Cerebral mechanisms underlying the automatic processing of the facial expression of pain

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"I live in the facial expression of the other, as I feel him living in mine…"

- Maurice Merleau-Ponty, *The Primacy of Perception*, 1964 -

To my parents

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CONTENTS

List of Abbreviations

ACC	Anterior Cingulate Cortex
ANOVA	Analysis of Variance
AU	Action Unit
BA	Brodmann Area
BEES	Balanced Emotional Empathy Scale
BOLD	Blood Oxygenation Level Dependent
BPM	Beats per Minute
DLPFC	Dorsolateral Prefrontal Cortex
DMPFC	Dorsomedial Prefrontal Cortex
DR	Defense Response
ECG	Electrocardiography
EDA	Electrodermal Activity
EMI	Electro Magnetic Interference
EPI	Echo Planar Imaging
FACS	Facial Action Coding System
FFA	Fusiform Face Area
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
FWHM	Full Width at Half Maximum
GLM	General Linear Model
GSR	Galvanic Skin Response
HP	Heart Period
HR	Heart Rate
HRV	Heart Rate Variability
IAPS	International Affective Picture System

IASP	International Association for the Study of Pain
IBI	Interbeat Interval
IRI	Interpersonal Reactivity Index
IRI-EC	Interpersonal Reactivity Index - Empathic Concern
IRI-PT	Interpersonal Reactivity Index - Perspective Taking
MFG	Medial Frontal Gyrus
MPFC	Medial Prefrontal Cortex
OR	Orienting Response
PAM	Perception Action Model
PCC	Posterior Cingulate Cortex
PCS	Pain Catastrophizing Scale
PET	Positron Emission Tomography
rCBF	Regional Cerebral Blood Flow
ROI	Region of Interest
RT	Reaction Time
RT	Reaction Time
SCR	Skin Conductance Response
SD	Standard Deviation
SE	Standard Error
SFG	Superior Frontal Gyrus
SI	Primary Somatosensory Cortex
SII	Secondary Somatosensory Cortex
SOA	Stimulus Onset Asynchrony
STAI	State Trait Anxiety Inventory
STS	Superior Temporal Sulcus
TE	Time of Echo
TMS	Transcranial Magnetic Stimulation

TR   Time of Repetition

VLPFC   Ventrolateral Prefrontal Cortex

VMPFC   Ventromedial Prefrontal Cortex

Zusammenfassung

Simon, D. (2005). Cerebrale Mechanismen der automatischen Verarbeitung des Gesichtsausdruckes des Schmerzes. *Dissertation. Fakultät der Sozial- und Verhaltenswissenschaften. Friedrich Schiller Universität, Jena.*

Gesichtsausdrücke übermitteln wichtige Informationen über den emotionalen Zustand eines Individuums. Obwohl ein schmerzverzerrtes Gesicht, das wohl dominanteste Merkmal nonverbalen Schmerzverhaltens, in der Literatur als einzigartig und distinkt von den Gesichtsausdrücken der Basisemotionen beschrieben wird, ist bisher nur wenig zu den neurobiologischen Grundlagen der Schmerzkommunikation bekannt. Umfassende Forschungsarbeiten der vergangenen Jahre identifizierten Gehirnregionen, die in den Prozess des Erkennens von Basisemotionen (z.B. Angst, Wut, Ekel, Traurigkeit, Freude und Überraschung) involviert sind. Dieses Netzwerk umfasst eine Vielzahl kortikaler und subkortikaler Strukturen wie den occipotemporalen Neokortex, die Amygdala, den präfrontalen Kortex und den rechten parietalen Kortex. Neben diesen beeindruckenden Entwicklungen auf dem Gebiet der Erforschung neuronaler Korrelate der Verarbeitung emotionaler Gesichtsausdrücke, wurde die Untersuchung der cerebralen Verarbeitung des 'Schmerzgesichtes' von kognitiven Neurowissenschaftlern vollständig vernachlässigt.

Mit Hilfe funktioneller Magnet-Resonanz-Tomographie (1.5 T) wurde in einem „mixed blocked/event-related" Design die neuronale Antwort auf dynamische Gesichtsausdrücke des Schmerzes im Vergleich zu wütenden und neutralen Gesichtern bestimmt. Darüber hinaus wurden Verhaltensdaten sowie peripherphysiologische Messgrößen erhoben.

Die Ergebnisse belegen eine signifikante Aktivierung verschiedener emotionsbezogener Areale, einschließlich der Amygdala, auf dynamische Gesichtsausdrücke des Schmerzes im Vergleich zu neutralen Gesichtern. Insbesondere widerspiegeln die Befunde eine Spezifik dieser Reaktion auf Schmerz, wie der Vergleich zu wütenden Gesichtern offen legt. Überraschenderweise unterlagen diese Aktivierungsmuster einer Interaktion mit dem Geschlecht des Darstellers.

Stichwörter: Gesichtsausdruck des Schmerzes, FACS, Gesichtserkennung, implizite Verarbeitung, RR-Interval, GSR, 'Schmerzempathie'.

Abstract

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Human facial expressions convey important information about subjective emotional states and cognitive processes. The facial expression of pain, the most prominent non-verbal pain behavior, is unique and distinct from the expression of basic emotions, yet, little is known about the neurobiological basis for the communication of pain and its recognition. Extensive research conducted over the past years has revealed brain areas involved in the recognition of facial expression of basic emotions (fear, anger, disgust, sadness, happiness and surprise). This network comprises various cortical and subcortical structures such as occipotemporal neocortex, the amygdala, the prefrontal cortex, and the right parietal cortices. In contrast to this exciting development in the investigation of neural correlates associated with the perception of emotional facial expressions, cognitive neuroscientists have completely overlooked brain responses to the expression of pain.

Neural responses to dynamic visual stimuli of male or female actors displaying pain, angry or neutral facial expression presented in a mixed blocked/event-related design were investigated while blood oxygenation level-dependent (BOLD) signal was acquired using whole-brain functional magnetic resonance imaging (fMRI) at 1.5 Tesla. Furthermore, behavioral data and autonomic measures were assessed.

Results confirm the significant activation of several emotion-related areas, including the amygdala in response to dynamic visual stimuli displaying facial expressions of pain as compared to neutral. Importantly, results indicate some specificity of pain-related responses as compared to anger. Surprisingly, there was an interaction of these activation patterns with the sex of the displaying actors.

Keywords: Facial expression of pain, FACS, face recognition, implicit processing, fMRI, RR-interval, GSR, 'pain empathy'

1   Introduction

How do mothers understand that their babies are amused by something? Why do we stay away from a furious looking guy? It is reading in faces. The detection and interpretation of facial expressions is critical to our appreciation of the social and physical environment. Individuals suffering from brain lesions in certain areas are impaired in this ability (e.g. Adolphs, Damasio, Tranel and Damasio, 1996). Hence, the neuronal correlates of emotion recognition have been intensively investigated. Especially the facial expression of pain, an important indicator for a highly distressing experience occurring in everyday life, which might sometimes even accompany life threatening events, is less examined concerning the neural correlates of its perception. The present work is aimed to contribute to a deeper understanding in this field.

This introduction provides an overview of the research on facial expressions of emotion and especially on the facial expression of pain. Afterwards, the neural system known to be involved in face recognition in general and in recognition of several emotions in particular is described. Finally, present fMRI-research on vicarious pain experience, which has often been linked to the term 'pain empathy', will be reported and critically discussed.

1.1   Facial Expressions and Their Measurement

The importance of the face in interpersonal communication is widely recognized in anthropology, psychology and the social sciences. Facial expressions are powerful social signals, which impart information about a person's emotional state. Therefore, they represent an essential aspect of social communication (Blair, 2003a) and might even have survival value in terms of recognizing potential threat (Darwin, 1872).

Around one-hundred years ago B. Duchenne gave attention to the question, which muscles are involved in certain facial expression. A crucial turning point in the research on facial expressions occurred as the anatomist Carl-Hermann Hjortsjö (1970) provided a detailed description of facial muscles and the influence of their contraction on the facial display (Eibl-Eibesfeldt, 1997). Based on his work, Ekman and Friesen (1978)

developed a technique of coding facial expression – the so called Facial Action Coding System (FACS).

Considerable evidence for a correspondence of specific activation patterns of these action units (AUs) to at least six different basic emotions (anger, disgust, fear, sadness, happiness and surprise) has been provided (Ekman, Friesen and Elsworth, 1982). According to the FACS Investigator's Guide one has to distinguish prototypes of emotions and their major variants (chapter 12, p. 174, Ekman, Friesen and Hager, 2002; Table 1). A prototype refers to a configuration of activated AUs, which have been observed to be commonly associated with a certain emotion. Usually not only <u>one</u> prototype for one emotion exists. Moreover, there is some degree of plasticity of these patterns in naturalistic contexts and therefore variants of the prototypes occur (Smith and Scott, 1997). These major variants are partial expressions of a prototype.

Although scholars engage in an ongoing controversy about innateness and the degree of universality of facial expressions and their recognition (Russell and Fernandèz-Dols, 1997), researchers agree on the account of 'minimal universality', which predicts a certain amount of cross-cultural similarity in the recognition of these emotional patterns without postulating an innate mechanism (Russell and Fernandèz-Dols, 1997). Moreover, there is robust evidence that facial expressions emerge early in childhood with morphological stability (Izard et al., 1995; cited in Izard, 1997) and can also be discriminated by infants in early months (Nelson and de Haan, 1997). Although debates on the right model of facial expressions continue, there is an overall agreement on the specificity of prototypical basic emotions that can be reliably recognized across a variety of cultures (Smith and Scott, 1997).

Ekman and Friesen (1976) provided a set of photographs – the 'pictures of facial affect', which include the prototypical facial expressions of the basic emotions mimicked by actors (Figure 1), who were trained using a discrete muscle training technique. This set has been widely used in past and present research (e.g. Morris, Öhman and Dolan, 1998b).
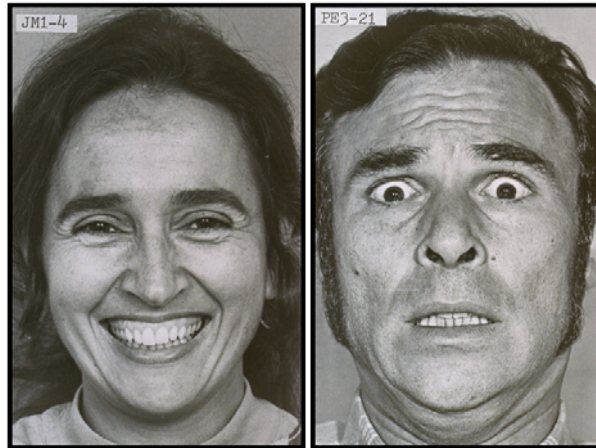
Figure 1:   Example of a prototypical happy and fearful face taken from Ekman and Friesen's Pictures of Facial Affect (1976).

1.2   The Facial Expression of Pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (International Association for the Study of Pain (IASP), 1994). Price has proposed a slightly different definition in which pain is "a somatic perception containing (1) a bodily sensation with qualities like those reported during tissue damaging stimulation, (2) an experienced threat associated with this sensation, and (3) a feeling of unpleasantness or other negative emotions based on this experienced threat" (Price, 1999, p. 1-2). Previous imaging studies on experimental pain revealed a network of multiple cerebral structures including the primary and secondary somatosensory cortices (SI and SII), anterior cingulate cortex (ACC), insular cortex and regions of the frontal cortex associated with this complex experience (e.g. Apkarian, Darbar, Krauss, Gelnar and Szeverenyi, 1999; Casey, Minoshima, Morrow and Koeppe, 1996; Kwan, Crawley, Mikulis and Davis, 2000; Peyron, Laurent and Garcia-Larrea, 2000; Rainville, Duncan, Price, Carrier and Bushnell, 1997; Talbot et al., 1991). Moreover, acute pain is accompanied by autonomic responses, e.g., heart rate (HR) acceleration and increase of Galvanic skin response (GSR) (Price, 1999). Besides sensory, affective and cognitive aspects, pain of certain intensity is characterized by a motor response including withdrawal reflexes and distinct facial expression related to this experience.

5

Indeed, these nonverbal expressions are essential aspects of pain behaviors used implicitly or explicitly by clinicians to evaluate pain. In the past decade facial expressions have been increasingly accepted as a valid diagnostic instrument. Especially pain in preverbal infants, in the cognitively impaired or during post-operative recovery is often misunderstood (Chambers, Giesbrecht, Craig, Bennett and Huntsman, 1999; Craig, Whitfield, Grunau, Linton and Hadjistavropoulos, 1993; Craig, Korol and Pillai, 2002; Hadjistavropoulos, Craig, Grunau and Whitfield, 1997; LaChapelle, Hadjistavropoulos and Craig, 1999; Nader, Oberlander, Chambers and Craig, 2004). These facts highlight the importance of understanding the expressive pain behavior and its neuropsychological correlates for both, fundamental theoretical purposes and practical clinical implications. Accrued knowledge about those correlates may contribute to the optimal care and to a deeper insight into clinical conditions where apparently still a lack of understanding of the nonverbal communication of distress exists (e.g. following brain injury or in psychiatric disorders).

The following annotations outlining the state of the art in research on facial expressions of pain will, however, solely refer to the ones following acute pain, since only these will be investigated in the present thesis.

According to Chapman and Turner (1990), the pain expression reflects both, emotional and sensory qualities of a pain experience, but there is little research on the extent to which it encodes intensity or affect. Evolutionary theories propose that the facial expression of pain following acute injury might play a role in survival by alarming onlookers in situations of immediate threat and/or by eliciting empathy and solicitous behavior towards the individual experiencing pain (Williams, 2002). Beyond this account, an operant model suggests that the facial expressions of pain as inviting help can also become maladaptive in chronic pain (e.g. Flor, Kerns and Turk, 1987).

Although pain behavior in general is determined by individual learning experiences, the social surrounding, the cultural background and certain personality factors (Chapman and Turner, 1990; Williams, 2002), several studies using FACS nevertheless reliably identified the co-occurrence of certain facial actions in a pain face (Table 1). They are characterized by brow lowering, cheek raising, lid tightening, nose wrinkling, upper lip raising and sometimes eye closing (e.g. Craig and Patrick, 1985; Prkachin, 1992; Prkachin and Craig, 1995; Williams, 2002). Furthermore, this pattern was observed

across lifespan (e.g. Craig et al., 1993; Grunau, Johnston and Craig, 1990; Johnston, Stevens, Craig and Grunau, 1993; Lilley, Craig and Grunau, 1997), as well as in subjects with different cognitive abilities (e.g. LaChapelle et al., 1999; Nader et al., 2004). Moreover, a consistency across various clinical pain conditions was reported (Prkachin, 1992). In general, observers are properly able to identify facial expressions of pain, especially those associated with extreme pain (e.g. Kappesser and Williams, 2002; Keltner and Buswell, 1996; Pillai Riddell, Badali and Craig, 2004; Xavier Balda et al., 2000). Yet, relative to the expressor's judgements observers, like health care professionals tend to underestimate pain in others (e.g. Solomon, Prkachin, and Farewell, 1997).

Facial expressions of pain are described as being unique and distinct from the ones of the basic emotions (Williams, 2002) and people are generally good in distinguishing pain from other emotions displayed in photographs (Kappesser and Williams, 2002; Keltner and Buswell, 1996). However, research in this area is still scant. With regard to gender differences of nonverbal pain behavior one has to note that males were generally found to display less facial pain expression than females in response to experimentally controlled acute pain (Sullivan, Tripp and Santor, 2000). Moreover, it was observed that pain experience and behavior may depend on individual pain catastrophizing tendencies, which is characterized by a lack of confidence in one's ability to cope with pain (Sullivan et al., 2001). Hence, greater catastrophizing seems to be associated with worse pain and more expressive pain behavior (Sullivan et al., 2000; Turner, Mancl and Aaron, 2004).

Although distinctiveness has been suggested and empirically confirmed, one has to note that the involvement of some AUs is common to multiple expressions (Table 1) as revealed with the help of FACS. Hence, most emotions, including pain are not characterized by the activation of a *single* distinct AU but a distinct *pattern*. According to the componential approach, which has been proposed by Smith and Scott (1997), the overall facial expression conveys the emotion's identity while involvement of single AUs might enrich and support this core information. Hence, an overlap of AUs involved in pain with disgust, anger or surprise might not lead to misidentification of pain for one of the other emotions, although real pain experiences might be accompanied by feelings of e.g. fear or surprise.

Table 1   Prototypical AUs, which occur with happiness, anger, disgust, fear, surprise, sadness and pain.

Emotion   AU

	1	2	4	5	6	7	9	10	11	12	15	16	17	20	22	23	24	25	26	27
	Inner brow raiser	Outer brow raiser	Brow lower	Upper lid raiser	Cheek raiser	Lid tighten	Nose wrink-ler	Upper lip raiser	Nasol. Furrow deepen	Lip corner puller	Lip corner de-pressor	Lower lip de-pressor	Chin raiser	Lip stretch	Lip funnel	Lip tighten	Lip pressor	Lips part	Jaw drop	Mouth stretch
Happin.					■					■										
Anger			■	■		■		□					□		■	■	□	■	■	
Disgust							■	■				□	□						□	
Fear	■	■	■	■										□			■	■	■	
Surprise	■	■		■															□	□
Sadness	■		■		□				□		■								□	□
Pain			■		■	■	■	■		□				□				□	□	□

Following Kappesser and Williams (2002) and FACS; ■ AU which occurs with prototype; □ may occur with prototype and / or major variant.

Furthermore, the specific information encoded in a pain face is not simply conveyed by the pattern of AUs per se, but more importantly by the dynamics of their co-occurrence. In general, communication between individuals is characterized by *dynamic* facial expressions. To date, the neural substrate of emotion recognition has been intensively investigated by means of static facial displays. However, the facial expression of pain, which is undoubtedly the most prominent nonverbal pain behavior, is neither included in any validated set of static nor of dynamic facial expression stimuli. Yet, research on brain mechanisms underlying certain emotions or pain using dynamic face clips is still rare (Botvinick et al., 2005; Kilts, Egan, Gideon, Ely and Hoffman, 2003; LaBar, Crupain, Voyvodic and McCarthy, 2003; Wicker et al., 2003). Hence, there is a need for a validated set of these stimuli in order to be able to further investigate the neural basis for the recognition and interpretation of pain and emotion. Therefore, an own set of dynamic visual stimuli of actors expressing pain and the six basic emotions will be developed, while solely the expression of pain and the basic emotion 'anger' will be used for this thesis (see Section 3.2.). In order to provide ecologically valid stimuli, which at the same time sufficiently meet the research criterion of standardization, actors have to be carefully trained using a discrete muscle training technique outlined by Ekman and Friesen (1975). A validation with FACS and subjective ratings in normal volunteers will be conducted. One might argue that the validity of those posed facial expressions is poor and the deception will be recognized by participants. However, while faked facial expressions of pain, as well as of basic emotions are indeed more asymmetric and less temporally contiguous related to the involved muscle actions than genuine (e.g. Craig, Hyde and Patrick, 1991; Gosselin, Kirouac and Dore, 1997; Poole and Craig, 1992), subjects generally have difficulties to detect the fake (Hadjistavropoulos, Craig, Hadjistavropoulos and Poole, 1996; Poole and Craig, 1992). Therefore, it is methodological reasonable to use deceptive facial expressions instead of genuine pain displays.

One can summarize that the facial expression of pain is clear and distinct from other emotional expressions and observers are generally able to reliably detect them. Nevertheless, in most studies on detection and judgment of pain, participants were aware of the painful procedures (e.g. clinical setting). Since the stimulus material used

in this study will not contain any contextual cues but only the facial information per se, this will be the first study which investigates how observers automatically respond to a prototypical pain face.

1.3 Neural System for the Recognition of Emotional Facial Expressions

It has to be pointed out that in the literature the term 'recognition of emotion' from facial expressions, which will also be used in the present thesis, is referred to as both explicit and implicit processing of emotion. Since the focus of this work will be on automatic detection of angry and pain contorted facial expressions, the distinction between both kinds of information processing will be pronounced.

Firstly, the neural system involved in face perception in general and subsequently the network of brain regions associated with emotion recognition will be described in detail. Since the present work focuses on the recognition of emotion from dynamic facial displays, studies using dynamic stimulus material will be highlighted.

1.3.1 <u>Face Perception</u>

The visual perception of faces draws on a specialized neural system (Haxby, Hoffman and Gobbini, 2000; 2002). Before the visual information from the retina reaches these highly specialized areas it is, like every other visual stimulus, transmitted via several interconnections to the striate visual cortex (see Carlson, 2004). The face information is afterwards further processed in extrastriate higher order visual areas of the temporal cortex. First evidence for the existence of face specific regions was provided by studies in patients with focal lesions in the ventral occipotemporal cortex. These individuals suffered from prosopagnosia – a syndrome which is associated with impaired ability to recognize familiar faces while object recognition is close to normal (e.g. Damasio et al., 1982, cited in Haxby et al., 2000). Further evidence derived from single-cell studies in monkeys that revealed face-selective neurons in the superior temporal cortex and the inferior temporal cortex (Perrett et al., 1992, cited in Haxby et al., 2000).

A hierarchical human neural system of face processing has been proposed. On the one hand this includes a core system consisting of these occipotemporal regions in extrastriate visual cortex comprising the lateral fusiform face area (FFA) and the superior temporal sulcus (STS) mediating the visual analysis of faces and on the other hand an extended system that extracts the meaning from faces (Haxby et al., 2002). This system's function in the recognition of emotional facial expressions will now be outlined in detail.

1.3.2   Emotion Recognition

Considerable evidence for the existence of a specialized neuronal system involved in the decoding of facial expressions' emotional content came from studies on brain damaged patients (e.g. Adolphs et al., 1996; Adolphs, Damasio, Tranel, Cooper and Damasio, 2000; Adolphs, Tranel and Damasio, 2003; Weniger and Irle, 2002) and patients suffering from various disorders like schizophrenia (e.g. Gur et al., 2002b; Phillips et al., 1999), autism (e.g. Adolphs, Sears and Piven, 2001; Critchley et al., 2000b; Hadjikhani et al., 2004; Hubl et al., 2003; Pierce, Muller, Ambrose, Allen and Courchesne, 2001), psychopathy (e.g. Blair, Colledge, Murray and Mitchell, 2001; Blair, 2003b), as well as Huntington's disease (Hennenlotter et al., 2004) and Williams syndrome (Gagliardi et al., 2003), who showed crucial impairment in face recognition and/or emotion recognition of certain or all basic emotions.

The variety of studies in patients and healthy controls (e.g. Morris et al., 1998b) revealed a neural system for the recognition of emotional facial expressions. Besides the above mentioned occipotemporal neocortex this system comprises also the amygdala, prefrontal cortex and right somatosensory cortices (reviewed in Adolphs, 2002). Moreover, the insula and the anterior cingulate cortex have been found to be activated during the processing of emotional facial expressions (Phan, Wager, Taylor and Liberzon, 2002). This system even showed dissociable neural responses to facial expressions of different emotions (e.g. Blair, Morris, Frith, Perrett and Dolan, 1999).

The most important regions of this system and their role in the recognition of emotional facial expressions will now be outlined in detail. The outlined studies investigated the

processing of emotional facial expressions with the help of explicit (e.g. labeling of emotion, rating of faces arousal and valence), implicit (e.g. distraction, subliminal presentation) or no tasks (passive viewing).

Since this thesis examines the automatic processing of pain faces investigated by a distraction task (see Section 3.5) the imaging results referring to implicit tasks will be particularly highlighted.

1.3.2.1 *Amygdala*

Electrophysiological, neuropharmacological, and lesion studies in animals, and studies in brain damaged and healthy humans provide considerable evidence for a central role of the amygdala, a brain structure located within the temporal lobes as part of the limbic system, in the processing of emotional stimuli (for details see Aggleton, 1992). Since this thesis investigates brain responses to visual stimuli, the annotations will mainly focus on empirical results occurring during visual induction (for review see Zald, 2003).

Amygdalar involvement in the processing of facial expressions has mainly been observed to biologically salient and/or threatening facial expressions. Considerable evidence has been provided by studies on patients with bilateral amygdala damage predominantly showing impairment in the ability to recognize fear in faces (Adolphs, Tranel, Damasio and Damasio, 1995; Anderson and Phelps, 2000; Broks et al., 1998; Sato et al., 2002; Sprengelmeyer et al., 1999). Additionally, enhanced activation of the amygdala to fearful facial displays has also been consistently demonstrated in healthy subjects (e.g. Breiter et al., 1996; Morris et al., 1996, 1998a; Morris, deBonis and Dolan, 2002; Phillips et al., 1997, 1998, 2001; Surguladze et al., 2003; Whalen et al., 2001; Yang et al., 2002). In line with these studies pronounced responding of the amygdala was also found to faces of strangers as compared with familiar faces (Gobbini, Leibenluft, Santiago and Haxby, 2004) and during rapid presented unfamiliar photographs of the racial outgroup vs. racial ingroup (Cunningham et al., 2004; Phelps et al., 2000).

This response of the amygdala to potentially threatening stimuli, investigated by using static photographs, has also been observed to dynamic fear morphs relative to neutral or happy faces (Sato, Kochiyama, Yoshikawa, Naito and Matsumura, 2004a), and in

contrast to static fear displays (LaBar et al., 2003). Moreover, PET results showed increased BOLD-response in the amygdala while viewing negative film clips (e.g. Reiman et al., 1997).

The amygdala also showed involvement in emotional memory characterized by enhanced responses to stimuli that predict an aversive event (e.g. Armony and Dolan, 2002; LaBar, Gatenby, Gore, LeDoux and Phelps, 1998; Morris et al., 1998b; Morris and Dolan, 2004; Phelps, Delgado, Nearing and LeDoux, 2004) as investigated in fear conditioning paradigms.

Moreover, in line with the amygdala's engagement in fear-relevant information processing, studies in spider and social phobic subjects detected amygdala response during exposure to phobogenic stimuli (e.g. Dilger et al., 2003; Straube, Kolassa, Glauer, Mentzel and Miltner, 2004).

Such emotionally salient information has been proposed to be processed by two routes of the brain, with the amygdala being a core structure (LeDoux, 1996). Hence, a fast subcortical 'retinocollicular-pulvinar-amygdalar' pathway and a slower cortical 'retinogeniculostriate-extrastriate-fusiform' path of information processing have been distinguished (for review see Amaral, Price, Pitkänen and Carmichael, 1992).

Applying this model to the processing of social signals from faces, one can assume two mechanisms of amygdalar engagement. Via the slow path, the amygdala receives highly processed information about the facial expression from the visual cortices. Once the amygdala considered them as relevant or even potentially threatening it can in turn influence the activation of those areas. On the fast path, the amygdala was shown to be able to regulate cortical processing before a cortical representation is fully built up (LeDoux, 2000). Remarkably, evidence for the feedback-projection of the amygdala to visual areas has been provided by Vuilleumier, Richardson, Armony, Driver and Dolan (2004), who observed lower emotional modulation of visual cortices in participants with amygdala lesion as compared to healthy subjects. Moreover, a patient with bilateral amygdala damage showing impaired fear recognition, returned to normal when being instructed to focus on the eyes of the presented facial expression as recently demonstrated by Adolphs and colleagues (2005). This intriguing finding suggests that

the amygdala does not only influence the *processing* of visual information at an early stage, but already the visual information that is *sought by the eyes*.

Hence, the amygdala is predisposed for a pivotal role in the automatic, preattentive detection of potential threat (Whalen et al., 2001), providing evolutionary advantages for the individual (Öhman, 1993). With its interconnections to various cortical areas (Amaral et al., 1992), as well as the brain stem and the hypothalamus, the amygdala participates in an alerting response and in the regulation of defense responses mediated by the autonomic nervous system (LeDoux, 1998; 2000).

Evidence for the amygdala's role in the rapid detection of threat via the subcortical path was confirmed in several studies. Enhanced activation of this structure was reported during subliminal processing of masked fear faces (e.g. Liddell et al., 2005; Whalen et al., 1998b; but see Phillips et al., 2004) and angry faces (e.g. Morris et al., 1998b). These studies argue for the amygdala's role in rapid responding to threat before conscious recollection. Intriguingly, an engagement of the amygdala was also observed when a patient with blindsight was required to discriminate facial expressions (de Gelder, Vroomen, Pourtois and Weisskrantz, 1999; Morris, de Gelder, Weisskrantz and Dolan, 2001). By guessing, this patient was more than accidentally able to discriminate these expressions in his blind hemifield. This has been confirmed recently in another patient (Pegna, Khateb, Lazeyras and Seghier, 2004).

However, the amygdala does not respond to negatively valenced stimuli or potential threat per se. For instance concerning the recognition of angry expressions the results of imaging studies are not consistent. While some found amygdalar involvement (Fischer, Fransson, Wright and Bäckman, 2004a; Sato, Yoshikawa, Kochiyama and Matsumura, 2004b; Straube et al., 2004; Whalen et al., 2001; Wright, Martis, Shin, Fischer and Rauch, 2002) others did not (Blair et al., 1999; Kesler-West et al., 2001; Kilts et al., 2003; Sprengelmeyer, Rausch, Eysel and Przuntek, 1998; Yang et al., 2002).

It has rather been assumed that the response to a potential danger is not only influenced by threatening content of the sensory stimulus, but seems to be also a function of *ambiguity*. While the emanator of an angry face might be a threat itself, fearful facial expressions represent a potential environmental danger without giving detailed information about the actual source. Whalen (1998) proposes an inverse relationship

between amygdala activation and information about the nature of threat. In line with this assumption, Adams, Gordon, Baird, Ambady and Kleck (2003) found right-sided amygdala involvement only during exposure to angry faces of averted gaze and to fear faces of directed gaze. Both variations of gaze direction in these particular emotions lead to a reduction of clarity of information regarding the source of threat and hence to increased ambiguity of the stimulus material (but see Sato et al., 2004b). Also in line with the theories of the amygdalae's involvement in the processing of ambiguous stimuli, Rotshtein, Malach, Hadar, Graif and Hendler (2001) observed BOLD-responses in the amygdala to bizarre as in contrast to normal faces (slightly smiling), which had been modified by selective inversion of the eyes and the mouth in the upright original faces.

Less often the amygdala was found to be activated by disgusted (Gorno-Tempini et al., 2001; Schienle et al., 2002), sad (Blair et al., 1999; Yang et al., 2002) and happy facial expressions (Breiter et al., 1996; Killgore and Yurgelum-Todd, 2004; Yang et al., 2002). A study by Canli, Sivers, Whitfield, Gotlib and Gabrieli (2002), who found enhanced amygdala responses to happy faces in more extraverted subjects, suggests that variability of amygdala activation might be due to individual personality differences. Moreover, amygdalar engagement might be influenced by the attractiveness of face targets in terms of their reward value. As reported by Aharon and colleagues (2001), who exposed male observers to photographs of male and female faces displaying neutral facial expressions with varying attractiveness, the amygdala responded more strongly to attractive females in contrast to both, attractive males and less attractive females. This 'opposite gender effect' has, however, not been investigated in a group of female observers.

Hence, it has been suggested that the amygdala might generally play a role in the processing of information that is relevant to *social cognition* (Brothers, Ring and Kling, 1990; Adolphs, 1999), especially to facial expressions that are positive or negative reinforcers.

Nonetheless, the amygdala response seems to be not only determined by stimulus valence but also by its arousal. However, most studies fail to distinguish both concepts since unpleasant stimuli like fearful facial expressions are also arousing. Some imaging

studies suggest stronger amygdalar involvement to stimuli of greater arousal for both pleasant and unpleasant pictures (Garavan, Pendergrass, Ross, Stein and Risinger, 2001) and odors (Anderson et al., 2003b). Amygdala activation was also found to be associated with the processing of emotionally arousing faces (e.g. Winston, o'Doherthy and Dolan, 2003a) investigating low or high intensity disgust, fear, happiness, or sadness under two task conditions. Bilateral amygdalar involvement was detected to high-intensity expressions of all emotions regardless of whether subjects focused on the emotionality or on the gender of the face.

Moreover, this involvement of the amygdala seems to be a function of attentional characteristics of the experimental task. An activation was predominantly observed when subjects were distracted by a task (e.g. gender discrimination task), were passively viewing facial expressions (e.g. Critchley et al., 2000a; Keightley et al., 2003) or when stimuli were perceptually suppressed (via binocular rivalry) (e.g. Williams, Morris, McGlone, Abbott and Mattingley, 2004). Hence, it has been suggested that the amygdala is more engaged at a sensory level and less associated with cognitively demanding tasks or cognitively elicited emotions (Phan et al., 2002). Fewer studies reported activation when conscious evaluation like labeling of the emotional expression was required (explicit processing) (e.g. Gorno-Tempini et al., 2001; Gur et al., 2002a). However, Winston et al. (2003a) also detected amygdala responses regardless of attention in high-intensity expressions. Additionally, for fearful expressions amygdala activation did not depend on the attentional condition (Anderson, Christoff, Panitz, de Rosa and Gabrieli, 2003a; Vuilleumier, Armony, Driver and Dolan, 2001; but see Phillips et al., 2004), which also seemed to be influenced by the subjects' anxiety level (Bishop, Duncan and Lawrence, 2004b). While in "high-anxious" participants enhanced responses were observed regardless of the attentional focus, in "low-anxious" participants the amygdala was solely engaged to attended fearful faces.

Additionally, one has to note that some sex differences in amygdala activation have been observed. Cahill and colleagues (2001), for instance, detected that enhanced memory for negative films was accompanied by stronger right-sided involvement in male and stronger left-sided activation of the amygdala in female observers. Killgore

and Yurgelun-Todd (2001) detected gender differences to happy, but not to fearful facial displays characterized by stronger right lateralized amygdala activation in male observers. Interestingly, McGlure and colleagues (2004) reported an increase of amygdala activity to unambiguous threat (angry faces) in female observers, which was not found for male observers. Fischer and colleagues (2004b) even found sex differences of amygdalar responses to neutral faces. They reported stronger involvement of the amygdala in male but not female observers to photographs of the opposite sex (in contrast to the same sex). In contrast to the study by McGlure and colleagues (2004), another report of the Fischer group did not find differences in amygdala activation to angry faces collapsed over actors' sexes (Fischer et al., 2004a).

Furthermore, a lateralization of amygdalar activation has been suggested by several studies. While the lesion literature supported a right-hemispheric dominance, the neuroimaging literature reported frequent left-sided or bilateral engagement during exposure to emotional facial expressions (for review see Zald, 2003). In order to integrate these contrary findings one has to take into account that repeated exposure to the same stimulus leads to rapid habituation of the amygdala response (Breiter et al., 1996; Phillips et al., 2001; Wright et al., 2001), being stronger in the right as compared to the left hemisphere as demonstrated for fearful facial expressions (Phillips et al., 2001; Wright et al., 2001). Thus, the laterality differences might rather be explained by lateralization of sustained (left amygdala) and transient (right amygdala) responses. However, habituation does not occur universally (e.g. Hart et al., 2000), but might be a function of ambiguity. According to these facts, one could assume that the faster face information can be sufficiently explored the stronger habituation effects should be observable.

Few imaging studies have also linked amygdalar activation to the pain experience. While some found enhanced activation in dependence of the pain intensity (Bornhövd et al., 2002; Schneider et al., 2001), some studies observed decreased BOLD-response (e.g. Derbyshire et al., 1997; Petrovic, Carlsson, Petersson, Hansson and Ingvar, 2004) explained as suppression of amygdala activity in terms of coping with the aversive

situation. A study by Botvinick and colleagues (2005) even detected engagement of amygdala, while participants were observing others in pain.

To summarize, the amygdala can be considered as a structure mainly involved in the automatic processing of socially relevant and/or potentially threatening facial expressions, especially (1) when they are ambiguous (Whalen, 1998), (2) intense (e.g. Winston et al., 2003a) and (3) when detailed stimulus analysis is prevented (e.g. Morris et al., 1998b).

1.3.2.2   Prefrontal Cortex (PFC)

Evidence for the involvement of the prefrontal cortex in social cognition has been provided by the famous historic accident of Phineas Gage who received bilateral frontal lesions (including the ventromedial PFC) and thereupon showed socially inappropriate behavior (Adolphs, 1999). Similarly, patients with lesions in the frontal lobes show impairments in the ability to infer mental states in others as investigated by visual perspective taking and detection of deception (Stuss, Gallup and Alexander, 2001).
A basic anatomical distinction divides the PFC in three subdivisions – a medial prefrontal (MPFC), a lateral prefrontal (LPFC), and an orbitofrontal area, which might contribute distinctively to affective processing (Davidson, 2002). Since the MPFC will be selected as a ROI for this thesis, reported empirical findings will mainly focus on this area. The role of the other areas will be outlined briefly.

Studies investigating the role of the orbitofrontal cortex suggest its engagement in decision making and choosing responses by using the reward value and risk for an appropriate selection of an action (Critchley, Mathias and Dolan, 2001; Elliott, Frith and Dolan, 2000). In line with these findings, O'Doherty and colleagues (2003) for instance reported activation in this region to attractive faces – stimuli of reward value, which was even more pronounced when faces were mildly smiling instead of being just neutral.

The literature regarding the LPFC and MPFC is more puzzling, since no common anatomical distinction has been used and thus both areas will be reported together. The

LPFC as well as the MPFC can be divided into a dorsal and a ventral portion (dLPFC, vLPFC / dMPFC, vMPFC).

It has been suggested that the LPFC plays a key role in emotional self regulation. For instance, the dLPFC was detected to be involved in the suppression of positive (sexual arousal) and negative emotional states (sadness) (Beauregard, Lévesque and Bourgouin, 2001; Lévesque et al., 2003). The MPFC is probably engaged in linking perceptual representation of stimuli to their emotional and social significance (Damasio, 1994). Also, patients with damage of the ventromedial cortex show socially inappropriate emotional expressions (Damasio, 1994).

During exposure to affective pictures (International Affective Picture System - IAPS by Lang, Bradley and Cuthbert, 1997a) a differential involvement of LPFC and MPFC in the explicit processing of arousal and valence information conveyed by those stimuli has been reported by Dolcos, LaBar and Cabeza (2004). While the left dLPFC and vMPFC were activated during exposure to positive pictures, the right vLPFC was engaged when participants viewed negative pictures. Regardless of valence information, the dMPFC was associated with the processing of arousal information. However, one has to note that this study did not include positive and negative pictures of lower arousal levels. Hence, all comparisons with respect to the valence information were still contaminated by high arousal.

There is a huge body of evidence showing that while the amygdala seems to be more engaged during implicit tasks, the PFC seems to be associated with explicit processing of emotion (e.g. Lane, Fink, Chau and Dolan 1997a; Lane, Reiman, Ahern, Schwartz, and Davidson, 1997b; Nakamura et al., 1999; Narumoto et al., 2000; Winston et al., 2003a). For instance, Nakamura and colleagues (1999), as well as Narumoto and colleagues (2000) found enhanced activation in the right portion of the LPFC when the task was associated with emotional appraisal (identification of emotion; facial emotion matching) in contrast to a control task (judgment of facial attractiveness and background color distinction; gender discrimination and rest). Similar evidence has been provided by Hariri, Bookheimer and Mazziotta (2000), who also found right-sided dLPFC activation when participants were asked to label angry and fearful faces. However, in contrast to Narumoto et al. (2000), Hariri and colleagues (2000) did not find prefrontal involvement when they requested facial emotion matching, which might be explained

by the fact that Hariri and colleagues' (2000) matching task was less cognitively demanding (two instead of six emotional facial expressions). Hence, participants probably did not need their categorical knowledge in this case and thus did not consciously evaluate the stimuli.

In line with the PFC's role in explicit processing of affective stimuli its engagement was also observed when the task implied self-referential judgements. Lane and colleagues (1997a) demonstrated that the MPFC was associated with subjects' internal attendance to their emotional state in contrast to focusing on spatial aspects of the same pictures. In accordance with this finding the left vMPFC was also engaged when subjects rated their personal association to presented pictures. Additionally, dMPFC was involved when they judged this self-relatedness as being high (Phan et al., 2004). Fitting into this literature, Gusnard, Akbudak, Shulman and Raichle (2001) suggested a role of the dMPFC in explicitly self-referential mental activity and proposed that the vMPFC might be influenced by attention-demanding tasks and associated with emotional processing. They found increases in this area when subjects directed their attention to self-referential or introspectively oriented mental activity like rating their feeling while exposed to pleasant and unpleasant pictures. This involvement of dMPFC in mentalizing has been confirmed by studies on 'theory of mind' (for review see Frith and Frith, 2003).

Although the MPFC seems mainly associated with explicit processing of emotional facial expressions, one study also reported an engagement during subliminal presentation of fear faces (Liddell et al., 2005). While other fear-masking studies did not explicitly examine the modulation of other cortical regions by subliminal fear (Morris, Öhman and Dolan, 1999; Whalen et al., 1998b) this was the first study suggesting the contribution of other areas in alerting during subliminal processing of biologically significant signals. Based on this observation, Liddell and colleagues (2005) propose a rapid 'alarm' system encompassing the superior colliculus, locus coeruleus, pulvinar and amygdala triggering activation of the anterior insula (see Section 1.3.2.4), the ACC (see Section 1.3.2.3) and the MPFC. Amygdalar modulation of prefrontal activation could also be transferred via direct projections to these areas (Amaral et al., 1992). Hence, for particularly threatening stimuli one could hypothesize an engagement of

MPFC also under conditions of reduced stimulus analysis (distraction, subliminal presentation).

Several studies have reported a reverse relationship of amygdalar and prefrontal activation mainly during explicit tasks but also during passive viewing conditions (Hariri et al., 2000; Hariri, Mattay, Tessitore, Fera and Weinberger, 2003; Kim, Somerville, Johnstone, Alexander and Whalen, 2003; Nomura et al., 2004; Taylor, Phan, Decker and Liberzon, 2003). Confirming these empirical findings, it has been shown that the glucose metabolic rate of the amygdala is inversely related to the one of the MPFC (Abercrombie et al., 1996, cited in Phan et al., 2002).

At first glance these findings of an inverse relationship of amygdalar responding to MPFC activity seem to contradict the concomitant activation of both areas during subliminal processing of fear faces (Liddell et al., 2005). However, on the one hand, none of the mentioned studies investigated these relationship for biologically significant stimuli and on the other hand an 'activation' of this area, which might also be due to less deactivation to fear faces relative to neutral faces, does not run counter to the proposed negative correlation between amygdala and MPFC engagement. Hence, this might rather quantify the above stated proposal than conflict with it.

According to Phan et al. (2002), the MPFC is commonly activated in various emotional tasks and its activation is not specific to any emotion or induction method. Thus, a more general role of the MPFC in emotional processing has been proposed. Hence, an involvement of the MPFC has been observed to emotional pictures, films, positive and negative emotions (Gray, Braver and Raichle, 2002; Kilts et al., 2003; Lane et al., 1997a; Lane et al., 1997b; Lane et al., 1997c; Leibenluft, Gobbini, Harrison and Haxby, 2004; Paradiso, Robinson, Boles Ponto, Watkins and Hichwa, 2003; Phan et al., 2004; Reiman et al., 1997; Teasdale et al., 1999; Wicker et al., 2003), and emotional facial expressions like surprised faces (Kim et al., 2003), fearful faces (Hariri et al., 2000; Sprengelmeyer et al., 1998), disgusted and happy faces (Gorno-Tempini et al., 2001), as well as angry faces (e.g. Blair et al., 1999, Hariri et al., 2000). An fMRI study by Carr, Iacoboni, Dubeau, Mazziotta and Lenzi, (2003) found right-sided MPFC activation

comprised across all six basic emotions while participants passively viewed static facial pictures.

A study by Harmer, Thilo, Rothwell and Goodwin (2001), applying transcranial magnetic stimulation (TMS) to the MPFC found substantial impairment in the processing of angry (longer reaction times) but not in happy facial expressions. This finding indicates that the MPFC seems to be essential for the identification of this expression. Moreover, the medial frontal gyrus was involved in the explicit processing of ambiguous faces in contrast to clear expressions (Nomura et al., 2003).

Summarizing these empirical results, the MPFC seems to be associated with the cognitive aspects of affective processing like evaluation/identification of different emotional facial expressions (Phan et al., 2002). Since the MPFC is connected with the ACC, which is engaged in cognitively-bound emotional tasks (Phan et al., 2002), it has been proposed that these two regions are involved in the regulation of combined emotional and cognitive tasks especially when this cognitive task is explicit to the emotional response. However, during implicit processing of biologically significant signals, the MPFC might even be engaged in the top-down modulation of intense emotional responses.

1.3.2.3 Anterior Cingulate Cortex (ACC)

The cingulate cortex (Figure 2) can be divided into an anterior and a posterior part, namely ACC and PCC and is known to be a part of the limbic system. The PCC comprises several Brodmann areas (BAs 23/29/30/31) and so does the ACC (BAs 24/25/32/33). According to Vogt, Finch and Olson (1992) the PCC is involved in assessing the environment and in mnemonic associations to sensory input and thus is believed to be 'evaluative'. On the contrary, the ACC is referred to as the 'executive' region and can be divided into functional subdivisions (Devinsky, Morrell and Vogt, 1995; Paus, Koski, Caramanos and Westbury, 1998; Vogt et al., 1992).

Cognitive and emotional information is known to be processed by two major subdivisions of the ACC – a dorsal cognitive division ACcd (BAs 24b-c/32) and a

rostral-ventral affective division ACCad (rostral BAs 24a-c/32 and ventral BAs 25 / 33; Figure 2) (for review see Bush, Luu and Posner, 2000).
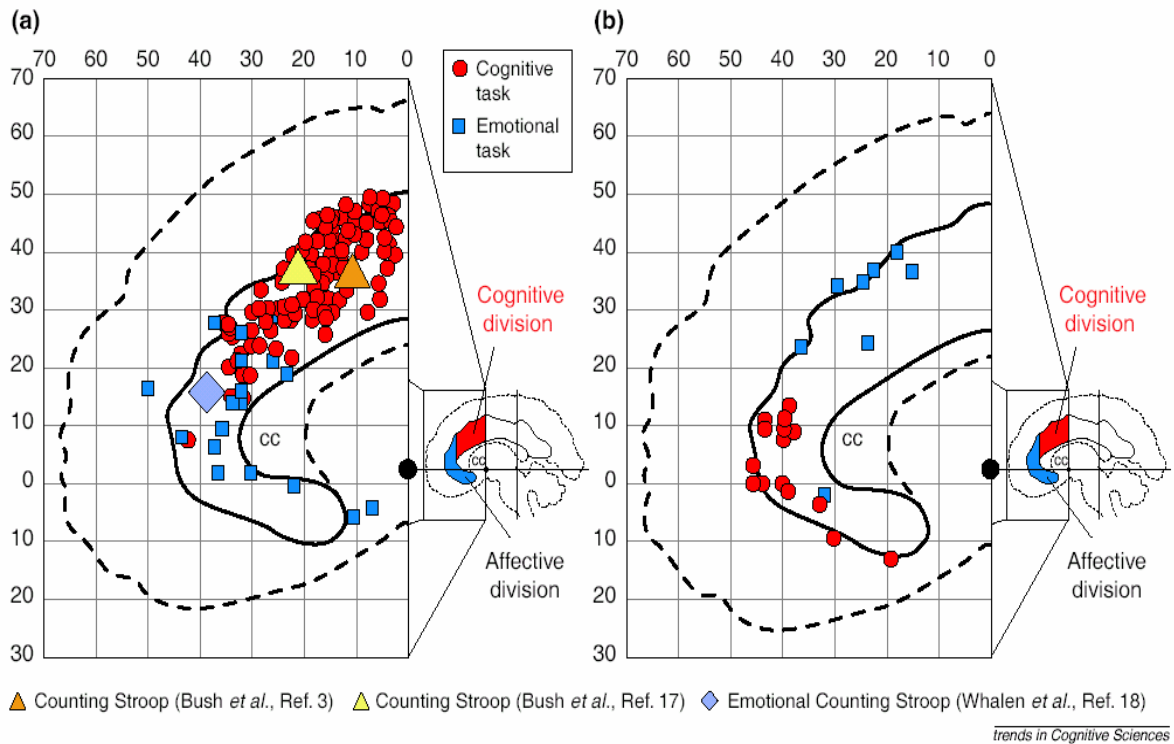
Figure 2:　　　The affective and cognitive division of the ACC (Bush et al., 2000).

Considerable evidence for such a distinction of the ACC into a cognitive and affective division has been provided. For instance, while Bush et al. (1998) confirmed involvement of ACcd during performance in a standard counting stroop paradigm, Whalen and colleagues (1998a) observed enhanced responses in ACCad when subjects performed an emotional counting stroop (emotional words like 'murder') paradigm. Furthermore, even reciprocal suppression of the affective division during performance of a cognitive task was reported (Drevets and Raichle, 1998, cited in Bush et al. 2000). Both the affective and cognitive subdivision are of course not acting in a vacuum but are part of a parallelly distributed emotional network. Nevertheless, for didactical purposes the empirical results will be reported separately.

The *cognitive division* is known to be interconnected to the LPFC, premotor and supplementary motor regions, as well as to the parietal cortex.

As stated by numerous studies, the anterior cingulate cortex, mainly the dorsal part (BA 24), is part of the nociceptive system (for review Peyron et al., 2000). The ACC's pain-related stimulus response function (SRF) further supports findings of its engagement in experiencing pain (Bornhövd et al., 2002). A study, which demonstrated that manipulation of pain unpleasantness via hypnosis alters ACC activation (e.g. Rainville et al., 1997) suggests that this region is especially associated with the emotional aspect of pain. Remarkably, results of Eisenberger, Lieberman and Williams (2003) revealed activation in the same spot of ACC when participants were unexpectedly socially rejected from participating in a virtual game. This activation was found to be correlated with the reported distress (social pain), which, according to the authors, suggested analogous neurocognitive functions of social and physical pain. In line with this idea, an engagement of this area has also been reported when participants witnessed pain in others (Botvinick et al., 2005; Hutchison, Davis, Lozano, Tasker and Dostrovsky, 1999; Jackson, Meltzoff and Decety, 2005; Morrison, Lloyd, di Pellegrino and Roberts, 2004; Singer et al., 2004). This will be outlined in detail in Section 1.4.

Involvement of this region also has been demonstrated in the modulation of the sympathetic nervous system and generation of efferent arousal responses (Critchley, 2003).

Moreover, this subdivision is activated during monitoring and controlling of goal-directed behavior. Hence, it has been found to be involved in cognitively demanding tasks, which required subjects to respond to competing information (e.g. Bush et al., 1998). This region also seems to exhibit error responses (Miltner et al., 2003; for review Bush et al., 2000). It has recently been demonstrated that an activation of the cognitive division occurred not only during errors, but even in trials without response conflict and error. This suggests that the ACcd learns to predict error likelihood in a given context for the purpose of early recruitment of cognitive control (Brown and Braver, 2005).

The *affective subdivision* with its interconnections to the amygdala, the nucleus accumbens, the periaqueductal gray, hypothalamus, anterior insula, hippocampus and the orbitofrontal cortex, as well as to autonomic, endrocrine and viceromotor structures is predisposed for a role in generating arousal responses and mediating feeling states

(Dolan, 2002). In line with this theory, Liddell and colleagues (2005) even observed activation of this division to subliminal presented fear faces.

A meta-analysis by Phan and colleagues (2002) showed that cognitively bound emotional tasks specifically engage this region. Involvement has been detected in studies on explicit processing of emotional stimuli (e.g. Dolan et al., 1996; Gusnard et al., 2001; Lane et al., 1997a; Phan et al., 2004). Moreover, inhibition of induced emotional states, e.g. by erotic clips, recruits the same area (Beauregard et al., 2001).

Furthermore, studies have revealed that ACCad is associated with the processing of emotional distractors (e.g. Bishop, Duncan, Brett and Lawrence, 2004a; Keightley et al., 2003; Vuilleumier et al., 2001; Whalen et al., 1998a). For instance, Vuilleumier et al. (2001) reported a distinction between ACcd and ACCad in the processing of fear and neutral faces depending on spatial attention. In a matching task participants were required to judge whether two stimuli (e.g. both horizontal) at a prespecified location were equal or not, while another pair was present at a task-irrelevant location (e.g. both vertical). These pairs of stimuli were either houses or faces. Whereas the ACCad was more engaged when the fear faces were task-irrelevant, the ACCcd was active when fear faces appeared in the prespecified region. The authors argue that while the cognitive subregion might be responsible for providing attention when evaluation is required, the affective division seems to inhibit attention towards the emotional faces when they are task-irrelevant. Hence, these studies suggest - analogous to the ACCcd - , a role of the ACCad in responding to unexpected processing conflict, but in this case arising from *emotionally* salient stimuli.

Furthermore, Fischer and colleagues (2004a) found a distinct pattern of activation in the affective and cognitive division depending on the actor's and observer's sex. According to the authors male observers showed enhanced responses in ACCad to male angry and fearful faces when compared to the female pendant. However, these results have to be treated with caution since the study had to deal with a severe methodological shortcoming. Participants in this study had prior to that attended in another experiment using the same fear faces.

Generally speaking, the ACCcd seems to be associated with working memory and engaged in response selection, as well as pain experience. The ACCad was shown to be

involved in the assessment of the salience of emotional and motivational information and moreover in the regulation of emotional responses (Bush et al., 2000) and their self-awareness (Lane et al., 1998).

1.3.2.4 Anterior Insula

The insular cortex is a sunken region closely located to the lateral fissure and is covered by the rostral superior temporal lobe and the caudal inferior frontal lobe (Carlson, 2004). For the purpose of this thesis the insular cortex has been divided into an anterior and a posterior part and hence empirical results will be reported in separate sections. Since many studies do not explicitly distinguish between two regions the reported Talairach coordinates have been especially examined.

As the posterior insula is closely located to the secondary somatosensory cortex, empirical results referring to this region will be outlined there. The function of the anterior insula and related findings will be reported separately in the next section.

The anterior insula is known to be reciprocally connected to brainstem and hypothalamic autonomic nuclei. Hence, this area seems to be involved in representation of bodily arousal states (Lane et al, 1997b; Reiman et al., 1997; for review: Critchley, 2003) and is believed to overall monitor the ongoing emotional state (Damasio et al., 2000; Craig, 2002). Moreover, the functional connectivity of amygdala and anterior insula has been confirmed by Keigthley and colleagues (2003).

As recently revealed by a study of Critchley, Wiens, Rotshtein, Öhman and Dolan (2004), the anterior insula seems to be a neural correlate of interoceptive awareness. On the one hand the authors requested subjects to sense whether their heartbeat was in synchronicity with a series of tones (interoceptive task), on the other hand they asked subjects to judge whether one of the notes had a different pitch (exteroceptive task). They detected individual differences in subjects' ability to accurately sense their own heart-beat, which was related to the activity and even the size (measured by voxel-based morphometry) of their anterior insula. Also the right-sided insular activity, as well as the accuracy was correlated with subject's anxiety scores. This favors the view that feelings are the consequence of body sensations, which has already been suggested by James and Lange (1884, cited in Birbaumer and Schmidt, 2003) long time ago.

Adolphs and colleagues (2003) observed impaired recognition of emotional facial expressions from static pictures in a patient with bilateral damage of the insula, which argues for a role of this area in the processing of emotion observed in others. Indeed, activation of this region was observed in several studies mainly during explicit processing of affective pictures and faces in healthy subjects (e.g. Gorno-Tempini et al., 2001; Leibenluft et al., 2004; Phan et al., 2004; Straube et al., 2004; Winston, Strange, O'Doherty and Dolan, 2002). For instance, Winston and colleagues (2002) asked subjects to rate trustworthiness of faces, which resulted - in contrast to an implicit task (age assessments) - in activation of the anterior insula when subjects judged the faces as being untrustworthy.

Moreover, the engagement of the anterior insula has predominantly been reported to recognition, as well as experience of aversive states like disgust, fear and pain. Several studies found activation of the anterior insula during exposure to unpleasant odors, but also to static pictures and dynamic clips of disgusted faces, mainly when explicitly processed (e.g. Anderson et al., 2003a; Gorno-Tempini et al., 2001; Schienle et al., 2002; Schröder et al. 2004; Sprengelmeyer et al., 1998; Wicker et al, 2003; but see Stark et al., 2003). Furthermore, the anterior insula has been shown to be involved in direct pain (Bornhövd et al., 2002; Peyron et al., 2000), as well as in the processing of vicarious pain under explicit task conditions or during passive viewing (Botvinick et al., 2005; Jackson et al., 2005; Singer et al., 2004). The latter aspect will be explicitly outlined in Section 1.4.

While most imaging studies suggest an involvement of the anterior insula mainly during explicit processing, biologically significant signals like implicitly processed intense fear faces (Morris et al., 1998a; but see Phillips et al., 1997) or subliminal presented fear faces (Liddell et al., 2005) can also elicit its engagement. Another study, also using an implicit processing task, reported enhanced BOLD-responses in the anterior insula when subjects' precise analysis of fear faces was hindered by the use of coarse low frequency images (Vuilleumier, Armony, Driver and Dolan, 2003). However, this was

not the case for high-frequency images, which provided precise information about the emotional cues.

In line with these findings Straube and colleagues (2004) found insular engagement during implicit processing of angry faces solely in a group of subjects known to be hypersensitive to this signal of social threat, namely social phobics, but not in healthy control subjects.

One can summarize that while the anterior insula seems to be mainly associated with explicit processing of emotional facial expressions, for particularly threatening stimuli it might also be activated under conditions of reduced stimulus analysis (distraction, subliminal presentation, impoverished images). This view is in line with the anterior insula's role in detection of homeostatic changes and internally perceived danger. Moreover, it appears to be associated with bringing them to consciousness (Craig, 2002).

1.3.2.5   Somatosensory Cortices (SI and SII)

The somatosensory cortices, especially those of the right hemisphere, are believed to be engaged in the recognition of emotional facial expressions (Adolphs, 2002). Adolphs suggests that facial displays may be interpreted by simulating this perceived expression using the somatosensory cortices, either overtly or covertly, and hence sensing the emotion by this simulation.

Firstly, a brief summary of the anatomy of the somatosensory cortex will be given. Afterwards the involvement of somatosensory areas in different processes and their engagement in the processing of facial expressions of emotion in particular will be outlined.

The term somatosensory cortex generally refers to the primary and secondary somatosensory cortex (SI and SII). According to Kolb and Wishaw (1996) SI is somatotopically organized and comprises the BAs 1, 2, 3a and 3b. These areas receive input from different peripheral neurons: BA1 from rapid adapting skin receptors, BA2

from pressure and joint receptors, BA3a from muscle receptors and BA3b from rapid adapting skin receptors and free nerve endings. The SII region, which appears also to be organized in a somatotopic manner, although less well structured than SI (Disbrow, Roberts and Krubitzer, 2000), is located along the upper bank of the Sylvian fissure and the parietal operculum and comprises parts of the posterior insula (Kolb and Wishaw, 1996). It receives input from somatosensory thalamus as well as from SI (Shi and Apkarian, 1995). Neurons in these regions are responsible for coding of spatial, temporal and intensity aspects of innocuous and noxious somatosensory stimulation (e.g. Kenshalo, Chudler, Anton and Dubner, 1988).

As outlined earlier, SI and SII are, besides the above mentioned engagement, part of the nociceptive system – a system that is crucial for the analysis of potentially life-threatening situations (Peyron et al., 2000). Both areas are involved in the processing of sensory-discriminative aspects of pain. As suggested by primate studies, the SI region encodes the intensity of tactile and nociceptive stimuli (e.g. Kenshalo et al., 1988). Bornhövd and colleagues (2002) further demonstrated that this region showed an intensity-related SRF, which slightly decreased at maximum pain intensities. Area SII, which often comprises the posterior part of the insula, also seems to be responsible for intensity coding during pain (Sawamoto et al., 2000). Indeed, Bornhövd and colleagues (2002) did not find a response of this region to the intensity of nonpainful stimuli, but only to pain intensity.

Striking evidence for the importance of the somatosensory cortices in emotion processing has been provided by lesion studies that describe impairment in recognizing especially negative emotions in patients suffering from focal brain damage in somatosensory areas (Adolphs et al., 1996). Importantly, this impairment did solely occur when the lesion comprised the right hemisphere, whereas patients with exclusively left-sided damage recognized the expressions normally. Adolphs and colleagues (2000) found highest impairment of emotion recognition from static pictures (six basic emotions) in a group of 108 patients when lesions were located in the right somatosensory-related cortices, namely the lower sector of SI and SII, anterior supramarginal gyrus and, to a lesser extent the insula.

Adolphs (1999) assumes that high-level cognition requires not only the representation of the individual's own state in response to a facial display, but also the ability to construct a mental model of the other individual's state. He argues for a mechanism that might even be innate, characterized by reactivation of the neuronal circuits (limbic and somatosensory), which had been previously engaged while oneself perceived a comparable emotional state. Thereby he emphasizes that this does not necessarily cause conscious feeling of the same emotion.

Such a mechanism of mirroring the other person's emotional state for precise analysis and recognition is supported by several findings. For instance, Wallbott (1991) reported that people mimic facial expressions, which they were requested to judge. However, only simple mimicry has been reported when people merely observed facial expressions of others. Furthermore, Levenson, Ekman and Friesen's (1990) findings of induction of emotional states by volitional contractions of face muscles, highlight the proposed importance of imitation in emotional experience.

The rare data basis on somatosensory activation during recognition of emotional facial expression might be partly due to habituation effects in this area. Feinstein, Goldin, Stein, Brown and Paulus (2002) reported signal attenuation across time in the right SI when subjects were exposed repeatedly to emotional faces while performing a gender discrimination task.

Hence, besides powerful lesion studies, only few works have explicitly described involvement of the somatosensory cortices in feeling or observing emotional states. For instance, Carr et al. (2003) who requested subjects to observe static pictures of the six basic emotions, as well as imitating and internally generating them, found bilateral SI activation during imitation but not during passive viewing of emotions. However, one has to note that these findings based on computations comprised across all emotions what could have possibly covered differential engagement of SI during observation of different emotions. Another study investigating somatosensory involvement during internal generation of emotion is the one by Damasio and colleagues (2000). They investigated recall of emotion (sadness, happiness, anger, fear) from autobiographic

memory in healthy subjects and reported distinct cortical and subcortical patterns of activation for different emotions. Thereby, SII showed differential engagement, which was characterized by right-sided activations during happiness, right-sided activation and left sided deactivation during fearful memories, right-sided decrease while experiencing sadness and bilateral signal decreases during recall of anger.

Besides somatosensory involvement while participants actively imitate or internally generate emotions, these brain regions also appear to contribute to explicit processing of emotional facial expressions as shown for instance by Winston and colleagues (2003a). In this study, subjects were presented morphed emotional faces displaying low or high intensities of disgust, fear, happiness, or sadness. BOLD-responses under an explicit emotion related task and an implicit gender-related task were investigated revealing right-sided engagement of somatosensory cortices (also of vMPFC) only during explicit emotional judgments. At an uncorrected threshold also bilateral activation of SII/posterior insula was reported. In line with Adolph's theory, the authors proposed a role of vMPFC and somatosensory cortex in explicit emotion processing through linking emotion perception with representations of somatic states previously elicited by similar emotional states. Recently, a study by Pourtois and colleagues (2004) applying single-pulse transcranial magnetic stimulation (TMS) to the right somatosensory cortices reported selective TMS-related interference in a matching task to fear but not to happy faces. This happened to occur at an early latency (<200ms) following stimulus onset supporting the findings of Adolphs and colleagues (2000).

In accordance with these results, Kilts and colleagues (2003) reported engagement of left SI (BA1/2) during explicit processing of static angry and happy faces as compared to neutral displays, while no difference in somatosensory activation occurred between both emotional conditions. No somatosensory involvement was found for dynamic happy and angry faces, which, as suggested by the authors, possibly reflects stronger reliance on motor simulation for successful decoding of emotions from static faces.

In contrast to this hypothesis, Wicker et al. (2003) observed somatosensory engagement during passive viewing of dynamic face stimuli. The authors detected enhanced activation in left SI (BA1) during passive viewing of disgusted face clips relative to neutral, but not for "pleasure faces" relative to neutral.

However, these findings do not necessarily contradict but might qualify the explanation by Kilts et al. (2003). One could for instance hypothesize a general lack of somatosensory activation to dynamic face stimuli involving only few AUs but automatic mimicry for facial displays comprising more facial action like disgust or fear. To date no imaging study, to the best of the author's knowledge, explicitly described or investigated involvement of the somatosensory cortices during processing of emotional facial expressions while participants were attentionally distracted. However, Liddell and colleagues (2005) found activation in left SI while subjects actively attended to subliminal presented fear faces in contrast to neutral faces. The authors argue for the contribution of this area in the processing of biologically salient stimuli as already suggested by other studies (Berns, Cohen and Mintun, 1997; Halgren and Marinkovi, 1995). Another investigation on 'unseen' fear in a blindsight patient also reported somatosensory activation, although not surviving the whole brain statistical corrections (Morris et al., 2001).

Besides activation of SI and SII also the posterior insula was found to be activated during static face processing (e.g. fearful, disgusted, familiar), however, when the task was either implicit (e.g. Gobbini et al., 2004; Pessoa, McKenna, Gutierrez and Ungeleider, 2002) or explicit (e.g. Phillips et al., 2004).

Reconciling these findings, engagement of the somatosensory areas (SI/SII) appears to occur during imitation, explicit judgements of emotion, as well as during passive viewing of more expressive facial categories. Although its engagement under distraction of attention has not been examined yet, a contribution of this area in subliminal processing of salient stimuli has been proposed. However, none of these studies differentiated somatosensory responses with respect to the actors' sexes.

1.3.2.6 Fusiform Face Area (FFA) and Superior Temporal Sulcus (STS)

Visual areas are organized as two functionally specialized processing pathways, both originating in the primary visual cortex. Hence, a ventral stream (occipotemporal) path associated with the identification of objects and a dorsal pathway (occipoparietal) crucial for the assessment of the spatial relation among objects and for visually guided

movements has been proposed (Goodale and Milner, 1992 cited by Carlson, 2004). While the FFA is part of the ventral path, the STS region belongs to the dorsal path.

Visual information of faces contains static-based information like facial structure and features (e.g. nose, distance between the eyes) and facial motion. Facial motion comprises both person-specific information and additionally social communicative information (e.g. gaze, facial expression).

Fusiform Face Area (FFA)

The FFA, part of the core system involved in face perception proposed by Haxby and colleagues (2000), is responsible for face recognition based on invariant aspects of faces as consistently shown in a variety of studies (e.g. Hoffman and Haxby, 2000; Kanwisher, McDermott, Chun, 1997; Kanwisher, Stanley and Harris, 1999; Yovel and Kanwisher, 2004). However, it has also been demonstrated that it is not exclusively involved during face perception but also during processing of non-face objects (Haxby et al., 2001; Ishai, Ungerleider, Martin, Schouten and Haxby, 1999). Moreover, its activation increased with expertise and learning (Gauthier, Skudlarski, Gore and Anderson, 2000; Grossman, Blake and Kim, 2004).

Besides the general engagement of FFA in face recognition its activity seemed to be modulated by the emotional importance of the facial displays. For instance, Golby, Gabrieli, Chiao and Eberhardt (2001) found stronger BOLD-increases in FFA to same-race than to other-race faces. Also it has been demonstrated that the face area was more activated when participants were required to attend to face identity than to gender or occupation of the model (e.g. Sergent, Ohta, MacDonald and Zuck, 1992, cited in Hoffman and Haxby, 2000; Turk, Rosenblum, Gazzaniga and Macrae, 2005). Although the FFA has been shown to be engaged in implicit (e.g. Anderson et al., 2003a; Iidaka et al., 2001; Morris et al., 1998b; Schröder et al., 2004; Sprengelmeyer et al., 1998; Williams et al., 2004), and explicit processing of emotional facial expressions (e.g. Gläscher, Tüscher, Weiller and Büchel, 2004; Narumoto et al., 2000) studies directly comparing both attentional foci found stronger involvement in explicit tasks (e.g. Critchley et al., 2000a; Pessoa et al., 2002). Moreover, one has to emphasize that effects of emotion intensity have often been reported for positive and negative facial

expressions (e.g. Gläscher et al., 2004; Morris et al., 1998b; Surguladze et al., 2003; Winston et al., 2003a; Winston, Vuilleumier and Dolan, 2003b). Since this arousal dimension is often contaminated by valence (unpleasant – highly arousing), empirical findings on FFA activation might underlie a negativity bias and therefore often report stronger responses in the "face area" to threatening than to neutral expressions.

Furthermore, in line with the fact that the amygdala is interconnected with FFA (Amaral et al., 1992), functional interactions of FFA and the amygdala have been described (e.g. Morris et al., 1998b; Winston et al., 2003b), reflecting modulatory feedback influences based on emotional significance from the amygdala on extrastriate cortical areas. Thus, although FFA activation is observed during a variety of tasks and types of emotional facial expressions its involvement might influences by amygdalar responding.

Besides an involvement of the FFA during processing of static faces, also dynamic stimuli elicited activation of this region via free viewing of complex movie sequences (Bartels and Zeki, 2004; Hasson, Nir, Levy, Fuhrmann and Malach, 2004) or exposure to fixed sets of face clips or morphs (Kilts et al., 2003; LaBar et al., 2003; Sato et al., 2004a; Wicker et al., 2003).

Superior Temporal Sulcus (STS)

The STS, also part of the core system of face recognition proposed by Haxby and colleagues (2000, 2002), is involved in the processing of variable aspects of a face and the evaluation of its social relevance (Allison, Puce and McCarthy, 2000). Hence, a role of this area in encoding of facial expressions and direction of gaze has been proposed (e.g. Hoffman and Haxby, 2000; Wicker, Michel, Henaff and Decety, 1998). Important evidence for this assumption came from studies using single-cell recordings of the STS region in monkeys (e.g. Sugase, Yamane, Ueno and Kawano, 1999).

Indeed, imaging studies consistently found enhanced responses in this area during processing of biological motion like eye and mouth movement (Puce, Allison, Bentin, Gore and McCarthy, 1998), hand (Bonda, Petrides, Ostry and Evans, 1996) and body movement (Bonda et al., 1996; Grossman et al., 2000). This was also observed during natural viewing of movies (Bartels and Zeki, 2004; Hasson et al., 2004). Moreover, still pictures, which imply intentions and intentional activity as used in studies investigating

'theory of mind', activated the STS (Gallagher et al., 2000; for review see Frith and Frith, 2003).

The STS region is directly (Amaral et al., 1992) and via frontotemporolimbic interfaces indirectly (Petrides and Pandya, 1999) interconnected to the amygdala, which also back-projects into this area (Allison et al., 2000). Considerable evidence for modulatory amygdalar influences on STS activation has recently been provided by Vuilleumier and colleagues (2004). Thus, emotional salience of stimuli as processed by the amygdala could enhance response of STS cells to emotional facial expressions.

According to its proposed role, STS activity was enhanced during recognition of emotional facial expressions from static stimuli (e.g. Carr et al., 2003; Narumoto, Okada, Sadato, Fukui and Yonekura, 2001; Winston et al., 2002, 2003a) as well as dynamic morphs or movie clips (Kilts et al., 2003; LaBar et al., 2003; Wicker et al., 2003). Responses elicited by dynamic stimuli furthermore seem to be stronger than the ones elicited by static facial displays (Kilts et al., 2003).

Similarly to FFA, the activity of STS seems to be modulated by stimulus valence and the attentional focus of the processing task. Thus, the comparison of negative with positive or neutral dynamic displays yielded stronger responses (Kilts et al., 2003; LaBar et al., 2003; Wicker et al., 2003) and, moreover, high intensity emotion was associated with enhanced STS involvement (Winston et al., 2003a). Furthermore, explicit processing elicited stronger BOLD-responses in this area (e.g. Narumoto et al., 2001; Pessoa et al., 2002; Winston et al., 2002, 2003a).

One can summarize that the FFA seems to be more associated with the processing of facial identity, whereas STS is involved in the processing of socially relevant signals. They furthermore seems to be either directly, or indirectly via regions (e.g. amygdala) associated with the processing of emotional salience, involved in the processing of emotional facial expressions.

However, one has to note that the activation within these areas underlies habituation effects. Ishai, Pessoa, Bikle and Ungerleider (2004) found signal attenuation in STS and FFA during repeated exposure to fearful and neutral facial expressions.

1.3.2.7   Autonomic Responses during Emotion Recognition

In general, one distinguishes autonomic orienting (OR) and defense responses (DR). An OR is associated with the processing of novel and significant stimuli and characterized by an increase of RR-intervals (HR deceleration) and phasic changes of the electrodermal activity (EDA) providing processing resources for a transfer of the information from preattentive to attentive levels. The DR occurs during exposure to painful or dangerous stimuli and is accompanied by a decrease of RR-intervals and phasic changes of the EDA (Stern and Sison, 1990). An autonomic response is characterized by a multiple level organization including higher rostral neural systems (hypothalamus, amygdala, MPFC) and lower reflex systems (brainstem). These systems are heterarchically interconnected, which means that besides hierarchical ascending and descending projections between these levels also long connections from the top to the bottom level exist, allowing for a flexible control by high level regions (Bernston and Cacioppo, 2002).

Cardiovascular Response (RR-interval)

The control of cardiovascular activity is an important aspect of adaptive behavior. While the parasympathetic activation is associated with fast decrease of heart beats (or vice versa) the sympathetic activation slowly increases the heart beats (Carlson, 2004). Dynamic interactions between these excitatory and inhibitory control mechanisms can be measured as heart-rate variability (HRV), which reflects changes in intervals between R-waves. The RR-interval is sensitive to stimulus novelty, significance and unpleasantness (increase) as well as to potential threat (decrease). Empirical data confirmed larger RR-interval increases during negative compared to positive stimulation (e.g. Bradley, Codispoti, Cuthbert and Lang, 2001; Lang, Greenwald, Bradley and Hamm, 1993). Other studies, which investigated cardiovascular responses to induced emotional states on a psychophysiological level revealed heart rate increases to sad, angry, fearful and happy emotion relative to a neutral state (Damasio et al., 2000). Furthermore, imitation of facial expressions led to a decrease of the RR-interval, which differed between emotions and was independent of the facial movement's

complexity (Levenson et al., 1990; Levenson and Ekman, 2002). Rainville, Bechara, Naqvi and Damasio (submitted) also find distinct patterns of cardiovascular activity (parasympathetic and sympathetic branch) for the processing of sad, angry, fearful and happy faces, which confirms the previous findings of Levenson and colleagues (1990).

Imaging studies, which examined cardiovascular responses to affective picture processing (e.g. International Affective Picture System - IAPS) also found RR-interval increases during passive viewing of negative pictures, as well as to positive IAPS photographs (Kuniecki, Urbanik, Sobiecka, Kozub and Binder, 2003). Another study by Gomez, Stahel and Danuser (2004b), as well using an explicit task, did not find an RR-interval increase with enhanced unpleasantness. According to the authors, the block-wise presentation of stimuli probably caused a reduction of the stimuli's affective novelty and hence led to the observed lack of valence modulation.

To the best of the author's knowledge, only one imaging study incorporated cardiac measures, while subjects were processing emotional facial expressions (Critchley et al., 2005). The authors demonstrated that explicit processing (reaction time task incl. emotion classification) of happy, sad, angry and disgusted faces elicited differential changes in RR-interval. While relative RR-interval decreases were detected to processing sad and angry faces, the cardiovascular response to happy and disgusted faces was characterized by relative increases. These findings are in line with the ones found in emotion induction studies. One might assume that explicit processing is more likely to induce the observed emotional state in the observer than during an implicit task (gender discrimination). Furthermore, these evoked visceral changes were coupled with activation of the brainstem, the amygdala, anterior insula, ACCcd and with activity in FFA and STS.

So far, no brain imaging study has investigated cardiac indices during implicit processing of static or dynamic facial expressions. However, Gomez, Zimmermann, Guttormsen-Schär and Danuser (2005) found stronger RR-interval increase during passive viewing of negative in contrast to positive film clips.

Electrodermal Response (GSR)

Changes in electrical conductance of the skin are referred to as electrodermal activity (EDA), which includes phasic changes – the so called galvanic skin response (GSR). The GSR is sensitive to stimulus novelty, intensity, emotional content and significance, and is hence a critical index of changes in sympathetic autonomic arousal (Dawson, Schell and Filion, 1990).

Previous studies investigating electrodermal response to affective pictures (IAPS) or movie clips consistently observed higher electrodermal activity during arousing as compared to calming stimuli regardless of valence (Anders, Lotze, Erb, Grodd and Birbaumer, 2004; Bradley et al., 2001; Gomez and Danuser, 2004a; Gomez et al., 2004b; Gomez et al., 2005; Lang et al., 1993). Moreover, considerable evidence has been provided for a role of the amygdala in the expression of GSRs (e.g. Critchley, Elliott, Mathias and Dolan, 2000c; Critchley, Mathias and Dolan, 2002). Further insights came from brain lesion studies, which found impaired GSRs during fear conditioning (e.g. Bechara, Damasio, Damasio and Lee, 1999) and during processing of arousing IAPS pictures (Gläscher and Adolphs, 2003) in patients with amygdala lesion.

Imaging studies simultaneously investigating the SCRs to emotional facial expressions are still rare. However, Williams and colleagues (2001) presented fearful and neutral static facial displays, while subjects were distracted by a gender decision task. In line with the above mentioned results, fear faces elicited increased SCRs, which were associated with enhanced BOLD-response in the amygdala and the medial frontal cortex. To date no brain imaging study has investigated SCRs during processing of dynamic facial expressions. Solely one study by Gomez and colleagues (2005), which presented movie clips, found higher skin conductance levels during passive viewing of arousing in contrast to calming film clips.

1.4   Neural System for Pain Recognition?

The next section summarizes the results of studies dealing with the neural correlates of observing pain in others. One has to emphasize that most of these studies compared a vicarious pain condition to an experience of experimental pain. Hence, in contrast to the

present work, these studies refer to a more explicit processing of pain in others, which has often been linked to the term 'pain empathy' by these authors.

On the one hand these studies investigated responses to pain faces, which will be reviewed in the first section and on the other hand they used cues independent of facial expressions that are reported in the second section. Finally, the term 'pain empathy' will be discussed critically.

1.4.1   Pain Recognition from Facial Expressions

In the past, research on recognition of facial pain expression was done using physiological measures like HR and GSR during direct (e.g. cold pressor test) and vicarious pain experience (e.g. Craig, 1968; Craig and Lowery 1969a; Craig and Wood, 1969b). Those studies revealed significant differences in the physiological response between these kinds of experiences as compared to a rest state. Whereas SCR tended to increase in the course of all pain related experiences, HR accelerated during direct or imagined, but decelerated during vicarious pain experience (e.g. Craig, 1968).

So far, one imaging study has investigated the neural response during exposure to pain contorted faces. Botvinick and colleagues (2005) compared subjects' BOLD-responses to alternating blocks of thermal painful stimulation (vs. non-painful) and visual stimulation with short movie clips showing shoulder pain patients undergoing active or passive motion exercises of the affected limb and displaying facial expressions of pain (vs. neutral). Advantageously, these clips comprised the facial behavior of 21 different individuals, however, poorly described in terms of models' age and ethnic group. Subjects were asked to passively attend to all stimuli. The authors found activation of ACCcd and bilateral anterior insulae to both direct and vicarious pain experience. Post-hoc exploratory analysis also revealed a bilateral involvement of the thalamus, medial frontal gyrus (MFG), occipital cortex and cerebellum, right-sided activation of FFA, STS and inferior parietal lobule (BA 40), as well as left-sided engagement of amygdala, orbitofrontal cortex and temporo-parietal junction during visual stimulation.

However, this study contains several methodological shortcomings. The most critical point is the fact that the authors did not include any other emotional facial expression

than pain, but aim to conclude on pain specificity of responses. Furthermore, they used a fixed block order with visual stimulation always followed by thermal stimulation. Hence, expectations and order effects might have been occurred and presumably contaminated the activation observed during visual runs. Moreover, since no study so far disproved observer sex differences in the processing of pain faces, results of this study, which solely investigates this in female observers, can not be generalized. Besides these critical aspects, some further questionable points have to be highlighted. Firstly, the group used an unusually liberal threshold for statistical analysis ($p<0.05$ uncorrected). Secondly, subject's attendance to the visual stimuli, especially to neutral faces, was not monitored throughout the experiment. Thirdly, the pain clips had different duration (mean duration: 1.10s; SD=0.50s). Lastly, the luminance of pain clips and blank screen in between (black) was not matched.

However, summarizing these results the dynamic facial expressions of pain elicit responses in brain areas that have been found to be involved in the processing of emotional facial expressions. Since this study failed to include any other emotional face it can not be concluded that the evoked response is pain-specific. Instead, the authors interpret their findings in terms of 'pain empathy'. This will be further discussed in the last section of the introduction.

1.4.2 Pain Recognition from Other Cues

An early electrophysiological study dealing with the subject of mental evocation of pain in others was conducted by Hutchison and colleagues (1999). This group measured single cell activity in the ACC of precingulotomy patients during painful stimulation in patients themselves (thermal and mechanical) and while they observed the application of these stimuli to the experimenter. Especially to painful pinpricks the authors found activation of the ACCcd when these stimuli were applied to the patients own hand, as well as to the experimenter's hand.

Recently, three imaging studies investigated vicarious pain relying on somatosensory or visual cues independent of facial expression to evoke the mental representation of pain in self and others (Jackson et al., 2005; Morrison et al., 2004; Singer et al., 2004).

Morrison and colleagues (2004) compared brain responses to blocks of 'feeling' a noxious tactile stimulation applied to the finger (vs. non-painful) with blocks of 'observing' this painful stimulation of an unknown person's hand (vs. non-painful) as presented via movie clips. Blocks were intermixed with a baseline rest condition. All of these stimulations were passively experienced by the subjects. After scanning, they provided unpleasantness ratings for perceived and observed painful stimulation resulting in equal levels of unpleasantness. During visual presentation of noxious experience as compared to baseline, activation in bilateral ACCcd, right MFG and left superior frontal gyrus (SFG) was observed. One has to note that the authors did not control for the observers handedness, which might have contaminated the data in terms of laterality. Unfortunately, Morrison and colleagues (2004) did not provide information about the visual pain specific contrast (movie noxious vs. movie non-noxious stimulation). However, a conjunction analysis revealed enhanced responses in right ACCcd commonly to both direct and vicarious pain experience compared to rest and non-noxious conditions.

Another study by Singer et al. (2004) studied neural responses to pain perception and pain observation in 16 couples (36% married; dating duration: 2.4±1.9 years) with the female being placed in the scanner and her partner being outside of the scanner in the same room. Via a mirror system the female was able to see her own and her partner's right hand, which was placed on a tilted board. Visual cues projected onto a screen indicated a weak or a sharp electrical shock (1sec) which was either delivered to the female's or her partner's hand. The participants judged the unpleasantness of all four conditions (pain - no pain in self - others). Painful trials were rated as being significantly more unpleasant than nonpainful trials, irrespective of whether the pain was direct or vicarious. During direct pain experience as compared to 'no pain' areas of the 'pain matrix' were activated. Observing the partner in pain, relying on the visual cue rather than on visual information of the hand itself, enhanced BOLD- responses were detected in anterior and posterior portion of the ACCad, bilateral anterior insulae, left brainstem and cerebellum. Furthermore, activation was observed in LPFC and FFA bilaterally, in superior frontal sulcus and inferior parietal cortex on the left as well as in occipital cortex and STS on the right. Conjunction analysis moreover revealed that ACCcd and the posterior part of ACCad, as well as bilateral anterior and mid insulae

were commonly activated during direct and vicarious pain experience. Interestingly, the time course of activation in those areas during the vicarious pain condition was characterized by two peaks – an early one after the cue and a late one, whereas the time courses during actual noxious stimulation only showed the late peak. The authors explained this first peak as an indicator of anticipation. Additionally, Singer et al. (2004) observed that activity in the left anterior insula and the posterior ACCad significantly covaried with post-scan measured empathy scores measured on two scales: Interpersonal Reactivity Index – Subscale Empathic concern (IRI-EC) by Davis (1983) and the Balanced Emotional Empathy Scale (BEES) by Mehrabian and Epstein (1972).

Another study investigating the vicarious pain experience by using a different approach without a direct pain experience is the one by Jackson and colleagues (2005). They presented blocks of static color photographs displaying right hands and feet in situations being likely to cause pain (e.g. finger caught in the door) and in similar situations without painful event intermixed with a baseline condition showing static crosses. During scanning the participants were asked to rate the perceived pain intensity on a visual analog scale (baseline task: indicating the cross position) and thus explicitly processed the visual stimuli. The pain intensity judgements to painful events were significantly higher than to no pain events. Contrasting pain against neutral pictures resulted in activation of ACCcd, bilateral anterior insula, cerebellum, thalamus and posterior parietal cortex. Additionally enhanced BOLD-responses were detected in the precuneus, inferior and medial frontal gyrus bilaterally, in supplementary motor area, as well as in the occipitotemporal junction on the right side. In contrast to Singer et al. (2004), empathy scores (IRI-scale) did not reveal a significant coactivation with any brain region's activity. This might be partly explained by the fact that Singer and colleagues (2004) solely investigated females while Jackson et al. (2005) studied responses in both sexes. Differences in the empathic ability, with females showing more empathy than males have been reported (e.g. Eisenberg and Lennon, 1983).

Summarizing these results, one can say that the vicarious pain experience, independent of the used stimulus material, elicited an activation of the ACC, especially in the cognitive division (Botvinick et al., 2005; Hutchison et al., 1999; Jackson et al., 2005; Morrison et al., 2004; Singer et al., 2004). Moreover, most of these studies report also

bilateral involvement of the anterior insula while subjects were observing pain (Botvinick et al., 2005; Jackson et al., 2005; Singer et al., 2004). All of these studies are part of a growing body of research investigating mind states like 'theory of mind' and empathy. These theoretical concepts assume a neural representation of what another person is experiencing in the observer. Applied to the pain experience researchers suggest an involvement of the 'pain matrix' also during witnessing painful events in others. The above described imaging studies on vicarious pain experience interpret their findings according to this idea of 'pain empathy' and propose an involvement of the areas associated with the affective-motivational component of pain, but not with those associated in sensory-discriminative aspects of pain. The concept of 'pain empathy' and its validity in the course of these experiments will be critically discussed in the next section.

1.4.3   From Pain Recognition to 'Pain Empathy'?

The idea of the research on 'pain empathy' stems from studies on the perception action model (PAM) reporting the existence of so called 'mirror neurons' in monkeys and humans, which are active during both, action itself and observation of this action performed by another individual (Buccino, Binkofski and Riggio, 2004; Meltzoff and Decety, 2003; for review see Rizzolatti, Fogassi and Gallese, 2001). This mechanism has also been observed in imaging studies comparing brain activity associated with the *imitation* of different facial expressions and the *observation* of static (Carr et al., 2003) or dynamic stimuli (Leslie, Johnson-Frey and Grafton, 2004) showing different emotional facial expressions. Moreover, also in line with this idea Wicker and colleagues (2003) observed enhanced BOLD-responses in the insula when subjects smelled an aversive odor but also when they watched movie clips of disgusted faces suggesting a common substrate for feeling and observing an emotion. According to Damasio and colleagues (2000), recalling emotions is accompanied by the engagement of several brain areas including upper brain stem nuclei, hypothalamus, somatosensory and orbitofrontal cortices, and the insula. There seems to be a clear overlap between feeling an emotion and viewing emotional facial expressions in others.

Based on the above described idea, researchers assume that the perception of other people in pain could involve the activation of brain regions associated with the experience of pain. Recent studies partly support this hypothesis, showing that the insula and the ACC (as well as regions of the prefrontal cortex) may be involved directly or indirectly in the anticipation of pain (e.g. Ploghaus et al., 1999) and in the mental evocation of pain in the absence of a noxious stimulus (Derbyshire, Whalley, Stenger and Oakley, 2004; Rainville et al., 2004). The above described studies on vicarious pain provide further evidence for this hypothesis. It is assumed that pain empathy occurs when the subject's own representation of the pain event is directly activated by perception of a target in pain. However, so far all studies failed to find activation of areas associated with sensory aspects of pain (SI and SII) and argued that a detailed sensory-discriminative representation of the noxious stimulus might not be necessary to understand another's pain (Singer et al., 2004). Instead an engagement of regions associated with the affective aspects of pain (ACC and anterior insula) was detected and assumed to reflect a state in the perceiver from which 'pain empathy' may stem. Two critical questions arise from these facts:

1. Is the evoked vicarious pain response 'just' an affective or a pain-specific affective response?
2. Can this response be interpreted as 'feeling in' another person's pain as suggested by the term 'pain empathy'?

With regard to the first question, one has to note that theses studies indeed provide some evidence for a partly shared network of direct and vicarious pain (Morrison et al., 2004; Singer et al., 2004). However, since the ACC and anterior insula are also involved in other emotional and cognitive processes alternative explanations have to be taken into account. One could also interpret the representation of other's pain as a special case of anticipation resulting in ACC's engagement. This might even occur in the absence of direct pain and could be referred to as an automatic mechanism crucial for one's own survival (Jackson et al., 2005). Moreover, the ACC's activation could also reflect mere attention and arousal to salient, aversive stimuli. One could argue that this should be accompanied by activation of the amygdala. However, as noted in Section 1.3.2.1., detecting activation of the amygdala crucially depends on the attentional focus of a task and moreover on scanning parameters like e.g. slice thickness. Hence, the lack of

amygdala involvement in three of the four studies (Jackson et al., 2005; Morrison et al., 2004; Singer et al., 2004) does not invalidate this alternative interpretation, but could be rather due to differences in experimental tasks and acquisition parameters between these studies. Additionally, both ACC and anterior insula have been observed to be associated with the representation of internal bodily states. But it still remains unclear whether this response reflects re-acting of the affective dimension of pain as suggested by Singer and colleagues (2004). Thus, in order to answer the first question one should not only compare vicarious pain to real pain experiences (Botvinick et al., 2005; Morrison et al., 2004; Singer et al., 2004) or to other vicarious pain conditions (Jackson et al., 2005), but also to other emotions.

Answering the second question seems to be more puzzling and requires refining the definition of 'pain empathy'. The term empathy (Greek: empátheia = passion) generally describes a person's ability (observer) to "feel in" another person (target), but it has been used differently across and within disciplines (for review Eisenberg and Lennon, 1983). However, two components in the definition of empathy seem to be consistent across concepts: (a) an affective response to another person's state (emotional empathy) and (b) the cognitive capacity to take another person's perspective (cognitive empathy). Moreover, other terms are often used as a synonym for 'empathy'. Table 2 shows a distinction of these terms.

Table 2:   Distinction between different terms used in the context of empathy (Preston and de Waal, 2002 - modified).

Term	Self-other distinction	State matching
Emotional contagion	Lacking	Yes
Sympathy	Intact	No (feeling sorry for the target)
(Emotional) empathy	Intact	Yes (but not feeling the same)
Cognitive empathy	Intact	Partial

Another typology by Thompson (2002) distinguishes several facets of empathy:

- passive involuntary coupling including = unconscious sensorimotor embodiment of empathy (PAM, 'mirror neurons')
- spatial transposition of perspective ('theory of mind')
- reciprocity of imagery in interindividual exchange
- ethical and moral aspects

It becomes obvious that neuropsychological studies like the reported imaging studies solely investigate a small, artificial aspect of the face-to-face intersubjective experience of empathy – the passive involuntary coupling. The term 'empathy' should therefore be used more cautious. All four studies on vicarious pain equalize neural correlates of observing and recognizing pain in another person with empathy for pain without assessing behavioral data referring to the above mentioned affective and cognitive aspect of empathy. Applying these different concepts of empathy on the pain experience one could assume a first-order affective response referred to as automatic mirroring response. This would comprise the perception and *automatic* recognition of another person in pain. One could further assume that this process is followed by retrieval of knowledge and memory on past pain experiences in order to *know* that the other person is in pain (perspective taking), which could be automatic as well. Moreover, the process of '*feeling in*' another person might be a second-order affective reaction requiring conscious processing. In this actual understanding of emotional empathy (Table 2) one could assume that the proposed affective response is accompanied by feelings of unpleasantness and arousal in the observer during witnessing a model in pain.

One could also suppose that empathy does not occur per se but might depend on the degree of potential threat emanated from the person in pain. This might decrease empathic behavior and prompt self protection behavior instead. However, those are solely assumptions which have to be further elucidated.

Hence, before examining 'pain empathy' it seems to be necessary to understand the first stage in this assumed empathic response – namely investigating how people automatically detect and perceive pain in others. The present study is aimed to contribute to this understanding.

2   <u>Objectives and Hypothesis</u>

The recognition of emotional facial expressions is an essential aspect of social communication and seems to rely on a network of subcortical and cortical brain regions (Adolphs, 2002; Phan et al., 2002). Although the facial expression of pain is the most prominent nonverbal pain behavior, which conveys crucial information both from a clinical and an evolutionary point of view (Williams, 2002), little is known about the neurobiological basis for the communication of pain and its recognition. However, one recent imaging study investigates females' brain responses to dynamic facial expressions of pain as compared to direct pain in terms of 'pain empathy' (Botvinick et al., 2005) and thereby completely overlooks examining mere recognition of pain in others. Also, Botvinick and colleagues' study aims to conclude on pain specificity of neural responses, failing to include any other emotional facial expression for comparison. Furthermore, it does not incorporate any behavioral and autonomic measures, in order to be able to relate the observed brain responses to participant's actual emotional experience.

Hence, in the course of two experiments (see Section 3.4.) the present thesis endeavors to quantify the mechanisms of automatic processing of male and female pain contorted faces in male and female observers. It moreover examines the distinctness of this process in contrast to another threat-relevant facial expression, namely 'anger', as well as to neutral control faces. During exposure to the different facial expressions and while performing a distracting gender discrimination task subjects' brain, autonomic activation and behavioral responses are acquired and related to each other. Moreover, since studies report a relationship between pain behavior and pain catastrophizing tendencies (Sullivan et al., 2001), as well as vicarious pain and empathic ability (Singer et al., 2004) questionnaires assessing these constructs are included. Furthermore, brain activity to threat-related facial displays seems to be related to participant's anxiety levels (Bishop et al., 2004a, 2004b) and therefore individual anxiety scores are measured. These questionnaires are additionally incorporated into analyses.

The following major assumptions are stated:

I. Behavioral Data:

1. There is an overall agreement on the specificity of prototypical basic emotions and facial expressions of pain that can be reliably recognized by individuals (Smith and Scott, 1997; Williams, 2002). Hence, subjects are expected to be able to clearly distinguish and recognize pain contorted, angry and neutral facial displays.

2. Since pain and anger are thought to, inter alia, signal threat it is assumed that they are, from the actor's point of view, rated as being more arousing und unpleasant than neutral faces.

3. Additionally, subjects' own experience of arousal and unpleasantness during exposure to angry and pain contorted facial expressions is presumed to show the same pattern as from the actor's viewpoint, but solely for highly empathic individuals.

4. Moreover, a positive correlation between interindividual differences in empathic ability and trait anxiety with valence and arousal (actor viewpoint), as well as intensity ratings to anger faces is hypothesized. The same patterns and additionally a positive correlation of pain catastrophizing with ratings to pain faces are proposed.

5. Finally, since research investigating emotion recognition from facial expressions in dependence of actor's and observer's sex is still rare, the behavioral data is investigated in terms of sex differences.

II. Peripheral Physiological Data:

Only few studies investigate cardiac and electrodermal autonomic responses to emotional facial expressions and even less during implicit task conditions. However, processing of salient stimuli is generally accompanied by an orienting response (Stern and Sison, 1990). For instance, passive viewing of negative static and dynamic affective stimuli independently of facial expressions yields RR-interval increases relative to

positive material (Kuniecki et al., 2003; Gomez et al., 2005). Explicit processing of angry faces, however, results in RR-interval decreases, possibly as a consequence of emotion induction (Critchley et al., 2005). Furthermore, both passive viewing of arousing film clips (e.g. Gomez et al., 2005) and exposure to fearful faces while distracted by a gender discrimination task elicits increased electrodermal activity (Williams et al., 2001). Additionally, passively observing another person in pain enhances both RR-intervals and SCRs (Craig, 1968, Craig and Lowery 1969a; Craig and Wood, 1969b).

1. Since both, angry and pain contorted faces are more salient and more likely to be arousing and unpleasant than neutral faces, an orienting response characterized by increases of the RR-interval (HR deceleration) and SCRs is hypothesized.

2. Additionally, given that repeated exposure to the same stimuli results in habituation of the orienting response (Stern and Sison, 1990) such an effect is expected for cardiac and electrodermal measures across the experimental session.

3. Moreover, it is examined whether male and female observers differed in their cardiac and electrodermal responses to the different emotional facial expressions.

III. Imaging Data

1. Taking the literature on emotional face processing into account (e.g. Carr et al., 2003; Hariri et al., 2000; Keightley et al., 2003; Morris et al., 1996; Wicker et al., 2003) an engagement of the same network of regions comprising STS, FFA, amygdala, MPFC, anterior insula, ACC, as well as the right somatosensory cortices (SI, SII/posterior insula) during exposure to pain and angry faces in comparison to neutral faces is expected.

2. Keeping in mind that the facial expression of pain is unique and distinct from the expression of basic emotions (Williams, 2002), differences in the activation of the amygdala and the interconnected visual face responsive regions (FFA and STS) are expected to facial pain expressions in contrast to anger expressions.

While angry facial expressions signal danger emanating from the expressor, pain contorted faces reflect an uncertain or indirect environmental threat perceived by the expressor, which is known to be associated with stronger amygdala response (Whalen et al., 2001). Moreover, the amygdala is able to modulate activity of visual cortices (Vuilleumier et al., 2004). Thus, stronger BOLD-responses in amygdala, FFA and STS to pain contorted facial displays as compared to angry faces are assumed.

3. As widely reported, the STS region is associated with the processing of variant aspects of faces (Haxby et al., 2000; 2002) and shows enhanced responding to dynamic as compared to static faces (Kilts et al., 2003). Hence, an additional difference of activation in this region for the comparison of dynamic (anger, pain) and almost static (neutral) stimuli is hypothesized.

4. Furthermore, the question of sex-differences in these BOLD-responses to male and female actors expressing emotional facial expressions is raised.

5. According to the findings of previous imaging studies (Singer et al., 2004; Bishop et al., 2004b) a relationship between subjects' empathic ability and BOLD-responses in the anterior insula and ACC, as well as between their state anxiety scores and the activity of the amygdala to facial expressions of pain contrasted against neutral is suggested. Moreover, an influence of pain catastrophizing on pain perception is proposed (Sullivan et al., 2001). Thus one can also assume that the neural activity in the network of areas that respond to pain faces as compared to neutral faces is related to subjects' pain catastrophizing tendencies.

6. No brain imaging study investigates co-variation of brain responses during implicit face processing with cardiac indices, but Critchley and colleagues (2005) observe coupling of RR-interval changes, inter alia, with activation of the amygdala, anterior insula and ACCcd during explicit processing of faces. Hence, a relationship between BOLD-responses in these ROIs with cardiac measures as observed to facial expressions of pain and anger is assumed. Given that the amygdala plays a role in the expression of GSRs (e.g. Williams et al., 2001) a relationship between GSR and amygdala's BOLD response is expected.

3   Materials and Methods

3.1   Subjects

Data of 24 subjects [(14 females; age= 23.2 ± 4.5; Caucasian (n=21), Asian (n=1), Arabs (n=2)] for the physiological measures and of another 17 [(9 females; age=23.1 ± 4.2; Caucasian (n=12), Blacks (n=3), Arabs (n=2)] for the brain imaging experiment was acquired. All subjects had no history of neurological and psychiatric impairment, were free of medication, were right-handed and with normal vision or corrected to normal vision. They were recruited at the campus of the Université de Montréal / Canada and were mainly students (experiment I: 96%; experiment II: 88%, the remaining were employees). For experiment II, subjects were informed about possible risks and inconvenience of participation in an fMRI – study and it was assured that no contraindication (e.g. pacemaker, implants) was met (DVD). All subjects provided informed written consent (DVD) and received money for their attendance (experiment I= 25$; experiment II= 40$). Both experiments were approved by the local ethics committee.

3.2   Stimuli

In the course of both experiments, dynamic visual stimuli (clips) of males and females displaying pain contorted, angry and neutral facial expressions were presented. Since there is no published set of dynamic stimuli including facial expressions of all basic emotions and especially facial pain expressions an own set had to be produced and validated for the present study (see Simon, Rainville, Gosselin, Belin and Craig; in preparation). A selection of those stimuli was used for the current study. The complete set of clips, as well as the subset, which was used in this study and its selection process will now be described in detail (see DVD).

For the production of the dynamic stimuli 11 drama students or lay actors (6 males, white Caucasians, mean age: 23.2 ± 6.6) of different theatrical schools in Montréal were

hired. They provided written informed consent and assigned the copyrights of the produced material to the research group.

The filming sessions took place in a special cabin at the Université de Montréal. Thus, the clips were standardized in terms of the background (light violet). Moreover, to avoid contamination of stimuli by special facial cues, actors with facial piercing, mustache or beard were excluded. Before the session started drama students had to remove earrings and make-up and were asked to wear a hairnet if necessary. A session per actor lasted around 1.5 hours and was paid with 100 CAN$.

The drama students were trained for the filming session using a training technique following Ekman and Friesen (1975, 1978). They were asked to express the six basic emotions (happiness, disgust, fear, anger, sadness and surprise) in three intensities (moderate, strong, extreme). Moreover, they generated facial displays, which would follow a phasic pain in four intensities (mild, moderate, strong, extreme), as well as a neutral face. Since little is known about dynamic stimuli and their potential to evoke a neurophysiologic response, the clips of the 'strong' intensity level were used for the current study. Thus, it was assured that the stimuli were neither too mild nor too exaggerated.

Figure 3 shows filmstrips of the used face categories with one example for neutral, angry and pain contorted expressions. The complete stimulus material compiled to movies is provided on the DVD.
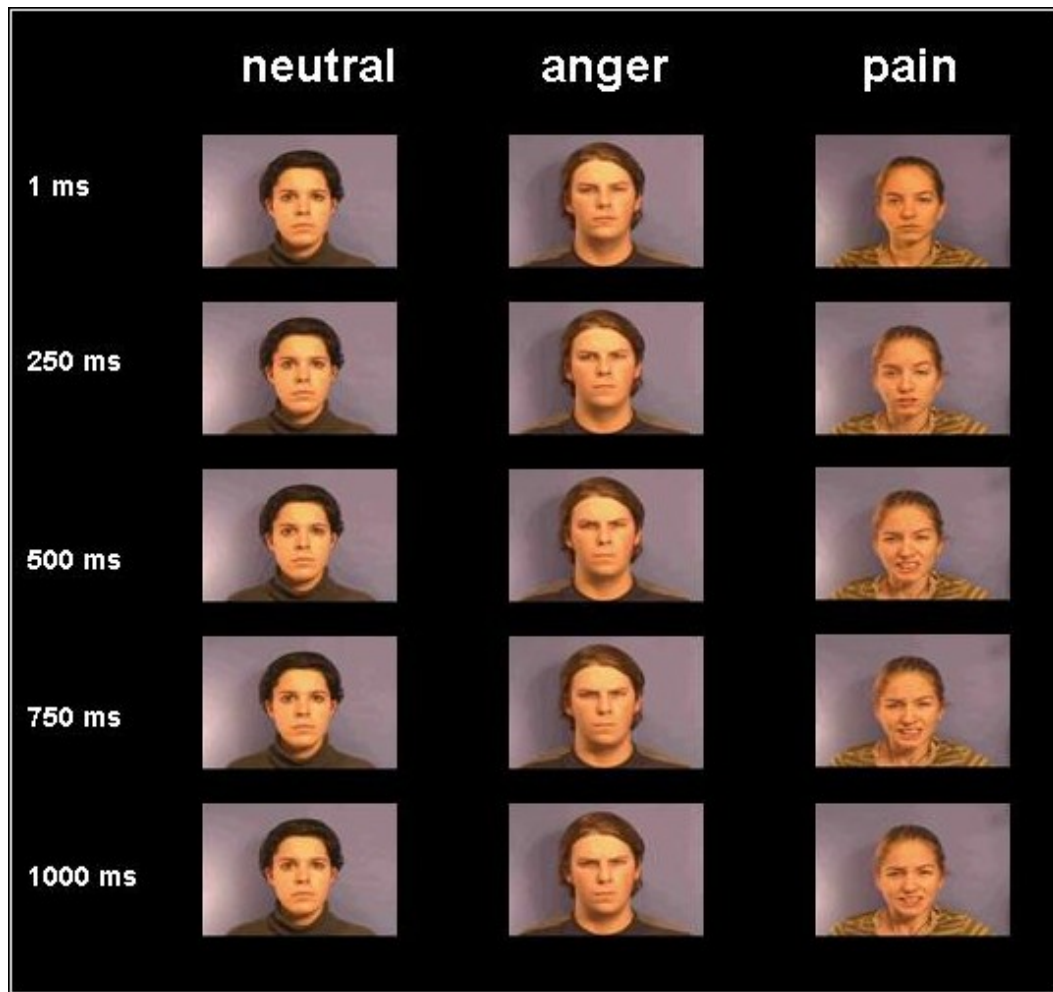
Figure 3: Examples of two female and one male actor expressing neutral, anger and pain; five time points in the clip (1ms, 250 ms, 500 ms, 750 ms, 1000ms) are displayed.

3.2.1 Subjective Rating

All clips of strong intensity were cut into 1 second movie streams using the software Adobe Premiere 6.5 and exported in Windows AVI movie format. In a pre-experimental session three independent raters (1 male, mean age: 25.3 ± 0.6) selected the best three clips per actor by emotional category for rating.

Subsequently, fifteen raters (11 males, mean age: 24.1 ± 3.4; students) evaluated valence, arousal, intensity and contamination of each clip. In total raters were shown 242 clips (three clips per six basic emotions and pain of 11 actors plus 11 neutral clips) in pseudo-randomized order and were asked to judge each clip on three different scales (DVD). First, the subjects evaluated the valence that the actor in the clip felt on an 8 -

point scale from -4 ("clearly unpleasant") to + 4 ("clearly pleasant"). Afterwards subjects were asked to rate the arousal felt by the person in the clip on an 8-point scale of -4 ("highly relaxed") to +4 (high level of arousal). Furthermore, subjects judged each facial expression with respect to the intensity of happiness, disgust, fear, anger, sadness, surprise and pain on a scale of 0 - 5 (0= not at all, 5= the most intense possible). For example, subjects were asked to rate a pain face not only with respect to the intensity of the label 'painful', but also to all the other labels. Thus, a score reflecting the intensity of the expressed emotion (to simplify the description pain will be labeled as 'emotion' too) was calculated. Using the intensity ratings on the non-target emotions additionally the contamination of each clip was determined. The rating session lasted 2 hours and was simultaneously done by all 15 subjects.

Using the results of the rating session, the best clips for each emotion and pain were selected for 8 actors (4 males, mean age: 24.4 ± 7.5) from the group of 11 actors. Taking the descriptive statistics into account only those clips were chosen, which fulfilled the following two criteria:

1. Intensity criterion: mean of the target category at least 2, but not higher than 4 (intensity strong, but not extreme requested - comparability)

2. Contamination criterion: mean of <u>each</u> "non-target category" less than 1

All selected clips (pain, anger, neutral), which were used during the present study, fulfilled both criteria (DVD). In order to validate the set of the best 8 actors expressing all three face categories, analyses of variance (ANOVAs) were calculated with SPSS for Windows version 12.0.2 (SPSS Inc., Chicago). For a general description of the statistical procedure utilized in the current study see Section 3.7. Since gender differences were of essential interest, the clips were analyzed with respect to the actors' gender. Thus, 3 x 2 analyses of variance (ANOVA) with repeated measures factor EMOTION (pain, anger, neutral) and SEX OF ACTOR (male / female actors) were calculated for intensity and contamination, as well as valence and arousal ratings.

Contamination analysis revealed a significant main effect of EMOTION only ($F_{(2;28)}=17.52$; GG-ε=0.54; GG-p=0.001). All clips fulfilled the mentioned criteria of low contamination (Figure 4), nevertheless pain clips were significantly more contaminated than anger and neutral clips (pain > anger: p=0.001; pain > neutral: p=0.001; p (cor)=0.02).

Contamination of Neutral Clips - rating session

Contamination of Anger Clips- rating session

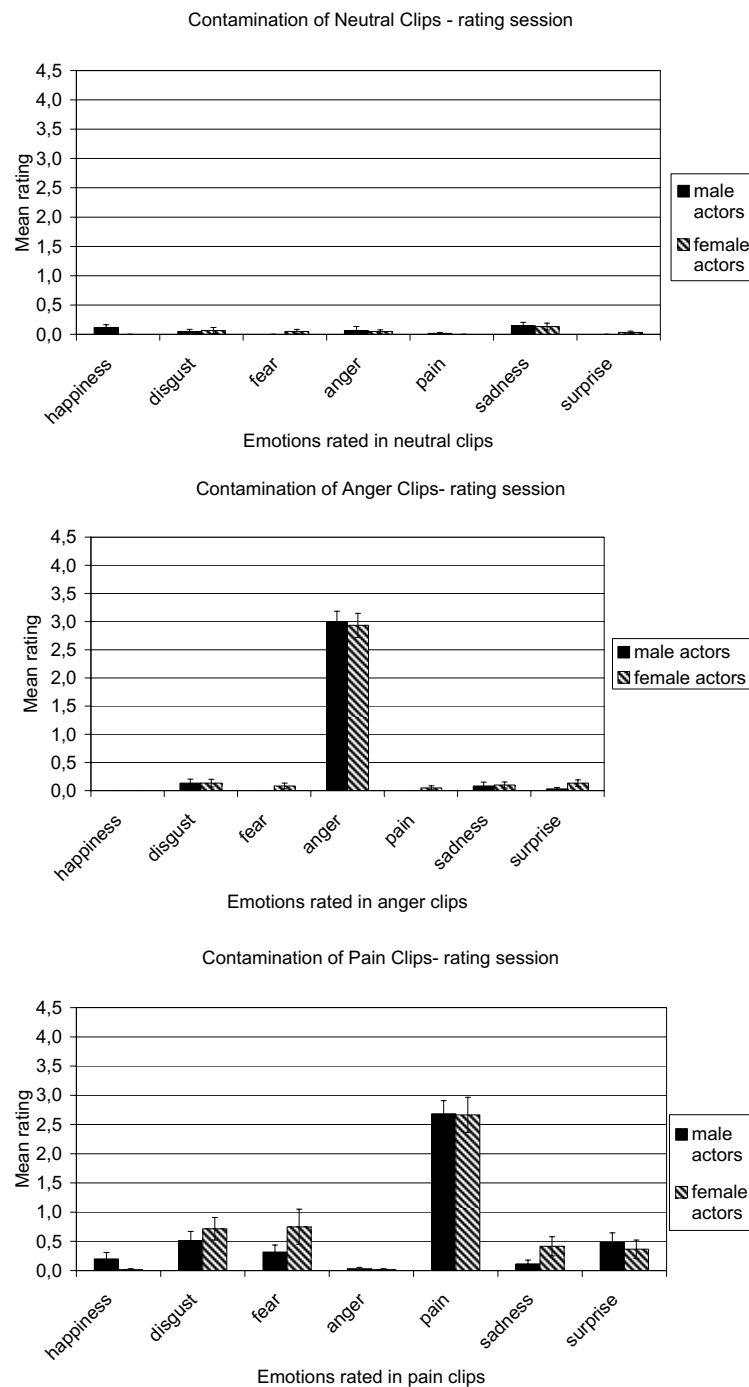Contamination of Pain Clips- rating session

Figure 4: Graphs displaying contamination of clips with other emotions displayed for male and female actors (mean±se).

With respect to the target emotion's *intensity* the clips showed the following ratings: angry (mean=3.0, SD=0.7), painful (mean=2.7, SD=1.0) and neutral (mean of intensity for all emotional labels=0.1, SD=0.1). Again, solely a main effect of the factor EMOTION ($F_{(2;28)}= 97.25$; GG-ϵ=0.84; GG-p<0.001) was detected due to the fact that

neutral clips were rated as less intense than the other categories (neutral < anger: p<0.001; neutral > pain: p<0.001; p(cor)=0.02), while pain and anger clips did not differ from each other (DVD).

Moreover, the clips differed from each other with respect to the *valence* ratings (Figure 5). Only a main effect of emotion was found ($F_{(2;28)}$=102.82; GG-ε=0.85; GG-p<0.001), since all three categories of clips differed significantly from each other with pain being the most unpleasant, followed by anger, and neutral as the least unpleasant one (pain < anger: p<0.001; pain < neutral: p<0.001; anger < neutral p<0.001; p(cor)=0.02) as revealed by post hoc contrasts.
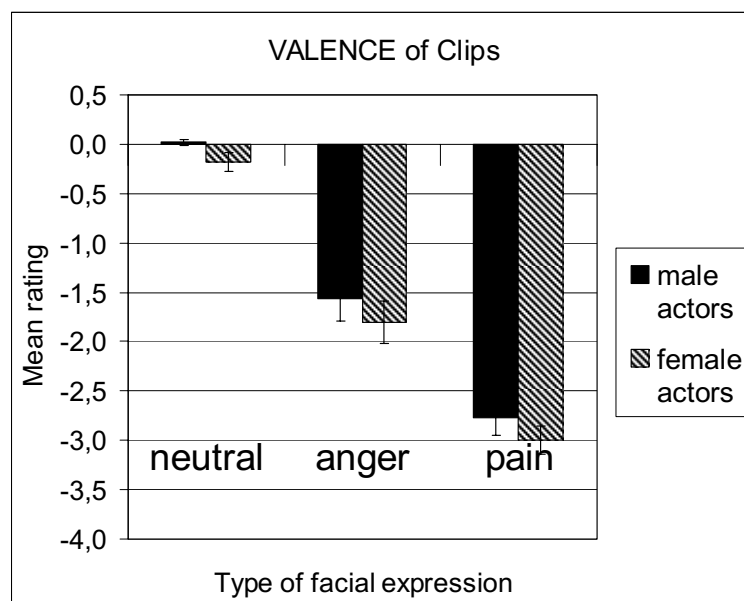

Figure 5: Graph displaying valence ratings for neutral, anger and pain clips of male and female actors (mean±se).

With respect to the *arousal* ratings again solely a main effect of emotion ($F_{(2;28)}$=65.01; GG-ε=0.97; GG-p<0.001) was shown (Figure 6). Post hoc contrasts showed a significant difference between all three categories of clips with pain being the most arousing, followed by anger, and neutral as the least arousing category (pain < anger: p<0.010; pain < neutral: p<0.001; anger < neutral p<0.001; p(cor)=0.02).
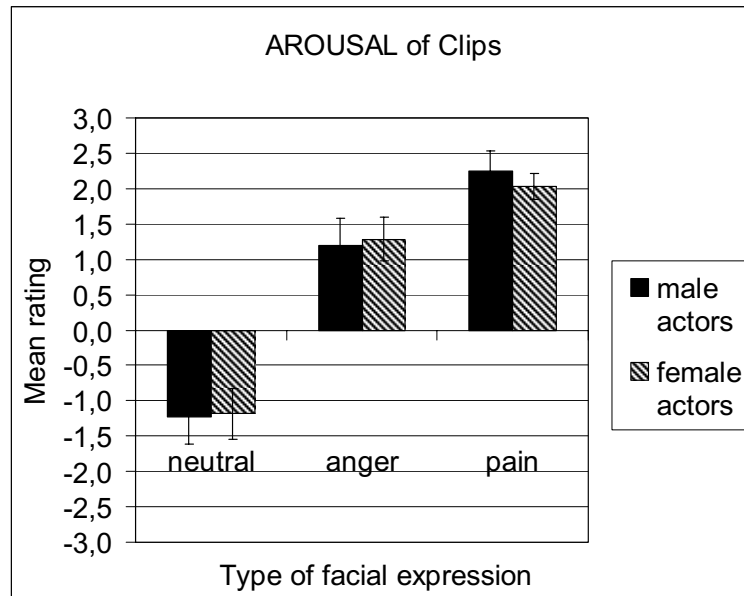
Figure 6: Graph displaying arousal ratings for neutral, anger and pain clips of male and female actors (mean±se).

It can be summarized that the set represented stimuli of low contamination, although pain seemed to be slightly more contaminated than anger and neutral face clips. Furthermore, the emotional categories were matched in terms of intensity. Due to the nature of the displayed emotional states (pain, anger and neutral) the clips were distinct from each other with respect to valence and arousal. Moreover, it has to be highlighted that there was no interaction with the sex of the actor on all three ratings for painful, angry and neutral facial expressions. Thus, the observed ratings were independent of the actors' sexes. As expected, neutral clips differed from the other emotional categories on all three ratings.

3.2.2   Facial Action Coding System (FACS)

Since it was important to have stimuli being as natural as possible, while providing as much standardization as possible, a second validation with the help of FACS was done. Assigned to the group of anatomically based classification systems, it is the most comprehensive (Ekman et al., 2002). This system of categorization describes a facial expression in terms of 46 unique actions the face is capable of. Besides coding the frequency of an action unit's (AU) involvement, the FACS manual outlines a scoring

procedure that allows for coding the intensity of each facial action on a 5-point scale (a=trace of the action, b=slight evidence, c=marked or pronounced, d=severe or extreme, e=maximum evidence; Ekman et al., 2002). This procedure offered the opportunity to compare the described faked facial expressions to real facial expressions reported by different studies.

Hence, the best clips, beforehand selected in the subjective rating session (in total 24: one clip per three categories of 8 actors), were evaluated by two independent accredited coders (1 male). For the coding a key was assigned to each clip assuring the coders were blind to the target emotion.

The coding procedure for the present set of dynamic stimuli consisted of two stages. During the first stage both coders provided one rating each. They achieved a frequency reliability of 86.7% (determined by 2x the number of agreements divided by the total number of AUs coded by both raters) and an intensity reliability of 89% (determined by 2x the number of intensity agreements ±1 divided by the total number of AUs the coders agreed about). Thus, their scoring reliability was satisfactory. During the second stage an agreed set was determined by reconciling the disagreements in frequency and intensity coding. The reported results refer to this agreed set.

Since a- and b-codings indicate only a trace or slight involvement of an AU, solely intensity levels of 'c' and above were taken into account for the actual analysis. Thus the sum of c-e ratings was calculated for each AU per face category, and the percentage of actors showing involvement of this AU in the group of 8 actors was determined (DVD). All AUs that were activated in 50% or more of the actors are reported in Table 3 and 4. Additionally, in each table a row displaying the prototypical AU for each emotion (see Table 1) is provided for comparison.

As expected, no AU was involved in the neutral facial expressions, confirming the validity of these expressions as being neutral. The lower row of Table 3 displays the results of the FACS coding for angry faces. The upper row shows those action units that are believed to be relevant for anger based on theoretical and empirical grounds. Besides the mentioned AU combinations major variants exist. Referring to the FACS Investigator's guide a combination of AU 4 and 23, is reported as being a major variant of these 'anger prototypes' (see Section 1.1.). Thus, it can be assumed that the dynamic stimuli of angry facial expressions are prototypical as confirmed by FACS.

Table 3: Comparison of prototypical and observed AUs in the produced clips.

ANGER	AU									
	4	5	7	10	17	22	23	24	25	26
	Brow lower	Upper lid raiser	Lid tighten	Upper lip raiser	Chin raiser	Lip funnel	Lip tighten	Lip pressor	Lips part	Jaw drop
Prototype	■	■	■	□	□	■	■	□	■	■
Observed	√						√			

■ AU occur with prototype; □ may occur with prototype and / or major variant; √ AU's activation occurred with an intensity of ≥ c in ≥ 50% of actors

Findings of the FACS coding for pain faces are shown in Table 4. The table compares the results of these clips (lower row) with those found in the literature on facial expressions of pain (upper row; see Table 1). Thus it can be assumed that the dynamic stimuli of facial pain expressions, including AU 4, 6, 7, 10, 20 and 25 were prototypical and valid as confirmed by the FACS.

Table 4: Comparison of prototypical and observed AUs in the produced clips.

PAIN	AU									
	4	6	7	9	10	12	20	25	26	27
	Brow lower	Cheek raiser	Lid tighten	Nose wrink-ler	Upper lip raiser	Lip corner puller	Lip stretch	Lips part	Jaw drop	Mouth stretch
Prototype	■	■	■	■	■	□	□	□	□	□
Observed	√	√	√		√		√	√		

■ AU occur with prototype; □ may occur with prototype and / or major variant; √ AU's activation occurred with an intensity of ≥ c in ≥ 50% of actors

60

In order to additionally investigate whether involvement of the determined AUs was dependent of actor's sex, the ratio of male and female actors contributing to this result for each AU was calculated. An impact of gender on the AU's activation frequency was stated in case a difference of more than ±1 occurred in this ratio. This gender dependence was only found for AU 23 in angry facial expressions, which happened to be activated more often in actors than in actresses. To investigate whether these prototypical AU were involved in each gender group to the same degree, the data was analyzed with respect to intensity differences in males vs. females. Therefore an "intensity sum score" of c, d, e – codings (c = 1, d = 2, e = 3) was calculated. If men and women showed the same intensity activation of a particular AU equality was indicated. Otherwise, a difference was stated. Intensity differences were found for AU 6 in facial pain expressions, which was more pronounced in male actors (DVD). It should be noted that the FACS intensity coding does not necessarily reflect the intensity of the emotion expressed but the clarity of the involvement of the AU in the expression.

All validated neutral, anger and pain clips were compiled to movies (Image size: 720 x 480 pixel, Frame rate= 29.97 frames per second) in Quick Time format (Quick Time 6.5. Pro, 2003 Apple Computer, Inc.). For further details about the movies' structure and duration see chapter 3.5.

3.3   Questionnaires

During the experimental session of both experiments different questionnaires were used to control for influences of certain variables that might be intertwined with the subject of the study. Hence, to examine whether processing of pain contorted faces elicits automatic empathic responses, indices measuring subjects' empathic ability were included. Moreover, to control for possible differences in response to pain faces due to subjects' pain catastrophizing tendencies, a scale measuring this construct was employed. Also to investigate whether individual responses were determined by reported anxiety, a corresponding questionnaire was used.

Depending on their purpose, these scales were handed out before or after the experimental procedure (see Figure 7). Since some of the subjects were not bilingual all questionnaires, except for one empathy scale, were available in English and French (see

PT) and to be able to assess emotional empathy the subscale 'empathic concern' (IRI-EC) was chosen for the present studies (DVD). Since not all subjects were bilingual the IRI-scale was also translated into French (DVD). To avoid that subjects were sensitized to the subject of empathy before performing the task, the questionnaire was handed out after the experiment.

3.3.2   Balanced Emotional Empathy Scale (BEES)

In order to have a well evaluated empathy-questionnaire and to be able to relate the less validated IRI-scale to the instrument, a second empathy questionnaire - the Balanced Emotional Empathy Scale (BEES) by Mehrabian and Epstein (1972) was included for experiment II. For this scale, an internal consistency coefficient of $\alpha = .87$ (Mehrabian, 2000) was established. Used as a description of a trait, Mehrabian defines "Emotional Empathy" as individual differences to feel and vicariously experience the emotional states of others (Mehrabian, 2000).

BEES is a 30-item self-report questionnaire and uses a 9-point agreement/disagreement scale (+4 = very strong agreement ... 0 = neither agreement nor disagreement ... -4 = very strong disagreement). In order to control for the acquiescence bias, 15 items are positively worded, such that agreement shows higher emotional empathy. The other half is negatively worded such that disagreement shows higher emotional empathy (see DVD). A total scale score is computed by subtracting the sum score of all 15 negatively worded items from the sum of responses to all of the 15 positively worded items (Mehrabian, 2000). Thus, scores can range from -120 to +120.

The aim of both empathy scales - IRI and BEES - was to distinguish subjects who typically experience more of others' feelings from those who are generally less responsive to the emotional expressions and experiences of others.

3.3.3   State-Trait Anxiety Inventory (STAI)

Since response to threat-relevant stimuli was of interest for the present study, there was a need to control the level of anxiety. These scores were later related to individuals'

behavioral and physiological responses (see Section 2). Thus, the STAI (Spielberger, 1983) was handed out. Additionally to the English version, a French adaptation was available.

The STAI offers alpha reliability coefficients for e.g. the English scales ranging from 0.86 to 0.95 (Spielberger, 1983). The self-report inventory consists of 20 items to assess state and another 20 items to assess trait anxiety on a 4 point scale (1= "not at all" – 4="very much so"). Thus, each form allows a minimum score of 20 and a maximum score of 80, and higher scores indicate greater levels of anxiety. Both subscales differ in item wording, response format (intensity vs. frequency), and instructions for how to respond (see DVD).

While the questionnaire assessing subjects' state of anxiety was handed out before the experimental procedure started, the trait anxiety inventory was filled in after the session (see Figure 7).

3.3.4   Pain Catastrophizing Scale (PCS)

According to Sullivan et al. (2001) pain catastrophizing can be defined as "an exaggerated negative mental set brought to bear during actual or anticipated painful experience". It can be assumed that catastrophizing might also influence the recognition of faces expressing pain. To investigate this question, the Pain Catastrophizing Scale (PCS) of Sullivan, Bishop and Pivik (1995) was used. As reported in the literature, pain catastrophizing involves focusing on pain, describing negative emotions such as fear and anger, expressing worry about harmful physical, emotional, and social effects of pain, and a lack of confidence in one's ability to cope with pain (Sullivan, 2004).

The PCS, existing in both English and French version (DVD), assesses the construct of catastrophizing by 13 items. The subjects are asked to reflect these items on painful experiences of the past ("I am in pain, I am afraid the pain will get worse" (see DVD) and indicate whether they agree with the statements on a 5-point scale (0= "not at all" – 4="all the time"; sum score range: 0-52). Besides a total score the PCS-scale yields three subscale scores, which assess rumination, magnification, and helplessness (Sullivan, 2004). Rumination and magnification appear to be related to the process of primary appraisal resulting in focusing on and exaggeration of threat of a painful

stimulus. Helplessness seems to be associated with secondary appraisal – reflected by negative evaluation of coping capacity for the painful stimuli (Sullivan et al., 1995). The scale provides a high internal consistency (total: α=0.87, rumination: α=0.87, magnification: α=0.66, helplessness: α=0.79; Sullivan et al., 1995). However, solely the total PCS-scores were used for computations in the present study.

In order not to prime the subjects they were asked to answer these questions after the session.

3.3.5   Questionnaire for Behavioral Ratings on Facial Expressions

To gain knowledge about subjects' experience while being exposed to the stimuli, a questionnaire to measure subjective ratings was developed (see DVD) and handed out after the experiment. Subjects judged each of the three categories of clips on three different scales: valence, arousal and intensity of the perceived "emotion". Therefore, subjects were again shown one block of angry, painful and neutral facial expressions for each of the three rating tasks. Since this rating had to be kept as less time consuming as possible, subjects were asked to create an average rating for all 8 actors in one block. In case an actor differed completely from all others in one block and his/her ratings did not fit to the average rating, subjects were requested to make an additional note.

Since the present study also aimed to test whether empathic responses to people expressing pain occur automatically, ratings of valence and arousal did not only base on the actor perspective ("Please take the perspective of the actor and spontaneously rate how the persons in each clip felt on the following scales:.."), but also on the observer perspective ("Please spontaneously rate how you felt while watching the clips on the following scales: .."). Thus, at first subjects evaluated their feelings of pleasantness/unpleasantness (valence) while observing the 8 actors in the movie clips on an 8 - point scale from -4 ("clearly unpleasant") to + 4 ("clearly pleasant"). Afterwards, subjects were asked to rate their arousal during exposure to the clips on an 8-point scale of -4 ("highly relaxed") to +4 (high level of arousal). Subsequently they used the same scales but changed the perspective for the rating task.

Furthermore, in order to make sure that subjects clearly recognized anger, pain and neutral faces they were requested to judge each block of facial expression with respect

to the intensity of happiness, disgust, fear, anger, sadness, surprise and pain on a scale of 0 - 5 (0= not at all, 5= the most intense possible). For example, subjects were asked to rate the pain faces expressed by the 8 actors not only with respect to the intensity of the label 'painful', but also to all the other labels. However, in contrast to the rating session, subjects saw three instead of seven categories of clips while again being asked to rate them for all labels. There is a risk of scaling biases, but since this is the first study evaluating dynamic facial expressions of pain it was necessary to receive information about possible contamination.

Finally, the aim was to relate subjects' empathy scores, as well as their peripheral physiological and imaging data to the subjective ratings.

3.4 Overview Experimental Procedure

The whole experimental procedure is displayed in Figure 7. If not outlined differently, the same sequence of events was used in both experiments.
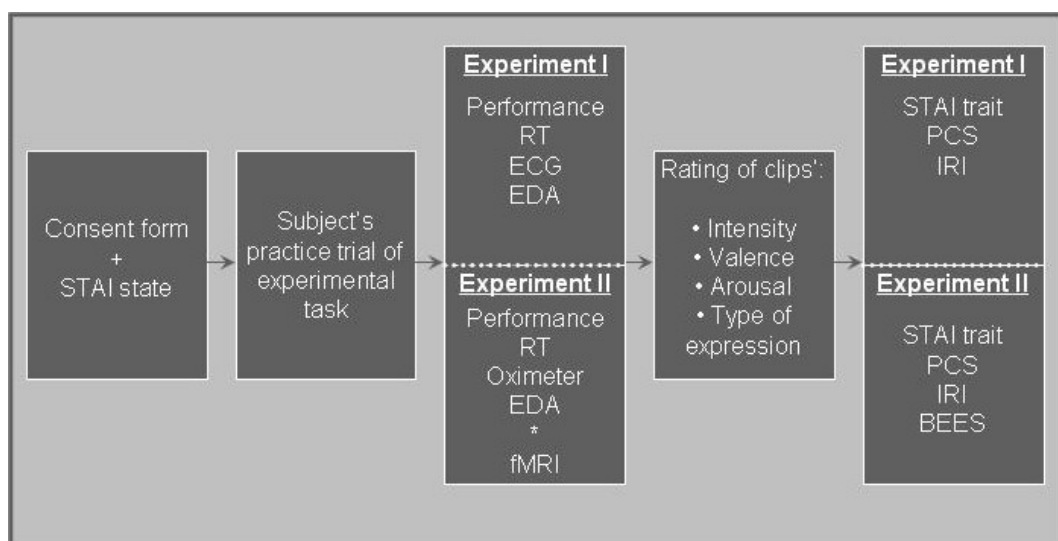

Figure 7:   Procedure of experiment I and II.

After providing written informed consent subjects were instructed and trained. To avoid habituation to the faces used in the experiment, different faces were taken for the practice session and subjects were allowed to perform the gender discrimination task until they were familiar with the procedure. They also had to fill in the state version of

the STAI in order to control the level of anxiety while attending the experiment. After further preparations (e.g. applying the electrodes to the skin, see Section 3.6.2.) the actual task including measurement of reaction time and performance correctness in the gender discrimination task, of ECG and EDA, and/or of brain activation began, which took around 35 minutes. Afterwards subjects filled in four or, in the case of experiment II, five questionnaires. For each experiment the entire process lasted around 2 hours.

3.5 Design

The present experimental paradigm combines both, block and event-related design to assess the impact of factors 'category of facial expression', 'sex of observer', and the factor 'sex of the observed person' (actor). The different emotional facial displays represent block-related information (e.g. block of faces expressing pain), the gender of model which expresses the emotional facial expression within one block depicts event-related information (e.g. female vs. male pain faces). Hence, using a mixed design (Figure 8) one is able to differentiate between sustained and transient BOLD-responses on emotional stimuli (Mechelli, Henson, Price and Friston, 2003; Visscher et al., 2003).
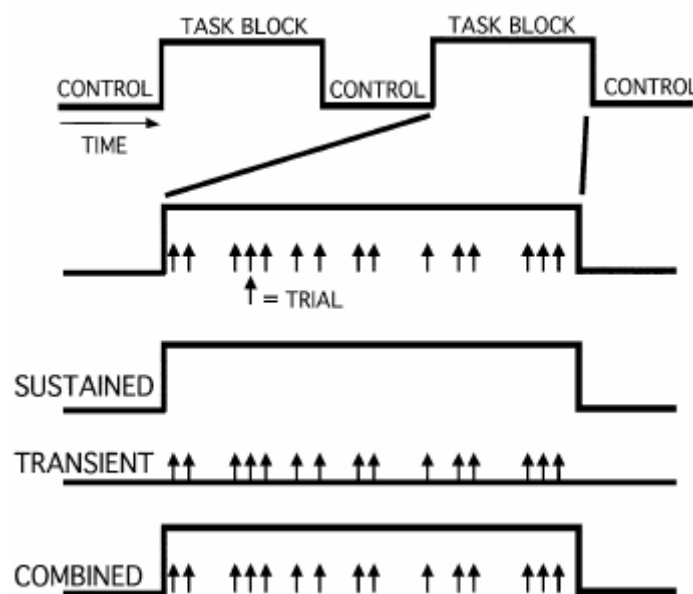

Figure 8: Diagram of a mixed blocked/event-related design. (A) In the mixed design, as in a blocked design, blocks of performance of a control task are interspersed with blocks of performance of a task. (B) Within task blocks, individual trials (arrows) are presented with different intervals between them, as in a rapid event-related design. (C) The mixed design includes sustained activity as well as transient trial-related activity combined in one design (taken from Visscher et al., 2003).

Since these two kinds of time courses (for a comparison see Chein and Schneider, 2003) might contribute differently to processing it seems to be essential to be able to discriminate between trial and epoch- related activity.

In the course of both, the peripheral physiological and the brain imaging experiment the same design was conducted, comprising three runs of about 8.5 min. As shown in Figure 9, one run included blocks of movie clips displaying painful, angry or neutral facial expressions interspersed with blocks of visual baseline (light grey screen with a fixation cross in the middle). In total a number of 31 separate 16 s presentation phases (baseline - 16x, angry - 5x, painful - 5x, neutral - 5x) was presented per run. The order of blocks was pseudo-randomized within and across runs. The order of runs was counterbalanced across subjects and notes concerning randomization were taken in a protocol sheet (for details see DVD).

Each block in turn included eight events, namely clips of four different male and four different female actors showing one category of facial expressions, e.g. anger. Each clip lasted 1s followed by a 1s interval in which a light grey blank screen was shown. Clips were randomized in terms of gender within, as well as across blocks of the same and different emotion. While the stimulus onset asynchrony (SOA) for each event was 2s, with respect to the gender categories SOAs of 2s - 8s occurred. Given these parameters applying a mixed blocked/event-related analysis should be valid according to Mechelli and colleagues (2003), as well as to Visscher and colleagues (2003).
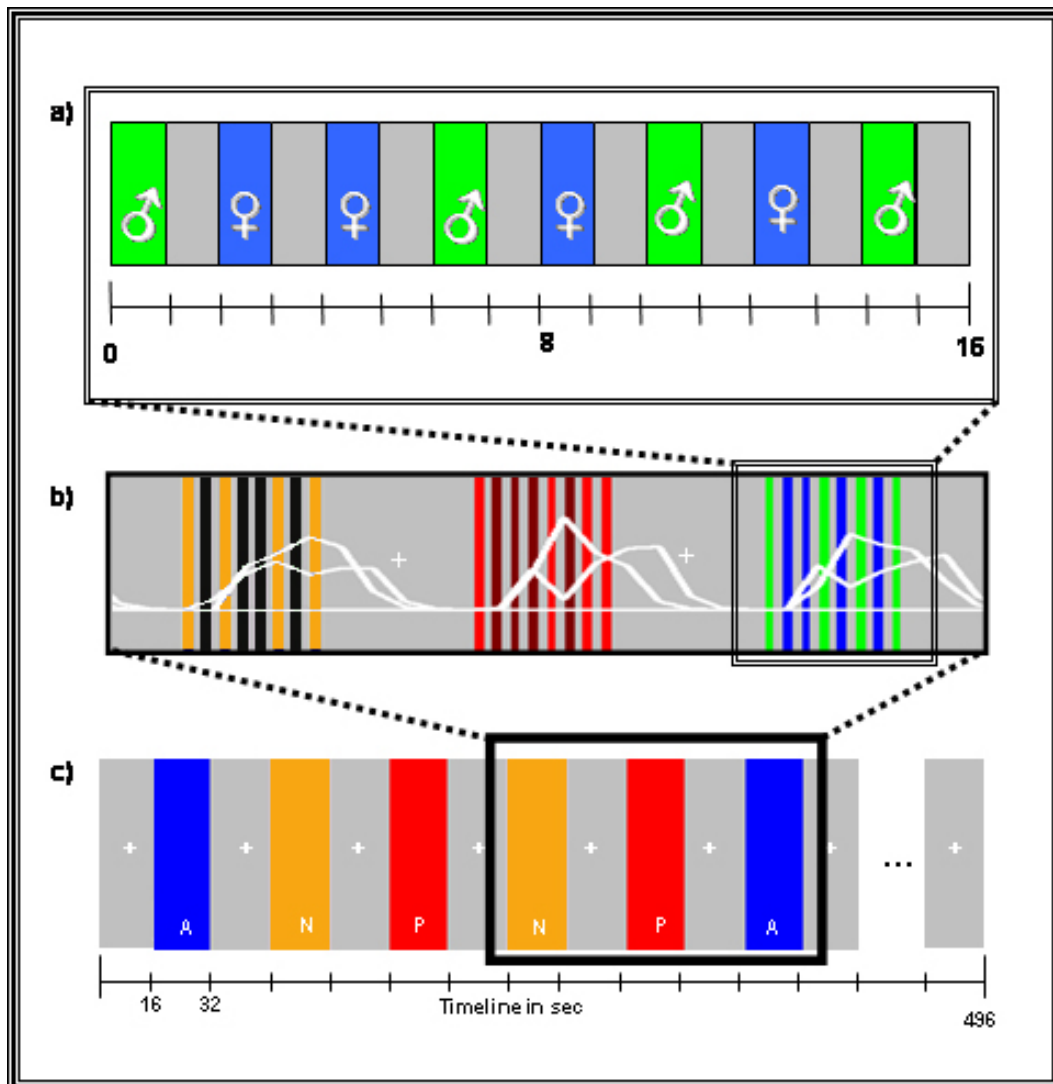
Figure 9: The mixed blocked/event-related design. a) Randomization of the sex of the model within blocks, b) single stimulus-event sequence within each of three blocks with white curves representing the expected BOLD-response modelled separately for male or female face stimuli (yellow/black, shades of red, or blue/green) c) blocks of pain (P), anger (A) or neutral (N) faces interspersed with blocks of visual baseline.

In the course of both experiments subjects performed a gender discrimination task. In response to every presented clip they made a sex classification by pressing one of two response buttons with the fingers of the left hand. There were minor changes in this instruction between experiment I and II. While during the first experiment subjects were asked to respond as fast as possible, subjects in the second experiment were only allowed to answer *after* the grey screen had occurred. This procedure had to be applied to the imaging experiment to avoid accrediting of differences in BOLD- response only

to RT differences. The implications of this instruction change for the interpretation of RT results will be discussed later (see Sections 4.2.2. and 5.1.).

This decision task allowed for an identical response across all conditions, because subjects were forced to focus on a perceptional feature that is independent of the kind of facial expression. Especially for the neutral blocks this seemed to be essential. Thus, we obtained a behavioral measure of subject's vigilance and attention to the stimuli by acquiring the accuracy of gender decisions. From the literature there is sufficient evidence, that there is a neural response to the facial expressions even though subjects are not explicitly asked to respond to those specific features (e.g. Phillips et al., 1997). Hence, subjects were informed about the aim of the experiment in a very general way and were told that the studies investigate the neural mechanisms of face perception using different facial displays.

3.6   Data Acquisition

3.6.1   Behavioral Ratings & Questionnaire Data

All questionnaires collecting behavioral ratings as well as personality features (empathic ability etc.), which were presented in conventional paper-pencil form, have been described in Section 3.3. The order in which these instruments were applied is outlined in Section 3.5.

3.6.2   Performance, Reaction Times & Peripheral Physiological Data

In the course of both experiments stimuli were generated on a portable computer using the software Windows Media Player (Microsoft Corporation). The following descriptions concerning the peripheral physiological measures are almost equal for both experiments. Therefore only differences (see Figure 7) will be outlined separately.

During both experiments, different physiological measures were assessed while subjects were performing the above described task. This was done with the help of MP System (BIOPAC System, Inc.) – a system including both software (Acq*Knowledge* 3.7.1) and

hardware (MP150) for acquisition as well as analysis of various data. The MP System is computer-based and converts incoming physiological signals (usually analog) into digital ones. Using the software Acq*Knowledge* data can be displayed on the computer screen and stored for further examinations. The system provides a maximum of 16 analog (=nature of incoming signal analog), 16 digital (=nature of incoming signal digital) and 16 calculation channels, which allow for online calculation e.g. smoothing (MP Systems Hardware Guide). For more details see www.biopac.com.

For the present study, six channels (5 analog, 1 digital) were defined. Additionally, three calculation channels were set up. Their purposes and technical features will now be outlined in detail.

To perform the gender discrimination task (see chapter 3.5) subjects were given a response key into their right hand (experiment II: additionally scanner alarm in the left hand). For a male actor subjects pressed the left, for a female actor they pressed the right button of the response key. In order to record these answers two analog channels, one for the label "female" and one for "male" were used. The button press resulted in a +5V signal in either the male or female channel, which was later used to calculate the correctness and latency of responses.

In order to additionally determine the on- and offset of each clip accurately and to relate the physiological responses of subjects to the stimuli, clips were linked with sound of different amplitudes (neutral=0 db, anger=-3 db, neutral=-6 db). The sound signal was sent to an audio channel (analog), which had been created in Acq*Knowledge,* indicating the occurrence of a clip.

While during experiment I the movie clips were presented directly on the screen of the portable computer in the course of the second experiment the laptop was additionally linked to a LCD video projector. This projector was positioned behind the scanner room in a separate chamber. Via a little whole in the chamber's wall the clips were back projected onto a screen behind the scanner. The subjects observed the stimuli through a tilted mirror attached to the head coil of the scanner.

Besides these measures two physiological measures were recorded; the heart period (HP) and skin conductance response (GSR). Acquiring these data in the magnetic environment during brain imaging presents itself as challenging. To prevent image

artifact certain things have to be taken into account and will be therefore outlined explicitly during this section.

For heart rate measurement during experiment I three adhesive disposable Ag/Ag-Cl electrodes (BIOPAC EL507) were attached to the throat, chest and the lowest rib arch forming a diagonal line. Via a pinch lead (LEAD110) they were connected to the Electrocardiogram Amplifier module (ECG 100C) of the BIOPAC system. In contrast, during experiment II a pulse oximeter (Nonin8600FO, Nonin Medical, Inc.) was used. The pulse probe was placed on the middle finger of the left hand and as described for experiment I, connected to the BIOPAC. Using a gain of 1000 the ECG raw signal was then amplified and displayed as analog signal. In order to compute the HP from this raw signal a calculation channel was set up, which determined the RR-interval (time between two R waves in seconds) of the smoothed signal by looking for peaks (interval window 0.33 – 1.5 sec).

Similar electrodes (MRI-compatible) and leads as described for the HP measures were used to measure GSR. Two of these adhesive electrodes were attached to the plantar surface of the left foot. Although GSR is usually recorded from the palmar surface, this procedure was chosen since the same measurement was employed during both experiments, which was a scanner environment with a strong magnetic field in the case of experiment II. Thereby it was assured that the electrodes would extend outside the magnet to avoid voltage differences between electrodes induced by the magnetic field. Moreover, the effect of the GSR measurement on the MRI images was thereby reduced. The scanning noise in the EDA signal was filtered out after acquisition by using additional median smoothing in Acq*Knowledge*.

All leads were connected to the Electrodermal Activity Amplifier module (GSR 100C). The GSR raw signal, amplified by a gain of 2-5 $\mu\Omega$/V, was recorded using an analog channel. Two calculation channels had been set up: firstly, a smoothing channel (factor: 1000 samples) and secondly, a channel recording the differences of consecutive SCRs by subtracting the data of the smoothing channel by itself shifted 1000 points (Smyser et al., 2002).

Lastly to be able to properly align stimulation and physiological responses for further analysis measures of the data acquisition's start were conducted. Therefore a digital

channel was created acquiring pressing of a foot switch (experiment I) or the scanners – TTL signal (experiment II).

All data was recorded using an acquisition rate of 1000 samples per second (1 kHz).

3.6.3 <u>Imaging Data</u>

Functional magnetic resonance imaging (fMRI) has become a widely used powerful non-invasive tool for investigating brain activity during a variety of sensory, motor, or cognitive tasks. Providing crucial advantages in comparison to other imaging techniques like PET (for details see Buckner and Logan, 2001) it even has turned into the method of choice in recent brain imaging studies.

While there is some controversy about the exact neural basis of the fMRI signal (for further discussions see Attwell and Iadecola, 2002; Bandettini and Ungerleider, 2001; Logothetis, Pauls, Augath, Trinath and Oeltermann, 2001) it is widely accepted now that there is a relationship between neural activity and cerebral haemodynamic changes, which underlie the blood-oxygen-level-dependant (BOLD) signal measured by fMRI. This signal reflects the loss of oxygen from haemoglobin, causing its iron to become paramagnetic. This process influences the magnetic field experienced by protons in surrounding water molecules (Ogawa, Lee, Kay and Tank, 1990) and results in a slight attenuation of signal intensity in brain regions containing deoxygenated blood. Brain areas, which are activated and therefore require more energy, show higher blood flow and thus contain more oxyhaemoglobin. Deoxyhaemoglobin can thus be considered as natural contrast agent. Thus, increases in neuronal activity are detected as an increase in the MR signal.

The present imaging experiment was performed using a 1.5 Tesla scanner with a standard head coil (Siemens Sonata, Erlangen, Germany). BOLD fMR images were obtained using a T2*-weighted gradient (GE) echo planar imaging (EPI) sequence (TR = 3500 ms, TE = 42 ms, flip angle = 90º, FOV = 192 mm, 64 x 64 matrix). Images were taken in 142 whole-brain volumes per run (3.5s/volume, ~8.5 min/run) with 40 contiguous interleaved axial slices of 3 mm thickness (0 mm gap, in plane resolution = 3 x 3 mm) parallel to AC-PC line. High-resolution structural T1*-weighted anatomical scans were acquired for each participant.

Subjects were placed in a comfortable position in the scanner; the head was immobilized with padded ear-muffs to prevent movement.

In order to minimize electro magnetic interference (EMI) with the scanning data created by high frequency signals (computer etc.), all equipment was set up in a separate room. To additionally assure a good image quality a radio frequency (RF) filter (= high frequency filter) was used. The EMI created by the scanner (low frequency), which compromised the physiological data, was eliminated later in Acq*Knowledge* software, which will be described below.

3.7   Data Analysis

Since similar statistical procedures were applied during analysis of: a) questionnaire data and behavioral ratings of facial expressions, b) performance, reaction times and physiological data and c) imaging data the procedure of statistical calculations will only be outlined once in the first section (3.7.1). All additional analyses conducted with the peripheral physiological measures and the imaging data are outlined separately in the second (3.7.2) and third section (3.7.3).

3.7.1   Behavioral Ratings & Questionnaire Data

Statistical analyses of questionnaire and rating data was conducted using SPSS for Windows version 12.0.2 (SPSS Inc., Chicago).

For each analysis the normality assumption was tested beforehand using a Kolmogorov-Smirnov-Test ($\alpha < 0.2$). This α-level was chosen to minimize the probability of a Type II error, whose consequences were considered to be more critical than a Type I error. In case that observations were not normally distributed on the dependent variable in each group, non-parametric tests were chosen where possible. As there are no multi-factorial non-parametric tests, ANOVAs were used in these cases. Since ANOVAs are robust with respect to Type I error (Stevens, 2002) violations of this assumption are not serious. Nevertheless, they are highlighted in the SPSS files (DVD).

In case effects of different groups had to be investigated, the homogeneity assumption of variance was tested using a Levene test. Results of this test are mentioned only in

case of violations. The ANOVA is conditionally robust against non-homogeneity, if the group sizes are equal or approximately equal (largest/smallest <1.5) (Stevens, 2002). In the case of dissimilarity of variances between groups and inequality of group sizes, the F statistic becomes more liberal if the large sample variance is associated with the small sample size (rejecting falsely too often) and more conservative if the other way around. These aspects are discussed if critical for particular results.

Moreover, for repeated measures designs the sphericity assumption was tested using the Mauchly Test of Sphericity. According to Diehl and Arbinger (2001) the equality of the covariance matrices is a sufficient condition of sphericity. If $\varepsilon = 1$ (p> 0.05) the data is spherical, while $\varepsilon < 1$ indicates the violation of this assumption. In case of violations one can still use the traditional test, but the degrees of freedom need to be adjusted. The Greenhouse-Geisser adjustment, which is a more conservative correction, seemed to be indicated since the sample size was small in the present study (Diehl and Arbinger, 2001).

If not outlined differently, the level of significance was set at $\alpha< 0.05$. Effects with an α -level of ≥ 0.05 and < 0.1 were interpreted as a trend and were just mentioned in case they seemed to be contentional meaningful. To avoid inflating the overall Type I error rate all dimensions of interest were included in one higher order analysis of variance. Afterwards only significant effects were further analyzed.

Main effects, if multi-leveled, underwent a post hoc contrast analysis using simple and repeated contrasts. While simple contrasts compare each level against the last level, repeated contrasts involve comparing each level with the adjacent level (Stevens, 2002). Results of these analyses are mentioned in the text but the concrete F-statistics is just listed in the SPSS files (DVD). Since these post hoc analyses comprised repeated testing a Bonferroni correction was applied. Significant interaction effects were also further analyzed in order to determine which variable contributed to the effect. Thus, contrast analysis was conducted as described above or in the case of three- or more-way interactions less factorial univariate ANOVAs were calculated. Furthermore, graphical displays were used to depict interaction effects.

The relationship between the different ratings was determined by the computation of Spearman's rho correlation coefficients. This non-parametric correlation coefficient was chosen since it is with regard to Type I the more conservative compared to the

parametric Pearson coefficient. Again, solely results surviving the Bonferroni corrected threshold were reported (DVD). Moreover, in order to investigate whether interindividual differences in empathic ability (IRI, BEES), anxiety (STAI state and trait) and pain catastrophizing (PCS) affected the behavioral ratings of the facial expressions again correlations were computed and a Bonferroni correction was applied.

3.7.2   Performance, RT & Peripheral Physiological Data

The peripheral physiological data was analyzed with the help of AcqKnowledge 3.7.1 software (Biopac System, Inc.), Excel 2002 (Microsoft Corporation) and SPSS 12.0.2 (SPSS Inc., Chicago).

One has to note that while performance and RT were analyzed both as block and event-related design, the peripheral physiological data, which characterize relatively slow responses, solely underwent the block-related analyses. Although current development in the field allows for e.g. analysis of overlapping GSRs obtained during short interstimulus interval designs (Lim et al, 1997; Williams et al., 2000, 2001) this approach does still not provide sufficient resolution for the 1s-clips used in the present experiments.

3.7.2.1   Performance & Reaction Time (RT)

In order to assure subjects attended equally to all clips and moreover to control for the influence of task performance on the peripheral physiological data, both – performance and RT were analyzed. To be able to determine the accuracy of judgements in the gender discrimination task the observed responses of each subject were compared with the expected ones. Firstly, for each individual (Experiment I: exclusion of subject 20-23 / broken response key) the order of presented clips was determined (neutral, anger, pain / male, female actors) for the entire time course of events (five blocks each face type/ run = 45 blocks). Since subjects sometimes corrected their wrong answer two responses occurred to one clip. Thus, prior to further analysis a correction of artifacts was done and only the first answer was kept. Trials in which no reaction occurred were excluded

from further analysis. In order to determine subjects' response to each clip, the sound files (indicating onset and offset of clips) were used to extract information about the time frame of each event. Subsequently, since subject's answer resulted in up to 5 Volt deflections in channel 'male' or 'female', an area of 2 sec covering clip presentation and blank screen was investigated by a peak detection - function (threshold level 0.1 Volt, detection of 360 peaks [8 clips x 15 blocks x 3 runs] per subject). For each peak the maximum (V) as well as absolute time on male or female channel was determined. Using an 'if-function' looking for peaks that show higher maximum on male than on the female channel (observed answer=male) or the ones that show higher max on female than on the male channel (observed answer=female), the subject's actual response was extracted. They were compared to the expected ones. This way, the percentage of correct answers as well as the number of errors was determined for each subject per block (out of 8). Therefore correctness and errors with respect to the category of facial expressions (neutral, anger, pain) and the sex of the actor (male and female) were calculated.

Aiming to identify the RT to the clips the delay of responses was determined by calculating the difference between clip onset and time of each peak (response). Later the mean-RT of the correct responses was determined for each subject and block. Data was then analyzed with respect to the entire sequence of stimulation (decrease of RT = learning effects) and with respect to the presented facial category (neutral, anger, pain), as well as the actor's sex.
Prior to the analysis, data values were classified as outliers and excluded from further analysis when a deviation of three or more standard deviations from the group mean occurred.

3.7.2.2 Cardiac Measures

There are two possible ways to measure cardiac activity. On the one hand one can determine heart rate (HR) and on the other hand one can use the heart period (HP) also named interbeat interval (IBI) (Schandry, 1998). While HR is defined as the number of heart beats per unit of time (e.g. beats per minute = bpm), HP is based on the time

interval (ms) between two consecutive R-waves (=RR-interval) (Cacioppo and Tassinary, 1990). Although both measures share *time* as a common base and can therefore easily be converted, a non-linear relationship exists between them (Graham, 1978, cited in Cacioppo and Tassinary, 1990, S. 475). Therefore, a decision for one or the other measure depends on the question of the study. As described in Stern, Ray and Quigley (2001) an increase in parasympathic nerve activity (fast responding nerves), which is e.g. associated with short-term responses investigated in psychophysiological experiments leads to a linear change in RR-intervals while to a non-linear for the HR. Therefore, RR-intervals are recommended as the metric of choice in the case that the cardiac changes are expected to be results of these short-term autonomic effects (Berntson et al., 1995, cited in Stern et al., 2001). Conversion from RR-intervals into HR could then be problematic by exacerbation of measurement errors. Hence, the analysis of cardiac activity for the present study was based on RR-interval data. Moreover, since this analysis is also commonly used at the lab the present study was conducted at, it was chosen to keep these results comparable to follow–up studies. Since HR is simply the reciprocal of the RR-interval interpretation can be easily done (increase of RR-interval = deceleration of HR / RR-interval decrease =acceleration of HR).

The cardiac activity (via RR-interval data) was analyzed in an interval of 0 - 20 s around each stimulus onset (=block of 8 clips). The interval [−12 s; 0 s] served as baseline. Three different chronometric indices were determined for each of these stimulation and baseline epochs for analysis in the present study. After a software threshold had been set for R-wave detection, the successive RR-interval values were determined from the artifact-edited ECG recordings for the defined intervals (see 'Read-me'- file on DVD). The times intervals between successive R waves (R-R intervals) were calculated in milliseconds, which form the RR tachogram (see Figure 10). As a first index, the mean RR-interval was determined (RR_{mean}) for each block independent of the presented facial category first and afterwards in dependence of the clip type. To determine the change of cardiac activity to stimuli in contrast to baseline RR-interval indices extracted for the baseline epoch were subtracted from the RR-intervals of the successive stimulation epoch. According to Graham (1978) averaging these heart rates per time interval over stimuli is valid. Only these "corrected" values entered the analysis.

Figure 10: Example of an RR tachogram derived from the ECG raw data. Intervals between two R-waves are displayed in ms.

Additionally, two indices measuring heart period variability, both baseline-corrected, were extracted from the RR tachogram. Since such measures of RR-interval variability are known to decrease as a function of mental effort and hence the heart beat becomes more regular (Manzey, 1998), they are believed to be indicators of mental demand. Although the reasons for it are not yet fully understood, a more precise central nervous control has been assumed as a reason for this (Manzey, 1998). Firstly, the overall variation in RR-intervals reflected by the standard deviation of RR (RRsd) was calculated (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). This index is a measure estimating the relative contribution of the parasympathetic (rapid onset) and sympathetic (slow onset) branches of the autonomic nervous system. Using spectral analytic methods (for details see Berntson et al., 1997) one can precisely define their contribution to an autonomic reaction. However, since the peripheral physiological data was not of central interest for this study, these indices were solely analyzed with standard statistical procedures. Secondly, the difference between the longest (RR_{max}) and shortest interval (RR_{min}) from each block (RR_{p-p}) was used as a control measure indicating the quality of heart beat detection (too long or to short intervals are sign of missed or falsely included heart beats).

Due to abnormalities found in the cardiac activity, subjects 1, 14, 20 (experiment I) and 11 (experiment II) had to be completely excluded from the analysis. Moreover, prior to the analysis outliers were identified by introspection of skewness and kurtosis of the sample distribution. Additional subjects had then to be excluded from the analysis of different indices (experiment I: RR_{sd} - 5, 8, 9, 12; experiment II: RR_{mean} - 2, 8; RR_{sd} − 2, 14). Furthermore, to avoid contamination of RR-interval measures caused by novelty effects, the first block of each emotional condition per run was discarded (4 instead of 5 blocks / condition and run or 12 blocks / run).

In order to investigate the hypothesized significant effects of pain and angry faces on cardiac activity as compared to neutral faces (see Section 2) several ANOVAs were calculated. According to the factorial structure displayed in the Table 5 below the following analyses were conducted for each of the indices:

a) habituation (analysis of sequence effect independent of facial category with factor RUN and BLOCK)

b) condition (analysis in dependence of facial category with factor EMOTION, RUN, BLOCK).

Table 5:   Structure of analysis applied to the ECG data.

	Overall experiment															
Run	**1**												**2**			**3**
Condition	N				A				P				N	A	P	
Block	1	2	3	4	1	2	3	4	1	2	3	4				
RR_mean																
RR_sd																

3.7.2.3 GSR – Measures

Since event-related SCRs usually show a latency of 1-3s after stimulus presentation and a recovery time between 2-10s (Dawson et al., 1990), the electrodermal activity to the STIMULUS was analyzed in an interval of 0 - 20 s around block onset. Accounting for the delay of GSR, an area of 12 seconds before each block was set to cover the BASELINE response.

Analysis was restricted to the investigation of phasic GSRs. According to Dawson and colleagues (1990) non-specific responses ("spontaneous") should be differentiated from specific ("event related") responses. Although the focus was on the analysis of event-related GSRs, no clear distinction between them was possible (no simultaneous breath monitoring). Since peripheral physiological measures were not the central research method in this work, but were used to support the imaging results, this does not seem to be critical. To determine phasic electrodermal activity, several measures like, for

example, latency of a GSR can be used (Boucsein, 1992). First, the index GSR_{mean} was chosen and extracted from the channel of smoothed GSR data (see Section 3.6; Dawson et al., 1990) for the above mentioned intervals. Moreover, to monitor the amplitude of changes in GSR response during exposure to the blocks of stimuli, the index $GSR_{diffarea}$ was extracted from the channel GSRdifference.

The GSR response of individuals showed high variablility (2-20 µS) and moreover, the distribution of GSRs were found to be skewed. Hence, all indices were logarithmized by log 10(1+*Stimulus*/*Baseline*). Since also GSRmean values of zero might occure "1+" has to be added, because the logarithm of zero is not defined (Venables and Christie, 1980, cited in Dawson et al., 1990). The following indices of interest were used: GSR_{mean}, $GSR_{log-mean}$, $GSR_{log-diff-area}$. Prior to the analysis these measures were baseline-corrected by calculating the difference between stimulus and baseline response for each indice (e.g. $GSR_{meanS-B}$ = $GSR_{meanStimulus}$ -$GSR_{meanBaseline}$). For reasons of simplicity the indices of these corrected values were labeled as GSR_{mean}, $GSR_{log-mean}$ and $GSR_{log-diff-area}$.

In order to avoid contamination of the GSR measures caused by novelty effects, the first block of each emotional condition per run was discarded (4 instead of 5 blocks / condition / run or 12 blocks / run) before further analysis was done.

Due to insufficient amplification, data of subjects 16 and 17 had to be completely excluded from the analysis of experiment I. Moreover, prior to the analysis outliers were identified by introspection of skewness and kurtosis of the sample distribution. Additionally, subject 18 had then to be excluded.

For the analysis of GSR signal acquired during brain imaging neither the quality of the images was decreased nor quantitative changes in the signal-to-noise ratio were detected. However, the GSR signal was contaminated by the gradient noise. An additional median filter of 1000 samples was applied to the smoothing channel before continuing with the above described extraction of the GSR indices. Although smoothing revealed satisfactory results, the data itself was of low quality. Thus, seven of 17 subjects (4, 7, 9, 10, 11, 14 and 15) had to be excluded due to technical problems during acquisition. The data of the remaining subjects showed responses below 0.6 MicroSiemens (µS) without meaningful variation (< 0.05 µS; see Cacioppo and Tassinary, 1990). Analysis of this data was although done, but will only be provided on

DVD. Possible reasons for this technical problem will be evaluated in the discussion of this thesis.

In order to investigate the hypothesized significant stronger GSR responses to pain and angry faces in contrast to neutral faces (see Section 2), the four indices were further analyzed for an effect of habituation and condition of facial expression following the structure applied to the ECG data (Table 5).

3.7.3   Imaging Data

Image processing and statistical analysis was performed with the software Brainvoyager QX (Version 1.2; Brain Innovation, Maastricht / Netherlands).

Since the first two volumes per run did not represent the steady state of magnetization, they were discarded from the time series resulting in a remaining number of 140 volumes per run. The time-series were corrected for slice timing, realigned, coregistered, motion corrected, and spatially normalized into standardized Talairach space (Talairach and Tournoux, 1988) using the subjects coregistered T1*-weighted image. In order to further increase the signal-to-noise ratio, data was spatially smoothed using a 10 mm FWHM isotropic Gaussian kernel. Temporal smoothing was done by using a high-pass filter of 5 cycles per time series and a Gaussian kernel of 2.8s.

Statistical analysis was performed on a voxel-by-voxel basis using the general linear model (GLM) (for details see Kiebel and Holmes, 2003). Thus, a three-by-two-by-two (neutral / anger / pain *versus* male / female actor *versus* male / female observer) repeated-measure ANOVA was conducted. As suggested by Friston et al. (1995), a separate GLM was specified for each subject including parameter estimates of block and event-related activity at each voxel for each regressor (block design: neutral, anger, pain; event-related design (+ factor: male/female actor): $neutral_{male}$, $neutral_{female}$, $anger_{male}$, $anger_{female}$, $pain_{male}$, $pain_{female}$). The expected BOLD signal change for each stimulation block and event was modeled by a canonical hemodynamic response function (modified gamma function of delta = 2.5, tau = 1.25). Contrast images were calculated by applying appropriate linear contrasts to the parameter estimates for the parametric regressor of each event. A *t* statistic resulted for each participant (Poline, Kherif and Penny, 2003). In order to account for variability among the different subjects

and runs, random-effects analysis was performed (Penny and Holmes, 2003). Thus, after z-transformation of the signal values, the individual single-subject contrasts were entered into a second-level random-effects analysis. One-sample t tests on individual contrast images obtained in each subject for each comparison of interest, treating subjects as a random variable, were conducted. This analysis estimates the error variance for each condition of interest across subjects, rather than across scans, and therefore provides a stronger generalization to the population from which data are acquired. In this random-effects analysis, resulting t statistic (df = 16) at each voxel were thresholded at $P < 0.005$ (uncorrected) corresponding to a t-score > 3.3 in regions where a priori hypothesis existed. Based on earlier studies on facial expressions of emotion, analysis was focused on the amygdalae, MPFC, fusiform gyrus, STS, anterior insula, ACC, somatosensory cortices (SI and SII / posterior insula), which were defined a priori as region of interest (ROI) using Talairach daemon software (http://ric.uthscsa.edu/ projects/talairachdaemon.html), except for STS. Following the suggestions of Winston et al. (2003a), a sphere of 12mm was used to investigate activation in posterior STS. For analyzing prefrontal activation, a ROI for the MPFC was defined including medial BA 9 and 10. Significant results in these ROIs are reported with respect to the precise anatomical location of the cluster as: dorsomedial (BA 9) and ventromedial (BA 10) PFC.

Moreover, to protect against type I error (e.g. false positives), only activation foci that survived the mentioned threshold with a cluster size of greater than four contiguous voxels (extent threshold) were accepted.

The following effects were investigated:

		ALL OBSERVER	
		Male Observer	Female Observer
Neutral	*Male Actor*		
	Female Actor		
Anger	*Male Actor*		
	Female Actor		
Pain	*Male Actor*		
	Female Actor		

According to this structure, different contrasts of interest, outlined below, were calculated:

Block design

To examine the effect of emotion versus neutral expressions, pain and anger faces were compared against neutral faces using the contrasts [**Pain-Neutral**] and [**Anger-Neutral**]. In order to identify regions specifically responsive to pain recognition, "pain" was also compared with "anger" using the contrast [**Pain-Anger**]. To examine possible effects of the observers' sex these contrasts were analyzed in the group of: (a) all observers (=male + female observer), (b) male observers, (c) female observers and were moreover compared directly by the computation (d) male > female observer.

Event-related design

To account for sex differences, the factor SEX OF ACTOR was included in this step of analysis. To investigate the effect of emotion versus neutral expressions, pain and anger faces were compared against neutral faces using the contrasts below:

$$[\textbf{Pain}_{\textbf{male}}\textbf{-Neutral}_{\textbf{male}}] \text{ and } [\textbf{Pain}_{\textbf{female}}\textbf{-Neutral}_{\textbf{female}}]$$
$$[\textbf{Anger}_{\textbf{male}}\textbf{-Neutral}_{\textbf{male}}] \text{ and } [\textbf{Anger}_{\textbf{female}}\textbf{-Neutral}_{\textbf{female}}]$$

To identify regions specifically responsive to pain recognition, "pain" was also contrasted against "anger" using the contrast:

$$[\textbf{Pain}_{\textbf{male}}\textbf{-Anger}_{\textbf{male}}] \text{ and } [\textbf{Pain}_{\textbf{female}}\textbf{-Anger}_{\textbf{female}}]$$

To examine possible effects of the observer's sexes as well as interactions between observer's and actor's sex, these contrast were analyzed in the group of: (a) all observer (=male + female observer), (b) male observers, (c) female observers and were moreover compared directly by the computation (d) male > female observer. However, only significant differences found for the contrast [Male > Female observer], which also met the extent threshold, were reported.

Furthermore, in order to gain more knowledge about the origin of certain results, all mentioned conditions (neutral, anger, pain, neutral$_{male}$, neutral$_{female}$, anger$_{male}$, anger$_{female}$, pain$_{male}$, pain$_{female}$) were post hoc compared to the visual baseline. Since this comparison was not of central interest but solely calculated for descriptive purposes, the resulting information (t-values) are provided in the appendix. Only in cases where these results seemed crucial for the understanding of effects, they are mentioned in the main text.

Moreover, to assess for habituation of BOLD-responses across the entire experimental session, additional regressors were included into the design matrix. They allowed for comparison of the fMRI-signal (parameter estimates at peak voxels for each ROI) between the first and the second half of the three facial expression runs using the same predictors as in the standard analysis plus the predictor TIME (first half, second half of the experiment). Only significant effects associated with the factor TIME are outlined in the results section, since the interactions and main effects of the remaining variables are already reported in the basic fMRI analysis. The level of significance was set at $\alpha <$ 0.05. All files of this habituation analysis are provided on DVD.

To explore whether individual differences in the observed activity covaried with individual ratings and questionnaire scores, correlation (Spearman's rho) between ROI parameter estimates for certain contrasts of interest and these individual scores were calculated. This was solely done for the most meaningful questions and not for each questionnaire and each region of interest (see Section 2). Hence, subjects' valence and arousal ratings (actor's view) reported to pain clips, as well as the questionnaire scores were correlated with the parameter estimates measured for the contrast [**Pain-neutral**] observed to male and female actors faces in the ROIs' peak voxels. Since these computations comprised repeated tests, a Bonferroni-corrected threshold was employed for each ROI (e.g. left and right amygdala treated as separate ROIs). Since some ROIs

underwent more correlation analyses according to the a-priori hypothesis, different corrected thresholds resulted for each ROI (see Section 4.3.9).

Moreover, this thesis aimed to link the BOLD-response in the amygdala, ACcd and the anterior insula with block-related cardiac measures, as well as amygdala activation with block-related GSRs. However, on the one hand in the case of GSR-data acquired during scanning, poor data quality made this analysis impossible. On the other hand, analysis of the block design did not yield sustained activation in these ROIs. Thus, this hypothesis remained to be unanswered.

4 Results

4.1 Questionnaire Data & Behavioral Ratings

4.1.1 IRI

For the two samples of subjects, a mean of 19.2 (SD=5.4) in experiment I and a mean of 19.0 (SD=4.5) in experiment II was measured for IRI-PT. For the subscale IRI-EC the following results were determined: experiment I - mean=22.3 (SD=3.8) and experiment II - mean=20.9 (SD=3.5). Significant intercorrelations between EC and PT were solely detected for the second experiment (experiment I: Spearman r=0.31, p=0.14, r^2=0.15; experiment II: Spearman r=0.70, p=0.002, r^2=0.37). After exclusion of outliers by inspection of the associated scatter plots, significant correlations occurred for both experiments (experiment I: Spearman r=0.44, p=0.045, r^2=0.25; experiment II: Spearman r=0.73, p=0.002, r^2=0.42). Figure 11 displays the mean empathy scores of male and female subjects for both samples (experiment I and II). A comparison of these sample values to the gender norms of a large college sample (579 men, 582 women) provided by Davis (1980) can be found in Appendix A-I. In relation to those, all scores observed in the present study, except for one, were slightly above average. This was especially true for male subjects.

IRI scores - experiment II
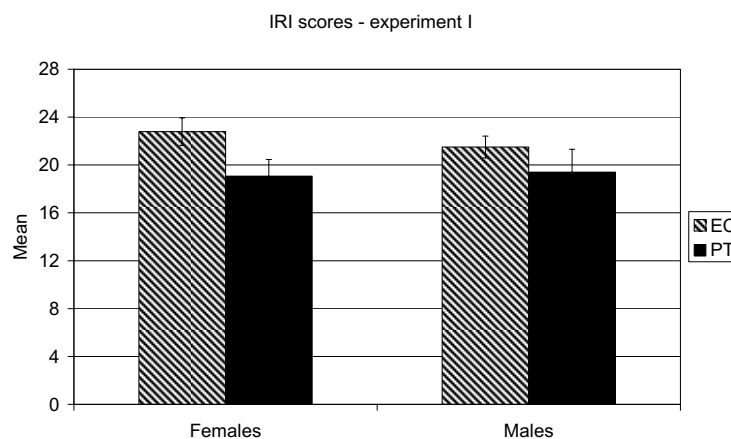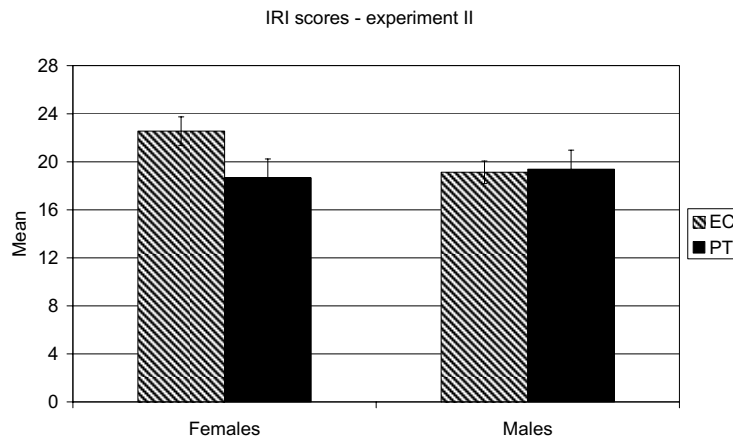
Figure 11:   Scores of male and female observers on IRI-subscales empathic concern (EC) and perspective taking (PT) observed in experiment I and II (mean ± se).

Females did not on all subscales score higher than males. In line with this descriptive data, a 2 x 2 ANOVA with between-subject factor SEX OF OBSERVER and repeated measures factor IRI-subscale (EC and PT) did not reveal a main effect of SEX OF OBSERVER. However, a significant main effect of IRI-subscale (experiment I: $F_{(1;23)}=8.00$; $p=0.010$; experiment II: $F_{(1;15)}=5.91$; $p=0.028$) was observed. Post hoc contrast analysis showed that EC scores were significantly higher than PT scores for both experiments (DVD). Only for experiment II an interaction between SEX OF OBSERVER and type of IRI-subscale was observed ($F_{(1;15)}=7.64$; $p=0.014$) (Figure 12).
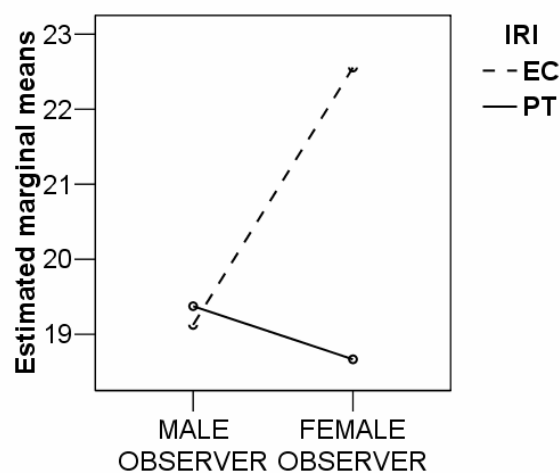
Figure 12:   Interaction effect of IRI-subscales and SEX of OBSERVER in experiment II (estimated marginal means displayed).

Inspection of Figure 12 displaying this interaction and post hoc contrasts showed that this was due to the fact that EC scores were higher than PT scores in female observers but that there was no difference between these subscales in male observers (DVD).

4.1.2   BEES

Results for the BEES-scale are solely reported for experiment II, since data was only acquired for this experimental setting. Compared to the norms reported by Mehrabian (2000) (mean = 45; SD=24), the values observed in the present sample corresponded to the average (mean$_{all}$=53.2; SD=22.8). Appendix A-IIa provides the z-scores for all subjects in relation to norms of z-scores and percentile equivalents found by Mehrabian (2000). Moreover, in the literature it has been described that women in general tended to be more emotionally empathic than men (Mehrabian, Young, and Sato, 1988). Thus, Mehrabian provided separate norms for males and females (mean$_{male}$=29; SD=28, mean$_{female}$=60, SD=21). Although, as shown in Figure 13, the present study confirmed that female observers showed on average higher empathy scores than males (mean$_{male}$=44.4, SD=19.7; mean$_{female}$=61.1, SD=23.5) the difference was not statistically significant (DVD).
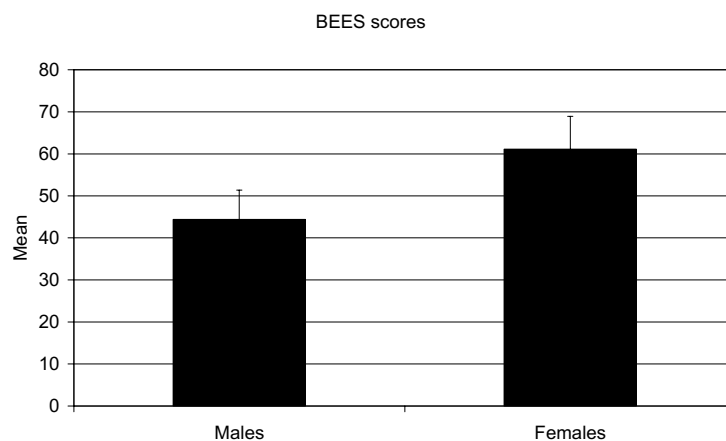
Figure 13:   Scores of male and female observers on the BEES-scale observed in experiment II (mean±se).

One can furthermore summarize that male subjects in the present sample were more empathic than males in general when taking the separate norms for males and females into account. Appendix A-IIb displays male and female empathy scores related to the norms of z-scores and percentile equivalents for each gender group as found by Mehrabian (2000).

4.1.3   BEES & IRI

In order to relate the less validated IRI-scale to the well evaluated BEES-scale, correlations were determined using the data of experiment II. It was shown that both IRI subscales were significantly correlated with the BEES-scale (BEES and IRI-EC: $r=0.74$, $p=0.001$, $r^2=0.58$; BEES and IRI-PT: $r=0.51$, $p=0.035$, $r^2=0.30$). Hence, one has to note that the correlation with the subscale IRI-EC was much higher than the one with the subscale IRI- PT, which was not surprising given the fact that both BEES and IRI-EC measure "emotional empathy". Thus one can use the EC-subscale as an indicator of emotional empathy in experiment I. Furthermore, additional information about cognitive empathy might be provided using the subscale IRI-PT.

4.1.4   STAI

The reported state of anxiety before the experimental procedure was on average 43.5 (SD=5.0) for experiment I and 44.1 (SD=3.4) for experiment II. For trait anxiety, mean scores of 46.5 (SD=5.3) were measured for experiment I and of 45.5 (SD=4.0) for experiment II. These scores are above the published norms for this age group (state: mean=36; SD=10; trait: mean=36; SD=10) as provided by Spielberger (1983).

A significant correlation was detected between state and trait scores for experiment I ($r=0.59$, $p=0.002$, $r^2=0.35$) but not so for experiment II ($r=-0.12$, $p=0.66$, $r^2=0.01$).

Figure 14 shows the mean state and trait anxiety scores, which were observed in the sample of male and female subjects. The scores and standard deviations for both experiments are provided by Appendix A-III.

STAI scores - experiment I

STAI scores - experiment II
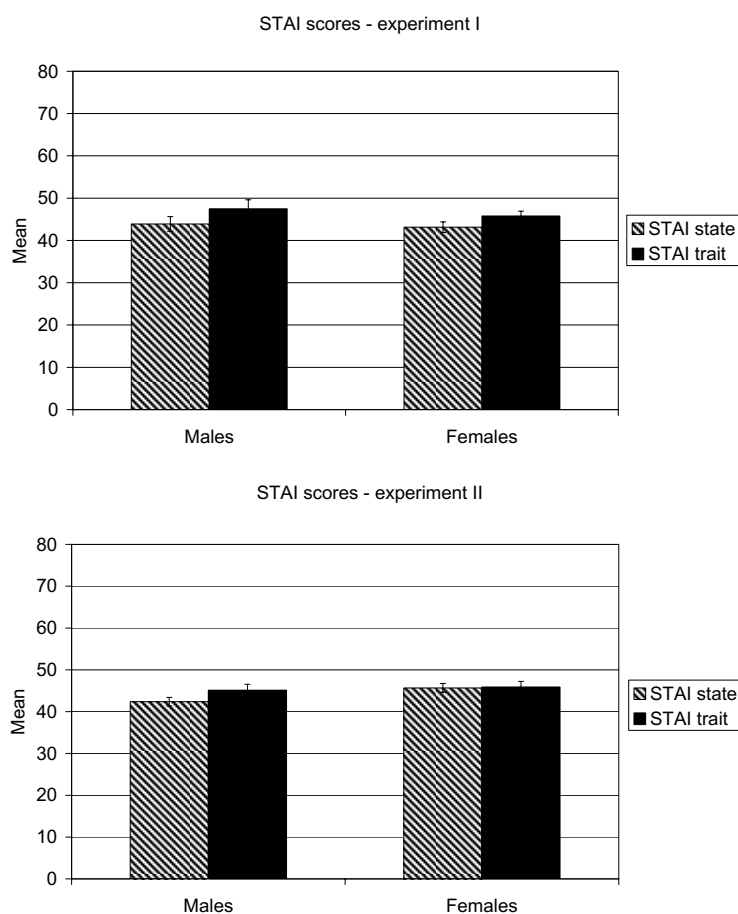
Figure 14:   Scores of male and female observers on STAI-subscales measuring state (STAI state) and trait anxiety (STAI trait) as observed in experiment I and II (mean±se).

A 2 x 2 ANOVA was calculated with between-subject factor SEX OF OBSERVER and repeated measures factor STAI-subscale (state and trait). There was no significant main effect of observer's sex found in both experiments (DVD). However, a significant difference was observed between state and trait anxiety for experiment I ($F_{(1;23)}$=10.36; p=0.004) due to the fact that STAI trait scores were higher than state scores (DVD).

4.1.5 PCS

While in experiment I subjects generally showed a total score of 23.3 (SD=10.8) on the PCS-scale, subjects in the second experiment reported a lower total score on average (mean=18.0, SD=9.2). Taking the percentile equivalents reported by Sullivan into account, mean PCS-score of experiment I corresponded with the 57th and mean PCS-

score of experiment II with the 47th percentile. Since only scores of 30 and higher are considered to be clinically relevant, the present samples showed non-clinical, average levels of catastrophizing (Sullivan, 2004). Figure 15 displays the mean PCS-scores of the subjects when taking the gender variable into account. The total PCS-score, as well as the scores for the three subscales for male and female subjects are provided in Appendix A-IV.
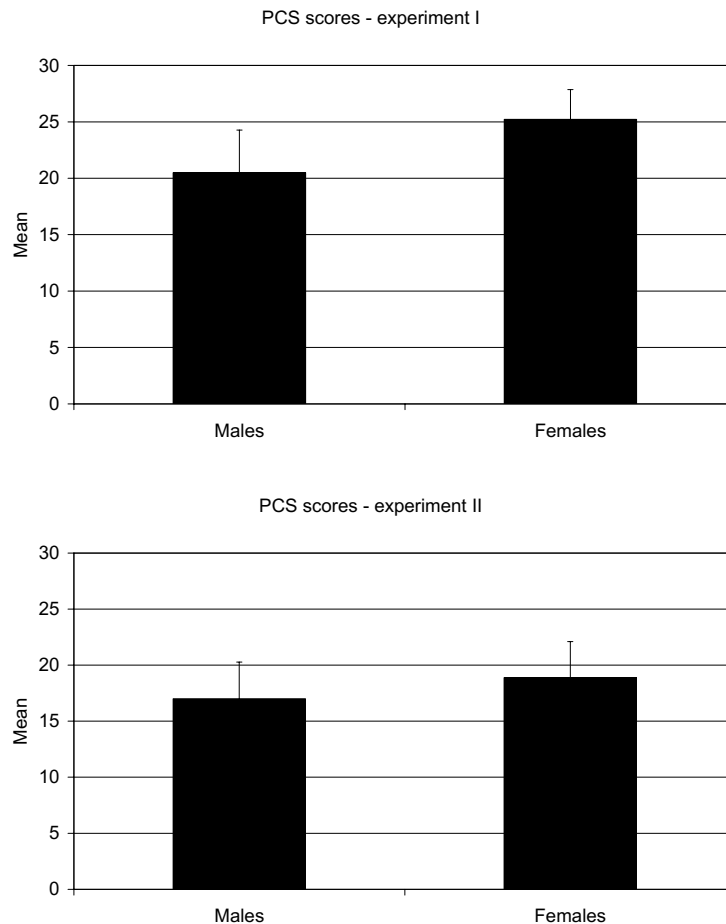
Figure 15:   Total PCS-scores of male and female subjects as observed in experiment I and II (mean ±se).

In contrast to the literature which reports higher PCS scores for females as compared to males (Sullivan et al., 1995), no such differences were detected for the PCS total score in the samples of both experiments. Also in contrast to the literature, no interaction was found between the three subscales and the observer's sex (DVD).

4.1.6 Behavioral Ratings

As described in section 3.3.5, during both experiments subjects were asked to judge the intensity, valence, and arousal of the anger, pain and neutral clips.

For intensity ratings, a 2 x 3 ANOVA with between-subject factor SEX OF OBSERVER and repeated measures factor EMOTION (neutral, anger, pain) was calculated. Since these ratings reflected an average for all 8 actors, no discrimination of the actor's sex was possible.

With respect to the *intensity* of the target emotion the clips showed the following ratings: angry (experiment I: mean=3.9, SD=0.9; experiment II: mean=3.6, SD=0.9), painful (experiment I: mean=3.2, SD=1.9; experiment II: mean=3.1, SD=1.8) and neutral (mean of intensity for all emotional labels in experiment I: mean=0.1, SD=0.2; in experiment II: mean=0.3, SD=0.3). One has to note that the homogeneity assumption of variance was violated for experiment II. However, this had no consequences since equality of group sizes was met. First of all, analysis of intensity ratings yielded a main effect of the factor EMOTION (experiment I: $F_{(2;44)}$=82.02; GG-ε=0.69; GG-p<0.001; experiment II: $F_{(2;30)}$=51.88; GG-ε=0.66; GG-p<0.001). Post hoc contrast analysis revealed that pain and anger did not differ significantly from each other, but from neutral (p(cor)=0.016; experiment I: anger > pain: p=0.029, pain > neutral: p<0.001; anger > neutral: p<0.001; experiment II: anger > pain: p=0.208; pain > neutral: p<0.001; anger > neutral: p>0.001).

Since males and females in general gave the same ratings in terms of intensity, no main effect of the observers' sex was found. Only marginal significance was detected in experiment II ($F_{(1;15)}$=4.39; p=0.054) due to the fact that females' intensity ratings were slightly higher than ratings of males. Also, the interaction between emotion and the observers' sex reached marginal significance for experiment I ($F_{(2;44)}$=3.60; GG-p=0.055) only. Figure 16 indicates that females rated pain clips as slightly more intense as compared to male observers (DVD).

Generally speaking, the ratings of male and female observers did not differ within each clip category.
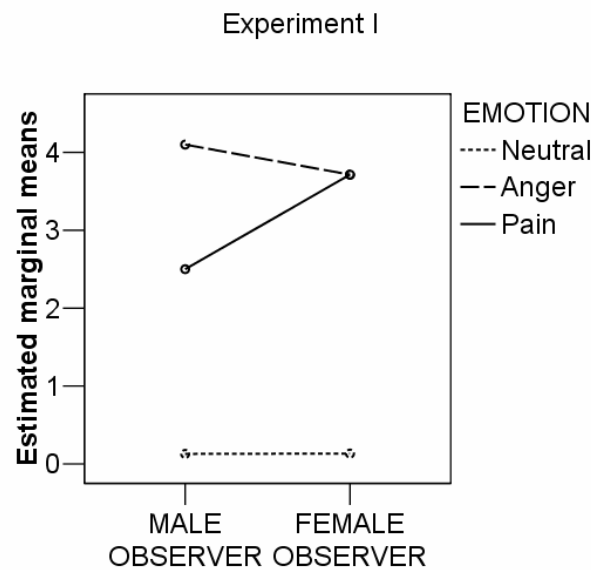
Figure 16: Interaction of the factor EMOTION x SEX of OBSERVER on intensity ratings as detected in experiment I (estimated marginal means displayed).

Differences in *contamination* between clips of angry, painful and neutral faces were determined. The complete descriptive statistics displaying the intensity ratings on all target and non target emotions for all three kinds of clips are provided on DVD. Analysis yielded a significant main effect of EMOTION in both experiments (experiment I: $F_{(2;44)}=37.77$; GG-ε=0.64; GG-p<0.001; experiment II: $F_{(2;30)}=$; GG-ε=0.78; GG-p<0.001). This was due to the fact that pain clips were significantly more contaminated than the other clips, while the other clip categories showed comparably low contamination levels (p(cor)=0.016; experiment I: pain > anger: p<0.001; pain > neutral: p<0.001; anger > neutral: p=0.703; experiment II: pain > anger: p<0.001; pain > neutral: p<0.001; neutral > anger: p=0.683). Figure 17 displays the contamination of pain clips. The same graphs are provided for anger and neutral clips in the Appendix A-V.
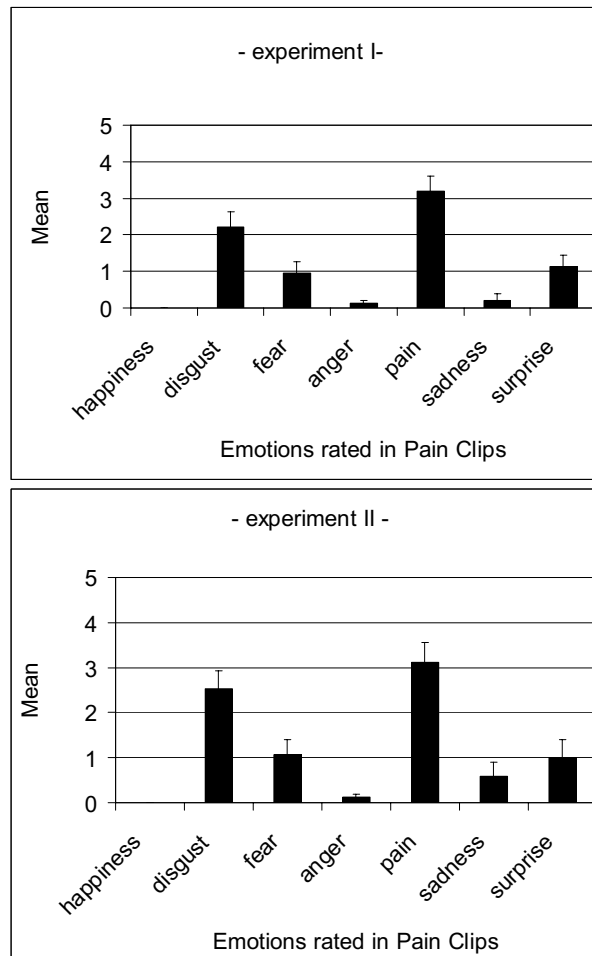
Figure 17: Contamination of pain clips with other emotions on a scale from 1-5 (mean±se).

Visual inspection of the graphs (Figure 17) and descriptive statistics demonstrated that pain was mostly contaminated with the following other emotions taking their means into account:

		Experiment I		**Experiment II**	
1.	disgust	2.2	(SD=2.1)	2.5	(SD=1.7)
2.	fear	1.0	(SD=1.5)	1.1	(SD=1.4)
3.	surprise	1.1	(SD=1.6)	1.0	(SD=1.7)

This contamination is due to the fact that 33% of the subjects in experiment I and 29% in experiment II recognized another emotion being more intense than pain in the clips displaying pain contorted faces or that even did not recognize pain at all (zero-rating for the pain label). Although mostly pain was recognized in the pain clips, these cases suggest that some people had difficulties to clearly recognize pain as the target emotion.

To test whether these interindividual differences for the recognized emotions in pain clips did alter the processing of pain clips as measured by fMRI, these ratings were taken into account and are described in the accordant section.

Furthermore, a marginally significant main effect of the observers' sexes on judgements of contamination was observed for experiment I ($F_{(1;22)}$=4.04; p=0.057), because male observers tended to rate more contamination in the clips than female observers did.

It has to be taken into account that the homogeneity assumption of variance was violated for both experiments. For experiment II, this was not crucial since the equality of group size was met (largest/smallest <1.5, Stevens 1996) and thus the ANOVA responded relatively robust. For experiment I, the group size was not equal, but since the resulting F statistic became more conservative due to the fact that the large sample variance was associated with the smaller group, no further consequences occurred.

There was no interaction effect of SEX OF OBSERVER and EMOTION (DVD) in experiment II, but this effect was significant (Figure 18) for experiment I ($F_{(2;44)}$=7.82; GG-p=0.006), due to the fact, that male observers, as revealed by subsequent one-way ANOVAs, rated significantly more contamination for pain clips than female observers, while their ratings did not differ for anger and neutral clips ($pain_{male}$ > $pain_{female}$: p=0.013; $anger_{male}$ > $anger_{female}$: p=0.525; $neutral_{female}$ > $neutral_{male}$: p=0.961; p(cor)=0.016).
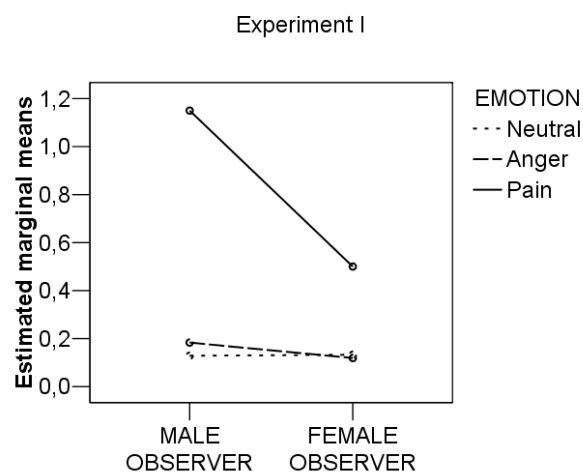
Figure 18: Interaction of EMOTION x SEX of OBSERVER on contamination indices found in experiment I (estimated marginal means displayed).

For the analysis of valence and arousal, the factor PERSPECTIVE, with the two stages actor's vs. observer's point of view, was additionally included. Thus, three way

univariate ANOVAs were calculated with between-subject factor SEX OF OBSERVER, repeated measures factors EMOTION (neutral, anger, pain) and PERSPECTIVE (actor and observer perspective).

In both experiments, it was observed that clips differed from each other with respect to their valence ratings (see Table 6 + Figure 19).
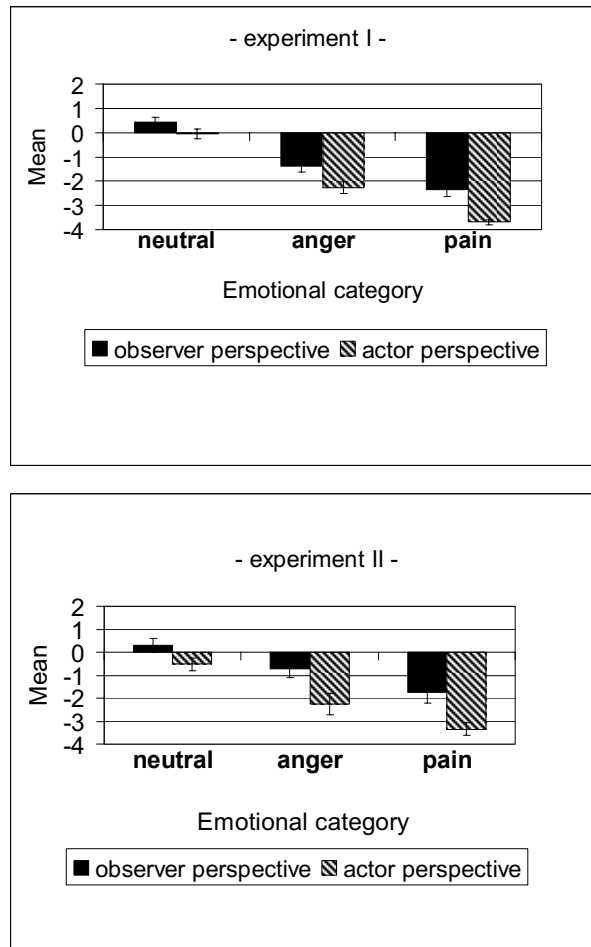

Figure 19: Valence ratings of neutral, anger and pain clips for experiment I and II (mean±se).

Table 6:   Valence ratings for neutral, anger and pain faces from the actors' and the subjects' point of view (mean±SD).

	Experiment I	Experiment II
ACTORS' PERSPECTIVE		
Neutral	-0.06 ± 1.0	-0.53 ± 1.2
Anger	-2.27 ± 1.2	-2.26 ± 1.5
Pain	-3.69 ± 0.5	-3.35 ± 1.8
OBSERVERS' PERSPECTIVE		
Neutral	0.42 ± 1.0	0.29 ± 1.2
Anger	-1.38 ± 1.2	-0.74 ± 2.0
Pain	-2.33 ± 1.4	-1.76 ± 1.1

The analysis of *valence* ratings revealed a main effect of EMOTION (experiment I: $F_{(2;46)}=140.18$; GG-ε=0.84; GG-p<0.001; experiment II: $F_{(2;32)}=23.32$; GG-ε=0.74; GG-p<0.001). Separate subsequent analyses of these means for the actors' and observers' point of view were computed (p(cor)=0.016; ACTOR PERSPECTIVE unpleasantness: experiment I - pain > anger: p<0.001; pain > neutral: p<0.001; anger > neutral: p<0.001; experiment II - pain > anger: p=0.046; pain > neutral: p<0.001; anger > neutral: p=0.009; OBSERVER PERSPECTIVE unpleasantness: experiment I - pain > anger: p=0.001; pain > neutral: p<0.001; anger > neutral: p<0.001; experiment II - pain > anger: p=0.026; pain > neutral: p<0.001; anger > neutral: p=0.061). Hence, in line with the hypothesis from the actors' viewpoint, subjects perceived anger, as well as pain faces as more unpleasant than neutral faces, which was shown in both experimental sessions. Moreover, in the case of experiment I, they even judged pain as being more unpleasant than anger. Subjects' own feelings of unpleasantness in response to all three types of facial displays differed from each other with pain being most unpleasant, followed by anger and neutral during experiment I. However, in experiment II solely ratings to pain clips showed a significant difference in comparison to neutral clips.

Moreover, as suggested by Figure 19, a main effect of PERSPECTIVE was detected in both experiments (experiment I: $F_{(1;23)}=15.49$; p=0.001; experiment II: $F_{(1;16)}=27.18$; p<0.001), resulting from the fact that subjects rated clips as more unpleasant when

taking the perspective of the actor as compared to their own point of view (DVD). This seemed to apply to male and female observers comparably, because no interaction and main effect of this factor was observed.

Moreover, the facial expressions differed from each other with respect to their *arousal* ratings throughout both experiments (see Table 7 and Figure 20).

Table 7:   Arousal ratings for neutral, anger and pain faces from the actors' and the subjects' point of view (mean±SD).

	Experiment I	**Experiment II**
ACTORS' PERSPECTIVE		
Neutral	-1.45 ± 1.6	-1.59 ± 2.3
Anger	2.13 ± 1.2	1.88 ± 1.7
Pain	3.17 ± 1.7	2.38 ± 1.4
OBSERVERS' PERSPECTIVE		
Neutral	-1.56 ± 1.7	-1.59 ± 1.9
Anger	0.96 ± 1.4	0.00 ± 1.7
Pain	1.25 ± 0.9	1.12 ± 1.5

As expected, statistical analysis of the *arousal* ratings also yielded a main effect of EMOTION (experiment I: $F_{(2;46)}=77.39$; GG-ε=0.96; GG-p<0.001; experiment II: $F_{(2;30)}=27.44$; GG-ε=0.69; GG-p<0.001). Separate subsequent analysis of these means for the actors' and observers' viewpoint were computed (p(cor)=0.016; ACTOR PERSPECTIVE: experiment I - pain > anger: p=0.007; pain > neutral: p<0.001; anger > neutral: p<0.001; experiment II - pain > anger: p=0.283; pain > neutral: p<0.001; anger > neutral: p<0.001; OBSERVER PERSPECTIVE: experiment I - pain > anger: p=0.475; pain > neutral: p<0.001; anger > neutral: p<0.001; experiment II - pain > anger: p=0.013; pain > neutral: p<0.001; anger > neutral: p=0.020). In accordance with the a-priori hypothesis, subjects rated anger and pain faces as more arousing than neutral faces taking the actors' viewpoint. This was confirmed by both experiments. In experiment I, they even perceived pain as being more arousing than anger. Subjects' introspection into their own arousal led to higher ratings for pain and anger as compared

to neutral clips for experiment I. However, in experiment II solely ratings to pain clips showed a significant difference in comparison to both clips of neutral and angry faces.
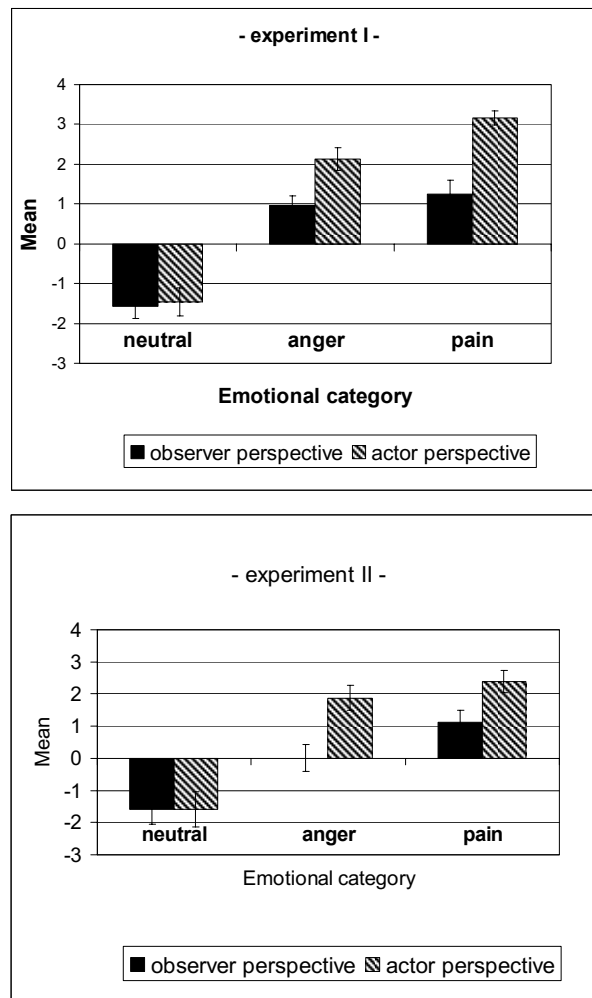
Figure 20: Arousal ratings of neutral, anger and pain clips for experiment I and II (mean±se).

While no main effect of the factor SEX OF OBSERVER had been found for experiment I, a significant difference was detected for experiment II ($F_{(2;15)}$=5.93; GG-p=0.028). This was due to the fact that females indicated in general higher levels of arousal perceived in the clips. Also, a main effect of PERSPECTIVE was observed for both experiments (experiment I: $F_{(1;23)}$=21.79; p<0.001; experiment II: $F_{(1;15)}$=8.54; p=0.011), due to the fact that subjects judged the presented clips as being more arousing taking the perspective of the actor as compared to their own perspective (see Figure 20). Also, a significant interaction between PERSPECTIVE x EMOTION (experiment I: $F_{(2;46)}$=6.77; GG-ε=0.91; GG-p=0.004; experiment II: $F_{(2;30)}$=4.23; GG-ε=0.87; GG-

p=0.030) was detected. Subsequent ANOVAs calculated for each facial category revealed that this was due to the fact that while no difference between actor and observer perspective occurred for neutral clips, this was the case for pain and anger clips (experiment I: $neutral_{actorP} > neutral_{observerP}$: p=1.000; $anger_{actorP} > anger_{observerP}$: p=0.008; $pain_{actorP} > pain_{observerP}$: p=0.007; experiment II: $neutral_{actorP} > neutral_{observerP}$: p=0.801; $anger_{actorP} > anger_{observerP}$: p=0.001; $pain_{actorP} > pain_{observerP}$: p<0.001; p(cor)=0.016).

One has to notice that the homogeneity assumption of variance was violated for experiment II. However, again this had no consequences since equality of group sizes was met.

Finally, it also has to be highlighted that subjects rated pain and anger clips also from their own perspective as more unpleasant and arousing than neutral clips. This might indicate some empathic contagion. However, in contrast to the a-priori hypothesis no correlation of the valence and arousal ratings to pain, anger and neutral faces was detected with subject's IRI-EC and IRI-PT scores (p(cor)=0.004), which was not due to outliers (see DVD).

4.1.7 Behavioral Ratings & Questionnaires

In order to investigate the proposed relationship of valence, arousal, and intensity ratings to anger, as well as pain faces with the questionnaires IRI-EC, IRI-PT and STAI and also of the same ratings for pain clips with the PCS-scale, correlations using a Bonferroni-corrected statistical threshold (p(cor)=0.002) were computed. In contrast to the a-priori hypothesis, no significant results occurred which was not due to outliers (see DVD). Hence, neither empathic ability nor trait anxiety or pain catastrophizing tendencies seemed to influence subjects' behavioral ratings.

4.2 Performance, Reaction Times & Peripheral Physiological Data

4.2.1 <u>Performance</u>

Individuals' responses during the gender discrimination generally showed high accuracy for both experiments, although subjects made more errors during experiment II. First, the correctness of responses is displayed descriptively. Second, incorrect responses (errors) were statistically investigated for effects of actors' as well as observers' sexes and displayed emotion on the error number.

The exact percentage values of correct answers for the entire experiment (total: 360 responses) as well as for each category of facial expressions (total: 120 responses) are displayed in Table 8.

Table 8: Accuracy of judgements (%) for the gender discrimination task for the entire experiment, as well as for each category of facial expressions separately (mean; SD).

	Experiment I	Experiment II
Overall	98 (1.7)	94.2 (5.7)
Neutral	98.5 (1.6)	96.7 (4.3)
Anger	98.5 (1.7)	93.3 (7.2)
Pain	97.0 (2.9)	93.1 (6.6)

With respect to the category of facial expression and the actors' sexes, the following means and standard deviations occurred for incorrect responses (Table 9):

Table 9: Number of errors during the gender discrimination task to male and female actors expressing neutral, angry and pain faces (mean; SD).

	Experiment I	**Experiment II**
neutral$_{male}$	0.9 (1.1)	1.5 (1.6)
neutral$_{female}$	0.9 (1.1)	3.2 (4.4)
anger$_{male}$	0.8 (1.0)	3.2 (3.6)
anger$_{female}$	1.0 (1.3)	4.9 (5.3)
pain$_{male}$	2.0 (2.2)	3.2 (3.7)
pain$_{female}$	1.6 (1.7)	5.0 (5.1)

Figure 21 shows the distribution of errors according to the type of facial expression and the sex of the actor who displays it.
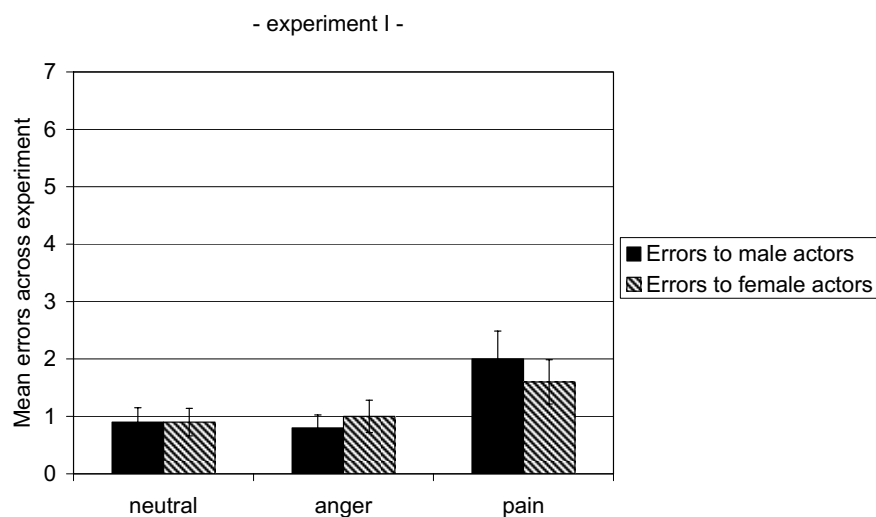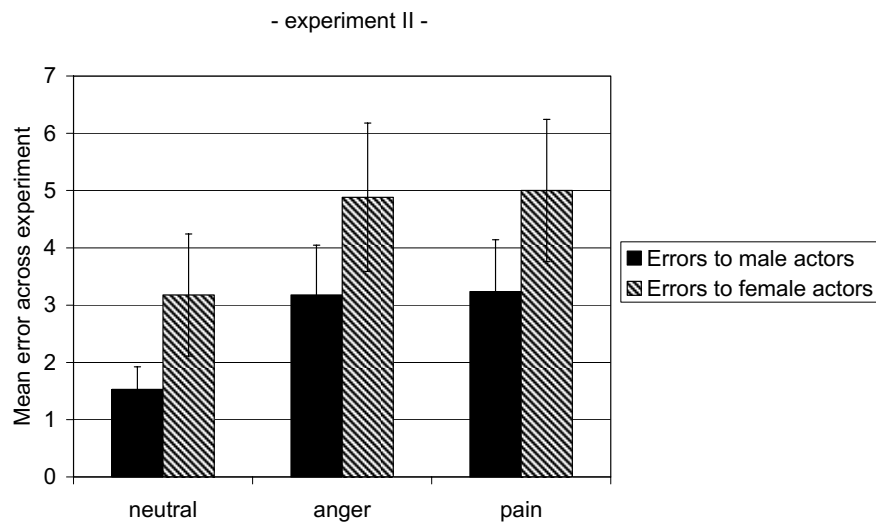
Figure 21: Graphs displaying performance errors to male and female actors expressing pain, anger and neutral during experiment I and II (mean±se).

To examine the influence of EMOTION and SEX OF ACTOR on the error number, a 3 x 2 x 2 ANOVA with between - group - factor SEX OF OBSERVER was performed. Analysis of experiment II revealed a main effect of EMOTION only ($F_{(2;32)}$=6.07; GG-ε=0.68; GG-p=0.015), due to the fact that subjects made significantly more mistakes while being exposed to pain contorted faces. However, the difference between errors to pain and anger, as well as to those between anger and neutral clips failed to reach significance (pain > anger: p=0.787; pain > neutral: p=0.015; anger > neutral: p=0.024; p(cor)=0.016). In the first experiment, also a main effect of EMOTION was found ($F_{(2;36)}$=11.41; GG-ε=0.69; GG-p=0.001), but additionally a main effect of observers' sexes ($F_{(1;18)}$=6.18; p=0.023) and also an interaction of EMOTION x SEX OF OBSERVER ($F_{(2;36)}$=6.30; GG-ε=0.72; GG-p=0.012) was detected. Subsequent analysis of the main effects of EMOTION revealed that significantly more errors were observed to pain faces in comparison to neutral and angry faces (pain > anger: p=0.003; pain > neutral: p<0.003; anger > neutral: p<0.607; p(cor)=0.016). The difference between errors made to angry and neutral clips failed to reach significance. Moreover, in general, male observers made conducted more errors than female observers as subsequent analysis of the second main effect confirmed (DVD). The interaction effect of EMOTION x SEX OF OBSERVER was further analyzed by subsequent one-way ANOVAs, which were calculated separately for male and female observers. The

analysis yielded no main effect of EMOTION for the group of female, but for the group of male observers ($F_{(1;12)}$=7.20; GG-ε=0.62; GG-p=0.026). This was due to the fact that males made more errors to pain clips as compared to anger and neutral clips (pain > anger: p=0.043; pain > neutral: p<0.026; anger > neutral: p<0.253; p(cor)=0.016). However, taken the corrected threshold into account, these effects failed to reach significance. Moreover, it has to be highlighted that the homogeneity assumption was not fulfilled in this case. Since the group of male and female observers was not equal in size for experiment I (7 vs. 13) and additionally the larger sample variance was associated with the small sample size (male observer), the F statistic became more liberal and this probably contributed to these significant results.

4.2.2 RT

It has to be highlighted that there were minor differences in the instruction to the sex discrimination task between both experiments, which has to be taken into account for the interpretation of the following results on RTs. As mentioned earlier, during experiment I subjects were asked to respond as fast as possible, while subjects in experiment II were, from a methodical point of view, only allowed to answer *after* the grey screen had occurred. Hence, RT of experiment I were much shorter (< 1000 ms) than those of experiment II (> 1000 ms). Introspection of the descriptive statistic (Table 10) showed that within both experimental settings almost equal RTs were observed.

Table 10: RT during the gender discrimination task to male and female actors expressing neutral, angry and pain faces (mean± SD in ms).

	Experiment I	Experiment II
neutral_male	645 (27)	1532 (88)
neutral_female	632 (28)	1510 (85)
anger_male	659 (32)	1554 (87)
anger_female	650 (30)	1531 (82)
pain_male	646 (31)	1553 (98)
pain_female	637 (27)	1537 (95)

Without taking the facial category into account, learning effects on RT values across the experiment were analyzed using a 2 x 3 x 15 ANOVA with between-subject factor SEX OF OBSERVER and repeated measure factors RUN (1-3) and BLOCK (1-15). During experiment I no decrease of RT and hence, no main effect was observed for the factor BLOCK and RUN. This was the case, however, for experiment II (RUN: $F_{(2;32)}$=5.33; GG-ε=0.88; GG-p=0.014; BLOCK: ($F_{(14;224)}$=2.56; GG-ε=0.47; GG-p=0.02). As post hoc analysis revealed, subjects generally responded faster during the last run as compared to the first run (run 3 < run 1: p=0.013; run 2 < run 1: p=0.056; run 3 < run 2: p=0.176; p(cor)=0.016). The variation of RT accounting for the main effect of BLOCK did not show meaningful patterns, but was characterized by increases and decreases across the whole experiment (DVD). For experiment I, only an interaction of RUN x BLOCK was observed ($F_{(28;532)}$=2.53; GG-ε=0.32; GG-p=0.010), which was not found for experiment II. Further analysis of this interaction showed a main effect of BLOCK for the first run only ($F_{(14;266)}$=3.87; GG-ε=0.41; GG-p=0.002). Since post hoc analysis for all 15 blocks would incorporate multiple testing resulting in p(cor)=0.0005, they were not calculated (accuracy of SPSS only p=0.000). Variation of RT during the first run can instead be inspected in Figure 22.
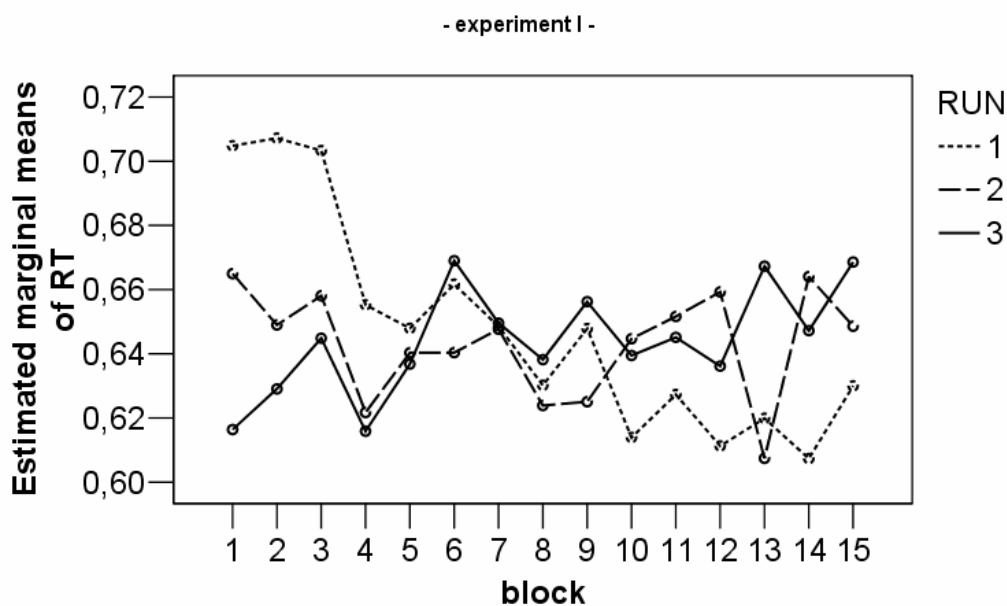
Figure 22:   Variation of RT across three runs independent of facial category observed during experiment I.

Introducing the factor SEX OF ACTOR and EMOTION resulted in 2 x 2 x 3 x 3 x 5 ANOVAs with between-subject factor SEX OF OBSERVER and repeated measures factors SEX OF ACTOR, EMOTION, (neutral, anger, pain), RUN (1-3) and BLOCK (1-5). Confirming the descriptive data of Table 10, no effect of the facial category on the RT was observed (experiment I: $F_{(2;38)}=2.44$; GG-ε=0.84; GG-p=0.112; experiment II: $F_{(2;32)}=2.49$; GG-ε=0.82; GG-p=0.11). Thus, besides the above mentioned learning effects (BLOCK, RUN), no further significant differences in RTs were detected for experiment II.

However, analysis of the RT acquired during the first experiment I, revealed a significant two-way interaction of SEX OF ACTOR x BLOCK ($F_{(4;76)}=15.94$; GG-ε=0.66; GG-p<0.001), as well as of EMOTION x RUN ($F_{(4;76)}=3.60$; GG-ε=0.79; GG-p=0.017). Additionally, a three-way interaction of SEX OF ACTOR x EMOTION x BLOCK ($F_{(8;152)}=9.12$; GG-ε=0.70; GG-p<0.001) was observed. Subsequent 3 x 3 x 5 ANOVAs (EMOTION x RUN x BLOCK) calculated for male and female observers separately, demonstrated that the interaction between SEX OF ACTOR and BLOCK was due to a decrease in RT to male actors from the first to the fifth block (BLOCK: $F_{(4;76)}=10.60$; GG-ε=0.86; GG-p<0.001; RT block 1 > block 4 and 5: p<0.001; p(cor)=0.005). To female actors, however, almost no changes in RT were present ($F_{(4;76)}=1.60$; GG-ε=0.48; GG-p=0.216) (see Figure 23).
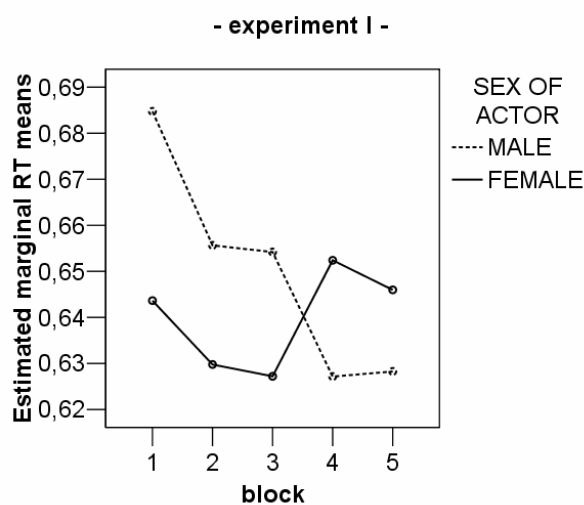
Figure 23:   Interaction of BLOCK x SEX of ACTOR on RT compiled across runs for experiment I (estimated marginal means displayed).

For a more comprehensive understanding of these differential learning effects, one has to further consider the three-way interaction SEX OF ACTOR x EMOTION x BLOCK. Therefore, six subsequent 3 x 5 ANOVAs (RUN x BLOCK) were calculated for each facial category and actors' sexes separately resulting in a main effect ("learning effect") of BLOCK for some emotional categories only (neutral$_{male}$: $F_{(4;76)}$=7.77; GG-ε=0.75; G-p<0.001, anger$_{male}$: $F_{(4;76)}$=5.30; GG-ε=0.79; GG-p=0.002, pain$_{male}$: $F_{(4;76)}$=8.77; GG-ε=0.84; GG-p<0.001, / neutral$_{female}$: n. s., anger$_{female}$: $F_{(4;76)}$=4.25; GG-ε=0.77; GG-p=0.008, pain$_{female}$: n.s.). Post hoc contrast analysis suggests that the above described decrease in RT from block 1-5 observed to male actors was only present for neutral and angry faces but showed increases <u>and</u> decreases to pain contorted faces (see Figure 24).
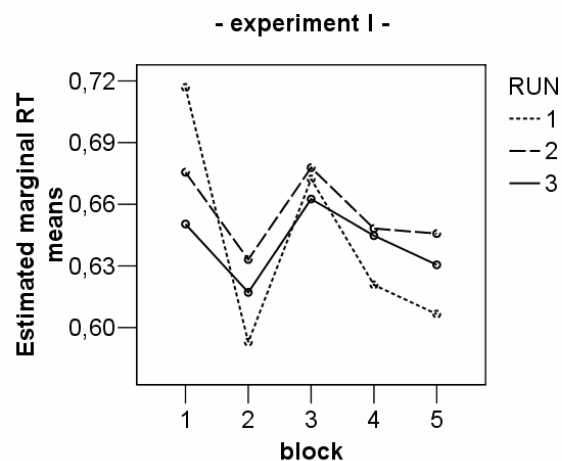
Figure 24: Variation of RT to male actors' pain faces across blocks 1-5 (estimated marginal means displayed).

Moreover, while (as already reported above) no changes in RT occurred to neutral and pain blocks of female actors, a significant learning effect to angry female faces was detected, which was characterized by a decrease of RT across blocks (DVD). This finding is furthermore emphasized by the two-way interaction between EMOTION x RUN, which had only become significant for female actors (male actors: $F_{(4;76)}$=1.25; GG-ε=0.82; GG-p=0.299; female actors: $F_{(4;76)}$=4.02; GG-ε=0.80; GG-p=0.010). In order to be able to explain these results, three one-way ANOVAs with repeated measures factor RUN (1-3) were calculated for female actors only. The analysis resulted in a significant main effect of EMOTION on RTs for the third run ($F_{(2;38)}$=6.57; GG-

ε=0.85; GG-p=0.006), while no differences were detected for the first two runs (DVD). Post hoc contrasts confirmed that this was due to the fact that during the third run, RTs to angry female faces were significantly longer than to female neutral or pain contorted faces (anger > pain: p=0.013; anger > neutral: p<0.001; p(cor)=0.016).

Thus, one can summarize that during experiment II a learning effect reflected by decreases in RT across runs was detected. In neither of the experiments RTs for the three facial categories differed from each other. However, in experiment I, a learning effect across blocks was observed to male actors' faces, which was especially pronounced for neutral and angry faces, but was interestingly characterized by increases and decreases of RT to pain faces. To female actors' faces RTs did solely decrease across blocks in the case of angry faces. Additionally, during the third run, longer RT occurred to angry female faces in contrast to neutral and pain contorted female faces.

4.2.3 RR-Interval

As outlined in section 3.7.2, the two chronometric cardiac indices RR_{mean} and RR_{sd} were chosen for the examination of cardiac activity. One has to note that these values are baseline corrected and hence describe changes relative to baseline activity. This will not be repeatedly mentioned.

The cardiac activity was firstly investigated for effects of habituation. Therefore, the data (per index) was submitted to a 2 x 3 x 12 ANOVA with the between-subject factor SEX OF OBSERVER and the repeated measures factors RUN (1-3) and BLOCK (1-12; first block of each emotion per RUN excluded).

Secondly, in order to systematically evaluate differences for the cardiac indices with respect to the face category, a 2 x 3 x 3 x 4 ANOVA was calculated with the between-subject factor SEX OF OBSERVER, the repeated measures factors EMOTION (neutral, anger, pain), RUN (1-3) and BLOCK(1-4, first block of each category was excluded).

Lastly, since habituation was strongest in the second and third run, as examined using descriptive data, an additional analysis restricted to run one was conducted. Hence, 3 x 4 ANOVAs were calculated for each index of the first run with repeated measures factor EMOTION (neutral, anger, pain) and BLOCK (1-4).

Habituation

While, in contrast to expectations on RR_{mean}, no habituation was observed for experiment I (DVD), a significant main effect of RUN was detected during experiment II ($F_{(2;26)}$=5.45; GG-ε=0.73; GG-p=0.021). As shown in Figure 25 and as contrast analysis reveals this was due to the fact that RR_{mean} – values increased from the first to the last run. This result is equivalent to a decrease of heart rate across the entire experiment (RR_{mean} run 1 < run 2: p=0.004; run 1 < run 3: p=0.037; run 2 < run 3: p=0.831; p(cor)=0.016). However, taking the corrected p-value into account, only the difference between the first and second run reached significance. Moreover, an interaction between RUN x BLOCK was detected ($F_{(22;286)}$=4.18; GG-ε=0.27; GG-p=0.001). Subsequent ANOVAs calculated for each run separately resulted in a main effect of BLOCK for run 1 ($F_{(11;165)}$=3.36; GG-ε=0.48; GG-p=0.007) and run 3 ($F_{(11;165)}$=5.56; GG-ε=0.36; GG-p=0.001) caused by the fact that RR_{mean} decreased during the last block of run 3 (HR increase), while it increased for the first run (HR decrease) (DVD).
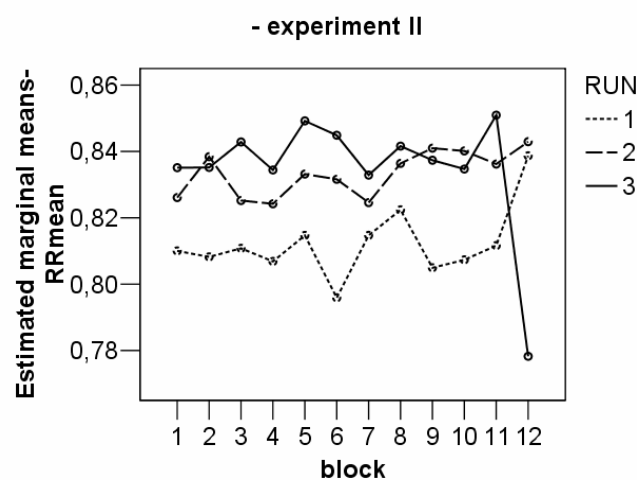
Figure 25: Increase of RR-intervals (HR deceleration) from the first to the last run (estimated marginal means displayed).

The analysis of the variability index RR_{sd} revealed a significant main effect of BLOCK for experiment I due to increases and decreases in variability across the experimental runs ($F_{(11;176)}$=2.45; GG-ε=0.53; GG-p=0.032). Detailed contrast analysis is provided on DVD.

Face Category

Figure 26 and Table 11 demonstrates the baseline corrected RR_{mean}, which was observed during the three conditions of face clips for both experiments. These values reflect increases of the RR-intervals (HR deceleration) during exposure to all clip types relative to the baseline, which became solely significant for experiment I (DVD).

Table 11: Adjusted means and SDs (in parentheses) of the peripheral physiological change scores (stimulus relative to baseline) RR-intervals (in ms) and GSR (in micromho).

Indices		Clip					
		Neutral		**Anger**		**Pain**	
RRmean	E I	8.84	(11.95)	11.55	(13.43)	9.50	(13.08)
	E II	5.46	(12.32)	5.57	(9.38)	1.23	(9.28)
RRsd	E I	-2.18	(4.92)	-0.92	(3.66)	-3.06	(8.21)
	E II	-7.77	(9.57)	-5.65	(6.32)	-5.49	(7.42)
GSRmean	E I	0.043	(0.089)	0.031	(0.110)	0.081	(0.089)
GSRlog-mean	E I	0.302	(0.002)	0.301	(0.002)	0.302	(0.002)
GSRlog-diff-area	E I	0.830	(1.041)	0.784	(0.988)	0.908	(1.177)

EI = experiment I; EII = experiment II; RR_{mean}= mean of RR-intervals; RR_{sd}= standard deviation of RR-intervals; GSR_{mean}= mean of GSR; $GSR_{log-mean}$= logarithmized mean of GSR and $GSR_{log-diff-area}$= logarithmized area under curve of GSR changes.

In contrast to the hypothesis no main effect of emotion was found on RR_{mean} for both experiments (experiment I: $F_{(2;40)}$=0.63; GG-ε=0.97; GG-p=0.531; experiment II: $F_{(2;26)}$=2.51; GG-ε=0.95; GG-p=0.105). After exclusion of run two and three, a significant main effect of emotion occurred for experiment II ($F_{(2;26)}$=3.71; GG-ε=0.99; GG-p=0.039).
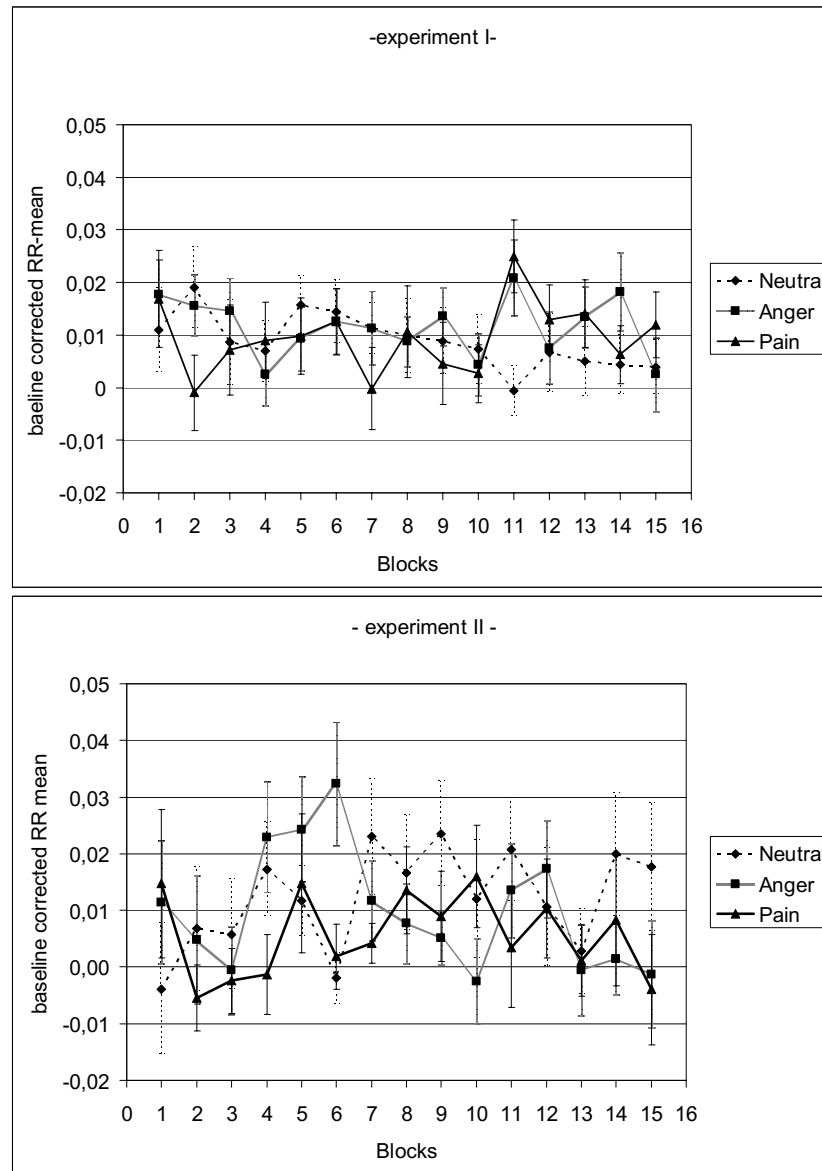
Figure 26:   Baseline corrected RR$_{mean}$ values during exposure to neutral, angry and pain faces for experiment I and II.

The contrast analysis provided on DVD showed that RR$_{mean}$ during presentation of pain clips was smaller than during presentation of anger and neutral clips (pain < anger: p=0.025; pain < neutral: p=0.054; neutral < anger: p=0.564; p(cor)=0.016). However, only the difference between pain and anger reached marginal significance. Introspection of the descriptive statistics even revealed that this was due to the fact that RR-interval increases (HR-deceleration) occurred during anger and neutral, whereas the intervals decreased (HR-acceleration) during pain clips (neutral: mean=5ms±5; anger: mean=8ms±4; pain: -5ms±3). Hence, subjects' cardiac responses to pain faces tended to

be characterized by acceleration as compared to the other faces. However, these findings have to be treated with caution since none of them survived the corrected threshold.

The descriptive statistics on RR_{sd} demonstrate decreases of variability during exposure to all three types of facial expressions relative to the baseline condition (Table 11). Solely the values measured during experiment II were significantly different from the baseline variability (DVD). Further analysis revealed a significant interaction between EMOTION x RUN x BLOCK for experiment I ($F_{(12;192)}$=2.20; GG-ε=0.51; GG-p=0.048). Subsequent analysis of this interaction by subsequent ANOVAs for each run showed an interaction of EMOTION x BLOCK for run 3 only ($F_{(6;96)}$=5.40; GG-ε=0.70; GG-p=0.001). This interaction found in run 3 was further analyzed by ANOVAs computed for each facial category separately. Only for neutral a marginally significant main effect of BLOCK was observed ($F_{(3;60)}$=2.97; GG-ε=0.68; GG-p=0.061). Post hoc contrasts revealed that this based on the fact that variability of RR – values in block 1 was significantly smaller than in the last block of the third run (block 1 < block 4: p=0.015; p(cor)=0.008). However, this difference did not survive the corrected threshold.

Summarizing the results, it may be said that during experiment II the heart beat in general became slower throughout the experimental procedure especially from the first to the second run. Additionally, within the third run an increase of the heart rate was observed during the last block. No such evidence was observed during experiment I. Moreover, the variability index did not show any meaningful pattern of habituation.

While the RR-interval during all conditions were increased relative to the baseline, solely the values of experiment I reached significance. Moreover, while the variability of the heart beat decreased in all conditions this was in contrast to baseline solely significant for the second experiment. Neither the heart beat nor its variability differed between the facial categories, the subjects were exposed to. However, after exclusion of the runs that were strongest affected by habituation (2, 3), RR-interval decreases (HR acceleration) were detected during processing of pain faces relative to the other facial expressions in experiment II. The variability index solely showed marginally significant changes across blocks for the third run (experiment I). No sex differences with regard to the observers' gender were observed.

4.2.4 GSR

Phasic electrodermal activity characterized by the three indices GSR_{mean}, $GSR_{log-mean}$ and $GSR_{log-diff-area}$ was investigated in terms of habituation and condition (neutral, anger and pain face presentation) by repeated measurement ANOVAs. To test for habituation effects a 2 x 3 x 12 ANOVA with the between-subject factor SEX OF OBSERVER and the repeated measures factor RUN (1-3) and BLOCK (1-12) was calculated for each GSR index. Analysis of condition effects comprised a 2 x 3 x 3 x 4 ANOVA with the between-subject factor SEX OF OBSERVER and the repeated measures factors EMOTION (neutral, anger, pain), RUN (1-3), as well as BLOCK (1-4).

The results of experiment I will be outlined in this section, while for the above mentioned reasons data acquired during experiment II is only provided on DVD.

Habituation

As hypothesized, a significant habituation effect was observed for GSR_{mean} reflected by a main effect of RUN ($F_{(2;38)}=6.84$; GG-ε=0.91; GG-p=0.004). As suggested by Figure 27, and as revealed by contrast analysis, this was due to the fact that run three showed significantly lower GSR_{mean} - values than run one and two (run 1 > run 3: p=0.004; run 2 > run 3: p=0.044; run 1 > run 2: p=0.077; p(cor)=0.016).
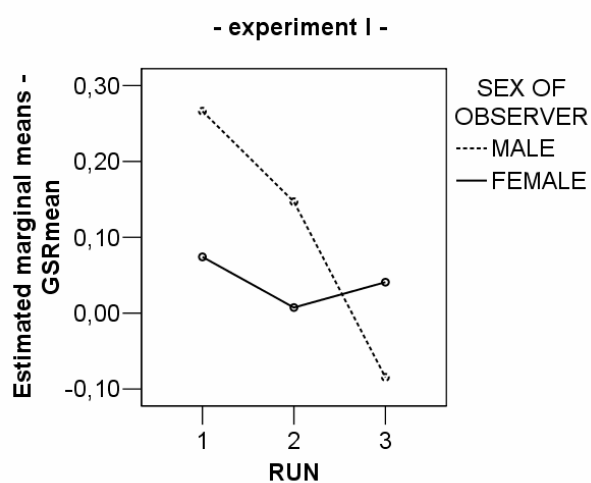
Figure 27: Interaction of RUN x SEX of OBSERVER on GSR_{mean} (in micromho) observed across the experimental setting (estimated marginal means displayed).

However, only the difference between the first and the last run survived the Bonferroni-corrected threshold. This effect has to be further interpreted by the significant interaction between RUN x SEX OF OBSERVER, which was detected ($F_{(2;38)}$=5.36; GG-ε=0.18; GG-p=0.011). Subsequent ANOVAs calculated for male and female observers separately resulted in a main effect of RUN in male observers ($F_{(2;14)}$=6.02; GG-ε=0.85; GG-p=0.019). Post hoc contrasts revealed that the observed differential habituation effect in male observers was due to smaller GSR_{mean} - values during run 3 in comparison to run 1 (run 1 > run 3: p=0.025; run 2 > run 3: p=0.077; run 1 > run 2: p=0.273; p(cor)=0.016). Although this effect reached only marginal significance this finding may explain the main and interaction effect reported above.

Investigation of the logarithmized GSR_{mean} also resulted in a main effect of RUN ($F_{(2;42)}$=7.55; GG-ε=0.88; GG-p=0.003) due to the fact that subjects' GSR response of run one was significantly higher than the one of run two and three (run 1 > run 2: p=0.011; run 1 > run 3: p=0.004; run 2 > run 3: p=0.247; p(cor)=0.016). Additionally, a tendency of a main effect of BLOCK ($F_{(11;231)}$=2.07 GG-ε=0.46; GG-p=0.074) was found, because four "peaks" of $GSR_{log-mean}$ occurred, namely during block 4, 5, 7, 8 (DVD). The index $GSR_{log-diff-area}$ did not show any significant habituation effect (DVD).

Face Category

As displayed in Table 11, the GSR_{mean} as well as $GSR_{log-mean}$ was characterized by increases relative to baseline for all categories of clips. However, post hoc contrast analysis showed that this increase did not reach significance (DVD). Moreover, in contrast to the hypothesis, these baseline corrected values did not show a main effect of EMOTION (GSR_{mean}: $F_{(2;38)}$=0.46; GG-ε=0.65; GG-p=0.552; $GSR_{log-mean}$: $F_{(2;42)}$=1.97; GG-ε=0.96; GG-p=0.152). After exclusion of run two and three, a marginally significant main effect of EMOTION was detected for GSR_{mean} ($F_{(2;40)}$=3.04; GG-ε=0.95; GG-p=0.059). The contrast analysis provided on DVD showed that GSR_{mean} during presentation of pain clips was significantly higher than during neutral clips (pain > neutral: p=0.011; pain > anger: p=0.223; anger > neutral: p=0.294; p(cor)=0.016), which was at least for 'pain' in accordance to the a-priori hypothesis (Figure 28). However, again no main effect of EMOTION occurred after exclusion of the second

and third run for $GSR_{log-mean}$ ($F_{(2;42)}$=2.39; GG-ε=0.91; GG-p=0.110). However, a tendency of a main effect of BLOCK ($F_{(3;63)}$=2.64; GG-ε=0.67; GG-p=0.083; block 2 > block 4) was found.
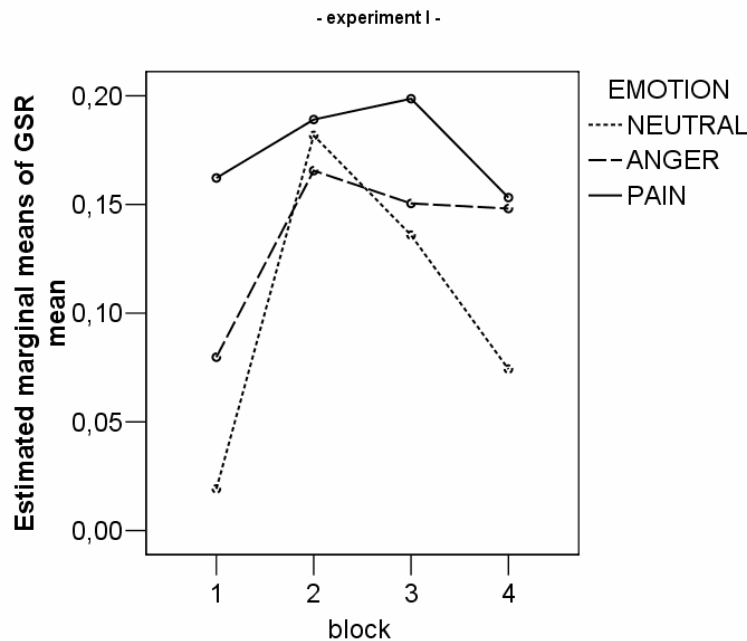

Figure 28: GSR_{mean} (in micromho) observed during run 1 to neutral, anger and pain clips in experiment I (estimated marginal means displayed).

The descriptive statistics (Table 11) of the index $GSR_{log-diff-area}$ suggested higher amounts of GSR changes during clip exposure than during baseline, which also reached statistical significance (DVD). Moreover, in contrast to the a-priori expectations, the analysis of these values did not reveal a significant main effect of EMOTION ($F_{(2;42)}$=0.23; GG-ε=0.74; GG-p=0.733). This was still the case after exclusion of the last two runs ($F_{(2;42)}$=1.47; GG-ε=0.96; GG-p=0.242) (DVD).

Summarized, in line with expectations, habituation across the experiment was detected for GSR_{mean} and $GSR_{log-mean}$. Although the mean GSRs were characterized by increases they were not significantly different from baseline. For none of the four indices, differences between the facial categories were found. However, exclusion of the last two runs (strongest habituation) revealed higher GSR_{mean} during pain trials in contrast to

neutral partly confirming the hypothesis. However, it has to be taken into account that the observed main effect of emotion was solely marginally significant.

4.3 Imaging Data

The following section reports the findings derived from the brain imaging. In order to reduce complexity, only results which were observed in the group of all observers will be described in detail. Results which occurred in the separate analysis of male and female observers, as well as during direct comparison of male and female observers, are available in Appendix B of this thesis. They are only mentioned explicitly in case male and female observer's BOLD-responses to the presented stimuli differed significantly (n>4 contiguous voxels) from each other. Moreover, regions which did meet the statistical but not the extent threshold are listed in the table, but will solely be mentioned in the main text, in case they seemed to be meaningful in relation to the literature. Furthermore, files containing the GLM-table, as well as the ROI details <u>for each voxel</u> are provided on DVD.

4.3.1 <u>Amygdala</u>

There was no evidence for sustained significant activation found in any contrast of interest in the group of all observers during the analysis of the block design (see Appendix B-I). However, contrasting conditions to visual baseline revealed slight activation of the amygdala to all stimuli, which even became significant, although not meeting the extent threshold, for the right amygdala to pain and anger expression (see Appendix B-II). However, as detected in event-related analysis, the strength of this activation depended on the type of facial expression and on the sex of the actor.

Detailed analysis of activation to the events revealed stronger bilateral activation of the amygdala to male pain faces as compared to both neutral (Figure 29-a) and, although to a lesser extent, to angry faces (Figure 29-b). As comparison of male and female observers confirmed, this response pattern occurred in all observers similarly independent of their sexes (see Appendix B-I). Moreover, the effect was more

pronounced in the right than in the left amygdala (Table 12). No involvement of the amygdala was observed to the perception of male angry compared to neutral faces.
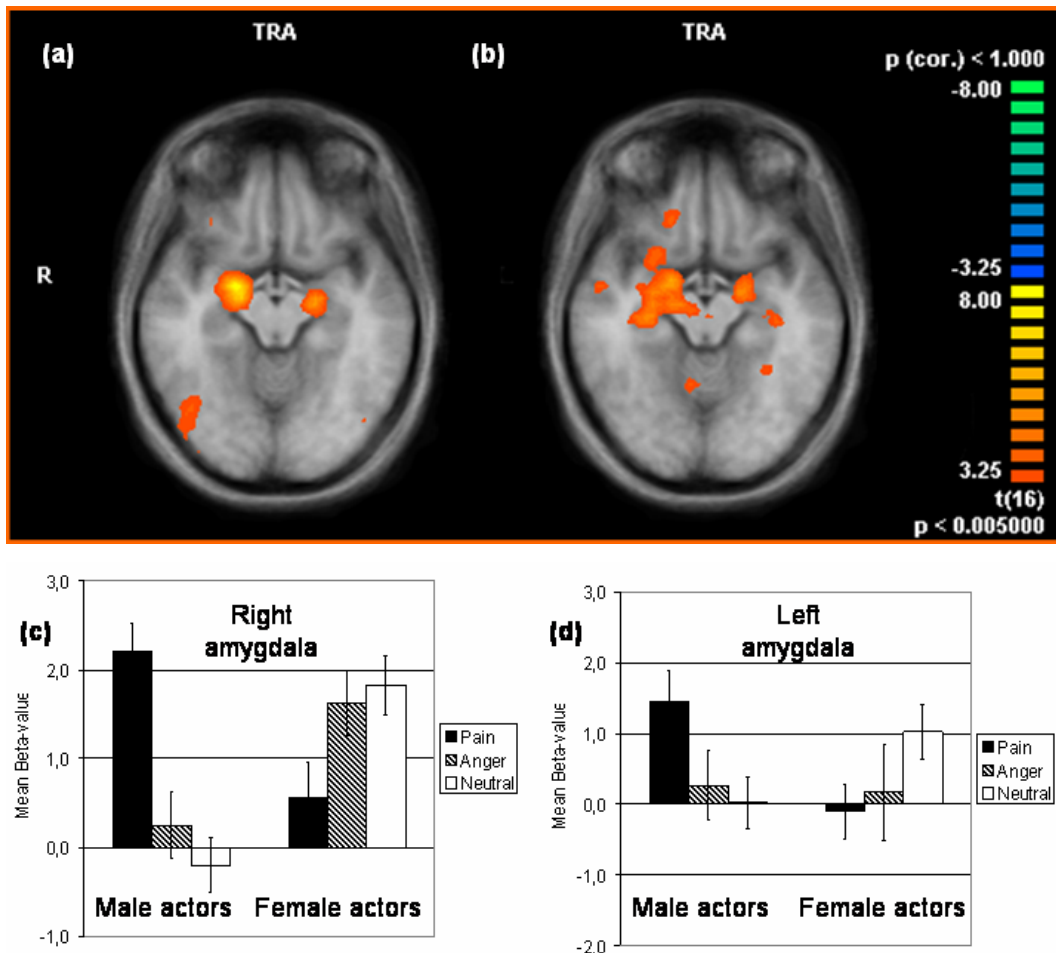

Figure 29: Transversal view of bilateral amygdala activation to male actors' pain faces relative to a) neutral and b) to angry male faces. The corresponding bar graphs show activation of c) right and d) left amygdala to all stimuli vs. visual baseline as determined by the mean betas (±SEM) in the peak voxel.

In contrast, pain expressed by females produced a significant bilateral *decrease* in amygdala activity (right-sided below extent threshold) relative to neutral faces in both male and female observers. Also the comparison of pain to angry faces resulted in a slight decrease bilaterally, but did not become significant. Direct comparison of BOLD-responses to male and female actors using the contrasts of interest confirmed the strength of the actor's sex effect (Table 12). Moreover, no amygdala activation was found when comparing BOLD-responses to angry with those to neutral female faces.

These results indicate that the activation of the amygdala to pain faces is (1) specifically induced by male facial displays and (2) not simply a non-specific response to the perception of emotional expression.

To further analyze the observed decrease to female pain faces, post-hoc statistical comparisons of each event with the visual baseline condition were conducted. As shown in Appendix B-II, it confirmed that all observers generally responded significantly stronger to male pain faces, as well as to female neutral faces.

Table 12: Summary of effects in AMY and MPFC for all observers.

AREA	SIDE	SIZE	TALAIRACH x	y	z	t-value	p-value
[Pain-Neutral] – event-related design							
male actors							
AMY	**R**	**(25)**	**19**	**-6**	**-13**	**10.83**	**0.000089**
	L	**(5)**	**-20**	**-10**	**-10**	**4.64**	**0.000270**
MPFC							n.s.
female actors							
AMY	R	(1)#	21	-4	-11	-4.04	0.000945
	L	**(7)**	**-21**	**-9**	**-11**	**-4.10**	**0.000836**
MPFC							n.s.
male > female actors							
AMY	**R**	**(20)**	**19**	**-6**	**-13**	**8.64**	**0.002010**
	L	**(11)**	**-20**	**-10**	**-10**	**4.52**	**0.000349**
MPFC							n.s.
[Pain-Anger] – event-related design							
male actors							
AMY	**R**	**(25)**	**19**	**-6**	**-13**	**5.61**	**0.000039**
	L	(5)	-17	-7	-11	5.04	0.000121
MPFC		**(13)**	**3**	**52**	**18**	**4.72**	**0.000232**
female actors							
AMY	R						n.s.
	L						n.s.
MPFC							n.s.
male > female actors							
AMY	**R**	**(17)**	**20**	**-3**	**-11**	**4.55**	**0.000325**
	L	**(4)**	**-21**	**-4**	**-11**	**4.63**	**0.000279**
MPFC		(3)#	-7	37	-9	3.58	0.002499

AREA	SIDE	SIZE	TALAIRACH x	y	z	t-value	p-value
[Anger-Neutral] – event-related design							
male actors							
AMY	R						n.s.
	L						n.s.
MPFC							n.s.
female actors							
AMY	R						n.s.
	L						n.s.
MPFC							n.s.
male > female actors							
AMY	R						n.s.
	L						n.s.
MPFC							n.s.

AMY=Amygdala, MPFC=medial prefrontal cortex (including medial parts of BA9, 10); side outlines the side where activation occurred (R=right, L=left); size shows the number of contiguous significant 3x3x3mm voxels in the region; Talairach *xyz* standardized stereotaxic coordinates of peak voxel, as well as corresponding t- and p- values are displayed; results which met the threshold of n≥4 voxel and p<0.005 (uncorrected) were considered significant; [#]Activations which did not meet extent threshold.

Amygdala – Habituation

Investigation of BOLD-response habituation in the left and the right amygdala was done by using a 2 x 2 x 3 x 2 x 2 ANOVA with the between-subject factor SEX OF OBSERVER (male - female) and the repeated measures factors SIDE (right and left amygdala), EMOTION (neutral, anger, pain), TIME (first half – second half) and SEX OF ACTOR (male - female). Analysis firstly yielded an interaction of SIDE x TIME ($F_{(1,15)}$=4.68; p=0.047). Additionally, a significant interaction of SIDE x EMOTION x TIME x SEX OF OBSERVER ($F_{(2;20)}$=3.88; GG-ε=0.89; GG-p=0.038) and of TIME x SEX OF ACTOR x SEX OF OBSERVER ($F_{(1,15)}$=10.31; p=0.006) was found.

To further analyze these interactions, subsequently separate ANOVAs for left and right amygdala were computed. Only for the right amygdala a marginal significant main effect of TIME was detected ($F_{(2;15)}$=3.33; p=0.088). This was due to the fact that the BOLD-response in this ROI decreased from the first to the second half of the experiment (Figure 30).
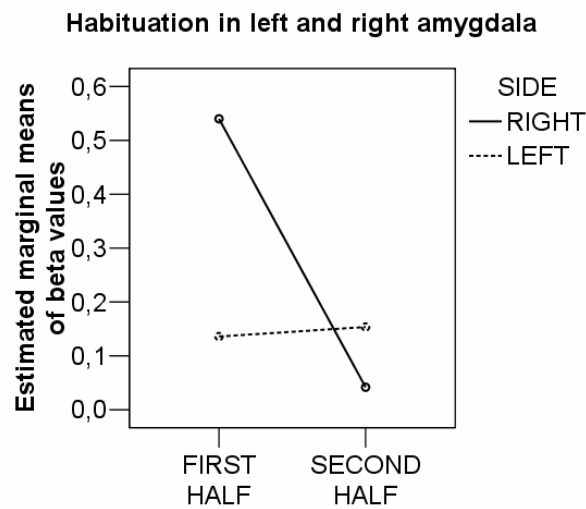
Figure 30: Interaction of SIDE x TIME characterizing more rapid habituation in the right than in the left amygdala from the first and the second half of the experiment (estimated marginal means displayed).

Additionally, an interaction of SEX ACTOR x TIME x SEX OF OBSERVER was detected bilaterally (AMY-R: $F_{(1;15)}$=9.10; p=0.009; AMY-L: $F_{(1;15)}$=5.46; p=0.034). Moreover, for the left amygdala a significant interaction of SEX ACTOR x TIME ($F_{(1;15)}$=5.48; p=0.033) was observed.

For a comprehensive understanding of these interactions, subsequent ANOVAs were calculated for male and female observers separately, resulting in a significant interaction of TIME x SEX OF ACTOR for female observers only (AMY-R: $F_{(1,8)}$=9.30; p=0.016; AMY-L: $F_{(1,8)}$=8.52; p=0.019). Furthermore, for the left amygdala an interaction of EMOTION x TIME x SEX OF ACTOR ($F_{(2;16)}$=4.72; GG-ε=0.67; GG-p=0.045) was detected.
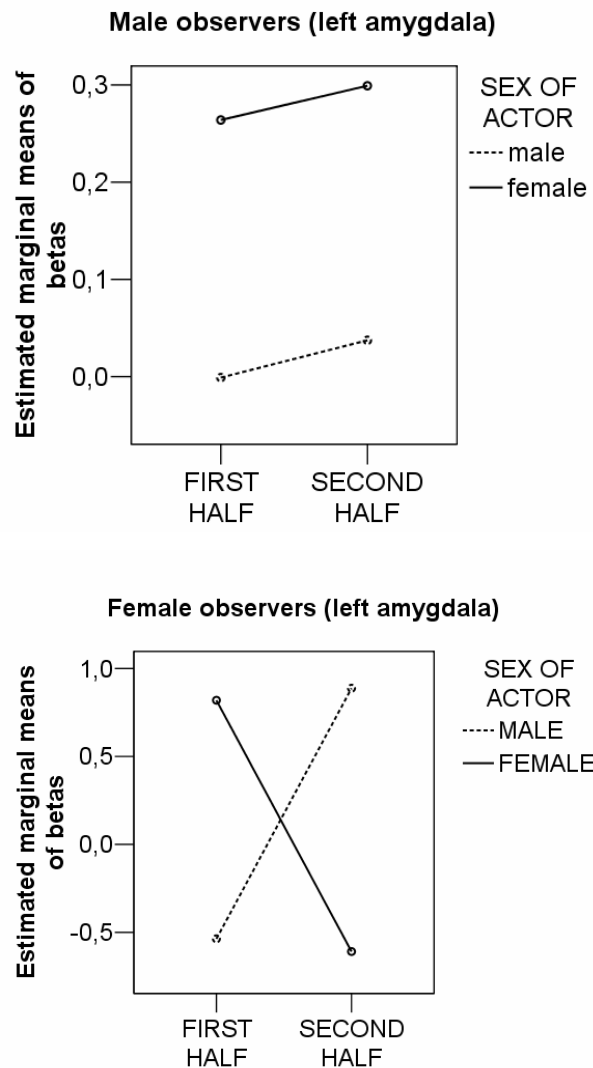
Figure 31: Interaction of TIME x SEX of ACTOR displayed for a) male and b) female observers in the left amygdala (same pattern in right amygdala; estimated marginal means displayed).

These interactions observed in female subjects were further investigated by separate ANOVAs for male and female actors yielding a main effect of TIME in BOLD-responses to female faces (AMY-R: $F_{(1,8)}$=10.10; p=0.013; AMY-L: $F_{(1,8)}$ =10.02; p=0.013) explained by a decrease of activation (Figure 31).

Furthermore, in the left amygdala an interaction of EMOTION x TIME ($F_{(2;16)}$=4.18; GG-ε=0.90; GG-p=0.040) was detected for female actors, which was due to significant signal decreases in female subjects to actresses' angry faces (neutral$_1$ > neutral$_2$:

$p=0.923$; $anger_1 > anger_2$: $p=0.007$; $pain_1 > pain_2$: $p=0.472$; $p(cor)=0.016$) as revealed by post hoc tests (Figure 32).
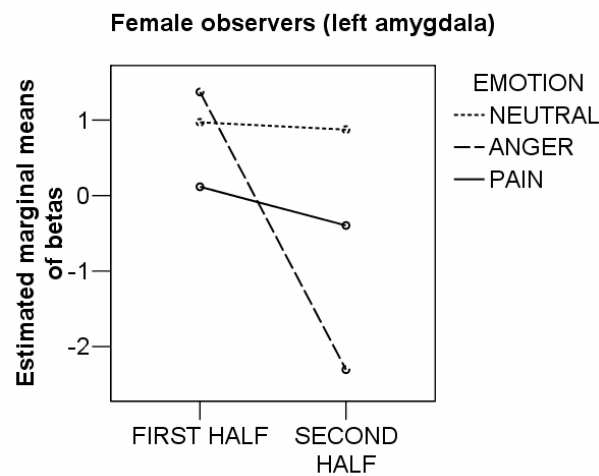
Figure 32: Interaction of TIME x EMOTION detected in female observers' left amygdala to female actors' faces (estimated marginal means displayed).

Additionally, for the left amygdala a main effect of TIME was also found for male actors, which reached marginal significance ($F_{(1,8)} =4.58$; $p=0.065$) and was caused by slight increases of the BOLD-response found in female observers.

Thus, a more rapid habituation effect was detected in the right amygdala. Moreover, a differential response pattern was observed for female subjects in the right and left amygdala. While for the right amygdala a habituation to female faces in general occurred, the pattern in the left amygdala was characterized by *decreases* in activation to female, especially angry actors' faces and *increases* to male actors' faces.

4.3.2 MPFC

Block design analysis of MPFC showed no significant sustained activation across all contrasts of interest (Appendix B-I). Further inspection of baseline contrasts revealed significant deactivation to pain, anger, and neutral faces relative to the visual baseline (Appendix B-II).

As depicted in Table 12 and Figure 33, taking the actors' sex into account, solely contrasting males' pain with males' angry faces resulted in a significant activation of dMPFC (BA 9).
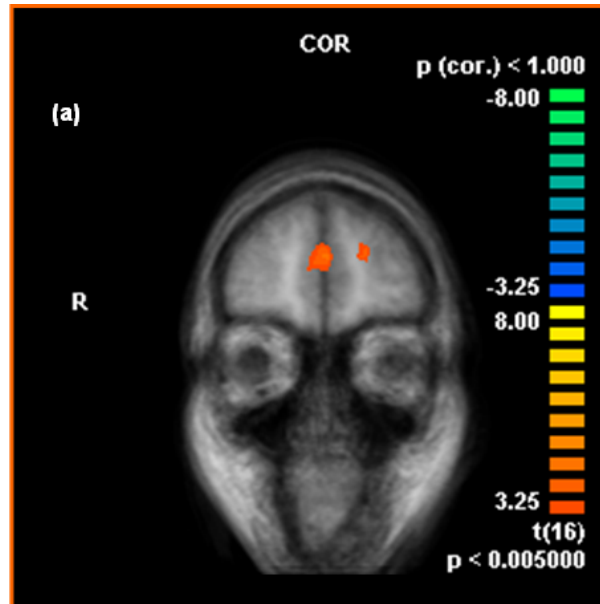
Figure 33:   Coronal view of MPFC activation to male actors' pain faces relative to male angry faces.

However, for interpretation of this 'activation' one has to consider the baseline contrasts (Appendix B-II), which are displayed in Figure 34. As analysis revealed, the BOLD-response in MPFC to all male and female faces of all three conditions is characterized by negative betas. Since the decrease of rCBF to angry male faces even reached significance, the contrast [Pain$_{male}$-Anger$_{male}$] yielded activation in MPFC due to less deactivation during perception of pain faces as compared to angry faces. No interaction or main effect of the observers' sexes was found (Appendix B-I).
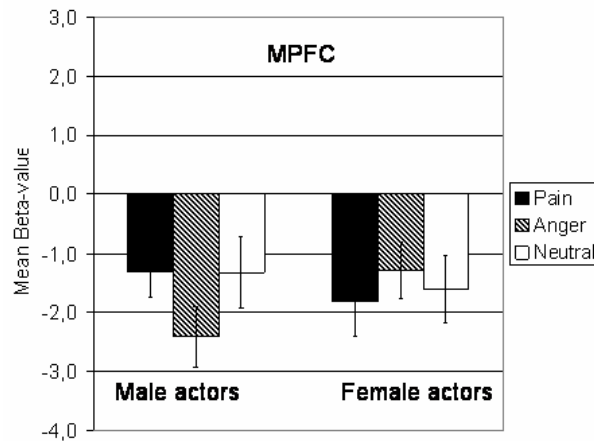
Figure 34:   Graph displaying activation to all stimuli vs. visual baseline in the peak voxel of the MPFC (mean±se).

MPFC – Habituation

Investigation of BOLD-response habituation in the MPFC ROI was done by using a 2 x 3 x 2 x 2 ANOVA with the between-subject factor SEX OF OBSERVER (male - female) and the repeated measures factors EMOTION (neutral, anger, pain), TIME (first half – second half) and SEX OF ACTOR (male - female). Analysis yielded a significant interaction of TIME x SEX ACTOR x SEX OF OBSERVER ($F_{(1;15)}$=7.39; p=0.016). In order to interpret this interaction subsequent ANOVAs were calculated for male and female observers separately resulting in a significant interaction of TIME x SEX OF ACTOR for female observers ($F_{(1,8)}$=9.32; p=0.016).

MPFC
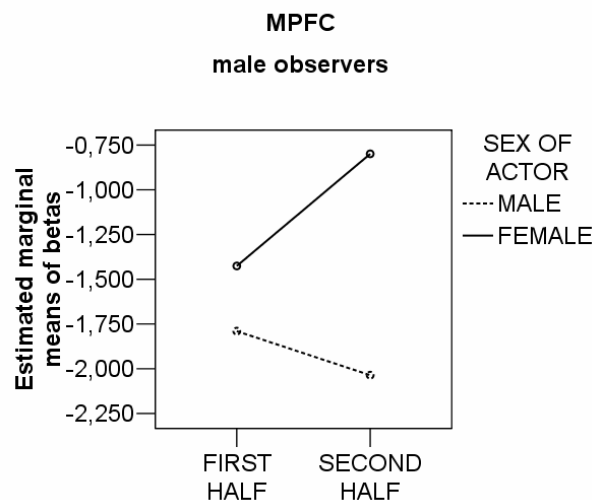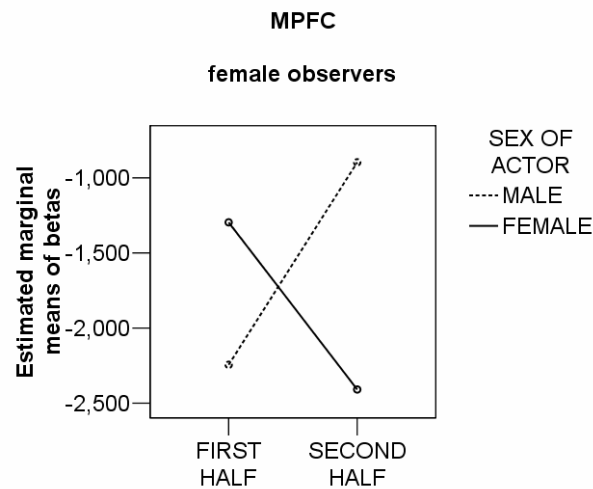
female observers

Figure 35:   Interaction of TIME x SEX of ACTOR displayed for a) male and b) female observers in the peak voxel of the MPFC (estimated marginal means displayed).

This interaction detected in female observers was further analyzed by calculating separate ANOVAs for male and female actors resulting in a main effect of TIME solely to male faces ($F_{(1,8)}$=5.91; p=0.041). This was due to an 'increase' (less deactivation during second half) of activation (see Figure 35).

Thus, while in general no strong habituation effect was found in the MPFC (lack of main effect TIME), a differential attenuation of deactivation was found in female subjects to male actors' faces.

4.3.3   ACC

Block design analysis did not show sustained activation of ACC for all contrasts of interest (Appendix B-III). The baseline contrasts (Appendix B-IV) were characterized by increases and decreases of comparable amount, which explained the findings described above.

However, during event-related analysis, engagement of ACC was observed depending on the type of facial expression and on the sex of the actor in the affective (rostral-ventral) and the cognitive division (dorsal) of the ROI.

Affective Division

As suggested by Figure 36, right-hemispheric BOLD-response increases to males' pain contorted faces, relative to neutral (Figure 37-a) and relative to angry faces (Figure 37-b) occurred. For the left hemisphere contrasting pain against anger also reached significance in two sub clusters of ACCad (Figure 39-a). This was due to less deactivation to males' pain relative male angry faces.
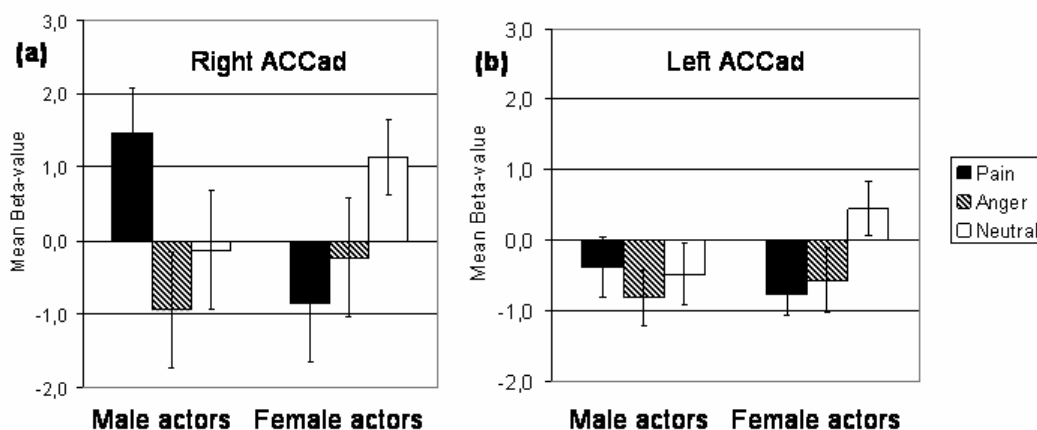

Figure 36:   Bar graphs show activation to the facial events compared to the visual baseline in a) right and b) left ACC (affective division) for event-related design as determined by the mean betas (±SEM) in the peak voxel.
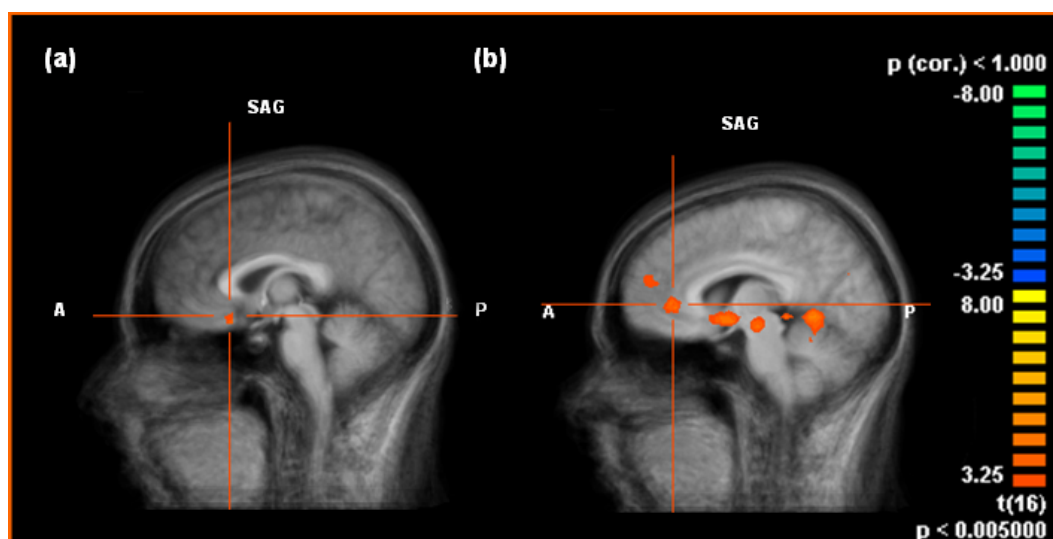
Figure 37:   Sagittal view of ACC activation (affective division) observed to male actors displayed for contrast a) P – N and for b) P – A for the right hemisphere.

During the exposure to females' pain faces bilateral deactivation relative to females' neutral faces was found (Figure 38-a). This was due to stronger signal increases to

neutral faces. This effect was even more pronounced in male observers' right hemisphere (Appendix-B-III). Direct comparison of male and female actors in this particular contrast (Table 13) confirmed stronger bilateral activation in ACC to male actors' as compared to female actors' pain faces contrasted against neutral, stronger in right ACCad for male observers (Appendix B-III). Similarly, explained by stronger responses to females neutral faces, contrasting BOLD-responses to females expressing anger resulted in significant right-sided signal decreases relative to neutral (Figure 38-b). However, BOLD-responses to pain relative to angry female faces did not reach significance. Thus, direct comparison of male and female actors (Table 13) in this particular contrast resulted in stronger bilateral responses to male actors' as compared to female actors' pain faces contrasted to anger.
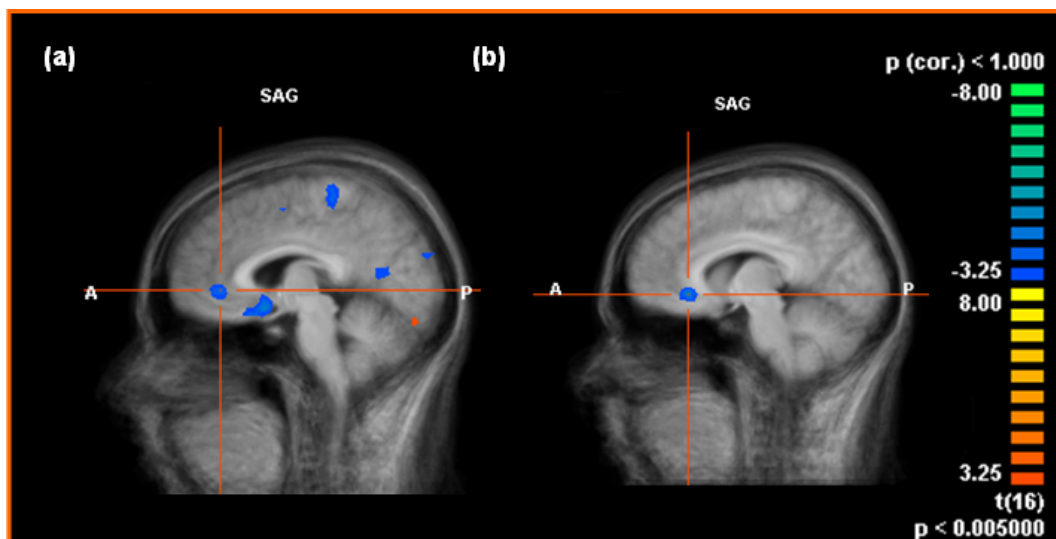
Figure 38: ACC activation (affective division) to female actors displayed in sagittal view for a) contrast P – N and b) for contrast A – N.

Cognitive Division

While comparison of males' pain faces to angry faces led to signal increases (Figure 39-b), contrasting males' angry faces to neutral faces resulted in a significant deactivation in this region (Table 13). As revealed by the baseline contrasts displayed in (Figure 40), this was due to the fact that BOLD-responses to both, pain contorted and neutral faces of male actors, were characterized by signal increases, whereas relative to those the signal to male angry faces showed clear attenuation.
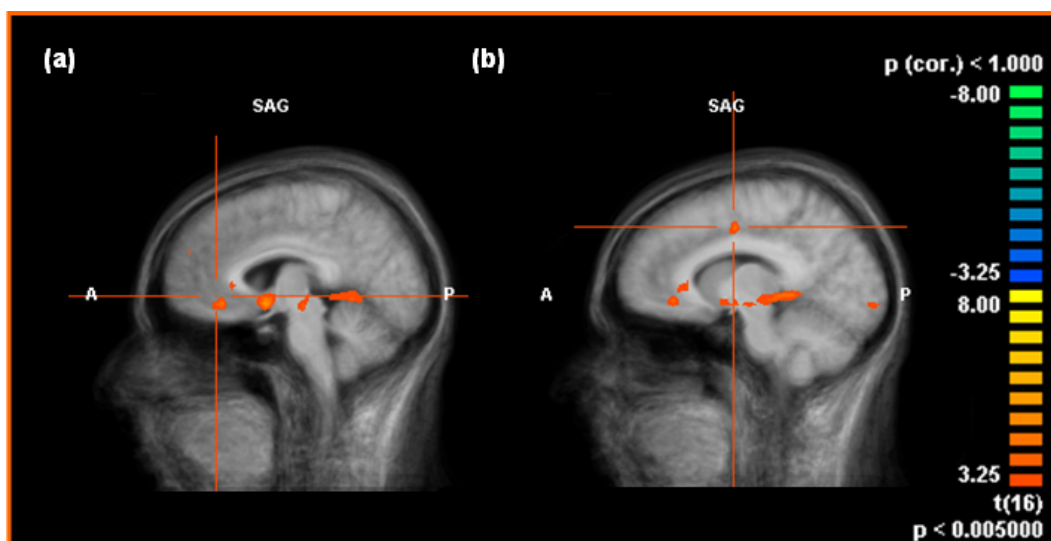
Figure 39: Sagittal view of ACC activation to male actors displayed for contrast P – A in a) the affective and b) the cognitive division in the left hemisphere observed.
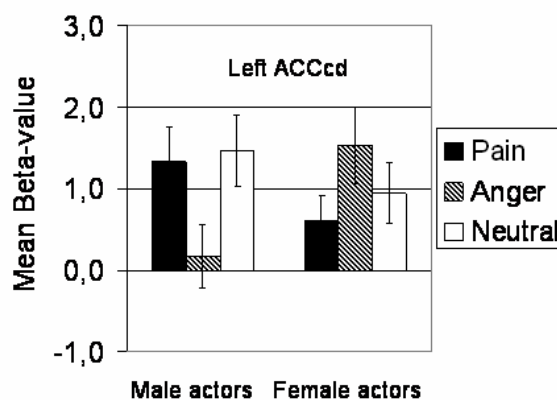

Figure 40: Bar graphs show activation to the facial events compared to the visual baseline in the left ACC (cognitive division) for event-related design as determined by the mean betas (±SEM) in the peak voxel.

ACC - Habituation

Investigation of BOLD-response habituation in the ACC was performed by using 2 x 3 x 2 x 2 ANOVA with the between-subject factor SEX OF OBSERVER (male - female) and the repeated measures factors EMOTION (neutral, anger, pain), TIME (first half – second half) and SEX OF ACTOR (male - female).

129

Affective Division

BOLD-responses in the affective division of ACC did show habituation (no main effect of TIME). However, an interaction of TIME x SEX ACTOR x SEX OF OBSERVER ($F_{(1;15)}$=6.96; p=0.019) occurred. In order to interpret this finding, subsequent ANOVAs were calculated for male and female observers yielding an interaction of TIME x SEX OF ACTOR for male observers ($F_{(1;7)}$=6.94; p=0.034). Separate ANOVAs were computed for male and female actors revealing a main effect of TIME (first < second half) to female actors' faces ($F_{(1,7)}$=13.03; p=0.009).

Hence, in general, no habituation but a sensitization was detected for male observers to female actors' faces in affective ACC.

Cognitive Division

Analysis yielded a significant main effect of TIME ($F_{(1;15)}$=4.59; p=0.049) caused by generally higher BOLD-responses during the first as compared to the second half of the experiment. Furthermore, an interaction of TIME x SEX ACTOR x SEX OF OBSERVER ($F_{(1;15)}$=5.01; p=0.041) was found. This result was further investigated by subsequent ANOVAs calculated for male and female actors. However, since this analysis solely yielded an interaction of TIME x SEX OF OBSERVER of marginal significance for both – male and female actors (female: $F_{(1;15)}$=4.08; p=0.062; male: $F_{(1;15)}$=4.42; p=0.051), no subsequent ANOVAs were calculated.

Thus, the BOLD-response in the cognitive division of the ACC was characterized by habituation across the experimental run.

Table 13: Summary of effects in ACC and anterior Insula for all observers.

AREA	SIDE	SIZE	TALAIRACH x	y	z	t-value	p-value
[Pain-Neutral] – event-related design							
male actors							
aINS	R						n.s.
	L						n.s.
ACC	**R**	**BA32 (2)**[#]	*ad*	**6**	**20**	**-8**	**3.76**	**0.001706**
	L						n.s.
female actors							
aINS	R						n.s.
	L						n.s.

AREA	SIDE	SIZE		TALAIRACH x	y	z	t-value	p-value
ACC	R	BA 25 (19)	*ad*	3	8	-8	-5.52	0.000046
	R	BA 24 (17)	*ad*	5	38	2	-4.70	0.000242
	L	BA 24 (10)	*ad*	-3	38	4	-4.53	0.000339
male > female actors								
aINS	R							n.s.
	L							n.s.
ACC	R	BA 32 (12)						
			ad	6	22	-8	5.23	0.000083
			ad	9	41	7	4.22	0.000647
	L	BA 32 (7)						
			ad	-6	44	4	4.70	0.000240
			ad	-4	24	-9	4.99	0.000134
[Pain-Anger] – event-related design								
male actors								
aINS	R	(9)		48	11	-2	4.13	0.000785
	L	(3)[#]		-42	14	13	4.12	0.000797
ACC	R	BA 25 (14)	*ad*	5	38	2	4.68	0.000249
	L	(16)						
		BA 25	*ad*	-3	5	-5	5.78	0.000028
		BA 32	*ad*	-3	32	-5	4.48	0.000378
		BA 24	*cd*	-9	-4	43	4.87	0.000168
female actors								
aINS	R							n.s.
	L							n.s.
ACC	R							n.s.
	L							n.s.
male > female actors								
aINS	R							n.s.
	L							n.s.
ACC	R	BA 32 (3)[#]	*ad*	12	41	4	4.13	0.000776
	L	BA 24	*cd*	-12	-5	46	4.59	0.000296
		BA 25 }(13)	*ad*	-2	8	-4	4.11	0.000822
		BA 32	*ad*	-6	35	-5	4.60	0.000295
[Anger-Neutral] – event-related design								
male actors								
aINS	R							n.s.
	L							n.s.
ACC	R							n.s.
	L	BA 24 (18)	*cd*	-4	-1	40	-4.51	0.000353
female actors								
aINS	R							n.s.
	L							n.s.
ACC	R	BA 24 (4)[#]	*ad*	6	29	-2	-4.70	0.000237
	L							n.s.
male > female actors								
aINS	R							n.s.
	L							n.s.
ACC	R							n.s.
	L							n.s.

aINS=anterior insula and ACC=anterior cingulate gyrus (ad=affective division, cd=cognitive division) ; side outlines the side where activation occurred (R=right, L=left); size shows the number of contiguous significant 3x3x3mm voxels in the region; Talairach *xyz* standardized stereotaxic coordinates of peak voxel, as well as corresponding t- and p- values are displayed; results which met the threshold of n≥4 voxel and p<0.005 (uncorrected) were considered significant; [#]Activations which did not meet extent threshold.

4.3.4   Anterior Insula

Block design analysis did not reveal any engagement of the anterior insula for all contrasts of interest (Appendix B-III).

Taking the actors' sexes into account, solely contrasting males' pain with males' angry faces resulted in a significant activation of the anterior insula bilaterally (Figure 41), while no such effect was found to female actors' faces.
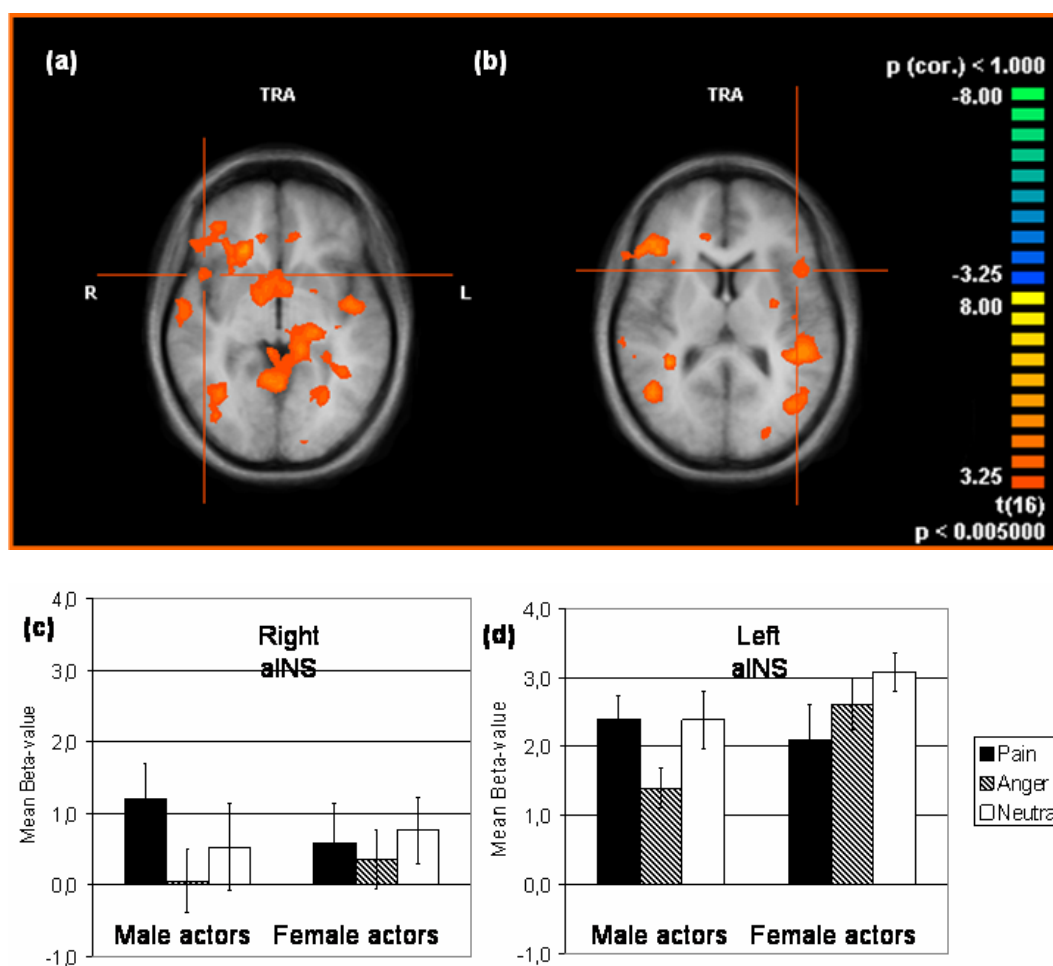

Figure 41:   Transversal view of anterior insula's activation to male actors' faces displayed for contrast P – A in the a) left and the b) right ROI. The corresponding bar graphs show activation to the facial events compared to the visual baseline for the c) right and d) left anterior insula show activation as determined by the mean betas (±SEM) in the peak voxel.

For none of the computed contrasts any interaction or main effect of the observers' sexes was found (Appendix B-III).

Anterior Insula - Habituation

Investigation of BOLD-response habituation in the anterior insula was performed by using a 2 x 3 x 2 x 2 ANOVA with the between-subject factor SEX OF OBSERVER (male - female) and the repeated measures factors EMOTION (neutral, anger, pain), TIME (first half – second half) and SEX OF ACTOR (male - female).

Analysis yielded a significant main effect of TIME ($F_{(1;15)}$=6.71; p=0.020) caused by generally higher BOLD-responses during the first compared to the second half of the experiment. Furthermore, an interaction of TIME x EMOTION x SEX ACTOR x SEX OF OBSERVER ($F_{(2;30)}$=4.18; p=0.031) occurred. However, an interaction of SIDE x TIME just reached marginal significance ($F_{(1;15)}$=4.20; p=0.058) due to the fact that right-sided habituation was stronger (main effect TIME: $F_{(1;15)}$=10.81; p=0.005).

In order to interpret the above reported four-way interaction subsequent, ANOVAs were calculated for each facial category separately resulting in a significant interaction of TIME x SEX OF ACTOR x SEX OF OBSERVER for neutral ($F_{(1;15)}$=4.83; p=0.044) and pain ($F_{(1;15)}$=6.87; p=0.019). Further analysis was conducted by means of separate ANOVAs calculated for male and female observers yielding an interaction of TIME and SEX OF ACTOR for female observers to pain faces only ($F_{(1;8)}$=5.42; p=0.048). As Figure 42 and subsequent ANOVAs for male and female actors revealed this is due to a main effect of TIME (first > second half) to males' pain faces ($F_{(1,8)}$=8.95; p=0.017).
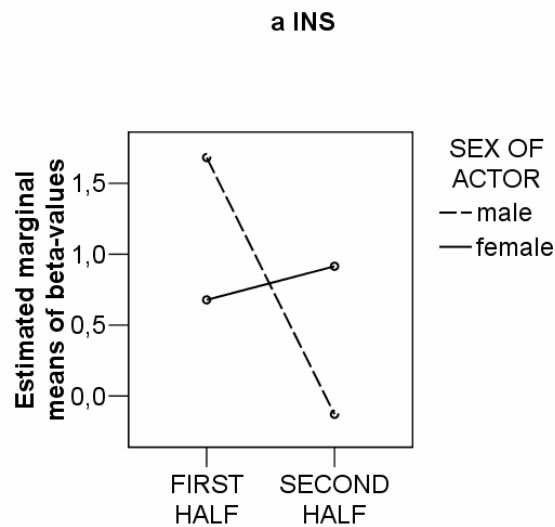
a INS

Figure 42: Interaction of TIME x SEX of ACTOR in the anterior insula (peak voxel left and right) of female observers detected to pain faces (estimated marginal means displayed).

Hence, while in general, habituation in the anterior insula occurred bilaterally, a differential attenuation of activation across the experiment was found in female observers to male actors expressing pain.

4.3.5   <u>SI</u>

Relative to the visual baseline, BOLD-response increases (not significant for pain) were observed in the sensorimotor cortex of the left hemisphere, hence, contralateral to the hand performing the key press. Interestingly, the responses in the right hemisphere were characterized by significant decreases as compared to the baseline condition (Appendix B-IV). While no significant differences between face conditions were detected for the right hemisphere, an involvement of SI during the processing of pain contorted and angry faces (not meeting the extent threshold) relative to neutral was found for the left hemisphere (Table 14). However, this engagement of SI was characterized by deactivations due to stronger activation to neutral in contrast to pain faces conditions. Comparison of faces displaying pain and anger did not yield a significant difference. Differences in activation occurred for none of the contrasts in the block design analysis when comparing female and male observers (Appendix B-III).

Event-related analysis further elucidated these findings by showing that the strength of activations and deactivations depended on the type of facial expression and on the sex of the actor (Figure 43).
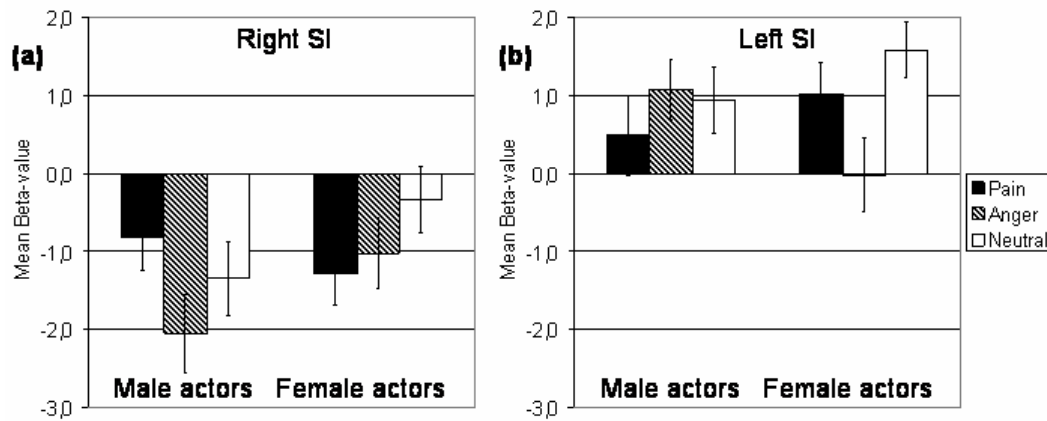

Figure 43: Bar graphs show activation to the facial events activation compared to the visual baseline in a) the right and b) the left SI for the event-related design as determined by the mean betas (±SEM) in the peak voxel.

Again, introspection of the baseline contrasts confirmed right-hemispheric deactivations and left hemispheric activations (Appendix B-IV).

While these BOLD-increases to male faces of all face categories did not differ from each other, no significant results were observed for the left hemisphere. However, for the right hemisphere significant activations in SI were detected due to less deactivation during exposure to males' pain contorted faces relative to both neutral (Figure 44-a) and angry faces (Figure 44-b). Contrasting responses to males' angry with male neutral faces did not result in involvement of SI.
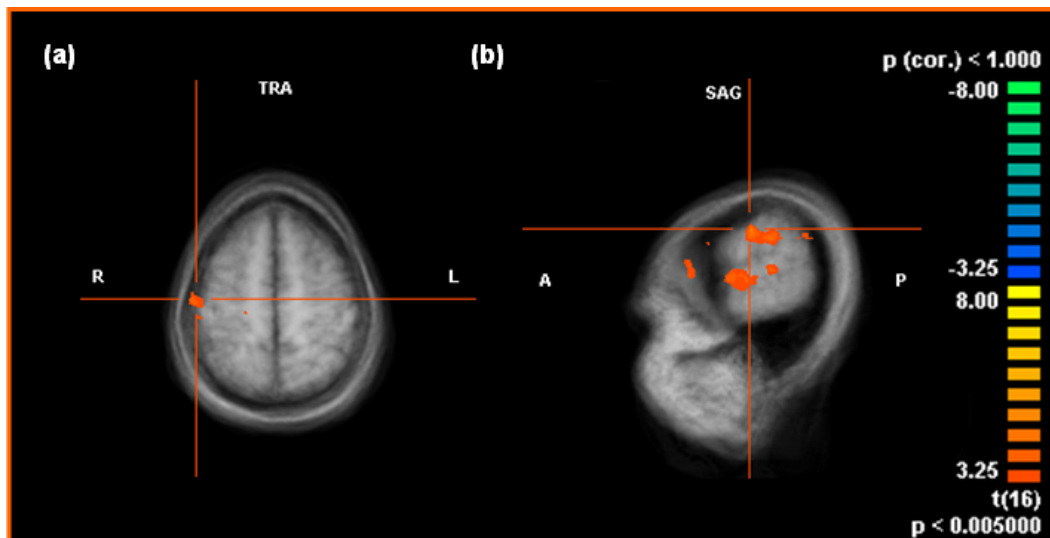
Figure 44: SI activation (right-sided) to male actors displayed for contrast a) P – N in transversal view and for b) P – A in sagittal view.

While the observed left-hemispheric increases for males' faces did not with respect to the facial category again stronger increases to females' neutral faces were also detected in this brain region. Thus, a relative signal decrease to angry compared to neutral faces of female actors was found in SI.

Moreover, due to the fact that stronger right-sided deactivation during exposure to females' pain than during females' neutral faces occurred a significant decrease of the BOLD-response was observed for SI (Figure 45-a). Direct comparison of male and female actors in this particular contrast confirmed stronger right-sided activation to male actors' compared to female actors' pain faces contrasted against neutral. Similarly, right-hemispheric signal decreases to angry female actors relative to neutral again yielded a significant SI-decrease (Figure 45-b; Table 14). Direct comparison of male and female actors in this particular contrast therefore led to stronger right-sided activation (less deactivation) to male actors compared to female actors' angry faces contrasted against neutral. The BOLD-responses decreases to pain relative to angry faces did not show significant differences. Thus, direct comparison of male and female actors in this particular contrast confirmed stronger right-sided responses to male actors' compared to female actors' pain faces contrasted against anger.
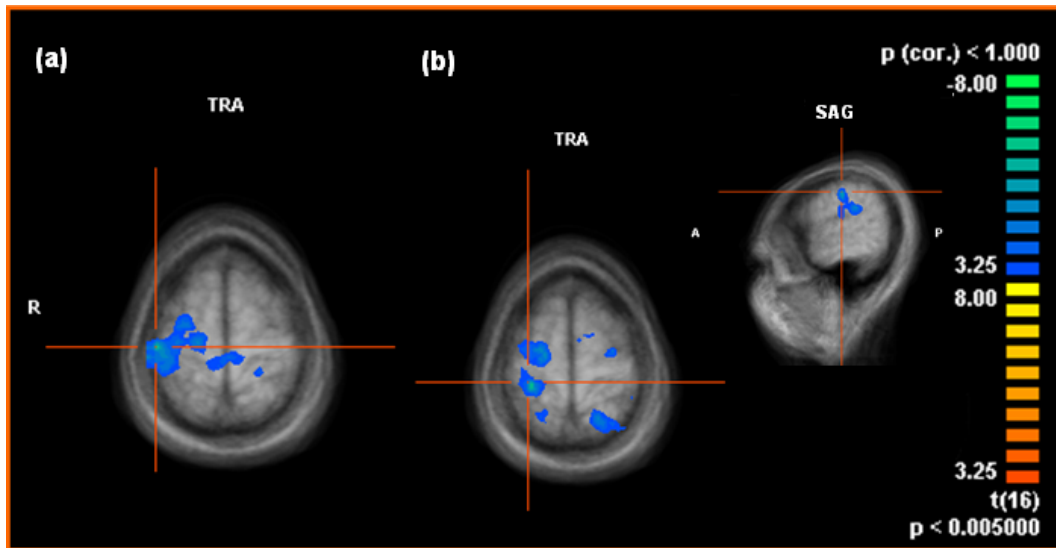
Figure 45: SI activation to female actors displayed for contrast a) P – N (right SI) in transversal view and for b) A – N in transversal (right SI) and sagittal view (left SI).

SI - Habituation

Computation of a 2 x 3 x 2 x 2 ANOVA with the between-subject factor SEX OF OBSERVER (male - female) and the repeated measures factors EMOTION (neutral, anger, pain), TIME (first half – second half) and SEX OF ACTOR (male - female) resulted in a significant main effect of TIME ($F_{(1,15)}$=21.32; p<0.001) indicating habituation in left and right SI during the experimental procedure (first half > second half). Additionally, an interaction of TIME x EMOTION ($F_{(2;30)}$=4.43; GG-ε=0.80; GG-p=0.030) and of TIME x EMOTION x SEX OF OBERVER ($F_{(2;30)}$=4.10; GG-ε=0.80; GG-p=0.037) was found. To further interpret these interactions separate ANOVAs for male and female observers were performed leading to a significant interaction of TIME x EMOTION ($F_{(2;14)}$=4.31; GG-ε=0.80; GG-p=0.047) in male observer, while only yielding marginal significance in female observers ($F_{(2;14)}$=3.81; GG-ε=0.78; GG-p=0.060). In order to be able to explain the interaction of TIME x EMOTION separate ANOVAs were calculated for neutral, anger and pain in male observers, which solely resulted in a main effect of TIME for pain ($F_{(1;7)}$=7.48; p=0.029) and neutral ($F_{(1;7)}$=8.03; p=0.025), due to habituation from the first to second half of the experiment. Hence, habituation effects in primary somatosensory cortex occurred bilaterally. However, a differential response was detected in male observers, which did not, in

contrast to the above described effect of habituation compiled across emotions, show any habituation to angry faces.

Table 14:   Summary of effects in SI and SII for all observers.

AREA	SIDE	SIZE	TALAIRACH			t-value	p-value
			x	y	z		
[Pain-Neutral] – block design							
SI	R						n.s.
	L	BA 1	(6)	-51	-19	49	-4.35	0.000492
SII/pINS	R						n.s.
	L						n.s
[Pain-Anger] – block design							
SI	R						n.s.
	L						n.s.
SII/ pINS	R						n.s.
	L		(8)	-45	-31	19	4.49	0.000364
[Anger-Neutral] – block design							
SI	R						n.s.
	L	BA2	(2)#	-45	-25	33	-4.24	0.000631
SII/pINS	R						n.s.
	L						n.s.
[Pain-Neutral] – event-related design							
male actors							
SI	R	BA3	(7)	55	-13	52	4.04	0.000950
	L						n.s.
SII/pINS	R						n.s.
	L						n.s.
female actors							
SI	R	BA3	(41)	42	-23	61	-6.48	0.000008
	L						n.s.
SII/ pINS	R		(24)	39	-10	-5	-4.22	0.000652
	L		(38)	-45	-10	13	-5.08	0.000112
male > female actors							
SI	R	BA3	(23)	43	-22	61	6.22	0.000012
	L						n.s.
SII/ pINS	R		(8)	45	-1	10	3.76	0.001704
	L		(4)#	-39	-22	16	3.93	0.001184
[Pain-Anger] – event-related design							
male actors							
SI	R	BA3	(14)	60	-16	33	4.92	0.000155
	L	BA2	(3)#	-36	-28	42	3.95	0.001149
SII/ pINS	R		(11)	36	-34	19	5.96	0.000020
	L	= 2	(98)	-42	-31	18	7.20	0.000002

AREA	SIDE	SIZE	TALAIRACH			t-value	p-value
			x	y	z		
female actors							
SI	R						n.s.
	L						n.s.
SII	R						n.s.
	L						n.s.
male > female actors							
SI	**R**	BA3	(3)[#]	60	-16	33	4.46	0.000391
	L						n.s.
SII/ pINS	**R**						n.s.
	L		(9)	-42	-13	1	4.25	0.000612
[Anger-Neutral] – event-related design							
male actors							
SI	R						n.s.
	L						n.s.
SII/pINS	R						n.s.
	L						n.s.
female actors							
SI	**R**	BA3	(60)	27	-31	64	-7.62	0.000001
	L	BA3	(37)	-55	-22	38	-5.30	0.000071
SII/ pINS	**R**		(16)	42	-19	13	-5.43	0.000055
	L		(69)	-42	-1	10	-5.39	0.000060
male > female actors							
SI	**R**	BA2	(9)	48	-27	55	4.45	0.000402
	L						n.s.
SII/pINS	R						n.s.
	L						n.s.

SI=primary somatosensory cortex and SII/pINS=secondary somatosensory cortex and posterior insula; side outlines the side where activation occurred (R=right, L=left); size shows the number of contiguous significant 3x3x3mm voxels in the region; Talairach *xyz* standardized stereotaxic coordinates of peak voxel, as well as corresponding t- and p- values are displayed; results which met the threshold of n≥4 voxel and $p<0.005$ (uncorrected) were considered significant; [#]Activations which did not meet extent threshold; = indicates the number of subclusters within the ROI.

4.3.6   SII / Posterior Insula

Analysis of the block design revealed in accordance to the expectations an involvement of the ROI during the processing of pain contorted relative to angry faces, although only left-sided (Figure 46). In contrast to the expectations, the comparison of pain and neutral blocks did not yield a significant difference (Table 14). For neither of the contrasts in the block design analysis differences in activation occurred when comparing female and male observers (Appendix B-III).
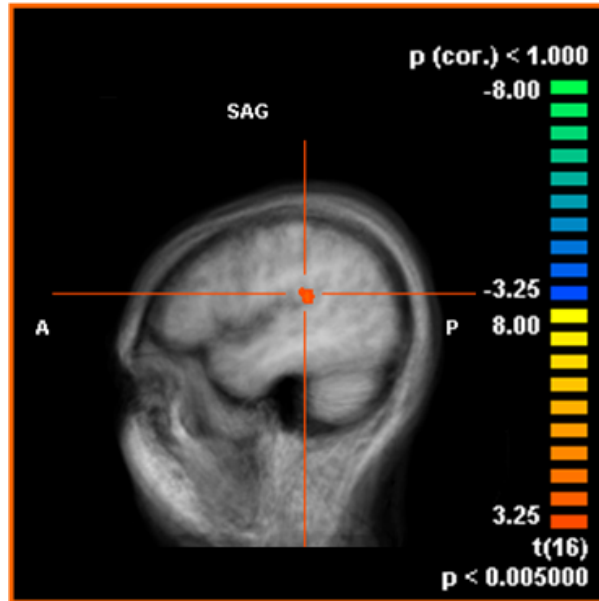
Figure 46: Left-sided SII/pINS activation for contrast P – A of the block design displayed in sagittal view.

As revealed by event-related analysis, the strength of the detected activations depended on the type of facial expression and the actors' sexes (Figure 47).
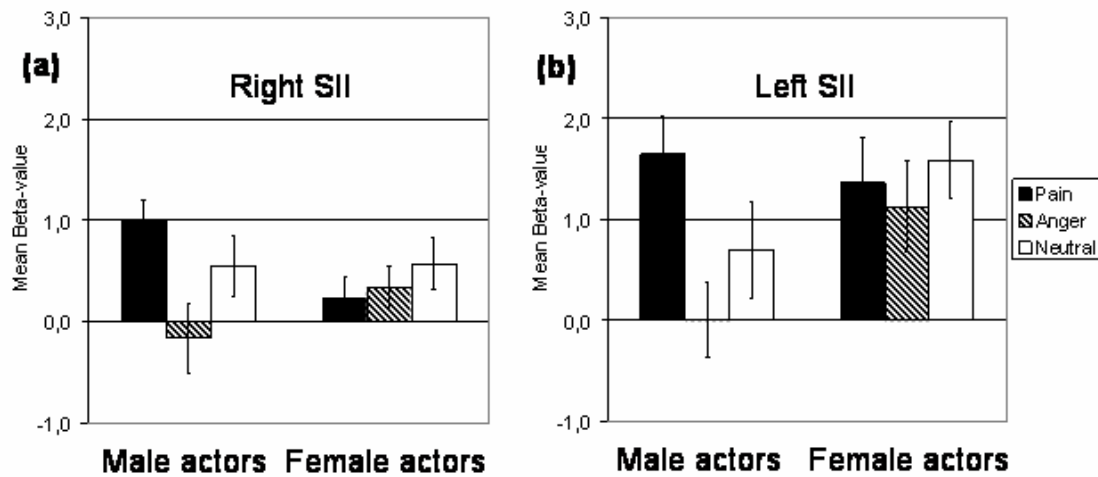

Figure 47: Bar graphs show activation to the facial events compared to the visual baseline in a) the right and b) the left SII/pINS for event-related design as determined by the mean betas (±SEM) in the peak voxel.

Exposure to males' pain contorted faces led to significant bilateral activations in the ROI relative to angry faces (Figure 48). However, contrasting pain$_{male}$ and anger$_{male}$ to neutral$_{male}$ did not result in involvement of the SII/posterior insula.
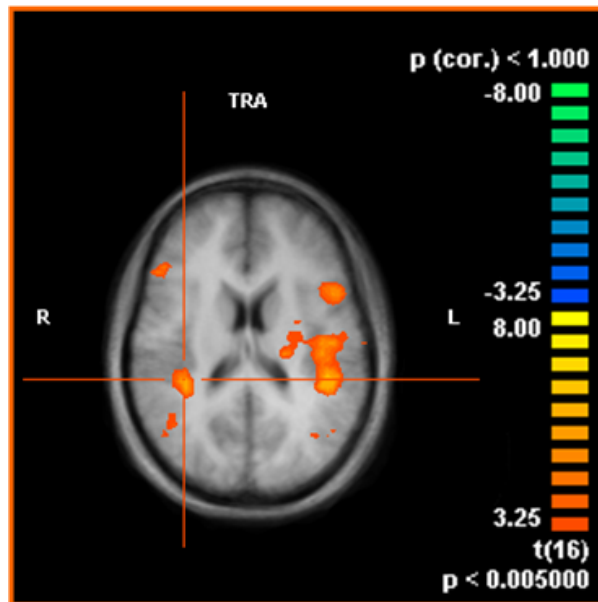

Figure 48:   Bilateral SII/pINS activation to male actors displayed for contrast P – A in transversal view.

Regarding to female actors, no significant difference was detected when comparing pain contorted faces to angry faces. Hence, comparing responses to male and female actors in this particular contrast directly revealed stronger left-sided responses to male actors compared to female actors' pain faces contrasted against anger. An engagement of SII/posterior insula during processing of females' pain faces in contrast to females' neutral faces, however, reached significance bilaterally, due to less activation during exposure to pain faces. This effect of deactivation was found to be especially pronounced left-hemispheric in male observers (Table 14). Direct comparison of male and female actors in this particular contrast confirms stronger bilateral activations (less deactivation) to male actors' compared to female actors' pain faces contrasted against neutral.

Moreover, BOLD-responses to females expressing anger were significantly smaller than to neutral facial displays of actresses (Figure 49).
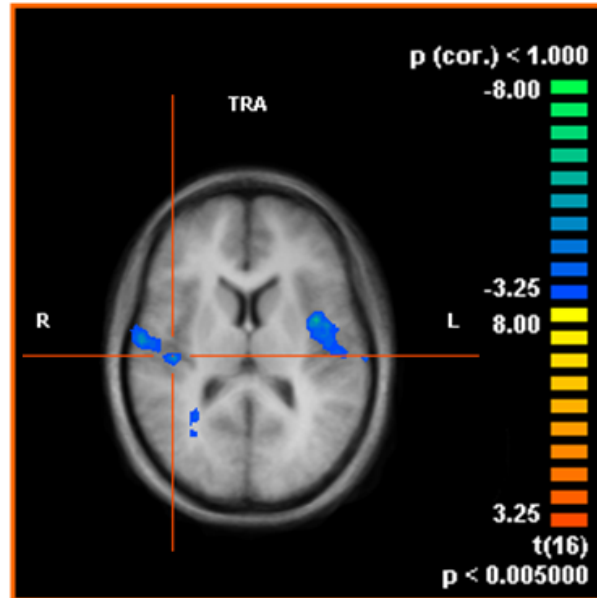
Figure 49: Bilateral SII/pINS activation to female actors displayed for contrast A – N in transversal view.

SII / Posterior Insula - Habituation

Investigation of BOLD-response habituation in the left and the right SII – posterior insula was done by using a 2 x 2 x 3 x 2 x 2 ANOVA with the between-subject factor SEX OF OBSERVER (male - female) and the repeated measures factors SIDE (right and left amygdala), EMOTION (neutral, anger, pain), TIME (first half – second half) and SEX OF ACTOR (male - female). Firstly, a main effect of TIME was observed ($F_{(1;15)}$=9.41; p=0.008), due to bilateral habituation (first half > second half). Moreover, significant interactions of SIDE x TIME ($F_{(1;15)}$=5.95; p=0.028), TIME x SEX OF ACTOR x SEX OF OBSERVER ($F_{(1;15)}$=6.20; p=0.025), SIDE x TIME x SEX OF ACTOR ($F_{(1;15)}$=5.28; p=0.036), SIDE x TIME x SEX OF ACTOR x SEX OF OBSERVER ($F_{(1;15)}$=4.65; p=0.048) and SIDE x TIME x EMOTION x SEX OF ACTOR ($F_{(2;30)}$=5.58; p=0.009) occurred.

In order to be able to interpret these findings subsequent ANOVAs were calculated for the left and right ROI separately, yielding a main effect of TIME ($F_{(1;15)}$=12.82; p=0.028; first > second half), as well as an interaction of TIME x EMOTION x SEX OF ACTOR ($F_{(2;30)}$=3.49; GG-ε=0.93; GG-p=0.048) for the left SII – posterior insula. For the right ROI solely an interaction of TIME x SEX OF ACTOR x SEX OF OBSERVER ($F_{(2;14)}$=11.78; p=0.004) was found.

These findings were further analyzed by separate ANOVAs calculated for male and female actors leading to a significant main effect TIME found for male actors ($F_{(1;15)}$=11.77; p=0.004; first > second half) and an interaction of TIME x EMOTION observed in female actors ($F_{(2;30)}$=4.09; GG-ε=0.81; GG-p=0.037) for the left ROI. In the right ROI an interaction of TIME x SEX OF OBSERVER for both male ($F_{(1;15)}$=6.53; p=0.022) and female actors ($F_{(1;15)}$=6.99; p=0.019) was detected.

The interaction of TIME x EMOTION observed in the left hemisphere was due to significant habituation to angry faces ($F_{(2;30)}$=9.54; p=0.007) as subsequent ANOVAs computed for each emotion separately revealed.

To further interpret the interaction of TIME x SEX OF OBSERVER separate ANOVAs were performed for the responses observed in male and female observers, which revealed a marginal significant habituation for female observers to male actors ($F_{(1;8)}$=4.32; p=0.071) and significant habituation for male observers to female actors ($F_{(1;7)}$=9.59; p=0.017).

Hence, in general a habituation effect was found bilaterally but more pronounced in the left hemisphere to male actors' faces in general and angry female faces in particular. For the right hemisphere specific differences in BOLD-responses were observed for male and female observers characterized by habituation to the opposite sex.

4.3.7 FFA

As revealed by the analysis related to the block design no significant sustained activation of FFA was observed for all contrasts of interest (Table 15 and Appendix B-V).

Further inspection of the baseline contrasts explained this finding. Analysis of these contrasts revealed highly significant bilateral (right > left) activation to pain, anger and neutral faces relative to the visual baseline (Appendix B-VI).

Taking the actors' sexes into account, contrasting males' pain with males' neutral faces resulted in right-sided, while contrasting it to males' angry faces results in a significant left-sided activation of FFA Figure 50. Comparison of males' angry with males' neutral faces did in contrast to the hypothesis not yield a significant activation in FFA. For

neither of these contrasts FFA indicated stronger activation in male compared to female observers (Appendix B-V).
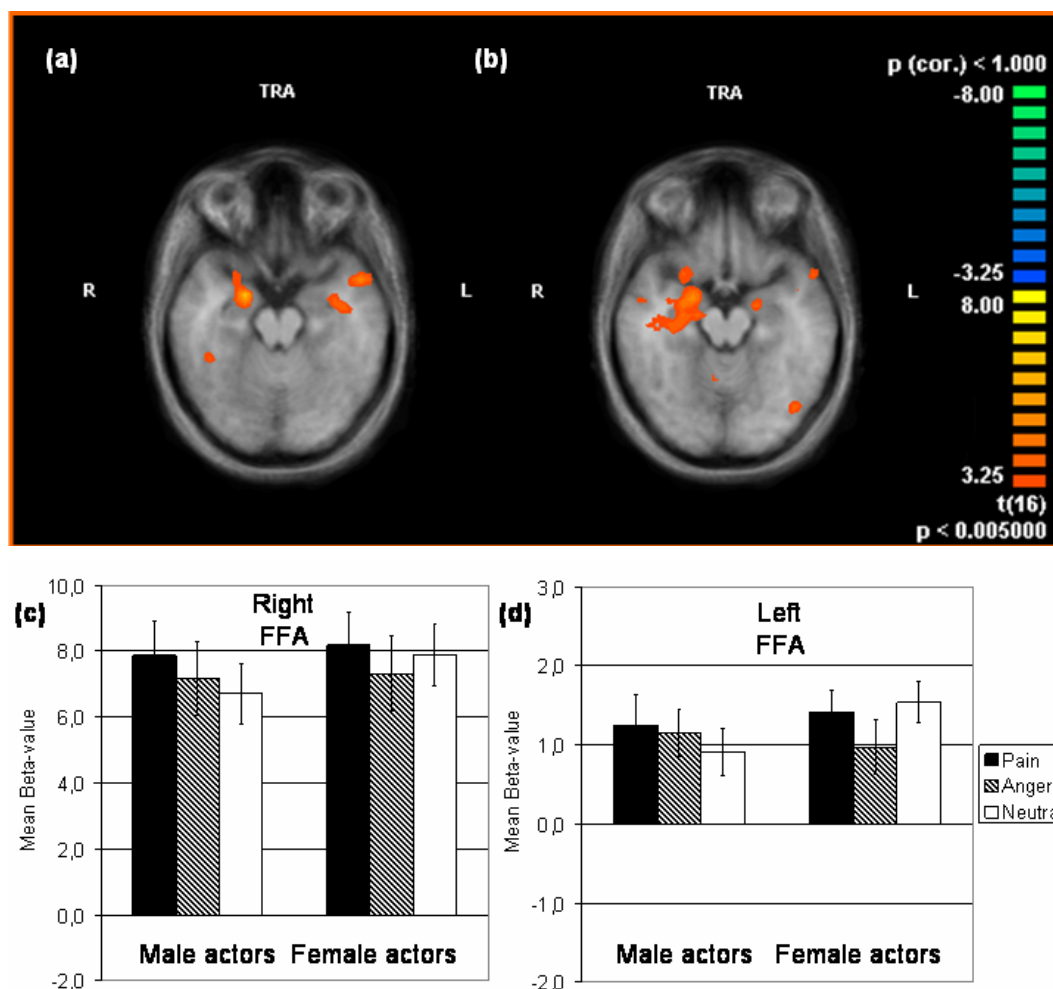

Figure 50: Transversal view of FFA activation displayed for contrast a) P – N (right) and b) P – A (left) to male actors faces. The corresponding bar graphs show activation to the facial events compared to the visual baseline in c) right and d) the left FFA as determined by the mean betas (±SEM) in the peak voxel.

For female actors' faces only comparing pain to anger yielded a significant right-sided activation (although not meeting the extent threshold). Moreover, female observers showed stronger activation of FFA bilaterally for this contrast (Appendix B-V). However, contrasting BOLD-responses to female angry and neutral faces indicated a significant deactivation in FFA (Table 15). Direct comparison of responses to actors and actresses confirmed stronger bilateral activation to male actors (although not meeting

the extent threshold) for [pain – neutral] and less deactivation in left FFA to male actors for [anger-neutral].

As demonstrated when inspecting the baseline contrasts for the peak voxel (Appendix B-VI) it became obvious that while FFA showed significant bilateral activation (right > left) to all conditions, the amount of activation depended on the actors' sexes and condition. In accordance with the hypothesis, observers showed strongest activation to pain, followed by anger and weakest to neutral male faces. Although as expected responses were stronger to actresses' pain than angry faces, the signal increase to females' neutral faces was strongest explaining the lack of activation or findings of relative deactivation.

Table 15: Summary of effects in FFA and STS for all observers.

AREA	SIDE	SIZE	TALAIRACH x	y	z	t-value	p-value
[Pain-Neutral] – block design							
FFA	R						n.s.
	L						n.s.
STS	R	(87)	51	-54	7	6.68	0.000005
	L	(116)	-54	-43	7	6.40	0.000009
[Pain-Anger] – block design							
FFA	R						n.s.
	L						n.s.
STS	R						n.s.
	L						n.s.
[Anger-Neutral] – block design							
FFA	R						n.s.
	L						n.s.
STS	R	(87)	51	-54	7	6.68	0.000005
	L	(94)	-48	-52	7	4.33	0.000004
[Pain-Neutral] – event-related design							
male actors							
FFA	R	(5)	42	-40	-17	4.35	0.000501
	L						n.s.
STS	R	(92)	56	-56	4	5.88	0.000023
	L	(43)	-49	-35	7	5.45	0.000053
female actors							
FFA	R						n.s.
	L						n.s.
STS	R						n.s.
	L	(7)	-54	-46	4	4.39	0.000455

AREA	SIDE	SIZE	TALAIRACH			t-value	p-value
			x	y	z		
male > female actors							
FFA	**R**	**(2)**[#]	**30**	**-46**	**-14**	**4.28**	**0.000571**
	L	**(2)**[#]	**-33**	**-49**	**-7**	**3.79**	**0.001619**
STS	**R**	**(1)**[#]	**57**	**-34**	**4**	**4.54**	**0.000333**
	L						n.s.
[Pain-Anger] – event-related design							
male actors							
FFA	**R**						n.s.
	L	**(9)**	**-42**	**-67**	**-14**	**4.34**	**0.000511**
STS	**R**	**(10)**	**53**	**-33**	**7**	**4.01**	**0.001008**
	L	**(20)**	**-51**	**-37**	**7**	**5.24**	**0.000080**
female actors							
FFA	**R**	**(1)**[#]	**33**	**-76**	**-14**	**3.99**	**0.001050**
	L						n.s.
STS	**R**						n.s.
	L						n.s.
male > female actors							
FFA	**R**						n.s.
	L						n.s.
STS	**R**						n.s.
	L						n.s.
[Anger-Neutral] – event-related design							
male actors							
FFA	**R**						n.s.
	L						n.s.
STS	**R**						n.s.
	L						n.s.
female actors							
FFA	**R**						n.s.
	L	**(5)**	**-42**	**-52**	**-11**	**-3.99**	**0.001057**
STS	**R**						n.s.
	L						n.s.
male > female actors							
FFA	**R**						n.s.
	L	**(7)**	**-39**	**-52**	**-11**	**4.5**	**0.000366**
STS	**R**						n.s.
	L						n.s.

FFA=FFAform face area, STS=superior temporal sulcus; side outlines the side where activation occurred (R=right, L=left); size shows the number of contiguous significant 3x3x3mm voxels in the region; Talairach *xyz* standardized stereotaxic coordinates of peak voxel, as well as corresponding t- and p-values are displayed; results which met the threshold of $n \geq 4$ voxel and $p < 0.005$ (uncorrected) were considered significant; [#]Activations which did not meet extent threshold.

FFA - Habituation

Computation of a 2 x 3 x 2 x 2 ANOVA with the between-subject factor SEX OF OBSERVER (male - female) and the repeated measures factors EMOTION (neutral,

anger, pain), TIME (first half – second half) and SEX OF ACTOR (male - female) solely resulted in a significant main effect of TIME ($F_{(1,16)}$=16.28; p=0.001) indicating habituation in left and right FFA during the experimental procedure (first half > second half).

4.3.8   STS

As expected a significantly higher bilateral activation to pain compared to neutral faces (Figure 51-a), as well as angry relative to neutral faces (Figure 51-b) was detected during analysis of blocks (Table 15). Both emotional conditions, however, did not differ significantly from each other. For neither of the contrasts in the block design analysis differences in activation occurred when comparing female and male observers (Appendix B-V).
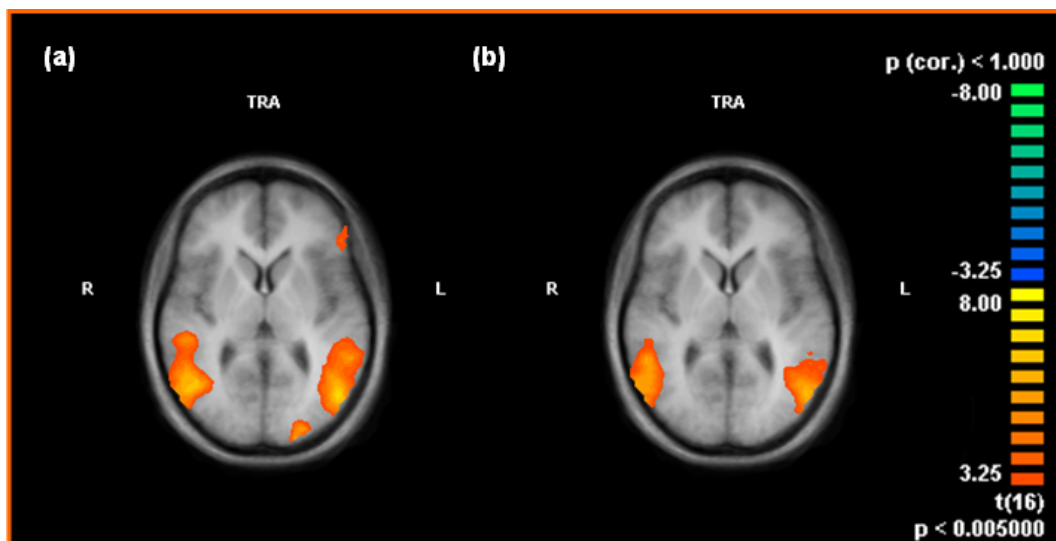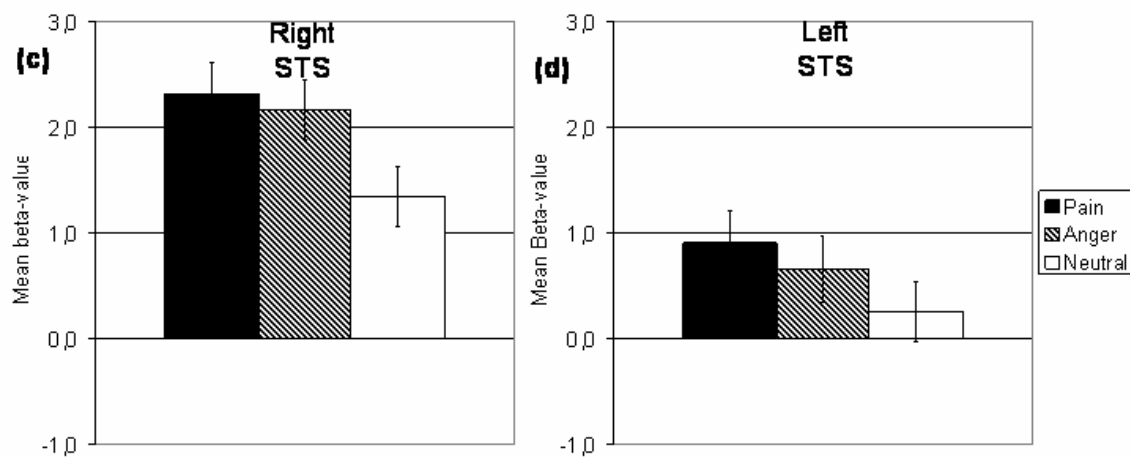
Figure 51: Transversal view of STS activation displayed for contrast a) P – N and b) A – N to all actors' faces (block design). The corresponding bar graphs show activation of c) right and d) the left STS to pain, anger and neutral in contrast to visual baseline as determined by the mean betas (±SEM) in the peak voxel.

Baseline contrasts (Figure 51-c,d) reflected stronger activation in pain and anger blocks than in neutral blocks particularly in the right hemisphere, which underpinned these results (Appendix B-VI).

As detected in event-related analysis, the strength of this activation depended on the type of facial expression and on the sex of the actor (Figure 52).
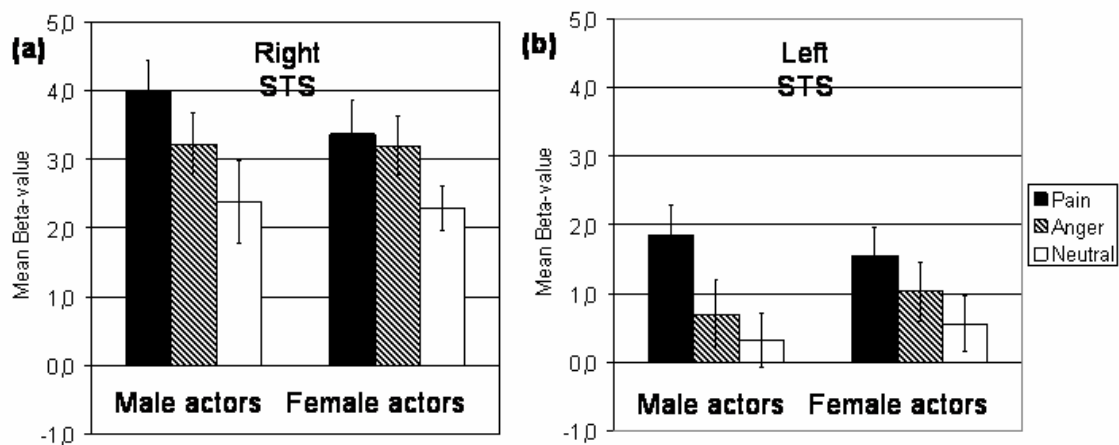

Figure 52: Bar graphs show activation to the facial events compared to the visual baseline in a) right and b) left STS for the event-related design as determined by the mean betas (±SEM) in the peak voxel.

Hence, significant bilateral activations in STS were detected when comparing BOLD-response to males' pain contorted faces to both neutral (Figure 53-a) and, although to a lesser extent, to angry faces (Figure 53-b). This involvement of STS in the processing of males' pain faces in contrast to the other conditions is even more pronounced in female observers' right hemisphere compared to male observers (Appendix B-V). However, contrasting anger$_{male}$ to neutral$_{male}$ did not result in involvement of the STS for all observers, but showed stronger engagement in the left STS in male observers for this particular contrast (Appendix B-V).

An involvement of STS in the processing of females' pain faces in contrast to neutral faces did only reach significance in the left STS (Table 15). Direct comparison of male and female actors in this particular contrast confirmed stronger right-sided responses to male actors' compared to female actors' pain faces contrasted against neutral.

Neither of the remaining contrasts did indicate differences in involvement of the STS (Table 15).
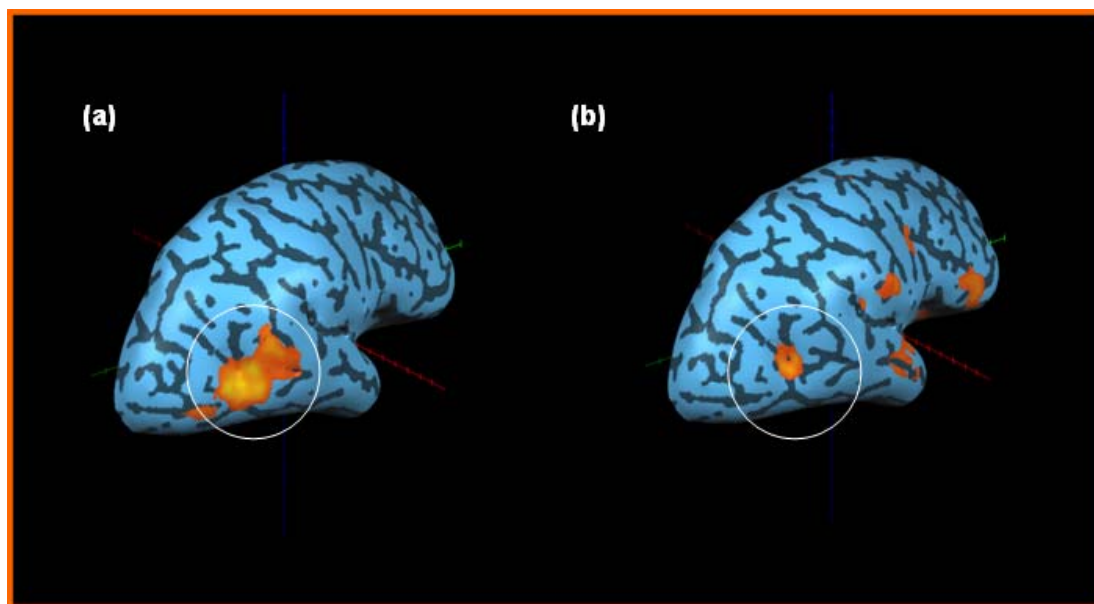

Figure 53:   Inflated occipotemporal cortex including STS activation (white circle) displayed for contrast a) P – N and b) P-A to male actors' faces exemplarily shown for the right hemisphere (light blue corresponds to gyri and dark grey to sulci).

STS - Habituation

To investigate possible effects of habituation in STS a 2 x 3 x 2 x 2 ANOVA with the between-subject factor SEX OF OBSERVER (male - female) and the repeated measures factors EMOTION (neutral, anger, pain), TIME (first half – second half) and SEX OF ACTOR (male - female) was conducted. Firstly, a main effect of TIME ($F_{(1,16)}$=8.14; p=0.012) occurred due to higher BOLD-responses during the first in contrast to the second half. Moreover, an interaction of SIDE x TIME ($F_{(1,15)}$=6.00; p=0.027), SIDE x TIME x SEX OF OBSERVER ($F_{(1,15)}$=4.94; p=0.042), TIME x EMOTION x SEX OF OBSERVER ($F_{(2;30)}$=3.97; GG-ε=0.74; GG-p=0.044) and TIME x SEX OF ACTOR ($F_{(1,15)}$=9.63; p=0.007) was found. Separate ANOVAs were calculated for right and left STS separately yielding a main effect of TIME for the right STS ($F_{(1,15)}$=9.52; p=0.008), which indicated habituation from the first to the second half for this particular ROI. For the left STS a marginal significant interaction of TIME x SEX OF OBSERVER ($F_{(1,15)}$=3.31; p=0.089) and a significant interaction of TIME x EMOTION x SEX OF OBSERVER ($F_{(2;30)}$=3.64; GG-ε=0.94; GG-p=0.042) were detected. For both right and left STS an interaction of TIME x SEX OF ACTOR was found (right: $F_{(1,15)}$=4.29; p=0.056; left: $F_{(1,15)}$=7.38; p=0.016). To further investigate these effects subsequent ANOVAs were computed for male and female actors separately. Bilaterally, STS showed higher BOLD-responses to male actors' faces during the first half compared to the second half of the experiment resulting in a main effect of TIME (right: $F_{(1;15)}$=16.11; p=0.001; left: $F_{(1;15)}$=16.20; p=0.006), while no such differences were observed to females' faces. Furthermore, a marginal significant interaction of TIME x SEX OF OBSERVER ($F_{(2;15)}$=3.40; p=0.085) was found in the left STS to male actors' facial expressions. Separate ANOVAs calculated for male and female observers revealed a main effect of TIME in the left STS for male observers ($F_{(1;7)}$=16.80; p=0.005) due to higher BOLD-responses to male faces during the first compared to the second half. The further analysis of the three-way interaction of TIME x EMOTION x SEX OF OBSERVER in the left STS did not reveal any significant results.

Hence, in general habituation effects were found for both – left and right STS, but they were stronger in the right hemisphere. These habituation effects were particularly pronounced to male actors bilaterally. Moreover, for the left STS this habituation effect to males' faces was stronger in male observers.

4.3.9   Relationship of Ratings and Questionnaires on BOLD-responses

Due to the fact that mainly event-related analysis yielded significant activation of the ROIs in the present thesis and hence solely here peak-voxel parameter estimates were extractable for analysis this section does not include block-related analysis.

Since the behavioral data revealed on the one hand that a small number of subjects had difficulties to clearly recognize the facial expression of pain and on the other hand valence and arousal ratings showed differences between pain and angry faces it had to be assured that these facts did not influence the observed results of BOLD-responses in the ROIs. This was done by the following analyses.

Recognized Emotion

While anger and neutral clips, as described in section 3.1.6, were clearly recognized as the intended target emotions, pain clips showed some contamination by other emotions. Namely, there were four subjects in experiment II which did not judge pain but another emotion being the most intense in the pain clips. Although, as already discussed, this might be due to a scaling bias there was still a need to test whether these subjects differed significantly from the group mean for each contrast of interest in each ROI. Therefore it was tested whether the beta values (e.g. pain-neutral to male actors' faces) observed in the four subjects deviated more than three SD from the group mean. Introspection of the descriptive statistics did not reveal an outlier in the group of the four subjects. Moreover, to examine whether exclusion of these four subjects would meaningfully change the group mean single t - tests for one sample were computed. The mean of each variable for the group after exclusion was therefore compared to the mean of this variable before exclusion treated as a constant. Analysis showed that the exclusion of these four subjects did not change the group mean and accordingly did not yield any significant result for the described procedure (DVD).

Hence, one can summarize that the results reported for each ROI are not influenced by the variability of subjects' ratings concerning the recognized emotions.

Valence & Arousal

In order to investigate whether BOLD-responses for the following contrasts in the ROIs corresponded with the valence and arousal ratings that subjects gave for the presented emotional clips (pain and anger) correlations were calculated. Since one computation for each ROI comprised 24 repeated tests (see Section 3.7.3) the Bonferroni-corrected threshold for a significant result was set to p(cor)=0.002. For neither of the investigated ROIs a significant correlation was detected throughout the analysis (DVD).

Questionnaire Scores

To determine possible relations between interindividual differences in empathy (IRI - EC and PT) and the BOLD response associated with the recognition of pain in the anterior insula and ACC correlations were computed (see Section 3.7.3). Solely for the left ACCad it was shown that the higher subjects' empathic ability was the stronger BOLD-responses occurred to male actor's expressing pain (relative to neutral) (IRI-EC: r=0.49, p=0.047; IRI-PT: r=0.61, p=0.009, p(cor)=0.008). In contrast the higher empathic ability the weaker BOLD-responses were observed to female actors' pain (relative to neutral) (IRI-EC: r=-0.56, p=0.019; IRI-PT: r=-0.51, p=0.037, p(cor)=0.008). However, none survived the corrected threshold.

Moreover, in order to examine whether the amygdala activation detected during the processing of pain in contrast to neutral clips to both male and female actors' faces was associated with individuals' STAI state scores, correlations with these scores were calculated (see Section 3.7.3). Solely for BOLD-response of the right amygdala to females' pain showed a marginally significant correlation with the state anxiety level (r=0.51, p=0.036, p(cor)=0.008). However, this finding did not survive the corrected threshold. Furthermore, no correlation of the individuals' pain catastrophizing tendencies with the BOLD-response in any ROI was detected.

Autonomic Measures

As mentioned earlier, on the one hand the low qualitative GSR-data acquired in experiment II and on the other hand the lack of sustained activation (block design) in

the a-priori ROIs made the intended analysis impossible. Hence, no results can be provided for the beforehand raised question.

5   <u>Discussion</u>

This chapter provides a detailed description and discussion of the results derived from the behavioral, peripheral physiological and imaging data in separate sections. Since facial expressions of pain and their recognition are the main focus of the present thesis conclusions with regard to these stimuli are given at the end of each section.

At the end of the chapter, all findings are integrated into an explanatory model. Finally, questions that remain to be answered by future research are outlined.

5.1   <u>Questionnaire Data & Behavioral Ratings of Face Clips</u>

This section firstly summarizes the main results of behavioral ratings, and subjects' performance in the gender discrimination task with respect to the hypotheses. It also provides an integration of these findings into the literature.

5.1.1   <u>Summary</u>

Subjects were presented lowly contaminated, prototypical neutral, anger, and pain face clips with the emotional categories being matched in terms of intensity.

1.   It was confirmed that subjects - both in the rating and the experimental sessions - were able to unambiguously recognize anger and neutral faces. Pain clips were clearly recognized throughout the rating session. In contrast to the expectations, in both experiments a small number of subjects also recognized a blend of other emotions (disgust, fear, and surprise), besides pain, in facial pain expressions.

2.   As expected, angry and pain contorted faces were consistently perceived as being more unpleasant and arousing than neutral clips taking the *actors*' point of view. Additionally, pain faces were also rated as being more unpleasant and arousing than anger faces throughout the rating session and in experiment I, but not in experiment II.

3. Exposure to pain clips as compared to neutral clips even elicited stronger arousal and feelings of unpleasantness in the *observer* in both experiments. However, only during experiment I the same was reported to anger faces in comparison to neutral faces. Additionally, pain faces were perceived as being even more unpleasant than anger faces in experiment I, and more arousing than anger faces in experiment II. These ratings were, in contrast to the expectations, independent of subjects' self-reported empathic ability. Compared to the actors' viewpoint, the ratings from the observers' perspective were lower, except for neutral faces (no difference).

4. It was not confirmed that empathic ability, anxiety level or pain catastrophizing tendencies influenced these behavioral ratings.

5. With regard to the actors' sexes no differences in subjects' intensity, valence and arousal ratings were detected throughout the rating session. Furthermore, taking the observers' sexes into account, no differences were detected with respect to the intensity and valence ratings in both experiments. During experiment I, however, male observers tended to rate clips displaying pain faces as more contaminated by additional emotions than female observers. Moreover, in experiment II female observers generally reported higher arousal ratings to the clips than male subjects.

During the gender discrimination task of both experiments, subjects made more errors to clips with pain faces relative to clips with neutral faces. Moreover, in the case of experiment II more errors to angry faces in contrast to neutral faces occurred, whereas this was not true for experiment I. It was shown throughout both experimental tasks that the performance was independent of the actors' gender. Higher error rates for male observers were generally observed in experiment I.

In none of the experiments did the RTs for the three facial categories differ from each other. Solely, a general learning effect (decreases of RT) was detected across runs of experiment II. In experiment I, RT-decreases across blocks were found to neutral and angry male actors' and female actors' angry faces, whereas male pain faces caused increases *and* decreases of RT across the entire experiment. Furthermore, longer RTs

occurred to angry female faces in contrast to neutral and pain contorted female faces during the third run.

5.1.2   Discussion

Hence, in line with expectations, subjects are able to clearly identify the prototypical neutral and angry facial expressions. Especially for angry faces, which were presented without any contextual information, the specificity of prototypical basic emotions that can be reliably recognized across individuals is confirmed (Smith and Scott, 1997). Moreover, the facial expression of pain was correctly identified by most subjects. However, in contrast to the a-priori hypothesis, 30% of the subjects in both experiments were not able to unambiguously detect the prototypical facial expression of pain. Pain faces were frequently contaminated with the emotions disgust, fear, and surprise. Past research on the recognition of pain faces provided reasonable evidence for their correct identification by subjects (e.g. Prkachin, 1992). However, only few studies have examined the distinction of pain from other emotional facial expressions. For instance, Kappesser and Williams (2002) asked health care professionals to judge static facial displays of pain and the basic emotions (without happiness). Similar to the rating session of the present study, on the labels 'pain', 'sadness', 'disgust' etc., they found, resembling the findings of the present study, that some subjects misidentified photographs of pain faces as disgust faces (18%) and as fear faces (2 %), while they clearly recognized faces of anger and moreover did not misidentify disgust as pain.

Taking this into account, two possible explanations for the results of this thesis can be stated. Firstly, as described in Table 1, faces displaying pain and disgust share AU 9 and 10 (nose wrinkler and upper lip raiser), which are the *only* prototypical AUs for disgust. Without contextual information (e.g. having an injection), this ambiguity of information might lead to higher disgust ratings for pain clips. Moreover, in naturalistic contexts, a co-occurrence of pain, fear, and surprise is likely and might explain the additional contamination of pain clips with both emotions. Secondly, these results might be due to a scaling bias as during the post-experimental rating subjects were not only required to judge pain and anger but also all other basic emotions in the three types of clips. This fact might explain the differences in the results between the subjective rating session

and the post-scanning data. However, there was no scaling bias observed to anger clips, which hence seem to be less ambiguous.

To summarize, while most of the research on recognition of pain faces was done in clinical settings giving context information (e.g. source of pain experience) this is the first study, which uses dynamic stimuli of pain facial displays without contextual cues. Although the results confirm that most individuals are able to automatically recognize pain from the pure facial expression, results also suggest that these faces, probably due to the described overlap of AUs with disgust and frequent co-occurrence of pain with other emotions, obviously convey some degree of ambiguous information. This ambiguity seems to decrease with the presentation of disgust faces as reference [rating session (+disgust) vs. experiment I+II (no disgust)], with the opportunity to rely on dynamic patterns of the AUs' co-occurrence [rating of static stimuli (Kappesser and Williams, 2002) vs. rating of dynamic stimuli (present thesis)] and might completely disappear when contextual information is provided. Future research, as suggested in section 5.5., should further investigate this question.

Furthermore, it was robustly confirmed by both experiments that angry and pain contorted faces were perceived as being more unpleasant and arousing than clips of neutral faces taking the actors' point of view. Additionally, pain faces were also rated as being more unpleasant and arousing than anger faces throughout the rating session and in experiment I, while this was not confirmed in experiment II. This inconsistent finding could simply reflect variations between different samples or could be due to the timing between experimental session and clip rating. While subjects judged the arousal and valence of the clips immediately after the stimulus presentation in the rating session or immediately after the experimental procedure in experiment I, subjects in experiment II underwent an anatomical scan and had to change their clothes before their ratings were acquired. Hence, one could hypothesize that this leads to less sensitive ratings in terms of distinction between anger and pain.

Compared to the actors' point of view, the ratings from the observers' perspective were much lower, which was not surprising considering that feeling vs. observing an emotion should intuitively differ in affective intensity. Nevertheless, the same pattern of results occurred. Thus, higher feelings of arousal and unpleasantness while observing pain

contorted faces (vs. neutral) were confirmed during both experiments. Only in experiment I subjects reported the same perceptions observed for pain clips as for angry face clips (vs. neutral). This might likely reflect variations between different samples or it could, as already mentioned above, be due to the difference in timing of ratings in the different experimental sessions. However, the findings of higher ratings to pain faces in contrast to angry faces for a) valence in experiment I and b) for arousal in experiment II seem to constitute no valid finding and need further validation. Against expectations, these results were observed in all subjects independently of their ability to 'feel in' or take another person's perspective. Hence, one could assume that to some degree viewing facial expressions of pain automatically elicits also an emotional response in the observer, while facial expressions of anger do not consistently. Since those scales explain only 50% of variance (Atkins and Steitz, 2002) the lack of correlation between behavioral ratings and reported empathic ability could also be due to the weak prediction of these scales.

An influence of any personality variable on the behavioral ratings could not be demonstrated. Since this lack of correlation was not due to outliers in the samples one could hypothesize that these results might be explained by the lower sensitivity of nonparametric correlations. Furthermore, singular explanations for each personality variables are conceivable. Although an influence of subjects' trait anxiety on behavioral ratings was intuitively expectable, the lack of a significant correlation is to some degree in line with the literature. For instance Stein, Goldin, Sareen, Zorrilla and Brown (2002) showed that the anxiety levels (however STAI state) of social phobics, did not modulate their 'harshness'-ratings of displayed faces (e.g. angry), while it did influence the BOLD-responses in certain brain areas (e.g. amygdala). The lack of correlation between empathy scores and behavioral ratings could be due to the weak prediction power of these scales. An alternative explanation could be derived from the fact that people, who have by definition "[…] a completely callous lack of empathy or concern for others [...]" (Hare, 1998) - namely psychopaths - nevertheless seem to be quite capable of taking the perspective of others (e.g. Blair, 2001). Hence, the finding that ratings from the actors' viewpoint were not necessarily dependent on subjects' empathic capabilities does not seem surprising. In the case of pain catastrophizing, the lack of a correlation might be due to the fact that the PCS-scores were not clinically relevant. Hence, a

significant interaction with perception of painful faces is unlikely and should be investigated in comparison to high- and low-catastrophizers in future research.

For the discussion of sex differences one has to take into account that behavioral data with respect to actors' sexes was solely acquired in the rating session (to time consuming for experiments) and with respect to the observers' gender only during both experimental sessions. During the rating session male and female actors' faces were matched for the intensity of the expressed emotion by both, subjective and objective measures (FACS-coding). However, according to the literature, one could have expected differences in valence and arousal ratings with regard to the actors' gender. Several previous findings showed that subjects of both sexes tended to rate angry faces of male actors, according to gender stereotypes, as being more angry, than of female actors, although objectively matched for intensity (Algoe, Buswell and DeLamater, 2000; Plant, Kling and Smith, 2004). Moreover, males are generally found to display less facial pain expression than females in response to experimentally controlled acute pain (Sullivan et al., 2000). Comparably intense male pain faces should therefore lead to more intense judgements, which was not the case. This question should be further addressed by future research. With regard to observers' gender generally no differences on intensity and valence were found, as robustly confirmed during both experiments. However, the remaining findings of sex differences for arousal and contamination, which were found in the first or second experiment, do not seem to reflect a valid pattern but variations between different samples

These behavioral findings also showed some accordance with the performance data measured during the gender discrimination task. Throughout both experiments subjects made more errors in response to pain clips, probably due to the arousal induced by the clips. During experiment II, where pain and anger faces had been judged as equally arousing, also more errors to angry faces occurred. However, this was not found within experiment I, despite the fact that angry facial displays had also been rated as being more arousing than neutral clips. This difference is probably due to the experimental setting in which the performance was acquired. Hence, the scanner environment itself might be more arousing than the lab situation resulting in generally higher error rates, which was confirmed by the descriptive data.

While the error number throughout both experimental tasks was, in line with the above described results, independent of the actors' gender, the performance data of experiment I showed higher error rates for male observers in general. This is probably a specific characteristic of the first sample. According to the literature, neither main nor interaction effects of observers' sexes on error rates to male and female faces have been reported (O'Toole et al., 1998). Moreover, one has to note that for both experiments the RTs of the three facial categories were not distinct from each other, which assured that observed differences between the facial categories are not due to subjects' performance.

CONCLUSION

Implicit processing of prototypical facial pain expressions, in accordance to the reported uniqueness and distinctness from the expression of basic emotions, generally led to correct identification. However, a small number of subjects in each sample gave contaminated ratings to pain clips, either due to a scaling bias or to a lack of contextual information, favouring the view that this facial expression nevertheless imparts stronger ambiguity than e.g. anger.

In line with the definition of pain as "[...] an unpleasant sensory and emotional experience [...]" (IASP, 1994) pain clips are consistently perceived as arousing and unpleasant, associated with stronger arousal and unpleasantness ratings than angry facial expressions (except for experiment II). Pain faces even elicit stronger feelings of arousal and unpleasantness in the observer and result in higher error rates regarding the task, however not different from the ones to angry clips (except for experiment I). These findings are independent of the measured personality variables and the observers' sexes.

5.2   **Peripheral Physiological Data**

5.2.1   Summary

1.   In contrast to the expectation, data did not clearly confirm an orienting response to pain and anger clips. Although, RR-intervals and GSRs showed increases relative to baseline, neither these indices nor their variability differed between pain, anger, and neutral clips. However, after exclusion of the last two runs, stronger GSRs (GSR$_{mean}$) occurred during pain trials as compared to neutral face clips in experiment I and RR-interval decreases (HR acceleration) were detected during processing of pain faces relative to angry faces in experiment II. However, all results solely reached marginal significance.

2.   While no habituation of RR-intervals across the entire experimental session was, in contrast to the expectations, detected in experiment I, heart beat in general became slower during experiment II. Also the GSRs (GSR$_{mean}$ and GSR$_{log-mean}$) showed habituation across experiment I.

3.   The electrodermal and cardiac responses to the three types of facial displays did not differ between male and female observers.

5.2.2   Discussion

For both cardiac and electrodermal measures solely weak overall effects were observed. Since different patterns of results were found during the experiments they will be reported separately and integrated afterwards.

5.2.2.1 Experiment I

The intervals between two R-waves significantly increased during viewing of all clips in comparison to baseline. Moreover, this orienting response showed no habituation across the experimental session.

Hence, in line with Craig's as well as Craig and Wood's findings (1968, 1969b), HR-decelerations were detected during the vicarious pain experience (Craig: 3-6 BPM; experiment I: 1-2 BPM). The smaller HR-changes in the present as compared to Craig's studies are eventually due to the fact that subjects in Craig's experiments were seated directly beside the person perceiving painful stimulation, whereas subjects in the present study solely saw movie clips and were moreover distracted by a task. However, Craig as well as Craig and Wood (1968, 1969b) did not include other facial expressions of emotion. Comparisons between different face categories, conducted in the present study, did not reveal increased HR-deceleration to pain faces and anger faces in contrast to neutral faces, as assumed beforehand. Thus, one could hypothesize that the observed results reflect a general response to faces while being distracted by the gender discrimination task. Furthermore, the lack of face type specific effects could be explained by the fact that subjects might develop expectations of the clips' affective content. Since the clips were presented in blocks, a reduction of the affective novelty might have occurred and subsequently have led to the observed lack of valence modulation (Bradley, 1998; Gomez et al., 2004b). An alternative explanation understanding the results as a function of errors could be rejected taking into account that no category specific results occurred, while more errors had been observed to pain clips.

The variability index of RR-intervals did not show a significant difference in contrast to baseline variations. Hence, taking into account that this measure decreases as a function of mental effort (Manzey, 1998) one could conclude that baseline and task do not differ in their mental effort during experiment I.

Moreover, as expected beforehand, increases of electrodermal activity were observed relative to baseline. This happened to be the case for all facial expressions and not as hypothesized, differentially for clips of pain and anger faces. However, these increases did not differ significantly from the baseline level. This was due to strong habituation

effects, which were, in line with the expectations (Boucsein, 1992), observed throughout the experiment. Indeed, marginally significant stronger GSRs to pain faces as compared to neutral face clips were detected after exclusion of the last two runs. This finding is in line with the literature (Craig, 1968; Craig and Lowery 1969a; Craig and Wood, 1969b; Gomez et al., 2005; Williams et al., 2001) and might be interpreted as a response to the most arousing and unpleasant clip type. However, besides the fact that these results were solely marginally significant, the described effect was not detected during analysis of logarithmized data. This favours the view that the effect is overemphasized by the skewness of the distribution and hence has to be validated with a larger sample. The variability index, reflecting the amount of GSR changes, did not reveal any differences between the types of clips but to the baseline conditions, suggesting a relative stability of autonomic responses to all clip categories.

Thus, while electrodermal changes with respect to the type of facial expression were observed during experiment I, this did not find expression in the cardiac measures. A similar pattern of electrodermal responses combined with a lack of cardiac responses was also found in a study by Gomez and colleagues (2004b). This suggests higher susceptibility of HR-measures than of GSR to the lack of affective novelty caused by a block-wise presentation of emotional facial expressions.

5.2.2.2 *Experiment II*

Although the RR-intervals showed slight increases during viewing of all clips in comparison to the baseline, this finding did not meet the significance threshold. This was due to habituation, which had, in line with the expectations (Stern and Sison, 1990), been observed.

Indeed, exclusion of the last two runs revealed differential effects to facial pain expression on the RR-intervals. Surprisingly, in contrast to the expectations (Gomez et al., 2005; Kuniecki et al., 2003), pain clips, rated as being unpleasant and arousing, led to RR-decreases (HR-acceleration) as compared to anger and neutral clips. This effect could not be interpreted as a function of the conducted errors since the same amount of errors to pain and anger clips had been observed. The results, although solely reflecting a tendency, rather suggested a distinct autonomic response to facial expressions of pain.

On the one hand, considering that imitation of facial expressions (Levenson et al., 1990; 2002), as well as induction of emotion (Damasio et al., 2000) led to HR-acceleration, one could assume that exposure to pain clips results in automatic mimicry of the facial expressions inducing an emotional state in the observer. On the other hand one could speculate that this effect of HR-acceleration reflects a defensive response mechanism elicited by the aversive pain clips. Since the effect was weak those are vague hypotheses that need to be further validated by gathering larger data sets.

The RR-interval's variability index reflected a general decrease in contrast to baseline for all conditions. The lack of face category specific effects supported the view that the response to all clips was equally mentally demanding.

Although some gender differences reflected by higher EDA to threat (electric shock) (Kopacz and Smith, 1971, cited in Boucsein, 1992) and increased HR to laboratory stressors (Fichera and Andreassi, 2000) have been reported in females, no such effects were detected in the present experiments.

Integrating the results of both experiments, one could conclude that the detected marginally significant results solely present in one of the two sessions do not reflect a meaningful response pattern, but variations between different samples. One could also assume that the differences of results between the experiments are very likely due to the characteristics of the settings. Thus, while participants of the first experiment were comfortably seated in a quiet room, subjects of the second experiment performed the task in a less comfortable and noisy scanning environment. Hence, one could argue that subjects in the first experiment were more relaxed from the beginning on, whereas the second sample might have entered the session with higher autonomic arousal. This view is favoured by the fact that more pronounced habituation effects and higher overall mental effort, reflected by decreased HR-variability, occurred during experiment II. While subjects in the scanner were exposed to a more challenging situation, developing expectation of the clips' affective content might have been less pronounced and therefore differential effects of face types could have been potentiated.

However, the overall weak effects are presumably due to the fact that subjects were distracted from the face clips and that clips were presented in a block design. However,

the few marginally significant differences between pain, anger and neutral suggested the need to gather larger data sets to further investigate these findings also in event-related presentation.

CONCLUSION

Implicit processing of facial pain expressions, partly due to habituation, resulted in overall weak effects. Regardless of the observers' sexes, the vicarious pain experience tends to elicit a defense rather than an orienting response. However, this is solely detected under more challenging conditions created by the scanner environment. This proposes a differential mechanism of autonomic responding to facial pain expressions in contrast to angry facial expressions.

5.3   Imaging Data

5.3.1   Summary

1.   Only a small part of the network known to be involved in emotional face processing, namely SI, SII/posterior insula and the STS region, showed sustained engagement during exposure of pain contorted and angry faces. However, in line with the hypothesis all proposed regions, namely amygdala, MPFC, ACC, anterior insula, SI, SII/posterior insula, FFA and STS were involved, showing either transient BOLD-increases or -decreases to those stimuli in dependence of the actors' sex.

2.   A stronger engagement of amygdala and the interconnected extrastriate areas (FFA and STS) to pain relative to angry faces could not be confirmed in the block-related analysis. However, for pain faces of male actors compared to angry faces of male actors such activation patterns were found.

3.   As expected, the STS region showed enhanced responses to both types of dynamic clips – anger and pain facial displays - in contrast to the rather static neutral face clips.

4.   Brain responses showed differential patterns mainly with respect to actors' but also regarding the observers' sex.

5.   In contrast to the hypothesis, no influence of pain catastrophizing tendency and the state anxiety level on the BOLD-response of proposed regions was detected. The activation in the left ACCad to male actors' expressing pain relative to neutral, however, showed marginally significant positive correlation with individuals' empathic ability. The BOLD-response in this ROI to female actors' pain faces relative to neutral resulted in marginally significant *negative* correlations with the empathy scores. Contrary to the expectations, no such covariations were found for the anterior insula and right ACCad.

6.   Low qualitative GSR-data acquired in experiment II and a lack of sustained activation in the a-priori ROIs made the intended analysis of relationship between BOLD-response and autonomic responses.

5.3.2 <u>Discussion</u>

5.3.2.1 *Amygdala*

While no activation of the amygdala was detected in the block design analysis of event-related data revealed engagement of this brain structure. Taking into account that subjects were distracted from the different facial expressions, the data of the event-related analysis is in line with studies that found stronger amygdalar responses in automatic, implicit than in explicit processing (e.g. Critchley et al., 2000a; Straube et al., 2004; but see Pessoa et al., 2002).

Interestingly, event-related analysis revealed an interaction between amygdala activation and the sex of the actor. Thus, bilateral activation of the amygdala in response to male expression of pain as compared to both neutral and angry faces occurred. In contrast, pain faces expressed by females produced *decreased* left-sided amygdala involvement relative to neutral faces. This opposite pattern observed to male and female facial expressions of pain was on the one hand explained by BOLD-decreases to female relative to male pain faces and on the other hand caused by an increase of activity to neutral faces of females in contrast to male neutral faces. The pattern was observed independently of the observer's sex, which was in contrast to a study that found stronger activity to threat-related stimuli in this region in female observers (McClure et al., 2004). This opposed pattern of activation to faces of male and female actors might have led to annihilation and explains the lack of significant results in the block design analysis.

Understanding a pain face as a signal of danger, the response to male expression of pain confirms previous findings that threat-related stimuli, especially fear faces, both static and dynamic, activate the amygdala (e.g. LaBar et al., 2003; Morris et al., 1998a). Although stronger habituation, as described in the literature (e.g. Phillips et al., 2001), was observed in the right amygdala still an enhanced right-sided response to males' pain was detected across time. This is in line with the right-hemisphere dominance hypothesis on emotional recognition (Damasio, 1994). The study by Botvinick and

colleagues (2005), in contrast, found sustained left-sided engagement of amygdala when observing clips of males and females expressing pain. Since the authors used a very liberal threshold $p<0.01$ (uncorrected) for this exploratory whole brain analysis, a comparison with the present data seems difficult.

The lack of a significant finding to angry faces in general as compared to neutral faces was as well in accordance with the inconsistent state of the current research on brain activation to angry faces. For instance, Kilts and colleagues (2003), also using dynamic stimuli of anger faces, failed to detect amygdalar engagement (but see Fischer et al., 2004a). Furthermore, the stronger response found to pain as compared to anger faces was consistent with the proposal that the amygdala responds more robustly when threat to the observer is uncertain, indirect or ambiguous (e.g. Adams et al., 2003; Whalen et al., 2001). The gaze of the actors in all stimuli of the present study was directed towards the observer. Hence, the threat conveyed by the anger expression might be considered less ambiguous. Observing another person expressing acute pain without knowledge about the source of pain, in resemblance to a fear face of direct gaze, might have been considered as more ambiguous and potentially threatening.

However, why were the same pain facial displays expressed by females not perceived as ambiguous threat? Interestingly, this interaction with the sex of the actor may relate to the different meaning that the facial expression of pain conveyed by males and females. Males are generally found to display less non-verbal pain expression than females in response to experimentally controlled acute pain (e.g. Sullivan et al., 2000). Hence, one could assume that observers are generally more used to females than to males expressing pain. This would be in line with studies demonstrating that health care professionals, i.e., people who often are exposed to pain expressions, tend to underestimate patients' pain (e.g. Solomon et al., 1997). Taking into account that the stimuli selected for this study were matched for intensity of facial expression, one could hypothesize that comparable male pain expressions may have signaled a more intense noxious stimulus and pain experience. From an evolutionary viewpoint one could also speculate that male expression of pain may be more strongly associated with situations of potential threat, and hence might produce a defense response more readily in the observer than female facial expressions of pain.

However, those explanations may not be sufficient to account for the reversed pattern produced by females' pain expressions as compared to neutral. The lack of amygdala response to this non-verbal pain behavior of females could then either be due to the fact that people are used to it or could even reflect a spontaneous top-down inhibition of the defense response. Such a response might possibly be associated with the promotion of helping behavior in situations of potential threat.

However, parallel to the weaker amygdala responses to females' pain faces, an increase of activity in this region was observed to female neutral faces. A possible explanation for this result stems from studies in children who were found to perceive still faces not as "socially neutral", but showed amygdala activation to them (Thomas et al., 2001). Developmental psychology reported the existence of the so called "still face phenomenon" investigated in children interacting with their mothers and strangers, which was in both cases characterized by a negative response within the child when the social partner suddenly showed a neutral face (Striano, 2004). Taking into account that gender of an actor influences the interpretation of the same emotional expressions (e.g. Plant, Hyde, Keltner and Devine, 2000; Plant et al., 2004) and that females are expected to display more emotions in general (e.g. Guinsburg et al., 2000) one could speculate that a female neutral face might have been perceived as unexpected and socially more salient than males' neutral faces. The contrast between the more dynamic facial displays (anger, pain) and the almost static neutral face might have additionally pronounced this effect. However, imaging research on this topic is still scant. Most studies on processing of emotional facial expressions did not provide data for the contrast neutral faces vs. baseline condition. One imaging study by Fischer and colleagues (2004b) investigated neural responses to male and female neutral faces using a block design. In contrast to the present data, the authors found stronger sustained involvement of the left amygdala to females' in contrast to males' neutral faces. The effect was, however, stronger in male observers, which was interpreted as mate-selection preferences. In line with this finding, Aharon and colleagues (2001) male observers' amygdala responded stronger to neutral faces of attractive females in contrast to both, attractive males and less attractive females. However, this was not investigated in a group of female observers.

Although actresses' attractiveness in the face clips seems to be average this has to be considered as an alternative explanation for the findings. Since no ratings of attractiveness were acquired in the present study this question has to remain open and should be investigated for further use of the stimuli set. Nevertheless, this explanation is still questionable since it seems unlikely that female observers also respond to an attractive female conspecific.

Another point that has to be highlighted is the data on calm vs. neutral face processing recently presented by Freed and colleagues (2004), as well as Tottenham et al. (2005). They reported increased amygdala response to neutral (severe) in contrast to calm (less eye-white, peaceful) faces in adults. People generally rated both stimuli as neutral when presented in isolation, but were able to distinguish them in a forced choice task. Hence, a systematic effect of this kind in females' vs. males' neutral faces can not be excluded and the stimuli set has to be further elucidated with respect to this question. One could even assume that gender stereotypes might have influenced the interpretation of the objectively similar neutral stimuli in terms of being perceived as more severe in female than male actors evoking the effect described by Tottenham and colleagues (2005).

Finally, one has to emphasize that the observed patterns and especially the gender difference can not simply be explained as an effect of arousal and valence as suggested by some studies (e.g. Winston et al., 2003a). As shown by the rating data of experiment II there was no difference between pain and anger face clips on this particular scale. Furthermore, according to the pre-experimental ratings, no difference in arousal with respect to the actor's sex was found. Additionally, motion-related influences of the clips' content on amygdalar responding seem unlikely. Although neutral faces clearly show less motion than pain and anger faces, both dynamic types of stimuli elicited different amygdala activation. However, although the clips met the criteria of standardization, there might still be slight differences between clips. Hence, for future studies, a physical measure of motion should be included for further validation of the stimuli set. Moreover, one might argue that pain faces could have been perceived as bizarre and thereby evoking a response in the amygdala (Rotshtein et al., 2001). However, this can not be considered as an alternative explanation since on the one hand the behavioral data confirm a high percentage of correct pain face identification and on

the other hand it seems questionable why objectively equivalent expressions (FACS coding) should be perceived as bizarre for male, but not for female actors.

Taken these findings together, male pain faces seem to be perceived as threat-relevant information and might, in line with the literature (e.g. Lang, Bradley and Cuthbert, 1997b; LeDoux, 2000), trigger an integrated response via amygdala's feedback modulation on sensory, motor and autonomic brain areas providing selective attention to these biologically salient stimuli.

Although less pronounced, female neutral faces also elicited amygdalar activation. This could, due to the mentioned reasons, reflect a response to behaviorally relevant facial expressions.

5.3.2.2 MPFC

The MPFC is known to be, inter alia, associated with cognitively-bound emotional responding to facial expressions (Phan et al., 2002). Subjects in the present study were not required to explicitly evaluate the face clips, but were distracted by a gender discrimination task. Thus, the overall observed MPFC deactivation (relative to the visual baseline) in both block and event-related analysis, which is not explained by habituation, is not surprising. These results are in line with studies examining the attentional modulation of MPFC activity by direct comparison of its engagement in explicit and implicit face processing (e.g. Winston et al., 2003a; Straube et al., 2004). These studies consistently failed to find MPFC involvement when subjects were distracted from the facial expression. In addition, considering the increased amygdalar involvement combined with decreased responding in MPFC to all clips relative to baseline, the proposed reciprocal relationship of MPFC and amygdala responses is confirmed (Hariri et al., 2000, 2003; Phan et al., 2002; Taylor et al., 2003).

However, due to less deactivation during perception of males' pain faces, a BOLD-increase in dMPFC was detected relative to angry faces. This effect and especially the gender difference can not simply be explained in terms of arousal (Dolcos et al., 2004) or valence, since pain and anger face clips do not differ in these aspects. Considering that biologically significant threatening signals seem to be able to modulate MPFC, one

might interpret this response to males' pain faces as part of an 'alerting' response triggering selective attention to those stimuli (LeDoux, 2000). Taking into account that the dMPFC has been shown to be engaged in studies on 'theory of mind' (for review: Frith and Frith, 2003), one could assume that subjects engage this area in order to understand the salience of facial expressions. This might have modulated the BOLD-response in the MPFC in terms of attenuating the decrease, which was observed relative to visual baseline and angry faces. However, the lack of an effect to pain faces of males in comparison to neutral faces contradicts this view. Further research has to validate and elucidate this finding.

The detected pattern seemed to apply to male and female observers similarly, since no differences in activation were detected on the part of the observer.

To summarize, data confirmed that the MPFC mainly seems to be involved in explicit processing of emotional facial expressions. However, particularly threatening stimuli, like male pain faces, might even elicit, via the described interconnections to other brain areas, MPFC engagement during implicit processing of these stimuli.

5.3.2.3   ACC

Sustained activation was neither detected for the affective nor for the cognitive division of the ACC. Thus, in contrast to studies on vicarious pain experience reporting activation of ACCcd during explicit (Jackson et al., 2005; Singer et al., 2004) or passive viewing (Botvinick et al., 2005; Hutchinson et al., 1999; Morrison et al., 2004), the present data does not support an automatic involvement of this area during distraction from pain faces. However, transient changes in BOLD-responses in the affective and the cognitive division of this area occurred as a function of actors' sex and the type of facial expression.

The exposure to male facial expressions of pain elicited stronger ACCad activation to neutral as well as to angry faces. These activations to males' pain resulted from stronger activation (right-sided) and from less deactivation (left-sided) in contrast to the remaining two categories of facial expressions. Viewing of both females' pain contorted and angry faces resulted in significant deactivations in this area, caused by stronger

increases to female actors' neutral faces. However, BOLD-responses to pain relative to angry female faces did not show significant differences.

These results and especially the detected gender effect can not simply be explained in terms of valence and arousal differences. Strikingly, the pattern of BOLD-responses in the affective division resembles the pattern observed in the amygdala characterized by stronger responses to male facial expressions of pain and female neutral faces. Since the ACCad is known to be associated with the unexpected processing of conflicts caused by emotional distractors (e.g. Keightley et al., 2003; Vuilleumier et al., 2001), the engagement of this region might reflect inhibition of attention towards these emotionally salient but task-irrelevant facial expressions. The lack of engagement to the pain nonrelated faces suggests that these stimuli might have been perceived as less distracting and salient.

On the side of the observer, sex differences in ACCad's activation were found. Male subjects, who generally showed sensitization to faces of female actors across the entire experiment, showed more pronounced activation to neutral female in contrast to females' pain contorted faces. In accordance to Fischer and colleagues (2004b), this could reflect males' mate-selection preferences and could have led to stronger emotional distraction by female neutral faces in male than in female observers.

For the cognitive division, only effects to faces of male actors were observed. Hence, stronger engagement of this region to pain in contrast to angry faces occurred. One could interpret this response in terms of error detection (Bush et al., 2000) or error prediction (Brown and Braver, 2005). However, the lack of performance differences between anger and pain runs counter to this explanation. One might also understand this finding as automatic mirroring of the vicarious pain experience (Botvinick et al., 2005; Hutchinson et al., 1999; Jackson et al., 2005; Morrison et al., 2004; Singer et al., 2004) to the more salient pain faces. Since an involvement of ACCcd was also found to males' angry in contrast to males' neutral faces (deactivation) - contradicting the idea of pain specificity - this seems unlikely. Thus, these results do not seem to reflect a meaningful pattern or at present, given the current literature, no sufficient explanation can be provided.

5.3.2.4 Anterior Insula

In accordance with the literature reporting involvement of the anterior insula mainly in explicit processing of emotional facial expressions (e.g. Anderson et al., 2003a), due to the attentional distraction no sustained activation for any of the face categories, compiled across actors' sexes, was found in this brain area. Thus, in contrast to studies on vicarious pain experience, which used either an explicit task (Jackson et al., 2004; Singer et al., 2004) or passive viewing (Botvinick et al., 2005), no evidence for an automatic engagement of this structure was observed during distraction from the pain faces. The lack of significant results of insular engagement to threat-relevant angry relative to neutral faces is in line with findings of Straube and colleagues (2004) who also failed to find activation of this region during implicit processing of static angry faces in healthy controls.

However, bilateral engagement was detected to males' pain faces relative to males' anger faces. Taking the behavioral ratings into account, this findings and the gender effect can not be explained by arousal or valence of clips. Considering the role of the anterior insula for the representation of bodily arousal states (for review: Critchley, 2003) and its engagement during implicit or even subliminal processing of biologically significant signals of threat (Liddell et al., 2005; Morris et al., 1998a; Straube et al., 2004), the implicit processing of male pain faces, perceived as threatening, might have via functional connection of the amygdala to this region (e.g. Keigthley et al., 2003) led to these results. This might reflect the process of integrating threat perception and bodily arousal states (Amaral et al., 1992). This detected effect might have been weakened by the habituation to males' pain observed in female observers and could possibly explain the lack of significant findings for males' pain faces relative to neutral faces. Thus, while the vicarious experience of pain, when explicitly processed or passively viewed, might evoke stronger responses in the anterior insula (Botvinick et al., 2005; Jackson et al., 2005; Singer et al., 2004), implicit processing solely seems to elicit this response to the most salient, namely to male pain faces. No such alerting response of the anterior insula was found to female faces.

These results seemed to occur similarly in male and female observers since effect of the observer's sex was not found.

5.3.2.5 SI

Since only a few imaging studies explicitly reported involvement of SI in processing of emotional faces during attentional distraction, an integration of the present findings into the literature proved to be difficult. A study that used a similar design as the one of this thesis, i.e. Winston and colleagues (2003a) presented static emotional faces under attentional distraction (gender decision). The authors did not find somatosensory activation to high- and low-intensity disgusted, fearful, happy or sad faces compiled across emotions and sex of the actor vs. a visual baseline condition. Botvinick and colleagues (2005) also did not report engagement of SI during passive viewing of facial pain expressions relative to neutral faces compiled across male and female clip targets. However, taking into account that clips of this study were excerpts from motion exercises with the affected limb by pain patients, the studies do not seem to be one-to-one comparable. While in line with these findings the present study did not detect right-hemispheric contribution of SI to automatic face processing, in contrast, a relative decrease of BOLD-responses to pain and anger faces against neutral faces was observed. However, an explanation of the findings is provided by data from the event-related analysis. Here, it becomes obvious that these right-sided increases and left-sided decreases, observed relative to baseline, crucially differ with respect to the face category and with respect to the actor's sex.

Contralateral to the motor response (left hemisphere), no significant differences between the face conditions were detected for male faces. In contrast, subjects showed differential responses in this hemisphere to female faces. Interestingly, again stronger responses to female still faces occurred. Hence, BOLD-response decreased to female angry, but not to female pain faces relative to neutral faces. This strong response to female neutral faces obviously led to the observed overemphasis of the neutral condition in the block-design.

The findings for the right hemisphere seem more puzzling. In contrast to the comparable responses to male faces on the contralateral side, differences in ipsilateral inhibition were found, which were weakest for pain faces. Thus, relative increases of somatosensory activation occurred relative to both neutral and angry faces, whereas it

was not different for angry as compared to neutral faces. To female faces, observers showed inhibition to both female pain and anger faces relative to female neutral faces.

For none of these contrasts, an effect of the observer's sex was found. Moreover, one has to emphasize the robustness of these findings, taking into account that in line with other studies habituation was observed bilaterally throughout the experimental procedure (Feinstein et al., 2002).

Since no study investigated sex differences of SI engagement in the processing of emotional facial displays, solely a hypothetical explanation of these findings can be given. Firstly, one could understand the pain-related involvement of this area to male faces as an evidence for sensory-discriminative encoding of the observed pain. However, considering the strong engagement of SI to neutral female faces in contrast to both emotional conditions questions such an explanation.

The observed pattern of significant responses to male pain faces and female neutral faces resembles the results found in other ROIs. Taking Adolphs' theory (2002) into account, one could understand SI engagement in terms of sensing the observed emotion by internal simulation or as 'mirror system' (Gallese and Goldman, 1998). This mechanism might be more crucial for biologically salient and/or ambiguous stimuli, which male pain and female neutral faces according to the data might constitute, than for the remaining face stimuli. According to Pourtois and colleagues (2004), this might occur at an early latency in the recognition of a visually presented emotion and even without involvement of the visual cortices (Liddell et al., 2005). As shown by Damasio and colleagues (2000), as well as by Pourtois and colleagues (2004), recognizing ambiguous facial expressions (e.g. fear) requires stronger activation of the right somatosensory system, whereas this is not the case for happy faces. In line with this theory, exclusively right-sided engagement to male facial pain expressions was detected, however, engagement associated with female neutral faces occurred bilaterally. Given the poor database on SI engagement in the automatic processing of emotional facial expressions, the reason for the detected lateralization of BOLD-responses remains unclear. One could simply assume distinct cortical maps of activation and deactivation characterizing different emotions, as previously shown by Damasio

and colleagues (2000) in a study on recall of emotion. However, these hypotheses remain to be elucidated by future research.

5.3.2.6 SII

In line with the expectations, a sustained left-hemispheric involvement of SII/posterior insula in the processing of pain contorted relative to angry faces was found. This pattern did not differ between male and female observers. This stronger response to the ambiguous in contrast to the unambiguous stimuli was in accordance with a study by Whalen and colleagues (2001). The authors, also using a block design, reported signal increases in both posterior insulae during passive viewing of static fear relative to angry faces, while this was not observed in contrast to neutral facial expressions. Botvinick and colleagues (2005) as well detected bilateral responses in the posterior insulae to pain contorted faces, however in contrast to neutral faces. This deviation from the present findings might be explained by the fact that these authors used a more liberal threshold. However, the results contradict the results of Winston and colleagues (2003a) who found somatosensory activation solely during explicit in contrast to implicit processing of emotional face pictures. One has to note that they report their results as a compiled activation across all emotions instead of comparing them between facial categories. Thus, a one-to-one comparison to the findings of the present thesis is not possible.

Moreover, distinct patterns of transient activation with regard to the type of facial expression and the actors' gender were detected. On the one hand male pain contorted faces elicited stronger bilateral activations in the vicinity of the SII/posterior insula relative to angry faces. On the other hand, significantly smaller BOLD-responses to female pain and angry faces relative to female neutral faces were observed bilaterally. The effect of stronger responses to neutral female faces relative to female pain faces was especially pronounced in male observers' left hemisphere.

Similarly to the results in SI, understanding the pain-related engagement of this area to male faces as intensity coding of the observed pain seems unlikely, considering the

strong engagement of SI to neutral female faces in contrast to both emotional conditions.

Strikingly, again the pattern of stronger responses to male pain faces and female neutral faces occurred, not weakened by the generally observed bilateral habituation. In line with the findings in the previous section and based on the interconnection of SI and SII/posterior insula one could assume that this activation pattern reflects the somatic representations derived from internal simulation of those salient stimuli (Adolphs, 2002). However, the lack of studies investigating somatosensory (incl. posterior insula) involvement in automatic processing of ambiguous faces with respect to sex differences underlines the need for future research to validate this result.

Increased left-sided responses to female neutral faces by male observers might be explained in terms of mate-selection preferences confirming the data of Fischer and colleagues (2004b). The described right-sided habituation to female faces in general, as well as left-sided signal attenuation to female angry faces in particular, being detected in male observers only properly explains the left-lateralized responses in contrast to female angry, but not female pain contorted facial displays.

5.3.2.7   FFA & STS

Although automatic processing of pain, anger and neutral faces led to sustained BOLD-increases in FFA, activity in this region did not differ between the three facial categories. According to the literature, activation of this area, known to be associated with face recognition (e.g. Kanwisher et al., 1997), is modulated by the valence of facial expressions and the attentional focus during face processing (e.g. Pessoa et al., 2002). Although pain faces and anger faces had been judged as more unpleasant than clips of neutral faces, implicit processing of pain faces and angry faces did obviously not yield differential FFA activation, when investigation was done compiled across sex. However, taking the gender into account, transient BOLD-increases to male pain faces relative to both neutral and angry faces were revealed on the one hand. On the other hand, comparing female angry and neutral faces indicated a significant deactivation in the face area, due to enhanced responding to neutral faces. Considering that female

neutral faces were rated as less unpleasant than male pain faces, but evoked similar responses in FFA, a simple interpretation of findings in terms of valence-related effects seems unlikely. Hence, one might rather understand this extrastriate involvement as a response to emotionally salient face stimuli. This response might have been potentiated by feedback influences of the amygdala (Amaral et al., 1992), where the same pattern of activation was observed. Moreover, male facial expressions of pain seem to be equally salient for male and female observers, which was not the case for female pain faces. They solely elicited stronger FFA activity (relative to anger) in the same-sex group – namely in female observers.

The STS, known to be in charge of processing variant aspects of faces and evaluation of the relevance of social signals (Allison et al., 2000), showed sustained bilateral engagement to both, pain and anger clips, in contrast to clips displaying neutral faces. These patterns were observed in both male and female observers. Considering that dynamic stimuli elicit stronger STS activation than static pictures (Kilts et al., 2003), and that neutral clips of the present study contained less facial movement, this response could reflect mere processing of motion. This might also characterize evaluation of socially relevant stimuli, suggesting that faces of pain and anger are equally relevant to the observer.

However, taking the gender of the actor into account, transient BOLD-increases, in line with the findings and explanation stated above, were found to male and, although to a lesser extent, to female pain faces as compared to neutral faces. Remarkably, male pain faces as compared to male anger faces additionally showed enhanced involvement of STS which was even more pronounced in female than in male observers. This specific effect to pain faces expressed by males could reflect a modulatory feedback influence of the amygdala (Amaral et al., 1992), showing the same response pattern to this kind of stimuli. For female pain faces such an effect was not observed suggesting that, although these faces were obviously more socially relevant than neutral faces, they were not perceived as salient as male pain faces. While the comparison of angry and neutral faces expressed by females did not yield transient BOLD-changes in STS, enhanced engagement of this area was detected for male angry faces (relative to neutral) in the

group of male observers. Thus, male angry faces seem to be more socially relevant for male than for female observers.

To summarize these results, pain expressed by male faces, in line with the findings for other ROIs, evoked stronger visual processing and evaluation by the extrastriate areas FFA and STS, possibly mediated by amygdalar interconnections with these regions. Moreover, enhanced extrastriate engagement was also found to female neutral faces. However, this was only demonstrated in FFA and not in STS, possibly due to the fact that the latter region is more strongly associated with the processing of variant face aspects than neutral faces.

5.3.2.8 Correlation with Personality Variables

In contrast to the expectations, only marginal significant correlations between empathy scores and left ACCad's response to male and female pain faces occurred. While Singer et al. (2004) had previously observed that activity in the left anterior insula and ACCad significantly covaried with empathy scores, Jackson et al. (2005) did not find such a co-variation, supporting the present results. Considering that participants of Singer and colleagues' study (2004) were only females and taking into account that females are known to show higher scores on empathy scales than males (Davis, 1980; Mehrabian et al., 1988), their results could be a specific characteristic of the sample chosen. This might also explain the lack of significant correlations in the study by Jackson and colleagues' (2005), as well as the weak findings in the present study, which both used mixed samples.

While a study by Bishop and colleagues (2004b) suggested a modulatory influence of subjects' state anxiety levels on amygdalar responding to threatening stimuli, no clear effect of this kind was found to pain faces, considered to be threat-relevant face stimuli. The weak correlation of right-sided amygdalar responses to female pain faces with subjects' anxiety levels seems not to constitute a robust result and has to be validated with the help of a larger sample.

Moreover, BOLD-responses in neither of the ROIs were associated with subjects' pain catastrophizing tendencies. This might be due to the fact that the PCS-scores were not clinically relevant. Hence, a significant interaction with perception of painful faces is unlikely and should be investigated in comparison to high- and low-catastrophizers in future research.

Finally, one could assume that the overall weak effects might be explained by the fact that nonparametric correlations are generally less sensitive than parametric correlations (Pearson product moment correlation coefficient). Future research should investigate these questions by using larger samples in order to be able to use more sensitive statistics.

CONCLUSION

Automatic processing of facial pain expressions solely resulted in sustained engagement of the somatosensory cortices and the extrastriate area STS. However, event-related engagement to male pain faces was robustly observed in the amygdala, MPFC, ACCad, anterior insula, somatosensory cortices and extrastriate areas. These findings do not reflect a non-specific response to the perception of an emotional expression, but are specific to male facial expressions of pain, whereas no such effect is detected for female pain faces.

In some of those areas - namely the amygdala, ACCad, somatosensory cortices and FFA - enhanced responses to female still faces, although to a lesser extent, occurred.

All results were mainly independent of the measured personality variables, except for some marginally significant covariations that occurred in the left ACCad (with empathy) and the right amygdala (with state anxiety).

5.4   Summary and Integration of Results

A vicarious pain experience by observing pain-relevant cues can on the one hand signal a potential threat in the onlooker's surrounding and/or on the other hand elicit solicitous behavior (Williams, 2002). The facial expression of pain is the most prominent non-verbal pain behavior. Hence, it is the ideal interface between another person's pain experience and the induction of a mental model of this person's state in the observer.

Thus, the facial expression of pain has recently been used in the investigation of 'pain empathy' (Botvinick et al., 2005). Researcher in this field assume that the neural basis of this mind state is characterized by an overlap of brain responses to experimental pain and responses associated with observed pain (e.g. Singer et al., 2004). Without exact knowledge about this process of pain recognition from the facial display, which might vary with the experimental task requirement, examining such high-level cognition based on these comparisons seems adventurous. Hence, the present thesis steps back and endeavors to quantify the mechanisms of mere recognition of pain from facial expressions and to determine its distinctness in contrast to another threat-relevant facial expression.

This is the first imaging study investigating automatic processing of prototypical facial pain expressions. Supporting the idea that the facial expression of pain is unique and distinct from the expression of basic emotions (Williams, 2002), the presented pain faces generally seem to be reliably recognizable. In resemblance to fear faces of direct gaze (Adams et al., 2003), the presented pain faces seem to constitute an ambiguous threat to the observer.

In line with this interpretation, clips of pain faces consistently resulted in stronger arousal and unpleasantness ratings relative to neutral faces, as well as to anger faces (except for experiment II). Pain faces even elicited stronger feelings of arousal and unpleasantness in the observer and resulted in higher error rates in the gender discrimination task. The error number, however, did not differ between pain and angry clips (except for experiment I).

While the block-related presentation of facial pain expressions did not imply activation of the neural circuit known to be engaged in vigilance and warning (Whalen, 1998) under attentional distraction, transient threat-related responses to male pain faces

occurred in the whole matrix of areas investigated in this thesis. This network comprised the amygdala, MPFC, ACCad, anterior insula, somatosensory cortices, as well as the extrastriate areas FFA and STS.

These findings for all reported areas can be integrated into an explanatory model reflecting an alerting response to threat-relevant stimuli. The proposed model has to be considered as hypothetical and might constitute a basis for future research.

Hence, exposure to different kinds of facial expressions results in the visual analysis of the facial display by the occipotemporal core system of face recognition (Haxby et al., 2000, 2002), comprising the extrastriate areas FFA and STS. In concert with this visual analysis, recognition of male pain faces seems to rely also on the engagement of somatosensory cortices. Activation of these areas possibly reflect the construction of a mental model of the other individual's state in the observer (Damasio, 1999), which seems to be more crucial for salient and ambiguous stimuli. The somatosensory cortices are known to project to the posterior and anterior insula (Friedman, Murray, O'Neill and Mishkin, 1986). This highly processed sensory input from the visual and somatosensory cortices presumably reaches the amygdala, the ROI that shows the described pattern most robustly. Hence, the amygdala might have been continuously updated with information about identity, the expressions' content and its social communicative value. The amygdala, capable of determining the potential threat emanating from sensory events, could have in turn, facilitated the processing of the stimuli being perceived as biologically relevant or even threatening via its back projections (LeDoux, 2000). Favouring this view, enhanced responses in visual and somatosensory cortices to male pain faces were observed. However, considering that the cortex and the amygdala are simultaneously activated by thalamic inputs, amygdalar modulation of the cortex might have even started before sensory information was fully processed by cortical areas (LeDoux, 2000).

The anterior insula also receives input from the amygdala (Amaral et al., 1992) and is engaged in the integration of threat perception and bodily arousal states (Critchley, 2003). Hence, the enhanced activation of this structure could reflect monitoring of the bodily arousal changes associated with those stimuli (Damasio, 1999). Although automatic processing of facial pain expressions resulted in overall weak autonomic responses, the vicarious pain experience tended to elicit a defense response in

experiment II. One could hypothesize that this effect is mainly due to internal bodily changes associated with the exposure to male facial expressions of pain, probably weakened by the block-related analysis. However, this effect remains to be elucidated by event-related analysis of such autonomic measures.

Furthermore, the amygdala sends projections to the anterior cingulate and MPFC cortex (Amaral et al., 1992). In consideration of task requirements, the engagement of those areas could be interpreted as top-down modulation of the emotional responses generated by the amygdala.

This overall response pattern was detected in male and female observers independent of personality variables, RT, and conducted errors and can not simply be explained by arousal and valence of the face clips.

Astonishingly, no such effect was found to female pain faces, which solely elicited stronger responses in extrastriate areas. However, the observed engagement of STS was found not to be pain-specific and involvement of the FFA region was solely evoked in female observers.

Taken together, these results indicated that the pattern of activation to facial pain expression is (1) induced by male facial displays, (2) can not be explained by a non-specific response to the perception of emotional expression, (3) is found in both male and female observers and (4) is robust across time. These possibilities suggest important sex differences in the cultural function of pain communication.

Remarkably, although less pronounced, in some of those areas - namely the amygdala, ACCad, somatosensory cortices and FFA - also enhanced responses to female still faces occurred. As stated in section 1.3.2.1. female neutral faces also seem to constitute salient stimuli that might conflict with task requirements. However, in contrast to male pain faces they obviously do not evoke bodily arousal as reflected by a lack of autonomic responses, as well as anterior insula's engagement.

Taken together, these findings imply that the engagement of the reported areas to still faces is (1) induced by female facial displays, (2) found in both male and female observers and hence might not simply be explained by actor's attractiveness and (3) is robust across time. This finding proposes sex differences in expectations on facial expressivity prompted by gender stereotypes. However, methodological reasons that

might have contributed to this effect need to be systematically examined in future research (see section 5.5).

Hence, in contrast to passive viewing of pain in others as examined by Botvinick and colleagues (2005), implicit processing of pain faces compiled across actors' sex does not elicit activation of the anterior insula and ACCcd. All studies on vicarious pain experiences that reported these activations used an explicit or a passive viewing task. Thus, the hypothesized mirroring mechanism characterized by an activation of areas associated with the affective-motivational component of pain, seems crucially to depend on the attentional focus of the task. In line with the literature, involvement of those areas has been more strongly associated with explicit processing (Phan et al., 2002). The presence of experimental pain conditions in some of those studies (e.g. Botvinick et al., 2005) might have, even under passive viewing conditions, led to a more conscious perception of the vicarious pain.

Although male pain faces evoked transient activation of the anterior insula, as well as of areas associated with the sensory-discriminative component of pain (SI, SII/posterior insula), the fact that these responses are accompanied by strong amygdalar engagement rather points to an alerting response than to an internal simulation of the pain. Moreover, the observed somatosensory activation to female neutral faces additionally runs counter to such an explanation.

Reconciling Botvinick and colleagues' findings (2005) of only weak amygdalar involvement to male and female pain faces with the findings of the present study, one could assume that threat-related response to pain faces seem to be modulated by attention and the contextual information provided. Hence, one could hypothesize that such activation patterns to facial expressions of pain, especially to the obviously more salient male pain faces, are likely when detailed stimulus analysis is hindered by the experimental conditions.

This study quantifies the process of mere recognition of facial expressions of pain and hence might provide a basis for the understanding of the mental representation of pain and the communication of this fundamental experience. These present findings might

further contribute to the advancement of research into the emerging field of the social neurosciences.

5.5   <u>**Future Directions**</u>

In line with the research on facial expressions of pain (Williams, 2002), the present study revealed that people are generally able to recognize pain from prototypical facial expressions. However, there was a small number of subjects that recognized, besides pain, also a blend of other emotions in facial pain expressions. Hence, it was assumed that these stimuli, presented without any contextual information, might also convey some ambiguity. In order to further investigate the conditions that support a clear recognition of facial pain displays one could parametrically modulate the degree of contextual information given to subjects (e.g. via stories, changes of clip background).

Evolutionary theories propose that the facial expression of pain following acute injury might play a role in survival by alarming others in situations of immediate threat and/or by eliciting helping behavior towards the individual experiencing pain (Williams, 2002). In general infants have been described to be able to discriminate facial features early in life (Nelson and de Haan, 1997). To further examine whether pain faces, in line with such theories, are already recognized in early childhood, behavioral ratings of adults to such stimuli should be compared with those of young children.

The data moreover implicated that although neutral and facial pain expressions objectively imparted the same information to the observer (FACS-coding), it was probably not encoded independently of gender stereotypes. In order to directly investigate this question, one could create two versions of a pain- and two versions of a neutral face by adding masculine and feminine hairstyle and clothing with the help of virtual makeover (see Plant et al., 2004). Those face stimuli would be identical regarding the facial expression, but not regarding the actors' sex and would hence be ideal to answer these questions using behavioral, as well as physiological measures.

In order to further elucidate the effect found to female neutral faces, the data set should be validated with respect to the question, whether systematical differences in terms of attractiveness (Aharon et al., 2001) and calmness (Tottenham et al., 2005) existed between male and female facial displays. Moreover, the whole set of clips should be further validated by a physical measure to be more properly able to control for motion related differences between the emotional stimuli.

Implicit processing of male pain faces elicited an alarming response in male and female observers. In order to further investigate facial pain displays' potential to trigger rapid processing via the fast amygdalar path one could incorporate these stimuli into an imaging experiment using a masking paradigm (Liddell et al., 2005; Whalen et al., 1998b). Additionally, one should include autonomic measures in a way that allows for event-related analysis of these responses by using greater ISIs between clips (Lim et al., 1997). Furthermore, in order to test whether this alerting response was due to the expressions content or simply to the ambiguity caused by the direct gaze, one should compare BOLD-responses to facial pain expressions of both averted and direct gaze (see Adams et al., 2003).

Moreover, the data implicated that the observed somatosensory engagement reflects simulation of the targets' emotional state. In order to address this question more directly, one could determine the observers' facial movement with the help of electromyography (EMG). One could also conduct a more detailed spatial analysis of somatosensory activation in a somatotopic manner. One could assume that simple mimicry of facial expressions would result in activation of the participant's somatosensory face area, whereas simulation of the other person's state might result in activation of the body part affected by the pain (e.g. "The displayed person hurt his/her left foot").

Reconciling the findings of previous studies on vicarious pain experience (Botvinick et al., 2005; Hutchison et al., 1999; Jackson et al., 2005; Morrison et al., 2004; Singer et al., 2004) with the results of the present thesis, one can assume that 'mirroring' might only occur when the attentional focus is explicitly directed to the facial expression of

pain. However, it remains unclear whether the observed activation reflects a mirror response of the affective dimension of pain or whether it is simply a non-specific affective response to salient stimuli. In order to answer this question, one should compare explicit processing of pain faces to other emotions in order to be able to test the pain specificity. Moreover, one could vary the intensity of pain contorted faces while subjects focus their attention to those stimuli in order to determine whether the proposed 'empathic response', mediated by the insula and ACCcd, turns into an alerting response.

Finally, it would be interesting to investigate the recognition of pain faces in populations of subjects known to have an impairment in the processing of facial expressions – namely psychopaths (e.g. Blair et al., 2001) and autistic people (e.g. Critchley et al., 2000b).

Appendix

A. Questionnaires – Means, Standard Deviations and Norms

A-I. Interpersonal Reactivity Index – IRI

Table A-I: Sample results for the IRI-subscales. Bold numbers are the mean and SD for male and female subjects of both samples displayed for experiment I and experiment II. Male and female norms for the subscales are provided in squared brackets (Davis, 1980).

IRI subscales		Males			Females		
		Exp. I	Exp. II		Exp. I	Exp. II	
Perspective	*mean*	**19.40**	**19.38**	[16.78]	**19.07**	**18.67**	[17.96]
Taking	*SD*	**(6.0)**	**(4.5)**	[4.7]	**(5.2)**	**(4.7)**	[4.9]
Empathic	*mean*	**21.50**	**19.13**	[19.04]	**22.79**	**22.56**	[21.67]
Concern	*SD*	**(2.9)**	**(2.6)**	[4.2]	**(4.3)**	**(3.5)**	[3.8]

Exp. I= experiment I; Exp. II= experiment II

A-II. Balanced Emotional Empathy Scale – BEES

Table A-IIa: Sample results for the BEES-scale. Bold numbers characterize the z-scores observed in the sample of subjects (n=17) during experiment II. Norms of z-scores and corresponding percentiles are provided for comparison (taken from the BEES manual, Mehrabian, 2000).

z-score subjects		z-score norms	percentil-score	label
		2.5	99.4	*Very extremely high*
		2.0	98	*Extremely high*
		1.5	93	*Very high*
1.6	*Very high*			
1.6	*Very high*			
1.7	*Very high*			
		1.0	84	*Moderately high*
1.4	*Moderately high*			
1.4	*Moderately high*			
		0.5	69	*Slightly high*
0.5	*Slightly high*			
0.7	*Slightly high*			
0.8	*Slightly high*			
		0.0	50	*Average*
-0.4	*Average*			
-0.3	*Average*			
-0.2	*Average*			
-0.2	*Average*			
-0.2	*Average*			
-0.1	*Average*			
0	*Average*			
		-0.5	31	*Slightly low*
		-1.0	16	*Moderately low*
-1.3	*Moderately low*			
-1.2	*Moderately low*			
		-1.5	7	*Very low*
		-2.0	2	*Extremely low*
		-2.5	0.6	*Very extremely low*

Table A-IIb: Sample results for the BEES-scale with respect to the subjects' gender. Males' (n=8) and females' (n=9) empathy and corresponding z-scores (experiment II) related to a label derived from Mehrabian's gender norms (Mehrabian, 2000).

z -score	BEES-score	label

males

z -score	BEES-score	label
-0.4	17	
0.2	35	
0.3	37	*Average*
0.4	41	
0.4	41	
0.5	42	*Slightly high*
1	57	*Moderately high*
2	85	*Extremely high*

females

z -score	BEES-score	label
-2.1	15	*Extremely low*
-0.9	41	*Slightly low*
-0.8	44	
0.1	62	*Average*
0.2	65	
0.9	78	*Slightly high*
0.9	79	
1.1	83	*Moderately high*
1.1	83	

A-III. State Trait Anxiety Inventory - STAI

Table A-III: Scores of male and female observers on the STAI subscales measuring state (STAI state) and trait anxiety (STAI trait) as observed in experiment I and II (mean and SD displayed).

	STAI scales	Males		Females	
		Exp. I	Exp. II	Exp. I	Exp. II
STAI	*mean*	43.90	42.38	43.14	45.67
State	*SD*	(5.5)	(2.9)	(4.7)	(2.9)
STAI	*mean*	47.50	45.13	45.79	45.89
Trait	*SD*	(6.6)	(4.1)	(4.2)	(4.1)

Exp. I= experiment I; Exp. II= experiment II

A-IV.   Pain Catastrophizing Scale - PCS

Table A-IV: Scores of male and female observers on PCS (total score & subscales) as observed in experiment I and II (mean and SD displayed).

	PCS scales	Males		Females	
		Exp. I	Exp. II	Exp. I	Exp. II
PCS	*mean*	**20.50**	**17.00**	**25.21**	**18.90**
total	*SD*	(11.9)	(9.3)	(9.9)	(9.6)
PCS	*mean*	**8.7**	**7.4**	**10.9**	**7.9**
rumination	*SD*	(4.4)	(3.7)	(4.2)	(4.5)
PCS	*mean*	**3.2**	**4.0**	**5.1**	**3.2**
magnification	*SD*	(3.0)	(2.6)	(2.1)	(2.7)
PCS	*mean*	**8.6**	**5.5**	**9.3**	**7.8**
helplessness	*SD*	(5.6)	(4.3)	(5.1)	(4.4)

Exp. I= experiment I; Exp. II= experiment II

A-V. Behavioral Ratings of Facial Expressions
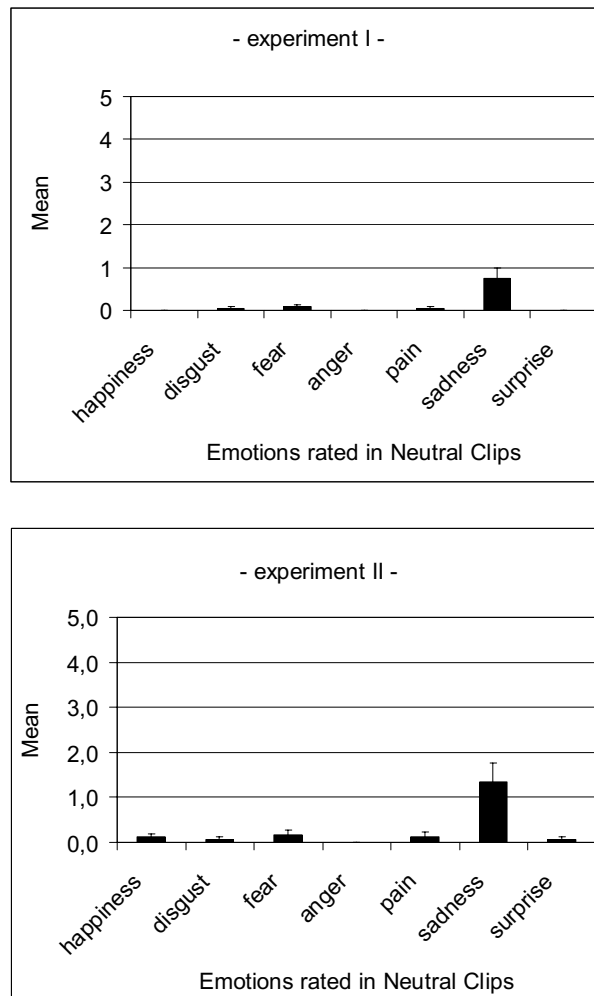
Figure A-Va: Contamination of neutral clips with other emotions observed in experiment I and II (mean±se).
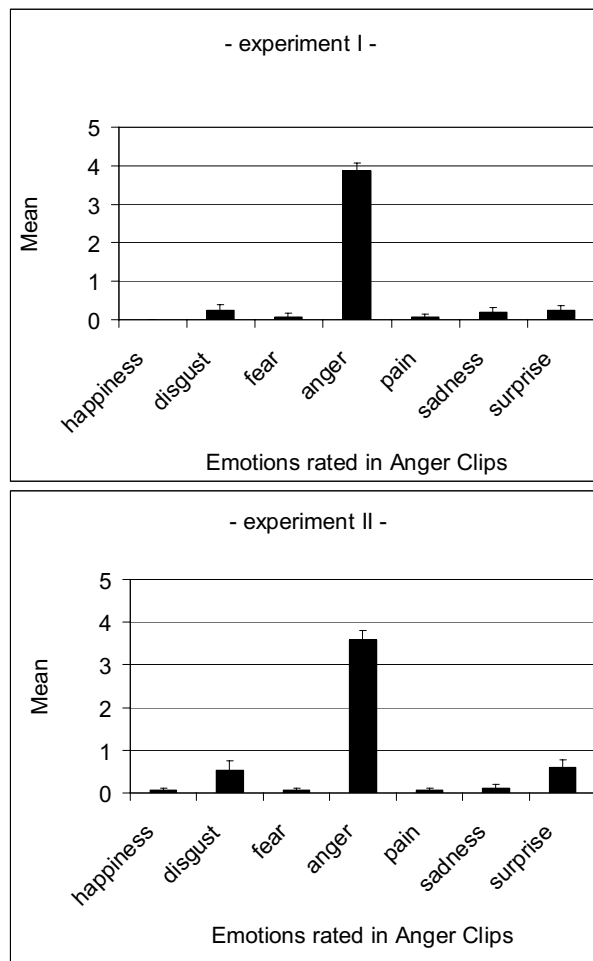
Figure A-Vb: Contamination of anger clips with other emotions observed in experiment I and II (mean±se).

B. <u>Imaging Results</u>

B-I. Summary of effects in AMY & MPFC

Block design

All observers	Male observers	Female observers	Male > Female observers
AMY			
All actors	*All actors*	*All actors*	*All actors*
P - N	P - N	P - N	P - N
A - N	A – N	A – N	A – N
P - A	**P-A -** l (-5.7)	P - A	P - A
MPFC			
All actors	*All actors*	*All actors*	*All actors*
P - N	P - N	P - N	P - N
A - N	**A – N (5.8$^\#$)**	A – N	A – N
P - A	P-A	P - A	P - A

Event-related design

Male observers	Female observers	Male > Female observers
AMY		
Male actors:	*Male actors*:	*Male actors*:
P-N - b (12.31 / 5.12$^\#$)	**P-N -** r (6.35)	P - N
A - N	A - N	A – N
P-A - r (5.09$^\#$)	**P-A -** l (5.16$^\#$)	P - A
Fem actors:	*Female actors*:	*Female actors*:
N – P - b (4.95$^\#$ / 6.58)	P - N	P - N
N – A	A– N	A– N
P - A	P - A	P - A
Male actors > Fem actors	*Male actors > Fem actors*	*Male actors > Fem actors*
P – N - b (8.48 / 6.20$^\#$)	**P – N -** r (5.31$^\#$)	P - N
A - N	A - N	A – N
P – A - b (4.70$^\#$ / 4.56$^\#$)	P – A	P - A
MPFC		
Male actors:	*Male actors*:	*Male actors*:
P-N	P-N	P - N
A - N	A - N	A – N
P-A	P-A	P - A
Fem actors:	*Female actors*:	*Female actors*:
P-N (-9.01)	P - N	P - N
A - N	A– N	A– N
P - A	P - A	P – A
Male actors > Fem actors	*Male actors > Fem actors*	*Male actors > Fem actors*
P – N (10.16)	P – N	P – N
A - N	A - N	A – N
P – A	P – A	P - A

AMY=Amygdala, MPFC=medial prefrontal cortex (including medial parts of BA9, 10) for male, female and male vs. female observers; highlighted in grey are contrasts that showed activation in the ROI for $p<0.005$ uncorrected; side of activation (b=bilateral; r=right / l=left) and t-values displayed; $^\#$Regions which did not meet extent threshold.

B-II. Baseline Contrasts (peak voxels) - AMY & MPFC

All observers		
All actors (≈ block design)	*AMY*	*MPFC*
Pain-Baseline	**3.52 / 1.84**	**-5.14**
Anger-Baseline	**3.44 / 2.71**	**-3.75**
Neutral-Baseline	**2.05 / 1.65**	**-3.98**
Male actors (event-related design)		
Pain-Baseline	**7.10 / 3.76**	**-1.92**
Anger-Baseline	**0.56 / 0.93**	**-4.55**
Neutral-Baseline	**-1.10 / 1.30**	**-1.84**
Female actors (event-related design)		
Pain-Baseline	**1.06 / 1.43**	**-3.18**
Anger-Baseline	**4.73 / 4.34**	**-1.62**
Neutral-Baseline	**7.76 / 7.06**	**-1.28**

AMY=amygdala and MPFC=medial prefrontal cortex (including medial parts of BA9, 10) for all observers; highlighted in grey are contrasts that showed activation in the ROI for $p<0.005$ uncorrected; t-values are displayed for right-sided / left sided part of AMY.

B-III.   **Summary of effects in SI, SII/pINS, aINS and ACC**

Block design

Male observers	Female observers	Male > Female observers
SI		
All actors	*All actors*	*All actors*
P - N	P - N	P - N
A - N	A - N	A - N
P-A	P - A	P - A
SII/pINS		
All actors	*All actors*	*All actors*
P - N	P - N	P - N
A - N	A - N	A - N
P - A	P – A - l (6.5)	P - A
aINS		
All actors	*All actors*	*All actors*
P - N	P - N	P - N
A - N	A - N	A - N
P - A - r (5.2)	P - A	P - A
ACC		
All actors	*All actors*	*All actors*
P – N - l (-5.0[#])	P - N	P – N
A - N	A - N	A - N
P - A	P - A	P - A

SI=primary somatosensory cortex, SII/pINS=secondary somatosensory cortex and posterior insula, aINS= anterior insula, ACC=anterior cingulate gyrus (ad=affective division, cd=cognitive division) for male, female and male vs. female observers; highlighted in grey are contrasts that showed activation in the ROI for p<0.005 uncorrected. Side of activation (b=bilateral; r=right / l=left) and t-values displayed; [#]Regions which do not meet extent threshold (same legend applies to the event-related table on the next page).

Event-related design

Male observers	Female observers	Male > Female observers
SI		
Male actors P − N - l (10.0[#]) A - N P − A - l (4.5[#])	*Male actors* P − N - r (4.8[#]) A - N P − A - r (7.3)	*Male actors* P − N A - N P - A
Female actors P − N - b (-6.3/-6.1[#]) A − N - b (-12.5 / -6.8) P - A	*Female actors* P − N - r (-4.4[#]) A − N - b (-4.9 / -5.9[#]) P - A	*Female actors* P − N A - N P - A
Male actors > Fem actors P − N- b (5.3 / 7.9) A − N - L (5.3[#]) P − A	*Male actors > Fem actors* P − N - r (4.6[#]) A − N - r (9.0[#]) P − A - r (5.2)	*Male actors > Fem actors* P − N A − N P − A
SII/pINS		
Male actors P − N - l (5.3[#]) A - N P − A - b (5.0 [#]/ 11.5)	*Male actors* P − N A - N - l (-6.2[#]) P − A - b (5.5[#] / 8.0)	*Male actors* P − N A − N P - A
Female actors P − N - B (-4.6 [#]/-9.9) A − N B (-8.4 / -9.2) P - A	*Female actors* P − N - l (-4.3[#]) A - N P - A	*Female actors* P − N - l (-5.2) A - N P - A
Male actors > Fem actors P − N - l (5.9) A − N - l (5.6[#]) P − A	*Male actors > Fem actors* P − N - l (5.5) A - N P - A	*Male actors > Fem actors* P − N A − N P − A
aINS		
Male actors P - N A - N P - A (5.4[#] / 5.4[#])	*Male actors* P - N A - N - l (-4.6[#]) P −A - l (9.2)	*Male actors* P - N A - N P - A
Female actors P - N A − N − b (-8.0 / -7.9) P - A	*Female actors* P - N A - N P - A	*Female actors* P − N A - N P - A
Male actors > Fem actors P − N - r (6.6[#]) A - N P - A	*Male actors > Fem actors* P - N A - N P − A - l (5.1[#])	*Male actors > Fem actors* P - N A - N P − A
ACC		
Male actors P − N - r (5.1) A - N P- A - r (6.6[#])	*Male actors* P - N A - N - b (-7.0 / -7.6) P- A - b (7.5 / 6.5)	*Male actors* P - N A - N P- A
Female actors P − N - b (-9.9 / -6.6) A - N - b (-5.1 / -5.3) P - A - r (-5.5[#])	*Female actors* P - N A - N P - A -l (-5.1[#])	*Female actors* P − N - r (-4.5) *ad* A - N P - A
Male actors > Fem actors P − N - b (7.3 / 5.2[#]) A - N P − A - b (6.1[#] / 6.0[#])	*Male actors > Fem actors* P − N - l (4.4[#]) A - N P − A - b (6.2 / 4.9[#])	*Male actors > Fem actors* P − N - r (4.8) *ad* A - N P − A

B-IV. Baseline Contrasts (peak voxels) - SI, SII/pINS, aINS and ACC

All observers				
All actors (≈ block design)	*SI*	*SII/pINS*	*aINS*	*ACC*
				ad / ad; cd
Pain-Baseline	-5.98 / 2.88	0.22 / 2.62	1.32 / 2.09	-3.23 / -2.04 ; 1.20
Anger-Baseline	-4.07 / 3.90	-1.01 / 1.09	0.40 / 0.70	-2.33 / -2.18 ; 2.37
Neutral-Baseline	-3.89 / 4.05	-0.12 / 1.73	0.36 / 2.49	-1.07 / -1.08 ; 1.90
Male actors (event-related design)				
Pain-Baseline	-0.38 / 1.48	6.17 / 6.42	2.81 / 3.77	3.37 / -0.36 ; 6.23
Anger-Baseline	-4.76 / 2.59	0.15 / 0.82	-0.27 / -0.85	-1.32 / -1.62 ; 0.63
Neutral-Baseline	-2.54 / 2.22	2.50 / 1.68	0.84 / 2.16	0.05 / -1.04 ; 4.44
Female actors (event-related design)				
Pain-Baseline	-1.74 / 2.91	1.05 / 3.18	1.51 / 2.56	-1.77 / -2.05 ; 2.11
Anger-Baseline	-1.26 / 0.60	2.59 / 3.12	1.71 / 3.14	-0.37 / -0.17 ; 7.83
Neutral-Baseline	0.80 / 4.63	3.40 / 4.41	1.98 / 5.31	1.11 / 2.06 ; 4.41

SI=primary somatosensory cortex, SII/pINS=secondary somatosensory cortex and posterior insula, aINS= anterior insula, ACC=anterior cingulate gyrus (ad=affective division, cd=cognitive division) for all observers; highlighted in grey are contrasts that showed activation in the ROI for $p<0.005$ uncorrected; t-values are displayed for right / left side of ROI.

B-V. Summary of effects in FFA and STS

Block design

Male observers	Female observers	Female > Male observers
FFA		
All actors **P – N** - r (-4.67#) **A – N** - b (6.12/ 5.85) P-A	*All actors* **P – N** – r (4.73#) A – N **P – A** – l (5.07#)	*All actors* **P – N** – b (4.10 / 4.41#) A – N P - A
STS		
All actors P - N **A – N** - b (11.70/10.58) P-A	*All actors* **P – N** – b (6.24 / 5.80) A – N **P – A** – b (6.42 / 4.25#)	*All actors* P - N A – N P - A

Event-related design

Male observers	Female observers	Female > Male observers
FFA		
Male actors: P-N A - N P-A	*Male actors*: P-N **A – N** – l (-4.77#) **P - A** - r (9.59)	*Male actors*: P - N A – N P - A
Fem actors: **P - N** - r (-5.70#) A – N **P – A** - r (5.59#)	*Female actors*: P - N **A– N** – l (-4.65#) **P – A** – r (6.88)	*Female actors*: P - N A– N **P – A** – b (3.75 / 4.63)
Male actors > Fem actors **P – N** - l (5.44#) **A – N** - r (-8.69#) P – A	*Male actors > Fem actors* P – N **A – N** – l (5.49) P – A	*Male actors > Fem actors* P - N A – N P – A
STS		
Male actors: **P - N** - l (5.54#) **A – N** - l (6.10#) P-A	*Male actors*: **P - N** – b (7.12 / 6.16) A - N **P – A** – b (5.14 / 8.13)	*Male actors*: P - N **A – N** – l (-4.07) **P – A** – r (4.61)
Fem actors: P - N A - N P - A	*Female actors*: **P – N** – l (7.39) **A – N** – l (4.59) P – A	*Female actors*: P - N A– N P – A
Male actors > Fem actors **P – N** – l (6.12#) **A – N** – l (6.17#) P – A	*Male actors > Fem actors* P – N A - N P – A	*Male actors > Fem actors* P – N A – N P – A

FFA=fusiform face area, STS=superior temporal sulcus for male, female and male vs. female observers; highlighted in grey are contrasts that showed activation in the ROI for p<0.005 uncorrected; side of activation (b=bilateral, r=right, l=left) and t-values displayed; #Regions which do not meet extent threshold.

B-VI. Baseline Contrasts (peak voxels) - FFA and STS

All observers		
All actors (≈ block design)	*FFA*	*STS*
Pain-Baseline	10.16 / 7.52	8.48 / 2.80
Anger-Baseline	8.80 / 6.85	8.26 / 2.27
Neutral-Baseline	10.54 / 7.49	5.84 / 1.13
Male actors (event-related design)		
Pain-Baseline	10.08 / 8.59	9.29 / 4.30
Anger-Baseline	8.85 / 7.31	8.24 / 1.20
Neutral-Baseline	7.42 / 5.67	3.85 / 0.56
Female actors (event-related design)		
Pain-Baseline	10.12 / 7.29	6.22 / 3.57
Anger-Baseline	8.03 / 6.78	6.39 / 3.11
Neutral-Baseline	13.48 / 10.27	6.18 / 2.69

FFA=fusiform face area and STS=superior temporal sulcus for all observers; highlighted in grey are contrasts that showed activation in the ROI for p<0.005 uncorrected; t-values are displayed for right-sided / left-sided part of FFA and STS.

List of Tables

List of Figures

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207

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Ehrenwörtliche Erklärung

Hiermit erkläre ich, dass mir die geltende Promotionsordnung bekannt ist und ich die vorliegende Dissertation selbst angefertigt habe. Ich habe dabei weder die Hilfe eines Promotionsberaters in Anspruch genommen, noch haben mich andere Personen entgeltlich oder unentgeltlich unterstützt. Alle von mir verwendeten Hilfsmittel und Quellen sind in der Arbeit aufgeführt.

Die Dissertation wurde weder in dieser noch in ähnlicher Form als Prüfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung vorgelegt, noch habe ich gegenwärtig oder früher eine Dissertation an einer anderen Hochschule oder Fakultät eingereicht.

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