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Prior knowledge and present events in the brain

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Abstract

Our experience the world is dependent on both the surroundings and the brain. In other words, perception is a synthesis of incoming signals, internal state, and previous knowledge rather than a mere reflection of the environment. Prior knowledge can be engendered from cues in the present context, from previous experiences, or in a wider sense by evolutionary processes effected in the organization of the brain. Knowing what is going to happen modulates the extent to which aversiveness induces stress and anxiety. Predictability is also of importance since it may improve the accuracy and speed of sensory processing as well as behavioral responses. As for evolutionary relevant threats, a perceptual and behavioral system has been organized around a fear module generating instant responses even outside of awareness. Accordingly, brain regions with altered activities and functions complement each other in constituting a system that allows for perceptions, reactions and behavioral planning at different time scales. In this thesis, we investigate the influence of prediction on perception of somatosensory and aversive events and the differential neural processing of phobic and fear-relevant stimuli, as measured by functional magnetic imaging (fMRI) and positron emission tomography (PET).

The network of activation and deactivation during anticipation of an expected somatosensory stimulus was found to be similar to that engaged during the actual sensory stimulation. These overlapping patterns of change furthers the idea that predictions are subserved by a neuronal network similar to that which subserves the processing of the actual sensory input. It also infers that anticipation may invoke a tonic top-down modulation of neural activity and in this way favor selective processing of relevant information. Correspondingly, predictive cues of painful stimuli that allowed for correct temporal estimation enhanced activity in relevant sensory-discriminative processing areas. Absence of cues predicting painful stimuli augmented the negative experience as well as neuronal activity in areas associated with the affective component of pain processing, such as the anterior insula, the caudal anterior cingulate cortex, and the orbitofrontal cortex. This context also prompted increased activity in the posterior parietal cortex and lateral prefrontal cortex that we attribute to enhanced alertness and sustained attention during unpredictability. An affective cortical network along with the amygdala and the periaqueductal gray was also active in response to phobic relative to fear relevant (but non-feared) stimuli. However, with non-conscious stimulus presentation only the amygdala was activated both to the phobic and fear relevant stimuli. With time to decide that the fear relevant stimuli in effect were not dangerous the dorsolateral prefrontal cortex was engaged, a region included in a system that has been identified in strategic selection of behavior and in inhibiting environmentally cued responses. These results thus reflect fast perceptual pathways favoring rapid responses to threat, top-down direction of attention contributing to enhancement of relevant information processing along with attenuation of anxiety and finally, activity in regions mediating goal-directed perception and behavior.

Keywords: Anticipation, prediction, predictability, attention, emotion, pain, tickle, fear, conscious, unconscious, awareness, amygdala, insula, functional magnetic resonance imaging (fMRI), positron emission tomography (PET)

List of publications

The thesis is based on the following papers, referred to by their Roman numerals:

I. Tickling expectations: Neural processing in anticipation of a sensory stimulus

Katrina Carlsson, Predrag Petrovic, Stefan Skare, Karl Magnus Petersson, and Martin Ingvar. *Journal of Cognitive Neuroscience*, 2000. 12:4 pp.691-703

II. Predictability modulates the affective and sensory-discriminative neural processing of pain

Katrina Carlsson, Jesper Andersson, Predrag Petrovic, Karl Magnus Petersson, Arne Öhman, and Martin Ingvar. In manuscript

III. Context-dependent deactivation of the amygdala during pain

Predrag Petrovic, Katrina Carlsson, Karl Magnus Petersson, Per Hansson, and Martin Ingvar. *Journal of Cognitive Neuroscience*, 2004. 15:7 pp. 1289-301

IV. Fear and the amygdala: Manipulation of awareness generates differential cerebral responses to phobic and fear-relevant (but non-feared) stimuli

Katrina Carlsson, Karl Magnus Petersson, Daniel Lundquist, Andreas Karlsson, Martin Ingvar, and Arne Öhman. *Emotion*, 2004. 4:4 pp 340-353

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List of abbreviations

ACC	Anterior cingulate cortex
BA	Brodmann's area
BOLD	Blood oxygen level dependent
CS	Conditioned stimulus
DLPFC	Dorsolateral prefrontal cortex
EPI	Echo planar imaging
fMRI	Functional magnetic resonance imaging
GLM	General linear model
MI	Primary motor cortex
OFC	Orbitofrontal cortex
PAG	Periaqueductal gray
PET	Positron emission tomography
PPC	Posterior parietal cortex
PPM	Posterior probability maps
rCBF	Regional cerebral blood flow
SAM	Self-assessment manikin
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SNR	Signal to noise ratio
SOA	Stimulus onset asynchrony
SPM	Statistical parametric mapping
TR	Repetition time
US	Unconditioned stimulus
VAS	Visual analogue scale

Prologue

Our experience of the world emerges from the meeting of the brain with the surroundings. That is, perception is not a simple reflection of the environment, but a synthesis of incoming information and prior knowledge. Prior knowledge derives from previous experiences of the individual as well as a long sequence of forerunners whose brains have been shaped by evolutionary processes. Thus, in this thesis prior knowledge includes and refers both to the results of recent learning as well as to information in the nervous system that has been coded through phylogenesis. The way that different regions of the nervous system respond to and represent different types of information, as well as the neural connectivity between these regions provide examples of innate knowledge. The concept of previous knowledge thus has here been given a wide interpretation.

Although the dynamics of emotional responses is attuned and formed by the environment and individual development, we have basic emotional systems that support the maintenance of life. Thus emotions may be seen as expressions of inherited knowledge that has served survival by allowing vital needs to be met and dangers to be avoided.

The direction of attention may be stimulus driven when it comes to danger, but attention may also be guided by cognitive operations that integrate attention in plans and strategies. To this end, predictions may guide the focus of attention and thereby improve the accuracy and speed of sensory processing. Knowing what will happen also modulates the extent to which aversiveness induces stress and anxiety.

In the project underlying this thesis, we investigated the influence of prediction on perception of somatosensory and aversive events and the differential neural processing of phobic and fear-relevant stimuli as measured by functional magnetic imaging (fMRI) and positron emission tomography (PET). By altering contexts in which stimuli were perceived, by providing cues that related to prior knowledge, and by manipulating the degree of awareness of stimuli we intended to contribute to the understanding of the interaction between previously acquired information and external events.

1 Background

1.1 Cognitive neuroscience

Cognitive neuroscience involves interdisciplinary research that integrates knowledge from fields such as neurophysiology, cognitive psychology and computational neuroscience. It is an approach to understanding mental activity from an information processing perspective and from ideas about how different cognitive functions are implemented in the neural processing structure.

1.1.1 Brief overview of the historical background to cognitive neuroscience

In the nineteenth century and the early twentieth century, one of the main questions in neurophysiology was whether the brain functioned as a whole, that is, if the whole brain participated in the control of behaviors and sensory processing or if individual processing parts of the brain carried out specific functions. The phrenologists Gall and Spurzheim advocated that the brain consisted of 35 independent parts with specific functions while psychologists as Lashley a century later presented experimental data to support that the whole brain worked as unit. The localizationist view was supported by clinicians such as Jackson, Broca and Wernicke, who observed that focal lesions in the cortex caused specific deficits. Around the turn of the century, the neuroanatomist Brodmann made the seminal contribution of organizing the cortex in terms of 52 distinct regions based on cellular architecture. The visualization of different cell types by tissue staining and microscope supported the suggestion that different regions indeed represent functionally distinct areas. By using Golgi's discovery that neurons could be stained by silver, Cajal argued that the brain was made up by discrete entities. Golgi and Cajal shared the Nobel Prize in Physiology and Medicine in 1906 for their discoveries. Their findings formed the basis for the neuron doctrine – the principle that the nervous system is made up of individual signaling elements, neurons, which contact one another at specialized points of interactions, called synapses.

Before the launching of experimental psychological science by Fechner and Wundt in the mid-nineteenth century, theories of the mind had primarily been a topic of discussion for philosophers. Empiricists and rationalists debated how we got access to properties of objects and their relations. The empiricists argued that

all knowledge had its origin in sensory experience, while the rationalists argued that we with mere thinking could gain a priori knowledge as for example in the mathematical venue. The empiricism laid the foundation for the associationism, the doctrine that complex knowledge reflects association between simpler ideas, and the behaviorism, which claimed that psychology could be reduced to studies of how associations are formed between stimuli and responses. Influenced by Darwin's idea of natural selection Thorndike asserted that a response that was followed by a reward would be stamped in as an association in the brain of a favored response. This was his famous “law of effect”. Behaviorists, e.g. Watson, also proclaimed that the brain had no pre-existing systematic structure, that everybody had the same neural equipment, and that the environment and training were the sole determinants for the development of the system. Thus, he saw the infant as a blank slate, *tabula rasa*, with no built-in knowledge or innate structure. In many respects the behaviorist standpoint was contrary to the view advocated by gestalt psychologists. With examples of visual perception they argued that built-in, unlearned properties of the brain determined the way visual stimuli were organized. Their central thesis was that the sum is more than the parts. They spoke of “gestalt laws”, that is, principles that organized perception to optimize regularity, order, simplicity, symmetry, etc. (Figure 1).

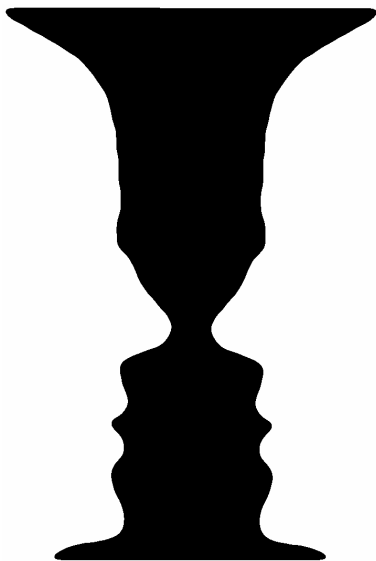


Figure 1. The central idea of the Gestalt psychologists is that the act of perception creates a figure or form that is not only a property of an object observed but also represents the brain's organization of the sensory input. Rubin argued that we have an innate tendency to perceive one aspect as the figure and the other aspect as the background.

Much earlier a similar idea was advocated by Kant (in 1781). He believed that our knowledge of external objects and their relations was dependent both of our perceptions and of the mind's capacity of processing them. Through basic

judgements of the mind, our perceptions were assigned characteristics such as numbers and causal connections. He also surmised that the brain automatically assigned locations in space and time to sensory input and that this was a necessary condition for the possibility of referring them to the external world. "It is an a priori representation, which necessarily underlies outer appearances". The object of our knowledge is not the outer world but our "processed" perceptions, *das Ding für mich*.

The dominance of behaviorism and stimulus-response psychology was challenged at midcentury. Computer science and artificial intelligence had been developed in parallel and contributed to insights into how learning may evolve. Chomsky made his famous proposal that the deep rules of language were built into the brain and shaped language learning according to principles that are universal for all different civilizations and languages.

This brief sketch of the historical background to cognitive neuroscience touches upon several fundamental issues in the history of the life sciences. They include the role of analysis in science, e.g., the gestalt psychologists' claim that psychological phenomena were governed by "holistic" principles rather than by "anatomic" behavioral entities. Further, there is the eternal discussion that may be framed as the empiricism-nativism debate at the philosophical level and the gene-environment issue at the psychobiological level. Finally, there is the role of subjective experience in science, whether a psychological science can be based on experience or whether psychology and cognitive neuroscience must rest on behavior observations.

1.1.2 Levels of analysis in cognitive neuroscience according to Marr

In trying to build a bridge between psychological phenomena and their neurobiological basis, Marr introduced a framework of descriptive levels (Marr 1982). According to his thinking there are three levels at which cognitive processes in terms of transformation of input to output can be described: (1) the computational level of abstract problem description; (2) the level of algorithms and codes, characterizing a procedure to perform the task of converting the input to the output as given by the computational specification; and (3) the level of physical implementation, that is the implementation of the process in terms of interactions between computational units (e.g. neurons).

An example of division into these levels could be a functional description of a cash register or a mini calculator adding integers. At the top level the problem is defined as adding integers, for example 532 and 1089. At the middle level an algorithm can be specified in terms of a table and an algorithm, for example first adding 9 and 2, resulting in 11, transferring 10 to the next addition of 8 and 3 and so on. The bottom level specifies how the representations and procedures of the algorithmic description are implemented in the physical system. In cognitive neuroscience accounts about the top level will come from studies of behavior such as reaction times. Development of theories about the nature of processing algorithms (middle level) must take into account both the behavioral evidence and knowledge about the neurophysiology. How the information representation and algorithms are implemented in the brain (bottom level) is one of the most central issues in the field of cognitive neuroscience.

1.2 Perspective on information

1.2.1 Information representation

Sensory receptors provide the interface between the neural system and the world. Receptors can respond to chemicals, photons, sound waves, temperature, mechanical stimuli such as pressure and so forth. The range of stimuli that a specific receptor responds to creates the first limitation of what the organism will detect. For example, the auditory system will respond to sound waves with frequencies of approximately 20 – 20000 Hz. Any pressure wave outside this interval will not by humans be registered as sounds. After responding to a stimulus, the receptor neuron either depolarizes or hyperpolarizes, that is, it transforms the data into a format that can be further processed by the neurons in the brain. Naturally, the types of receptors that humans have, together with the organization of further processing depend on the ecological niche in which we evolved. A bee can represent light in the ultraviolet range, and a rattlesnake can detect infrared light. These organisms have systems that enable them to detect certain colors of the flowers or rodents in the dark.

The next question is how this kind of information is represented in the brain. Two seemingly different hypotheses can be called “local coding” and “distributed coding”. The local coding theory has also the nickname “grandmother cell theory” since it implies that one neuron or one unit represents one concept, composite or simple. The distributed coding uses many cells or units to code for

a representation. A simplified example of the latter theory could be: consider four neurons, each with five activity levels ranging from 0 to 4. A vector of $\langle 3, 1, 0, 4 \rangle$ then specifies a particular pattern of activity at a certain time point, $\langle 4, 2, 0, 1 \rangle$ specifies another distinct pattern. Note that the 0, that is a neuron that is not firing, also carries information in this type of vector coding (Churchland and Sejnowski 1992). Another way of exemplifying distributed coding is to draw a parallel to musical chords. A C-major chord consisting of the tones C, E and G, and a C-minor chord with the tones C, E-flat and G are perceived as quite different harmonies. Distributed representations may be coded either coarsely, which permits overlap in response selectivity of the unit, or finely, which implies that the unit responds only to a very narrow range of stimuli. In either case, distributed representations are patterns of activation across a set of units.

However, the distinction between local and distributed coding theory is not as distinct as it may seem. Even when conceptualizing information representation as distributed, the units (vectors) represents symbols down the line. We come to the inevitable conclusion that bigger chunks of information are constructed by the combination of smaller chunks of information, or in other words, high-level effects depend on low-level phenomena (Churchland and Sejnowski 1992). Clearly, an important issue of neuroscience is related to questions about the neural code and how functional descriptions are translated into this code.

1.2.2 Information processing and learning

In processing the input information, the nervous system executes functions that perform vector-to-vector mapping. This is accompanied by a dynamic change in the neural activity over time. Which representation that prevails at a certain time can be seen as a function of the input information (for example from the receptor cells) and the configuration of weights in the connections between the cells. Considering it this way, the weight or the synapse strength between two units represents prior knowledge that will enhance or reduce the activity level in the next mapping. That is, the weight configuration of synapses is a kind of matrix, through which vectors can be pushed to give appropriate outputs destined for the next layer of processing. Generally speaking, neural processing consists in convolving representations (vectors) through a matrix of synapses. This suggests both that weight configurations can connote similar things and also that they can be sensitive to fine differences between things. At the experiential level, the result would be that we could distinguish between apples and oranges and also between

varieties of apples. The weights can also be seen as memory that can be changed by new experience and learning, a good learning algorithm allowing changes in the weights so that the network finds a point where errors are minimized (Churchland and Sejnowski 1992).

Innate predispositions can be described as specified architecture of neural connectivity. Accordingly, different areas of the brain respond to specific types of input and have a domain-specific way of processing the data. The incoming data from the environment will with time affect the architecture. However, the learning algorithms specifying how the input will change the connectivity are also part of the starting state. These learning algorithms may also vary between different areas and process units of the brain (Karmiloff-Smith 1994). One way of thinking of these inherited learning algorithms is that they belong to the prior knowledge provided by evolution. That is, evolutionary knowledge contains flexibility and we have inherited a strong capacity to learn. Learning on the ontological level can in this way be seen as a fine-tuning of what humans as a species has learned on a phylogenetic level.

The brain receives information through input surfaces in terms of sensory receptors and implements output information for example through generating movements or glandular and endocrine responses. This may be described as a perception-action-cycle: sensory input → perceptual processing → cognitive processing → planning and temporal organization of motor output → action (Figure 2) (Arbib 1981; Petersson 2005).

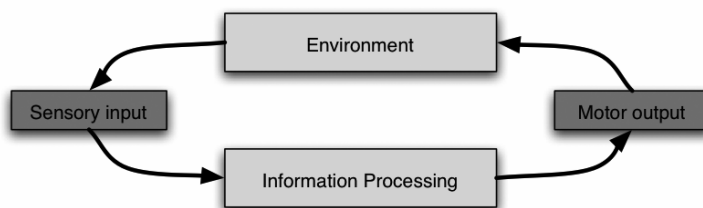
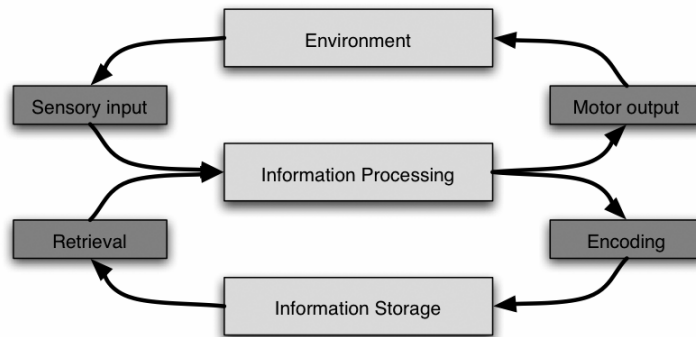


Figure 2. Perception-action cycle: The brain interfaces the environment through sensory input surfaces and motor output effectors.

Learning is a dynamic process that is instantiated in neural changes that modulate responses when the learning context is again encountered. Learning is thus conceptualized as the dynamic consequence of the processing of information and network plasticity. The stored information (i.e. the memory trace) can be viewed as the resulting changes in the processing system. In order to incorporate the capacities for learning, adaptation and memory, the perception-action-cycle needs to be complemented with an encoding-retrieval cycle (Figure 3). These

cycles interact through cognition/information processing, as for example attentional, working memory, emotional processes (Pettersson 2005).

Figure 3. Interaction between perception-action cycle and encoding-retrieval cycle: Learning takes



place when the brain's processing networks and its cognitive representations are restructured by experience. The cognitive representation and processing of information from the environment as well as the behavioral output will be influenced by the information already stored in the brain.

1.2.3 Functional organization of the brain

The connective anatomy of the perception-action cycle involves a synaptic hierarchy including the primary sensory, upstream unimodal, downstream unimodal and heteromodal association cortex for sensory processing and the equivalent organization for the motor output (Fuster 1997; Mesulam 1998). The connectivity is denser within than between the modules (Rumelhart and McClelland 1986). Actually, functional segregation arises precisely because of this structure of intense connectivity within a region and because every region is not connected directly to every other region (Frith 1997).

The principle of functional segregation is complemented by the principle of functional integration by the interaction of modules. Unimodal areas elaborate information coming from the primary sensory cortices, encoding basic features of sensation such as color, pitch or touch. Downstream unimodal areas, containing more coarsely tuned neurons, receive input from several upstream unimodal areas and will encode complex sensory experiences such as faces and spatial locations. The heteromodal association cortex may in turn combine information coming from multiple unimodal and other heteromodal areas into integrated representations (Mesulam 1998).

The flow of information between the modules is reciprocal allowing higher level modules to exert feedback influence on earlier levels of processing. This top-down flow of information is important for attentional modulation of early

cortices as well as for learning (Figure 4). There is also parallel connectivity, that will contribute to the possibility of each sensory event to initiate multiple cognitive and behavioral outcomes (Fuster 1997; Mesulam 1998).

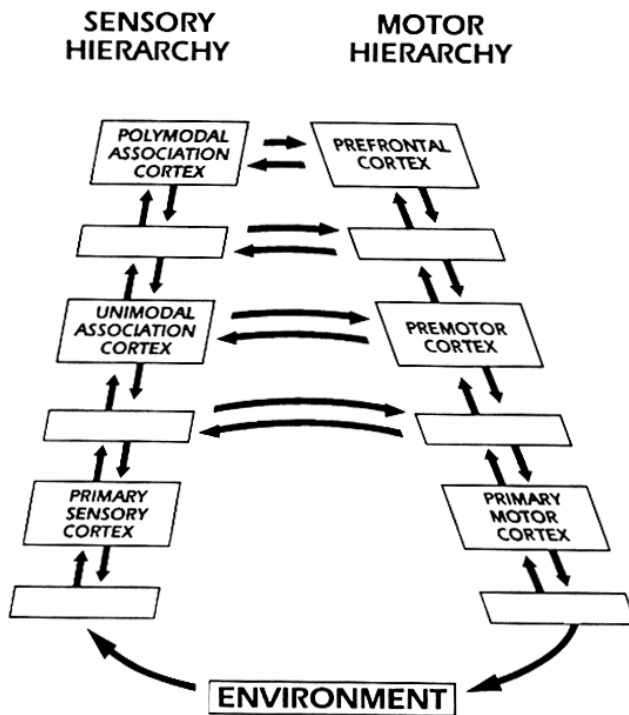


Figure 4. Flow of connections between cortical regions participating in the perception-action cycle.

1.2.4 Structural organization of the brain

The brain is composed of about 10¹⁰-10¹² neurons, each supporting around 10³-10⁴ axonal output connections and about the same number of input connections. To get a sense of the magnitude of these numbers we can imagine counting 10 neurons per second, which will take us 3000 years of computing time. The complexity of the brain is also reflected in the structural composition of the neuron, including the cell body, the axon sending signals, that is giving rise to the output, the dendrites receiving input, and the synapses – the points of contact between the cells. The cells are essentially electrochemical devices, receiving and transmitting signals. The synapses show a number of different forms of chemical keys as well as plasticity characteristics, allowing for changes in time-scales ranging from milliseconds to weeks (Koch and Laurent 1999).

In general terms, we can say that the posterior part of the brain processes input information and that the anterior part mainly is involved in the planning and

organization of the output. The five lobes are processing different kinds of information (visual, somatosensory, auditory, motor, etc.). The lobes are further functionally and structurally segregated and the different regions function in integrated systems (Frith 1997).

1.2.4.1 Subcortical input to the cortex

The major input to any cortical area is from other cortical areas. Only about 1 in 100 or 1 in 1000 fibers in the white matter is involved in subcortical projections (Shepherd 1998). The thalamus is the major source of subcortical input to the cortex. It is a relay nucleus receiving input from the periphery and furthering the information centrally. Its projections are highly ordered so that the sensory input is represented in the cortex in such a way that their topographic arrangement in the periphery is preserved. The primary sensory and motor areas usually preserve the highest detail of the topography, which degrades progressively through secondary and higher order of cortex. There are about 20 other different subcortical structures providing input to the neocortex including the amygdala, the periaqueductal gray (PAG), and the striatum, each pathway having a distinct neurochemical signature (Shepherd 1998).

1.3 Somatosensory processing

Sensory input is characterized by modality, intensity, time and location of signals. Already the architecture of the receptor filters the input to reflect the specific sensory modality. Somatosensory modalities have a central representation with a detailed mapping of incoming signals.

1.3.1 Receptors mediating somatosensory input

Touch is mediated by mechanoreceptors in the skin placed at different depth, with different profiles with regard to what they react to. The two principal receptors in the superficial levels of the skin are the Meissner's corpuscle and the Merkel disk receptor. The Meissner's corpuscle is a rapidly adapting receptor signaling onset and offset of stimulation while the Merkel disk receptor is a slowly adapting receptor maintaining information throughout longer periods of time. The Pacinian corpuscle and the Ruffini ending are the two mechanoreceptors found in the deep subcutaneous tissue. The Pacinian corpuscle responds to rapid indentation of the skin and vibration, and the Ruffini endings

sense stretch of the skin at the joints. Tactile sensitivity is greatest on the hairless skin on the fingers, the palmar surface of the hand, the sole of the foot and the lips.

Temperature is mediated by specific thermal receptors that modulate their firing as a function of temperature. Proprioception refers to the position of the limbs and the sense of movements. The peripheral receptors that mediate proprioception are located in the muscle spindles, in joints and in skin.

The receptors that respond selectively to stimuli that can damage tissue are called nociceptors; they are located both in the skin and in the viscera. They respond directly to some noxious stimuli and indirectly to others by means of chemical releases from cells in the traumatized tissue. Mechanical nociceptors require sharp, strong stimuli in order to respond and they mediate sharp or pricking pain. Thermal nociceptors are excited by extremes of temperature, above 45°C or below 5°C and polymodal nociceptors respond to a variety of destructive mechanical, thermal and chemical stimuli (Kandel et al. 2000).

1.3.2 Pathways for somatosensory stimuli

The different modalities of somatic sensation converge to the so-called dorsal root ganglion cells. These cells differ in the size and conduction velocity of their axons. Large-diameter myelinated axons of mechanoreceptors and proprioceptors conduct action potentials rapidly, while small-diameter (C and A• fibers) myelinated or unmyelinated axons of thermal receptors and nociceptors have a slower conduction velocity.

The axons of the thermal and nociceptors enter into the spinal cord and synapse in the posterior horn where the second-order neurons are located. The axons of these second order neurons cross the spinal cord at the same level and enter into the ascending anterolateral system. There are several pathways within the anterolateral system conveying nociceptive information, one example being the spinothalamic tract terminating in the thalamus. The C and A• fibers also project to other nuclei, as for example the PAG, which in turn is heavily interconnected to the hypothalamus and the amygdala (Craig 2002).

The tactile sensation and proprioception are transmitted to the thalamus in the dorsal column and – the medial lemniscal system. In brief, the thalamic neurons mediating touch and proprioception send their axons to the primary

somatosensory cortex (SI) and the secondary somatosensory cortex (SII) while thalamic neurons sensitive to pain and thermal stimuli project also to the insula and the caudal ACC (Kandel et al. 2000).

1.3.3 Somatosensory cortical areas

The body surface is represented in the SI by the somatotopic arrangement of sensory inputs. The above mentioned sensory submodalities have each a cortical projection of their own. Sacral segments are represented medially, lumbar and thoracic segment centrally, cervical segments more laterally and the trigeminal representation at the most lateral position of the SI cortex. An important feature is that the regions of the body of highest receptor density have the largest representation in the cortex. That is, the image of the body in the brain exaggerates for example the lips, fingertips, and sole of the feet. About 100 times as much cortical tissue is devoted to a cm² of the skin on the fingers as to a cm² of skin on the back (Kandel et al. 2000). The somatotopic maps are also not fixed but can be altered by experience so that for example a violinist will develop a larger proportion of cortical neurons representing the left hand, especially if the practice begins before about 9 years of age (Pantev et al. 2001).

The SII is anatomically connected to SI, but receives also input directly from the thalamus. The term “second” thus does not imply a hierarchical processing position to the SI, only that it was the second somatosensory area to be identified. The SII is located in the upper bank of the lateral Sylvian sulcus behind the insula. The SII has also a cutaneous map of the body even though it is cruder than that of the SI. The topography is aligned from lateral to medial – face to foot (Craig 2002). Area SII also has connections to other areas processing somatosensory information, for example Brodmann’s area (BA) 7, and the insula, but not to BA 5.

The posterior insula receives information about visceral sensation, that is, from the interoceptive systems. Results from neuroimaging and lesion studies indicate that the posterior insula also receives input from C and A• fibers in the exteroceptive system. As mentioned above these fibers transmit information about nociception and temperature. A key feature of pain and temperature is that they signal physiological conditions of the tissue and consequently contain affective, motivational aspects. In addition these small-fibers have been shown to be sensitive to slow, weak mechanical stimuli that evoke sensual touch, slow

brush (tickle) as well as histamine (itch). These fibers also convey signals for example about slow variations in local metabolism (acidic pH, hypoglycemia, lactic acid) and immune and hormonal activity (cytokines and somatostatin). Accordingly, the posterior insula receives information about the physiological condition of the entire body, including interoceptive and exteroceptive information. This region has thus been postulated to process information related to homeostasis. This cortical image of the condition of the body is subsequently re-represented in the anterior insula (Craig 2002).

1.3.4 Tickle

Usually, by tickling we mean a touching of a part of the body that results in uneasiness, laughter, spasmodic movements or withdrawal. Tickle is different from itch in that a tickle is outside of us and induces attempts to move away from it. An itch is on us and leads to an urge to scratch. Darwin noted certain specific requirements for a touch to be perceived as tickle, namely that the tickler must be a familiar person, but someone other than the tickled must do the tickling, the tickled part must be a body part not commonly touched, and the touch must be light (Mintz 1966). There has been theories that tickle and itch are light versions of pain, that the nerve endings are just less intensely stimulated, but more recent theories speak for classes of receptors that respond selectively to tickle and itch stimuli. For instance, selectively histamine-responsive cells has been demonstrated to constitute pathways for the sensation of itch as well as another class responding to mechanical “slow brush” (tickle) (Craig 2002).

1.3.5 Pain

Pain perception has been described and divided into sensory-discriminative, emotional-motivational and cognitive-evaluative components (Melzack and Casey 1968). Also, the definition maintained by the International Association for the Study of Pain reads “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IAPS, 1994). The pain experience involves thus both sensory and emotional aspects that are reflected in the central processing of pain.

Some supraspinal subcortical structures that participate in the processing of nociceptive information include the PAG, the amygdala, the hypothalamus, the thalamus and the basal ganglia. Cortical structures containing neurons that

respond to noxious stimulation include the SI, the SII, the anterior cingulate cortex (ACC) and the insula (Ingvar 1999). The ACC can be divided into specific processing regions for emotion, cognitive and pain processing, with the pain processing region located caudally (Bush et al. 2000; Hsieh et al. 1995). Early reports from patients having gone through cingulotomy as a final treatment to chronic pain indicate that they continue to “feel the pain” but it does not bother them or trigger any adverse emotional reaction (Foltz and White 1962). Also imaging studies have related the ACC to pain affect (Rainville et al. 1997) and the ACC has been shown to respond not only during the personal experience of pain but also during an empathetic understanding that a loved one experiences pain (Singer et al. 2004). Empathy for pain also activated the anterior but neither the posterior insula nor the SI and the SII (Singer et al. 2004). The anterior insula (as well as the orbitofrontal cortex (OFC)) has also shown correlation with subjective magnitude ratings of temperature, rather than to physical increases in temperature (Craig 2002) (see also chapter 1.4.5.1). In summary, the SI and the SII/posterior insula has been presumed to be important of the sensory-discriminative aspect of the pain processing and the ACC and the anterior insula part of affective aspects.

1.4 Emotion

Emotions can be viewed and defined in different ways, but in this thesis emotions are conceptualized in terms of a complex of responses that include physiological reactions, behavioral changes and verbal reports of subjectively experienced feelings. The role of response systems becomes apparent when emotions are viewed from a perspective of what functions they have served throughout evolution. From an evolutionary outlook, the primary task for biological organisms is the furthering of genes across generations. Emotions promote behaviors that assisted the forefathers in fulfilling this task (Öhman et al. 2000). That is, emotions play a life-regulatory role and help to create circumstances advantageous to the organism experiencing them (Damasio 1994). Darwin's theory of the natural selection provides a basis for these assumptions. The competence for emotional responses is inherited and the responses in real-time are caused by so called emotionally-competent stimuli (objects or situations, actual or in the mind). In this way, emotions give value to stimuli, value referring to the organism's ability to perceive whether events in its environment are more or less desirable (Dolan 2002).

1.4.1 Fear

Some emotional stimuli must be urgently dealt with. Fear is an emotional state that serves to motivate the organism to cope with threatening events (Öhman 2000b). The subjective experience of fear can be described as a powerful urge to get out of the situation. The physiological and behavioral responses are different depending on the proximity of the threat. If the threat is not imminent, the typical response is immobility, associated with enhanced attentive scanning of the environment and deceleration of the heart. If the threat approaches, there is a mobilization of the sympathetic branch of the autonomic nervous system leading to heart rate acceleration, increasing blood pressure and release of hormones like epinephrine and cortisol, physiological responses that support the behavioral flight or fight responses (Öhman 2000b; Öhman and Wiens 2003).

1.4.2 Fear stimuli

Events or situations that provide a threat to the integrity of the organism are likely to be fear provoking. There are stimuli that can be regarded as innate fear stimuli, for example obstructed breathing, heights, potentially poisonous animals, e.g. spiders and snakes, and highly intense stimuli like loud noise or pain. Other stimuli in our contemporary environment that it would be reasonable to perceive as dangerous, such as fast driving or handling broken electronic devices, do not trigger immediate fear in the same way. It is evident that the responses to fear stimuli that have provided threats throughout evolution owe some of their fear-provoking power to evolutionary contingencies.

1.4.3 Phobic stimuli

Phobic fear is typically elicited by stimuli that are fear-relevant from an evolutionary perspective. This has promoted assumptions that phobias reflect evolutionarily-derived readiness to easily learn to escape and avoid situations that endangered the survival of our ancestors (Seligman 1971; Öhman and Mineka 2001). From a survival point of view, it is advantageous that threat and danger is detected rapidly and automatically escaped and avoided. Studies on visual search has provided evidence that there is a more rapid detection of emotional stimuli, for example faces with negative or positive expressions compared to neutral faces and spiders and snakes compared to mushrooms (Öhman et al. 2001a; Öhman et al. 2001b). It is reasoned that evolution has shaped systems that deal with

dangerous situations quickly and that it is likely that parts of these systems are innate and “hard-wired” (Öhman et al. 2001a). Threats should be possible to identify and react to with only minimal training. Since speed in perception and automaticity in reaction are prioritized instead of elaborate accurate processing, these systems seem to be prone to false positive reactions, for example fleeing a situation that actually turns out to be harmless, rather than to false negative ones, possibly resulting in failure to escape a dangerous stimulus. The latter may lead to death while the former only leads to waste of energy. Mineka (Mineka 1992) has used the term “evolutionary conservatism” to describe the cautiousness of evolution in the design of systems to handle potential threats. Phobias have been defined as intense, irrational fears of specific objects or situations that cannot be controlled by conscious reasoning and that lead to avoidance of the phobic situation (Marks 1969). There are reasons to believe that the phobic irrational fears originate in the neural systems designed through phylogenetic learning to effectively and rapidly deal with threats.

1.4.3.1 Backward masking and non-conscious emotion

Individuals with phobic fear for snakes or spiders show strong physiological responses specifically to pictures of the feared animal. When viewing their feared animal they show for example enhanced skin conductance responses, heart rate acceleration, blood pressure increase and potentiation of the startle reflex (Globisch et al. 1999). Öhman and Soares (1994) provided data that supported the hypothesis that these responses reflect an automatic process that does not require conscious recognition of the feared stimulus. They used a backward masking technique whose potential as a tool for examining non-conscious information processing was introduced by Marcel (1983). With this method, the visual information processing of a target stimulus is interrupted by an immediately following masking stimulus. The extent to which the target stimulus is perceived is dependent on the interval between the onsets of the target and the masking stimuli, the so-called stimulus-onset-asynchrony (SOA) (Esteves and Öhman 1993). Öhman and Soares (1994) (Öhman and Soares 1994) demonstrated that even when the SOA is sufficiently short (30 ms) to effectively block conscious recognition of the target stimulus, targets affect both emotional ratings and skin conductance responses, thus showing that conscious recognition of a fear stimulus is not necessary for activating fear responses.

The everyday understanding of the word emotion is usually equivalent to the subjective experienced feeling. In the scientific study however, emotion is preferable viewed as a complex response with many observationally accessible components than as an exclusively felt inner state (Lang 1978). Physiological responses of skin conductance and heart rate, facial expressions, gestures and overt motor responses are example of such components of the emotional expression. One advantage of this perspective is that these physiological and behavioral responses allow for studying of unconscious processing of emotional stimuli. That is, the processing of an emotional stimulus can be measured, even if the subject is unaware of the content of the stimulus and any feeling experience.

1.4.4 Fear learning and conditioning

Stimuli that not inherently trigger a fear response can by learning acquire a fear value. Learning of events allows for predictions when encountering similar events later on. A prototype for fear learning is Pavlovian conditioning. Through conditioning, an innate fear trigger may transfer its value to a new, previously neutral stimulus, thus turning it to a learned trigger. Pavlov described the phenomenon of conditioning in the early twentieth century and since then many studies have been performed on the subject and there have been controversies on what conditions that have to be fulfilled in order to bring about conditioning. Öhman (Öhman 1983) defines Pavlovian conditioning in procedural terms in delineating the empirical criteria required for its observation. In this framework Pavlovian conditioning occurs when there is a systematic contingency between two stimuli, the unconditioned stimuli (US, the stimulus that possess the natural emotional triggering capacity) and the conditioned stimuli (CS, the neural stimulus acquiring a value through the conditioning process). The effect is measured in behavior or in verbal reports. Thus, for a change in the behavioral effect of the CS to qualify as “conditioned”, it is necessary that it can be linked to the larger US likelihood immediately after the CS than at any other point in time during the experiment. Also, to be able to attribute a response to CS to a conditioning through a previous CS-US contingency, control procedures are necessary. This control should consist of CS without a history of contingent US presentation either in a between-subject or within-subject control (Öhman 1983).

1.4.5 The neurophysiology of fear

The amygdala is a key structure in emotional processing. It is an almond shaped complex, located in the temporal lobe, consisting of lateral, basal and central nuclei. Extensive research has been made on the amygdala and there is still a lot to learn about this intricate complex. A generalized model presents the lateral nuclei of the amygdala as receiving the sensory input, the basolateral nuclei as convergent processing areas and the central nucleus as providing the output (Whalen 1998). The input to the lateral nucleus comes from sensory cortices. A direct input from thalamus to the lateral nucleus has been demonstrated in rodents (LeDoux et al. 1984). The central nucleus projects to various effector systems involved in the expression of emotion: The bed nucleus of stria terminalis influencing the pituitary gland and stress hormone release; the parabrachial nuclei relating to parasympathetic activation; the PAG effecting emotional behavior and pain suppression; the hypothalamus relating to sympathetic activation; the nucleus basalis facilitating cortical arousal; the ventral striatum and basal ganglia affecting motor output, etc. (Davis 1992; LeDoux and Muller 1997; Rolls 1999). The amygdala has also numerous cortical connections to the frontal lobe as for example, the anterior insula, the OFC and the ACC (Amaral et al. 1992).

The amygdala also sends reentrant projections to, for example, the visual cortex, involving both early striate cortices as well as late higher order areas (Amaral et al. 1992). It may well be that these inputs promote enhanced sensory processing of stimuli once their emotional value has been detected in the amygdala. Increased processing activity in relevant sensory cortices is a common finding in neuroimaging studies when comparing the response to emotional significant and neutral stimuli (Dolan and Vuilleumier 2003). For instance, Vuilleumier et al (Vuilleumier et al. 2001) detected enhanced activity in the amygdala in response to fearful compared to neutral faces, regardless whether the faces appeared in attended or unattended locations.

Another region proved important in emotional processing is the ACC. This gyrus encompasses subdivisions with diverse cytoarchitecture, patterns of connectivity and functions. The rostral ACC is the region mostly connoted with affect. Apart from the amygdala, this subdivision is anatomically connected to the PAG, the ventral striatum, the hippocampus and the OFC, etc. The more dorsal division is connected to the dorsolateral prefrontal cortex (DLPFC),

parietal cortex and supplementary motor cortex and has been ascribed functions of modulating attention or executive functions, monitoring competition and novelty for example (Bush et al. 2000). The caudal ACC has been shown to be involved in pain processing (Hsieh et al. 1995).

The caudal OFC has strong reciprocal connections with the amygdala. In addition to the mediodorsal nucleus of the thalamus, the OFC receives input also from the olfactory, the auditory, and the visual cortex, the SI, the SII, the insula and the ACC (Rolls 1999). Like the amygdala, the OFC is central in decoding and representing the emotional value of stimuli. It is also involved in processes of learning and reversing associations between values and stimuli. While memory in terms of working memory functions of DLPFC is held by continuing neuronal activity, the stimulus-value associations are held in the OFC as functions of synaptic modifications. Values of a large number of stimuli can in this way be stored for long periods and be recalled whenever each stimulus is seen again without any neuronal firing to hold the representation active. These stimulus-value associations of the OFC can rapidly be reversed which is adaptive in a changing environment, whereas reversal of associations held in the amygdala seem to be more difficult, holding more of stable learned values (Rolls 1996; Rolls 1999).

Animal models describe defensive behavior divided into three stages, pre-encounter defensive behavior, post-encounter defensive behavior and cirka-strike defensive behavior with a continuum in decreased distance between predator and prey and increased level of fear. When rats see their predator in post-encounter phase, they freeze in order to reduce the likelihood to be detected. Activity in the amygdala and the ventral part of PAG seem to be important for this phase. In the cirka-strike phase, physical contact between predator and prey happen and the rat engages in more active defenses such as biting and jumping, a defense system involving dorsolateral PAG (Fanselow 1994). There is evidence that PAG is involved also in human emotional processing. (Panksepp 1998).

1.4.5.1 Emotion, subjective feelings and insula

Emotional reactions are related to profound changes in both the body and brain. The collection of these changes is suggested to constitute the substrate for the feeling of emotions so that a feeling to a great extent is formed by the perception of a certain state of the body (Damasio 1994; Damasio 1999).

Already at the turn of last century, the James-Lange theory of emotion proposed that the subjective experience of emotion depends on afferent feedback of bodily responses to emotive stimuli (James 1894; Lange 1922). Thus, you feel scared partly because your heart races and your muscles activate as the bear approaches. As mentioned in chapter 1.3.3, information from the entire body - muscles, joints, skin as well as viscera reaches the posterior insula. The afferent signals that reach this region relate to the homeostatic the state of the body as for example, pain, itch, muscle burn, thirst, and visceral sensations. This cortical representation of the condition of the body is re-mapped in the anterior insula. The anterior insula has in neuroimaging studies recurrently been associated to the processing of subjective feelings (Craig 2002). The close relationship between the body's needs, homeostasis, and feelings is thus reflected in the common processing activity of these aspects in the anterior insula (Craig 2002).

1.4.6 Anxiety

Compared to fear, anxiety is more future oriented and the threat is more uncertain and uncontrollable. The states of fear and anxiety are very closely related, the only factors that will influence whether a situation provokes anxiety or fear are the timing of the threat and its controllability (Öhman 2000a).

1.4.7 Control

Control and predictability are two important factors that will modulate to which extent the aversive events will induce fear and anxiety. Control usually refers to being able to do something in order to change a situation and predictability relates to knowledge about a given situation or environment (Miller 1981).

Pain, a signal of potential tissue damage, is an example of an aversive stimulus inducing fear and anxiety. As pain normally should generate instant withdrawal, processing is assigned high priority, but it can also be subject of modulation. The degree of behavioral control is one potent modulator of the impact of nociceptive input, one reason being that it is a reliable way to reduce the expected consequences of the aversive event input (Maier and Watkins 1998). Also, control insures a lower maximum danger than no control (Miller 1980).

There are three principal ways of assessing if control (or predictability) has affected the processing of aversiveness. (1) To give a choice of control or not or to ask for the preference after having being exposed to both conditions. (2)

Estimation of anxiety and arousal, either physiologically, via electrodermal galvanic skin response, startle response and cardiovascular responses, or by asking the subjects of their experience of anxiety. (3) Impact arousal, that is whether or not a controllable painful event hurts less. Impact arousal can be measured physiologically, subjectively and behaviorally (Miller 1980).

Studies on the effect of control on pain or aversive events generally show that reduced arousal, as well as ratings of experienced pain, are consequences of having control (Miller 1980). However, there are also exceptions, as for example when control entails solving a difficult task or effortful responding of some sort, that lead to increased stress (Contrada et al. 1982). The perceived ability to manage to control the aversive events, termed self-efficacy by Bandura (1977), will also have influence on the level of stress. Individuals that perceive themselves as inefficacious in handling the aversive situation expect more discomfort and maintain a higher level of anxiety and arousal compared to individuals with a high sense of self-efficacy (Bandura 1977).

1.4.8 Predictability

Like control, prediction is central in modifying to what extent aversive stimuli induce stress and anxiety (Miller 1981). Even though the control and predictability often coincide it appears that the effects of predictability are somewhat distinguishable from those of control.

Miller (1981) describes two classes of predictability: (1) Contingency predictability, knowing the when and under what conditions an event will occur and (2) what-kind-of-event predictability referring to what the event will be like and what effects it will have. Contingency predictability can further be operationalized through three main procedures. (1) A non-aversive stimulus can regularly precede the stimulus (tone or visual stimulus) as to yield the predictability. (2) The temporal pattern that is employed for delivery of the stimuli may hold properties that allow the subject to find e.g. a rhythm that predicts the coming events. (3) A countdown procedure is an alternative when the interval between the events is too long to keep track of the time well enough to predict the next event (Miller 1981).

When moving in an ever-changing environment, our sensory systems receive an abundance of information. A search for coherence, patterns and predictability, as an inherent mechanism of the nervous system, would generally be adaptive for

the organism in supporting avoidance of redundancy and processing only what is new and for the moment most relevant. A too high informational load without apparent relatedness may in itself give rise to stress, and impending, threatening unorganized information will even more so contribute to a negative experience. Even if an individual cannot make an overt response to reduce an aversive event, predictability offer a possibility to make a model of the aversive situation, what to expect. This may lead to less focus on danger as well as a reduction of conflict and surprise that in turn lessens the anticipatory and impact arousal (Berlyne 1960; Miller 1981). Another theory holds the arousal to be proportional to the perceived momentary probability of the aversive event. Perpetual danger induces vigilance and heightened arousal of the aversive event. That is, a signal that reliably predicts a threatening stimulus grants safety and relaxation during the absence of the signal, whereas lack of such predicting signals entails lack of safe intervals (Seligman 1968).

Despite this theoretical basis for an expected advantageous effect of predictability, studies on predictability show diverse results. Preference for predictability has been indicated, even when the information about the upcoming event had no apparent instrumental value (e.g. Lanzetta and Driscoll 1966; Pervin 1963). Data are sparse and also divergent as to the effects of predictability of aversive events on arousal and anxiety. It appears that a longer anticipatory interval leads to higher subjective arousal comparing predictable and unpredictable conditions (Miller 1981), while shorter anticipatory intervals instigate lower anxiety and impact arousal during predictability (Miller 1981; Pervin 1963). A study on the effect of noise on efficiency in solving a puzzle implied a lower tolerance for frustration and impaired performance after unpredictable noise compared to predictable noise (Glass 1969).

Thus, the context and the nature of the aversive event as well as individual differences in the subjects receiving the event seem to have effect on the preferences regarding predictability (Miller 1981). When an aversive event is controllable, monitoring is a preferred strategy, since it enables the individual to influence the situation more effectively. For predictable situations, however, i.e. when the information has no instrumental value, monitoring and alertness to threat relevant information, may theoretically lead to unwanted heightened arousal and fear. Therefore, distraction and “tuning out” the threat may be more valuable in these situations. Also, aversive events of low frequency, low intensity, and short duration would possibly favor a blunting mode more frequently

compared to those of high frequency, high intensity and long duration (Miller 1981). Explicit instruction of monitoring versus blunting would possibly also have an affect in the laboratory situation.

Miller (1981) has summarized these hypotheses: (1) Predictability will be preferred under conditions when the aversive events are invasive and of high frequency. (2) Unpredictability will be preferred when a subject can more effectively reduce arousal by ignoring warning signals, that is under conditions when the aversive events are noninvasive. (3) A minority of subjects will choose unpredictability under conditions apparently not favoring distraction as will a minority of subjects choose predictability under conditions supporting distraction.

Another aspect of predictability is that a high degree of repetition will also induce stress (cf. Frankenhaeuser and Johansson). Monotonous work has been subject to research concerning psychosocial stressors and factors such as understimulation, underutilization of skills and few opportunities to learn new things. The results suggested that these factors were associated with perceived strain, heightened sympathetic nervous system activity and morbidity (cf. Johansson 1989). Hence, uneventful monotony as well as excessive unordered stimulation lead to stress. Somewhere in between, there is an optimal level of novelty and predictability for subjective well-being, inspiration and health.

1.4.9 Fear, anxiety and pain

This review suggests that the degree of control and predictability will modify the experienced anxiety and arousal provoked by aversive or painful stimuli. Looking at how some of these factors interact from a different angle we note that the level of fear and anxiety in turn will influence the way pain is processed. That is, pain is not simply determined by the intensity of nociceptive input, but will also depend on the context and the emotional state of the organism.

Animal studies suggest that fear inhibits pain and anxiety enhances it (cf. Rhudy and Meagher 2000). Since fear mobilizes the organism to take action here and now, it has been argued that fear and pain are mutually inhibiting states, fear having priority to promote fight and flight (Bolles and Fanselow 1980). Anxiety, on the other hand, leads to increased environmental and somatic scanning that facilitates sensory receptivity (cf. Rhudy and Meagher 2000) and increases the painful experience. For example, in a behavioral study, Rhudy et al (2000)

showed that fear, induced by three electrical shocks, decreased pain reactivity to a different pain exposure (radiant heat) while anxiety, elicited by the threat of a shock led to increased reactivity. A previous functional imaging study showed that uncertain expectation enhanced anxiety and pain experience (Ploghaus et al. 2001). They compared anxiety ratings to one visual signal, which reliably predicted pain of moderate intensity, to another visual signal that was followed by the same moderate-intensity stimulation on most of the trials, but occasionally by a stronger noxious stimulus. The anxiety ratings were higher to the latter visual signal and the physical identical noxious stimulation was also perceived as more painful.

Anxiety, when the focus of anxiety is related to something else than the pain, has in some studies not induced increased pain ratings and arousal (al Absi and Rokke 1991; Arntz et al. 1994). This may lead to the suggestion that the focus of attention rather than anxiety interacts with the pain processing (Arntz et al. 1994; Janssen and Arntz 1996). Weisenberg formulated the “attribution theory” suggesting that anxiety relevant to pain increases pain, whereas anxiety irrelevant to pain does not (Weisenberg et al. 1984). Yet other studies found increased pain also as an effect of pain-irrelevant anxiety and in line with these data, it has been reasoned that anxiety in general enhances pain perception (cf. Cornwall and Donderi 1988).

1.4.10 Coping and stress

Coping may in general terms be defined as thoughts and behaviors used to manage the internal and external demands of situations appraised as stressful (cf. Folkman and Moskowitz 2004). The coping process is initiated in response to the individual's appraisal that important goals are lost or threatened and comprises both the external environment as well as internal dispositions of appraisal of stress and resources for coping.

Coping responses can be conceptualized into four categories. (1) Problem-focused coping involves addressing the problem causing distress. (2) Emotion-focused coping aims at ameliorating the negative emotions associated with the problem. (3) Social coping will include both the seeking of instrumental and emotional support. (4) Meaning-focused coping that may involve a positive reinterpretation (e.g. ”I learn something from the experience”) (cf. Folkman and Moskowitz 2004). This thesis addresses only the first two categories.

Under conditions where nothing useful can be done to change the situation that causes the stress, that is, when there is no possibility to control the situation, emotion-focused efforts offer the better coping choice of the two (cf. Lazarus 1993). Emotion-focused strategies involve the task of handling stressful negative emotions and can either be avoidant or nonavoidant, to be compared with Miller's (1981) terminology of blunting and monitoring mentioned above. Avoidance strategies include distraction, ignoring, suppressing, denying whereas nonavoidant strategies imply focusing on the event and the emotional reaction connected to it. The nature of the stressful event, the context in which the stressful event occurs and personality factors will influence the outcome of the coping choice. Coping is moreover a process that may involve different types of strategies over a period of time. Hence, there may be no universally good or bad coping processes, though some may work better or worse than others in specific situations (Lazarus 1993).

1.5 Attention

Attention involves something more than sensation and perception. The often-cited passage written by James (1890, pp 403-404) reads: "Everyone knows what attention is. It is the taking possession of the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought." This short statement includes the aspect of the voluntary control of what to direct attention to, the inability to attend to many things at once, hence the selective aspect of attention, and that attention can be directed to outside as well as inner processes.

Attention is influenced both by top-down, and bottom-up factors. Top-down processing refers to the influence of factors, such as prior knowledge, internal state, and current goals on lower level processing conveying knowledge derived from previous experience to the processing of present sensory input. Bottom-up factors relate to the information processing evoked by incoming sensory stimulation including both for example unexpected, novel, salient, threatening events as well as more subtle aspects of the environment. The dynamic interaction between these factors will determine the direction of attention (Corbetta and Shulman 2002).

Attention is an inclusive term for a heterogenous collection of processes as for example (1) selective attention (giving priority to the processing of one stimulus

in favor for another); (2) temporal attention (attentional orienting to a particular instant in time); (3) sustained attention (attending to infrequent stimuli over a period of time); (4) arousal (the state of physiological reactivity, ranging from sleep to excitement); (5) attentional orienting (the direction of attention to a certain stimulus); (6) attentional capture (stimulus driven attention), and (7) divided attention (dividing attention between two or more different stimuli); (modified from (Coull 1998).

1.5.1 Sources and sites

The interaction between prior knowledge and sensory input is suggested to involve the “site” where the analysis of the incoming signals occurs and the “source” which applies to the relevant prior knowledge (Frith and Dolan 1997). The “sources” refers thus to the brain regions where the modifying signals appear and the sites are the regions where activity is altered by these signals. The activity in the “sites” can get modified by incoming bottom-up signals as well as by modifying top-down signals whereas the “source” regions are not affected by changing sensory input.

1.5.1.1 Sites

In the classic positron emission tomography (PET) study of Corbetta and colleagues (1991) subjects were asked to pay attention to specific features of the same visual arrays. The results exemplify the modulation of activity in “sites” since selective attention to either feature modulated distinct regions of the extrastriate cortex suggested to be specialized for processing the selective features (Corbetta et al. 1991). There is multiple other evidence that attention can modify the neural response in a “site”. This modulatory influence can take different forms. Activity in a sensory area can be enhanced directly by “gain” or “phasic” mechanism, analogous to amplifier gain control, such that the response in an attended condition is equal to the response in the unattended condition multiplied by some gain factor. It can also be regulated through “tonic” or “bias” modulations such that there is an additive baseline shift (Kanwisher and Wojciulik 2000; Rees et al. 1997). Both mechanisms are most likely implemented in the brain. Evidence of bias modulation comes from studies showing increased activity in relevant sensory processing areas in absence of stimulus input (cf. Kanwisher and Wojciulik 2000). Attentional modulation without sensory input has been found even in the earliest cortical phase of

sensory processing as shown for vision, audition, and recently olfaction (cf. Zelano et al. 2004).

Another question regarding the effect of attention on neural activity has been whether it exerts its influence by enhancing the neural activity of the attended stimulus or by inhibiting the activity of the unattended stimulus, or both. Behavioral experiments indicate that both mechanisms exist, since performance is both improved by a valid location cue and disrupted by an invalid cue, in each case compared with a non-informative neutral cue (Posner et al. 1980). On a neuronal basis this may correlate to decreases in activity in sensory areas outside the areas representing the relevant stimuli. Drevets and colleagues (1995) could show that even in anticipation of a touch, activity decreased in parts of the SI located outside the representation of the skin area that was the target of the expected stimulus (Drevets et al. 1995). Also, task-irrelevant auditory input concomitant to the performance of a cognitive demanding task, correlated with relative decreases in the auditory cortex (Ghatan et al. 1998).

The detection and processing of predictable sensory events that occur as a consequence of our actions is a functional distinct phenomenon. It has been reasoned that as a motor command is sent, a parallel “efference copy” is sent to the sensory areas that predict the sensory consequences of the movement (Von Holst 1954). This efference copy results in attenuated sensory processing, in turn supporting the sharpening of features of importance, those due to external events (e.g. Blakemore et al. 1999). Only if the discrepancy between intended and actual consequences of movement is rather large do representations of the actual state of our motor system reach the threshold needed to enter awareness, to support learning and adjusting for the next movement (Frith 2004; Wolpert et al. 1995). Another suggested significance of the internal model of our motor commands is that it serves to distinguish the sensory consequences of our own actions from externally produced sensory stimuli (Wolpert et al. 1995).

1.5.1.2 Sources

The nature of the neural system that directs the attention toward selected stimuli has been of longstanding interest. Mesulam and Posner conceptualized in the 1980's two influential theories of the neural correlates of attentional sources (Mesulam 1981; Posner and Petersen 1990). Posner divided the attentional system into two sub-systems, an anterior that was involved in detecting signals of

relevance and a posterior that was involved in orienting to relevant sensory events. The ACC was designated as an important area for target detection and whereas the posterior parietal lobe together with the superior colliculus and the thalamic lateral pulvinar were thought to be responsible/implicated for visual orienting (Posner and Petersen 1990). Mesulam described the system in a slightly different way, designating the parietal regions as relevant in representation of space, the lateral frontal regions (frontal eye-field) as important in motor responses to spatial stimuli, and the ACC involved in determining whether a stimulus is motivationally salient or not (Mesulam 1981). Both shared the idea of an underlying reticular arousal system. The reticular formation is a diffuse network of neurons distributed throughout the core of the brain stem, one important nucleus being locus coeruleus containing noradrenergic neurons, crucial for vigilance and arousal. Furthermore, Mesulam's idea that ACC is involved in motivational salience is in agreement with Posner's suggestion of its involvement of target detection and both shared the idea of the importance of posterior parietal cortex in spatial processes (Coull 1998).

The fronto-parietal network of the right hemisphere has long been implicated as attentional source. Lesion studies show that damage to these regions lead to attentional deficits, single unit studies show stronger responses in neural activity in conditions with directed attention compared to passive viewing and numerous functional imaging studies find involvement of this network in tasks requiring attention (cf. Kanwisher and Wojciulik 2000). The exact location of the areas in the frontal and parietal lobe is less clear. Different groups propose that different parts may participate in attention, but most suggest locations within the regions of posterior parietal cortex, DLPFC and frontal eye fields (cf. Nobre 2001).

Working memory is closely related to attention since it involves the temporary holding of information on line. Tasks that require subjects to detect a target and then to maintain attention in order to determine its relatedness to a subsequent target will involve both attentional and working memory processes. The function of working memory to keep information active and to temporarily store the outcomes of intermediate computations is helpful when solving a problem or planning an activity (Baddeley 1998). This is not a unitary function implemented in a unitary region, however, the DLPFC is one of the regions designated as important for working memory (Smith and Jonides 1999).

The literature reveals the involvement of ACC in a multitude of emotional, attentional and cognitive processes (Bush et al. 2000; Devinsky et al. 1995; Vogt et al. 1992). When a situation is novel or highly competitive, a supervisory attentional system intervenes and provides the appropriate activation and inhibition of systems. It is necessary when routine functions are insufficient for the task at hand or when subsystems must be overridden due to environmental or goal changes. In order to accomplish this, the supervisory attentional system should have access to the overall representation of the environment and the goals of the organism. That is, in order for a brain area to perform a supervisory function it must influence widely distributed parts of the brain in which computations related to the task are performed (Norman and Shallice 1986). As described in chapter 1.4.5, the ACC has reciprocal connections with basically the whole brain and is also consistently activated in attentional and executive tasks. The ACC has consequently been designated as central in attention.

The ACC may be divided into three regions with different projections and functions (see chapter 1.4.5). Studies with tasks involving common attention and executive tasks as for example planning, monitoring, anticipation of events, error detection, conflict, novelty, not well-learned responses, or overcoming habitual responses, activate the dorsal cognitive division. The rostral affective ACC has shown involvement in assessing the salience of emotional and motivational information and the caudal ACC more significant for pain processing (Bush et al. 2000; Hsieh et al. 1995).

1.5.2 Selective attention

Selective attention may be described in terms of the process that determine which of several possible inputs that will be analyzed past the level at which all inputs are processed in parallel. Selection systems are of importance since there at each time point is a limitation in the amount of information that can be processed. The conceptualization of selective attention has undergone several transformations.

Broadbent's (1958) theory made analogies between selection and a filtering mechanism. He suggested that sensory stimuli were selectively filtered, based on their physical properties before stimulus identification had occurred. Unattended stimuli thus were supposedly filtered out at an early point (Broadbent 1958). This "early selection theory" was criticized a few years later by the "late selection

theory”. It is a common experience that even when attending closely to a conversation filtering out external stimuli, the mentioning of one's name in another unattended conversation will attract awareness. Deutsch and Deutsch (1963) (Deutch and Deutch 1963) suggested accordingly that all stimuli are non-selectively and involuntarily processed to the stage of object identification or semantics. This would support the perception of unattended but relevant stimuli. This theory was in turn criticized since this procedure would overload the processing resources. Treisman developed Broadbent's theory and suggested that the selection mechanism was not all or nothing, but rather resembled attenuation of unattended stimuli (Triesman 1964).

Desimone and Duncan (1995) developed the “biased competition model” of attention in which they address the brain's limited capacity for processing information. They suggested that the input competes for representation somewhere along the line of processing and that this competition is biased towards the stimuli that are currently relevant to behavior. This competition for neural representation can be biased both through goal-directed top-down signals and sensory-driven bottom-up mechanisms such as stimulus salience (Desimone and Duncan 1995). That is, somewhere between input and response, some sensory stimuli will not be further processed, only some will have impact on motor and memory systems.

Lavie (1995) introduced the concept of “perceptual load” and suggested that the extent to which unattended stimuli are processed depends on how much of the processing resources the attended processes use (Lavie 1995). This concept takes into account that perceptual processing is limited but argues that processing proceeds automatically until the mechanism runs out of capacity. That is, when relevant stimuli do not demand all of the available processing capacity, irrelevant stimuli will automatically be processed and reach awareness.

1.5.3 Temporal attention

Attentional orienting in time concerns the ability to focus resources at a particular moment in time in order to optimize behavior (Coull et al. 2000). Temporal attention will depend on elementary time perception processes that in turn strongly imply the involvement of the basal ganglia. Patients with Parkinson's disease have impairments in basal ganglia function along with disrupted motor functions that depend on precise timing (Narabayashi and

Nakamura 1985). The patients' behavioral impairments will be improved by dopamine treatment that restore some of their basal ganglia function as will their affected time perception (cf. Meck and Malapani 2004). Functional imaging studies have added further evidence by showing increased activity in the striatum in attention demanding temporal conjunction tasks compared to spatial conjunction tasks (Coull et al. 2000), during encoding of time intervals (Rao et al. 2001) and in attention to time (Coull et al. 2004). Another aspect of striatal function is the responsiveness to unexpected reward (Schultz 2002) and to violations to a learned sequence of events (Berns et al. 1997). This may further imply the involvement of striatum for learning about and prediction of aspects of the outer world, including temporal aspects.

Breaches in temporal expectancies have shown correlation with engagement of the OFC as well as left parietal cortex and right lateral frontal areas (Coull et al. 2000; Nobre et al. 1999). The left parietal cortex has previously been implied in temporal orienting (Coull and Nobre 1998), and engagement of the OFC and the right frontal areas was further interpreted as required for endogenous shifting of attention from one time-point to another and for the inhibition of responses (Coull et al. 2000). Attention to time seems thus to rely in a distributed processing network including the basal ganglia, and regions within the parietal and frontal cortex.

1.5.4 Sustained attention

Sustained attention involves the maintenance of attention to a particular stimulus or location for a prolonged period of time (Coull 1998). Although sustained attention often is used synonymously with the term “vigilance”, Coull (1998) suggests vigilance to refer to a longer-term process in the region of minutes to hours and sustained attention rather to refer to the time-span of seconds to minutes. Sustained attention relies on both arousal and attention. The level of arousal may be higher in the beginning. As the vigil continues the arousal usually declines somewhat and process will depend on an increased level of attention (Coull 1998). The early PET study by Pardo and colleagues (1991) on sustained attention towards subtle visual and somatosensory stimuli revealed the fronto-parietal network of the right hemisphere, that now is acknowledged as fundamental for processes involving sustained attention. The somatosensory task involved detecting brief pauses in suprathreshold touches with von Freys hair and in the visual task the subjects were asked to detect near-threshold luminance

changes of a dim central fixation mark, both situations typically requiring focus and maintained alertness for a period of time (Pardo et al. 1991). The midline ACC does not seem to be of primary implication in this type of attentional processes.

1.5.5 Attention, emotion and attentional capture

One inherent property of the stimuli that through evolutionary mechanisms have gained emotional value, is the capacity of capturing attention (Öhman et al. 2001a). There is evidence indicating that emotional stimuli will automatically break through to access processing resources, independent of the current direction of attention (cf. Dolan 2002). In visual search paradigms emotional stimuli are more rapidly detected compared to neutral stimuli. The time needed to find a specified neutral target is proportional to the number of irrelevant distractors indicating a serial search, whereas the time taken to detect an emotional stimuli is independent of the number of distractors suggesting a fast automatic search working on low-level features (Öhman et al. 2001a). Also, the results from backwards-masking paradigms indicating differential physiological responses to fear-relevant compared with fear-irrelevant stimuli support the theory that evolutionarily relevant threats are “tagged” to get priority for processing. This property of emotional stimuli to automatically capture attention makes it possible for the brain to deal with two opposing demands: the selection for goal-relevant stimuli for privileged processing and the detection of potentially significant events that occur unpredictable outside the focus of attention (Vuilleumier et al. 2001).

Apart from the aspect of automatic perception, there is evidence of enhanced sensory processing of stimuli of emotional significance as compared to neutral stimuli (cf. Dolan and Vuilleumier 2003). Vuilleumier (2001) presented a study that implied that this enhancement appears independently of current direction of attention. They manipulated the effect of spatial attention and emotion by examining how neural responses to fearful facial expressions were influenced by whether faces were inside as opposed to outside the focus of attention. Thus, they compared the effects of the same emotional stimuli in attended and unattended conditions. On each trial, subjects were briefly shown two faces, of either fearful or neutral expressions, and two houses in a cross format, with the pair of faces either horizontally or vertically aligned. The subjects had to focus their attention either vertically or horizontally and decide whether the stimuli

were the same or different pictures. In this way, the neural responses to fearful emotional expression could be compared for faces at task-relevant position (inside the focus of attention) and faces as task-irrelevant position (outside the focus of attention). As expected, the visual processing “sites” specific for faces and houses showed increased activity when each type of stimuli appeared at attended locations, as the known enhancing effect of top-down directed selective attention. The more specific finding was that activity in the fusiform cortex, an area representing faces, was enhanced for fearful faces compared to neutral faces and that this enhancement occurred when the faces were at both the attended and unattended locations. Also, the amygdala responded to fearful compared to neutral faces, independent of attentional direction (Vuilleumier et al. 2001). Thus, the effects of attention and emotion were additive in the fusiform cortex.

Anatomically, the amygdala receives input from visual cortex and sends feedback projections to all levels of ventral visual processing stream, from early striate cortex to late higher-order areas. It is likely that the amygdala in this way modulates and enhances visual processes related to emotional stimuli (Vuilleumier et al. 2003). The basal forebrain also receives input from the amygdala as well as the OFC. It might be that the cholinergic neurons of this region, that project widely to the cortex including posterior parietal areas, involved in attentional shifts, and early sensory areas, provide an alternative source of cortical sensory modulation (cf. Dolan and Vuilleumier 2003).

2 Aims

The general aim of this thesis was to study the neural responses to the interaction of present information with previous knowledge. As conceptualised here, prior knowledge can be engendered from cues in the present context, from previous experiences, or in a wider sense by evolutionary processes effected in the organization of the brain.

The specific objectives were:

- To study the neural network active during anticipation of a sensory event. In other words, to characterize the neural activity generated by top-down processes, induced by a contextual cue, without intramodal sensory input (study I).
- To investigate the influence of temporal predictability on the neural processing of aversive events (study II).
- To describe the neural response to a manipulation of the expected duration of a standard painful stimulus (study III).
- To compare aware and unaware fear processing in response to phobic and merely fear-relevant stimuli (study IV).

3 Methods

3.1 Subjects

All subjects gave their informed consent to participation. Recruitment was done by advertisement locally and subjects were subsequently screened for general health, signs of addictive disorder, handedness etc. Details of the selection procedure are given in each of the studies 1-4.

In study 4 the subjects were initially screened for animal fears by answering short versions of the specific snake and spider fear questionnaires (Klorman et al. 1974). Those scoring above the 90th percentile for either snake or spider fear and below the 50th percentile for the other fear, met with a clinical psychologist who checked that they fulfilled the criteria of specific phobia given in the Diagnostic and Statistic Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1994).

3.2 Ethics

All procedures were pre-approved by the local ethical committee of the Karolinska Hospital as guided by the Declaration of Helsinki prior to the commencement of each study. Pertinent pre-information was given to all subjects including the option of discontinuing the participation at any time during the experiment. Subjects were acquainted with all procedures prior to the commencement of the experimental protocol. Payment to subjects for participation was done with moderation according to the guidelines of the ethical committee as to not provide improper influence on the subject's decision to participate or not in the experimental procedures.

3.3 Behavioral methods

3.3.1 SAM

The Self-Assessment Manikin (SAM) is an iconic differential rating system that Lang (1980) (Lang 1980) designed to measure emotional properties of stimuli. It is based on the tradition of describing emotional responses into three dimensions: evaluation, activity and potency (EPA). An early contribution to this line of thinking was made by Osgood and colleges (Osgood et al. 1957) (1957).

They performed factor analyses on a vast number of semantically contrasting adjective pairs and extracted the three major semantic dimensions (EPA) suggesting that they underlay the formation of affective impressions. Since then the EPA-structure has been validated as a way of conceptualizing responses to emotional properties in for example facial expressions, words, affective pictures and music (cf. Heise 1992). Lang and colleagues established further a link between the EPA-measures and emotional psychophysiological response system by demonstrating a link between rated valence (evaluation) and the magnitude of the startle response, and between rated activity (arousal) and the magnitude of skin conductance responses (Lang et al. 1997).

3.3.2 VAS

The Visual Analogue Scale (VAS) is another self-report measurement instrument that can be used to measure the magnitude of internal states, such as emotional responses and pain (Wewers and Lowe 1990). Conventionally, the VAS is a 100-mm line anchored by word descriptors at each end. The participants place a mark somewhere along the line that they feel best represent their perception of their current state. The anchor words used in study II and III were referring to pain experience, no intensity – highest imaginable intensity, no negative valence (unpleasantness) – highest imaginable negative valence (unpleasantness), no anxiety – highest imaginable anxiety.

3.4 *Interventions*

3.4.1 Tickle

The tickling somatosensory stimulation in study I was applied manually with a small artist's brush. The experimenter brushed the subject's sole of the right foot with light strokes.

3.4.2 Electrical stimulation

Electrical shock stimulation was administered by an electrical amplifier positioned outside the scanner room (SD 9 Stimulator, Grass Instruments, Astro-Med Inc, USA).

Before entering the scanner the subjects chose two levels of a 70 ms electrical shock stimulation (study II). The intensity of the stimulation was set by the

subject following the instruction that the low level should be as low as possible but still a clearly detectable stimulus whereas the high intensity should be painful but acceptable. The shocks were delivered via surface ECG-electrodes placed with approximately 4 cm distance from one another on the palmar aspect of the right wrist. To minimize interference with the scanner, the electrical current applied to the subject was filtered with a low-pass filter. All visual presentation and delivery of the electrical shocks were controlled and synchronized to the MR image acquisition using the ERTS software running on a laptop computer (BeriSoft Cooperation, Frankfurt, Germany).

3.4.3 Cold-pressor test

In Cold-pressor test the subject's hand is in water for a standard period of time. The water was in study III mixed with glycol and cooled to a temperature between 0°C and 1°C (painful) or the water was mixed with cooled with crushed ice to the same temperature, to contain a more tactile component. The control condition was cool water (19°C).

3.4.4 Backward masking

With this method, the visual information processing of a target stimulus is interrupted by an immediately following masking stimulus. The subjects are thus exposed to pairs of stimuli, one target and one mask. In study IV there were three different types of targets: phobic, fear-relevant and neutral. For subjects with specific fear for snakes the phobic stimuli consisted of snakes and the non-phobic fear-relevant stimuli of spider pictures. For subjects with specific spider fear the stimuli were reversed. The neutral stimulus was a picture of a mushroom and the masking stimulus was a picture constructed by randomly reassembling pieces of the snake and spider pictures. The targets were exposed for 14 ms and the mask 56 ms. The extent to which the target stimulus is perceived is dependent on the interval between the onsets of the target and the masking stimuli, the so-called stimulus-onset-asynchrony (SOA). The SOA was either 14 ms (short, masked) or 308 ms (long, non-masked). This means that in the short condition, the mask appeared right after the target offset, and that there were 294 ms between the target offset and mask onset in the long condition.

3.5 Functional neuroimaging

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are two functional imaging methods that detect changes in metabolism or blood flow as an indirect measure of neural activity. The neurophysiological basis of this inference is the roughly linear coupling between the regional cerebral blood flow (rCBF), the metabolic activity and the neural activity (Logothetis et al. 2001; Scannell and Young 1999).

The brain is a metabolically highly active. At rest the human brain consumes approximately 20% of the oxygen and metabolic supply needed by the body, although the brain accounts for only approximately 2% of the body mass. This energy turn-over in the brain is necessary to maintain the ionic concentration differences across membranes and thereby the membrane potentials at the appropriate levels. The dominant use of energy stems from maintenance of these membrane potentials. This implies that the total blood flow to the brain as an entity varies only a little between the time when the brain is most active and when it is at rest. However, the blood flow varies within and between regions depending on the intensity of neuronal activity at each time point.

Signal transmission between neurons implies changes in local field potentials, to a large extent in the postsynaptic dendrites. This results in large ionic fluxes that need restoration. Increases in neural activity in a given brain region will thus increase the energy requirements. However, the energy and oxygen consumption will be accompanied by a local increase in blood flow that exceeds the increase in oxygen consumption (Fox and Raichle 1986). This means that the relationship between the oxygen consumption and the blood flow is linearly coupled within the physiological range but not on par with one another. The local oxygenation will increase in an area of increased metabolic rate and this provides the basis for the signal in fMRI (see below).

There remains an unresolved question regarding the relationship between the type of brain activity and the signals measured with fMRI and PET. Are they related to excitation, inhibition, or both? The signal is a composite net-activity and it is difficult to imagine any regional activity that is not a mixture of both excitatory and inhibitory components. However, given that inhibitory signals give rise to hyperpolarization and less ionic leakage post-synaptically, it is suggested that the recorded signal might be more closely related to local excitatory activity (Shinohara et al. 1979).

3.5.1 PET acquisition procedures

The functional neuroimaging data presented in studies number III and IV were acquired with PET. In functional PET studies, a radioactive isotope (in study III, [15-O]-H₂O (Shinohara et al. 1979) and in study IV, [15-O]-butanol (Berridge et al. 1990) with a half-life of approximately 2 min is injected into the venous blood stream. For each subject, between 10 to 15 bolus injections of 400-500 MBq (10-15 mCi) [15-O]-butanol or [15-O]-H₂O were performed. In the basic PET scanner set-up used, the primary PET data acquisition started automatically when a predetermined activity threshold was passed upon bolus arrival to the brain. PET data was then acquired for the subsequent 40 s. In order for the injected radioactivity to return to the background level at least 5 x the half-life of [15-O] was allowed to pass (i.e., approximately 10 min between consecutive PET scans).

The tracer-molecules follow the blood flow and emit positrons that interact with electrons in their vicinity. Each positron-electron pair decays into two photons which then trace out a line-of-response in opposite directions. Hence, the photon radiation intensity along the different lines-of-response, determined by the field-of-view (i.e., the number and position of the detector rings of the PET scanner) depends on the tissue distribution of the tracer-molecules, which in turn is determined by the rCBF. Data were sampled with a 3D ECAT EXACT HR PET scanner (Wienhard et al. 1994). Attenuation correction was routinely performed based on a transmission scan for each participant.

3.5.2 fMRI

MRI is based on the hydrogen atom containing a positively charged proton in its nucleus and that it precesses around its own axis. In other words, the hydrogen atom has a quantum mechanical spin associated to it. The spinning of the charged protons creates a microscopic electromagnetic field. This electromagnetic property of the protons causes them to be aligned in the strong electric magnetic field provided by the MR scanner. The field strength of the external magnetic field will determine the precession frequency of the hydrogen atoms, also called the Larmour frequency. Brief electromagnetic radiofrequency pulses of a frequency that matches the frequency of a spinning proton will affect its alignment temporarily. When returning to the direction of the magnetic field of the scanner, the protons emit an electromagnetic signal that may be measured by a detector.

Functional MRI uses the blood oxygen level dependent (BOLD) effect to generate contrast between conditions within a given region of the brain, whose level of neural activity differ between the conditions (Ogawa et al. 1992). Oxyhaemoglobin is diamagnetic (that is, essentially nonmagnetic) while deoxyhaemoglobin is paramagnetic, a quality that will disturb the local alignment of protons and hence consequently lead to lower net signal emitted by the returning protons. Since the oxygen consumption of an active region will be accompanied with a disproportionate increase (as described above) in the supply of fully oxygenated blood, active regions will generate higher net signal.

While the temporal resolution is based on the bolus delivery of the isotope to the brain, i.e. between 20 sec to 40 sec for PET, a rapid sequence called echo-planar imaging (EPI) will allow for acquisition of a whole brain in seconds with fMRI. The EPI acquisition mode capitalizes on the usage of fast switching magnetic gradients to sample all the necessary frequency information to reconstruct a single MR image in less than a tenth of a second (Mansfield and Maudsley 1977). Thus, the time resolution for fMRI is largely depending on the trait of the biological signal (change in blood flow) and less on the mode of signal acquisition. The first fMRI studies of the human brain using sensory stimulation was reported only a little more than a decade ago (Ogawa et al. 1992).

One disadvantage of the EPI sequence is that it is sensitive to susceptibility artifacts. Magnetic susceptibility is defined as the extent to which a material becomes temporarily magnetized when placed in a magnetic field. Compared to brain tissue, air is more readily magnetized. At the boundary between brain tissue and air, as for example close to the ear canal or the facial sinuses, the slightly different magnetic fields create gradients that will cause dephasing between protons. This may contribute to signal drop-out and geometric distortions.

The changes in the signal induced by the BOLD effect are quite small, generally less than 5% of the total signal from the tissue. In order to increase the signal-to-noise ratio (SNR), paradigms that allow for repeated stimulus presentations are often used. A common arrangement is a block design with periods of one conditions interspersed with periods of a different condition or rest. In the subsequent analysis of the signal changes, one searches for correspondence between changes in the MR signal and a tentative response in the brain. In this thesis we have used block designs (study I and II).

The imaging was performed on a 1.5 T GE signa Exhospeed MR scanner with a standard circular head coil. In study I, the image volumes contained 13 axial 6-mm-thick slices positioned to cover the upper 7.8 cm of the brain. One volume were scanned in 3 s (repetition time (TR), TR=3 s). The sessions were 3 min long and the subjects each performed 4 sessions. At the time when study II was performed, the MR-scanner could acquire images at a higher rate, allowing a full brain acquisition with 42 axial 3-mm-thick slices, with the TR of 4.2 s. Also, an increased capacity for sampling the data, allowed for longer sessions of 7-8 min. For more specific details about the designs, please see the methods sections of the studies.

3.6 Image preprocessing and statistical analysis

3.6.1 Realignment

In a functional neuroimaging study several image volumes are acquired over time for a given participant. The subjects are asked to lie as still as possible throughout the experiment, that is for over 2 hours for PET and for 1 1/2 in an fMRI experiment. To help the subjects with this, they got an individually fitted plastic helmet (PET), an individual molded bite bar (study I, fMRI) or foam-rubber between head and head-coil (study II, fMRI). Nevertheless, small head movements on the order of a few mms still occur. In order to compensate for this movement, the images are automatically realigned (cf. Ashburner and Friston 1997). Through this step, the time-series that would have been acquired if the subject had remained absolutely still is obtained.

3.6.2 Normalization

The brains of different individuals are different in shape and size. Anatomical normalization is a method to warp images of individual brains into a standard brain shape. This procedure will adjust for anatomical differences and thus allow data to be averaged across subjects, a necessary requirement in group studies. The standard brain shape used in our studies is an approximate Talairach space (Talairach and Tournoux 1988), as defined by the statistical parametric mapping (SPM) template (www.fil.ion.ucl.ac.uk). In study I, the Computerized Brain Atlas of Greitz was additionally used (Greitz et al. 1991).

In study I, the morphological image from each individual was used for the calculation of normalization parameters. The realigned functional images were then normalized and resliced using these parameters. In study II, spatial normalization was based on finding the warping parameters between the mean EPI volume of a given subject and an EPI template in the Talairach space and applying these parameters to all the individual EPI images. Preceding the normalization step, a slice timing correction was performed to the middle slice to correct for the sequential sampling of the brain in the slice-direction.

For PET data, the mean of the 10-15 scans in each subject was directly normalized to the SPM PET template. The resulting parameters were then used to reshape the individual realigned scans.

The use of different templates (the templates have also small differences in the different versions of SPM) give rise to different coordinate localizations. Hence, minor difference between the anatomical designations of certain coordinates may exist.

3.6.3 Spatial filtering

There is a remaining anatomical variability after the normalization procedure. Deviations between subjects of peak activations can be on the order of 5-10 mm. The reduction of the impact of misregistration due to this residual functional-anatomical variability is therefore of importance, especially in group studies. Spatial filtering is one way to reduce such effects.

Spatial filtering or smoothing is the convolving of data with a smoothing kernel, that is each voxel is replaced by an average of that and the surrounding voxels. If the spatial-scale of the filter matches the inherent scale of functional-anatomical variability in the population, no (or little) spatial information is lost. In other words, a mapping of function onto anatomy may be meaningful only at a resolution that is not confounded by organizational details unique to a given individual.

Another important objective of spatial smoothing is that it increases SNR. The neurophysiological effects we are looking for are expressed in a spatial scale of several millimeters, whereas noise contains higher spatial frequencies. A spatial filter will hence favor physiological effects over noise. The nature of the technique means that SNR is inherently poorer in PET studies and PET data are

therefore often smoothed more. In our studies, we have filtered the data with a 3D isotropic Gaussian kernel of 8 mm (fMRI) or 10 (study III, PET) 13 mm (study IV, PET) full-width-at-half-maximum (FWHM).

3.6.4 Statistical modeling and inference

Statistical modeling corresponds to dividing the observed variability of the signal into effects of interest, confounds of no interest and an error term. Statistical inference is the process of comparing the size of the effects of interest to the error term. If the effect of interest, i.e. the effect invoked by our experiment, is large compared to the error we infer that an activation is at hand.

3.6.4.1 *Statistical modeling.*

A hypothesis about the changes in brain activity is constructed based on the paradigm that the subject has been exposed to. The data can be viewed as a large set of time-series, one for each voxel. Consequently, the hypothesis formulated is in the form of a tentative time-series. If the experiment consists of several different conditions there will be a separate tentative time-series for each condition.

Study I may serve as an example. The subjects were exposed to repeated periods of rest, anticipation and tickle. A tentative time-series to identify a voxel that is active during the anticipatory state would then have the value one during periods of anticipation, and zero during periods of rest or tickle. Similarly, a tentative time-series for identifying voxels active during tickle would have the value one during periods of tickle, and zero during the other periods. These tentative time-series are called stimulus functions or regressors.

Taken together the regressors define our model, as embodied by a design matrix that is a concatenation of the regressors. The model is subsequently used to identify, or classify, the voxels of the brain into those that are active during anticipation, tickle, both, or those that are not active in either condition. This is done by finding the linear combination of regressors that best mimic the time-series observed for a given voxel, i.e. finding how much is needed of each of the regressors to adequately describe the data. If we need “much” of the regressor corresponding to anticipation to model a certain time-series (voxel) it is likely that this particular voxel is involved in anticipation. Similarly if we need “much”

of both the anticipation-regressor and the tickle-regressor that particular region (voxel) is probably involved in both.

This framework, together with an assumption about normal distributed errors, is known as the General Linear Model (GLM) (Friston 1997).

3.6.4.2 Statistical inference and hypothesis testing

In classical hypothesis testing we calculate a statistic (e.g. a t-statistic) from our data that is designed to include all the factors that are believed to have an effect in our data.

In the example of study I, we want to infer if a given voxel (time series) is involved in for example) anticipation or not. From the process of modeling, as described above, we will know how much of the anticipation-regressor was needed to model the data of a particular voxel. If “much” is needed it will increase our belief in that voxel being involved in anticipation, if “little” is needed it will decrease that belief. In addition, there will be an error associated with each voxel. Due to measurement errors, the model will never exactly match the data, and the degree of mismatch gives information about the size of the measurement errors. If the errors, for a given voxel, are large it will decrease our belief in the voxel. Finally, we will tend to put greater trust in long time-series than in short time series. That is, the more measurements we have performed the more trust we have in the results.

A t-statistic is simply a function of the data that take all these factors into consideration, yielding a single value (per voxel) that quantifies our belief in the voxel.

When deciding if a t-statistic is significant, we start out by assuming that it is not, i.e. that there is no effect of the experiment. This (non-intuitive) assumption of no response is known as the null-hypothesis. When rejecting the null-hypothesis at a 5% level ($P=0.05$), it means that only 5 times out of 100 would one observe such data given that the null hypothesis is true. In other words, the smallness of the P-value is viewed as a measure of the strength of the empirical evidence against the null hypothesis. We can also say that we control type-1 errors at the 5% level, i.e. false positive errors.

In order to control for the family-wise type-1 error (i.e. control for the effect of testing at each voxel) a correction of threshold is introduced. If there is a 5% risk

of finding a t-statistic of e.g. 1.96, or larger, when there is no effect present then clearly there is a much higher risk of finding such a value somewhere among hundreds of tests. This means that the threshold for controlling family-wise error will be higher than for controlling voxel-wise error, often much higher. Precisely how much higher will depend on how many voxels one is testing (search volume) and on the shape of the volume that the voxels are in. It will also depend on how closely related adjacent voxels are, i.e. on the smoothness of the data. There are several approaches to handle the problem of calculating the threshold that will yield a 5% family wise error and this will not be entered upon here. In the present work this has been performed using SPM.

3.6.4.3 *Classical versus Bayesian inference*

In classical inference testing, we can assign probabilities to the data under some assumptions about the true state of affairs. Typically we say, “the probability of observing these data is 5% (or less) assuming that the null hypothesis is true”.

What one cannot do in classical inference testing however, is to assign probabilities to the parameters of the model. The Bayesian framework is a vehicle for going from probabilities of the data under the null hypothesis to probabilities of the parameters.

In order to take this leap one needs a “prior-distribution”, i.e. already before we do the experiment we should have some information about the effects that can be quantified in a mathematical sense. Critics of Bayesian methods claim that this introduces an element of subjectivity (that the prior is nothing but a quantitative form of your own bias). However, the prior does not need to introduce any bias. One may for example use non-informative, or flat, priors that consider every value of the parameter equally likely. In this case there can of course be no bias and a Bayesian point estimate (i.e. the single most likely value of the parameter) is identical to a classical (Maximum-Likelihood) estimate. However, the Bayesian calculations will yield a “posterior” distribution of the parameter, a distribution that allows us to assess just how likely or unlikely each possible value for that parameter is.

Another form of prior, one which is used in SPM, is a shrinkage prior. The term shrinkage prior refers to the assumption that the most likely value for any parameter (or effect) is zero, and hence any observed effect will “shrink” towards zero. In that sense it is not unbiased, but it is biased in such a way we will be

more conservative, i.e. it will make us more prone to underestimate any effect. Its usefulness comes from the fact that in a Bayesian framework “precisions add together”.

The precision of an estimate is the inverse of the variance. There is a variance, and hence a precision, associated with our prior belief and there is a precision associated with our data. If we add up these precisions, by combining the prior and the data, the precision will be greater and the variance, or uncertainty, consequently smaller.

Therefore, although a shrinkage prior will tend to diminish the size of our parameter/effect it will also increase its precision, i.e. decrease the uncertainty of it. The prior that is used by SPM has by definition a zero expectation (i.e. the most likely parameter value is zero) and it will estimate its variance (precision) from the surrounding voxels. If the surrounding parameter estimates vary wildly between them it is likely that there is large uncertainty associated with their values and the prior will have large variance (small precision). So, in a sense the prior is not really a “prior” at all since it is derived from that data, rather than from our prior beliefs. Therefore it represents a sort of “half-way Bayesian” approach known as Parametric Empirical Bayes.

The method we have used is known as Posterior Probability Maps (PPM) in SPM. It is based on the shrinkage prior described above and yields maps with expectation (most likely value) and uncertainty of the parameters we are interested in. For example if we use a contrast to find out the difference between painful shock and non-painful shock the PPM will constitute one map that describes, for each voxel, the most likely value for that difference and another map that describes how uncertain that value is. One can then use SPM for to show all voxels where there is a 95% likelihood that this difference is greater than zero, or any other value.

It has been claimed that the use of Bayesian inference eschews the problem of multiple comparisons. Since there is no longer a null-hypothesis, and hence no longer a type-1 error how can it be a problem? This is possibly a slightly ingenious claim though. In practical terms, if one uses a flat prior for the parameters and threshold ones PPM to show all voxels where there is a 95% likelihood that the effect is greater than zero we would see the same voxels as when performing a classical t-test and thresholding at the 5% level uncorrected for multiple comparisons. In a pragmatic perspective, the difference lies in the

shrinkage prior that will pull the “uncertain voxels” towards zero, and also in the factor λ that allows us to specifically look for voxels where, with 95% certainty, the parameter/effect is larger than λ . It is recommended that one chooses λ to signify a “physiologically meaningful” effect size. However, to date there is no information that would allow us to determine such a limit, and at any rate it would depend on irrelevant factors such as e.g. the field strength of the scanner. Therefore, in the present study we have chosen to look for effects larger than zero.

The final judgement on the usefulness of these methods will be determined by time and collected experience.

4 Results

4.1 *Anticipation of tickle (study I, fMRI)*

The uncertainty regarding the onset time of the tickle induced an anticipatory state. The upcoming tickle was known with regard to nature and location, the sole of the right foot, and this allowed for a specified, directed anticipation. The overall neural response to this anticipatory state was notably similar to the response to the actual tickle. The areas that were activated during both states included the area of the contralateral primary sensory cortex representing the right foot as well as the secondary somatosensory cortex (SII). Common decreases were seen in sensorymotor cortex located outside the area of the right foot. The right anterior insula was also active comparing anticipation with rest. That is, enhancement of activity was seen in relevant sensory processing areas and suppression of activity in irrelevant areas. We interpret the activity of these networks as a top-down modulation of activity in “sites”, a tonic regulation of neural activity without intramodal input, during anticipation.

Activity in both states were seen in the ACC (BA 32) and in the posterior parietal cortex (PPC) (BA 40/7) possibly part of the network supporting spatial attention and the sources of attentional modulation.

The overlapping patterns of change during the anticipation and the tickle furthers the idea that predictions/anticipation of a relevant stimulus, sufficiently specified in location and nature, is subserved by a neuronal network similar to that which subserves the processing of the actual sensory input. It also infers that anticipation may invoke a top-down modulation of neural activity and in this way favor selective and focused processing of relevant information.

4.2 *Predictability of pain onset (study II, fMRI)*

The temporal predictability was manipulated by means of rhythmicity (pilot, behavioral study) or a visual cue (main study) while maintaining the same amount of somatosensory input. Subjects reported lower levels of anxiety, negative valence and pain intensity during the predictable aversive events (electric shocks).

In addition to attenuate focus on danger, predictability allows for a correct temporal estimation of the sensory input. In line with the results from study I,

this increased selective attention related to enhanced activity in the “sites” of relevant sensory-discriminative processing areas, such as the SI, the SII and the posterior insula.

The unpredictable more aversive context correlated to brain activity in the anterior insula, the OFC and the caudal ACC, areas associated with the affective component of pain processing. This context also prompted increased activity in the PPC and lateral prefrontal cortex that we attribute to enhanced alertness and sustained attention during unpredictability.

4.3 Expectation of pain duration (study III, PET)

Preceding a noxious stimulation (cold pressor test), subjects were informed whether the stimulation would last for 1 or 2 min. The brain activity was measured during the first minute of the stimulation. In analogy to study II, a similar noxious stimulation was thus delivered during the scanning period, but the context, here the expectation of pain duration, varied.

The activity in the amygdala showed a more expressed decrease in the context of 2 min painful stimulation compared to the 1 min painful stimulation, compared with the same subtraction of the cold water stimulation. Also, the subjects reported that they perceived the anticipation period before the noxious stimulation as more aversive when they knew that the stimulation would last for 2 min. As the amygdala is a nexus in fear processing we suggest that the altered amygdala activity may be part of a mechanism to attenuate the pain-related stress response in the context perceived as more aversive. Other areas with decreased activity in the 2 min context included the OFC, a region that has been suggested to be of significance representing valence of stimuli, and the posterior insula.

The ACC was active in the simple effect of 2 min painful context to 1 min painful context.

4.4 Unawareness of fearful stimuli (study IV, PET)

The participants in study IV had been selected to be specifically afraid of either snakes or spiders, but not of both. The visual target stimuli consisted of snakes, spiders and mushrooms, that is phobic, fear relevant (e. g. a spider to snake phobics) and neutral. The subjects were unaware of the stimuli exposed when the target stimulus were shown for 14 ms and immediately followed by a masking

stimulus. The left amygdala/anterior medial lobe responded to both phobic and fear relevant stimuli with this exposure time only allowing for very rapid incomplete visual processing. In other words, exposure to fearful stimuli with a timing that did not allow for awareness activated the left amygdala/anterior medial lobe.

4.5 Awareness of phobic and fear-relevant (but non-feared) stimuli (study IV, PET)

Behavioral ratings of negative valence and arousal in response to aware exposure of the visual stimuli showed an interaction reflecting a double dissociation for groups and type of stimuli (phobic, fear relevant). The snake-fearful participants rated snakes as more arousing and more negatively valenced than spiders, whereas spider-fearful participants showed a significant difference in favor of spiders over snakes. The groups did not differ in their ratings of mushrooms.

When the exposure time allowed for aware processing, the phobic stimuli activated the amygdala together with an affective processing network of the ACC, the anterior insula, the OFC, and the PAG, whereas neither amygdala nor any of the cortical areas was significantly activated in the fear-relevant condition. Thus, when the phobic stimulus became more completely processed as compared to the short unaware exposure, a fear network that included both cortical and subcortical nodes were recruited as well as the subjective fear response. With time to apprehend that the fear-relevant stimulus was of a non-feared type, no significant subcortical or cortical areas were recruited. When contrasting the phobic and fear-relevant conditions, this difference in brain activity was confirmed.

In the reverse comparison, the right DLPFC and OFC appeared. The prefrontal cortex, and specifically the DLPFC, is a region that hold representations on line to promote goal-oriented behavior as well as to inhibit environmentally cued responses. These regions may therefore be considered to be “sources” in top-down modulation of the affective information processing of the non-feared fear-relevant stimuli.

5 Discussion

5.1 *Prior knowledge*

One of the main theses in this dissertation is that our experience of the world depends on both the surroundings and the brain. In other words, our percepts evolve from an interaction between the incoming signals and previously acquired knowledge. Prior knowledge can relate to previous experiences of the individual or just recently learnt information. However, in this thesis prior knowledge is referred to as including also a wider meaning of previous coded information contained within the nervous system. The design of the sensory receptors receiving incoming signals is one example of a built-in property of the system that carries information and determines the type of information that reaches the brain. The specified way in which the different regions in the nervous system respond and represent different types of information and even the learning algorithms that influence how the environment modifies connectivity and processing may be part of the starting state. Emotions may also be seen as expressions of inherited knowledge that has supported the meeting of needs throughout evolution. Emotions protect us by allowing dangers to be avoided or by endorsing the approach of favorable situations. As such, the emotions often operate along the dimensions of simple approach or withdrawal without resorting to the time consuming labors of reasoning and deliberated considerations of facts and options. Naturally, only a few aspects of this extensive interpretation of prior knowledge are discussed here.

In study I, the known nature of the tickle and the known location (the sole of the right foot) was part of the previous knowledge. Also, the correspondence between the foot and its corresponding site in the primary cortical representation is part of this. The visual cues (green and red squares) provided the contextual information that allowed for anticipation and activation of this prior knowledge.

Sensory information caused by self-initiated movements is well known in time, nature and location and its processing is usually attenuated by the intervention of an “efference copy” that blocks incoming information based on previous coding (see chapter 1.5.1.1). This is an example of how processing of one sensory stream may be diminished in order to make possible for processing of other incoming signals. In this study however, the sensory stimulus was externally generated and the ticklish subjects were impelled to notice and process the tickle. The

information of the upcoming event in terms of location and nature and the less specific information about the timing allowed for a selective direction of attention and the anticipatory state.

Information about the nature and location of the somatosensory stimuli was also granted in study II and III. However, the degree of temporal information varied between the unpredictable and predictable conditions (study II) and expected duration (study III). This difference in context turned out to influence the experience and the neural processing of similar sensory input.

Participants in study IV had a disposition to react with phobic fear to either snakes or spiders but not to both. Our data implies that the amygdala respond to both phobic and fear-relevant (but non-feared) stimuli when the stimuli were presented so that the participants remained unaware of them. This supports the suggestion that stimuli of survival relevance are “tagged” to automatically evoke an emotional response and thus to get priority for processing (Öhman 2000c). This match between stimuli and neural response may be conceptualized as a prior knowledge of the nervous system.

The disposition to react with phobic fear is a combination of inherited and learned factors. However, there are reasons to believe that fear to situations or animals that have constituted a threat throughout evolution may be implemented in the nervous system and more readily activated than fear to other stimuli. Whether the phobic response is phylogenetically or ontogenetically learned, it was a disposition that the nervous system had acquired by the time that the participants took part in the study. By choosing subjects with specific fear to either snakes or spiders we were able to rule out material specific effects and instead map responses reflecting this previously learned reference to the stimuli.

5.2 Top-down modulation of processing

The distinction between top-down and bottom-up is not without complication. “Top” and “bottom” can have evolutionary connotations such that the “top” would refer to the evolutionary younger frontal regions and the “bottom” to evolutionary older and deeper structures as for example in the brain stem. Usually, the model refers to the relationship between the organism and the environment. In this sense, “bottom” is the information that comes from the outside and via the sense-organs reaches central processing systems, while “top” is the knowledge that the organism already has. “Top” and “down” can also relate

to what is controlling and what is controlled (cf. Roepstorff and Frith 2004). Even if the model of “top-down” and “bottom-up” is very helpful in describing cognitive operations, a few things are to be kept in mind. The first to remember is that there is no region with only outputs and no input; also a region denoted as a “top” will be influenced by incoming information. This reasoning is likewise relevant to remember when using the model of “sources” and “sites”. That is, a region functioning as a “source” from one viewpoint may also be a “site” of modulation. Secondly, if we think about what is the “top”, we are confronted with the problem of what or who makes the choice of modulation. The abstraction of a homunculus, a little brain inside the bigger brain, is moving closer (Roepstorff and Frith 2004).

Roepstorff and Frith (2004) offer a complementary conceptualization that may add clarity to these putative predicaments, that of “shared scripts”. “Script-sharing” refers to the common understanding of the nature of an experiment that the experimenter and the participant has. Instructions to the participant are coming from the outside, via the senses, that is bottom-up, their main purpose being to allow for the establishment of a model of how are to interpret the situation, that is top-down. Via communication the experimenter and the participant will come to share the representation about the nature of the task, a representation that in turn will contribute to the top-down modulatory operations (Roepstorff and Frith 2004). This reasoning can carry over to the everyday life where the culture, that which can be shared and understood, and the interchange with other minds will contribute to the top-down operations. The idea that the incoming signals from the environment provide the script/representation that underlie actions adds another perspective to the figures 2 and 3 (chapter 1.2.2). From this perspective, the DLPFC-PPC network and the ACC, regions that traditionally carry the connotation of top-down activity, may be seen as significant regions for facilitating implementation of scripts (Roepstorff and Frith 2004).

5.2.1 The DLPFC, the PPC and the ACC

In study I the PPC and the dorsal ACC were active in the anticipation of, as well as during tickle. The PPC and the DLPFC were active together when comparing the processing of fear-relevant (but non-feared) and phobic stimuli in study IV. These are conditions that include operations with top-down controlling characteristics. In the state of anticipation, the visual cue, in combination with

the preceding verbal instructions, was holding and conferring information of where to direct attention and what brain regions to modulate. Possibly the PPC and the ACC contributed to this.

The parieto-frontal network active in study IV may be interpreted in a slightly different framework. Whereas the phobic stimuli are associated with uncontrollable fear, the processing of fear-related stimuli involves the cognitive reframing of the fear stimuli and the cessation of the fear reaction. The cognitive transformation of an emotional experience comprises several processes (Ochsner et al. 2002). One of them would involve generation of a strategy for reframing the emotional event in unemotional stimulus analysis terms and keeping that strategy on line. This process also supports higher order cognition, planning and inhibition of environmentally cued responses. As the DLPFC is associated with holding representations on line and exert top-down influences (Smith and Jonides 1999), we reason that the activity in this area, seen in response to the non-feared stimuli, may represent such operations. A second process in the cognitive transformation may involve monitoring of the interference between the top-down modulating strategy and the incoming affective information that generates the emotional response. This is a task that may contain components of conflict monitoring and has been attributed to activity in the ACC (Carter et al. 2000). Thus, the relative deactivation of DLPFC during phobic stimulation may be attributed to a failure of applying a non-fearful cognitive reframing strategy to the situation. Likewise, the relative activation of DLPFC during exposure of the non-feared stimuli may represent a successful implementation of such a strategy. The concurrent dorsal ACC activation in the phobic conditions may be related to the continuous monitoring of the situation in which the bottom-up-induced fear reaction was developing unconstrained by failed attempts to cope by cognitively transforming the threat to a less serious one.

These results and interpretations relate to studies of conflict using versions of the Stroop paradigm (Carter et al. 2000; MacDonald et al. 2000). In this classical cognitive paradigm the subjects are faster to name the color in which a color word is printed when the meaning of the word is congruent than when it is incongruent with the color of the print. This increased response time reflects the fact that word reading interferes with the color naming when the word and the color conflict, and is referred to as the Stroop effect. Carter and colleagues manipulated subjects' expectancies for congruent (that is, word and color are the same) and incongruent trials (word and color are different). When expectancy for

incongruent stimuli was high and strategic processes implementing a high degree of top-down control were engaged, the conflict was reduced and response times lowered. In the reverse condition, expectancy for congruent stimuli was high, top-down control was less engaged, less control was exerted over the prepotent response tendency, and consequently conflict associated with responding to incongruent stimuli was increased. This latter condition was related to an increased ACC activity relative the former condition, in line with the theory that the ACC performs evaluative and monitoring functions and that other regions, presumably the lateral frontal cortex, support the implementation of strategies resolving the conflict.

The dorsal ACC was also more active in response to unpredictable than to predictable low intensity electric shocks, a condition presumably involving increased monitoring (study II). The ACC was also active in response to 2-min pain compared to 1-min pain (study III). The activation was denoted to be located within the rostral part of ACC in study III. However, the coordinate is located such that it also can be described as belonging to the dorsal division (Bush et al. 2000). The activity related to the more aversive 2-min pain situation can be understood in line with the reasoning above, that is, in terms of a response to an increased demand of monitoring in the more aversive situation.

5.2.2 The amygdala: A "site" and a "source"

An intriguing finding of study III was a relative deactivation of amygdala/anterior MTL in the more aversive 2-min context of pain as compared to the 1-min pain. We reasoned that the amygdala, known to respond to fear and stress, was relatively inhibited in dealing with this more stressful situation. The self-reports indicated higher experienced stress during the anticipation period as well as more intense coping efforts in the 2-min context, but we have no objective measure of the subjects' coping efficiency. A general consideration, when studying stress and coping, is the difficulty to find independent indicators of the two factors. When relying on self-reports on both factors it may be troublesome to discern whether the stress is high or the coping efficiency is low and vice versa, if the stress is low or the coping is successful. Ways around this dilemma is to control and alter the coping strategies or to introduce startle eyeblink magnitude measurements as an indicator of emotionality, or endocrine and physiological indicators of stress. The heart rate measurements in study III showed that heart rate was increased in the 2-min context. This may be

interpreted in several ways, for example as resulting from an increased coping effort or as resulting from the increased perceived aversiveness. This physiological indicator does therefore not provide conclusive evidence of the stress level. The DLPFC was not engaged in this paradigm and the source of attenuation of activity is uncertain, the ACC being a possible candidate. However, the data of a less active amygdala in the 2-min compared to 1-min context remain and may be interpreted as if the amygdala is a site of modulation in the more aversive context.

In other situations the amygdala may function as a source of modulation. It is critical that potentially significant stimuli (e.g. emotional) are detected even when these are unexpected or outside the focus of attention. The amygdala has been suggested to respond to emotional stimuli and contribute to rapid and automatic detection of stimuli, even when these stimuli are presented at unattended locations or outside awareness (cf. Dolan and Vuilleumier 2003). Also, activity in relevant visual processing areas has been enhanced in response to stimuli with emotional content. This enhancement occurred when the stimuli were at both attended and unattended locations (Vuilleumier et al. 2001). One explanation for this effect of emotionality on visual processing areas is that it may reflect influences from amygdala onto extrastriate cortex. In other words, feedback connections from the amygdala may exert modulatory influences enhancing the visual processing of emotionally relevant stimuli. The concept of top-down and bottom-up is more constrained than that of source and site. Even if top-down control may be mediated by incoming information as explored by Roepstorff and Frith (2004), top-down is still characterized as a concept driven system, whereas bottom-up processes are stimulus driven (Norman 1976). Enhancement of activity as influenced by the amygdala is accordingly a bottom-up effect, even if the amygdala is a source in the modulative process. In study IV, the amygdala responds to the emotionally significant stimuli when presented outside awareness. The amygdala responds also to aware phobic stimuli as did other parts of an affective processing network. It is not possible to discriminate the direction of the flow of information in a subtraction analysis of the data, but it may be that the amygdala contributes to enhancement of activity in affective processing areas as well as that the cortical affective processing areas send reciprocal enhancing signals to the amygdala during phobic fear.

5.2.3 The OFC

The OFC respond to emotional values of stimuli, both positive and negative, and is involved in learning about as well as in reversal of acquired associations between values and stimuli (Rolls 2004; Schultz et al. 2000). The activation in the lateral OFC in study II related to unpredictable aversive stimuli may be understood as related to the more aversive and disturbing condition. However, the OFC is a heterogeneous region related to several other functions, such as the withholding of prepared responses and in operations linked to behavioral flexibility (Elliott et al. 2000). Nobre et al. (1999) reported for instance OFC activations in conditions when cues carried invalid predictive information, that is, when expectancies failed (Nobre et al. 1999). This result can be compared to the recruitment of lateral OFC (study II) when the visual cues and the relevant somatosensory stimuli were uncorrelated. These findings may thus also be interpreted as to provide further support for the role of OFC in neural processes that allow for flexible adaptations to changing conditions and situations.

The increased OFC activity in the conditions of unpredictable pain can further be understood in terms of top-down modulation of pain processing. This region has been implicated in the altering of perception and emotional experience during hypnosis, both during suggestion of increased as well as decreased pain unpleasantness (Rainville et al. 1999). Distraction from pain resulting in reduced pain experience has been associated with OFC activity (Bantick et al. 2002; Petrovic et al. 2000), as has placebo analgesia (Petrovic et al. 2002; Wager et al. 2004). Conceivably, the OFC may be involved in modulating pain perception in both directions. If so, the OFC response to the unpredictable shocks may be interpreted as representing a process involved in “top-down” modulation reflected in a higher anxiety and increased negative valence related to the unpredictable aversive stimuli. It is likewise somewhat intricate to interpret what process the OFC activation in the comparison of 1-min and 2-min pain context (study III) relates to. Possibly it relates to either the affect or the modulation of affect.

Lieberman (2004) has proposed in his “disruption theory” that the reflection on automatic affective processes may lead to their disruption or inhibition. He suggests further that the OFC region is central in supporting the labeling, interpretation and thought about the negative affect rather than the generation or the experience of the negative affect itself. (Lieberman et al. 2004). In line with

this theory, Cunningham et al. (Cunningham et al. 2003) observed activity in lateral OFC related to explicit judgments of affect compared to automatic evaluative processes. In study IV, the OFC was more active in response to the aware fear-relevant as compared to phobic stimuli, as was the DLPFC. We interpreted this OFC activity as being a part of the processes that attenuates the emotional expression.

5.2.4 Enhancement and attenuation of sensory information processing

Attentional direction enhances activity in relevant sensory processing areas (e.g. Rees and Frith 1998; Shulman et al. 1997). The visual cue predicting the aversive stimuli in study II allowed for the adequate direction of spatial as well as temporal attention. This condition induced increased activity in relevant somatosensory processing sites, that is, sensory-discriminative processing areas of the SI, the SII and the posterior insula. The SI and the SII as well as the anterior insula was active also in anticipation of tickle (study I). In addition, decreases were seen in the SI and adjacent parts of the MI located outside the area representing the target of the upcoming stimulus.

What we perceive depend in most cases upon the interaction between the top-down signals and the information coming from the sense organs. However, during anticipation or the act of imagination, the mental activity is the result of solely top-down signals. In the like manner as we can create a mental image of an object in its absence, we can imagine making movements in the absence of any overt behavior. This mental activity can have detectable consequences. For example, motor imaginary training has effects of movement precision as well as muscular strength (cf. Frith et al. 2000). Imagery has been suggested to act on most of the same neural network as perception, including low-level anatomical substrates (cf. Ganis et al. 2004). Changes in brain activity during imagery of movements of fingers, toes and tongue seem to draw on the same regions of the primary motor cortex representing the specific body parts (Ehrsson et al. 2003). There are data suggesting that even the topography of the activation pattern in primary visual cortex during visual imagery is similar to the topography obtained with a corresponding visual perceptual task (Klein et al. 2004). Indeed, the earliest cortical phase of olfactory processing was recently found to respond in the anticipation of an odor (Zelano et al. 2005).

The attentional modulation of neural activity in the absence of stimulus presentation can be described in terms of a bias signal (Rees and Frith 1998). A bias signal is assumed to improve the computational efficiency in the area of interest and to suppress responses outside the focus of attention. It is likely that a bias signal is one way to compensate for the limited human capacity to perform real time information processing and the relatively slow flow of neural transmission.

5.3 The role of the anterior insula in affective processing

The anterior insula was active during phobic fear (study IV), unpredictable shocks (study II) and during the anticipation of tickle (study I). As mentioned in chapter (1.3.3 and 1.4.5.1), the anterior insula is suggested to reflect the physiological condition of the body, and to correlate with changes in autonomic arousal as well as respond to subjective experience of feeling states (cf. Critchley et al. 2004).

Two recent studies discuss additional aspects associated with representations held by the anterior insula. Critchley and colleagues (2004) related the accuracy of subjective perception of heartbeat to anterior insula activity. In this test, a signal was delivered either in synchrony with each heartbeat or after a fixed delay. The subjects were asked to report whether the signal occurred in time with their heartbeat or not. Activity in the anterior insula as well as individual gray matter volume within anterior insula correlated with interoceptive awareness as reflected in performance accuracy (Critchley et al. 2004). The anterior insula activity was also related to measures of the subjective emotional experience (Critchley et al. 2004). These results provide further evidence for the central role of the anterior insula in interoceptive awareness. They are also consistent with the proposed contribution to subjective feeling states arising from representations of bodily responses.

The study reported by Singer and coworkers (2004) considered the affective dimension of pain experience. They assessed brain activity while female participants experienced a painful stimulus and compared it with the neural activity in response to observing their partner receiving a similar pain stimulus. The partner was seated so that the scanned subject could see him and his hand. While the SI/MI, the posterior insula, the SII, and the caudal ACC were active

specifically when the participants received the painful stimulus, the anterior insula and rostral ACC were activated both when the participants experienced the pain and when their partner received pain. Empathic experience can be described as based on the imagination of the other person's particular emotional state and as involving a representation of that state in the observer. The subjects who scored higher on general empathy scales showed stronger activations in the anterior insula and the rostral ACC when they perceived their partner in pain, results that are in line with the suggested affective processing functions of these areas.

The anticipatory state induced by the visual cue in study I may reflect an internal bodily state of arousal and possibly also the affective representation of what the tickle is going to feel like, analogous to the empathetic state. Anticipation of pain has previously been implied to activate the same region of anterior insula (Ploghaus et al. 1999). The unpredictable pain (study II) and the phobic stimuli (study IV) induced a higher negative valence and anxiety relative the predictable pain and fear-related stimuli, and their affective responses were associated with activity in the anterior insula.

We interpret the activity in the anterior insula in our data as a response to the affective quality of the stimuli. Given the previous research and theories about subjective experience of emotion we assume that the observed anterior insula responses are related to representations of the associated bodily state.

5.4 Sensory-discriminative and affective-evaluative pain processing

Sensory information from the body is conveyed to the thalamus and the cerebral cortex by two ascending pathways. The dorsal column medial lemniscus system mediates information of touch and proprioception, while the anterolateral system carries information of visceral sensations and about the physiological condition of the rest of the body, including for example signals of pain, temperature, slow weak mechanical stimuli, and local changes in metabolism (see chapter 1.3). The signals of the condition of the tissue are related to aspects of ongoing homeostasis and needs of the body and consequently also to affective and motivational aspects.

The thalamic neurons receiving input from the lemniscus system project primarily to the SI and SII, while the thalamic neurons of the anterolateral

system terminate mainly in the posterior insula but also in the SI and the caudal ACC. In line with this, the SI and SII are usually described as responding mainly to exteroceptive information and the posterior insula to information about the homeostatic state of the body. The projections to the SI, the SII and are arranged somatotopically and the representations of the different sensations of pain, itch, sensual touch etc are highly resolved within the posterior insula. These regions are hypothesized to process the discriminative aspects of the exteroceptive and homeostatic states. The representation in the posterior insula is subsequently re-mapped in mid- and anterior insula, a re-representation that has been suggested to lead to processing associated to more general affective and autonomic information in the region of anterior insula (Craig 2002).

Comparing a condition when a visual cue offered predictability of electrical shocks to a condition of unpredictable shocks, the processing network of the SI, the SII and posterior insula was active (study II). Electrical stimuli activates a multitude of sensory afferents, which may mean that the detected SI and SII activations can be attributed to both general somatosensory and pain processing. We attribute the activity of these areas and of the posterior insula as sensory-discriminative representation of the noxious somatosensory input. The visual signal predicting the aversive stimulus allowed for correct direction of attentional focus in time and space. This enhanced selective attention leads to increased activity in the somatosensory processing areas, in line with the multitude of evidence from functional imaging studies of attentional enhancement of relevant sensory processing.

The unpredictable pain stimuli resulted in increased ratings of anxiety and negative valence and increased activity in the anterior insula, the lateral OFC and the caudal ACC, areas postulated to relate to affective processing. These results relate partly to the study of empathy for pain (Singer et al. 2004). The understanding of someone else's emotional reaction to pain activated the anterior insula. However the SI, the SII/posterior insula was only active when the subjects themselves received the noxious stimulus, presumably since empathy does not necessitate the detailed sensory-discriminative representation relevant to the subjective pain experience (Singer et al. 2004).

We suggest that the design in study II provides a distinction between anxiety as well as sustained attention on the one hand and selective attention on the other. While the unpredictable situation induced more anxiety and higher alertness

towards aversiveness, the visual cues in the predictable conditions allowed for selective attention and correct estimation of the stimulus onset. This distinction was reflected in an opposing engagement of the affective and sensory-discriminative processing networks of the noxious input.

5.5 Ventral striatum and unpredictability

Predictions of stimuli of value involve systems that allow for temporal estimation as well as for the representation of the value. A key signal in the learning about stimuli and the temporal estimation of stimuli arrival is the prediction error in the estimate. Single-unit recordings suggests that activity changes in dopamine neurons in the ventral tegmental area and substantia nigra represent prediction errors in the time and amount of value events, that is, changes in spike rate in this system encode a difference between experienced value and predicted value (cf. Montague and Berns 2002). The dopamine neurons project to the striatum and to the frontal cortex where synaptic modifications may take place as a result of learning from the prediction errors.

A paradigm using juice as a rewarding stimulus could show an activity difference in the ventral striatum when the juice was withheld at the expected time of delivery (Pagnoni et al. 2002). This region was also active when comparing unpredictable delivery of juice to predictable delivery (Berns et al. 2001). The same region showed activity during prediction errors of the magnitude of electric shock delivery (Seymour et al. 2004) supporting the idea that this region respond to both appetitive and aversive information. We interpret the activation in the ventral striatum during the uncorrelated conditions (study II) as reflecting attempts to develop a model that would make the aversive stimuli more predictable by recruiting areas responsible for learning about temporal cues.

Humans are equipped with learning mechanisms that have the capacity to implicitly extract structural regularities from experience (cf. Petersson et al. 2004). That is, models for predictability and sequence structure may operate also outside of awareness. Berns and colleges (1997) performed an experiment in which participants were trained in a reaction-time task in which, unknown to them, stimuli followed a complex sequence. A subtle and unperceived change in the nature of the sequence, that is, a violation of an implicit expectation, resulted in increased reaction times as well as activity in the ventral striatum. As the stimuli in this experiment was neutral (numbers), the response in the ventral

striatum could be interpreted as correlating to breaches in expectation of a familiar pattern of stimuli in general. Another study using artificial grammar of letter sequences exposed the subjects to positive examples of the grammar (Elwér et al. submitted). In a later classification task positive as well as negative examples of the grammar were shown. They found that when the subjects merely used a “gut feeling” for if a sequence of letters was of their liking or not, performed better than chance in classifying whether a string, not previously seen, belonged to the artificial grammar (Elwér et al. submitted). One could hypothesize that the ventral striatum is part of an innate system in the brain proficient in detecting patterns and that this system performs also in the absence of awareness. If one takes this a step further, it could be that this system provides a basis for finding coherence in the abundance of stimuli reaching our senses and that the right amount of predictability, pattern and meaning appeal to our sense of preference and beauty.

5.6 *Aware and unaware processing*

The study of the neural correlates of awareness is based on the fundamental assumption that for every mental aware state there is an associated neural state, but that there is not an associated aware experience for every shift in neural activity (Frith et al. 1999). So a major task in the study of neural correlates of consciousness is to distinguish between aware-unaware processing. Also it will be useful to distinguish between three different kinds of neural activity: (1) neural activity associated with aware mental representations; (2) neural activity associated with changes in a sensory stimulus, in the absence of changes in mental representations; and (3) neural activity associated with behavior in the absence of mental representations (Frith et al. 1999).

Study IV examined the first two of these categories. We manipulated the level of awareness in the processing of phobic and fear-relevant stimuli by the method of backwards masking. The design allowed the analysis of three different states: unaware processing of fear, aware processing of phobic fear, and aware processing fear-relevant, but non-feared stimuli.

The left amygdala was activated in response to the fearful stimuli, both phobic and fear-relevant, when the exposure time allowed for only rapid incomplete and unaware visual processing. These activations are consistent with the assumption that the amygdala is part of an early warning or vigilance system.

In the aware phobic condition, in which the stimulus presentation allowed for more elaborate stimulus processing, the amygdala response was bilateral and associated with a cortical affective processing network including the ACC, the anterior insula and the OFC.

It is suggested that the amygdala is involved in the generation of autonomic arousal to intrinsically aversive stimuli as well as to conditioned stimuli, while the insula registers the changes in bodily autonomic arousal (cf. Critchley et al. 2002). By using the technique of backwards masking, Critchley and colleagues (2002) investigated to which degree the awareness of threat modulates neural activity associated with fear conditioning. The amygdala activity was enhanced during conditioning to both aware and unaware stimuli, whereas the insula activity was modulated by awareness. This fits the idea that the evaluation of the state of the body in response to a salient stimulus serves as a basis for the aware feeling (Craig 2002; James 1894; Lange 1922) and that the insula is central in this process, as are the ACC and the OFC (Craig 2002). Also, neural activity in anterior insula and individual gray matter volume predicted subjects' accuracy in the heartbeat detection task (Critchley et al. 2004), providing further indications that the insula supports a representation of the bodily state accessible to awareness.

It is often assumed that information processed outside awareness leads to more automatic responses that cannot be controlled by the perceiver, whereas aware perception allows individuals to use the information to guide their actions. One example of this is a study using a version of a Stroop-interference in combination with backwards masking, indicating that prediction about the upcoming experimental trial improves reaction times in aware but not in unaware conditions (Merikle and Joordens 1997). When subjects predicted that word/color pairings would be incongruent and the words were consciously perceived, it took even less time to name a color when it followed an incongruent color word (e.g. word GREEN/color red) than when it was followed by a congruent color word (e.g. GREEN/green). That is, the predictive information facilitated the performance on aware incongruent trials and slowed performance on aware congruent trials. However, the predictive information was ineffective in changing the standard Stroop interference effect when the words were unconsciously perceived. In other words, unaware perception leads to automatic reactions whereas aware perception allowed the participants to use the predictive information to respond in a more flexible manner.

This relates to the response seen in the fear-relevant aware condition. With time to decide that the fear-relevant stimulus was of the non-feared type, the initial amygdala response (as detected in the unaware condition) was relatively disengaged (not significant) and no cortical areas were recruited. Instead, the DLPFC and the OFC was active in the fear-relevant condition compared to the phobic condition (as also was mentioned in chapter 4.5). It is likely that the engagement of these regions inhibits inappropriate environmentally cued, that is automatic, responses, allowing for more flexible behavior.

Whereas the frontal cortices are of importance for goal-oriented behavior on the basis of aware elaborate representations, this type of processing may not be sufficiently rapid to manage real-time requirements in threatening situations. In such situations, it is functionally appropriate to relinquish control to evolutionary history, as distilled in time-proven defense systems. The three different types of neural responses exemplified in study IV can be conceptualized as systems that complement each other in allowing for reactions and responses at different time scales.

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