that a fish has consciousness”. While this sounds logical, practically the approach is hindered by two obstacles:

- what do we actually mean – in biological terms – when we talk of “consciousness”; and
- how do we assess consciousness, what operational indicators can we use to demonstrate presence or absence of consciousness?

In the following, it will be attempted to review shortly the ongoing discussion on the existence of fish consciousness, with the focus on the biological literature. The philosophical dimension of the question will not be addressed here, as this is excellently done in the study of Wild (2012).

The term of animal consciousness has a “tumultuous history” (Cottee 2012) in life sciences. In the Cartesian view, only man was considered to have a conscious mind while animals were understood as non-conscious “automatons”. Early in the 20th century, reductionist approaches of neurobehaviourists tried to explain animal behaviour on the basis of reflexes, “tropisms”, instinct or associations, and were sceptical towards a concept of animal consciousness (Greenspan and Baars 2005). Consciousness as a study object of life sciences

became accepted only later in the 20th century, and it is now getting increasingly important in animal welfare research, although the term remains controversial due to the problems in empirically demonstrating the existence of animal consciousness. These controversies are still reflected in the current literature on animal consciousness in general and fish consciousness in particular (e.g., Dawkins 2000, Chandroo et al. 2004b, Arlinghaus et al. 2007, Cottee 2012).

An instrumental approach to make the term consciousness accessible to biological research is to discriminate different levels or forms of consciousness. Rose (2002), as many other authors, distinguishes two forms of consciousness, primary and secondary. Primary (or feeling) consciousness refers to the moment-to-moment awareness of sensory and emotional experiences. Secondary consciousness (or self-awareness) includes awareness of one's self as an entity that exists separately from other entities. In this system, secondary consciousness is restricted to man and probably some other primates, while it is primary consciousness which matters in the case of fish.

Braithwaite (2010) adopted a scheme developed by Ned Block who distinguishes three forms of consciousness:

- *access consciousness*, as the capability to think about a mental state. This would include the capability to generate a mental map by combining diverse pieces of information, and to deduce from this mental map guidance for decisions, for instance, to use a mental map of the spatial environment to plan a route for moving from A to B;
- *phenomenal consciousness*, as the capability to sense environmental and social information and to connect it with affective-emotional information, that is seeing, smelling, feeling the world. Specifically for the ability to feel and experience emotions, some authors in the biological literature use the term “sentience”;
- *monitoring or self-consciousness*, as the capability to think on one's own actions.

Also Panksepp (2005) distinguishes several tiers of animal consciousness. Importantly, he understands the various tiers as an evolutionary continuum, thus, it is not a question of having or

not having a specific form of consciousness but there are multiple layers of emergence. According to Panksepp (2005):

*“Primary consciousness may reflect raw sensory/perceptual feelings and (various) types of internal emotional/motivational experiences. Secondary consciousness may reflect the capacity to have thoughts about experiences, especially about how external events relate to internal events. Finally, there are tertiary forms of consciousness – thoughts about thoughts, awareness of awareness – much of which is unique to humans and requires expansive neocortical tissues that permit linguistic-symbolic transformation of simple thoughts and remembered experiences. Those who are not willing to give animals any consciousness are probably thinking about the tertiary human-typical linguistic variants. They may also be generalizing too readily from human perceptual consciousness, which is clearly dependent on neocortical functions, to an affective consciousness whose locus of control is largely sub-neocortical. There are reasons to believe that affective experience may have provided an evolutionary platform for the emergence of more complex layers of consciousness”.*

One lesson to be learned from the discussion above is that consciousness can mean rather different things, and it needs a clear definition what we mean when we talk of consciousness in fish. It is evident that it does not refer to something like self-consciousness, but it deals with “simple” consciousness (corresponding to what has been said above about the “simple” pain experience of fish) – some form of basic cognitive and emotional awareness. A second lesson from the discussion on forms of consciousness is that conscious awareness of internal and external states is probably not an all-or-nothing phenomenon but rather a gradually evolving property. Its evolution may even be limited to specific subject matters which are appropriate for the animal's ecology (Chandroo et al. 2004b). As stated by de Gelder et al. (2011):

*“Viewed from an anthropocentric perspective, emotions are intrinsically linked to the highest human mental faculties seated in the neocortex. However, from another perspective, emotions are essentially adaptive action dispositions, and phylogenetic continuity is the central heuristic principle of affective neuroscience.”*

The discussion on what consciousness actually is in biological terms leads to the second important question: how can we assess that an animal is conscious, what are the neural correlates of consciousness and which operational indicators do we have to “measure” the presence of consciousness in an organism? In man, the standard behavioural indicator for consciousness is “accurate report”, the ability to being aware of and to report – verbally or non-verbally – a sensory event (Seth et al. 2005). Behavioural tests such as accurate report are difficult to interpret when used in animals. Here, alternative behavioural tests are needed for assessing consciousness in animals. The accurate report test is based on the assumption that consciousness is a perceptual state in which the individual does report the presence of a stimulus and/or its attributes such as the emotional content, while a non-conscious perception is a state when the individual does not report the presence of a stimulus or its attributes, even though there is evidence, for instance from neurophysiological measurements, that the stimulus has been processed by the individual (Tamietto and de Gelder 2010). One may train an animal to non-verbally report a sensory signal, for instance, by pushing a button, however, it is difficult to distinguish if this represents conscious perception or conditional learning. An example of a powerful behavioural test is the behaviour of animals towards psychoactive drugs: Many humans find drugs that activate opioid receptors in the brain or facilitate dopamine activity to be pleasurable. For a number of animal species it has been shown (for instance, in “self-rewarding” experiments) that they are also responsive to such hedonistic drugs and express strong desire for them. In addition, neurophysiologically the drugs act similarly in the brains of animals and man. The behavioural response of animals towards psychoactive drugs clearly suggests that affective consciousness is present in these animals, because otherwise the behaviourally expressed desire of the animals for these drugs is difficult to explain (Panksepp 2005). Nevertheless, already these two examples may illustrate that the distinction between conscious and non-conscious perception is not a straightforward exercise if it comes to animals, and the borderlines between the two perception types are fluent, depending to a large extent on the methods used.

A frequently used approach to assess consciousness in non-human species is a comparative approach which uses parameters which have been shown to be associated with human consciousness as a reference and benchmark. Principally, this is the same approach as already described for pain assessment in non-human species (see above). This approach yields the more conclusive results, the more closely the evolutionary relationship is between the species under question and man. The operational indicators of consciousness in animals rely on structures and functions which are analogous and homologous to neural correlates of human consciousness. Neuroanatomical correlates of conscious perception in man are the thalamocortical system as well as the mesencephalic reticular formation, while certain neurotransmitter and opioid systems as well as certain EEG patterns represent key neurophysiological correlates (Baars 2005, Edelman et al. 2005, Seth et al. 2005). Edelman et al. (2005) give a nice illustration of the scopes and limits of the comparative approach. They examine the possibility that (primary) consciousness exists in birds and in cephalopods (*Octopus*). The neuroanatomy of birds is distinguished from the human brain in a number of aspects, for instance, the presence of the pallial “Wulst” instead of the neocortex. However, histological, molecular and ontogenetic markers identify numerous structural homologies and suggest that many of neuronal properties and circuitry that underlie the mammalian cortical system are already in place in birds (Edelman et al. 2005). For instance, the somatomotor circuitry within the avian dorsal pallium appears to be homologous to the mammalian basal ganglia-cortico-thalamic loop. For several other structures, like the layers of the avian Wulst, the identification of homologies remains contentious. The overall evidence from this homology approach, however, suggests that birds have at least some of the necessary substrates and conditions for primary consciousness (Edelman et al. 2005). The situation gets much more complicated if it comes to cephalopods. Here, due to the distant phylogenetic paths mammals and cephalopods have taken in their evolutionary history, the search goes not for homologous but for analogous neuroanatomical structures and neurophysiological functions. Although cephalopods undoubtedly are able of higher sensory and cognitive functions, the currently available knowledge is by far not sufficient to come up with any conclusive

statement on the possibility of consciousness in this animal group. Available knowledge on fish appears to be somewhat halfway between birds and cephalopods - although the available information strongly increased over the last 10 to 20 years. Nevertheless, there remain significant knowledge gaps what makes all statements on the presence of consciousness in fish fairly speculative.

According to Rose (2002), consciousness and pain perception in man depend critically on the presence of the neocortex. Therefore, this author took the absence of a neocortex homologue in fish as a main argument to dispute the possibility of consciousness and pain perception in fish. Rose (2002) says that subcortical and brainstem regions may be able to modulate perceptive processes in the cortex, but without cortex they are not capable of conscious perception of stimuli. He supports his view with observations from humans with cerebral cortex destruction or congenital cortex deficit, who appear to be in a vegetative state, with conscious awareness being abolished. However, these data have to be considered cautiously, since the decorticate patients have also compromised thalamocortical activity, what makes it difficult to distinguish between the role of the neocortex and the non-cortex structures (cf. Chandroo et al. 2004b). Also findings on the effects of cortical, thalamic and brainstem lesions on human consciousness (Seth et al. 2005) are in contradiction to the logics of Rose (2002). Current day evidence challenges the view of Rose (2002) and suggests that it is too one-dimensional (Pessoa 2008, Tamietto and de Gelder 2010). Consciousness is understood to depend more on an interaction of different brain regions – with the neocortex having a prominent role in this interaction – rather than on one specific region alone (Baars 2005, Panksepp 2005, Tamietto and de Gelder 2010) – a view that is in line with current understanding of pain arising from the pain matrix rather than from the neocortex alone. There is increasing evidence that evolutionary old, non-cortical brain regions are involved in maintaining the state of consciousness while the neocortex regions, (in interaction with the thalamus) sustain conscious content. The concept that consciousness is a network property rather than the property of one particular brain structure is also supported from the observation of widespread brain activation during conscious perception (Seth et al. 2005).

Brain regions other than the neocortex may functionally substitute in non-mammalian vertebrates if it comes to generation of consciousness. The sub-cortical regions may be able to generate simple levels of consciousness such as affective consciousness (Panksepp 2005, 2011). Major loci for affective experiences in both non-mammalian vertebrates and mammals including man are situated in very similar and very ancient regions of the vertebrate brain, such as thalamus, amygdala, hippocampus or brainstem, and it is within these circuits where emotional responses can be triggered (Panksepp 2005, 2011, Pessoa 2008, Tamietto and de Gelder 2010). Also in fish, there exists good experimental evidence of a role of these evolutionary old brain areas in cognitive and emotional processes (e.g., Portavella et al. 2004, Vargas et al. 2009). Rose (2002) rejected the generation of consciousness through brain regions other than the neocortex on the following grounds:

*“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 cortex and thalamus, and enough non-sensory cortical mass and local functional diversification to permit regionally specialized, differentiated activity patterns.”*

Even with respect to non-human mammals, Rose (2002) argues that they may have little capacity for consciousness and, thus, for pain perception:

*“The type of neocortex most essential to consciousness, the non-sensory association cortex, comprises the vast majority of human cerebral cortex, but it is a very small proportion of the neocortex in most mammals. Even great apes, having substantially less non-sensory association cortex than humans, would be unlikely candidates for human-like higher consciousness.”*

The argumentation of Rose (2002), however, is biased in two ways. First, his view of the role of the “non-sensory association cortex” is not appropriate in the light of recent research. As discussed in the chapter on human brain, cortical areas which are involved

in “non-sensory association” such as the anterior cingulate cortex or the insular cortex are nowadays seen as having much broader functions than “non-sensory association”; actually, key to their function is to integrate diverse processes. Thus, the argumentation on the basis of relative brain mass reserved for the non-sensory association function appears to be somewhat flawed. Second, Rose (2002) denies the presence of “human-like higher consciousness” in non-mammalian vertebrates (and perhaps even in many mammalian species), but the question is not whether fish have a human-like consciousness, but whether fish are capable of a simple form of consciousness.

Given the difficulties to argue for the presence of consciousness in fish on the basis of neuroanatomical data, several authors took the demonstration of higher cognitive capabilities, as evidenced in a number of behavioural studies (see above), as argument to support the possibility of consciousness in this animal group. However, as emphasized by Rose (2002, 2007) and Chandroo et al. (2004b), higher cognitive processing is not synonymous with conscious cognition. What we know for fish is that they are able to create mental representations of their environment and their social relationships – a fact that would fit Braithwaite’s (2010) description of access consciousness. Rich Moccia, Ian Duncan, Stephanie Yue and their colleagues have discussed intensively the available evidence for the existence of phenomenal consciousness in fish (Chandroo et al. 2004a, b, Cottee 2012). The general tenor of these discussions is that adult fish probably do experience some of the adverse states that humans associate with pain and emotional distress, and that they have the cognitive capacity necessary for conscious suffering. The main arguments to support this conclusion are (cf. Huntingford et al. 2006):

- fish are capable of complex learning, and they can form mental representations of their environment, using forebrain structures that are homologous to those in birds and mammals;
- fish process different types of information in different areas of the forebrain, suggesting that these experiences can be integrated and enable the fish to generate appropriate and flexible adaptive responses (Portavella et al. 2004, Yue et al. 2004);
- fish can remember emotive experiences;

- fish produce endogenous opioids;
- fish display a complex and in no way stereotyped behaviour, particularly social fish species.

Overall, the answer of the various authors on the question of fish consciousness is positive, although many aspects remain uncertain and are subject of equivocal interpretation. The question is what level of confidence we actually can achieve and what level of uncertainty we have to accept, given the limitations in the available operational indicators to assess consciousness. In this context, we must not overlook that also in man the term consciousness has some vagueness and is not always unequivocally defined (Bateson 1991). Self-reflective awareness is of course present in adults; however, children appear to gain full awareness of themselves as an entity distinct from others only around the second year of life. A child of less than two years does not have full reflexive consciousness, although when being hurt, it is aware of the pain. Another example is the learning of language by young children which is a unique feature of man, but as adults we do not consciously remember how we learned the language (but we realize how difficult it can be to consciously learn another language). Thus, are young children conscious or not? The question cannot be answered by a simple yes or no, and the same may apply when asking on consciousness of animals.

Finally, a critical question is whether the discussion on consciousness is indeed helpful to answer the question of pain perception in fish. Many of the arguments used in the discussion on fish consciousness are “*déjà vu*” arguments and have already been used in the discussion of pain perception in fish. Instead of introducing new aspects, it appears that the consciousness discussion is partly repetitive to the pain discussion and thus does not really promote our understanding of pain perception in fish (this, however, applies only for the biological aspects of the discussion and differs clearly from the philosophical discussion on fish consciousness – see Wild 2012).

## 5. Conclusions

The previous chapters discussed neuroanatomical, neurophysiological and behavioural data which are used as operational indicators to assess the capability of fish for conscious pain perception. They also address the existence of consciousness in fish and to what extent this discussion furthers our understanding of pain perception in fish. Pain is a human experience and as such, the term cannot be directly transferred to fish, but we have to rely on diverse constructs, all of them with strengths and weaknesses in accessing animal minds.

The discussion in the biological literature on pain perception and consciousness in animals centers roughly around two concepts, the all-or-nothing concept and the continuity concept. In simplified form, the all-or-nothing concept says that in the absence of certain properties like e.g. neocortex, pain perception is impossible. A basic assumption behind this concept is that “all the systems involved in the detection of pain have evolved as unitary package, which is either present and works in its entity, or is absent and does not work at all” (Bateson 1991). The continuity concept emphasizes the evolutionary, stepwise development of pain perception; it assumes that already sub-systems can provide some level of function, even if they do not support the full functional level as achieved in man but only a restricted or simple form of pain perception. What is clear, however, is that the quality of pain experience in animals like fish is different from pain experience in man. Basically, the question is not “does fish feel pain?” but “which pain does fish feel?”

If a animal species displays analogies and/or homologies of the operational indicators which are correlated with pain perception in man – as the species serving as benchmark –, this provides evidence that the species has the capability of pain perception. This will never be a yes or no-decision, as no animal species will be

identical to man, but will show more or less pronounced differences of the indicator parameters. A decision is more easy to achieve with species closely related to man, e.g. other primates, as these species have many similarities to man. The results of the comparative approach will get more disputable, the more phylogenetically distant the species under consideration is. The key question is where to draw the line: when are the similarities still sufficient to assume that the species is able of at least a simple pain sensation, and when is this no longer the case? It appears that currently there exists no general agreement on the scientific criteria where to draw this line, and on the basis of what considerations.

As outlined above, the assessment of pain perception in fish on the basis of structural and functional analogies and homologies bears considerable uncertainty. Therefore, such an assessment should not rely on a single, stand-alone parameter but should build on multiple lines of evidence. Bateson (1991) as well as EFSA (2009) listed a series of parameters which they considered to be useful in providing evidence for or against pain perception in animals including fish. All these criteria were addressed in the present review, and they are summarized in the following table. Fish fulfill all criteria in the list above except for the presence of the neocortex. It is indeed this fact that has been put forward as main argument against the existence of pain perception and consciousness in fish. As discussed above, presence of the neocortex is essential for human pain perception and consciousness, however, it is under debate to what extent the neocortex alone drives pain perception, and whether the presence of phylogenetically older parts of the pain matrix would be sufficient to create a simple form of pain experience. It is clear that the question on pain perception in fish is not a matter of majority decision (six criteria pro pain perception, one criterion contra pain perception), still it is debatable if the single “no”-criterion – absence of the neocortex – has such a weight that it outrules all the other criteria, and if it is indeed a strong enough argument to exclude that fish have the capability of pain experience. In this context, it needs to be emphasized how much our picture of cognitive capabilities of fish has changed over the last two decades. If the table below would have been set up 20 years ago, in many cases the answer to the question “present in fish?” would have been a “no” or a question mark.

Criterion:	Present in fish?
Existence of functional receptors sensitive to noxious stimuli (nociceptors)	Yes
Existence of brain structures homologous or analogous to the human brain structures involved in pain perception (pain matrix)	No in the case of the neocortex, yes for subcortical structures like amygdala and hippocampus; yes for thalamus and brainstem
Existence of nervous pathways connecting peripheral nociceptors to higher brain centres	Yes
Existence of endogenous opioids and opioid receptors in the central nervous system	Yes
Analgesics act in reducing the response to noxious stimuli	Yes
Existence of complex forms of learning including avoidance learning of noxious stimuli	Yes
Suspension of normal behaviour under impact of noxious stimuli	Yes

In conclusion, the overall balance of evidence from the available published information indicates that fish or at least some fish species have the capability to experience pain.

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Andreas Bachmann  
*Nanobiotechnologie*  
Eine ethische Auslegeordnung  
2006

126 Seiten  
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Die Nanobiotechnologie verfügt über ein enormes Potenzial. Dies lässt sich anhand von breiten (möglichen) Anwendungen in der Biomimetik, Medizin, Landwirtschaft und Ernährung («Nano-Food») verdeutlichen. Das Buch legt die in der Literatur diskutierten ethischen Aspekte der Nanobiotechnologie dar. Es handelt sich hierbei um die Aspekte Risiken für Mensch und Umwelt, Gerechtigkeit («Nano-Divide»), militärische Anwendungen, Datenschutz, Nanomedizin und Enhancement. Es liefert keine Antworten, sondern soll helfen, die Diskussion über den ethisch angemessenen Umgang mit der Nanobiotechnologie besser zu strukturieren.



Jürg Stöcklin  
*Die Pflanze*  
Moderne Konzepte der Biologie  
2007

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Die Schweizerische Gesetzgebung verlangt, dass nicht nur bei Tieren, sondern auch bei Pflanzen die Würde der Kreatur geachtet wird. Bei Tieren gibt es gewisse Anhaltspunkte, worin ihre Würde besteht. Bei Pflanzen stellt sich die Frage, welche ihrer Eigenschaften Würde begründen könnten. Das Buch befasst sich aus der Sicht der modernen Biologie mit Pflanzen und deren Unterscheidung von Tieren. Auch wenn sie sich in ihrer Organisation grundsätzlich unterscheiden, so sind sie sich hinsichtlich ihrer zellulären Strukturen und dem Grad ihrer Komplexität doch sehr ähnlich. Das Buch beschreibt die Fähigkeiten von Pflanzen, Informationen aus ihrer Umgebung aufzunehmen, zu speichern und darauf zu reagieren. Vor diesem Hintergrund wird argumentiert, dass die Unterschiede zwischen Pflanzen und Tieren lediglich gradueller Natur sind. Aus biologischer Sicht kann keine Höherentwicklung von Tieren im Vergleich zu Pflanzen postuliert werden.



Andreas Brenner  
*Leben*  
Eine philosophische  
Untersuchung  
2007

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«Was ist Leben?» Zunächst wird gezeigt, warum diese Frage so schwierig zu beantworten ist und warum auch die Biowissenschaft wenig zur Aufklärung dieser Frage beiträgt. Im Unterschied dazu beschäftigt sich die Philosophie seit ihren Anfängen intensiv mit der Frage nach dem Leben. Biophilosophische Theorien des 20. Jahrhunderts greifen auf diese Positionen zurück und machen von unterschiedlichsten Ansätzen ausgehend die Selbstbezüglichkeit von Leben deutlich. Der so gewonnene Lebens-Begriff wird an Entwürfen «Künstlichen Lebens» getestet, z.B. an Projekten der Synthetischen Biologie. Dabei wird untersucht, ob und inwiefern der Lebens-Begriff hier anwendbar ist. Zum Abschluss der Untersuchung wird die Selbstbezüglichkeit von Lebendigem noch einmal aufgegriffen. Jüngste naturwissenschaftliche Beobachtungen lassen sich dahingehend deuten, dass Leben sich in der Stiftung von Sinn und Bedeutung artikuliert.



Benjamin Rath  
*Ethik des Risikos*  
Begriffe, Situationen,  
Entscheidungstheorien  
und Aspekte  
2008

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ISBN: 978-3-905782-03-5

Welchen Risiken darf eine Person sich selbst und andere aussetzen? «Ethik des Risikos» befasst sich mit der ethischen Bewertung von Handlungsentscheidungen, deren Umsetzung mit Unsicherheit verbunden ist. Im ersten Teil werden die wesentlichen risikoethischen Begriffe definiert und verschiedene Risikosituationen voneinander abgegrenzt. Im zweiten Teil werden drei unterschiedliche Entscheidungstheorien der Risikoethik (Bayesianische Entscheidungstheorie, Maximin-Prinzip, Precautionary Principle) diskutiert. Diese umfassen Positionen, die von einem durch Rationalität geprägten Ansatz reichen bis hin zu einem, der die Vermeidung des worst case anstrebt. Im dritten Teil werden weitere für die risikoethische Debatte bedeutende Aspekte ansatzweise ausgeführt, z. B. die Funktion der Zustimmung und der Kompensation, Individualrechte sowie die Eigentumsrechte an Risiken und deren Verteilung.



Joachim Boldt, Oliver Müller,  
Giovanni Maio  
*Synthetische Biologie*  
Eine ethisch-philosophische  
Analyse  
2009

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ISBN: 978-3-905782-04-2

Synthetische Biologie hat, ähnlich wie Physik und Chemie, nicht nur die Analyse, sondern auch den Nach- und Neubau ihrer Gegenstände zum Ziel. Mit der Vision von der Erschaffung neuer einzelliger Lebensformen rückt dieses Forschungsfeld Lebendiges in den Bereich technischer Erzeugbarkeit. Die Autoren differenzieren Forschungsfeld und Anwendungsgebiete der Synthetischen Biologie und systematisieren die zentralen ethischen Fragen. Anhand von Metaphern wie «living machine» verdeutlichen sie, wie unklar der ontologische Status des neu geformten Lebendigen werden kann. Darüber hinaus argumentieren sie, dass der Schritt von der gentechnischen Manipulation zur Kreation neuer Lebensformen Konsequenzen für das menschliche Selbstverständnis haben kann. Missbrauchsgefahren werden ebenso diskutiert wie die Notwendigkeit der Prüfung von Risiken einer unkontrollierten Verbreitung synthetischer Organismen.



Bernard Baertschi  
*La vie artificielle*  
Le statut moral des êtres  
vivants artificiels  
2009

122 pages  
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Ce volume pose la question du statut moral des êtres vivants artificiels. Il est important de déterminer ce statut, car c'est sur lui que nous nous appuyons pour savoir comment nous devons les traiter et quelles limites la morale imposera à l'usage que nous en ferons. Jusqu'à présent, les êtres vivants que nous connaissons étaient tous naturels, mais si nous produisons des organismes artificiels, ce caractère artificiel aura-t-il un impact sur leur statut moral?

Pour pouvoir y répondre, cet ouvrage commence par préciser ce que signifie l'attribution d'un statut moral à une entité. Puis, défendant une conception de la vie qui se veut en accord avec les sciences biologiques, il examine les différentes significations que prend l'opposition du naturel et de l'artificiel. En conclusion, il établit que le fait qu'un organisme vivant soit naturel ou artificiel n'a aucun impact sur son statut moral.



Arianna Ferrari, Christopher Coenen, Arnold Sauter  
*Animal Enhancement*  
 Neue technische Möglichkeiten und ethische Fragen  
 2010

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Die Debatte über ethische Aspekte des «Human Enhancement» wirft auch ein neues Licht auf die wissenschaftlich-technische «Verbesserung» von Tieren. Zwar ist «Animal Enhancement» in vielerlei Hinsicht ein altbekanntes Phänomen. In der Landwirtschaft werden Tiere seit langem gezielt verbessert, und einige Tierversuche lassen sich gleichfalls so begreifen. Während aber die Debatte um «Human Enhancement» stark von der Basisunterscheidung zwischen Heilen und Verbessern geprägt ist, ist diese Unterscheidung im Tierbereich weitgehend irrelevant. Durch aktuelle wissenschaftlich-technische Tendenzen ändern sich aber zumindest die Interventionstiefe und potenziell auch die ethische Bedeutung der Eingriffe. Dieses Buch bietet einen breiten Überblick über Entwicklungen im Bereich der konvergierenden Technologien und Wissenschaften, die für «Animal Enhancement» relevant sind, und diskutiert zentrale ethische Fragen.



Peter Kunzmann, Nikolaus Knoepffler  
*Primaten*  
 Ihr moralischer Status  
 2011

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Die «Primaten» als Tierordnung wurden in den letzten Jahren in ihrem rechtlichen und moralischen Status teils erheblich aufgewertet. Worauf gründet sich diese Neubewertung? Was leisten die ethischen Argumentationen, die ihr zugrunde liegen? Ist es der «Affen» Nähe und Ähnlichkeit zum Menschen, die sie so besonders im Tierreich machen? Oder sind sie ethisch gar nicht mehr als «Tiere» zu behandeln, sondern als «Personen»?

Die vorliegende Studie argumentiert auf dem Grund jener einzigartigen Fähigkeiten und Eigenschaften, die Primaten zu ganz besonderen Subjekten ihres Lebens macht. Von hier aus rechtfertigt sich ihr moralischer Status, ihre Würde, die sich vor neuen technischen Eingriffen zu bewähren hat.



Markus Wild  
*Fische*  
Kognition, Bewusstsein  
und Schmerz  
Eine philosophische  
Perspektive  
2012

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Das Bild vom Fisch hat sich durch die Forschung der letzten 20 Jahre erheblich verändert. Fische gelten nicht mehr als Reflexmaschine, sondern als kognitive Wesen. Sie leben in komplexen sozialen Gemeinschaften, können Individuen unterscheiden, ihren Status verfolgen, kooperieren und voneinander lernen. Neben kognitiven Fähigkeiten ist auch das Bewusstsein bei Fischen in den Fokus der Aufmerksamkeit gerückt worden. Fische verfügen über die Voraussetzungen, um Schmerzen zu empfinden. Diese Entdeckung hat zur Debatte geführt, ob Fische wirklich Schmerzen empfinden. Das wirft nicht nur biologische, sondern auch philosophische Fragen auf: Was ist Schmerz? Was ist Bewusstsein? Wie können wir erkennen, ob ein Wesen bewusste Empfindungen hat? Dieser Band diskutiert das neue Bild vom Fisch und argumentiert, dass Fische tatsächlich Schmerzen empfinden.