Thesis

Cognitive mechanisms in pain processing

- Assessed with functional imaging methods

by

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This book is dedicated to Zoran, Danica, Nenad and Karin,
who supported me in good and bad times.

ко на брдо, ак' и мâлō, стоји,
више види но онај под брдом.

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Abbreviations:

BA	-	Brodmann area
FMRI	-	functional magnetic resonance imaging
GSR	-	galvanic skin response
lc	-	locus coeruleus
MTL	-	medial temporal lobe
obfc	-	orbitofrontal cortex
PAG	-	periaqueductal gray
pfc	-	prefrontal cortex
PET	-	positron emission tomography
rACC	-	rostral anterior cingulate cortex
rCBF	-	regional cerebral blood flow
RF	-	receptive field
S1	-	primary somatosensory cortex
S2	-	secondary somatosensory cortex
STT	-	spinothalamic tract
VAS	-	visual analogue scale
vmPFC	-	ventromedial prefronatal cortex

1. Cognitive mechanisms in pain processing: an introduction

The intensity and unpleasantness of a painful experience is often described as correlating well with the degree of noxious stimulation. However, the perception of pain is not a linear phenomenon, reflecting the signal from the peripheral neuron. Rather, the noxious input may be modulated at every level of the neural axis. One of the most potent sources of modulation is the brain, although the related mechanisms have not been studied in detail. Supraspinal modulatory influences involve both lower order automatic processes and higher order cognitive mechanisms. It may be suggested that this organizational pattern has developed as an evolutionary-driven adaptation, in which both fast hardwired responses and slower dynamic responses increased the chance for survival.

In line with the presented hypothesis above, it has been suggested that the brain initially processes noxious input in the brainstem thereby supporting the demand for a fast response (Price 2000). Apart from autonomic changes and a wide range of defense reactions, the brainstem may induce powerful analgesia in direct response to noxious stimuli (Fanselow 1994) and thereby alter noxious input and pain perception. At a higher hierarchical level, cognitive processes may also dramatically modulate the perception of pain (Melzack and Casey 1968; Weisenberg et al. 1996). In fact, the perception of pain has been suggested to be composed of sensory-discriminative, affective-motivational and cognitive-evaluative dimensions (Melzack and Casey 1968). In the present thesis we have focused on cognitive interactions with pain processing that may be described as belonging to the cognitive-evaluative dimension of pain, although the included studies also cover other aspects of pathological and normal pain processing.

In this context it becomes necessary to define the term cognitive dimension. Cognition concerns perception, action, memory, language and selective attention, i.e. processes that pertain to higher order central nervous system function. The brain is a dynamical system that produces behavior with the signature of chaos, which implies that any action is preceded by a myriad of inputs all of them with influence on the final decision (van Vreeswik and Smolensky 1996). The term cognitive neuroscience may be defined as the study of processes that act upon and interact with the information reaching the brain.

The prefrontal cortex is an interconnected set of neocortical areas that have a unique, but overlapping, pattern of connectivity with virtually all sensory and motor systems and a wide range of subcortical structures (Barbas and Pandya 1991; Fuster 1997). Thus, it provides an ideal infrastructure for synthesizing the diverse range of information needed for complex behavior and is often referred to as a higher order cortical area implying that not only does it access information from a multitude of sources, it also interacts and thereby influences these sources via top-down mechanisms (Mesulam 1998; Mesulam 1990). This top-down processing is more than simple adaptive influence of e.g. inhibition. Peripheral signals may be enhanced, suppressed, filtered or skewed. This model for higher order brain function implies parallel distributed processing

(Goldman-Rakic 1988) in sets of neuronal assemblies, meaning structurally distributed areas that interconnect on a need only basis (Mesulam 1998; Mesulam 1990). The general nature of this organization has been emphasized by the ability to develop computational models that account for strategies in decision-making in complex behaviors. (Dehaene and Changeux 1991; Churchland and Sejnowski 1992, Cohen and Servan-Schreiber 1992) Also, in pain research frontal brain functions have been emphasized in the cognitive-evaluative dimension of pain processing (Melzack and Casey 1968). Cognitive interactions with nociceptive signals may totally abolish the perception of pain (Melzack and Casey 1968) and suggest that the top down mechanisms outlined above are, strong determinants for the pain experience. As will be shown in the present thesis subdivisions of the prefrontal cortex such as the orbitofrontal cortex and the medial prefrontal cortex / ACC are suggested to have a crucial involvement in cognitive interactions with pain processing.

An understanding of this system is crucial if we want to; 1) develop new strategies for analgesic therapies in the future, 2) increase our theoretical knowledge of the cognitive mechanisms important in pain perception, and 3) shed new light upon general theories of cognition and attention. Functional imaging tools such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) may help us in this understanding.

2. Central pain processing: a review

2.1 Anatomy and the neurophysiology

Although cognitive aspects of pain processing cannot be understood only by studying the anatomy and physiology of nociceptive pathways, it is of crucial importance to understand the basic research in this field in order to appreciate higher order mechanisms in pain processing. Therefore, a short review is included of the anatomy and physiology of the nociceptive systems in the brain and the brainstem. This review, while not complete, attempts to include the most important features in order to understand the thesis. Some references concerning general pain physiology have been omitted in the text of this chapter. In the case where no specific references are stated, the reader is referred to several excellent reviews in this field (Albe-Fessard et al. 1985; Bromm et al. 2000; Craig and Dostrovsky 1999; Fields and Basbaum 1999; Schnitzler and Ploner 2000; Vogt and Sikes 2000; Vogt et al. 1993; Willis and Westlund 1997).

2.1.1 Spinal cord

Peripheral sensory neurons carrying nociceptive information reach the dorsal horn in the spinal cord. The dorsal horn may be divided into different laminae where lamina 1 is the most lateral. Small diameter nerve fibers (C and A∂) end in the 1st lamina, which contains nociceptive specific, polymodal nociceptive and thermoceptive-specific neurons. The nociceptive specific cells respond only to nociceptive signals of different classes and have small receptive fields. The polymodal nociceptive cells also respond to nociceptive signals from deeper tissues. Lamina 4 / 5 contains low threshold neurons that respond only to non-nociceptive stimuli, and wide dynamic type neurons (WDR) that respond to both innocuous and noxious signals in a graded manner. These neurons contain larger receptive fields than the lamina 1 neurons. The activity of both the spinal WDR and the nocicpetive specific neurons correlate with the aversive response in primates. Finally, lamina 7 / 8 contains neurons that respond in a complex way to noxious and innocuous stimulation and have large and sometimes bilateral receptive fields.

The axons from the dorsal horn neurons cross the spinal cord and follow two different pathways in the spinothalamic tract (STT). The lateral STT contains neurons that mainly originate from the lamina 1, and the anterior STT contains neurons that originate in the lamina 4 / 5. Apart from the STT there are several other spinal tracts that may be important for pain processing in the brain, such as the spinobulbar tract, spinohypothalamic tract, postsynaptic dorsal column system, spinocervicothalamic pathway and spinoparabrachial tract. The spinobulbar tract, including the spinoreticulart and the spinomesencephalic tract, has been well studied and may be especially important for the nociceptive processing in the brainstem.

2.1.2 Brainstem

The spinobulbar tracts project to mainly four different areas: 1) cathecolaminergic nuclei (situated in the ventrolateral medulla, the nucleus of the solitay tract and dorsolateral pons) 2) the parabrachial nucleus 3) the periaquductal gray and 4) the reticular formation (see figure 1). These regions may interact with both the cortex and other nuclei in the brainstem, and it has been suggested that some of these regions are especially important for the initial processing of noxious input (Price 2000).

The cathecolaminergic nuclei are generally involved in the integration of cardiorespiratory and homeostatic functions and in the drive of the sympathetic outflow. Several nuclei, e.g. the A7 cell groups, project directly to the spinal cord and are involved in noradrenergic modulation of ascending noxious input. The locus coeruleus (A6) has only about 6000 neurons but these neurons send noradrenic axons to 30 - 50 % of the whole brain and may thus be involved in adjusting the set threshold for general processing in the brain (Aston-Jones et al. 1999; Snyder 1996). In line with this, it has been shown that the locus coeruleus is generally involved in vigilance and attention, and that nociceptive information may drive its activity (Aston-Jones et al. 1999).

The parabrachial nucleus has a role in homeostasis and cardiovascular integration. It has direct connections with the central nucleus of the amygdala and the hypothalamus. Moreover, it may serve as a relay to the insular cortex through the ventrobasal thalamus. Thus, it has a role in the autonomic response to nociceptive input as well as mediating an indirect nociceptive pathway to the cortex.

The periaqueductal gray (PAG) is involved in automatic behavioral coping strategies during fearful contexts and noxious stimulation (Carrive 1993). The dorsolateral PAG may exert a fight or flight behavior including cardiovascular changes. It may also be involved in non-opioid dependent analgesia. The ventral PAG is involved in passive and freezing behavior, and exerts an opioid dependent analgesia. Both sub-nuclei have major reciprocal projections from the amygdala, the thalamus (reticular nucleus, parafascicular nucleus and the centromedian nucleus) and the hypothalamus. Also, the anterior cingulate cortex (ACC), the insula and the orbitofrontal cortex (obfc) project to the PAG (see also chapter 5.3 and 5.4). The PAG seems not to project directly to the spinal cord, but influences the activity of neurons in the rostral ventromedial medulla (RVM), which in turn projects to the spinal cord where it may modulate the nociceptive input.

A large number of other nuclei in the brainstem may directly or indirectly process nociceptive input and interact with cortical regions. For example, the cholinergic nuclei in the upper brainstem, such as the laterodorsal tegmental nucleus and the pedunculopontine nucleus may interact with the reticular nucleus in the thalamus, which is involved in the regulating cortical activity (Parvizi and Damasio 2001). Also, dopaminergic neurons in the ventral tegmental area (VTA) may control learning and motivational / emotional behavior in the striatum, the ACC and the prefrontal cortex (Fuster 1997; Panksepp 1998; Parvizi and Damasio 2001; Paus 2001). Other subcortical structures such as the basal forebrain may induce arousal in vast regions of the cortex

(Kapp et al. 1992).

2.1.3 Thalamus, amygdala and cortex

Nociceptive signals reach a wide range of different thalamic nuclei before reaching cortical structures (figure 1). The ventral thalamus encompasses three nuclei, all of which receive nociceptive information but are differently organized, i.e. the ventral posterior nucleus, the ventral medial nucleus and the ventral lateral nucleus. The ventral posterior nucleus may be further subdivided into the ventral posterior lateral (VPL), ventral posterior medial (VPM) and the ventral posterior inferior (VPI). The VPL receives nociceptive signals mostly from the lamina 4 / 5, contains almost exclusively WDR neurons with small receptive fields. The VPM is similar to the VPL but receives information from the trigeminal tract, i.e. the head region. The VPL / VPM neurons project further to the primary somatosensory cortex. The VPI receives input from both the lamina 1 and lamina 4 / 5, and projects further to the secondary somatosensory cortex (S2). The posterior part of the ventromedial nucleus (VMpo) receives primarily noxious input from lamina 1 and projects further to the anterior insula. The ventral lateral nucleus receives nociceptive input from lamina 5 and 7 and projects to the motor cortex. Similarly, the central lateral nucleus and the parafascicular nucleus project to motor areas, including the motor cortex and basal ganglia. The ventral caudal part of the medial dorsal thalamic nucleus (vcMD) receives nociceptive information from lamina 1 and projects to area 24c in the ACC. It should be noted that several other medial and intralaminar thalamic nuclei that respond to nociceptive stimuli also seem to project to the ACC (see further Vogt et al. 1993). Also, such nuclei as the reticular and the intralaminar nuclei may affect large parts of the brain (Parvizi and Damasio 2001; Paus 2000).

In the primary somatosensory cortex (S1; BA3b and 1) the neurons that respond to noxious stimulation are intermingled with neurons that respond only to innocuous stimuli (Kenshalo and Isensee 1983). As in the VPL, these are mostly WDR neurons with small contralateral RF that are highly somatopically organized. The S1 connects anatomically to the S2 and the posterior parietal cortex (Friedman et al. 1986).

S2 and surrounding somatosensory association areas have only a few neurons that respond to nociceptive information (Robinson and Burton 1980). This study has shown that only about 2% have been observed in the S2, while approximately 10% have been observed in the area 7b of the monkey (inferior parietal cortex in humans). The neurons in S2 seem to be only nociceptive specific and have contralateral or bilateral RF, although there is a clear somatotopic organization. In area 7b the neurons often respond both to noxious stimulation and another modality such as visual or auditory stimulation. The S2 has anatomical connections with the S1, area 7b and the insula (Friedman et al. 1986).

In area 24c of the ACC in the monkey about 25% of the neurons have been found to respond to noxious stimulation. These neurons have large and often bilateral RF. Moreover, they are often polymodal neurons. Thus, the ACC is not in a

position to process a localizing or sensory-discriminative dimension of noxious input. However, lesion studies and cingulotomies, i.e. cutting thalamic input to the ACC, have effectively lowered the affective expressions of chronic and acute pain perception. In the thesis a distinction is made between the caudal ACC (cACC) that is activated in the main effects of pain and more rostral sub-divisions of the ACC (rACC) that seem to be involved in pain modulation. The cACC has anatomical connections especially with the posterior and anterior insula, while the rACC has anatomical connections with the medial and lateral obfc, the posterior and anterior insula, the amygdala and the PAG (An et al. 1998; Mantyh 1982; Vogt and Pandya 1987). The limbic connections including the obfc connections are less developed for the cACC (Devinsky et al. 1995; Vogt and Pandya 1987).

Recently, nociceptive neurons have also been described in the insula (Robinson and Burton 1980; Treede et al. 2000; Zhang et al. 1999). Many of these neurons also respond to autonomic stimuli, which indicate a combined function of autonomic and nociceptive cortical processing. Lesions to this part of the cortex have changed the emotional perception of pain (Greenspan and Winfield 1992; Greenspan et al. 1999). The insula has anatomical connections with the lateral obfc, the ACC, the amygdala and the S2 (Friedman et al. 1986; Mufson and Mesulam 1982).

Finally, nociceptive specific neurons have been observed in the amygdala (Bernard et al. 1996) and the basal ganglia (Chudler and Dong 1995). Nociceptive signal may reach the amygdala through the thalamus, the insula or the parabrachial nucleus (Bernard et al. 1996; Shi and Davis 1999). The amygdala has anatomical connections with the obfc, the ACC, the anterior insula, the hypothalamus and the PAG (Aggleton et al. 1980). Moreover, some data indicates that the subdivision of the insula that receives S2 input connects to the amygdala (Friedman et al. 1986).

Although there is yet no data showing neurons that specifically respond to nociceptive input in the lateral obfc of the primate this region is important for the hypothesis presented in the present thesis. Specifically, the lateral obfc may be important in regulating other regions of the pain matrix. Therefore, it is of interest that the lateral obfc has anatomical connections with the rACC, the insula, the amygdala, the PAG and the hypothalamus (Aggleton et al. 1980; An et al. 1998; Carmichael and Price 1995a; Cavada et al. 2000; Morecraft et al. 1992; Vogt and Pandya 1987). Also, the obfc is in a position to interact with sensory association areas such as secondary somatosensory cortex and area 7b (Carmichael and Price 1995b).

2.2 The concept of the medial and the lateral pain system

The concept of the medial and the lateral pain system (Vogt et al. 1993) was inspired by the theoretical framework that stated that pain perception might be divided into sensory-discriminative, emotional-motivational and cognitive-evaluative sub-processes (Melzack and Casey 1968). Moreover, it was founded on the suggestion by Alber-Fessard that the lateral thalamic nuclei may be involved in noxious localization while the medial thalamic nuclei may be involved in the affective pain response (Albe-Fessard et al. 1985). The

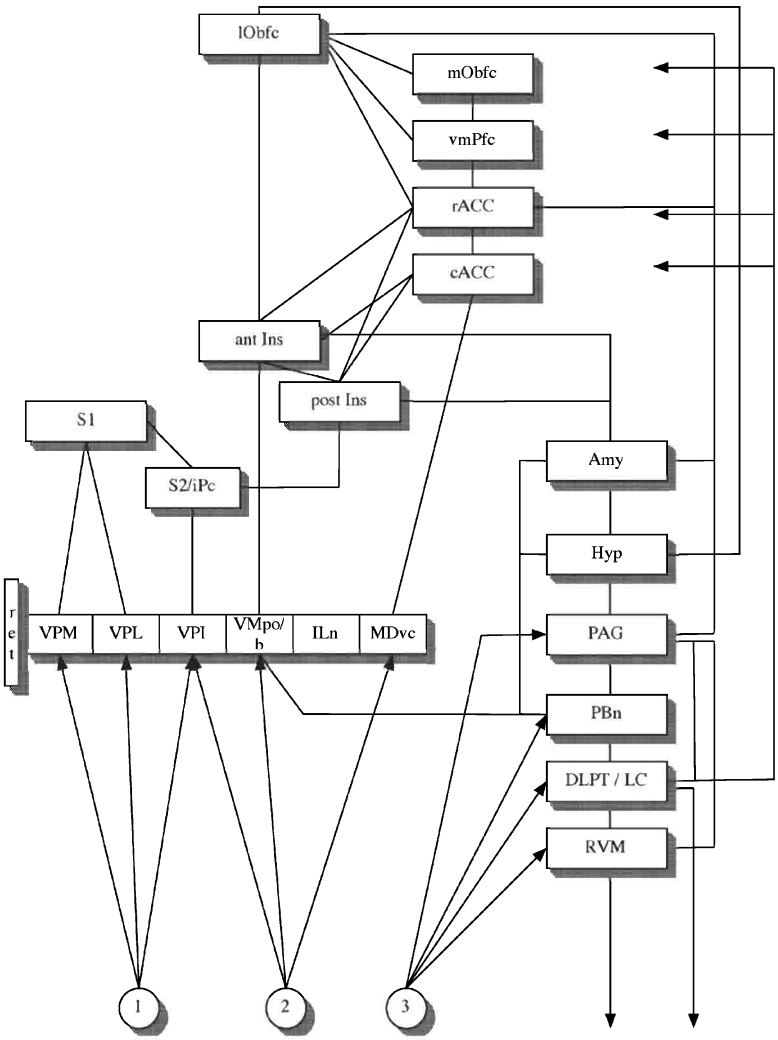
structures that were thought to project from these thalamic nuclei were then included in the medial and lateral pain system, respectively. This anatomical division was in line with data that indicated that the insula and the ACC are more involved in the affective pain processing, while the S1 and the S2 are more involved in the sensory-discriminative dimensions of pain processing.

It may be argued that the insula receives nociceptive information from the VMpo thalamic nucleus, which is a part of the ventral thalamus also projecting to the S1 and S2 and not a part of the intralaminar or medial thalamic nuclei. However, data indicating that the insula and the ACC are involved in affective pain processing, and that these regions are more connected with the limbic system and each other than the S1 and S2, still makes the concept of a medial and lateral pain system relevant. Moreover, these regions actually are situated medially in the cortex. However, it should be emphasized that this division is more conceptual than exact. Possibly, a better division would be that those systems receiving lamina 1 nociceptive specific input should be divided from those receiving lamina 4 / 5 WDR input.

2.3 Imaging the pain system

The present thesis will not discuss the large number of functional imaging studies, i.e. PET, fMRI (functional magnetic resonance imaging), MEG (magnetoencephalography) and EEG (electroencephalography) studies that have been performed, but focus on those relevant to cognitive processing of pain. Functional imaging studies have shown involvement of the thalamus, the S1, the S2 and related sensory association regions, the insula, the ACC, the amygdala, the temporopolar cortex, the brainstem and orbitofrontal cortex (see further Bushnell et al. 1999; Ingvar 1999; Peyron et al. 2000; Schnitzler and Ploner 2000; Treede et al. 2000; Treede et al. 1999). Although there are some inconsistencies, these studies suggest that a widespread network may be activated during pain indicating a parallel and distributed processing in the brain (Ingvar 1999).

Figure 1. A schematic drawing of the large-scale network in the brain that processes nociceptive signals and pain. The nociceptive input may reach the thalamus through the lateral (1) or anterior (2) spinothalamic tract. Most input to the brainstem derives from the spinabulbar tracts (3). VPL = ventral posterior lateral nucleus. VPM = ventral posterior medial nucleus. VPI = ventral posterior inferior nucleus. VMpo = posterior part of the ventromedial nucleus. VMb = basal portion of the ventromedial nucleus. vcMD = ventral caudal part of the medial dorsal nucleus. ILn = intralaminar nuclei. ret = reticular nucleus. S1 = primary somatosensory cortex. S2 = secondary somatosensory cortex. iPc = inferior parietal cortex (includes area 7B in monkeys). ant Ins = anterior insula. post Ins = posterior insula. lObfc = lateral orbitofrontal cortex. mObfc = medial orbitofrontal cortex. vmPFC = ventromedial prefrontal cortex. rACC = rostral anterior cingulate cortex. cACC = caudal ACC. Amy = amygdala. Hyp = hypothalamus. PAG = periaqueductal gray. PBn = parabrachial nucleus. DLPT = dorsolateral pontine tegmentum. LC = locus coeruleus. RVM = rostral ventromedial medulla.



3. Methodology - What can functional imaging teach us?

Functional imaging tools such as positron emission tomography (PET) and fMRI (functional magnetic resonance imaging) are used to investigate how the neuronal activity in the brain changes in parallel to behavioral or perceptual changes in human subjects. The methods have many drawbacks and the interpretation must be cautious for several reasons stated below. Nevertheless, these studies provide a powerful mean to investigate how networks in the brain act on a large-scale level. Asking the relevant questions, incorporating the findings with results of other methods and complementing the studies with pharmacological investigations may lead to a better understanding of the processes in the brain underlying the human mind.

3.1 Coupling between neural activity and regional blood flow

The basis of functional imaging tools is a relatively linear relationship between the regional blood-flow and neural activity (Gusnard and Raichle 2001; Raichle 1998; Scannell and Young 1999). One hypothesis for such a coupling is based on the glutamate transmission (i.e. the dominant neurotransmitter in the brain released by ≈ 90 % of the neurons) and metabolism in the synapse (see further Magistretti and Pellerin 1999; Magistretti et al. 1999). In short the glutamate that is released in the synapse will be recycled by a neighboring astrocyte (a process which is energy dependant). The astrocyte makes contact with capillaries in the proximity from which it will take up glucose. The glucose molecule will be used partly for the glutamate recycling (2 adenosine tri-phosphate; ATP). The remaining energy, i.e. 2 lactate molecules, will be delivered to further energy consumption in the neuron (34 ATP). Thus, the more the neuron is active, i.e. releasing glutamate, the more glucose will be used. The Crebs cycle will consume oxygen in a linear relation to this process and the oxygen is transported by the regional blood flow, i.e. there is a coupling between blood-flow and neuronal activity.

It should be noted that all regions in the brain show a spontaneous activity during resting state, and the activity may both increase and decrease from this state (Gusnard and Raichle 2001; Raichle 1998). These changes in metabolism should be regarded as changes of the net-activity of different brain regions. Thus, it is not possible to show if the net-activity change represents excitatory or inhibitory activity.

3.2 Coupling between isotopes and blood flow

In functional PET studies, a radioactive isotope such as [^{15}O]-H_2O or [^{15}O]-butanol with a half-life of ≈ 2min is injected into the blood stream. Usually up to 15 bolus injections of 400-500 MBq [^{15}O]-butanol (Berridge et al. 1990) or [^{15}O]-H_2O are injected. The 1min scan was starts automatically upon bolus arrival to the brain. A period of ≈ 10 min passes between the scans to allow for a degradation of the previous tracer. The tracer-molecule will follow the blood flow and release a positron (see Gazzaniga et al. 1998). This

particle will collide with an electron very shortly after it has been released and produce 2 photons and each photon will move in opposite direction after the collision. When the PET scanner registers two simultaneous photons with a 180 degrees difference it will register the activity as a true event (Gazzaniga et al. 1998). In a region where the blood flow is increased due to increased neural activity a higher number of photon pairs will be released (Gazzaniga et al. 1998). This is the base to reconstruct an image of areas having high regional blood flow. The images from the present studies were reconstructed using the factory supplied back projection tool and standarized filter setting (Hann 5). Attenuation was corrected for based on data from a transmission scan obtained with the subject in the same position.

3.3 Image analysis

The raw image goes through several steps of analysis before the result is interpreted (see further Friston 1997a). Most PET-studies are based on a group of subjects in order to increase the signal to noise ratio. SPM99 (and SPM95/96) is a statistical tool used in the processing of imaging data (see also http://www.fil.ion.ucl.ac.uk/spm/) and has been used in the studies that are included in the present thesis.

3.3.1 Realignment

Every subject has often made 12 scans with ≈ 10min in-between each scan lying in a more or less comfortable position with a plastic helmet designed to minimize movement. Nevertheless, movement has occurred and to compensate for the movements the scans are spatially adjusted into the position of the first scan (Friston 1997a).

3.3.2 Spatial normalization

The brains of different subjects may vary considerably. A pre-requisite to make statistical analysis on several subjects is to use the same spatial representation. Therefore every subjects' brain is warped into a standard brain using spatial transformations algorithms (Ashburner and Friston 1997). This transforms the images of the individual subjects into a standardized anatomical space that are approximate to the Talaraich-Tournoux atlas. SPM99 uses a template that is based on a group of individual subjects and called the MNI-template (http://www.fil.ion.ucl.ac.uk/spm/).

3.3.3 Spatial smoothing

In order to minimize individual anatomical and physiological differences between subjects the images are smoothed (Friston 1997a). Smoothing also increases signal to noise ratio because noise has usually has higher spatial frequencies (Friston 1997a). Also, convolving the rCBF data with Gaussian filter during the smoothing procedure conditions the data to conform more closely to a Gaussian field model, which is used for the

statistical inference (Friston 1997a). The smoothing of the Gaussian filter is usually between 10 and 16 mm FWHM (full width half maximum).

3.3.4 Statistical analysis

The statistical analysis models the data into components of interest, confounds of no interest and an error term. In essence the same analysis may be made as t-tests, regressions or ANOVAs. However, the General Linear Model is used to perform these analyses for each voxel of the brain. A t-value is then given for each voxel that also is transformed into a z-value (Holmes et al. 1997).

3.3.5 Statistical inference

In order to correct for all the voxels in the brain, the theory of Gaussian fields is used, since classical correction would yield a data set that is too conservative. This allows a stepwise analysis. First, a limited search can be applied to those regions that are part of the initial main hypothesis. In the predefined network a change in activity with a Z-value of 3.09 is accepted as a significant. Thereafter, a general volume search may be performed in those regions where no a priori hypothesis has been made. A corrected p-value is given for each voxel of this search.

3.4 Method considerations

There are many factors that make the interpretation of data difficult. As mentioned above, we do not know how much of the increases or decreases in rCBF represent excitatory or inhibitory events. Moreover, at a processing level, increases in activity are not the only indication of involvement of a region in a network. Sometimes regression analysis or structural equation may indicate such involvement but these analyses also have several drawbacks. There is also a large intra-individual variability both in anatomy, physiology and processing strategies. When individuals are grouped together in order to increase the signal to noise ratio, some of information may be lost. Most importantly, activity itself can never show the underlying mechanisms in the processes. Therefore functional imaging can only be used as a complementary tool to studies on the cellular level of neuro-physiology, neuro-pharmacology, receptor imaging, tracing studies, studies of neural networks, neuro-psychology and behavioral level. Thus, by using functional imaging methods we may understand some of the processing in the brain at a systematic level only if we also use knowledge from other fields of research.

4. Aims of the thesis:

• To test whether the brainstem is specifically involved in early noxious processing, indicating the lowest nociceptive hierarchical processing of pain.

• To test whether there are pain specific co-variation between regions processing pain, and discuss the relevance of parallel distributed networks in pain processing.

• To describe regions in the pain network that may be altered due to cognitive interactions during distraction, placebo analgesia and coping (e.g. somatosensory regions, insula and amygdala).

• To describe the neural circuits (e.g. ACC and obfc) and processes that may be involved in cognitive modulations of pain processing during distraction and placebo analgesia.

• To investigate whether chronic pain involve similar processes.

• To generate a hypothesis that describes how enetrocpetive information is processed in a hierarchical network in the brain, in which the rACC / vmPFC and the obfc belong to the highest order levels of the network.

5. Discussion of the studies

5.1 The brainstem and the first response to noxious input

In this chapter we discuss the benefit for the division between an immediate automatic response and a later more complex one to aversive stimuli. It is suggested that the brainstem is involved in the first processing and that cortical networks are involved in the later processing of noxious input. We show functional imaging data indicating this functional division, and also nociceptive-specific interactions between the two networks.

5.1.1 Pain networks in the brainstem and the cortex

Supraspinal processing of noxious input has been divided between processes in brainstem networks and the cortex (Price 2000). Although these systems are highly interactive it has been postulated that they can be more or less involved in different processing phases. While the brainstem seems to be important in the early immediate pain response, higher order regions seem to be involved in the later response (Price 2000). It may be suggested that the brainstem response is hardwired to be as fast as possible in order to increase the chance for survival during an acute life-threatening event. The later response may depend on the interaction with sophisticated processes in the brain such as abstract relative motivation, long-term goals, cognitive attention demands, long-term memory and working memory. The interaction between noxious input and cognition produces more flexible behavior but yields also slower responses. The complexity and dynamics of these higher order processes are mainly localized to neo-cortical networks and will be discussed in later chapters.

5.1.2 Automatic defense behaviors

The brainstem function during acute pain may be viewed as a processing and reaction to a complex situation, which may not just consist of pain. Instead, it is a way for the organism to cope in a threatening situation with a set of pre-packaged behaviors (Bolles 1970; Fanselow 1994; Timberlake 1993). These automatic defensive behaviors have been divided into different modes depending on the threat in the context, i.e. pre-encounter phase, post-encounter phase and circa strike phase (Fanselow 1994; Timberlake 1993). While the pre-encounter phase is activated during a potential but undirected threat, the threat has been identified in the post-encounter phase, and has been executed in the circa strike phase. These states have been described for experimental animals both in encounters with predators (Blanchard et al. 1990; Fanselow and Sigmundi 1986) but also elicited by noxious stimulation (Fanselow 1982). The post-encounter phase involves passive behavior, opioid analgesia and seems to be dependent upon the interaction between amygdala and the ventrolateral PAG (Fanselow 1994). The circa-strike phase

involves fight or flight behaviors and non-opioid dependent analgesia, and is elicited by the dorsolateral PAG (Fanselow 1994). During a noxious stimulation the circa-strike phase is primarily switched on but shifts quickly into a post-encounter phase, and it has been suggested that these phases have an inhibitory interaction (Fanselow 1994). The circa-strike phase may be directly initiated by nociceptive stimuli (Fanselow 1982; Fanselow 1994), which ascend to the PAG (Blomqvist and Craig 1991). Thus, this phase may represent predominantly brainstem processing.

5.1.3 Brainstem networks processing pain

The studies above indicate that the dorsolateral PAG may mediate an early behavioral and autonomic response to noxious input independent of the cortex. However, it is unlikely that the dorsolateral PAG is the only brainstem region involved in this response. Several other brainstem nuclei, such as the parabrachial nucleus, the locus coeruleus and the hypothalamus, also receive direct nociceptive information from the spinobulbal tract (Craig and Dostrovsky 1999). There is data suggesting different roles for these regions in the early response to noxious input.

As an example, the parabrachial nucleus may integrate nociceptive information with the body state (Blomqvist and Craig 1991; Craig and Dostrovsky 1999) and projects directly to the amygdala (Bernard et al. 1996) and via the thalamus to the posterior insula (Cechetto and Saper 1990). The parabrachial nucleus seems also to be involved in autonomic responses in general (Chamberlin and Saper 1992; Chamberlin and Saper 1994), and in an interaction with noxious input (Allen and Pronych 1997; Baffi and Palkovits 2000).

The hypothalamus receives dense noxious input in rat but more sparse input in cat (Craig and Dostrovsky 1999). Such a putative connection would be significant since the hypothalamus may be important for the release of hormones such as CRF (cortical releasing factor) and activate the sympathetic nervous system in direct response to noxious input in order to increase alertness.

The locus coeruleus (lc) consists of only approximately 6000 neurons (Snyder 1996). However, it may affect a majority of the neurons in the whole neuro-axis by the release of noradrenaline (Aston-Jones et al. 1999). Thus, it has both descending and ascending noradrenic projections. It is well established that the descending projections are involved in spinal modulations of nociceptive input (Fields and Basbaum 1999). However, a unifying theory of the locus coeruleus must consider both projection pathways and their physiology. The tonic lc activity in the ascending pathway correlates with wakefulness (Aston-Jones et al. 1999; Grant et al. 1988). The neurons in the lc are also phasically active in response to novel stimuli (Aston-Jones et al. 1999). It has been proposed that it is involved in the arousal due to novel stimuli in order to increase the signal to noise ratio (Aston-Jones et al. 1999; Grant et al. 1988). Thus, it may increase the attention to a novel peripheral stimulus. In this view it is of great interest that the locus coeruleus is most potently activated by noxious stimulation (Aston-Jones et al. 1999; Chiang and Aston-Jones 1993). Based on these findings it may be suggested that the lc is

involved both in alerting the subject, i.e. increasing the signal noise ratio to incoming stimuli, and modulating the spinal activity in response to acute noxious input. In line with this the lc has dense connections with the nucleus paragigantularis, which is involved in activating the peripheral sympathetic response (Chiang and Aston-Jones 1993). Thus, this mechanism may alert both cognitive systems and peripheral systems but may also be involved in the circa-strike analgesia by modulating the noxious input from the spinal cord (Craig and Dostrovsky 1999; Fanselow 1994; Fields and Basbaum 1999; Van Bockstaele and Aston-Jones 1995).

5.1.4 Brainstem and the early response to noxious input

In summary, several lines of research suggest that the brainstem is highly involved in the first response to noxious input. In order to probe this hypothesis the early phase of a tonic nociceptive stimulation was compared with the later phase of the same nociceptive stimulation in a PET study (study 1; Petrovic et al 2002d). The cold pressor test was used as noxious stimulation, i.e. the left hand was lowered into water of approximately 0^{o} C. The first minute of a noxious stimulation which always had the duration of two minutes, was compared with the second minute of the stimulation. The control condition consisted of the same conditions but cold non-painful water of 19^{o} C was used. The galvanic skin response (GSR) was measured in parallel as an index of the sympathetic response (Dawson et al. 2000; Hugdahl 1995). This response habituated for both the nociceptive and the control stimuli, but tended to be more increased during the painful events (figure 2A). The subtraction analysis showed that the early processing of pain compared with later pain processing activated areas in the brainstem (Figure 2B). This finding was not observed for the control condition. Although it is spatially impossible to resolve exact which nuclei were involved, the activated region included the hypothalamus, the PAG, and the pons. The area in the pons approximately encompassed the parabrachial area and the locus coeruleus. Thus, these data support the hypothesis that the brainstem areas are mostly important in the early pain processing which is combined with an autonomic response.

Similar regions, including the hypothalamus and the PAG, have been activated during traumatic painful event that included an intense emotional experience with concomitant autonomic and somatic outflow (Hsieh et al 1995). This experience may also be described as a circa-strike processing and behavior (Fanselow 1982; Fanselow 1994) where the automatic brainstem activity contributes to a high degree.

One previous PET study has compared the late with early processing of noxious stimulation (Casey et al. 2001). This study did not find any increased activity in the brainstem during the early vs. late stimulation. However, a crucial difference between the studies was that they used phasic stimulation while we used tonic stimulation. According to the hypothesis described above (Aston-Jones et al. 1999), each novel noxious input of the phasic stimulation will reactivate the brainstem both during the early as well as during the late phase. Thus, contrary to the tonic stimulation, no or only minor differences are expected in the brainstem between early and late phasic stimulation.

An fMRI study observed increased activity in the PAG during early pain processing, but decreased activity in a similar region during a later phase of the noxious stimulation (Becerra et al. 2001). In this study also a tonic stimulation was used with the duration of 25 seconds. However, the drawback in this study was that the difference in the neuronal response between the two phases was not statistically tested. Thus, although the findings are in line with our study, the data is not conclusive.

Our findings are in line with other functional imaging studies looking at arousal in general (Paus 2000). For example, it has been shown that there is a correlation between the alert state and the activity in the thalamus and the brainstem (Paus et al. 1997). Similar correlations have been found as a function of wakefulness during sleep (Hofle et al. 1997) as well as during different levels of general anesthesia (Fiset et al. 1999) and these regions have been found to be more active during alert as compared to relaxed waking (Tracy et al. 2000). Also, cardiovascular arousal correlated with the activity in the brainstem (Critchley, et al.2000a). These studies indicate that the brainstem, possibly including the locus coeruleus, is more activated in aroused conditions and correlates with the sympathetic activity during the aroused conditions. Thus, these studies support an involvement of the brainstem in the early painful condition of our study that also involved a high GSR.

Previous studies have indicated that several spinal nococeptive neurons respond most intensively to noxious stimulation during the acute phase of the stimulation, i.e. the first 5-30 seconds; (Coghill et al. 1993; Kenshalo et al. 1979). However, behavioral studies indicate that pain ratings increase approximately the first forty seconds and then stabilize during tonic pain (Rainville et al. 1992). Thus, there seems to be a lack of congruence between the perception of pain and the noxious input. Possibly, the early signals are more important for the acute response of the brainstem, which also is activated to a higher extent during the earliest phase of noxious stimulation.

5.1.5 Interactions between networks in the brainstem and the cortex

Given the anatomical and general physiological data for the parabrachial nucleus, locus coeruleus and other brainstem nuclei an interaction between the brainstem and the cortical networks seems to be fundamental for noxious processing (Parvizi and Damasio 2001). Thus, the neuromodulatory effects and the alternative noxious input should reach cortical regions through these nuclei specifically during noxious stimulation. In line with this suggestion we observed significant co-variations between the pons and the posterior insula during pain vs. control for the first minute of stimulation (figure 2C). This finding was then replicated for the second minute of stimulation (figure 2E). Importantly, this analysis shows no causality. Thus, the findings do not indicate whether the pons controls the insular region, vice versa, or whether both regions are controlled by a third signal, e.g. the noxious input. However, the fact that other regions involved in noxious processing do not correlate with the activity in the pons, and the existence of anatomical projection from the parabrachial nucleus to the insula (Craig and Dostrovsky 1999) implies a specific interaction between these regions. The posterior insula is involved in autonomic

processing (Cechetto and Saper 1990) and it has been suggested as a region processing enteroceptive information about the status of the body (Craig et al. 2000). This information could be relayed from the parabrachial nucleus via thalamic nuclei (Cechetto and Saper 1990; Craig and Dostrovsky 1999). During the second minute of noxious stimulation specific co-variations were also observed between the pons and the ventromedial PFC, the rostral ACC and the orbitofrontal cortex (figure 2E; figure 4H). This finding may be an indication of neuro-modulatory effects of the locus coeruleus. However, this suggestion is less likely since the effect is only observed during the late phase of the noxious stimulation when the autonomic response has habituated. Possibly, the observed functional connectivity represents a prefrontal cortex control of the brainstem. It has been postulated that the prefrontal cortex is involved in the habituation of the autonomic responses during cold pressor test (Lovallo 1975), i.e. the same stimulation that was used in study 1. For example, patients with frontal lesions after leucotomy have shown later habituation of the blood pressure response during cold pressor test. This mechanism would thus be similar as the proposed rostral ACC control over brainstem regions during opioid analgesia (see further chapter 5.4).

The hypothalamus showed a pain-specific co-variation with the primary sensorymotor region for the somatotopic area of the stimulated hand for the first minute of stimulation (figure 2D). This pattern of co-variation was replicated during the second minute of stimulation, i.e. a completely different set of scans (figure 2F). During the second minute of stimulation also the ipsilateral side of the somatotopically hand region co-varied with the hypothalamus (figure 2F). The findings indicate that there is an positive interaction between the hypothalamus and the stimulated primary sensorymotor region in the painful conditions but not in the cold control conditions.

One critique of the present study would be that the duration dependent activity in the brainstem and the hypothalamus must not be pain specific. Although the activity is more expressed during pain it may just represent a higher signal frequency regardless of input modality. However, the regression analysis showing pain-specific interactions between the pons and the hypothalamus with neocortical networks that are known to process pain, indicates that these regions are specifically involved in processing noxious input.

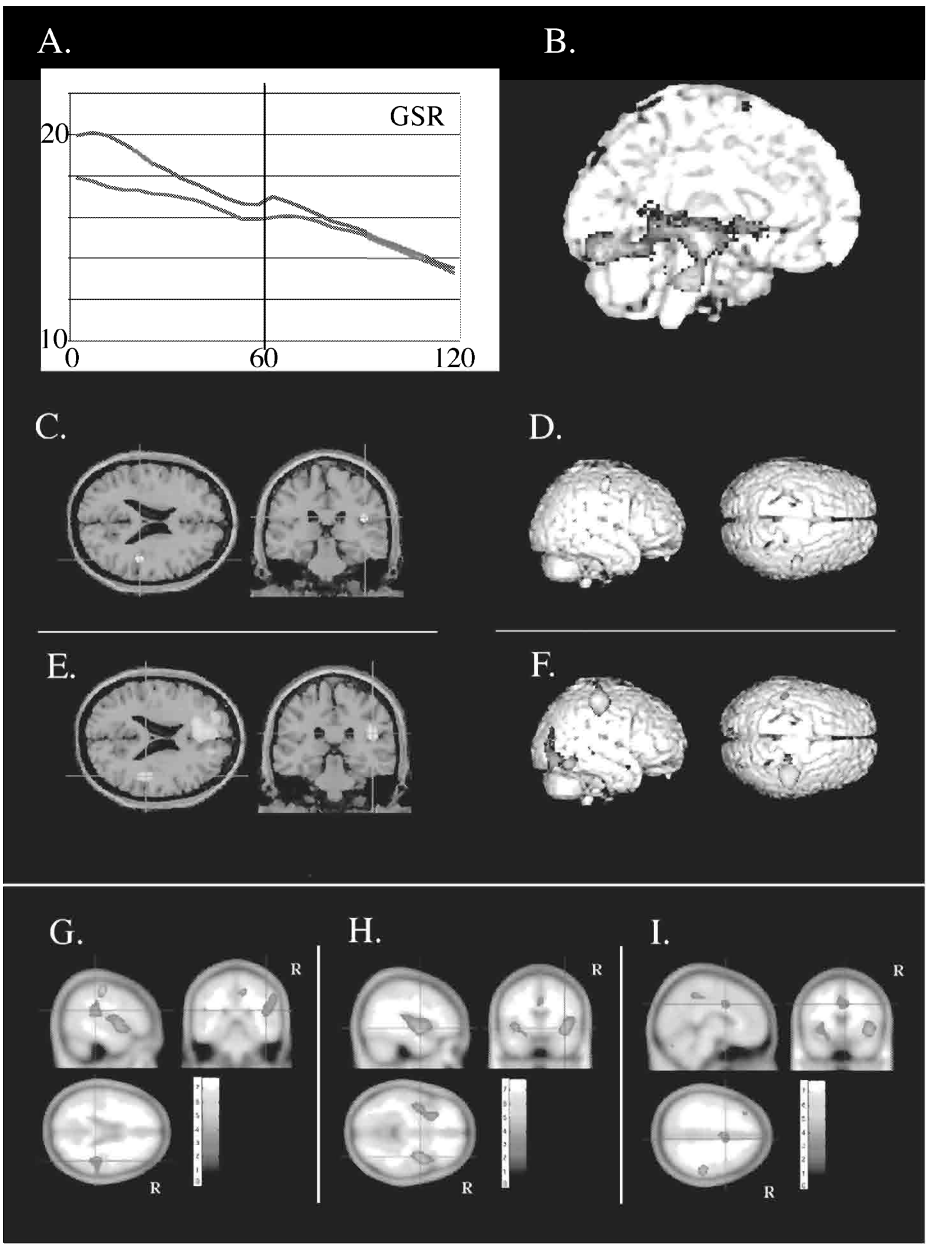


Figure 2. A) The galvanic skin response (GSR) decreased during the two minutes of pain stimulation (red) and cold stimulation (blue) in study 1. Y-axis indicates the GSR response in µSiemens and the X-axis indicates the stimulus duration in seconds. The subjects were either scanned the first or second minute of stimulation. B) Areas in the brainstem, including the hypothalamus, the PAG and the pons, showed an increased activity during the first minute of pain as compare with the second minute of pain. The pons showed pain specific co-variation with the posterior insula during the first (C) and the second minute of stimulation (E). The hypothalamus showed pain specific co-variation with the sensorymotor cortex during the first (D) and the second minute of stimulation (F). In study 2 it was shown that the S1 co-varied with the contralateral posterior insula / S2 (G), the anterior insula bilaterally (H) and the cACC (I) during the second minute of pain.

5.2 Network processing - a fundamental mechanism for cognitive pain processing

The involvement of the somatosensory cortex in pain processing has been extensively debated during the last decade. Using regression analysis we show that the primary somatosensory cortex may be involved in pain processing although there is no increased activity in this region during pain. We further discuss why a region may co-vary with other regions during a specific condition, such as pain, and conclude that the findings may indicate that pain is processed in a distributed and parallel network. It is suggested that such computations are fundamental for higher order cognitive interactions.

5.2.1 The involvement of S1 in pain processing

In two studies of the present thesis (study 1 and study 4; Petrovic et al. 2002d; Petrovic et al. 2002b) no increased activity was observed in the somatosensory cortex, as well as in several other imaging studies of pain (for review se Bushnell et al. 1999; Ingvar 1999). It has been postulated that the somatosensory cortex is involved only in specific processing of a noxious stimuli (Treede et al. 1999). However, a lack of significantly increased activity as compared to the control stimulus does not exclude the involvement of the somatosensory regions in the pain processing. Such findings would be obscured if the control stimulus also activated these regions, or if the pain dependant increase was too variable or too small. In fact, it has been shown that also cold stimulus, which was used in the control condition of our study, tends to augment the rCBF activity in the somatosensory regions (Craig et al. 2000; Craig et al. 1996).

In order to better understand the involvement of S1 during pain in studies not showing increased activity in somatosensory regions during noxious input, we re-analyzed the data from study 1. We employed a regression approach, in which we probed for co-variation of the activity of the putative S1 region for the stimulated hand and the rest of the brain (Petrovic et al. 2002d). We hypothesized that if the S1 is involved in pain processing it will co-vary with other regions also involved in pain processing during the pain conditions but not during the control conditions. These differences in co-variation could also be tested between the different conditions (Friston 1994; Friston et al. 1997b). We postulated that this was a more sensitive method since it was less dependent on increases in the S1 during the control stimulation. We observed that the patterns of co-variation were very different in the control conditions vs. the pain conditions. Whereas the S1 co-varied with other ipsilateral and contralateral parts of the sensorymotor cortex in the cold conditions, no such findings were observed in the pain conditions. Instead, the S1 co-varied with regions involved in pain processing (including the insula, S2, ACC and obfc bilaterally) during the second minute of noxious stimulation (figure 2G, H, I). The differences in the co-variations were significant between the pain vs. cold condition

bilaterally in the obfc and the insula. Similar, but sub-significant co-variations were observed during the first minute of pain stimulation.

Thus, it was established that there was a significant difference in the regression pattern between the S1 and the rest of the brain in the noxious vs. the control condition. This finding implies that somatosensory regions may be involved in pain processing although no significant differential activity increases are observed. The findings of increased S1 activity during allodynia (study 6; Petrovic et al. 1999) which may be criticized as being more motor driven than driven by the nociceptive input, may be analyzed in a similar way. However, it would require a new study in which the allodynic patients have similar localization of the neuropathic pain.

5.2.2 Parallel and distributed processing

A more interesting question is what these co-variations actually represent. Our analysis does not indicate any causal relationship. Thus, it is not possible to say which region or signal is driving the activity in another region. There are two general ways to explain the findings. The first alternative is that peripheral input is driving all the regions. The other alternative is that the regions interact in order to compute the complex processing leading to pain perception and behavior. Most probably the observed co-variation pattern results from both alternatives.

For every perception there are many different regions processing different aspects of the total perception. In visual perception, which is the most widely studied perception in neuroscience, over 30 regions interact in the primate cortex (Gazzaniga et al. 1998; Kolb and Whishaw 1996). These are distributed over large parts of the occipital, parietal and temporal cortex, and many of these regions are parts of different processing streams and thus parallel with each other. Although widely distributed, these regions are also highly interconnected in both directions, i.e. reciprocally connected. This seems to be a general feature of the cortex (Mesulam 1998). Thus, it is suggested that the brain is working in a parallel and distributed fashion (Goldman-Rakic 1988), using large-scale networks of highly interconnected regions (Mesulam 1998).

Using this hypothesis, a general model for processing cognitive aspects of different perceptions has been suggested by Mesulam (Mesulam 1998). In this model the input signal reach the primary sensory cortex and continues to unimodal association regions which have a more complex processing of the same perception. These regions are considered as upstream regions. The processed signals then reach heteromodal association areas, where they may be integrated with other perceptions. From here the signals may continue to paralimbic and limbic regions, which are considered as downstream regions. As discussed above this stream of processing is both serial and parallel. The strong reciprocity enables downstream modulation of upstream processing, which is fundamental for cognitive modulation of the upstream regions, for example in attention tasks. However, the processing in this stream may not be thought of as a single signal serially transferred from region A to B. Instead it may be better conceptualized as a continuum of processing which is changed by an input signal. Different regions may have

a special profile although processing the same information. Thus, the total percept may be constructed by the simultaneous activity in all the regions in the network. The regions upstream are highly differentiated and considered to reflect the outside world, while the regions downstream deal with "regulation of emotion, motivation and autonomic-endocrine function" and are therefore considered as processing the internal milieu (Mesulam 1998). This construction makes it possible for regions processing the internal milieu to modulate regions that more strictly reflect the outside world.

Thalamic nuclei may have a role in binding together sub-regions into a functional unity, i.e. a large-scale network. This has been especially proposed for the intralaminar thalamic nuclei because their axons reach most parts of the cortex (Paus 2000). It has further been suggested that neuronal synchrony between regions may be relevant in grouping together regions into large-scale networks and thus, also shifting between networks (Singer 1993; Singer 1998; Singer 1999; Singer 2001). However, also an increased neuronal activity is proposed for regions included in the network. The increased activity in one region may then interact with, and drive another region. This would be the basis for context specific co-variation between regions in a functional network It has also been suggested by Mesulam (Mesulam 1998), that "individual cortical areas can dynamically shift affiliation from one network to another depending of the overall goal of the task". This would be an efficient use of the computational capacity of the brain.

5.2.3 Parallel and distributed processing of pain

The outlined model of parallel and distributed processing in large-scale networks may partly be applied for noxious processing. The primary and secondary somatosensory regions have highly somatotopic organization and may be viewed as unimodal regions. The insula, the ACC, the orbitofrontal cortex, and the amygdala may be considered as a part of the downstream limbic and paralimbic cortex. Similarly, as suggested above these regions are highly and reciprocally interconnected. However, a unique organization for noxious processing is that not only the upstream regions receive peripheral noxious input, but also the paralimbic and limbic regions receive peripheral input. However, these processes are less somatotopically organized, and these regions are more directly involved in emotional, motivational and autonomic aspects of pain perception (Vogt et al. 1993). Thus, although they also receive noxious input they may be considered as part of the system reflecting the enteroceptive state of the organism, a suggestion that also has been put forward for processing warm and cold stimuli (Craig et al. 2000).

The results in study 2 indicate that S1 may be part of different processing networks during cold as compared with cold pain. It would then shift networks during the different conditions and work serially and in parallel with a different set of regions. The correlational pattern would then reflect the large-scale network S1 is a part of during the different conditions.

However, as stated previously, an important bias is that most of the regions in the pain matrix receive noxious input from the periphery. Theoretically, the activity in these

regions may co-vary only because the input is the same and not due to interaction between each other. The proposition that S1 is a part of different networks depending on the overall processing demands may be stronger if it is possible to show that its activity is differently regressed although the input is the same. This cannot be shown in study 2 since the first minute of pain may differ in noxious input compared with the second minute of pain. However, in study 5 (Petrovic et al. 2002a) the context was changed while the noxious input was the same. When the subjects expected a longer painful event (2 minutes) they also decreased the amygdala and insula activity during the first minute of pain. However, when they expected a shorter painful event (1 minute) no decreased amygdala activity was observed during the same stimulation time. Thus, the network was differently activated although the peripheral noxious stimulation was the same (see further chapter 5.5). Importantly, it was also shown that both amygdalae co-varied more strongly with other areas processing pain during the short painful context as compared with the long painful context. This difference was significant for the co-variation between the right amygdala and the somatotopic S1 hand region contralateral to the stimulus side. This finding indicates that the S1 may change the strength of co-variation with other regions processing pain although the noxious stimulation is the same. However, even this analysis cannot exclude that the input has changed due to descending modulatory processes. Analysis of rCBF data such as structural equation modeling (SEM) or transcranial magnetic stimulation (TNS) studies can further indicate if and how these regions interact.

5.3 The orbitofrontal cortex – an attentional source involved in the modulation of pain processing

Certain networks in the brain can modulate the activity of distant regions that process peripheral input. Here, we suggest that the lateral orbitofrontal cortex is involved in modulation of networks processing pain perception. This mechanism is proposed to be a part of a general function of the orbitofrontal cortex in regulating distant neural activity during emotional and motivational contexts.

5.3.1 Sites and sources of attention

Conscious perceptions are not an accurate reflection of the outside world but an integration of signals from the outside world with prior knowledge (Frith and Dolan 1997) and with the motivational state of an organism (Mesulam 1998). This suggestion has been indicated in behavioral experiments ranging from studies of corollary discharge (Kolb and Whishaw 1996) to studies of color constancy (Zeki and Marini 1998; Zeki and Moutoussis 1997), the brains ability to fill in missing information (Ramachandran 1999) and attentional modulations of perception (Gazzaniga et al. 1998).

Electrophysiological and functional imaging studies have shown neural correlates of changes in the perceived perception during an unchanged peripheral input (Coull 1998; Frith and Dolan 1997; Gazzaniga et al. 1998). These modifications of activity have been reported in regions crucially involved in the processing of the percept per se, also called the sites of modulated activity (Frith and Dolan 1997). However, it has been hypothesized that other regions or groups of regions may modulate the neuronal activity in the sites. Such a network may be referred to as a source and is able to inhibit (i.e. attenuate) or excite the activity of the different sites, and thereby change the processing of a peripheral input (Frith and Dolan 1997).

5.3.2 The lateral and the medial orbitofrontal cortex

The orbitofrontal cortex has been defined as the part of the prefrontal cortex above the orbital / ventral surface including both lateral and the medial regions (see further Elliott et al. 2000a; Roberts and Wallis 2000). However, there are differences in projections between the medial and the lateral obfc (Carmichael and Price 1995a; Carmichael and Price 1995b; Cavada et al. 2000; Morecraft et al. 1992). Although there are vast amount of interconnections between specific sub-regions of the medial obfc and the lateral obfc, respectively, the general interconnections between the lateral and medial obfc are sparse (Carmichael and Price 1996).

5.3.3 Orbitofrontal cortex and reward association

Neurophysiological evidence show that the orbitofrontal cortex is involved in associating cues with primary and secondary re-inforcers (Thorpe et al. 1983). Evidence from lesion

studies indicate that the medial obfc is involved in associating a previously non-rewarded stimulus with a reward, and that the lateral obfc is involved in inhibiting the choice of a previously rewarded stimulus (Iversen and Mishkin 1970). The associations seem to be highly dynamic and relative in their nature (Critchley and Rolls 1996; Tremblay and Schultz 1999; Tremblay and Schultz 2000; Tremblay and Schultz 2000). These suggestions are partially supported by functional imaging studies (Elliott et al. 2000a). The medial obfc has more often been activated in studies when there is a requirement to make associations between a stimulus and a rewarded response, especially when subjects had to hold different reward values in mind (Elliott et al. 2000a). Therefore it may be suggested that the medial obfc function may be viewed as a prefrontal working memory for reward values (Elliott et al. 2000a; Schoenbaum and Setlow 2001). Similarly as in animal studies, the lateral obfc is activated when the tasks include a suppression of previously reinforced responses in humans (Elliott et al. 2000a). In line with these studies the medial obfc has been activated by reward feedback while the lateral obfc was activated by negative feedback, i.e. punishment (O'Doherty et al. 2001). Also, the activity was correlated to the magnitude of reward and punishment, in the medial and lateral obfc, respectively.

5.3.4 Orbitofrontal cortex and affective state

Apart from association and inhibition of association between responses and perceptions during motivation dependant tasks, functional imaging studies have indicated that the obfc is more directly involved in normal and pathological emotional processing. This is especially evident for patients suffering from depression, bipolar disorders and obsessive-compulsive disorder (Drevets 2000b), but also when different emotional states have been induced in healthy subjects (Baker et al. 1997; Pardo et al. 1993). These studies have shown increased activity in the lateral obfc during experimentally induced elevated or depressed mood in healthy subjects and in patients with primary major depressive disorder. However, the elevation of the lateral obfc resting activity during depression was mood state dependent and disappeared after effective treatment with anti-depressive drugs (Drevets 2000a; Drevets 2000b). Moreover, although the lateral obfc activity was increased during depression it correlated inversely with ratings of depression severity and negative thought frequency (Drevets 2000a; Drevets 2000b). These observations have led to the hypothesis that the lateral obfc participates in the modulation or inhibition of emotional processes during depression (Drevets 2000a). The putative role of the lateral obfc in modulation of perceived emotions is in line with its role in suppression of a previously reinforced / rewarded response (Elliott et al. 2000a; O'Doherty et al. 2001). Similarly, physiological and lesion studies have previously suggested that the obfc may exert inhibitory control over sensory processing and behavior based on motivational values (see further Fuster 1997).

5.3.5 Interaction between the orbitofrontal cortex and limbic structures

The obfc has anatomical possibilities to directly interact with and modulate several limbic structures involved in emotional processing and autonomic regulation. Especially, the connectivity between the obfc and the amygdala may be emphasized. These regions have reciprocal anatomical connections (Aggleton et al. 1980; Amaral and Price 1984; Barbas and De Olmos 1990; Carmichael and Price 1995a; Porrino et al. 1981) and physiological interactions have been indicated between these structures (Baxter et al. 2000; Morris and Dolan 2001; Morris et al. 1999; Schoenbaum et al. 2000; Zald and Pardo 1997). The left obfc rCBF increase correlated positively with the left amygdala rCBF increase during presentation of aversive odorants (Zald and Pardo 1997). The right obfc co-varied negatively with the right amygdala during presentation of masked faces conditioned to an aversive stimulus (Morris et al. 1999). Thus, the functional relation between the obfc and the amygdala may both be positive and negative depending on the context. Functional relations between these structures have also been observed during pain, i.e. in study 5 (Petrovic et al. 2002a) we observed that the right amygdala activity co-varied significantly different with the obfc in two pain contexts (see further chapter 5.5).

The amygdala activity is elevated during major depression like the obfc activity (Drevets 2000a; Drevets 2000b). It is directly involved in various autonomic, endocrine and behavioral stress responses (see further chapter 5.5). Conversely to obfc activity, the amygdala activity is positively correlated to the severity of the depression, and the glucose metabolism between the amygdala and the obfc is inversely correlated in depressed humans (Drevets 2000a; Drevets 2000b). Based on these observations it has been suggested that the obfc modulates the amygdala activity during depression (Drevets 2000a; Drevets 2000b). This hypothesis is supported by the finding that behavioral and autonomic responses, which are elicited through amygdala stimulation, are attenuated by simultaneous stimulation of the obfc (Timms 1977). Interestingly, non-pharmacological treatments of depression such as cognitive behavioral therapy increases the rCBF in the obfc, suggesting that the therapeutic mechanism may depend upon an increased obfc (Brody et al. 1998; Brody et al. 1999). Also, brainstem structures such as PAG may be modulated by the obfc (Dong et al. 1999; Huang et al. 2001), which is in line with the finding of opposite interaction in the PAG vs. the obfc during analgesia due to cognitive distraction (Petrovic et al. 2000).

5.3.6 Overall functions of the orbitofrontal cortex

Altogether the different lines of research suggest that the obfc may act as an attentional source in contexts that involve processing of emotional or motivational material. Apart from modulation of other processes, the obfc is suggested to be involved in monitoring the reward value of stimuli and responses so that these may be used to choose an appropriate action. Thus, the function of obfc may also be conceptualized as an emotional working memory holding the relative emotional values in a short-term memory. Finally,

the obfc may be a part of a network producing the subjective emotional experience, which also may include the ACC, the insula and subcortical structures.

5.3.7 The orbitofrontal cortex and pain processing

The perception of pain involves intense emotional components (Price 2000). It may therefore be suggested that the obfc is involved in similar modulatory influences during pain processing. Activation of the lateral obfc has most consistently been observed in functional imaging studies of sever clinical pain states (see chapter 5.6). Given that these pain states are a real threat to the organism and that some chronic pain states involve a high frequency of depression and depressive symptoms (Fishbain et al. 1997), a similar relation between the obfc activity and the clinical pain conditions would be expected as in major depression. It would thus be possible that the obfc is involved in regulating the emotional systems, which have been induced and are potentiated by the chronic pain.

Increased activity in the lateral obfc has also been observed in functional imaging studies of experimental pain. Several of these studies involve a modulation of the pain perception (figure 3C; Bantick et al. 2002; Petrovic et al. 2000; Petrovic et al. 2002b; Rainville et al. 1997; Rainville et al. 1999; Willoch et al. 2000). Two of the studies involve hypnosis and suggestion (Rainville et al. 1997; Rainville et al. 1999; Willoch et al. 2000), two involve cognitive distraction during pain processing (Bantick et al. 2002; Petrovic et al. 2000) and one involves placebo analgesia (Petrovic et al. 2002b).

In the study by Rainville et al, hypnosis was used as a cognitive tool in order to modulate the perceived unpleasantness of a standard noxious stimulation (Rainville et al. 1997). The caudal ACC activity increased significantly more when the noxious stimulation was perceived as highly unpleasant as compared to when the noxious stimulation was perceived as only mildly unpleasant. The authors also performed an analysis in which they subtracted the hypnosis conditions involving a noxious stimulation from those hypnosis conditions involving both a noxious stimulation and a suggestion that the painful perceptions would be altered (Rainville et al. 1999). The suggestions included both the condition where the unpleasantness was increased and decreased. Thus, this network was interpreted as "reflecting processes specifically involved in the response to the suggestions to alter perception" (Rainville et al. 1999). Among the regions, which increased their activity in these conditions, were the rostral ACC, the insula and the lateral obfc (BA47). Decreased activity was noted in medial obfc.

In the study by Willoch et al (Willoch et al. 2000), hypnotic suggestion was used to induce an intense perception of pain in an amputed extremity, i.e. phantom limb pain. Although no peripheral noxious stimulation was used, the pain matrix was activated (including the S1, the thalamus and the ACC) supporting the hypothesis that phantom limb pain is induced in the brain as a pathological consequence of neural denervation. Similarly as in the study by Rainville et al the lateral orbitofrontal cortex increased its activity as a consequence of pain induction through hypnotic suggestion.

In order to efficiently solve a cognitive task, the processing of irrelevant perceptions is often attenuated (Chawla et al. 1999; Coull 1998; Frith and Dolan 1997;

Ghatan et al. 1998; Rees and Frith 1998). This was also shown for the processing of experimental pain (study 3; Petrovic et al. 2000). When subjects simultaneously solved an attention demanding cognitive task, the computerized maze task, they perceived the noxious stimulation as less intense and less unpleasant. As a neural correlate to the behavioral results the activation of the somatosensory association areas (including S2) and the PAG decreased relatively during pain and the cognitive task as compared with the pain only condition. However, when the subjects solved the maze task and therefore perceived less pain, the activity in the lateral obfc increased relatively (figure 3A). A similar study has shown that when subjects were distracted away from the pain using a Stroop task, the obfc (and rACC) activity increased (Bantick et al. 2002) while the caudal ACC, which was activated by pain decreased its activity.

In placebo analgesia, i.e. a condition that included noxious stimulation and a placebo treatment vs. a noxious only condition, increased activity was observed in the lateral obfc (figure 3B; study 4; Petrovic et al. 2002b). Also, general opioid effects showed an increased activity in the obfc (activity continuum from temporopolar regions). However, the obfc activity was more rostral and more expressed during placebo analgesia as compared to the general opioid effects. This finding may mirror the higher cognitive complexity during placebo analgesia as compared with general opioid effects (se further chapter 5.7 and Kringelbach 2002). Also, the obfc increases were especially expressed in right (contralateral) prefrontal regions. The interpretation is uncertain since it may just mirror a threshold effect. However, low - but not high - doses of remifentanil activate the right lower prefrontal cortex (Wagner et al. 2001), which also may be due to a placebo effect. Thus, there may be a right obfc dominance during processing of placebo analgesia.

These studies indicate that the lateral obfc is activated in conditions involving both an experimental noxious stimulation and a higher order cognitive modulation of the painful perception. This modulation included decreased pain perception (Petrovic et al. 2000; Petrovic et al. 2002b), increased pain perception (Willoch et al. 2000) and a combination of increased and decreased pain perception (Rainville et al. 1999). Thus, the obfc activity may be more related to the general modulation of pain perception than specific modulations (increases or decreases of pain perception). In line with the suggestion that the obfc may exert modulatory influences on pain processing, it has been shown that stimulation of the lateral obfc induces analgesia in animal studies (Oleson et al. 1980; Zhang et al. 1997). This effect is at least partly regulated through the thalamic nucleus submedius and the PAG (Dong et al. 1999; Huang et al. 2001), which is in line with study 3 (Petrovic et al. 2000) in which the PAG activity relatively decreased while the obfc activity increased when the pain perception was modulated.

In conclusion, it is hypothesized that motivational signals, such as pain, which must be overridden in order to solve a cognitive task will be suppressed by the lateral orbitofrontal cortex. This general idea may be applied to any stimulus from the internal / enteroceptive environment.

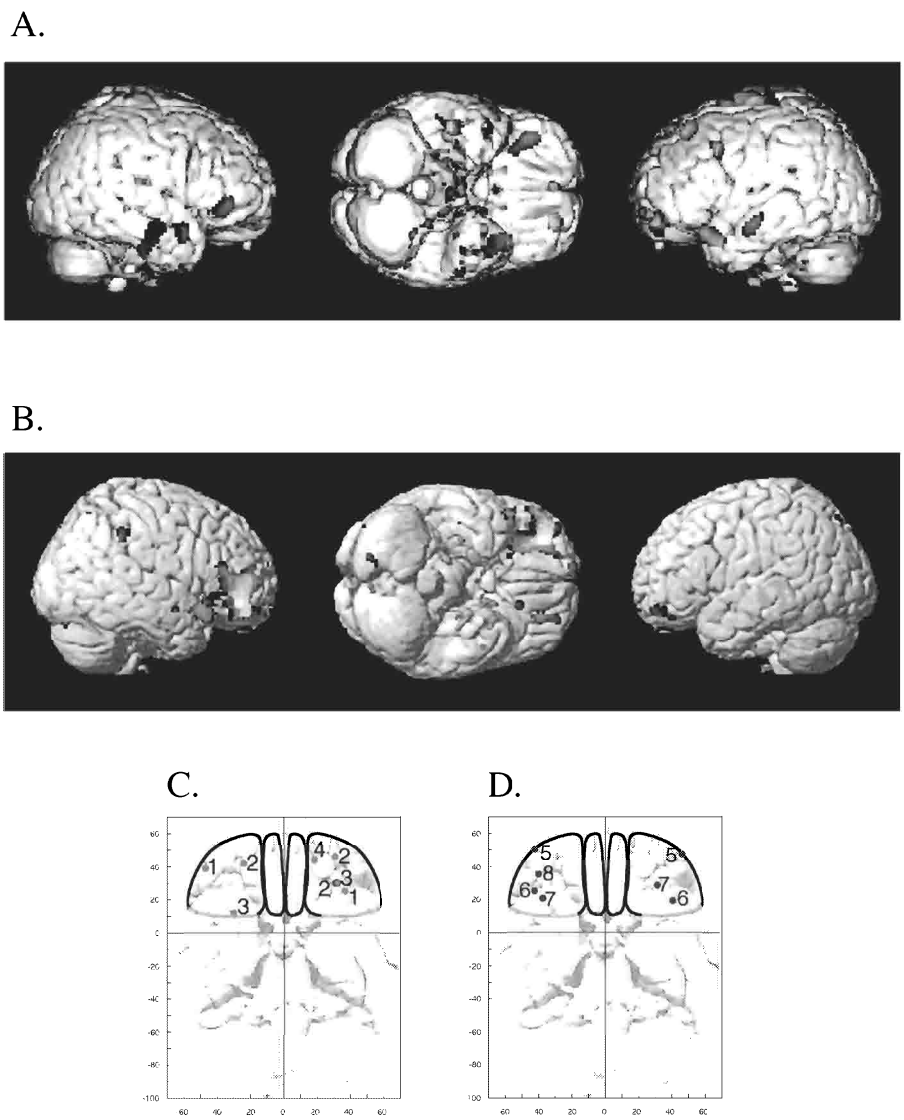


Figure 3. The orbitofrontal cortex showed increased activity when the pain perception was decreased in a cognitive distraction task (A; study 3; SPM96-template) and during placebo analgesia (B; study 4; SPM99-template).
A plot of the maximal increased activity in the orbitofrontal cortex during cognitive modulation of the pain perception that was controlled for non-modulated pain (C; 1 = Rainville et al. 1999; 2 = Petrovic et al. 2002b; 3 = Petrovic et al. 2000; 4 = Bantick et al. 2002) and during chronic pain (D; 5 = Hsieh et al. 1995; 6 = Hsieh et al. 1996; 7 = Rosen et al. 1994; 8 = Peyron et al. 1998).

5.4 The involvement of rACC and the brainstem in opioid and placebo analgesia

In this chapter a relationship is suggested between the endogenous opioid system and the network involved in placebo analgesia. It is indicated that the rostral ACC and the brainstem are similarly involved in opioid and placebo treatment, and it is further hypothesized that these processes are a part of a general attentional mechanism that partly involves the anterior cingulate cortex.

5.4.1 The brainstem opioid network

Opioid receptors in the CNS are found in the entire neuro-axis, for example in the cortex, the brainstem and the spinal cord (Fields and Basbaum 1999; Jones et al. 1991; Price 1999a; Willoch et al. 1999; Zubieta et al. 2001). Although these receptors are widespread throughout the CNS, the localization is not diffuse but highly regional. It has been proposed that the networks containing opioid receptors may exert the analgesic effect through several different mechanisms (Jackson et al. 2000). These include modulation of the spinal noxious input (on the spinal input level or on the ascending pathways), direct control of cortical or brainstem structures that are involved in pain processing or regulation of the ascending forebrain systems (Jensen 1997). At present the modulation of the spinal cord has been best described (Fields and Basbaum 1999).

In the brainstem opioid receptors are mainly found in the periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM) (Fields and Basbaum 1999; Price 1999a). Both stimulation of the PAG and microinjection of opioids into the PAG may induce analgesia. The PAG receives nociceptive input directly (Craig and Dostrovsky 1999) but has no major direct output to the spinal cord (Fields and Basbaum 1999). Instead PAG projects to the RVM (Fields and Basbaum 1999). This connection is critical for pain modulation, i.e. if the RVM is lesioned stimulation of the PAG does not induce analgesia (see further Fields and Basbaum 1999). The RVM consists of several structures, which have opioid receptors and which are involved in pain modulation, e.g. the midline nucleus raphe magnus and adjacent nuclei in the reticular formation (Fields and Basbaum 1999; Price 1999a). There are major projections from the RVM to the dorsal horn, mainly laminae 1, 2 and 5. Stimulation of the RVM inhibits nociceptive dorsal horn neurons, an effect that is thought to be expressed through inhibitory interneurons in the spinal cord containing GABA and / or enkephaline (Fields and Basbaum 1999).

5.4.2 The cortical opioid network and pain modulation

The opiod receptor network is less characterized in the cortex, especially in the more developed human brain. However, auto-radiographic studies of post-mortem human and primate brains, and PET studies of opioid receptors in human subjects have started to reveal a cortical opioid receptor network. The auto-radiographic studies indicate high concentrations of opioid receptors in the periaqueductal gray, the intralaminar and medial

thalamic nuclei, the cingulate cortex and prefrontal cortex (Atweh and Kuhar 1983; Pfeiffer et al. 1982; Wamsley et al. 1982). These studies have suggested that the anterior cingulate has one of the highest levels of opioid receptor bindings in the cortex (Vogt et al. 1993). Recent PET-studies using radioactive opioid, i.e. [^{11}C]-Diprenorphine, which indicates the mu-, delta- and kappa-opioid receptor availability, have confirmed previous animal and human auto-radiography findings (Jones et al. 1991; Sadzot et al. 1991; Willoch et al. 1999). Although no quantitative analysis of the entire brain has been presented, the opioid receptor images from these PET–studies suggest a high opioid receptor concentration in the insula and the prefrontal cortex (Jones et al. 1991; Sadzot et al. 1991; Willoch et al. 1999). Raw data indicates that the binding potential is highest in the rostral parts of the ACC (figure 4; Willoch et al. 1999). Also the basal ganglia and the thalamus seem to express a high opioid receptor concentration.

A similar network has showed increased rCBF activity during treatment with opioid like compounds, such as remifentanil and fentanyl (Adler et al. 1997; Casey et al. 2000; Firestone et al. 1996; Wagner et al. 2001). In line with these studies we were also able to show that remifentanil, an opioid compound with short half-life, increases the activity in several regions known to be involved in pain processing and containing high concentrations of opioid receptors (study 4; Petrovic et al. 2002b). Increased activity was observed in the caudal and rostral ACC (figure 4A), mid- anterior insula, stretching into the orbitofrontal / temporopolar cortex, and in the brainstem (i.e. the pons; figure 4A). Common for all the presented rCBF studies of opioid effects was an observed activity increase in the rostral ACC during the opioid treatment. Also, the activity in the ACC increased in the conditions where pain was induced simultaneous with administration of opioids to induce analgesia (Adler et al. 1997; Casey et al. 2000). Thus, it may be suggested that a relationship exist between opioid analgesia and the rACC.

Several PET-studies involving stimulus induced analgesia (Davis et al. 2000; Garcia-Larrea et al. 1997; Garcia-Larrea et al. 1999; Peyron et al. 1995; Willoch 2001), nitrous oxide-induced analgesia (Gyulai et al. 1997), and hypnotic modulation of pain perception (Faymonville et al. 2000; Rainville et al. 1999) have also shown an increased activity in the rACC associated with a change in the pain perception. Also, a study using distraction has shown relatively increased activity in the rACC during the distraction induced analgesia (Bantick et al. 2002). We have post-hoc reviewed (Petrovic and Ingvar 2002) our study (Petrovic et al. 2000) in which the maze-test was used to induce distraction analgesia. Apart from the previously shown relative increase in the obfc during modulation of pain we also observed a sub-significant interaction in the rACC (using the same contrast). Finally, stimulation of the ACC / vmPFC has induced analgesic like behavior in rats (Hardy 1985; Hardy and Haigler 1985). In conclusion, these studies suggest that the ACC / vmPFC, and especially the rostral ACC may be involved in pain modulation.

5.4.3 Conditions that activate the endogenous opioid system

It is well established that opioids are potent analgesics and that a complex endogenous system exists which includes at least three receptors subtypes (my, delta, kappa) and several opioid like compounds, e.g. enkephalines, endorfines and endomorphines, which all have a different regional specificity (Fields and Basbaum 1999). The complexity of the endogenous opioid network indicates that it is an important regulatory system for the organism. However, it is less elaborated in which situations these systems are active and their role for increasing the chances of the survival of the organism. Apart from the analgesic function the opioid sub-systems may be specifically involved in different motivational and mood regulations (Fanselow 1994; Filliol et al. 2000). Thus, its role is not just to regulate pain perception, but to modulate the general state of the organism, which also includes a change of the perceived pain. This implies that the opioid effect can be understood only in relation to the external context and the internal state (e.g. motivation and emotion). It has been hypothesized that several contexts may be important for activating endogenous opioid systems for the induction of analgesia (Fields and Basbaum 1999; Price 1999a).

In animal studies, contexts that induce fear and stress have been described as important for the activation of the endogenous opioid system, i.e. fear- or stress related analgesia (Fanselow 1984; Fanselow 1994; Terman et al. 1984). This state has been induced either using noxious shocks (Bellgowan and Helmstetter 1996; Fox and Sorenson 1994), conditioning a noxious shock with an neutral stimulation (i.e. conditioned stress induced analgesia (Fanselow 1984; Fanselow 1994; Fox and Sorenson 1994; Helmstetter 1992; Watkins et al. 1993) or setting up a context in which fear is thought to be induced in the animal, e.g. putting an animal in the same cage as its predator (Fox and Sorenson 1994). These type of triggers will activate the opioid system through the amygdala network which then activates the brainstem opioid system (Fanselow 1994; Fox and Sorenson 1994; Helmstetter 1992; Watkins et al. 1993).

In humans several types of unnatural triggers, e.g. acupuncture analgesia as well as electro-stimulation, are suggested to be opioid dependent (Fields and Basbaum 1999; Price 1999a). However, about a third of the studies have not shown naloxone interactions. Moreover, placebo effects cannot be ruled out as one of the mediators of the analgesia (Price 1999b). It has also been suggested that pain thresholds and pain in stressful situations may be dependent on endogenous opioids, although there is a high variability between subjects (Price 1999a). However, a correlation between different fear-states and naloxone attenuation of an analgesic response, have yet not been performed. The most intriguing opioid dependent trigger of analgesia is when a context induces a belief that will reduce pain perception, i.e. placebo analgesia (Levine et al. 1978; Price 1999b; Wall 1999).

5.4.4 Placebo analgesia

There are several known contextual triggers that may induce placebo analgesia possibly through different mechanisms. Some of these mechanisms are reversed by naloxone, i.e. an opioid antagonist, which indicates that placebo analgesia may depend on endogenous opioids (Levine et al. 1978; Price 1999b; Wall 1999). Expectations of an analgesic response and opioid conditioning are two potent placebo triggers that have been described (Amanzio and Benedetti 1999; Price 1999b; Wall 1999). The first placebo analgesic effect (i.e. expectations) may induce a placebo response when subjects are informed that they will receive a potent analgesic drug before giving the placebo (Amanzio and Benedetti 1999). The latter placebo analgesic effect (i.e. opioid conditioning) may be induced if an inactive placebo drug has been associated with the active drug (Amanzio and Benedetti 1999). Both of these placebo mechanisms appear to be highly opioid dependent since they may be abolished by the opioid antagonist naloxone (Amanzio and Benedetti 1999). The endogenous opioid response during placebo treatment involves higher order processing of external cues and internal demands (Price 1999b; Wall 1999). For example expectations involve analysis of the relative emotional relevance in an upcoming condition. In conditioning analgesia similar complex cognitive analysis may be crucial, although some mechanisms may be part of a lower hierarchy conditioning.

Given the fact that placebo needs a complex analysis of a specific situation we hypothesized that placebo analgesia would activate higher order cortical networks in study 4 (Petrovic et al. 2002b). Moreover, we proposed that the involved cortical networks in placebo analgesia would be similar to those activated by exogenous opioids corroborating the similarities between opioids and placebo analgesia previously observed at a behavioral level (Amanzio and Benedetti 1999; Levine et al. 1978; Price 1999b; Wall 1999). Especially we focused on the rostral ACC, given its involvement in pain modulation (Davis et al. 2000; Faymonville et al. 2000; Garcia-Larrea et al. 1997; Garcia-Larrea et al. 1999; Hardy 1985; Hardy and Haigler 1985; Peyron et al. 1995; Rainville et al. 1999; Willoch 2001) and opioid effects (Adler et al. 1997; Casey et al. 2000; Firestone et al. 1996; Wagner et al. 2001). The subjects were told that the placebo drug, i.e. saline injected intravenously, was a potent pain-reducing drug. Thus, an analgesia expectation had been induced. In some conditions the subjects also received the opioid (remifentanil injected intravenously). Since the subjects were not told when the treatment consisted of the opioid drug or the other analgesic drug (i.e. the placebo) and the opioid drug had an inherent potent analgesic effect also an opioid conditioning placebo effect was induced. Both opioid conditioning and expectancy placebo are highly reduced by naloxone (see above). We therefore expected that the cortical opioid system should be activated. Most subjects reduced their pain ratings during the placebo analgesia condition (figure 5D). Concomitantly, increased activity was observed in orbitofrontal regions (figure 3B) and the rostral ACC (figure 4C), partly corresponding to the same network as the activations in the opioid conditions. Thus, these findings indicate similarities in the neuronal processing between the opioid effect and the placebo

analgesia in several regions including the rostral ACC and the subregions of the obfc. Thereby this is the first study in which previously observed similarities between opioid- and placebo analgesia at a behavioral level are shown on a brain processing level.

5.4.5 Interaction between the cortical and the brainstem opioid network

The endogenous opioid system seems to, at least partly, be dependent on descending opioid modulatory mechanisms in the brainstem. Therefore, we hypothesized that more complex cognitive processes in the cortex that activate the endogenous opioid system, such as placebo analgesia, will induce a top-down control of the brainstem opioid network (figure 4E). In line with this hypothesis it has been suggested that ACC plays a key role in the cortical control of the brainstem during opioid analgesia (Vogt et al. 1993) via tracts projecting directly to the PAG (Hardy and Leichnetz 1981) or via the medial thalamic nucleus (Royce 1983). Furthermore it has been shown that stimulation of the ventromedial prefrontal cortex exerts its analgesic response through the PAG in rat (Hardy 1985; Hardy and Haigler 1985).

The rostral ACC showed increased co-variation with two regions in the brainstem during the opioid analgesia condition (figure 4F; study 4; Petrovic et al. 2002b). One of these regions included the PAG and the other was situated in the border between pons and the medulla. These co-variations were not observed during the pain condition containing no treatment, and the difference between the regressions in the two states was significant both in PAG and in the pons. Thus, the findings are in line with an ACC control of opioid modulating systems in the brainstem (Vogt et al. 1993). As discussed above, the functional relation between the cortex and the brainstem during opioid treatment should have an endogenous counterpart during complex cognitive processing such as placebo treatment. In line with this suggestion a similar co-variation was observed between the rACC and the same region in the pons / medulla also in the placebo analgesia condition (figure 4G). This effect was also significantly stronger than in the pain only condition. The pons and the medulla includes several nuclei involved in opioid processing such as the parabrachial nucleus and the rostral ventromedial medulla (RVM) (Fields and Basbaum 1999). Other nuclei such as the locus coeruleus and the A5 and A7 noradrenergic cell groups may also influence the RVM (Fields and Basbaum 1999; Willis and Westlund 1997). Moreover, this region was activated in the subtraction analysis of study 4 when the opioid conditions were compared with the control conditions, indicating an increased activity during opioid processing. It is noteworthy that the rACC also had a sub-significant co-variation with the PAG during placebo analgesia as in the opioid analgesia condition. Thus, also the regression results indicate similar networks and processing in the placebo analgesia condition as in the opioid analgesia condition.

In study 1 we showed that the brainstem is preferentially activated in the early phase of pain (Petrovic et al. 2002d; see also chapter 5.1). During the late phase of the painful stimulation we observed a pain specific positive co-variation between the pons and the rACC. In the light of the presented results this may also indicate a control mechanism upon the brainstem initiated by the rACC. Possibly, the subjects activate

cortical opioid regulatory systems (Price 1999a) in a prolonged painful event. This hypothesis could easily be tested by the use of naloxone.

5.4.6 rACC in attention and pain

Pain may be viewed as an irrelevant perception yielding contra-productive responses in certain conditions. Filtering out irrelevant sensory input and inhibiting further processing of such stimuli has been recognized as a fundamental attentional mechanism (Coull 1998). We propose that an opioid network in the cortex may modulate noxious processing in order to efficiently share attentional resources during specific situations. The supervisory attentional system (SAS) is a theoretical framework proposed by Shallice and Norman, which deals with how and in which situations higher order cognitive systems may control lower order processing in the brain (Stuss et al. 1995). It proposes that basic cognitive operations are carried out in units, and that these units are controlled by routine programs called schemata (Stuss et al. 1995). If a schemata is activated it will automatically inhibit other competing schemata. However, when there is a conflict between competing schematas without an obvious conflict resolution, or other situations in which the stronger schemata has to be overridden the SAS will interact (Stuss et al. 1995).

Noxious stimulation will automatically recruit lower order responses in the brainstem and activate cortical schemata involved in pain processing (see chapter 5.1). Also, a very intense inhibition will be executed on other processes in the brain. This is indicated during the perception of allodynia (study 6; Petrovic et al. 1999), when areas processing various auditory and visual stimuli decrease in activity although the peripheral input is the same. However, in certain circumstances other cognitive schemata can compete for the attentional space during pain processing. According to the SAS theory, schemata are controlled by specific supervisory systems (Stuss et al. 1995). For example they may be accentuated or inhibited according to the need of the organism. There are lesion studies suggesting that the ACC and frontal regions are involved in such control (Stuss et al. 1995). The ACC has been suggested to be a nexus in attentional modulations in the two most cited attentional theories, i.e. the Posner attentional model (Fernandez-Duque and Posner 2001; Posner 1994; Posner and Dehaene 1994; Posner and Rothbart 1998) and the Mesulam attentional model (Mesulam 1998; Mesulam 1981; Mesulam 1990; Mesulam 1999). Although both these models are based on spatial attention, a general mechanism may be proposed for the ACC. Posner suggests that the ACC (as a part of the anterior attentional system) is important in selection of targets from competing inputs. Similarly, Mesulam suggests that ACC is involved in motivational salience of a stimulus, which is important for the choice of response or processing. Thus, both hypotheses suggest that the ACC may be involved in selection of responses or cognitive processes. Several functional imaging experiments that have manipulated the attentional load support these hypotheses (see further Coull 1998). Modern theories of attention focus on the involvement of the ACC in monitoring task conflicts (see further chapter 5.7), which also may be incorporated in the present reasoning.

A recent meta-analysis of functional imaging studies indicate that the ACC may be divided in an emotional and a cognitive division (Bush et al. 2000), whereas functional imaging studies of pain indicate increased activity in a region posterior to the cognitive division in the ACC (Hsieh et al. 1995). However, the involvement of the ACC in stimulus induced pain modulation is anterior to the region that most often shows increased activity during pain (Willoch 2001). Also, cognitively induced pain modulation is expressed in this region (Figure 4D; Petrovic and Ingvar 2002). Actually, this region of the ACC seems to be the same portion that is involved in emotional paradigms, i.e. anterior to the cognitive division. Using two variants of the same attentional paradigm, one emotional (emotional counting Stroop) and one cognitive (counting Stroop), it has been shown that the ACC has a similar role both in cognitive attention and in the emotional attention (Bush et al. 2000). Whereas the cognitive attentional task activated the cognitive division of the ACC, the emotional attentional task activated the emotional division of the ACC. We suggest that the ACC has a similar role during pain modulation as during emotional and cognitive attentional tasks. In conclusion, the ACC may be divided into three regions based on the presented meta-analyses. The caudal ACC (figure 5A) is activated when pain is subtracted with a control condition. The mid-caudal ACC (figure 5B) is involved in various pure cognitive attention demanding tasks. Finally, the rostral ACC (figure 5C) is involved in emotional processing including cognitive tasks that depend on emotional / motivational signals. This area is also involved in pain modulation.

The proposed ACC involvement in the control of attentional resources in general would be in line with the modulation of pain related processes in more complex cognitive situations, such as the placebo response, using the opioid system. A further proposition derived from this view would be that pain related processes also might be augmented through the ACC. It is known that compounds such as CCK and nociceptine may facilitate pain processing (Fields and Basbaum 1999) and that there is a high concentration of CCK receptors in the ACC (Beinfeld et al. 1981; Kritzer et al. 1987). In summary, the modulatory effect that the ACC is exerting on pain perception may be a part of a general attentional system, which is involved both in augmenting and attenuating these processes using opioid and other neuro-modulatory systems.

5.4.7 Placebo responders and rACC

It has been shown that both placebo analgesia effects and opioid analgesia effects are highly variable between subjects (Price 1999a; Price 1999b). Interestingly, there is a correlation between how well a subject responds to opioids and how well the subject responds to placebo (Amanzio and Benedetti 1999). Thus, opioid analgesia responders tend also to be placebo analgesia responders. In the placebo study (study 4; Petrovic et al. 2002b) we compared the five subjects that we classified as placebo responders (five subjects that responded with more than 10 % pain intensity relief on the VAS) with the placebo non-responders (four subjects that responded with less than 10 % pain intensity relief on the VAS) (figure 5D). Although, no significant differences were observed

during the placebo condition between these two groups (perhaps because the low number of subjects in each group) the two groups activated the rACC differently during opioid treatment. The placebo responders had a pronounced activation in the rACC (figure 5E) while the non-responders did not activate this structure significantly when they were given opioids (figure 5F), and the difference between the two groups was significant. This indicates that placebo responders may have a more efficient opioid system in the ACC. It has been shown that opioid receptor binding potential is highly variable between subjects (Zubieta et al. 2001). A large variability has been observed in other modulatory systems, e.g. the dopamine system in which the receptor concentration correlates with some aspects of personality (i.e. detachment) (Breier et al. 1998; Farde et al. 1997; Laakso et al. 2000). In line with this we propose that opioid receptor concentration in the ACC may correlate with the degree of placebo analgesia. This hypothesis directly links the placebo response to the individual endogenous opioid system, and would explain why placebo responders also respond well to opioid analgesia.

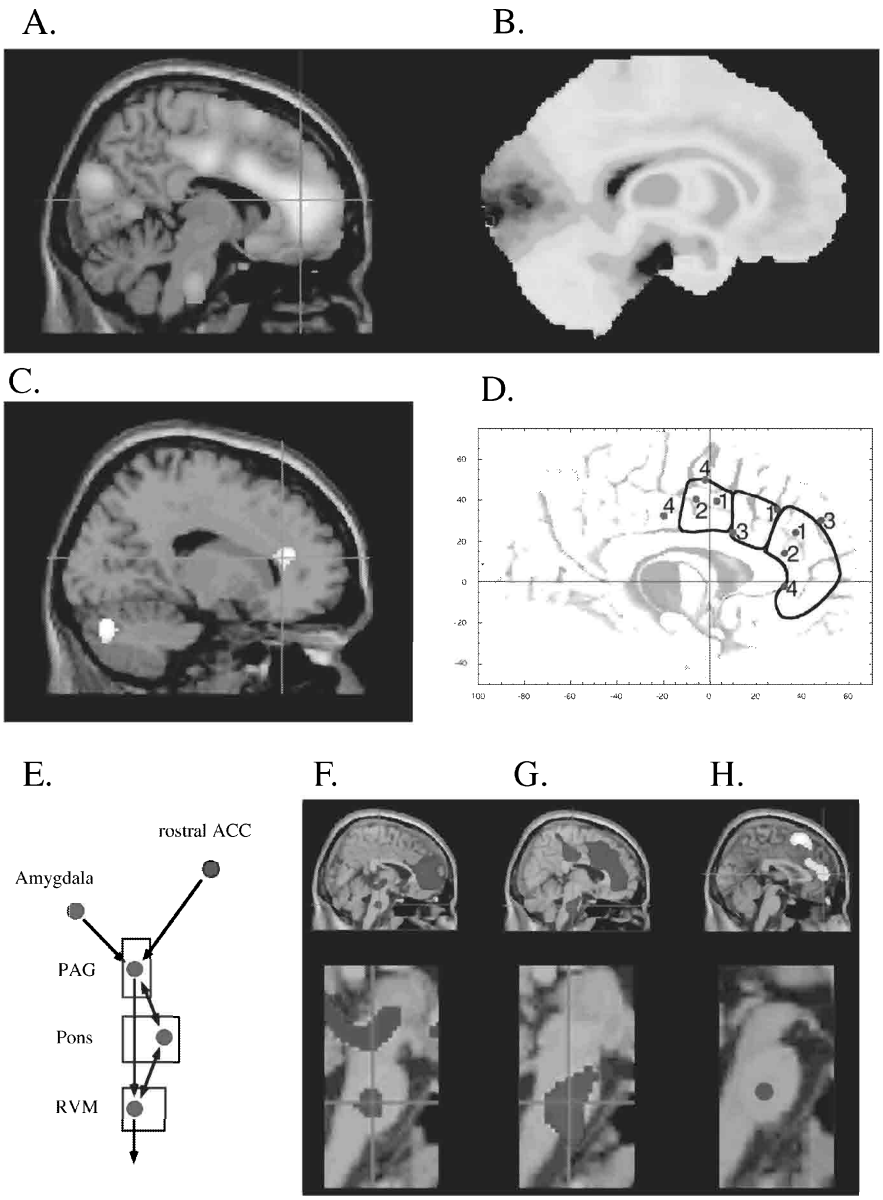


Figure 4. A short lasting opioid (remifentanil) increased the activity in the ACC, especially in the rostral ACC, and in the brainstem in study 4 (A). Also, a receptor imaging study using [11C]-Diprenorphine (Willoch et al. 1999) has previously shown high opiod receptor aviability (red) in the rACC (B). Placebo analgesia activated the rACC in study 4 (C). Cognitive modulation of pain has shown increased activity in the rACC (red dots) when the pain perception was altered but increased activity in the cACC (blue dots) during pain in general (D). The included studies are 1 = Rainville et al. 1999; 2 = Petrovic et al. 2002b; 3 = Petrovic et al. 2000; 4 = Bantick et al. 2002. A schematic drawing (E) of brainstem opioid system (including the PAG, the pons and the RVM) and the regions that are hypothesized to control this system (rACC and amygdala). In line with this the rACC co-varied with the brainstem during opioid analgesia (F) and placebo analgesia (G) in study 4. In study 1 similar regions in the pons co-varied pain specifically with the rACC during the second minute of stimulation.

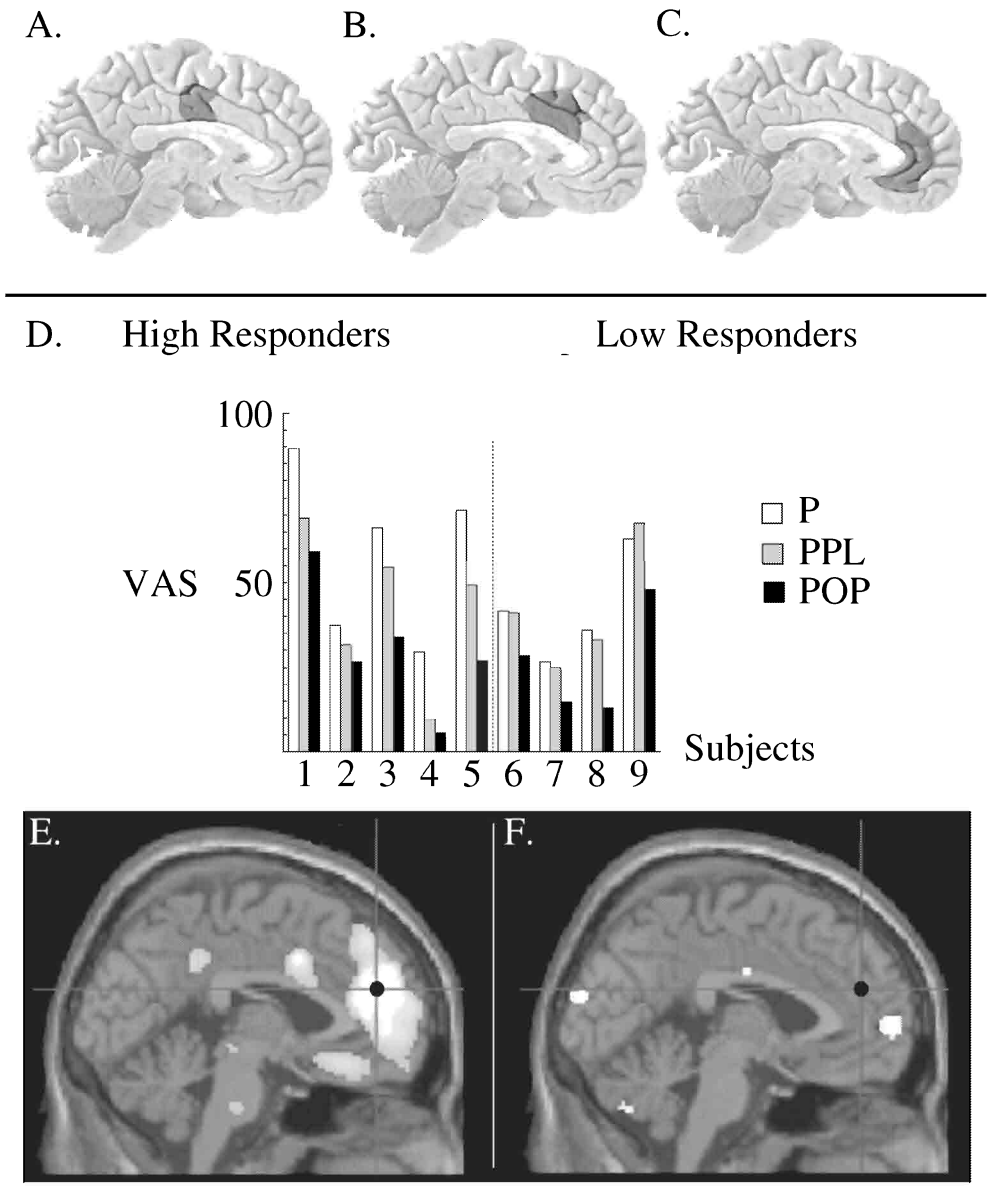


Figure 5. Pain has been shown to increase the activity in the caudal ACC (A). Pure attention demanding tasks activate the mid-caudal ACC (B). Emotions, cognitive tasks in the emotional domain and pain modulation activate the rostral ACC (C). In study 4 the subjects were classed as placebo responders or non-responders depending on how much the pain intensity (VAS) ratings decreased during placebo analgesia (D). P = Pain. PPL = Placebo analgesia. POP = Opioid analgesia. The placebo responders activated the rACC while the non-responders did not show any significant rACC activation when they were given opioid treatment.

5.5 Amygdala and pain processing

The amygdala is involved in processing a wide range of stimuli leading to negative emotions as well as in processing noxious input. Functional imaging studies have shown that fear-relevant material has been associated with an increased amygdala activity. In contrast, the amygdala displays decreased activity during noxious processing. In this chapter the paradoxical involvement of the amygdala during pain is discussed. It is hypothesized that its reduced activity mirrors a coping mechanism, and this suggestion is supported by a study showing that the deactivations are dependent on the context in which we tried to increase the need for effective coping.

5.5.1 Amygdala involvement in fear processing

The involvement of amygdala in emotional and cognitive processing has been widely discussed during the last decade (Aggleton 2000). Apart from more elaborated animal and primate studies, imaging studies have indicated new aspects of the amygdala function (Dolan 2000). Although the amygdala has been postulated to be involved in positive valanced functions and in the response to ambiguous situations of potential biological relevance (Davis and Whalen 2001), the main field has focused on its involvement in negative emotional processing (Aggleton 2000, Davis, 2001). For example, the amygdala is considered a central constituent in the evaluation of potential threats as well as in fear processing, including both fear conditioning and the control of behavioral, autonomic, and arousal responses during fear (Davis 1997a; Davis and Whalen 2001). Recently, these suggestions have been corroborated by functional imaging data indicating increased activity in the amygdala during the processing of fear relevant material (Dolan et al. 2001; Morris et al. 1996; Morris et al. 1999; Vuilleumier et al. 2001; Whalen et al. 1998) and fear conditioning (Buchel et al. 1998; Critchley et al. 2002; LaBar et al. 1998).

5.5.2 Amygdala anatomy

When discussing amygdala it is of importance to remember that this is a heterogeneous structure consisting of a large number of nuclei. Basically, the basolateral and the lateral nuclei receive information from association and frontal regions, while the central nucleus may be viewed as an output nucleus (Davis and Whalen 2001; LeDoux 2001). The basolateral amygdala is different both in histology and connectivity compared with the central nucleus (Davis and Whalen 2001). The central nucleus is often grouped together with structures outside the core of amygdala such as the bed nucleus of the stria terminalis (Davis and Whalen 2001). The output structures are very similar for the central nucleus of amygdala as for the bed nucleus of stria terminalis, indicating similar modulatory functions (Davis et al. 1997b).

5.5.3 Amygdala and processing of noxious input

Neurons responding to noxious input have been observed in the lateral (Romanski et al. 1993) and central nucleus (Bernard et al. 1996; Bernard et al. 1992) of the amygdala. The noxious input may reach amygdala via the parabrachial nucleus, the thalamus or via insula (Bernard et al. 1996; Shi and Davis 1999). These signals may contribute to several aspects of the amygdala function. First, pain is a potent unconditioned stimulus in fear conditioning (LeDoux 2001; Shi and Davis 1999). Second, amygdala is in a central position for regulating some of the autonomic and behavioral responses since it executes control over the PAG, the hypothalamus and other nuclei in the brainstem (Bohus et al. 1996; Davis 2000; LeDoux et al. 1988). Third, amygdala is involved in fear related analgesia (Fanselow 1984; Fanselow 1994; Helmstetter 1992; Helmstetter 1993; Helmstetter and Bellgowan 1994). The amygdala is probably involved also in more complex processing (Aggleton 2000; Davis and Whalen 2001) which is not discussed in this chapter, since the relation to pain is uncertain.

5.5.4 Fear conditioning

As stated above nociceptive stimuli are fundamental for many conditioning paradigms. In general, conditioning takes place when an aversive event, which induces a fear like response, is paired with a neutral event, which normally does not produce any such response (for further references in this section see LeDoux 2000; LeDoux 2001). The conditioned neutral event will now induce a similar fear response as the aversive stimulus itself. One of the most potent aversive events leading to conditioning is a noxious signal. In general, conditioning of simple stimuli is dependent upon an intact neural pathway from the peripheral receptor to the amygdala via the thalamus. For example, in auditory conditioning the pathway reaches the inferior colliculus via the acoustic nuclei in the brainstem, and then the pathway continues to the medial geniculate body of the thalamus from where direct pathways reach the amygdala. In contextual conditioning both the amygdala and the hippocampus are necessary, and in more complex conditioning there is an interaction with the cortex. Also, an intact pathway for the unconditioned aversive stimulus, such as the noxious input, is necessary (Shi and Davis 1999). The pairing of the aversive and neutral stimuli, i.e. the conditioning process, appears to occur in the lateral / basolateral nuclei while data indicate that the response is executed from the central nuclei of the amygdala (LeDoux 2001). Thus, the noxious input to the lateral nucleus has been suggested to be involved in the conditioning process (LeDoux 2001; Romanski et al. 1993). On a cellular level the conditioning mechanisms are NMDA-receptors dependent.

Several functional imaging studies have disclosed an increased activity in the amygdala during conditioning and extinction (Buchel et al. 1998; Critchley et al. 2002; LaBar et al. 1998). Consistently in these studies a habituation of the amygdala response has been observed in line with experimental animal studies (Quirk et al. 1997).

When a simple or complex stimulus is conditioned fear specific responses will be induced by the central nucleus of the amygdala via different nuclei in the brainstem and the hypothalamus (Davis 2000; LeDoux 2000; LeDoux 2001). These responses are similar with the unconditioned responses (se below).

5.5.5 Regulation of fear responses

The amygdala may be seen as a nexus from which many different emotional responses originating from several anatomically separated areas are orchestrated (Bohus et al. 1996; Davis 2000; Davis et al. 1997a). These responses seem to be induced by the central nucleus of the amygdala, and include responses both to conditioned and unconditioned stimuli during fear and anxiety (Davis 2000; Davis et al. 1997a). However, some data implicate that the related bed nucleus of stria terminalis is more involved in anxiety (Davis and Shi 1999; Davis et al. 1997b; Lang et al. 2000). Fanselow postulated a hypothesis that the amygdala may induce specifically the postencounter phase, which includes passive behavioral responses and opioid analgesia elicited via the ventrolateral PAG (Fanselow 1994; see chapter 5.1). However, Davis argues that both passive and active responses may be induced by the amygdala (Davis 2000). In any circumstance, it is a consensus that amygdala may modulate the activity in other regions. For example, the central nucleus may alter autonomic, endocrine and behavioral responses through regulation of the brainstem and the hypothalamus (Bohus et al. 1996; Davis 1997a; Davis 2000; LeDoux 2000; LeDoux 2001; LeDoux et al. 1988). Amygdala may also modulate cholinergic and noradrenergic systems that induce arousal in the cortex such as the RAS and the basal forebrain (Kapp et al. 1992), and memory processing systems (Cahill 2000). The bodily responses may in turn influence cortical areas via feedback either from proprioceptive or visceral signals or hormones (Damasio 1994; LeDoux 2001; McGaugh et al. 1995).

Similarly, the amygdala may be involved in activating or modulating behavioral, autonomic, arousal responses during pain. A holistic approach would suggest that this response is a fear-pain response or a fear response that is induced by pain. Possibly, this modulation is more complex than the fast automatic initial circa strike response, which seems to only be dependent upon the brainstem (Fanselow 1994).

5.5.6 Stress and fear related analgesia

The involvement of amygdala in stress and fear related analgesia has been extensively studied in animals and analgesia in similar conditions has been described in humans (Fanselow 1994; Price 1999a). This form of amygdala dependent analgesia has been described in relation to conditioning (Fanselow and Helmstetter 1988; Helmstetter 1992) but also in relation to unconditioned aversive stimuli (figure 4E; Bellgowan and Helmstetter 1996; Fox and Sorenson 1994; Helmstetter and Bellgowan 1994). These studies indicate that stress induced analgesia is opioid dependent and relies not only on the amygdala but also on opioid dependent processing in the ventrolateral PAG and the

rostral ventromedial medulla (Foo and Helmstetter 1999; Foo and Helmstetter 2000; Helmstetter et al. 1995; Helmstetter and Tershner 1994; Pavlovic et al. 1996; Tershner and Helmstetter 2000). Benzodiazepines seem to have an anti-opioid effect in stress induces analgesia (Fanselow and Helmstetter 1988; Willer and Ernst 1986) (Helmstetter 1993).

5.5.7 Paradoxical activity decreases in amygdala during pain

If the amygdala produces conditioned and unconditioned fear responses in general, a similar involvement is expected in the unconditioned (fear) response during pain. However, the majority of pain-imaging studies have disclosed a decreased activity in the amygdala during pain in contrast to the increased activity observed during conditioned and unconditioned fear (Becerra et al. 1999; Becerra et al. 2001; Derbyshire et al. 1997; Petrovic et al. 1999; Petrovic et al. 2002c). We have observed decreased amygdala activity both in experimental pain (figure 6A; study 1; Petrovic et al. 2002d) and allodynia (figure 6B; study 6; Petrovic et al. 1999). How should these paradoxical findings be interpreted?

Although pain and fear are closely linked to each other and to the amygdala, the two entities may rely on different processes. It has been proposed that the amygdala may receive noxious information from the insula, the thalamus and the parabrachial nucleus (Bernard et al. 1996; Shi and Davis 1999). Different classes of neurons in the amygdala respond in a complex way to the nociceptive signals including both increased as well as decreased neural firing (Bernard et al. 1992), and it can not be excluded that the negative effects on neural activity dominate. It is therefore possible that a more negative rCBF-response in the amygdala represents an increased processing of nociceptive signals deriving from the noxious input sources. Thus, the decreased activity in amygdala during pain (Becerra et al. 1999; Becerra et al. 2001; Derbyshire et al. 1997; Petrovic et al. 1999) may represent the normal response pattern during noxious stimulation. Below, we show indications from our data set that this is probably not the case.

Another hypothesis states that the observed deactivations in amygdala may represent a physiological habituation response observed both in functional imaging of conditioning (Buchel et al. 1998; LaBar et al. 1998; Whalen et al. 1998) and in animal studies (Quirk et al. 1997). Since the amygdala response in activity habituates very rapidly during conditioning the observed suppressed activity during pain may predominantly represent the later phases of the amygdala involvement. However, the habituation effect hypothesis has to provide plausible suggestion as to why this habituation is present.

A third hypothesis has stated that the amygdala may respond with a decreased activity when a mild experimental painful stimulus is perceived as less negative than anticipated (Davis and Whalen 2001). However, this suggestion appears inconsistent with the finding of robust amygdala deactivations during tactile allodynia (figure 6B; study 6; Petrovic et al. 1999). This acute neuropathic pain, which is experienced daily by the patients, is rated as extremely intense.

Finally, we hypothesized that since amygdala is a nexus for induction of fear-like responses, fear induced arousal and possibly also a component of the production of fear perception, a cognitive regulation of its activity would efficiently attenuate most of these responses (figure 6C; study 5 and study 6; Petrovic et al. 2002a; Petrovic et al. 1999). Such a regulation may be indicated by the decreased amygdala activity. This would also be a plausible explanation for the habituation response in functional imaging studies of fear processing, i.e. the observed attenuation over time may depend on the development of coping mechanisms.

5.5.8 Cognitive modulation of amygdala

Data from widely different fields of research are in line with the general hypothesis that the amygdala activity may be regulated and suppressed depending on the context and cognitive coping mechanisms.

First, functional imaging studies on pain anticipation have suggested that limbic deactivations in general may depend on cognitive coping processes in aversive situations (Hsieh et al. 1999; Simpson et al. 2001). A deactivation of the medial orbitofrontal cortex and the subgenual ACC was observed during anticipatory anxiety (Simpson et al. 2001). This deactivation correlated inversely with anticipatory ratings such that subjects that experienced low anxiety also expressed the largest decreases. It has also been shown that subjects that know what to expect decrease the activity in the medial orbitofrontal cortex and the ACC during anticipation of pain, while subjects that never have encountered the noxious stimulation previously, increased their activity in similar regions during the anticipation phase (Hsieh et al. 1999). Thus, both studies suggest that the coping efficiently in these anticipatory situations may involve a down-regulation of limbic regions.

Secondly, the amygdala and the related bed nucleus of stria terminalis are key structures for the action of anxiolytic agents during stressful situations (Davis 2000; File 2000; Heilig et al. 1994). Correspondingly, it has been shown that the amygdala is involved in behavioral and endocrine adaptation to normally stressful events (Thorsell et al. 1999).

Third, both behavioral and imaging studies have suggested that the amygdala may specifically be regulated by cognitive coping strategies. More specifically, a behavioral study has indicated that the emotional potentiation of the startle reflex, which is amygdala dependent (Davis 1992; Davis 1997a), may be voluntary suppressed (Jackson et al. 2000). A recent study has shown that while sexual arousal induces amygdala activity, the voluntary suppression of sexual arousal diminishes this activation (Beauregard et al. 2001). Thus, cognitive mechanisms may also regulate the amygdala output in order to suppress an emotional or a stress response during a normally fear evoking context as well as during the suppression of sexual functions.

5.5.9 Cognitive modulation of amygdala during pain

In line with these studies it is reasonable to suggest that a regulation of amygdala activity would potentially also influence the experience of different fearful and anxious states during a painful event. This hypothesis is directly supported by behavioral studies showing that subjects that encounter a painful stimulation frequently report cognitive coping strategies, which may alter perception and autonomic responses (Thompson 1981). It has also been shown that the duration a subject can tolerate a painful stimulation correlates with the coping efficiency (Weisenberg et al. 1996). In order to probe whether cognitive coping would influence limbic and amygdala activity the reversed strategy was used, i.e. the expected duration of pain stimulation was externally manipulated increasing the need for a more effective coping during the longer noxious stimulations (study 5; Petrovic et al. 2002a).

Specifically, in this PET study the subjects were informed prior to the start of each scanning that the noxious stimulation (standard cold pressor test) would last for either 1 minute or for 2 minutes. To ensure that a similar noxious stimulation was delivered during the scanning period the brain activity was always measured during the first minute of stimulation. In order to induce the development of cognitive coping mechanisms the subjects had experienced the stimulations in a pre-training session. As a control condition we used non-painful cold stimulation. We hypothesized that the longer painful stimulation would be perceived as being more aversive compared with the shorter stimulation during the anticipation phase, i.e after the information about the upcoming stimulation was given but before the stimulation started. We also hypothesized that in response to this anticipation a more intense coping strategy would be adapted in the longer painful context.

In line with our hypothesis we showed that the amygdala was significantly more deactivated during the longer pain context in which a majority of the subjects also indicated a more intense coping. This finding was corroborated by different autonomic responses, in which the heart rate showed a relative increase during the longer pain context.

A key factor in effective coping is cognitive appraisal that may be viewed as evaluating a given context in order to choose the most efficient strategy to handle the situation (Folkman and Lazarus 1988; Hsieh et al. 1999). We suggest that the cognitive appraisal and the choice of strategy take place during the anticipation phase and include a down-regulation of the responsiveness of the amygdala in the condition that is interpreted as potentially more threatening. The net-effect would then be an altered processing of pain in the different contexts. This interpretation is also a plausible suggestion for the showed habituation of amygdala activity in imaging studies of fear relevant material discussed above (Buchel et al. 1998; LaBar et al. 1998; Whalen et al. 1998).

We also suggest that if the amygdala activity is suppressed also its potential of modulating of the brainstem is decreased. When the amygdala influence is attenuated the brainstem may work independently of higher order structures, since this network has an intrinsic mechanism for processing noxious input (see chapter 5.1). Therefore, we suggest

that the relatively increased heart rate during the longer 2-minute context mirrors the intrinsic brainstem processing of the noxious input (study 5; Petrovic et al. 2002a). Regression data are in favor of this hypothesis, since the left amygdala co-varies less with the brainstem during the more intense coping context.

A relative decrease of activity was also observed in the contralateral mid-insula in the long context as compared to the short context of painful stimulation (study 5; Petrovic et al. 2002a). The contralateral insula is one of the main structures processing pain and may be an important relay for noxious input from the somatosensory cortex to the amygdala (Shi and Davis 1999). Although no differential activity was observed in the somatosensory areas between the two pain contexts, as in the amygdala, there was a difference in the regression analysis indicating a changed relationship between the two structures. A region in the contralateral S1, where the somatotopic hand-region is expected to be found, and that was activated during the main effect of pain, co-varied more with the right amygdala during the one-minute context pain than with the two-minute context pain (study 5; Petrovic et al. 2002a). The changed co-variation pattern indicates that the noxious input from the S1 may be attenuated when the amygdala activity is suppressed. Since these signals are relayed in the insula (Shi and Davis 1999), this may be the cut-off site for the information flow. Thus, the finding of the relative decreased activity in the insula during the long pain context suggests the possibility of an attenuated processing of pain perception per se and an inhibition of noxious input to the amygdala directly from the insula and indirectly from the S1 (relayed through the insula).

As discussed previously cognitive attentional processes may be divided between sites and sources (see chapter 5.3 and 5.4). If the amygdala is viewed as a site, which is modualted as a coping strategy during pain, there should be networks involved in modulating the amygdala. No obvious source of modulation was observed in the subtraction analysis. One of the most probable sites, the lateral orbitofrontal cortex, even decreased in activity in the longer pain context. The lateral orbitofrontal cortex also showed a differential co-variation with the right amygdala during the two contexts. The right amygdala co-varied more positively with the lateral orbitofrontal cortex bilaterally during the short context as compared with the longer context. The lateral orbitofrontal cortex has been implicated both in the generation of negative emotional states (Baker et al. 1997) and in cognitive modulation of pain related processing (Petrovic et al. 2000; Petrovic et al. 2002b; Rainville et al. 1999). The relative deactivation during the longer context may be viewed as a part of the attenuated activity of limbic areas in general, possibly modulating the affective state. A regression analysis showed that the amygdala shifted from a more positive relation with the orbitofrontal cortex during the short pain context to a more negative relation during the longer pain context. Possibly, this could be interpreted as a minor need for amygdala modulation from the obfc during the second minute when the amygdala activity already is suppressed.

As stated previously, it cannot be excluded that the decreased activity in amygdala during pain represents the normal response pattern during noxious stimulation due to a complex response of the amygdala to nociceptive stimuli (Bernard et al. 1992). Thus, it is possible that a negative rCBF-response in amygdala / anterior MTL represents

an increased processing of nociceptive signals deriving from the noxious input sources. However, it should be noted that also other regions known to be involved in pain processing, for example the insula decreased its activity in the two-minute context, which does not support the suggestion that the relative deactivation in amygdala / anterior MTL mirrors a general increase of pain processing.

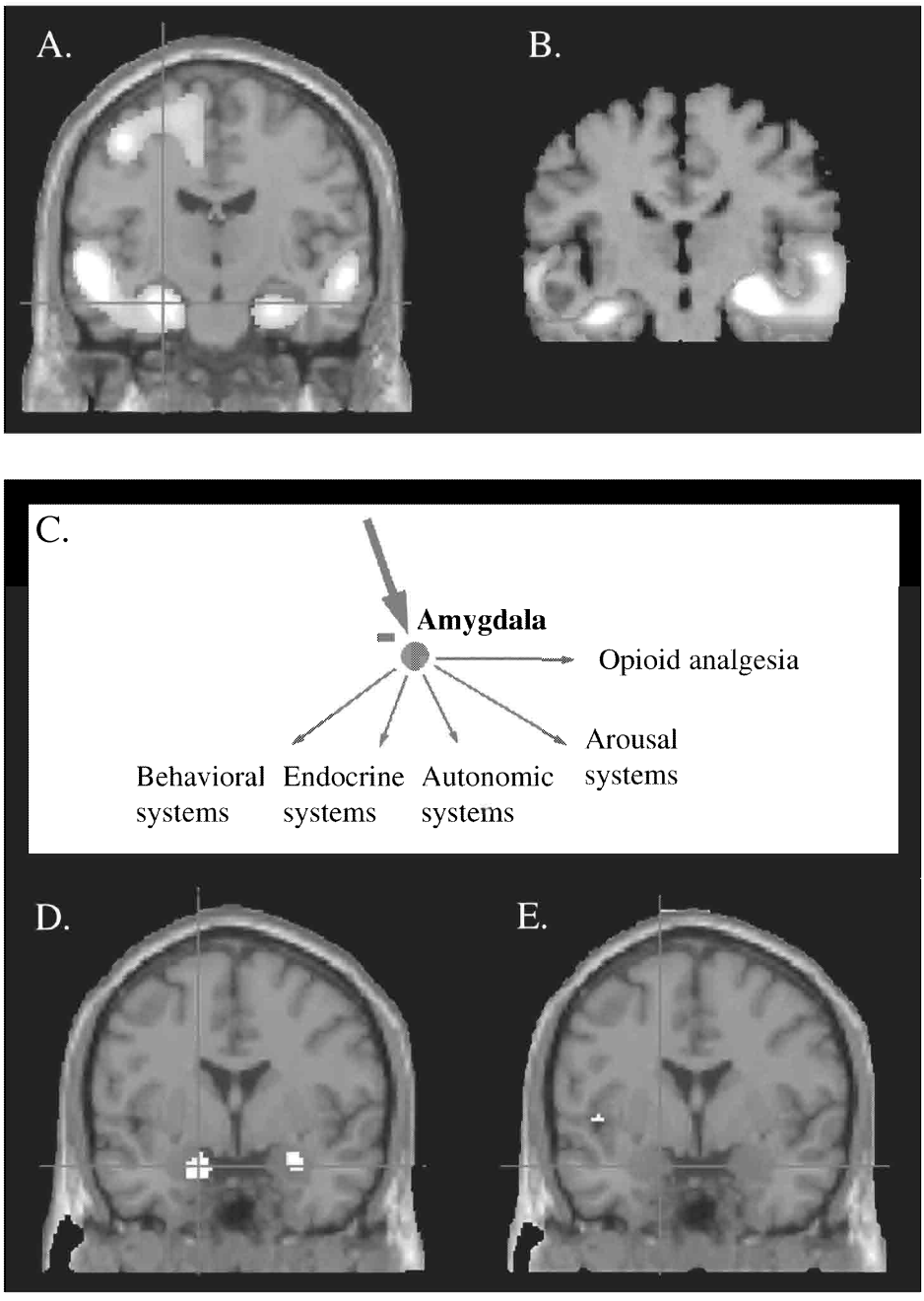


Figure 6. Decreased activity in the amygdala was observed in study 1 (A; experimental pain) and study 6 (B; allodynia). If the amygdala activity is suppressed a wide range of output systems may be controlled (C). When subjects expected a longer painful stimulation in study 5, the activity was decreased in the amygdala (D), while no amygdala decreases were observed when the same subjects expected a shorter painful stimulation (E) although the stimulus was exactly the same during the scanning phase.

5.6 Chronic pain and cognitive processing

In this chapter we show that some of the suggested mechanisms associated with cognitive modulation of experimental pain, such as the involvement of the lateral orbitofrontal cortex in pain regulation and amygdala activity suppression, are also found in chronic pain syndromes. We speculate that these changes of neuronal activity mirror cognitive coping strategies.

5.6.1 The involvement of the lateral orbitofrontal cortex in chronic pain and depression

Several studies have indicated that some chronic pain patients have an overrepresentation of clinical depressions (Dworkin and Gitlin 1991; Fishbain et al. 1997). Meta-analysis and theoretical data suggest that depression is a consequence of chronic pain, and not vice versa (Blackburn-Munro and Blackburn-Munro 2001; Dworkin and Gitlin 1991). It has also been shown that depression scores and catastrophizing thoughts correlate with the experience of heightened pain and emotional distress during experimental pain (Sullivan et al. 2001). Thus, there seems to be a reciprocal relation between pain and depression. Clinical material shows that patients with chronic pain may be categorized into dysfunctional patients who report that their pain affects a broad range of functioning and adaptive copers who deny significant negative affects of pain (Turk and Rudy 1988). Moreover, beliefs and coping strategies are associated with various measures of pain intensity in chronic pain patients, and changes in beliefs and coping strategies are associated with changes in pain intensity measures after cognitive-behavioral treatment (see further Turner et al. 2000). These behavioral studies indicate that there is a clear relation between depression and chronic pain, both in association between the two disorders and in cognitive treatment. In line with this reasoning it is interesting that some anti-depressives are associated with pain relief in chronic pain patients in general (Onghena and Van Houdenhove 1992) and neuropathic pain specifically (McQuay et al. 1996).

Functional imaging studies also show striking similarities between depression and chronic pain. The ACC is an important component in both pathological states and is therefore a candidate for such interactions. Another similarity is that both depression (Drevets 2000a; Drevets 2000b) and chronic pain (figure 3D; Hsieh et al. 1995; Hsieh et al. 1996; Peyron et al. 1998; Rosen et al. 1994; Willoch et al. 2000) often have increased activity in the lateral obfc. Hsieh et al found bilateral activation of BA 47 / 10 in the lateral obfc in patients with ongoing neuropathic pain (Hsieh et al. 1995) and cluster headache (Hsieh et al. 1996). Similarly, activation of the lateral orbitofrontal cortex was observed by Rosen et al in a group of patients with angina pectoris (Rosen et al. 1994), by Peyron et al in patients with central post stroke pain (Peyron et al. 1998) and by Willoch et al during hypnotic suggestion induced phantom limb pain (Willoch et al. 2000). Thus, the reviewed imaging studies of chronic pain show activation of the lateral orbitofrontal cortex, an activation that is rarely seen in imaging studies of experimental pain (see also Petrovic et al. 2000). Possibly, the neural circuits that are involved in

processing some emotional aspects of pain, are involved also in producing depression. Since it has been indicated that the obfc may be involved in regulating and modulating emotional networks that produce the depressed mood in depression (Drevets 2000a; Drevets 2000b), such a putative role may also be relevant in chronic pain. Experimental work on placebo analgesia and cognitive interaction with pain in experimental pain studies indicate that the orbitofrontal activity may be involved in regulation of pain processing (Petrovic et al. 2000; Petrovic et al. 2002b; Rainville et al. 1999), and not mirror the depression induced by pain.

Such findings were not observed in the allodynia study (study 4; Petrovic et al. 1999). However, two of the subjects experienced also spontaneous ongoing pain, and since an increase in the obfc activity has been described for these patients the variability of the patient material may have precluded such data. However, increased activity in these regions has been described in central post stroke pain (Peyron et al. 1998) which also is an acute neuropathic pain.

5.6.2 Decreased activity in amygdala during dynamic mechanical allodynia

The allodynia study showed robust decreases of activity bilaterally in the anterior medial temporal lobe including the amygdala (figure 6B; study 4; Petrovic et al. 1999). Touch evoked allodynia evokes a very intense and emotional pain (Hansson and Kinnman 1996). However, it may be experienced many hundred times each day. Thus, the patients know very well what to expect and have therefore the chance to develop cognitive strategies in order to cope with the painful event. Cognitive coping strategies in general may include a down regulation of the distress output (Thompson 1981). This would be in line with observed down regulation of limbic regions during anticipatory anxiety (Hsieh et al. 1999; Simpson et al. 2001), and decreased amygdala activity when the expected aversiveness for a painful event was enhanced (study 5). Thus, one interpretation is that the amygdala deactivation during allodynia indicates a coping mechanism with the acute neuropathic pain.

5.6.3 Other regions showing reduced activity during chronic pain

In general, deactivations during chronic pain have often been shown in the thalamus (Di Piero et al. 1991; Hsieh et al. 1995; Iadarola et al. 1995). It has been suggested that this may represent a mechanism in order to attenuate or filter out upcoming noxious stimuli, possibly with a GABA-receptor action upon the spinothalamic input. One of these studies represented ongoing neuropathic pain (Hsieh et al. 1995). However, in the study of dynamic mechanical allodynia (study 6; Petrovic et al. 1999) activity was increased in the thalamus. A possible filtering mechanism may be present tonically in the thalamus, but allodynia differs from these pain states since it represents acute noxious input.

Also, regions normally involved in processing visual and auditory stimuli showed a decreased activity in the allodynia study (study 6; Petrovic et al. 1999). Dynamic mechanical allodynia is an intense emotional experience that is hard to be distracted from

(Hansson and Kinnman 1996). According to the attentional theory of Shallice (Burgess and Shallice 1996) (se chapter 5.4). Allodynia represents a strong schemata that would automatically inhibit other schemata. The decreased activity in other perceptual modalities may be viewed as such inhibitions. Thus, these findings indicate that processing of irrelevant stimuli is automatically suppressed during an intense painful experience, such as dynamic mechanical allodynia.

Interestingly, there are some paradoxical observations indicating a cognitive control in allodynic patients, which involves decreased pain ratings. For example, many patients with allodynia rate the percept less bothersome when they induce it themselves (Hansson and Kinnman 1996). This may be in line with of the specific cognitive process of canceling out self-induced sensations (Blakemore et al. 1998a; Blakemore et al. 1998b), but may also indicate a higher degree of pain modulation described in previous chapters. In a PET study both the suppressed allodynia induced activity and the modulatory activity may be studied.

5.7 Conclusion

In the present review we have shown data indicating that areas involved in processing pain are prone to cognitive modulations. We have also suggested that the lateral orbitofrontal cortex and the rostral ACC may be involved in controlling the activity in those areas. In this chapter we try to integrate the functions of these areas and propose a modulatory network based on the enteroceptive signals and the internal milieu.

5.7.1 Rostral ACC and the lateral orbitofrontal cortex in pain modulation

The reviewed studies in the previous chapters indicate that regions belonging to the pain matrix may be altered when cognition interacts with the perception of pain. This has been shown for somatosensory areas (Petrovic et al. 2000), the ACC (Bantick et al. 2002; Rainville et al. 1999), the PAG (Petrovic et al. 2000) and the insula. Similarly, the amygdala and the insula activity were altered during a noxious stimulation when the expectation of pain was changed but the input remained the same (Petrovic et al. 2002a). It is well known that these regions may be involved in the perception of pain. Thus, the activity in the sites involved with processing the perception of pain may be modulated in analogy with the changed perception of pain.

In contrast to only pain perception the lateral orbitofontal cortex and the rostral ACC are activated during cognitive modulation of pain processing. This is in line with the proposal that the lateral orbitofrontal cortex and the rostral ACC are involved in suppressing motivation-dependant behavior and emotional processing during pain. However, what are the differences between the functions of these two regions? Moreover, how should these processes be incorporated into an integrated function of a modulatory network?

There is a large amount of reciprocal connections between the rostral ACC and the orbitofrontal cortex (Carmichael and Price 1995a; Vogt and Pandya 1987). Thus, it is unlikely that these two regions work separately. However, it has to be recognized that the functions of regions belonging to a network are in general neither completely segregated nor completely integrated (Mesulam 1998; Mesulam 1990). Therefore, it may be proposed that although both structures have unique processing capacities, there is some overlap between functions of the rostral ACC and the lateral orbitofrontal cortex. Thus, both structures may be involved in modulating distant activity during pain but may have different specific roles.

5.7.2 The mid-caudal ACC and the dorsolateral prefrontal cortex in pure cognitive functions

Similar to the putative interaction between the lateral orbitofrontal cortex and the rostral ACC, questions have been raised for pure cognitive, i.e. non-emotional, frontal functions that activate both the mid-caudal ACC and the dorsolateral prefrontal cortex (Duncan and Owen 2000). In this meta-analysis it was shown that a wide range of pure cognitive tasks such as response selection, executive control, working memory, episodic memory and problem solving recruited both the mid-dorsal prefrontal cortex and the mid-caudal ACC. However, several lines of studies suggest some specific roles for the two regions.

Fuster has suggested that there are several mechanisms related to the lateral prefrontal cortex, which are fundamental for performing new and complex goal-directed tasks (Fuster 1997; Fuster 2001). He emphasizes that the lateral prefrontal cortex is involved in cross-temporal contingencies, which may be conceptualized as holding both sensory / perceptual processing as well as plans of action on line. These ideas are based on animal studies showing neuron specific ability to signal in the delay period of tasks that depend on previous information (Fuster 1997; Fuster 2001). This would then be the fundament for both working memory as well as for goal-directed behavior, which are both impaired after prefrontal lesions (Fuster 1997; Fuster 2001). Miller also underlines the prefrontal cortex ability to enhance and suppress distant neural activity such that relevant material may be attended while task irrelevant material may be disregarded (Miller 2000; Miller and Cohen 2001).

The mid-caudal ACC is associated to situations in which there is a conflict of competing alternative responses and a response selection has to be made in the cognitive domain (Bush et al. 2000; Carter et al. 1999; Mesulam 1999; Paus 2001; Posner 1994; Posner and Rothbart 1998). It is a matter of debate whether the ACC only detects conflicts or whether it also is involved in conflict resolution (Paus 2001). Recent theories based on functional imaging studies suggest that the ACC is specifically involved in monitoring possible conflicts (Botvinick et al. 1999; Carter et al. 2000), while the lateral prefrontal cortex may be involved in increasing or inhibiting neural activity within distinct brain-areas (Bush et al. 2000). However, this hypothesis fails to account for the anticipatory nature of the ACC (Bush et al. 2000).

A core idea in the Fuster model of cognitive processing is that there are parallel hierarchies of perception and action, i.e. the perception-action cycle (Fuster 1997; Fuster 2001). According to this model all adaptive behavior is based on a circular processing between the organism and the environment, in which sensory information leads to motor actions that produce changes in the environment which in turn changes the sensory input. Complex or new behaviors depend on the highest hierarchies, i.e. the prefrontal cortex, while lower levels process automatic and over-learned responses. Importantly, Fuster recognizes that there must be a motivational aspect driving the cycle, which partly is based in the orbitofrontal cortex.

5.7.3 Entereoceptive information and emotional / motivational processing

Nociceptive information, as well as temperature and other sensations, has been suggested to signal the physiological status of the body tissue, i.e. the enteroceptive representation of the body (Cechetto and Saper 1990; Craig et al. 2000; Craig and Dostrovsky 1999). Although, most regions in the pain network receive nociceptive information, the ACC and the insula mostly receive lamina 1 input. Similarly, the insula receives lamina 1 thermosensory information, and the insula and the orbitofrontal cortex correlate with the subjective ratings of thermal intensity (Craig et al. 2000). Thus, the lamina 1 input seems to be used for mapping the enteroceptive state of the body (Craig et al. 2000). Also, several imaging studies indicate that these regions, including the insula, the ACC and the obfc, are involved in monitoring the autonomic status of the body (Critchley et al. 2000a; Critchley et al. 2000b; Critchley et al. 2001a; Critchley et al. 2001b; Critchley et al. 2001c; Critchley et al. 2002). The enteroceptive representation of the body has also been called the internal milieu or the internal state of the body when discussing processes in large-scale neurocognitive networks (Mesulam 1998). The internal state of the body is suggested to be a fundament for motivational and emotional processing (Mesulam 1998). However, the bodily states may also be important for direct cognitive computations. This suggestion is in line with the somatic marker hypothesis by Damasio in which the internal state is used as a bias signal in cognitive tasks used for a response selection, and which is dependent on an intact ventromedial prefrontal cortex / orbitofrontal system (Damasio 1994; Damasio 1999).

5.7.4 Two parallel cognitive systems

Based on the presented data we propose that there is a system for prefrontal processing of emotional and motivational signals, which is parallel to processing pure cognitive tasks, consisting of the orbitofronatal cortex and the rostral ACC (vs. the lateral prefrontal cortex and the mid-caudal ACC in the cognitive domain). In much we suggest that these two systems are alike. The main difference is that the processes in the orbitofrontal cortex and rostral ACC, are based on the internal state of the organism as opposed to the external world.

The orbitofrontal cortex is involved in representing the relative motivational value (Tremblay and Schultz 1999; Tremblay and Schultz 2000) for both primary and secondary reinforcers (Rolls 2000; Thorpe et al. 1983). This information is highly correlated with behavior leading to a motivational goal and it may therefore be proposed that it is used for goal-directed behavior (Schoenbaum and Setlow 2001; Tremblay and Schultz 1999; Tremblay and Schultz 2000). Similarly as in the lateral prefrontal cortex, delay-selective neuronal activity has been reported in the orbitofrontal cortex (Schoenbaum and Setlow 2001). However, while the delay-selective activity in the lateral prefrontal predominantly represents features such as identity, spatial location or color, delay-selective activity in the orbitofrontal cortex represents the incentive value or significance of the cues during the delays (Hikosaka and Watanabe 2000; Schoenbaum

and Setlow 2001). Functional imaging studies are in line with these proposals (see further Elliott et al. 2000a).

The ACC may also be divided into a cognitive, i.e. the mid-caudal ACC, and an emotional / motivational section, i.e. the rostral ACC (figure 5B, C; Bush et al. 2000). Although the rostral ACC is involved in strict motivational / emotional processing it is also involved in similar cognitive processing as the cognitive ACC but associated with motivational / emotional factors (Bush et al. 2000; Elliott et al. 2000b; Elliott et al. 2000c).

5.7.5 The hierarchical cognitive network based on emotional and motivational processing

The emotional / motivational network is also a hierarchical system (figure 7A) much alike the perception action cycle (figure 7B) describe by Fuster (Fuster 1997). However, its sensory information is based on the internal state of the organism. Recent reviews indicate that the orbitofrontal cortex is hierarchical organized with the complex information being processed more rostrally (Kringelbach 2002). Based on cyto-architectual maps on primates and humans (Carmichael and Price 1995a; Carmichael and Price 1996; Ongur and Price 2000) a hierarchical organization of the orbitofrontal cortex has been suggested (Kringelbach 2002). A similar division may be attributed the ACC / vmPFC (Paus 2001).

The pure cognitive and the emotional / motivational network must cooperate in many situations, e.g. a high incentive value must induce more effective pure cognitive working memory processes. In fact, we propose that the emotional / motivational network is fundamental for the pure cognitive perception action cycle at every hierarchical level. External input leading to visual, somatic or auditory perception will not automatically activate responses. A motivational drive is needed at every stage and we propose that it is mediated via the emotional / motivational network at the same stage of processing.

If one accepts that the pure cognitive and the emotional / motivational networks are much alike, hypothesis may be generated about one system from knowledge of the other. As discussed above a debated issue focuses on whether the ACC is involved only in detecting / monitoring conflicting processes or if it is also actively involved in conflict resolution (Paus 2001). The high concentration of opioid and CCK receptors in the ACC and the increased activity in the ACC during opioid treatment indicates an active role in conflict resolution when pain is one of the processes competing for attentional / processing space. In fact nociceptive processing may be viewed as one of the processes, which had to be controlled for at an early evolutionary stage. Thus, other conflict resolutions and response selections may have evolved from this control.

There are also lower stages in the emotional / motivational hierarchy. The insula has been proposed as a key structure representing the internal state of the organism including body temperature, damage (i.e. nociception) and gustatory information (Cechetto and Saper 1990; Craig et al. 2000; Craig and Dostrovsky 1999). Few studies have attributed its involvement in the highest cognitive computations. However, it is

highly involved in interaction with both the ACC and the orbitofrontal cortex, possibly representing a form of secondary sensory association area for signals of the internal state. Further below in the hierarchy, structures as the amygdala, the hypothalamus, the medial thalamus and related structures may be found. These have both input (sensory) and output regions, and are involved in more automatic emotional / motivational processes directly affected by the homeostatic and allostatic load (Panksepp 1998). Lowest in the hierarchy are the brainstem sensory and output nuclei. However, complex (although automatic) behavioral and autonomic responses may be elicited here, and there is a possibility that also these structures are highly involved in emotional perception. Moreover, the brainstem has great potential of affecting processes in the rest of the brain (Parvizi and Damasio 2001). The prime difference is that the brainstem will operate more automatically, if no control is elicited from regions belonging to higher hierarchies.

The presented studies have indicated an involvement of the brainstem during the early response to noxious stimuli, which probably also is more automatic. Moreover, cognitive computations based on enteroceptive signals will induce the involvement of the orbitofrontal and the rostral ACC, much as complex pure cognitive computations will induce activity in lateral prefrontal cortex and the mid-caudal ACC.

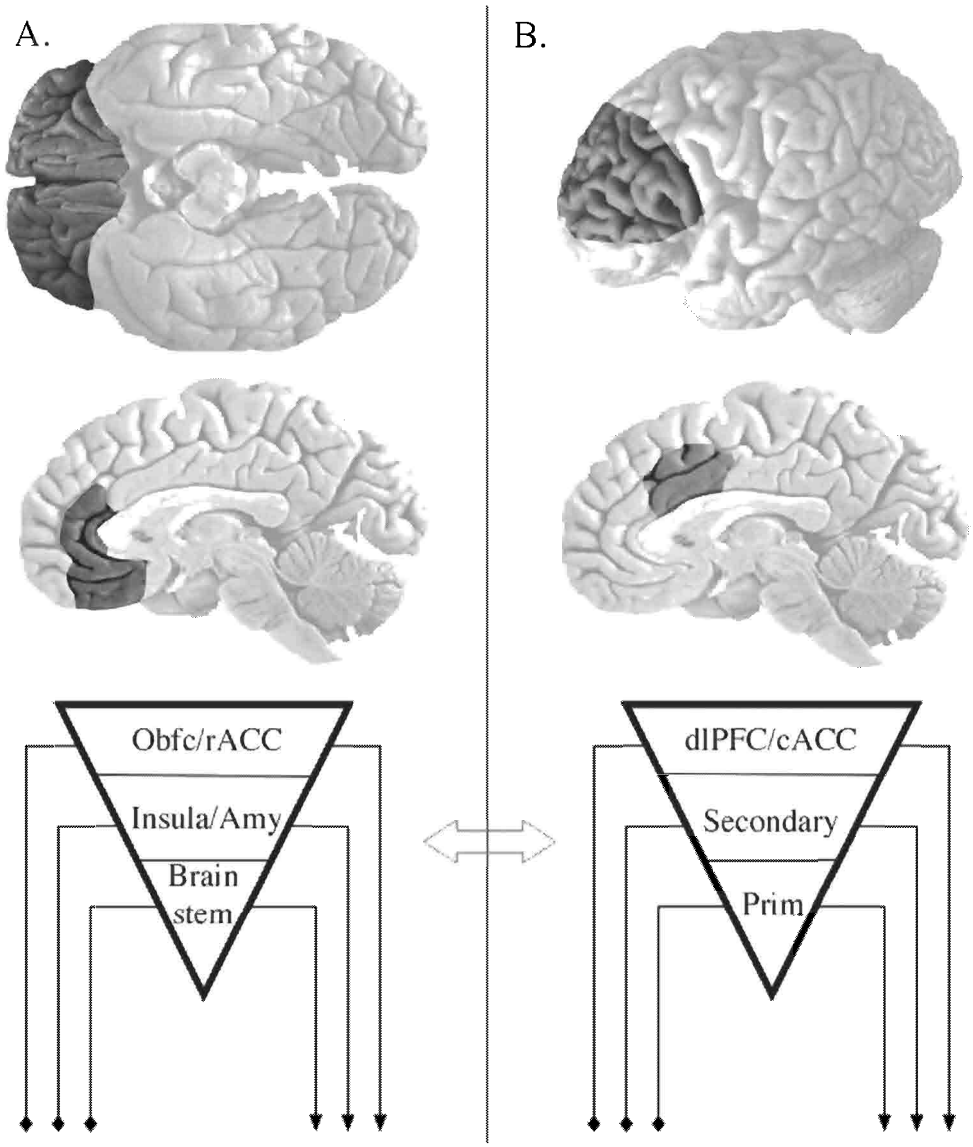


Figure 7. The orbitofrontal cortex (Obfc) and the rostral ACC (rACC) are suggested to be the highest processing areas in an input-output hierarchical network based on the internal (enterocepetive) world (A). The dorsolateral prefrontal cortex (dlPFC) and the (mid-) caudal ACC (cACC) are suggested to belong to a similar input-output hierarchical network based on the external world (B). Amy = Amygdala. Secondary = secondary association areas. Prim = primary sensory areas.

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