NEURAL SYSTEMS FOR RECOGNISING EMOTION FROM FACIAL EXPRESSIONS

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CONTENTS

1 SUMMARY (GERMAN)

Menschen sind wahrscheinlich einzigartig in dem Ausmaß, in dem sie sich auf sozial vermittelte Informationen in der täglichen Auseinandersetzung mit ihrer physikalischen und sozialen Umgebung verlassen. Emotionale Gesichtsausdrücke als sichtbare Signale sowohl der Intentionen als auch der internen Zustände anderer Menschen spielen eine wichtige Rolle bei sozialen Interaktionen. Die Erforschung der neuronalen Prozesse, die der Wahrnehmung dieser nonverbalen Signale zugrunde liegen, ist das Ziel der vorliegenden Arbeit. Unter Verwendung der Methode der funktionellen Magnetresonanztomographie (fMRT) sollten in drei Untersuchungen sowohl neuronale Korrelate der Wahrnehmung spezifischer Emotionen (Erstaunen: Experiment 1, Ekel: Experiment 2) als auch die Mechanismen, die dem Verständnis emotionaler Gesichtsausdrücke zugrunde liegen (Experiment 3), untersucht werden.

Neuropsychologische und funktionell-bildgebende Untersuchungen liefern Hinweise auf spezifische neuronale Korrelate für die Wahrnehmung einzelner Basisemotionen (Freude, Erstaunen, Angst, Ekel, Trauer, Wut) aus emotionalen Gesichtsausdrücken. Diese Gesichtsausdrücke sind angeboren und durch spezifische, kulturell unabhängige Konfigurationen von Gesichtsmuskelkontraktionen charakterisiert. Obwohl dies auch auf den Gesichtsausdruck von Erstaunen zutrifft, wurde diese Emotion in neurowissenschaftlichen Untersuchungen zur Wahrnehmung emotionaler Gesichtsausdrücke bisher weitgehend vernachlässigt. Das erste Experiment konzentrierte sich daher auf die Fragestellung, ob der Wahrnehmung sozial-kommunikativer Signale für Erstaunen ein spezifisches neuronales Korrelat zugrunde liegt. Als potentiell relevante Strukturen wurden medial temporale Areale diskutiert, denen im Zusammenhang mit der Verarbeitung kontextuell neuer oder unerwarteter Reize eine wichtige Rolle zugeschrieben wird. Im Rahmen eines impliziten Emotionswahrnehmungsparadigmas, bei dem gesunde Probanden eine Geschlechter-entscheidungsaufgabe während der fMRT-Untersuchung durchführten, wurden Bilder mit erstaunten, angeekelten und neutralen Gesichtsausdrücken von unterschiedlichen Individuen präsentiert. Die Ergebnisse unterschiedlicher Subtraktionsanalysen (Kontrastierung von erstaunten mit neutralen Gesichtsausdrücken und direkte Kontrastierung von erstaunten Gesichtsausdrücken mit Ausdrücken einer anderen Emotion) weisen auf die spezifische Bedeutung des parahippocampalen Gyrus für die Wahrnehmung von Erstaunen hin und

zeigen eine enge Verbindung zwischen der Wahrnehmung sozial-kommunikativer Signale für Erstaunen und der Verarbeitung neuer oder unerwarteter Reize.

Ergebnisse aus Untersuchungen zur Wahrnehmung emotionaler Gesichtsausdrücke bei neurologischen Patienten enthüllen eine beeindruckende doppelte Dissoziation: Während Läsionen in der Amygdala zu einem selektiven Defizit im Erkennen von Angst führen, zeigen Genträger der Huntigton'schen Erkrankung eine überdurchschnittlich starke Einschränkung im Erkennen von Ekel. Da die Huntington'sche Erkrankung nicht durch fokale Läsionen charakterisiert ist, sind die neuronalen Prozesse und Strukturen, die dem selektiven Defizit im Erkennen von Ekel bei Huntington-Genträgern zugrunde liegen, bisher nicht bekannt. Zur Untersuchung dieser Frage wurde eine kombinierte neuropsychologische und funktionell-bildgebende Untersuchung durchgeführt (Experiment 2). Dabei wurden neuropsychologische Maße der Emotionserkennung und neuronale Korrelate der Ekelwahrnehmung zwischen einer Gruppe prä-symptomatischer Huntington-Genträger und einer Gruppe gesunder Kontrollprobanden verglichen. Basierend auf Befunden zu neuropathologischen Veränderung bei Morbus Huntington und funktionell-bildgebenden Untersuchungen zur Wahrnehmung von Ekel bei gesunden Probanden, wurden verminderte Aktivierungen im Bereich der Basalganglien und/oder der anterioren Insel erwartet. In einer ausführlichen neuropsychologischen Testung wurden sowohl Emotionserkennung als auch grundlegende kognitive Funktionen und Wahrnehmungsleistungen der Huntington-Genträger überprüft. Während der fMRT-Untersuchung führten Huntington-Genträger und gesunde Kontrollprobanden eine Geschlechterentscheidungsaufgabe durch. Dabei wurden Bilder mit erstaunten, angeekelten und neutralen Gesichtsausdrücken von unterschiedlichen Individuen präsentiert. Ausschließlich bei der Wahrnehmung von Gesichtsausdrücken, die Ekel signalisieren, zeigten Huntington-Genträger eine im Vergleich zu gesunden Kontroll-probanden signifikant verminderte Aktivierung im Bereich der linken anterioren Insel (primär gustatorischer Kortex). In der neuropsychologischen Testung zeigten die Huntington-Genträger ein selektives Defizit im Erkennen von Ekel, das nicht aufgrund von Störungen in grundlegenden kognitiven oder visuellen Funktionen erklärt werden kann. Die Ergebnisse liefern eine Erklärung für das klinische Defizit dieser Patienten im Erkennen sozial-kommunikativer Signale für Ekelempfinden. Des weiteren bestätigen die Befunde, dass eine enge Verbindung zwischen der Wahrnehmung sozial-kommunikativer Signale für Ekelempfinden und der Wahrnehmung gustatorischer Reize besteht.

Sowohl die Ergebnisse des ersten als auch des zweiten Experiments unterstützen emotionstheoretische Ansätze gemäß derer einzelne Emotionen als distinkte psychologische

Kategorien repräsentiert sind („kategoriale Emotionstheorien“) und zeigen in Einklang mit Befunden aus frühren Untersuchungen, dass die Wahrnehmung unterschiedliche Emotionen mit Aktivierungen in teilweise getrennten neuronalen Subsystemen assoziiert ist. Die Ergebnisse beider Untersuchungen ermöglichen jedoch keine Rückschlüsse auf die Mechanismen, die dem Verständnis emotionaler Gesichtsausdrücke zugrunde liegen. Im dritten Experiment sollte die Verarbeitung emotionaler Gesichtsausdrücke deshalb aus einer unterschiedlichen Perspektive, der Perspektive der „Intersubjektivität“, untersucht werden: Verstehen wir Gesichtsausdrücke indem wir sie simulieren? Ergebnisse aus psychologischen Untersuchungen weisen darauf hin, dass im kognitiven System Reize und entsprechende Reaktionen in vergleichbaren Formaten repräsentiert sind. Die Befunde aus psychologischen Untersuchungen werden durch die Entdeckung sogenannter „Spiegelneurone“ im ventralen prämotorischen und posterior parietalen Kortex bei Affen unterstützt, die sowohl bei der Ausführung als auch bei der Observation zielgerichteter Griffbewegungen aktiv sind. Elektrophysiologische und funktionell-bildgebende Befunde weisen auf ähnliche Spiegelneuronensysteme beim Menschen hin und legen zusammen mit Befunden aus Verhaltensexperimenten nahe, dass neuronale Spiegelmechanismen auch bei der Wahrnehmung emotionaler Gesichtsausdrücke eine Rolle spielen könnten. Basierend auf diesen Befunden wurde die Hypothese aufgestellt, dass die Wahrnehmung emotionaler Gesichtsausdrücke motorische und somatosensorische Strukturen aktiviert, die auch mit deren Ausführung assoziiert sind. Während der Untersuchung führten gesunde Probanden abwechselnd entweder positive emotionale Gesichtsausdrücke selbst aus oder beobachteten kurze Videosequenzen, die Gesichter anderer Personen zeigten, während sie die gleichen Gesichtsausdrücke ausführten. Zur Vermeidung von durch Gesichtsbewegungen induzierten Bewegungsartefakten wurde ein „sparse sampling“ Paradigma konzipiert, bei dem die Gesichtsbewegungen der Probanden ausschließlich während Pauseintervallen zwischen den einzelnen Phasen der Bildakquisition auftraten. Überlappungen neuronaler Aktivierungen der Observations- und Ausführungsbedingung zeigten sich im rechten prämotorischen Kortex und *pars opercularis* des inferior frontalen Gyrus, im rechten parietalen Operculum (SII) und der linken anterioren Insel. Die Ergebnisse zeigen, dass die Wahrnehmung emotionaler Gesichtsausdrücke sowohl Aktivierungen in prämotorischen als auch in somato- und limbisch-sensorischen Gehirnarealen erzeugt, die mit der Ausführung der mimischen Gesten und deren somatosensorischen Konsequenzen assoziiert sind. Ein solcher neuronaler Simulationsmechanismus könnte dem Beobachter einen Eindruck davon vermitteln, wie sich

der Gesichtsausdruck anfühlt, wenn er ihn selber ausführen würde und damit eine wichtige Rolle für das empathische Verstehen der Gefühle anderer spielen.

2 INTRODUCTION

The formal evolutionary treatment of human facial expressions began with Charles Darwin's *The Expression of the Emotions in Man and Animals* (Darwin, 1872). Darwin found evidence for continuity in bodily movements and facial gestures that humans shared with animals. He used these resemblances across species to argue for common descent. Darwin's view of facial expressions, however, was not 'evolutionary' at all, because he did not consider them as adaptations but accidents or vestiges of earlier evolutionary stages in which the intellect was of less importance (see Fridlund, 1994). While the argument for phylogenetic continuity plays an important role in contemporary explanations of emotions, Darwin's vestigialism has largely been replaced by the view that expressions of emotion are adaptive and had been selected for social communication (Schmidt & Cohn, 2001). Emotion that is manifested by facial expression, to a greater or lesser degree, signals occurrences of value, and being able to transfer and receive such information undoubtedly confers a survival advantage. Motivated by advances in cognitive neurosciences where the idea of the brain as an information processing system provides a highly influential metaphor (Dolan, 2002), there has been considerable progress in emotion research over the last years. Thereby, findings from lesion and functional imaging studies as well as investigations of disorders associated with impairments in social and emotional functions have provided new insights into the neural basis of facial emotion processing that are in general consistent with an adaptive view of facial expressions and underscore the importance of nonverbal communication in everyday social life.

The present contribution is concerned with the neural basis of facial emotion processing. It focuses on the neural substrates involved in the processing of specific emotional expressions as well as on neural mechanisms that mediate the extraction of emotional content. Both issues are addressed by three functional magnetic resonance imaging (fMRI) studies. Before we present details of the empirical data, we will give a short overview to models of face processing and emotion followed by a summary of findings from neuropsychological and neuroimaging studies of facial emotion processing. A separate chapter focuses on possible neural mechanisms involved in face-based emotion recognition. After a brief introduction to the technique of functional magnetic resonance imaging (fMRI) the chapter closes with an outline of the thesis.

2.1 Models of face processing

Face perception may be the most highly developed visual skill in humans involving the recognition of individuals and the processing of information that facilitates social communication. Both functions can be impaired, when, for example, patients cannot recognise familiar faces or emotional facial expressions. In some patients, the ability to recognise facial expressions is intact but they fail to identify the person bearing the expression (Tranel, Damasio, & Damasio, 1988), whereas other people can identify the person but their ability to recognise facial expressions is impaired (Adolphs, Tranel, Damasio, & Damasio, 1994; Anderson & Phelps, 2000; A.J. Calder et al., 1996; Young et al., 1995). This double dissociation between facial identity and facial expression processing, together with evidence from psychological investigations, led to the development of the influential cognitive model of face recognition by Bruce and Young (1986) (Figure 2.1). At an early stage of processing, the representation still depends on both the viewing condition (angle of profile, lighting) and facial configuration (expression, eye gaze, mouth position). During structural encoding that captures the aspects of the configuration of a face, a view invariant representation of the face is established and forwarded to the face recognition units for further identification. The model emphasizes distinct processes involved in the recognition of identity and in the recognition of expression and speech-related movements. Facial expressions are treated as view-centred descriptions and are consequently analysed separately by the cognitive system for their affective content.

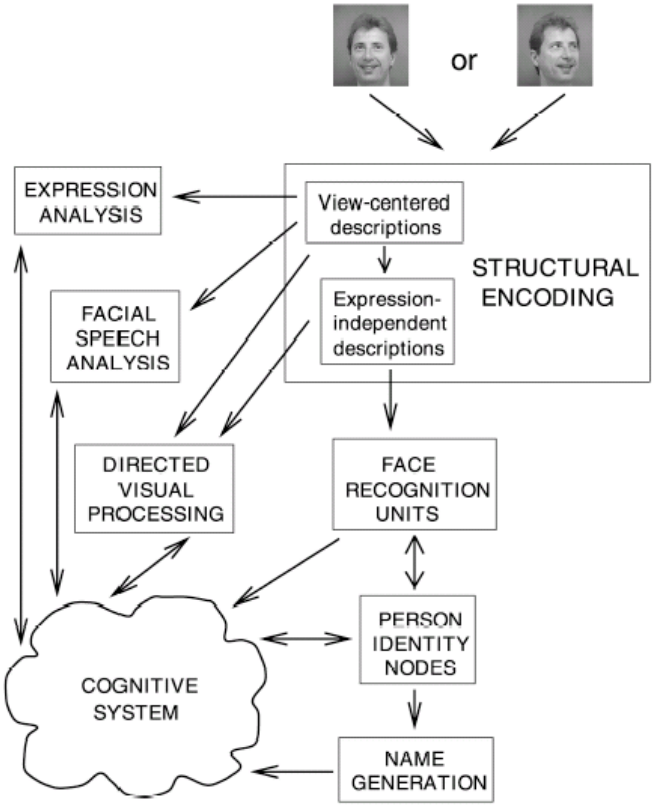

Figure 2.1: The Bruce and Young model of face recognition (from Bruce & Young, 1986)

In the course of the rapid developments in functional neuroimaging methods in the last decade, several research groups have used PET and fMRI to investigate various aspects of face processing. Based on findings from these studies, ERP studies, as well as animal studies, Haxby et al. proposed a 'distributed human neural system for face perception' (Haxby, Hoffman, & Gobbini, 2000, 2002) (Figure 2.2) that shares important features with the Bruce and Young model. The model is divided into a core system composed of three bilateral regions in the occipitotemporal visual extrastriate cortex and an extended system comprising various cortical and subcortical regions. The core system includes the inferior occipital gyri involved in the early perception of facial features which provide input to the lateral fusiform gyrus and the superior temporal sulcus. The fusiform gyrus processes the invariant aspects of faces or identity, whereas face-responsive regions in the superior temporal sulcus mediate the processing of changeable aspects of faces, such as facial expression, eye gaze, and lip movement important for social interactions and communication. The extended system supports further processing in concert with other neural systems, for example emotional content is processed by the amygdala, the insula, and the limbic system.

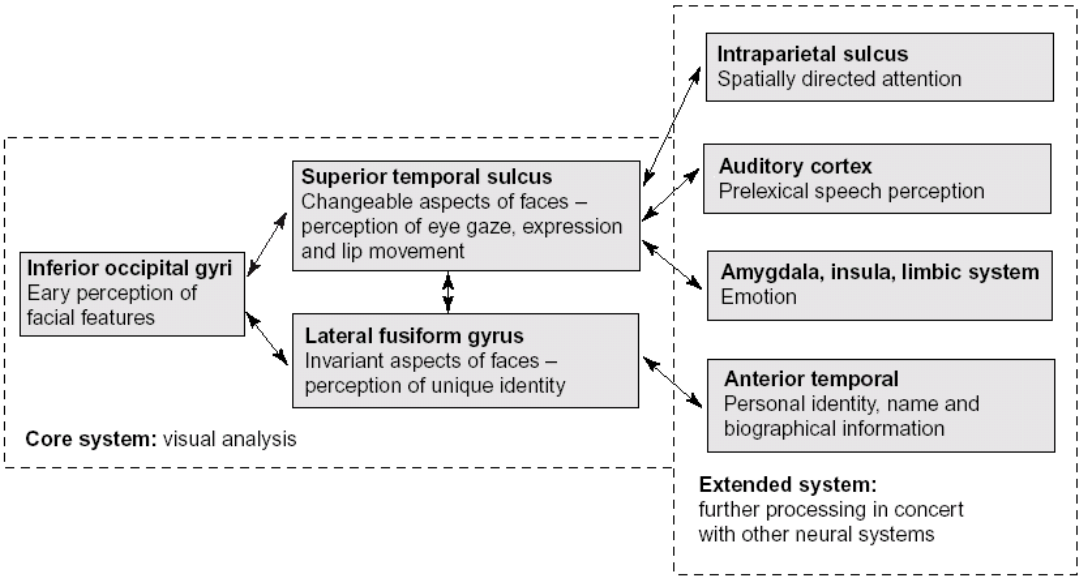

Figure 2.2: The Haxby model of a 'distributed human neural system for face perception' (from Haxby et al., 2000)

2.2 Models of emotion

There is a general psychological debate concerning whether emotions are best described in terms of category-based frameworks or unifying dimensional accounts. Category-based accounts postulate the existence of a limited number of 'basic emotions', generally including happiness, surprise, sadness, anger, fear and disgust (Figure 2.3) that are identified by the activation of discrete categorical representations. The six basic emotional expressions have been shown to be universal in their performance and in their perception. There is strong evidence that the recognition of these emotions from faces is carried out similarly by members of both literate and preliterate cultures (Ekman & Friesen, 1971; Ekman, Sorenson, & Friesen, 1969), even though those cultures have different 'display rules' for expressing the same emotions under various circumstances (Ekman & Friesen, 1969).

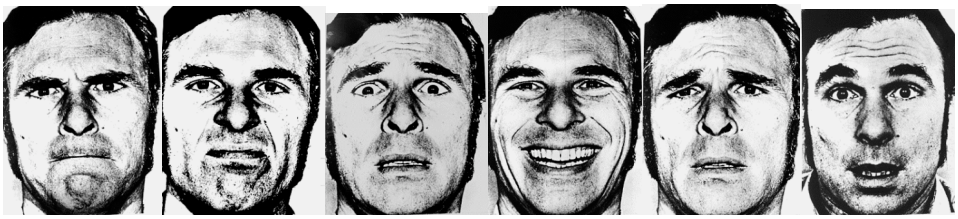

Figure 2.3: Prototypical facial expressions of the six basic emotions (Ekman & Friesen, 1976). Going from left to right the pictures show anger, disgust, fear, happiness, sadness and surprise

Dimensional models of emotion, on the other hand, propose that all emotions can be represented in a single integrated system with a limited set of dimensions. They are based on the observation that human errors in recognising facial expressions form consistent patterns that can be accommodated by a model in which facial expressions are recognised by registering their positions in a continuous two-dimensional space coding pleasure-displeasure and arousal-sleepiness (Russell, 1980) or on states elicited by positive and negative instrumental reinforcers (Rolls, 1999), for example presentation of reward (pleasure, elation, ecstasy) or punishment (apprehension, fear, terror) and withholding of reward (frustration, sadness, anger, grief, rage) or punishment (relief) (see Figure 2.4 and also Calder, Lawrence, & Young, 2001).

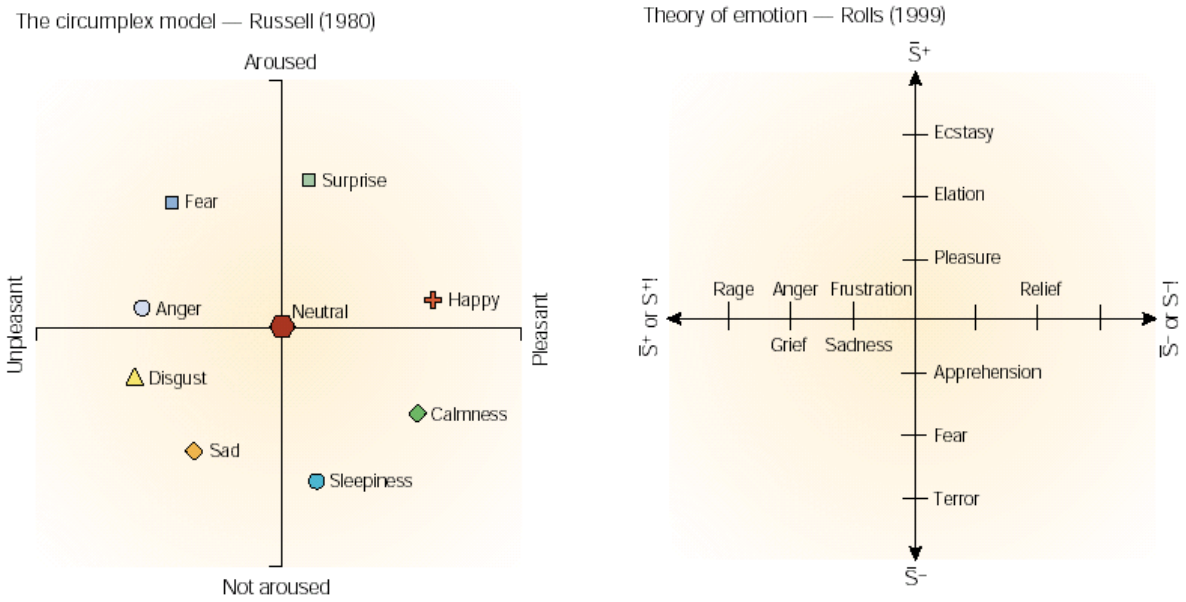

Figure 2.4: Dimensional models of emotion in psychology (Russell, 1980) and neuroscience (Rolls, 1999) (taken from A.J. Calder et al., 2001)

Proponents of both the categorical and the dimensional views make reference to the adaptive utility of the proposed psychological features. However, while the discrete emotion theorists argue that unitary mechanisms associated with different emotions determine the behavioural and physiological responses to an emotional stimulus, dimensional theorists point out that these responses depend on the costs and benefits of different courses of action, suggesting the existence of a complex and flexible problem-solving system.

2.3 Separable neural systems for recognising basic emotional expressions

Findings from investigations of the neural correlates that underlie perception of facial signals of emotion have made a significant contribution to the general psychological debate concerning whether emotions are best described in terms of category-based frameworks or unifying dimensional accounts. In support of the category-based framework, lesion studies and studies with neurological patients have provided evidence for selective impairments in recognising facial signals of fear and disgust. Further, functional imaging studies have uncovered partly separable and specialized neural systems for recognising several emotions in healthy individuals. The following sections will briefly review processing of the six basic emotions based on findings from both patient studies and functional neuroimaging studies with healthy subjects.

2.3.1 Fear

The emotion of fear has been closely linked to the amygdala. The fear system involves parallel subcortical and cortical transmissions to the amygdala from the superior colliculus and pulvinar thalamus, and the visual neocortex (LeDoux, 1996). Subliminally presented facial expressions of fear activate the amygdala (Whalen et al., 1998) via the subcortical route (Morris, Ohman, & Dolan, 1999) and subjects with blindsight, due to striate cortex damage, activate structures in the subcortical route during discrimination of emotional facial expressions (de Gelder, Vroomen, Pourtois, & Weiskrantz, 1999; Morris, DeGelder, Weiskrantz, & Dolan, 2001). Human lesion studies have consistently found impaired recognition of fearful facial expressions following bilateral amygdala damage (Adolphs et al., 1994; Adolphs et al., 1999; Anderson & Phelps, 2000; A.J. Calder et al., 1996; Sprengelmeyer et al., 1999; Young et al., 1995). The amygdala has therefore been suggested to be implicated in the processing of stimuli related to threat and danger (Adolphs et al., 1999), in resolving ambiguity in the environment (Davis & Whalen, 2001) or in the processing of emotions related to behavioural withdrawal (Anderson, Spencer, Fulbright, & Phelps, 2000). A recent study elucidated the mechanism by which amygdala damage compromises fear recognition: Adolphs and colleagues (Adolphs et al., 2005) showed that the impairment of a patient with bilateral amygdala damage (SM) to recognise fear from facial expressions is caused by an inability to make normal use of information from the eye region of faces when judging emotions.

Numerous functional imaging studies have corroborated the notion that the amygdala is disproportionately involved in the recognition of facial expressions of fear (e.g. Breiter,

Etcoff et al., 1996; Morris et al., 1998; Morris et al., 1996; Phillips et al., 1998). Amygdala activation associated with the perception of fearful facial expressions, however, appears to depend on passive or implicit processing of facial expressions, since explicit tasks, such as labelling the emotion expressed by faces, can result in reduction of amygdala responses (Critchley et al., 2000; Hariri, Bookheimer, & Mazziotta, 2000). Most functional imaging studies using fearful facial expressions have reported left amygdala activation. This might be explained by the finding that the habituation rate to facial expressions of fear is more rapid for the right than for the left amygdala (Phillips et al., 2001; Wright et al., 2001).

2.3.2 Disgust

The first evidence that perception of disgusted facial expressions might be associated with a particular neural substrate came from investigations of people with Huntington's disease, which results in a disproportionate impairment in recognising disgust from facial expressions (Sprengelmeyer et al., 1996; Sprengelmeyer, Young, Sprengelmeyer et al., 1997; Wang, Hoosain, Yang, Meng, & Wang, 2003), even in the absence of manifest symptomatology (Gray, Young, Barker, Curtis, & Gibson, 1997). Since initial neural degeneration in Huntington's disease primarily affects the basal ganglia (Goto, Hirano, & Rojas-Corona, 1989), it is informative that further disorders associated with abnormal metabolic activity in these brain regions, that is, obsessive-compulsive disorder (OCD), Wilson's disease and unmedicated Parkinson's disease have also been shown to produce impairments in recognising facial expressions of disgust (Sprengelmeyer et al., 2002; Sprengelmeyer, Young, Pundt et al., 1997; Wang et al., 2003). It is important to notice, however, that Huntington's disease, OCD and Wilson's disease are not characterized by focal neuropathology. So the actual brain regions involved in this deficit are still unclear.

A role for the basal ganglia and also the insula in recognising disgust has been proposed by findings from functional imaging studies, showing that these structures are specifically involved when healthy subjects view facial expressions of disgust (Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998). Since the insular cortex has been implicated in gustatory processing (Frey & Petrides, 1999; Small et al., 1999), recognition of disgust in others has been linked to the evaluation of distasteful stimuli (Phillips et al., 1997). This notion is supported by a lesion case of a patient with damage to the left insula and basal ganglia who showed selective impairments both in the ability to recognise facial expressions of disgust and in the ability to experience the emotion himself (Calder, Keane, Manes, Antoun, & Young, 2000).

2.3.3 Sadness and Anger

Compared to the emotions of fear and disgust, there is less evidence for a specific neural substrate associated with the perception of sad and angry facial expressions. Two studies have reported selective impairments in recognising facial expressions of anger. In the first study, Lawrence et al. show that after administration of the dopamine antagonist sulpiride subjects are significantly worse at recognising angry faces, though there are no such impairments in recognising facial expressions of other emotions (Lawrence, Calder, McGowan, & Grasby, 2002). Various lines of evidence suggest that the dopamine system has evolved as a neural subsystem involved in the processing of aggression in social-agonistic encounters, and that this system plays a role in mediating the processing of anger.

In a second study (Schroeder, Kuehler et al., 2004) we investigated facial expression processing in Parkinson's disease patients with subthalamic nucleus (STN) deep brain stimulation (DBS). DBS is an accepted form of treatment for patients with Parkinson's disease who have medically intractable motor symptoms. STN stimulation facilitates movement related frontal activity (Ceballos-Baumann et al., 1999; Limousin et al., 1997), but is not necessarily coupled with improvement in non-motor functions. Studies in patients with STN stimulation show subtle cognitive impairments paralleled by dysfunctional activations within the respective neural systems (Schroeder et al., 2002; Schroeder et al., 2003). Furthermore, there is evidence for emotional changes, affecting social interaction – for example, STN stimulation can lead to poor behavioural control (Saint-Cyr, Trepanier, Kumar, Lozano, & Lang, 2000), depression, anxiety, emotional lability, and social maladjustment (Houeto et al., 2002). In the study of Schroeder and colleagues (2004), we found that STN stimulation selectively reduces recognition of angry faces, known to signal discontent with the behaviour of others in order to discourage socially inappropriate and unexpected behaviour (Averill, 1982). Since the STN in animals is also targeted by limbic cortices (Parent & Hazrati, 1995), such as the orbitofrontal and anterior cingulate cortex (Canteras, Shammah-Lagnado, Silva, & Ricardo, 1990), the results of the study point to a possible role of these structures in recognising angry facial expressions. In fact, a patient with acquired sociopathy resulting from damage to the right frontal region, including the orbitofrontal cortex, showed difficulties in recognising angry and fearful facial expressions (Blair & Cipolotti, 2000). The patient's impairment was attributed to a reduced ability to generate expectations of others' negative emotional reactions and to suppress inappropriate behaviours. Results from functional imaging studies are in agreement with these findings revealing activation of the orbitofrontal (Blair, Morris, Frith, Perrett, & Dolan, 1999) and cingulate cortex (Blair et al.,

1999; Sprengelmeyer et al., 1998) during perception of angry facial expressions in healthy subjects.

Perception of sad facial expressions has been associated with activation in the amygdala and middle/inferior temporal gyrus (Blair et al., 1999).

2.3.4 Happiness

Smiling is the most easily recognised expression. According to the norms published by Ekman and Friesen (1976) (Ekman & Friesen, 1976), mean accuracy for recognition of facial expressions of happiness reaches 100% (Young, Hellawell, Van De Wal, & Johnson, 1996). So far, no patient groups have displayed problems in recognising happy facial expressions (e.g. Adolphs, Damasio, Tranel, & Damasio, 1996). Two patients with bilateral amygdala damage performed at normal levels in processing happy facial expressions (Adolphs et al., 1994; A.J. Calder et al., 1996; Young et al., 1995). One patient was impaired in her appraisal of happiness to a lesser extent (Anderson & Phelps, 2000).

Findings from neuroimaging studies of the perception of happy facial expressions revealed no consistent pattern of activation. Various neural structures have been implicated in the perception of happy facial expressions, including the basal ganglia (Morris et al., 1998; Morris et al., 1996), inferior/orbitofrontal cortex (Dolan et al., 1996; Gorno-Tempini et al., 2001), anterior cingulate cortex (Dolan et al., 1996; Kesler-West et al., 2001) and the amygdala (Breiter, Etcoff et al., 1996; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Winston, O'Doherty, & Dolan, 2003; Yang et al., 2002). Whereas some studies reported signal increases in the amygdala to positively valenced facial expressions (Breiter, Etcoff et al., 1996; Pessoa et al., 2002; Winston et al., 2003; Yang et al., 2002) others do not or have found signal decreases in the amygdala (Morris et al., 1996; Whalen et al., 1998). Given that the amygdala's activity is enhanced by faces containing dynamic information (LaBar, Crupain, Voyvodic, & McCarthy, 2003), inconsistencies in findings concerning its involvement in pleasant facial affect may be related to the lack of temporal cues in static facial displays that have mostly been used in these studies. Findings from more recent neuroimaging studies, however, suggest a generalized response of the amygdala to emotionally valenced stimuli (Winston et al., 2003), modulating the vigilance level during the perception of both positive and negative facial expressions (Yang et al., 2002).

2.3.5 Surprise

So far, no major studies have focused on the neural correlates associated with the perception of surprised facial expressions. Data on the recognition of surprise, collected in

conjunction with the assessment of other basic emotions have shown that bilateral amygdala damage may also impair the recognition of expressions judged to be similar to fear, such as surprise (e.g. Adolphs et al., 1994). However, behavioural data available on the classification of emotional facial expressions verify a categorical recognition of the six basic emotions by revealing high recognition rates for all emotions (approximately 80% correct in six-way forced choice), including recognition of surprised and fearful faces (Young, Perrett, Calder, Sprengelmeyer, & Ekman, 2002). If there is any confusion between surprised and fearful faces, the latter is confused with the former, that is, afraid faces are sometimes misinterpreted as surprised faces, while nearly all surprised faces are identified correctly (Adolphs, Tranel, & Damasio, 2003). Behavioural evidence therefore suggests partly separable neural substrates for the perception of facial expressions of surprise as well.

2.4 Mechanisms for recognising emotion from faces

Adolphs distinguishes between three possible mechanisms for recognising emotions from facial expressions that are linked to specific neural structures and their interconnections (Adolphs, 2002b). *Recognition as part of perception* means that emotions are recognised solely on the basis of information present in the geometric properties of the stimulus image. Such information might be linked directly to language-related regions of the brain to produce the name of the emotion, in the absence of retrieving any other information associated with the stimulus. Mathematical analyses suggest that the structure present in images of facial expressions is sufficient to generate some of the structure of the emotion categories that humans perceive (Calder, Burton, Miller, Young, & Akamatsu, 2001). Moreover, there is evidence for categorical perception of facial emotion from studies investigating the categorization of morphed images generated from the expressions of two different emotions (Calder, Young, Perrett, Etcoff, & Rowland, 1996; de Gelder, Teunisse, & Benson, 1997).

This notion of recognition, however, does not account for the *generation of associated knowledge* that is not present in the structure of the stimulus itself. The representation of the different properties of the stimulus may reactivate representations that were originally associated with one another when the knowledge was acquired, for example, linking a face of fear to a scream. Such associated knowledge could be implemented in terms of language, so that the subject can articulate her/his concept of the perceived emotion.

Another mechanism might attempt to *simulate* in the observer components of the emotional response shown in the stimulus. A representation of the emotional response in the observer could in turn trigger conceptual knowledge. ‘Simulation theory’ (ST) (Harris, 1992)

has been applied primarily in the context of typical mindreading tasks, such as identifying others' beliefs and desires (Goldman & Sripada, 2005). In contrast to the 'theory-theory' (TT) (Gopnik & Wellman, 1994) according to which mental-state attributors deploy a naïve psychological theory to infer mental states in others, ST holds that an attributor arrives at a mental attribution by simulating in his own mind the same state as the target's. ST has recently received considerable attention due to the detection of 'mirror neurons' in the monkey's premotor and posterior parietal cortex that discharge both when the monkey performs a specific goal-directed action and when it observes a similar action performed by another individual (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Fogassi, Gallese, Fadiga, & Rizzolatti, 1998; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). Neurophysiological and functional imaging findings support the notion that a similar mirror mechanism exists in humans (see Rizzolatti & Craighero, 2004) and might also be involved in our capacity to understand emotions expressed by others (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Keysers et al., 2004; Leslie, Johnson-Frey, & Grafton, 2004; Singer et al., 2004; Wicker et al., 2003). There is, however, a debate concerning the precise simulation mechanism involved in facial emotion recognition (see Wicker et al., 2003). According to the 'cold' hypothesis, observation of the facial expression of another person triggers a similar neural motor representation and its associated somatosensory consequences in the observer that underlie the understanding of the meaning of the observed facial expression. The 'hot' hypothesis on the other hand postulates, that in order to understand the facial expression displayed by others, a feeling of the emotion must occur also in the observer. Based on findings from clinical and experimental studies that display a pattern of paired deficits between 'hot' emotional experience and facial emotion recognition, Goldman and Sripada have proposed several simulation mechanisms by which the perception of emotional facial expressions could evoke an experience of the emotion in the observer (Goldman & Sripada, 2005). Following these theoretical accounts, brain areas associated with the experience of a specific emotion should become active during the observation of others' emotional facial expressions. So far, there is only direct evidence for the hot hypothesis: Wicker et al. found that the same sites in the left anterior insula are activated when subjects observe facial expressions of disgust and when they experience the same emotion induced by the perception of disgusting odorants (Wicker et al., 2003). The cold hypothesis is, however, indirectly supported by findings from behavioural studies, showing that when people are exposed to emotionally expressive faces, they spontaneously respond with distinct facial electromyographic (EMG) reactions in emotion-relevant facial

muscles even when facial expressions are not consciously perceived (Dimberg and Petterson, 2000; Dimberg et al., 2000).

2.5 Functional MRI

Functional MRI measures hemodynamic signals related to neural activity in the brain. In chapter 2.5.1 we will briefly summarize some of the most important physical and physiological principles underlying fMRI. In the following section (chapter 2.5.2) we describe two different types of experimental design used in fMRI research, that is, block design and event related design, and give a short overview of the different steps involved in the data analysis. For a complete introduction to fMRI we refer to the book of Toga and Mazziotta (Toga & Mazziotta, 2002). More detailed descriptions of the designs and analyses applied in this contribution are given in the respective chapters (chapters 3-5).

2.5.1 Physical and physiological principles

The fMRI technique monitors changes in the inhomogeneity of the magnetic field, which are a result of changes in the level of oxygen present in the blood. Deoxyhaemoglobin is paramagnetic, causing an inhomogeneity in the magnetic field, while oxygenated haemoglobin is diamagnetic and has very little effect on the magnetic field. Therefore changes in blood oxygenation can cause changes in the MR decay parameter T2*, leading to changes in image intensity in T2*-weighted MR images. The signal intensity of oxygenated blood is greater than that of deoxygenated blood in T2*-weighted images, which is also referred to as the blood oxygenation level dependent (BOLD) response (Ogawa et al., 1992). The function of the BOLD response against time in response to a temporary increase in neural activity is known as the haemodynamic response function (HRF) (see Figure 2.5). Initially the HRF decreases, because active neurons use oxygen thereby increasing the relative level of deoxyhaemoglobin in the blood. Following the initial decrease, there is a large increase in signal intensity due to an oversupply of oxygenated haemoglobin, reaching its maximum after 4-6 seconds. Finally, since the concentration of oxygenated haemoglobin returns to its normal level, the signal decays and reaches its original baseline level after an undershoot 20-30 seconds poststimulus.

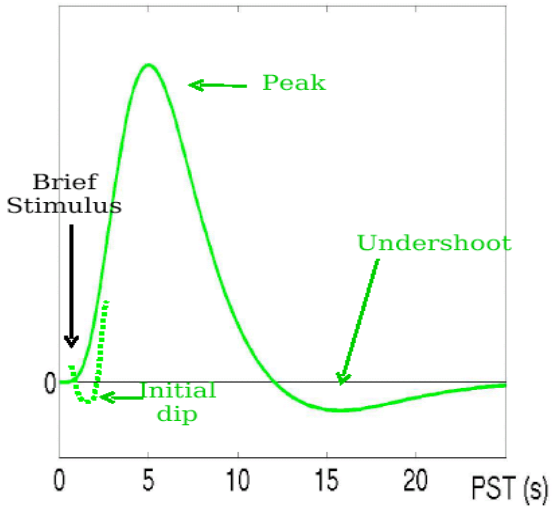

Figure 2.5: Time course of the HRF in response to a brief stimulus

It is important to note that the BOLD signal is an indirect measure of the underlying neural activity and that the relationship between various aspects of neural processing and the changes in BOLD activity is poorly understood. The predominant hypothesis is that BOLD activation reflects synaptic inputs and local processing within an area, rather than action potentials (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Moreover, the magnitude of the BOLD effects measured during fMRI is very small. This has commonly been reported to be in the 1-4% range for imaging at the magnetic field strength of 1.5 Tesla. Noise in fMRI comes from a variety of sources. Besides thermal noise from the subject (ions and electrons generating electromagnetic noise), attention or alertness dependent effects, variations in the received signal correlate strongly with the respiratory and cardiac cycles. Another significant source of signal variations in fMRI is head movement, since a complete fixation of the head is impossible. Especially at tissue borders, motion can cause signal changes that are mainly a result of variations of the scanned region.

There are a number of approaches to improve the signal-to-noise ratio (SNR) in fMRI data. Here we will only mention the most significant ones. First, the use of rapid acquisition techniques such as 'echo planar imaging' (EPI) and spiral imaging (Noll, Cohen, Meyer, & Schneider, 1995) allows for a large number of images to be averaged in order to reduce the undesired physiologic variations and also to freeze physiological motion. Secondly, the number of hydrogen nuclei that align with the magnetic field depend directly on the field strength of the magnet. Therefore, a higher field strength theoretically increases the signal to measure and allows to collect images of the brain more rapidly due to shorter echo times (TE). Unfortunately, at a higher field strength, inhomogeneity artefacts become more severe. Poor normalisation of images due to image distortion may result in an inability to measure

some regions of the brain such as the medial temporal lobe and ventral frontal lobe also important in facial emotion processing. Thirdly, for fixed field strength, with increasing voxel size, the SNR rises simultaneously. One can thus trade off image resolution for signal quality. The elimination of effects resulting from the subject's head movements is another challenge for functional MRI. To account for it, various forms of head restraints are used, such as bite-bars, foam packing, or surgical pillows. Moreover, head movement can be estimated and motion correction algorithms can be applied to calculate the original position of the subject. For fMRI experiments involving task-correlated facial movements, such as the investigation of overt speech or generation of facial expressions, specific imaging techniques can be applied to overcome motion artefacts (e.g. 'sparse temporal sampling' or 'compressed image acquisition'), where facial action is timed to coincide with a scan-free time interval between the acquisition of successive image volumes (Amaro et al., 2002) (see also chapter 5.3.3). Finally, the statistical power can be maximized by optimising the experimental design, for example using a block design or running longer fMRI sessions.

2.5.2 Experimental design and analysis

Most neuroimaging experiments rely on subtraction logic, that is, brain activation levels must be considered relative to another condition. Subtraction logic is based on the assumption of pure insertion, meaning that two conditions differ only in one critical component. In a block design, two or more conditions are alternated in blocks of several trials, resulting in an uniquely identifiable MR signal time course. The fMRI signal in response to a stimulus is additive. Because within each block only one stimulus type is usually presented, block designs offer considerable statistical power at the cost of high stimulus predictability and low flexibility in the design of the fMRI paradigm. In an event related design (Buckner & Braver, 1999), the response to a single event is examined. In contrast to block designs, event related designs allows for randomisation of trials, thereby cancelling out potential confounds like habituation and anticipation of stimulus properties. Though the statistical power of event related designs can be maximised by optimal spacing in time between the onsets of successive stimulus presentations (Dale, 1999), it is still low compared to block design paradigms. Several alternative approaches that can be applied to the block- and event related designs, such as factorial designs (Friston et al., 1996), parametric designs or cognitive conjunction designs (Price & Friston, 1997) have as their goal a reduction in the reliance upon the assumption of pure insertion. Moreover, one can decide between a voxelwise approach where statistical comparisons between two or more conditions

are performed on a voxel-by-voxel basis across the whole brain and a region of interest (ROI) approach which focuses on the role of previously described regions.

After obtaining EPI data from the scanner, several analyses have to be performed on the dataset (Friston, 1997), that can roughly be divided into pre-processing and voxel-based statistical analyses. Pre-processing usually includes spatial realignment of the data to ensure that the voxels are in the same anatomical space and to remove movement-related signal components that persist after realignment. During spatial normalisation individual brains are matched to a template that conforms to a standard anatomical space. Spatial smoothing of the data is performed to satisfy the requirements for applying Gaussian Field Theory in the ensuing statistical analysis and to remove noise present in the high spatial frequencies. In order to correct for the false assumption of uncorrelatedness of activations at successive points in time corrections for serial correlations are applied. After smoothing, the General Linear Model (GLM) is typically employed to estimate the parameters of the model and derive the appropriate univariate test statistic at every voxel. The voxelwise test statistics, usually *T* or *F* statistics, constitute a three-dimensional statistical parametric map (SPM). Due to the huge number of statistical tests, corrections for multiple spatial comparisons are applied to select an appropriate statistical threshold. Less conservative methods than the Bonferroni correction are available based on the Gaussian Random Field Theory that estimates the number of independent samples in spatially smoothed data or on the false discovery rate (FDR) which adjusts the threshold according to the amount of signal present in the data (Genovese, Lazar, & Nichols, 2002). Finally, the use of random effects analyses allows generalization of effects from the group of tested subjects to the population from which the subjects are drawn (A.P. Holmes & K.J. Friston, 1998).

2.6 Outline of the thesis

Subject of the thesis is the neural basis of facial emotion processing. By using functional MRI we aim to explore the neural substrates involved in the perception of specific emotional expressions as well as the neural mechanisms that mediate the extraction of emotional meaning. The first study focuses on the facial expression of surprise. Although this expression is characterized by a specific and universal configuration of facial muscle contractions and has a high recognition rate (see chapter 2.3.5), it has generally been neglected in neuroscientific investigations of facial emotion processing. As outlined in chapter 2.3, neuropsychological and functional imaging studies provided evidence for partly separable neural circuitries associated with the perception of specific emotional expressions.

Is there also a specific neural substrate for the perception of facial expressions of surprise? This question is addressed in chapter 3 where we present the findings of an fMRI experiment (Schroeder, Hennenlotter et al., 2004) that explores brain regions specifically associated with implicit processing of facial expressions of surprise.

As outlined in chapter 2.3.1 and 2.3.2, evidence from patient-based research reveals a striking double dissociation, showing that damage to the amygdala causes a disproportionate impairment in recognising facial signals of fear whereas carrying the gene for Huntington's disease is associated with a selective impairment in recognising facial expressions of disgust. In contrast to the findings of impaired fear recognition derived from patients with relatively selective lesions to the amygdala, however, Huntington's disease, associated with impaired disgust recognition, is not characterized by focal neuropathology. Thus, the actual brain regions involved in this deficit are still unclear. To address the question of which brain regions are associated with impaired disgust recognition in Huntington's disease gene carriers we conducted a combined neuropsychological and fMRI study (Hennenlotter et al., 2004) where facial recognition abilities and neural correlates associated with facial expression processing were compared between a group of pre-symptomatic Huntington's disease gene carriers and a group of healthy control subjects. This study is described in chapter 4.

Recently, catchwords like 'empathy', 'mind reading' or 'simulation' have become increasingly popular in the field of cognitive neuroscience, primarily owing to the detection of 'mirror neurons' in monkeys' premotor and posterior parietal cortex that discharge both when the monkey performs a specific action and when it observes a similar action performed by another individual (see chapter 2.4). Neurophysiological and functional imaging findings have subsequently supported the existence of a similar mirror mechanism in humans (see Rizzolatti & Craighero, 2004). Originally, thought of as a means to understand goal-related motor actions performed by others (Rizzolatti, Fadiga, Gallese et al., 1996), neural mirror mechanisms have also added a new perspective to the study of facial emotion processing. Do we understand what others feel by an internal mechanism that simulates in the observer components of the emotional response shown by others? Or more specifically: Does the perception of emotional facial expressions involve neural circuitries associated with their production? This question was addressed by a third fMRI experiment (Hennenlotter et al., 2005) where we aimed to explore the shared neural basis for perceiving and expressing pleasant facial affect.

Though many other interesting issues have to stay untouched, the present contribution addresses important aspects in the study of facial emotion processing, namely the neural basis of categorical expression recognition and the neural mechanisms that mediate the understanding of others' feelings. Both issues will be addressed in the following chapters.

3 THE FUNCTIONAL NEUROANATOMY OF PERCEIVING SURPRISED FACES[1]

3.1 Summary

Surprise is one of six emotions having a specific and universally recognised facial expression. Functional imaging and neuropsychological studies have uncovered partly separable neural substrates for perceiving different facial expressions; however, the functional neuroanatomy of perceiving surprised faces has not yet been investigated. Using functional magnetic resonance imaging (fMRI), we aimed to identify the neural substrate of surprise perception from facial expressions. Based on the assumption of unexpectedness and novelty as elicitors of facial surprise reactions, we hypothesized recruitment of medial temporal lobe structures implicated in novelty detection during the perception of surprise in others. Healthy subjects were scanned while they were presented with surprised faces. As control they viewed faces depicting neutral or disgust expressions. Activations during the emotional conditions were contrasted with each other and with the neutral face condition. Compared to both control conditions perception of surprised facial expressions yielded consistently increased signals in the parahippocampal region, an area associated previously with novelty detection. Our findings therefore suggest a close relation between perceiving surprise in others and the response to novel events. Additionally, we confirmed activation of the insula during perception of disgust expressions.

KEY WORDS: surprise; facial expression; fMRI; novelty; medial temporal lobe; disgust; insula

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3.2 Introduction

Facial expressions provide important indicators of emotion and contribute to the appreciation of the physical environment. Six basic emotions (happiness, surprise, fear, sadness, anger and disgust) have a distinct facial expression and are recognised universally (Ekman, 1992).

Recognition of facial expressions comprises multiple processes, including a perceptual analysis of facial features and extraction of emotional meaning (Adolphs, 2002a; Haxby et al., 2000). The perceptual analysis of facial characteristics has been linked to the occipital and posterior temporal cortices (Hoffman & Haxby, 2000; Kanwisher, McDermott, & Chun, 1997; Sergent, Ohta, & MacDonald, 1992). Extraction of emotional meaning from faces involves the orbitofrontal/inferior frontal cortex as shown by a neuropsychologic study (Hornak, Rolls, & Wade, 1996). Consistent with this, functional imaging studies revealed orbitofrontal and inferior frontal activation while viewing emotional facial expressions (Nakamura et al., 1999; Narumoto et al., 2000; Sprengelmeyer et al., 1998).

More important, imaging and neuropsychologic studies have uncovered partly separable and specialized neural systems for recognising different facial expressions. The amygdala is involved primarily during perception of fearful faces (Adolphs et al., 1994; Morris et al., 1996; Sprengelmeyer et al., 1999; Whalen et al., 1998; Young et al., 1995), whereas the processing of disgust has been linked to the insula and the basal ganglia (Calder, Keane, Manes et al., 2000; Krolak-Salmon et al., 2003; Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998; Sprengelmeyer et al., 1996). Moreover, the medial-frontal cortex has been implicated in perceiving angry faces (Blair et al., 1999; Harmer, Thilo, Rothwell, & Goodwin, 2001). Evidence concerning neural correlates of perceiving facial expressions of happiness and sadness is less clear cut. Functional imaging studies have pointed to activation of various neural structures during perception of happy faces, including the basal ganglia (Morris et al., 1998; Morris et al., 1996), the inferior frontal cortex (Dolan et al., 1996), the anterior cingulate cortex (Dolan et al., 1996; Kesler-West et al., 2001) and the amygdala (Breiter, Etcoff et al., 1996; Pessoa et al., 2002). A study investigating the neural substrate of perceiving sad faces suggests an involvement of the temporal pole and the amygdala (Blair et al., 1999).

The facial expression of surprise has been neglected in neuroscience, although this expression was described already by Charles Darwin in 1872, who proposed novelty and unexpectedness as its elicitors: “Attention, if sudden and close, graduates into surprise. […] Attention is shown by the eyebrows being slightly raised; and at this state increases into

surprise, they are raised to a much greater extend with the eyes and mouth widely open. [..] As surprise is excited by something unexpected or unknown, we naturally desire, when startled, to perceive the cause as quickly as possible…" (Darwin, 1999; p 278). Psychological theories conceive surprise as an adaptive mechanism to restructure and extend cognitive concepts after analysing an unexpected event (Schutzwohl, 1998); however, the neural substrate involved in the perception of surprise and its significance to the observer has not yet been investigated.

Using functional magnetic resonance imaging (fMRI), we aimed to identify the neural substrate that mediates the perception of surprise in others. Based on the assumed association of surprise and novelty (Darwin, 1999; Schutzwohl, 1998), we hypothesized that besides temporal and occipital cortices subserving the perceptual analysis of facial features (Haxby et al., 2000, 2002), perception of surprised facial expressions involves the medial temporal lobes, which have been implicated previously in the response to contextually novel or distinctive stimuli (Gabrieli, Brewer, Desmond, & Glover, 1997; Stern et al., 1996). Furthermore, we aimed to validate our experimental paradigm by reproducing the association of disgust perception with insular activation (Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998).

3.3 Methods

3.3.1 Subjects

The study subjects comprised 20 right-handed, healthy individuals (10 men, 10 women; mean age 32.5 ± 8.3 years). All volunteers were free of neurologic or psychiatric diseases and gave written informed consent to take part in the experiment. The study was approved by the Ethical committee of the Technische Universität München.

3.3.2 Stimuli and paradigm

Volunteers viewed greyscale pictures of faces from the *Facial Expressions of Emotions: Stimuli and Test* (FEEST) (Young et al., 2002), which displayed disgust, surprise or neutral expressions. As a neutral face, we used a morphed image with slightly happy expression (25% happy, 75% neutral) produced by computer graphic manipulation, because 100% neutral faces appear slightly cold and threatening (Phillips et al., 1997). Each picture was presented individually against a grey background for 3 s with an interstimulus interval of 0.76 s. Eight faces (3 male/5 female) of the same expressions were ordered randomly and

constituted one block. Ten blocks with alternating emotional (surprise or disgust) and neutral faces constituted one run. Participants performed four separate runs in a counterbalanced order: two runs including surprised and neutral and the other two disgusted and neutral faces. In line with previous studies of emotion perception (Blair et al., 1999; Morris et al., 1996; Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998), an implicit paradigm of facial expression perception was applied with volunteers pressing left or right response buttons in a gender decision task. To familiarize subjects with the stimuli, they viewed each picture once before fMRI scanning.

3.3.3 Image acquisition and analysis

Echoplanar MR brain images were acquired using a 1.5 Tesla Siemens Symphony Scanner (Erlangen, Germany) with a standard head coil. During each run, 110 T2*-weighted images were acquired at each of 33 slices of 4 mm thickness parallel to the intercomissural line (AC-PC), covering the whole brain (TR = 3 s, TE = 50 ms, flip angle = 90 degrees, matrix = 64 x 64, field of view (FOV) = 200 mm). The first five volumes of each session were discarded, to allow time for the longitudinal magnetization to reach a steady state. High-resolution T1-weighted anatomic images were also acquired for each subject at the end of the sessions.

Statistical analysis was carried out using SPM software (SPM99; Wellcome Department of Cognitive Neurology, London, UK) based on the general linear model (Friston, 1997). Images were realigned to the first scan of the session, stereotactically normalised into a standard space approximating that of Talairach and Tournoux (Talairach & Tournoux, 1988) and smoothed with an isotropic Gaussian kernel of 8 x 8 x 8 mm. Low frequency confounds were removed by a high pass filter with individually adjusted cutoffs. Data analysis was carried out by modelling the different conditions as reference waveforms, using boxcar functions convolved with a canonical hemodynamic response function (HRF).

A second level random effects approach was applied for statistical analysis. This approach takes into account between-subject variability, allowing a more critical exploration of blood oxygenation level-dependent (BOLD) responses than fixed-effects models (A. P. Holmes & K. J. Friston, 1998). On the first level, the four functional sessions were entered into an individual design matrix for each subject. Here, surprise and disgust conditions were defined explicitly with the neutral face conditions modelled implicitly. To show areas particularly involved in the perception of a specific emotional expression, both emotion conditions were contrasted against two different baselines: (1) surprise and disgust conditions

were compared to the neutral face condition (surprise vs. neutral, disgust vs. neutral); and (2) both emotion conditions were compared directly to each other (surprise vs. disgust and disgust vs. surprise). For a region to be denoted as specifically involved in perception of either surprise or disgust expressions, it thus had to fulfil the strict criterion of corresponding results across two different baseline conditions. For each of the four comparisons, individual contrast images were entered into a second level (random effects) analysis applying a one-sample *t*-test. Significance was accepted for voxels surviving a statistical threshold of $P < 0.001$, uncorrected. To avoid false positives, only clusters of 20 or more contiguous voxels were considered (Forman et al., 1995). All coordinates reported are based on the Talairach atlas and were transformed by applying procedures developed by M. Brett (available online at http://www.mrc-cbu.cam.ac.uk/Imaging; accession date 10 April 2003).

3.4 Results

Mean accuracy of gender classification during scanning was 95% (*SD* = 7%) for 17 subjects (data of 3 subjects were not recorded due to technical problems). Contrasting surprise with the neutral face condition was associated with increased activations in the right parahippocampal gyrus, right cerebellum, middle temporal gyrus (Brodmann's area (BA) 21) and adjacent posterior superior temporal sulcus (STS) as well as in occipital regions (BA18) (Table 3.1, Figure 3.1). The crucial role of the parahippocampal gyrus in the perception of surprise was underscored further by direct comparison of the 'surprise' with the 'disgust' condition, revealing significant activation exclusively in the right parahippocampal gyrus (Table 3.1, Figure 3.2).

Table 3.1: Activations in response to the perception of surprise expressions

Region	Side	*x*	*y*	*z*	*t**
Surprise versus neutral					
Parahippocampal gyrus (BA30/35)	Right	16	-31	-7	3.74
Middle temporal gyrus / STS (BA 21)	Right	57	-44	8	5.28
Lingual Gyrus (BA 18)	Left	-22	-95	-5	5.36
Inferior occipital gyrus (BA 18)	Left	-24	-88	-7	4.64
Cerebellum	Right	12	-35	-8	5.24
Surprise versus disgust					
Parahippocampal gyrus (BA 35)	Right	20	-24	-14	4.47

Regions activated by surprise versus neutral condition and surprise versus disgust condition. Talairach coordinates refer to each regional cluster and the associated *t*-values are shown. *$P < 0.001$, uncorrected, extent threshold = 20 voxels. BA, Brodmann area; STS, superior temporal sulcus.

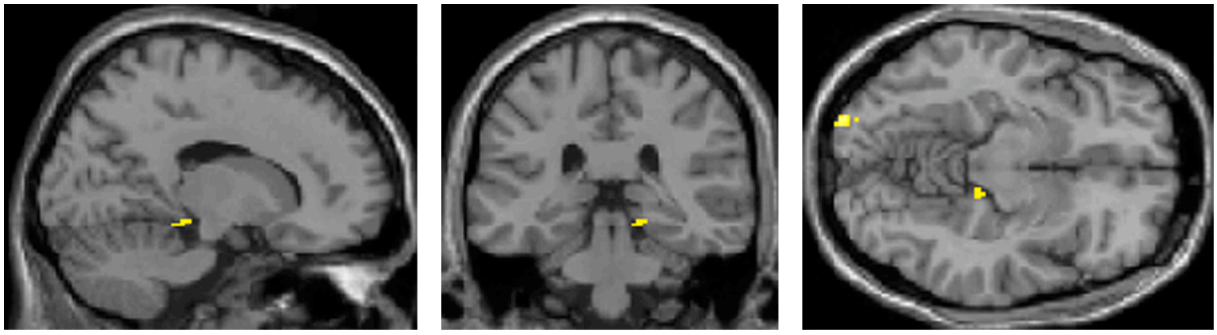

Figure 3.1: A statistical parametric map (SPM) showing significant activation of the right parahippocampal gyrus and left occipital gyrus in the surprise condition relative to the neutral condition ($P < 0.001$, uncorrected, extent threshold = 20 voxels).

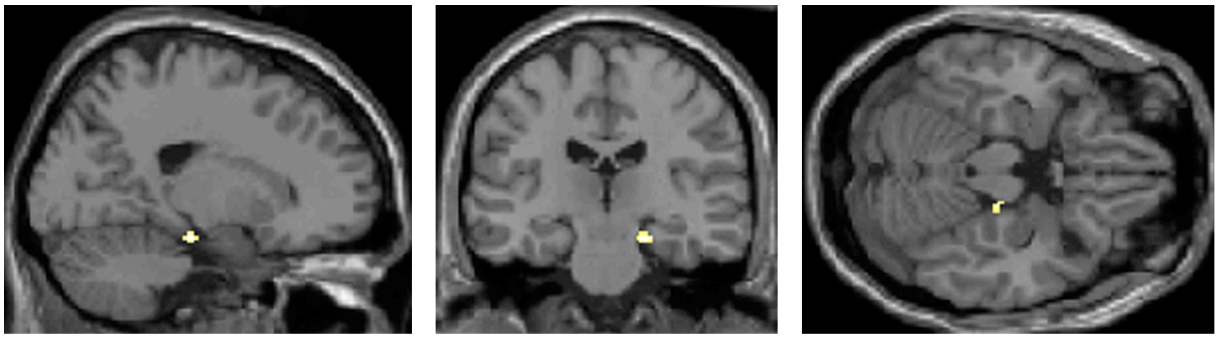

Figure 3.2: A statistical parametric map (SPM) showing significant activation of the right parahippocampal gyrus in the surprise condition relative to the disgust condition ($P < 0.001$, uncorrected, extent threshold = 20 voxels).

We found insular activations during perception of disgust for both contrasts (disgust vs. neutral and disgust vs. surprise). Perception of disgust when compared to the neutral face condition yielded additional activations in inferior frontal, postcentral, temporal, and occipital regions (Table 3.2). Besides insular activation, the contrast of disgust with the surprise condition demonstrated further activations within the claustrum, inferior frontal gyrus, thalamus, postcentral and paracentral gyrus, inferior parietal gyrus, cerebellum, brainstem, and occipital cortices (see Table 3.2).

Table 3.2: Activations in response to the perception of disgust expressions

Region	Side	*x*	*y*	*z*	*t**
Disgust versus neutral					
Insula (BA 13)	Right	38	5	15	4.64
Inferior frontal gyrus (BA 45)	Right	51	18	10	5.09
Inferior frontal gyrus (BA 46)	Right	50	43	9	4.88
Postcentral gyrus (BA 3)	Right	36	-32	53	4.53
Fusiform gyrus (BA 20)	Left	-38	-41	-13	4.56
Middle temporal gyrus (BA 39)	Right	51	-73	20	5.63
Inferior and middle occipital Gyrus (BA 19)	Right	46	-80	-3	6.00
Middle occipital gyrus (BA 18/19)	Left	-42	-81	15	4.16
Inferior and middle occipital gyrus (BA 18)	Right	-38	-93	0	5.56
Cuneus (BA 18)	Left	-22	-97	10	5.64
Disgust versus surprise					
Insula (BA 13)	Right	34	-3	19	4.09
Claustrum	Right	30	-3	17	5.02
Inferior frontal gyrus (BA 46)	Right	53	39	13	5.73
Thalamus (medio-dorsal)	Left	-6	-13	6	5.34
Postcentral gyrus (BA 2)	Left	-59	-25	44	4.76
Inferior parietal gyrus (BA 40)	Left	-36	-35	39	5.98
Paracentral gyrus (BA 5)	Left	-12	-38	55	4.58
Middle occipital gyrus (BA 37)	Right	50	-63	-7	4.00
Inferior occipital gyrus (BA 19)	Right	44	-78	-3	5.67
Cuneus (BA 19)	Left	-16	-88	25	5.06
Cerebellum	Right	12	-59	-22	5.20
Brainstem	Right	12	-19	-29	4.34

Regions activated by disgust versus neutral condition and disgust versus surprise condition. Talairach coordinates are referring to each regional cluster and the associated *t*-values are shown. *$P < 0.001$, uncorrected, extent threshold = 20 voxels. BA, Brodmann area.

To explore whether gender had an influence on the neural responses within our regions of interest, we conducted *post hoc* two-sample *t*-tests on second level to show differences between men ($n = 10$) and women ($n = 10$) in perception of surprised and disgusted facial expressions when compared to the neutral face condition. These analyses revealed no significant gender effects for perception of surprised and disgusted facial expressions within the medial temporal lobes and insular cortex.

3.5 Discussion

The results presented here provide evidence that the perception of surprised facial expressions consistently recruits structures within the medial temporal lobes, namely the right parahippocampal gyrus. Furthermore, they confirm the proposed association between the insula and facial expressions of disgust (Phillips et al., 1998; Phillips et al., 1997;

Sprengelmeyer et al., 1998). Our findings thus corroborate further the notion of partly distinct neural systems for extracting meaning from different facial expressions. In support of this interpretation, activations within the parahippocampal gyrus and the insular cortex during processing of surprise and disgust expressions, respectively, satisfied our strict criterion of corresponding responses across two different high-level baselines (neutral expressions and surprise/disgust expressions).

We also found support, however, for the idea of a common neural system for perceptual analysis of facial features, within temporal and occipital cortices (Haxby et al., 2000, 2002). In line with previous studies (Phillips et al., 1997; Vuilleumier, Armony, Driver, & Dolan, 2001), activation of the temporal and occipital cortices was more pronounced when the emotional (surprise/disgust) conditions were compared to the neutral condition than when compared to each other. Increased activation of these areas may represent top-down modulatory effects on the visual processing stream, reflecting attentional enhancement due to emotional significance (Pessoa et al., 2002; Vuilleumier et al., 2001). Furthermore, the posterior part of the STS, as implicated during perception of surprised relative to neutral expressions, has been previously related to perception of static images of changeable aspects of the face (Hoffman & Haxby, 2000) including facial expression (Critchley et al., 2000; Kanwisher et al., 1997; Narumoto, Okada, Sadato, Fukui, & Yonekura, 2001; Phillips et al., 1998).

Previous neuropsychologic and functional imaging studies have underscored the importance of the inferior frontal/orbitofrontal cortex in the extraction of emotional meaning from the face (Hornak et al., 1996; Nakamura et al., 1999; Narumoto et al., 2000; Sprengelmeyer et al., 1998). The inferior frontal/orbitofrontal cortex has been suggested to play an essential role in social reinforcement processes (Rolls, 1996) and to be a common endpoint of networks of emotion recognition (Sprengelmeyer et al., 1998). We found inferior frontal/orbitofrontal activation, however, during perception of facial expressions of disgust but not of surprise. This might be explained by the fact that surprise has no definite positive or negative valence as suggested by Ekman and Friesen: "…surprise itself is neutral in hedonic tone. It is rather the following emotion that gives it a positive or negative tone to the experience" (Ekman & Friesen, 1975; p 35).

The results of our study further support the idea of partly independent neural representations for distinct basic emotions, mediating the processing of different information crucial for survival and environmental adaptation. Accordingly, we demonstrate activation of the parahippocampal gyrus during surprise, but not disgust perception. Functional

neuroimaging studies have implicated the parahippocampal gyrus (Gabrieli et al., 1997) or posterior hippocampus and parahippocampal gyrus (Stern et al., 1996) in processing of novel compared to familiar visual stimuli. Consistent with this, Hunkin et al. found medial temporal lobe activations centred in the parahippocampal gyrus during processing of verbal associative novelty (Hunkin et al., 2002). Findings from lesion studies and single-unit recordings in monkeys further support the role of the parahippocampal gyrus in novelty detection, showing perirhinal involvement during processing of contextual novelty (Brown & Aggleton, 2001). In addition, the parahippocampal region receives prominent projections from unimodal and polymodal high-level visual temporal and occipital cortices (Suzuki & Amaral, 1994), also implicated in the present study. The perception of facial expressions of surprise in others may therefore be related to detection or evaluation of novel stimuli in the environment, which is thought of as an initial step in memory formation subserved by the parahippocampal area (Fernandez et al., 1998). This notion is in accordance with a psychological model of surprise, proposing an evolutionary old mechanism to analyse unexpected events in order to update knowledge for successful individual-environmental transaction (Schutzwohl, 1998).

An alternative explanation would be that activations in the parahippocampal gyrus might have been caused merely by unfamiliar faces per se. We feel that this is unlikely, however, as no such activations occurred during the presentation of disgusted when compared to neutral faces and all individual faces were presented repeatedly. Another objection might be that surprised faces might have been confused with fearful faces. We therefore conducted a *post hoc* behavioural assessment using a set of morphed faces from the FEEST, each showing two of the six basic emotions with different degrees of intensity (Young et al., 2002; for a detailed description please refer to the FEEST handbook). Subjects were instructed to categorize each morphed face according to one of the six basic emotions with a maximum score of 20 correct responses for each emotion. An errors analysis of surprise recognition scores revealed only a few confusion errors with happiness (0.75 ± 0.91) and fear (1.65 ± 2.16), both being part of the surprise morphs. A paired *t*-test revealed no more confusion of surprised with fearful than with happy expressions (t = -1,67; P = 0.11). Activations of the parahippocampal gyrus in response to surprised faces are thus unlikely due to confusion of surprised with fearful expressions. Moreover, the parahippocampal responses during surprise perception observed in our study can be distinguished clearly from amygdala activations implicated in the perception of fearful faces (Morris et al., 1996; Whalen et al., 1998). Even with clearly defined regions of interest for the bilateral amygdala (defined as spheres of 10-mm radius centred at ±24, -4, -16, based on the location of the amygdala in the Talairach

atlas) and small volume correction, we could not find significant responses within this region during perception of surprised faces when compared to either neutral or disgusted faces.

Insular activation found during perception of disgusted facial expressions converge with evidence from studies based on insular lesions (Calder, Keane, Manes et al., 2000), depth electrodes (Krolak-Salmon et al., 2003), and functional imaging (Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998), thus confirming the robustness and reliability of our findings. A metaanalysis carried out by Murphy et al., including four imaging studies that used facial expressions of disgust (Phillips et al., 1999; Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998), revealed that the insula was the only neural structure consistently activated across all studies (Murphy, Nimmo-Smith, & Lawrence, 2003). As the insular cortex has been implicated in gustatory processing (Frey & Petrides, 1999), recognition of disgust in others has been linked to the evaluation of distasteful stimuli (Phillips et al., 1997). Accordingly, a recent fMRI-study by Wicker and colleagues (2003) provided evidence for involvement of the insula during both perceiving facial expression of disgust and experiencing disgust. In our study, we further validated the association between the anterior insula and the processing of facial disgust, showing that the insula is also activated when the perception of disgusted faces is compared directly to the perception of a different emotion (surprise). By contrast, findings concerning the role of the basal ganglia in disgust are less consistent, given that imaging studies have revealed activation within different (sub)structures of the basal ganglia, that is, putamen, globus pallidus and nucleus caudatus (Phillips et al., 1999; Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998). Despite these heterogeneous results, the metaanalysis by Murphy et al. (2003) also pointed to a role of the globus pallidus in perception of facial disgust. Even at a more liberal statistical threshold, however, using small volume correction ($P < 0.05$) based on the coordinates provided by Murphy et al. (2003), we could not find significant neural responses within this region during the processing of disgusted faces when compared to either neutral or surprised faces.

In conclusion, our findings demonstrate robust medial temporal lobe activations, during perception of surprised facial expressions, that are focused in the parahippocampal gyrus and further corroborate the role of the insula in the emotion of disgust. We suggest that surprise perception in others subserves a specific adaptive function, related to novelty

detection. Furthermore, these findings support the concept of partly distinct neural system for perceiving different emotional facial expressions[2].

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4 NEURAL CORRELATES ASSOCIATED WITH IMPAIRED DISGUST PROCESSING IN PRE-SYMPTOMATIC HUNTINGTON'S DISEASE[1]

4.1 Summary

Disturbances in recognising facial expressions of disgust have been reported previously in pre-symptomatic and manifest Huntington's disease. Given the substantial role of the insula and basal ganglia in the perception of disgust as revealed by functional imaging, lesion studies and intracerebral recordings, we propose dysfunction within the insula and/or basal ganglia as the underlying neural substrate. Using functional MRI (fMRI), we studied a group of nine pre-symptomatic Huntington's disease gene carriers and nine healthy controls, matched for age, gender, intelligence and years of education, while they were viewing disgusted facial expressions. As control conditions, surprised and neutral expressions were presented. Compared with healthy controls, Huntington's disease gene carriers showed reduced responses within the left dorsal anterior insula during processing of disgusted facial expressions. Moreover, processing of disgust was associated with significant activation of the left dorsal anterior insula and putamen in healthy controls, but not in Huntington's disease gene carriers. Furthermore, behavioural assessment revealed a selective impairment in recognising facial expressions displaying disgust in Huntington's disease gene carriers. Our finding of dysfunctional decreased insula activation in pre-symptomatic Huntington's disease provides an explanation for the clinical deficit in recognising facial expression of disgust. Furthermore, it underscores the role of the insula in the emotion of disgust.

KEY WORDS: Huntington's disease; fMRI; disgust; facial expression; insula

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4.2 Introduction

Huntington's disease is a dominantly inherited neurodegenerative disorder primarily affecting the striatum with a generalized loss of medium-sized spiny neurons (Goto et al., 1989). The clinical picture is characterized by involuntary choreiform movements and cognitive and emotional dysfunctions (Lawrence, Sahakian, & Robbins, 1998; Speedie, Brake, Folstein, Bowers, & Heilman, 1990) including impairments in the processing of faces and emotional facial expressions (Jacobs, Shuren, & Heilman, 1995). In a study using prototypical emotion expression stimuli and morphed emotional expressions produced from six basic emotions (happiness, surprise, fear, sadness, disgust and anger), patients with manifest Huntington's disease showed problems in recognising several emotional expressions, but a disproportionately severe impairment in recognising facial expressions of disgust (Sprengelmeyer et al., 1996). The finding that Huntington's disease particularly affects recognition of disgust has been corroborated by a case study of two manifest Huntington's disease patients (Sprengelmeyer, Young, Sprengelmeyer et al., 1997) and a study with Chinese patients suffering from Huntington's disease (Wang et al., 2003). Furthermore, there is evidence for impaired recognition of facial disgust in the absence of manifest Huntington's disease symptomatology. Gray et al. investigated face processing in pre-symptomatic people at risk of carrying the gene mutation associated with Huntington's disease (Gray et al., 1997). Participants subsequently identified as gene carriers were compared with the non-gene carriers and a group of healthy controls. Compared to both groups, gene carriers showed a selective impairment in the recognition of disgusted faces, which could not be explained by basal visual and cognitive deficits.

Together with evidence from patients with amygdala lesions suffering from a selective deficit in recognising facial expressions of fear (Adolphs et al., 1994; Sprengelmeyer et al., 1999; Young et al., 1995), these findings support the notion of partly separable and specialized neural systems for recognising different facial expressions. Furthermore, perception of disgusted but not fearful facial expressions has consistently been associated with activations of the insula and putamen, as revealed by means of functional imaging (Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998). These findings converge with evidence for impaired disgust recognition in a case study of a patient with left hemisphere infarction involving the insula and putamen (Calder, 2003; Calder, Keane, Manes et al., 2000). Moreover, Krolak-Salmon et al. demonstrated intracerebral event-related potentials to facial expressions of disgust from insular contacts in patients suffering from drug-refractory temporal lobe epilepsy (Krolak-Salmon et al., 2003).

However, the neural substrate underlying the deficit of recognising disgust in Huntington's disease has not been investigated yet. Given the prominent interconnections between the striatum and insular cortex (Chikama, McFarland, Amaral, & Haber, 1997) and their implication in the perception of disgust (Calder, Keane, Manes et al., 2000; Krolak-Salmon et al., 2003; Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998), we hypothesized that the selective impairment of processing disgusted facial expressions in pre-symptomatic Huntington's disease is associated with decreased activation of the insula and/or putamen. In the current study, we tested this hypothesis using blood oxygenation level-dependent (BOLD) functional MRI (fMRI) to compare the response of the insula and putamen during perception disgusted facial expressions in pre-symptomatic Huntington's disease gene carriers with that in age-, gender-, education- and intelligence-matched healthy subjects.

4.3 Methods

4.3.1 Subjects

Nine pre-symptomatic Huntington's disease gene carriers (mean number of CAG repeats: 43.7, *SD* = 1.7), four females and five males, took part in the study. The mean age of the gene carriers was 37.4 years (*SD* = 5.4 years), mean duration of schooling was 10.7 years (*SD* = 1.9 years) and mean intelligence quotient (IQ) was 112.9 (*SD* = 11.1) as measured with the MWT-B German vocabulary recognition test (Lehrl, 1977). All gene carriers were right-handed following the criteria of the Edinburgh Handedness Inventory (Oldfield, 1971) and showed no signs of manifest choreic movements (for individual data, see Table 4.1). For all gene carriers, T1-weighted anatomical MRIs were acquired. Subcortical and cortical atrophy in frontal, parietal and temporal lobes was evaluated by two experienced neuroradiologists, naive about the results of neuropsychological testing and functional MRI. Furthermore, the caudate index (CI) was determined as a measure for subcortical atrophy, defined as the ratio of maximum and minimum distance between both side ventricles at the level of the interventricular foramen. The CI of one gene carrier (Huntington's disease subject 05) was scored pathological (CI < 1.8) (see Table 4.1). There were no signs of cortical atrophy within the insular cortex in all Huntington's disease gene carriers. In two gene carriers, minimal cortical atrophy was detected in parietal areas.

Table 4.1: Characteristics of gene-positive participants

Code	Sex	Age (years)	Education (years)	IQ	CAG	CI	Handedn.
01	Female	42	9	118	43	1.9	Right
02	Male	42	10	118	43	2.0	Right
03	Male	33	9	100	46	2.7	Right
04	Female	36	13	118	45	2.1	Right
05	Male	46	14	124	42	1.7	Right
06	Male	36	10	130	45	2.1	Right
07	Male	36	9	100	41	2.4	Right
08	Female	38	12	104	45	1.8	Right
09	Female	28	10	104	43	2.4	Right

Handedness was measured with the Edinburgh Inventory (Oldfield, 1971), IQ with the MWT-B (Lehrl, 1977).

The control group consisted of nine healthy adults free of neurological and psychiatric disorders, matched to the Huntington's disease group according to age (t = -1.20, P > 0.1), education (t = 1.79, P > 0.05), IQ (t = 1.52, P > 0.1) and gender (four female, five males). All controls were right-handed according to the criteria of the Edinburgh Handedness Inventory (Oldfield, 1971). Informed written consent according to the Declaration of Helsinki was obtained from each subject. The local Ethics Committee of the Technische Universität München gave approval for this study.

4.3.2 Neuropsychological background assessment

To ensure that any problems in facial expressions processing could not be explained by deficits in basal visual and cognitive functions, gene carries were tested with a number of standard neuropsychological tasks. The Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was given for dementia screening. Global intellectual function was measured with a German short version of the Wechsler adult intelligence scale (WIP, Wechsler, 1987), consisting of the subtests 'Information', 'Similarities', 'Picture Completion' and 'Block Design'. The Vistech VCTS 6000 contrast sensitivity chart, measuring visual accuracy and contrast sensitivity, was applied to test for basic visual processing. To ensure that early processing stages of perception of faces were intact, the Benton Facial Recognition Test (Benton, Sivan, Hamsher, Varney, & Spreen, 1983) was used. In this test, subjects are asked to pick a photograph of a target face from amongst six simultaneously presented faces of the same person. Items include identical photographs, as well as transformations of orientation or lighting.

In summary, there were no signs of dementia (MMSE; M = 28.8, SD = 1.2) or impairments in global intellectual function (WIP; M = 103.4, SD = 7.2). Gene carriers showed

normal contrast sensitivity and visual acuity for all spatial frequencies (Vistech VCTS 6000), and early stages of face processing were intact (Benton; $M = 45.8$, $SD = 4.7$).

4.3.3 Recognition of facial expressions of emotion

Immediately after fMRI scanning, facial expression recognition abilities of gene carriers and controls were assessed. A set of morphed pictures showing faces of the actor J.J. taken from the *Facial Expressions of Emotions: Stimuli and Test* (FEEST) (Young et al., 2002) was used. Each face shows two of the six basic emotions (happiness, surprise, fear, sadness, disgust and anger) with different degrees of intensity (e.g. 90% happiness/10% surprise, 70% happiness/30% surprise, 50% happiness/50% surprise, 30% happiness/70% surprise and 10% happiness/90% surprise; for a detailed description, please refer to the handbook of the FEEST). A set of 30 morphed photographs, spanning the six basic emotions, was presented five times, adding up to a maximum score of 20 for each emotion. Subjects were instructed to categorize each morphed face according to one of the six basic emotions. Responses were made by pressing one of six buttons labelled with the names of the six possible emotions. To ensure their understanding of the meanings of verbal emotion terms used for responses, participants gave verbal examples for each emotion. There was no time restriction, and no feedback was given as to the appropriateness of any responses. Before statistical analysis, the data were screened for homogeneity of variance. Differences among group means for each emotion were assessed using Student's *t*-tests. Welch's approximation to the *t*-test for unequal variances was used when group variances were not homogeneous (Welch, 1947). Since we predicted impairment of recognising disgusted faces, these comparisons were based on one-tailed probabilities.

4.3.4 fMRI stimuli and paradigm

Gene carriers and controls viewed grey-scale pictures of faces from the FEEST (Young et al., 2002), displaying disgust, surprise or neutral expressions. As a neutral face, we used a morphed image with slightly happy expression (25% happy, 75% neutral), produced by computer graphical manipulation, because 100% neutral faces appear slightly cold and threatening (Phillips et al., 1997). Each picture was presented individually against a grey background for 3 s with an interstimulus interval of 0.76 s. Within one block, eight faces (3 male/5 female) of the same expressions were presented in randomised order. Ten blocks with alternating emotional (disgusted or surprised) and neutral faces constituted one session. Participants performed four separate sessions in a counterbalanced order, two sessions including disgusted and neutral and the other two surprised and neutral faces. In line with

previous studies of emotion perception (Blair et al., 1999; Morris et al., 1996; Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998), an implicit paradigm of facial expression perception was applied, with subjects pressing left or right response buttons in a gender decision task. To familiarize subjects with the stimuli, they viewed each picture once before fMRI scanning.

4.3.5 Image acquisition and analysis

Echoplanar brain MRIs were acquired using a 1.5 T Siemens Symphony Scanner (Erlangen, Germany) with a standard head coil. During each run, 110 T2*-weighted images were acquired at each of 33 slices (at 4 mm) parallel to the intercomissural line (AC-PC), covering the whole brain [repetition time (TR) = 3 s, echo time (TE) = 50 ms, flip angle = 90°, matrix = 64 x 64, field of view (FOV) = 200 mm]. The first five volumes of each session were discarded to allow time for the longitudinal magnetization to reach a steady state. High-resolution T1-weighted anatomical images were also acquired for each subject at the end of the sessions.

Statistical analysis was performed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK) based on the general linear model (Friston, 1997). Images were realigned to the first scan of the session, stereotactically normalised into a standard space approximating that of Talairach and Tournoux (1988) and smoothed with an isotropic Gaussian kernel of 10 mm full-width at half-maximum (FWHM). Data analysis was performed by modelling the different conditions as reference waveforms, using box-car functions convolved with a canonical hemodynamic response function. For individual subject analyses, the four functional sessions were entered into an individual design matrix. Subject-specific low frequency confounds were removed by a high pass filter with individually adjusted cut-offs. Subjects of both groups (Huntington's disease gene carriers and controls) were analysed contrasting emotion conditions with the neutral face condition (disgust/neutral, surprise/neutral). Individual images for both contrasts subsequently were entered into separate second level (random effects) analyses. To study involvement of the insula and putamen during disgust processing within groups, we conducted second level one-sample *t*-tests for each group separately. A two-sample *t*-tests was applied for calculating differences in disgust responses between groups (controls versus Huntington's disease gene carriers). In order to establish the discriminant validity of our findings, that is to check if activation differences between both groups are specific for the processing of disgusted facial expressions, the same analyses were conducted for perception

of surprise expressions. According to our *a priori* hypothesis, Huntington's disease gene carriers were expected to show significantly decreased activation within the insula and/or putamen only during perception of disgust expressions but not while processing of a different emotion (surprise).

For the insula and the putamen, regions of interest (ROIs) were defined by spheres of 10 mm radius centred on mean coordinates derived from previous studies of disgust perception (Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998) (see Table 4.2). Reported *P* values are corrected for the number of comparisons made within each *a priori* ROI. Significance was accepted for clusters of five or more contiguous voxels exceeding a statistical threshold of $P < 0.05$. For non-predicted regions, significance was accepted for voxels surviving false discovery rate (FDR) correction ($q < 0.05$) for multiple spatial comparisons across the whole brain. All coordinates reported are based on the Talairach atlas and were transformed from Montreal Neurological Institute (MNI) space to Talairach stereotactic space applying procedures developed by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging).

Table 4.2*:* Coordinates for *a priori* ROIs

Region	Talairach coordinates		
	x	*y*	*z*
Insula			
left	-35	8	8
right	37	-3	7
Putamen			
left	-26	-19	9
right	23	-5	2

Mean coordinates for *a priori* regions of interest (insula and putamen), based on previous fMRI studies contrasting disgusted with neutral face perception (Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998). The coordinate for the left putamen is based on a single observation (Phillips et al., 1998).

4.4 Results

4.4.1 Recognition of facial expressions of emotion

Results for identification of morphed facial expressions of emotion are presented in Figure 4.1, showing mean identification rates and SEMs for each of the six basic emotions by Huntington's disease gene carriers and controls. Huntington's disease gene carriers performed significantly worse than controls in recognising disgust ($t_{10.59} = 2.03$, $P < 0.05$, one-tailed).

However, the groups did not significantly differ on recognition of any other emotion (happiness: $t_{16} = 0.00$, $P > 0.1$; surprise: $t_{16} = 1.40$, $P > 0.05$; fear: $t_{12.08} = 0.49$, $P > 0.1$; sadness: $t_{16} = -0.34$, $P > 0.1$; anger: $t_{16} = 1.72$, $P > 0.05$; all one-tailed).

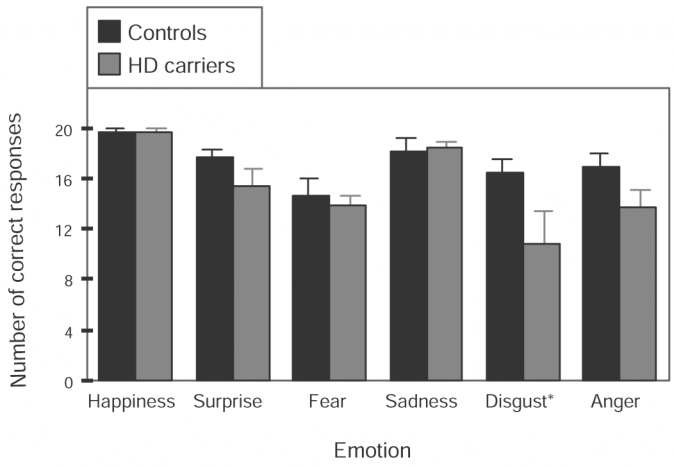

Figure 4.1: Mean number of faces correctly labelled for each of the six emotions in the expression recognition task, in controls and Huntington's disease carriers. Error bars represent SEMs. *$P < 0.05$ (one-tailed).

4.4.2 fMRI results

Consistent with previous reports involving healthy subjects (Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998), controls showed significant signal increases within the left dorsal (intermediate) anterior insula/opercular region and left putamen during processing of disgusted relative to neutral facial expressions, that were absent in Huntington's disease gene carriers (Table 4.3). More importantly, Huntington's disease gene carriers showed reduced responses within the left dorsal (intermediate) anterior insula and adjacent opercular region during processing of disgusted faces, as revealed by a two-sample *t*-test (see Figure 4.2, Table 4.3). Note that all reported within- and between-group differences in activation for our ROIs were specific for the emotion of disgust, since they were not apparent for the surprise contrasts. Furthermore, between-group comparisons of the neural responses to the neutral face condition alone (Huntington's disease gene carriers versus controls, controls versus Huntington's disease gene carriers) revealed no significant differences between groups within ($P < 0.05$, small volume corrected) and outside our ROIs ($q < 0.05$, FDR-corrected across the whole brain). Thus, the observed between-group differences in neural response to disgusted versus neutral faces within the left anterior insula were clearly the result of signal

decreases in this region to disgust expressions rather than increases to neutral expressions in the Huntington's disease gene carriers. Moreover, the exclusion of Huntington's disease subject 05 showing a CI that was scored pathological (CI = 1.7) had no influence on the results of our ROI analyses as revealed by *post hoc* between- and within-group comparisons for emotion (disgust/surprise) versus neutral expression contrasts.

Table 4.3: BOLD responses within ROIs (insula and putamen) to disgusted versus neutral expressions in within- and between-group comparisons

Brain region/group	Talairach coordinates			*Z* score*
	x	*y*	*z*	
Insula				
Controls				
Left dorsal anterior mid-insula	-42	6	13	4.31
Huntington's disease gene carriers	-	-	-	NS
Controls versus Huntington's disease gene carriers				
Left dorsal anterior mid-insula	-44	5	13	4.21
	-40	1	11	3.43
Putamen				
Controls				
Left putamen	-28	-15	12	3.62
Huntington's disease gene carriers	-	-	-	NS
Controls versus Huntington's disease gene carriers	-	-	-	NS

x, y, z express the position of the voxel(s) with peak activation level within a cluster in mm relative to the anterior commissure (AC) in stereotactic space (Talairach & Tournoux, 1988), *x* = lateral distance from the midline (- right, + left), *y* = anteroposterior distance from the AC (+ anterior, - posterior), *z* = height relative to the AC line (+ above, - below). NS, not significant. **P* < 0.05 corrected for multiple spatial comparisons across a small volume of interest.

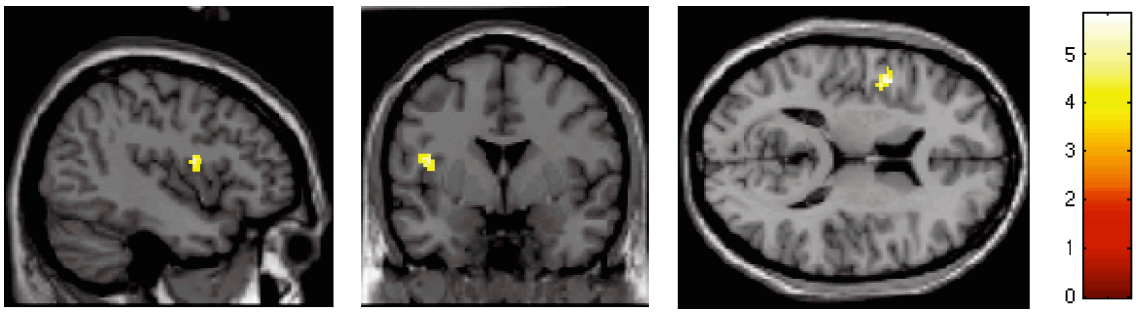

Figure 4.2: Statistical parametric map illustrating differences in BOLD response between Huntington's disease gene carriers and controls during perception of disgusted facial expressions. Huntington's disease gene carriers show significantly decreased activation in the left dorsal anterior mid-insula and adjacent opercular region (*P* < 0.05, small volume corrected). Activation is displayed superimposed onto three orthogonal sections of the MNI brain.

To identify areas of significant activation for the disgust and surprise condition relative to the neutral face condition, independent of specific ROIs, an additional whole brain analysis ($q < 0.05$, FDR-corrected) was conducted. For the disgust versus neutral expression contrast, this analysis revealed further signal increases within the middle occipital gyrus bilaterally [Brodmann area (BA) 18/19], right middle temporal gyrus (BA 19) and right precentral gyrus (BA 4) in controls and within the right cerebellum in Huntington's disease gene carriers (see Table 4.4). There were no sites of activation that survived correction across the whole brain volume in the between-group comparison of the disgust versus neutral expression contrast or the within- and between-group comparisons of the surprise versus neutral expression contrast.

Table 4.4: BOLD responses within non-predicted regions to disgusted versus neutral expressions in within- and between-group comparisons

Brain region/group	Talairach coordinates			*Z* score*
	x	*y*	*z*	
Controls				
R mid. occipital gyrus BA 18	38	-93	3	5.27
R mid. occipital gyrus BA 19	44	-81	11	4.83
R mid. temporal gyrus BA 19	46	-60	12	4.67
R precentral gyrus BA 4	46	-15	52	4.62
L mid. occipital BA 19	-40	-79	15	4.55
Huntington's disease gene carriers				
R cerebellum	36	-36	-30	5.09
Controls versus Huntington's disease gene carriers	-	-	-	-

x, y, z express the position of the voxel(s) with peak activation level within a cluster in mm relative to the anterior commissure (AC) in stereotactic space (Talairach & Tournoux, 1988), *x* = lateral distance from the midline (- right, + left), *y* = anteroposterior distance from the AC (+ anterior, - posterior), *z* = height relative to the AC line (+ above, - below). *$q < 0.05$ FDR-corrected across the whole brain volume. R = right; L = left.

4.5 Discussion

This study aimed at investigating the neural correlate of the selective impairment of processing disgust in pre-symptomatic Huntington's disease. Using a hypothesis-driven ROI approach, we demonstrate for the first time that this deficit is associated with altered neural activity in a circumscribed brain region: compared with healthy controls, an age-, gender-, education- and intelligence-matched group of pre-symptomatic Huntington's disease gene carriers showed reduced activations within the left dorsal anterior mid-insula during perception of disgusted facial expressions, that were absent while processing a different

emotion (surprise). Moreover, only in controls was perception of disgusted when compared to neutral faces was associated with activations of the left dorsal anterior insula and putamen. In contrast, Huntington's disease gene carriers failed to show activations within our ROIs. These imaging data are consistent with the results of the behavioural assessment revealing that Huntington's disease gene carriers were selectively impaired in recognising facial expressions displaying disgust.

Our finding of reduced responses within the dorsal anterior insula during disgust processing in Huntington's disease gene carriers is well in line with findings from previous imaging studies reporting very similar regions for processing of disgusted expressions in healthy subjects (Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998). Though there is converging evidence for a role for the insula in the emotion of disgust, findings concerning the laterality of insula responses are not consistent. Whereas some studies have demonstrated left-sided insula activation (Sprengelmeyer et al., 1998; Wicker et al., 2003), being well in line with our results, others have shown bilateral involvement of the insula (Phillips et al., 1998; Phillips et al., 1997). The left lateralised decreased activation in the posterior part of the anterior insula found in our study, however, is in agreement with evidence for impaired disgust recognition in a case study of a patient with left hemisphere infarction involving the posterior part of the left anterior insula (Calder, Keane, Manes et al., 2000).

The insular cortex is divided into three cytoarchitectonic areas: an intermediate dysgranular compartment that is closely associated with gustatory functions; a rostroventral agranular part related to olfactory and autonomic processing; and a caudodorsal granular part linked to somatosensory, auditory, and visual functions (Friedman, Murray, O'Neill, & Mishkin, 1986; Mesulam & Mufson, 1985; Penfield & Faulk, 1955; Schneider, Friedman, & Mishkin, 1993). Processing of disgusted facial expressions previously has been linked to the intermediate 'gustatory' (Phillips et al., 1998; Phillips et al., 1997; Sprengelmeyer et al., 1998) and rostroventral 'olfactory' insula (Krolak-Salmon et al., 2003). The primary cortical gustatory area in the monkey is located in the anterior insulo-opercular (intermediate) region (Scott, Yaxley, Sienkiewicz, & Rolls, 1986; Yaxley, Rolls, & Sienkiewicz, 1990). In humans, functional imaging has revealed activations within the insular/opercular primary taste cortex during gustatory stimulation (Frey & Petrides, 1999) and perception of pleasant and unpleasant tastes (O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001). Our finding of impaired performance in disgust recognition and decreased activation within the 'gustatory' (intermediate) insula and adjacent opercular region is therefore consistent with the notion that

perception of others' disgust and that of taste are closely linked (Rozin & Fallon, 1987) and share a similar neural substrate (Phillips et al., 1997).

Given that the striatum shows pathological changes even in early Huntington's disease, interruption of basal ganglia-thalamocortical loops (Alexander, DeLong, & Strick, 1986) at the level of the ventral striatum has been proposed as a possible explanation for the selective impairment in recognising disgusted facial expressions (Gray et al., 1997). A role for the striatum in this deficit is supported by the finding of impaired disgust recognition in people with Wilson's disease (Wang et al., 2003), obsessive-compulsive disorder (Sprengelmeyer, Young, Pundt et al., 1997) and unmedicated Parkinson's disease (Sprengelmeyer et al., 2002), since these disorders are also associated with abnormal metabolic activity in fronto-striatal regions (Ceballos-Baumann, 2003; Saxena, Brody, Schwartz, & Baxter, 1998; Tankanow, 1991). In fact, lack of significant striatal activation during perception of disgusted faces in our group of Huntington's disease gene carriers, as revealed by separate within-group analyses, indicates that the basal ganglia might also play a role in impaired disgust recognition. Functional neuroimaging applied to other disorders characterized by a selective loss of disgust such as obsessive-compulsive disorder, may help to clarify further the importance of the basal ganglia in this deficit.

However, pathological changes in Huntington's disease are not confined to the striatum, but also affect cortical regions (de la Monte, Vonsattel, & Richardson, 1988; Jernigan, Salmon, Butters, & Hesselink, 1991). Recently, neural loss in the insular cortex detected by means of voxel-based morphometry in a pre-clinical sample of Huntington's disease gene carriers (Thieben et al., 2002) has been considered a more plausible explanation for the selective impairment in recognising disgust and might also explain dysfunctional insula activations found in later stages of Huntington's disease (Boecker et al., 1999; Weeks et al., 1997). Moreover, the insular cortex has also been implicated in other disorders associated with impaired performances in recognising disgust, such as obsessive-compulsive disorder (Breiter, Rauch et al., 1996) and Wilson's disease (Duchen & Jacobs, 1992).

Recognition of facial expressions comprises multiple processes, including top-down modulatory projections from hetero- or transmodal regions onto the visual processing stream, that have been interpreted in terms of an allocation of attentional resources to the visual modality due to emotional significance (Pessoa et al., 2002; Vuilleumier et al., 2001). Consistent with this notion, an additional whole brain analysis, independent of specific ROIs, revealed signal increases within occipital/posterior temporal cortices during processing of disgusted compared with neutral faces in healthy controls. In contrast, Huntington's disease

gene carriers yielded no significant signal increases within these regions, probably due to dysfunctional back-projections from higher order hetero- or transmodal regions (e.g. the insular cortex) on the visual processing stream. However, this finding has to be interpreted cautiously since the between-group comparison for the disgust versus neutral contrast did not reveal decreased activations within posterior occipital/temporal regions in Huntington's disease gene carriers.

In conclusion, the present study offers a neural substrate for impaired performances in recognising disgust associated with pre-symptomatic Huntington's disease. Our findings provide evidence that this deficit is closely related to dorsal anterior insula dysfunction, as indicated by reduced activation of this area in Huntington's disease gene carriers only during perception of disgusted faces. Furthermore, they emphasize the role of the anterior insula in the processing of this emotion, supporting the concept of partly separate neural subsystems for perceiving different emotional facial expressions. The results of the current study may be limited by the small sample size of our groups, given that the number of pre-symptomatic and genetically tested Huntington's disease gene carriers is generally small. However, they provide a fruitful basis for future studies with larger samples to elucidate further the neural networks implicated in this deficit[2].

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5 A COMMON NEURAL BASIS FOR RECEPTIVE AND EXPRESSIVE COMMUNICATION OF PLEASANT FACIAL AFFECT[1]

5.1 Summary

There is accumulating evidence suggesting that the visual representation of facial affect is closely linked to its motor representation. To examine whether perception of pleasant facial affect involves neural circuitries associated with its production, we performed an fMRI experiment with 'compressed image acquisition' where subjects smiled and observed movies depicting other people smiling within scan-free time intervals between the acquisition of each image volume. Overlaps between the brain activation during observation and execution of smile expressions were located in the right premotor cortex and *pars opercularis* of the inferior frontal gyrus, right parietal operculum (SII) and left anterior insula. Observation of smile expressions further yielded signal increases within the posterior superior temporal sulcus (STS), fusiform gyrus and ventral amygdala. The results show that perceiving and expressing pleasant facial affect share a common neural basis in areas concerned with motor as well as somato- and limbic-sensory processing. In concert with temporal regions serving the visual analysis of facial expressive features, a mapping of the observed expressions onto neural circuitries associated with the production of these expressions and its somatosensory consequences could provide a description of what the expression would feel like if produced in the observer. Such a mechanism is suggested to be important for empathic understanding of others' feelings.

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5.2 Introduction

The mental representation of facial expression includes both a visual code to describe the physical structure of the face and a motor-program code that provides a description of how to produce the expression (Calder, Keane, Cole, Campbell, & Young, 2000). Separate lines of investigation have provided evidence that the visual representation of facial affect is closely linked to its motor representation. First, humans tend to show emotional facial expressions that are congruent with the expressions displayed by the sender. When people are exposed to emotionally expressive faces, they spontaneously react with distinct facial electromyographic (EMG) reactions in emotion relevant facial muscles even when facial expressions are not consciously perceived (Dimberg & Petterson, 2000; Dimberg, Thunberg, & Elmehed, 2000). Second, in the monkey's premotor and posterior parietal cortex, neurons have been described that discharge both when the monkey performs a specific goal-directed action and when it observes a similar action performed by another individual (di Pellegrino et al., 1992; Fogassi et al., 1998; Gallese et al., 1996; Rizzolatti, Fadiga, Gallese et al., 1996). Most importantly, mirror neurons located in lateral area F5 of the monkey's premotor cortex have been described that are triggered by the observation of communicative mouth gestures, that is, lip smacking ('communicative mirror neurons', Ferrari, Gallese, Rizzolatti, & Fogassi, 2003). Further evidence suggesting that the visual representation of facial affect may be intimately related to its motor representation comes from two recent functional imaging studies that addressed the neural correlates involved in imitation of static (Carr et al., 2003) and dynamic facial expressions (Leslie et al., 2004). These studies revealed that neural activation within several regions associated with observation of emotionally expressive faces including premotor and superior temporal areas as well as the insula and amygdala is modulated during imitation.

Together these findings suggest that the perception of emotional facial expressions in humans may incorporate neural circuitries implicated in their production. The actual brain regions involved in a shared representation network for perceiving and expressing specific emotions, however, are unclear. Whereas a recent functional imaging study has focused on the role of emotional experience and its somatosensory representation in recognition of negative facial affect (Wicker et al., 2003), the present fMRI study addresses the possible involvement of expressive aspects in recognising facial expressions. In contrast to previous imaging studies investigating modulatory effects of imitative facial movements on neural activity associated with observation of facial expressions (Carr et al., 2003; Leslie et al., 2004), the present study aimed to directly test for regions implicated in both observation and

execution of emotional facial action. More specifically, we were interested in whether observation of a facial action pattern expressing pleasant emotion activates neural circuitries also involved in its execution.

To this purpose BOLD-signal changes were monitored in 12 healthy subjects while they took part in four separate functional sessions. In two 'observation sessions' participants passively viewed movies depicting different faces with smiling or neutral expressions. During both 'execution sessions' they were asked to generate smile expressions by themselves or to keep their facial muscles relaxed and fixate on a static cross. Whereas the voluntary, non-imitative production of different negative facial expressions is difficult and involves complex coordination of various facial muscles, voluntary smiles can easily be produced within a short time interval by pulling the bilateral lip corners upward and are unambiguously recognised as signals of pleasant emotion (Floyd & Burgoon, 1999). Further, since voluntary smile expressions can easily be generated, the risk that subjects use different strategies (e.g., imagining facial expressions or emotionally arousing events) to generate facial expressions can be minimized. The investigation of pleasant facial affect therefore allows a close matching between observed and executed facial expressions which constitutes a prerequisite for the identification of shared neural representations involved in both observation and execution of emotional facial signals. Unlike voluntary smiling, the investigation of involuntary (emotion-induced) smiling or laughing does not allow to separate neural circuitries involved in action representation from those associated with the appreciation of humour and emotional experience. Since we aimed to examine the action representation system involved in the generation of emotional facial signals, emotion-induced facial expressions were not considered in the present study.

The occurrence of motion artefacts induced by facial movements was avoided using a compressed image acquisition protocol (Amaro et al., 2002), where facial action was timed to coincide with a short gap between the acquisition of each image volume where no data were acquired. To identify regions implicated in both perception and expression of pleasant facial affect, statistical analyses were focused on overlaps between the activations determined by smile observation and execution. Based on the findings reviewed above, we hypothesized that perception of smile expressions activates sensorimotor circuitries also involved in their production.

5.3 Methods

5.3.1 Subjects

Twelve healthy volunteers (6 females, 6 males, mean age 24.5 years), all right handed according to the criteria of the Edinburgh inventory (Oldfield, 1971) participated in the study. Subjects gave written informed consent according to the Declaration of Helsinki. The study protocol was approved by the local Ethical Committee ('Ethikkommission der Medizinischen Fakultät der Technischen Universität München').

5.3.2 Facial expression stimuli

Stimuli were selected and edited from video sequences (30 frames/s) of 4 female and 4 male face models (24-32 years), comprising one smiling and one neutral expression sequence (frontal view) of each of the eight face models, displayed from the neck up (see Figure 5.1a). Using a mirror, models were trained to contract the zygomaticus major muscles by pulling their bilateral lip corners upward with parted lips and to relax their facial muscles according to the instructions given by the experimentators. While they were filmed, the models were instructed by visual prompts displayed on a monitor, to tense and relax their facial muscles within a time window of 2 s. In order to maximise the congruence between observed and executed movements, the models were instructed to produce their smiles according to the same visual paradigm that was used to trigger the subjects' facial expressions (for a detailed description of visual cues, see next section). All video stimuli were matched for face orientation and foreground/background illumination.

5.3.3 Experimental design

The investigation of tasks associated with facial movements has previously resulted in significant image artefacts (Birn, Bandettini, Cox, Jesmanowicz, & Shaker, 1998; Hajnal, Bydder, & Young, 1996; Yetkin et al., 1996). Especially during blocked stimulus presentation, motion-induced signal changes overlap with BOLD signal changes and make it difficult to distinguish motion artefacts from 'real' fMRI signal (Birn, Bandettini, Cox, & Shaker, 1999). Approaches to solve the problem of movement artefacts used event-related fMRI and discarded scans during which movements occurred (Birn et al., 1999; Gosain, Birn, & Hyde, 2001). As BOLD signal changes are delayed relative to motion-induced signal changes that primarily occur during the actual performance of the task, the subsequent scans still contain enough BOLD signal. However, this approach does not account for differential spin history effects and image deformations caused by misalignment of slice selection relative

to the brain (Henson, Shallice, Josephs, & Dolan, 2002) and the remaining scans might therefore still be influenced by task-correlated facial movement. To overcome this problem, we interleaved a short gap between the acquisition of successive image volumes where no data were acquired ('compressed image acquisition', Amaro et al., 2002). Facial action was timed to coincide with this scan-free time interval, allowing us to minimize the risk of motion artefacts and to further improve sensitivity of our analyses. Variations of this acquisition procedure have previously been described as 'behaviour interleaved gradients (BIG)' (Eden, Joseph, Brown, Brown, & Zeffiro, 1999), 'clustered volume acquisition' (Edmister, Talavage, Ledden, & Weisskoff, 1999) or 'sparse imaging' (Hall et al., 1999) and have mainly been used for auditory tasks so far.

All volunteers underwent two observation and two execution sessions with the first block (smile/move or neutral/rest) counterbalanced within and the sequence of sessions permuted between subjects. For each observation session, images were acquired while subjects passively observed 36-s periods of repeatedly presented 2-s video sequences displaying smile expressions of different individuals (condition 'smile') alternated with 36-s periods of repeatedly presented neutral expressions of the same individuals (condition 'neutral') to control for visual input (Figure 5.1b). Video sequences were followed by a 2.5-s interstimulus interval of image acquisition. One period consisted of either eight smile- or neutral-expression videos-sequences presented in randomised order. An additional period of four smile- or neutral-video-sequences was presented at the beginning of each observation session to allow subjects to get accustomed to the experimental setting. While being scanned, subjects were asked to carefully concentrate on the expressions of the faces. Subjects were also explicitly told not to avert their gaze from the stimuli and to remain from imitating the facial expressions.

Execution sessions were identical to observation sessions concerning timing of stimulus presentation and image acquisition (Figure 5.1c). Images were acquired during 36-s periods of repeated smiling (condition 'move'), alternated with 36-s periods of visual fixation (condition 'rest'). Instead of the video sequences, a small cross was presented, indicating volunteers to generate and hold a smile expression as long as it was displayed on the screen or to fixate on it keeping their facial muscles relaxed, depending on whether the cross was preceded by an upright (move-periods) or an inverted triangle (rest-periods). The cross was presented for 1 s at the beginning of each scan-free period to allow subjects to tense and relax their facial muscles within the whole time window of 2 s, thus preventing the occurrence of facial motion during the subsequent 2.5-s interstimulus interval of compressed sequence

acquisition. Triangles were presented within the interstimulus intervals 0.5 s before the appearance of the cross in order to minimize effects of motor inhibition and prolonged reaction times at the beginning of a new period. All visual symbols were grey, presented against a light background and were viewed by projection onto a mirror placed onto the head coil in the scanner. Prior to fMRI scanning, subjects were familiarized with the meaning and timing of the visual cues. Similar to the face models, the subjects were trained to pull their bilateral lip corners upward with parted lips and to relax their facial muscles in front of a mirror. They were not explicitly asked to simulate a smile due to different strategies they might use to produce this expressions (e.g., imagining a funny situation, imagining a smiling person) (Wild, Erb, Eyb, Bartels, & Grodd, 2003). Participants were instructed to attend to the succession and timing of the visual cues, generating smile expressions during move-periods and fixating on the cross while keeping their facial muscles relaxed during rest-periods.

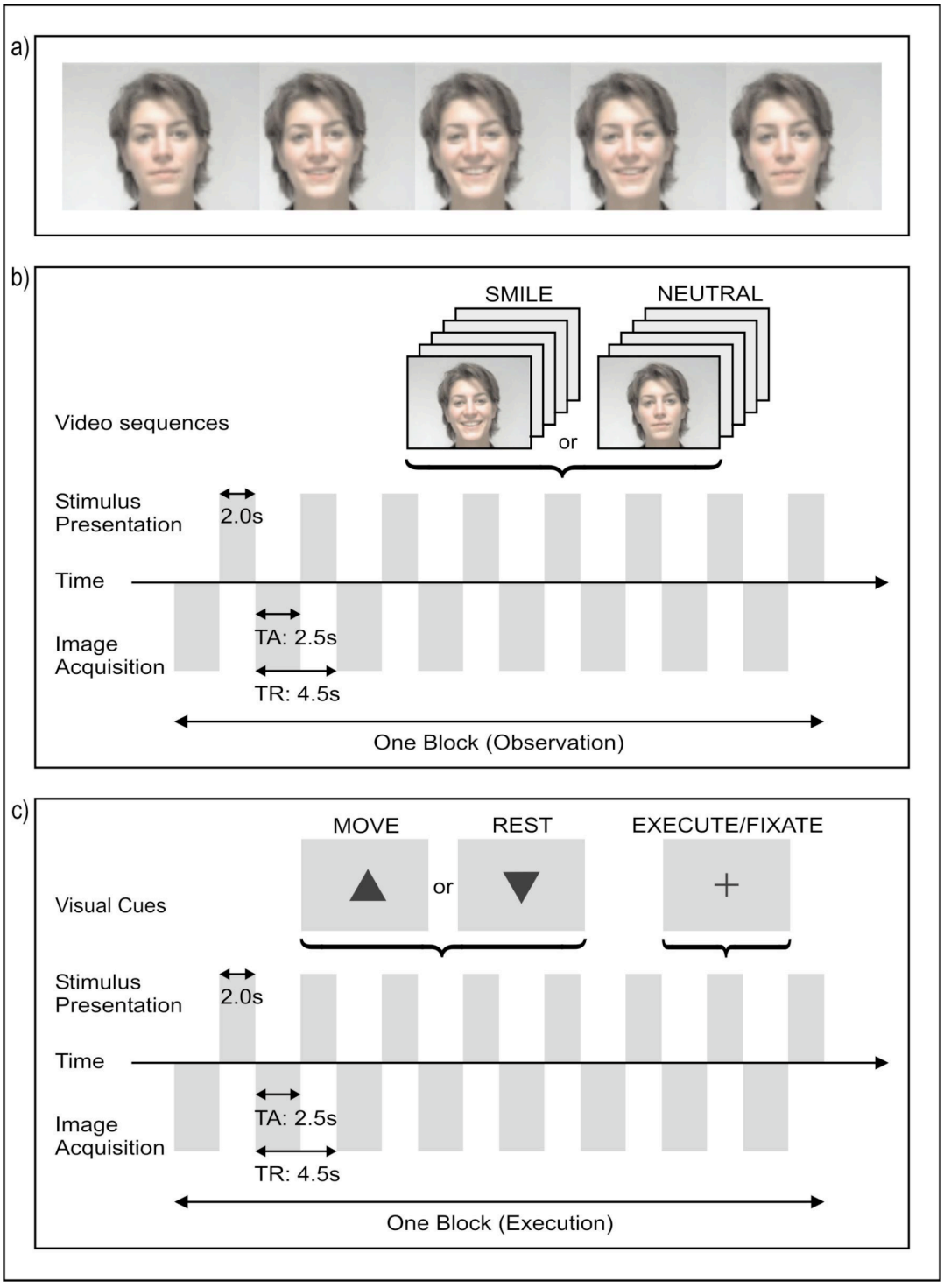

Figure 5.1: Experimental paradigm. (a) Five frames extracted from the 'smile' video sequence (30 frames/s) of one of the eight face models. (b, c) Stimulus presentation and compressed image acquisition protocol. Volumes were acquired continuously every 4.5 s (TR = repetition time) within the first 2.5 s (TA = acquisition time) of each TR. Visual execution prompts and video sequences were timed to coincide with the resulting 2.0-s gap between scans. Subjects took part in four 7 min and 48-s sessions (two observation/two execution) each consisting of alternating 36-s blocks of either (b) six 'smile' and six 'neutral' conditions during observation sessions or (c) six 'move' and six 'rest' conditions during execution sessions (see Methods for more details).

5.3.4 Image acquisition and data analysis

Echoplanar MR brain images were acquired using a 1.5-T Siemens Symphony Scanner (Erlangen, Germany) with a standard head coil. Firm foam pads were used for head fixation to minimize movement artefacts. During each session 104 T2*-weighted echo-planar images depicting BOLD contrast were acquired (TE = 50 ms, flip angle = 90°). A volume of 28 slices (FOV = 192 mm, matrix = 64 x 64) parallel to the intercomissural line (AC-PC) with a single slice thickness of 5 mm covering the whole brain was recorded during each scan. We used a compressed pulse sequence where volumes were acquired continuously every 4.5 s (TR = repetition time) within the first 2.5 s (TA = acquisition time) of each TR (see Figures 5.1b/c). The first four volumes of each session were discarded to allow time for the longitudinal magnetization to reach a steady state. High-resolution T1-weighted anatomical images were also acquired for each subject at the end of the four sessions.

Statistical analysis was performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 6.1 (Mathworks Inc., Sherborn, MA, USA) on PCs running LINUX. For each functional session, images were realigned to the first scan of the session to account for head-motion in time. Images were then stereotactically normalised into a standard space approximating that of Talairach and Tournoux and spatially smoothed with an isotropic Gaussian kernel of 8 mm at full-width at half-maximum (FWHM). Data analysis was performed by modelling the different conditions as reference waveforms, using box-car functions convolved with a canonical hemodynamic response function (hrf). To allow inferences to be extended to the population from which the subjects were drawn, a second level random effects approach was applied for all statistical analyses. On the first level, the four functional runs were entered into an individual design matrix with the two activation conditions (smile/move) and the respective baseline conditions (neutral/rest) modelled explicitly. To capture residual motion-related artefacts, movement parameters estimated during realignment pre-processing (three rigid-body translations and three rotations per session) were also included in the model. Subject-specific low frequency confounds were removed by a high pass filter with individually adjusted cut-offs. On the first level, two different contrasts were defined for observation (smile-neutral) and execution of emotional facial action (move-rest), respectively.

Analyses on the group level were based on the comparisons (1) ‘smile-neutral’ to show areas associated with observation of facial action, (2) ‘move-rest’ to show areas associated with execution of facial action and (3) a conjunction analysis of the contrasts ‘smile-neutral’ and ‘move-rest’ to test for regions involved in both observation and execution

of facial action patterns expressing pleasant emotion. Therefore, individual contrast images from the single subject analyses for each comparison (smile-neutral and move-rest) were entered into second level (random effects) analyses to determine task-specific regional responses using one-sample *t* tests. In accordance with previous imaging studies (Keysers et al., 2004; Wicker et al., 2003) using similar methods as those applied in the present study to assess overlaps of neural activation across several experimental conditions, we chose a joint intensity and spatial threshold ($P < 0.005$ uncorrected, $k = 20$ voxels) to avoid false-positives (Forman et al., 1995).

Overlaps between the smile observation (smile-neutral) and execution (move-rest) contrasts were determined by creating the intersection of the thresholded ($P < 0.005$ uncorrected, $k = 20$ voxels) three-dimensional statistical maps, using procedures provided by Thomas Nichols (http://www.sph.umich.edu/~nichols/Conj). In contrast to previous tests for conjunction (Friston, Holmes, Price, Buchel, & Worsley, 1999; Price & Friston, 1997), this method provides a valid test for a logical AND of effects as it allows to reject the null hypothesis that one or more of the comparisons has not activated even under dependence between the tests (Brett, Nichols, Andersson, Wager, & Poline, 2004). This analysis was performed at the second level, that is, on contrast images obtained from the single subject analyses, and is therefore a random-effects analysis.

5.4 Results

5.4.1 Visual action network: smile observation

Activations related to observation of dynamic smiles compared to observation of neutral facial expressions (smile-neutral) are shown in Figure 5.2 (green colour) and local maxima of activated foci in Table 5.1. This contrast revealed prominent activations in the region of the bilateral occipito-temporal junction mainly corresponding to motion-sensitive visual area V5 (BA 19/37) (Watson et al., 1993) that extended caudally into earlier visual areas (BA 18) and ventrally into the fusiform face area of both hemispheres. Significant signal increases were also found within the biological-motion-sensitive area of the right posterior superior temporal sulcus (STS) (Allison, Puce, & McCarthy, 2000) (see Figure 5.2c, *right*). Two activation foci were noted in the right premotor cortex. One was located in the ventral premotor cortex and *pars opercularis* of the inferior frontal gyrus (area 44/PMv), the other in the dorsal part of the right ventral premotor cortex with an extension into the rostral section of the dorsal premotor cortex (PMv/PMd). Activation within somatosensory-related regions

included area SI of the left hemisphere, right parietal operculum (SII) and left anterior insular cortex. Activations of the ventral amygdala were noted bilaterally extending into the bilateral parahippocampal region (Figure 5.2c, *left*). Further activated sites were located within bilateral area 47 of the inferior frontal gyrus and the temporal poles.

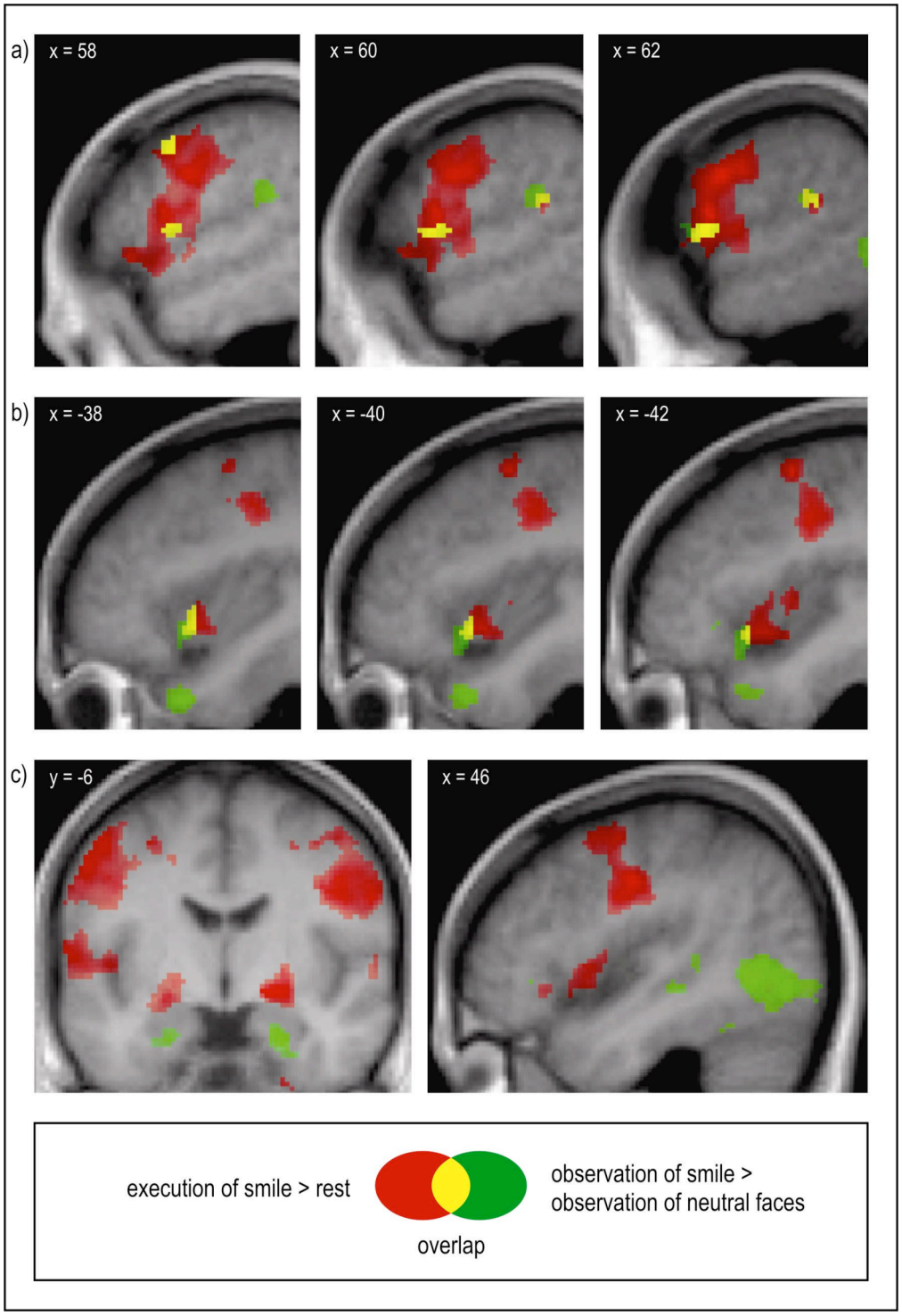

Figure 5.2: Illustration of the shared representation network for perceiving and expressing pleasant facial affect. Overlaps (yellow) between the activations during smile observation (green) and execution (red) are superimposed on the averaged T1 anatomical image of the 12 participants. Sagittal slices showing significant overlaps within (a) the dorsal (PMv/PMd) and ventral section (PMv/*pars opercularis*) of the right ventral premotor cortex, right parietal operculum (SII) and (b) the left anterior insula. (c) Left: coronal slice illustrating activation of the bilateral pallidum and adjacent dorsal amygdala/SI region during smile execution (red) and the ventral amygdala extending into the parahippocampal region during smile observation (green). (c) Right: sagittal slice showing two activation foci within the right posterior STS during smile observation (green).

Table 5.1:Smile observation

Anatomical Description	Hem	MNI			TAL			Size	*t*
		x	*y*	*z*	*x*	*y*	*z*		
Smile - Neutral									
Precentral gyrus (PMv/PMd)	R	56	8	40	55	10	36	61	5.05
Postcentral gyrus (SI)	L	-52	-26	32	-51	-24	31	28	4.56
Postcentral gyrus (SI)	L	-60	-18	24	-59	-16	23	36	4.57
Parietal operculum (SII)	R	58	-34	22	57	-32	22	73	4.51
Middle occipital gyrus	L	-42	-68	4	-42	-66	7	1052	9.22
Middle temporal gyrus	L	-34	-96	-2	-34	-93	3		9.76
Precentral gyrus (PMv)/*pars opercularis*	R	60	8	6	59	8	5	52	4.84
Inferior occipital gyrus	R	48	-62	0	48	-60	3	1425	6.84
Middle temporal gyrus	R	44	-74	-6	44	-72	-1		7.16
Superior temporal sulcus (STS)	R	52	-40	-2	51	-39	0	42	3.91
Superior temporal sulcus (STS)	R	46	-26	-6	46	-25	-4	21	4.17
Inferior frontal gyrus	L	-52	26	-8	-51	25	-8	54	4.25
Anterior insula/inferior frontal gyrus	L	-38	16	-10	-38	15	-9	103	6.10
Inferior frontal gyrus	R	36	34	-12	36	32	-12	41	4.67
Fusiform gyrus	L	-42	-52	-20	-42	-51	-14	270	6.49
Ventral amygdala/parahippocampal gyrus	L	-24	-8	-22	-24	-9	-18	127	4.48
Ventral amygdala/parahippocampal gyrus	R	22	-6	-26	22	-7	-22	122	6.62
Middle temporal gyrus	L	-52	8	-36	-51	6	-31	112	10.71
Superior temporal gyrus (temp. pole)	L	-40	14	-36	-40	12	-31	133	5.41
Middle temporal gyrus (temp. pole)	R	36	14	-44	36	12	-38	34	3.68

Local maxima of activated foci expressed in Montreal Neurological Institute Standard Brain (MNI) and Talairach space (TAL) ($P < 0.005$, $k = 20$). Hem =Hemisphere.

5.4.2 Motor action network: smile execution

Activations related to execution of smiles (move-rest) are shown in Figure 5.2 (red colour) and local maxima of activated foci in Table 5.2. This contrast revealed activation within a wide-spread bilateral sensorimotor network including parts of the mesial premotor cortex (ACC, pre-SMA), dorsal premotor (PMd) and primary sensorimotor face area (M1/S1), ventral premotor cortex and *pars opercularis* of the inferior frontal gyrus (area 44/PMv), posterior cingulate and cerebellum (hemispheres, vermis). Signal increases were also noted in the right parietal operculum (SII), left superior temporal gyrus, left posterior and anterior insula and right mid-to-anterior insula extending into area 47 of the inferior frontal gyrus in both hemispheres. Subcortically, activations were located within the bilateral striatum, thalamus and globus pallidus plus the adjacent dorsal amygdala and substantia innominata (SI) region.

Table 5.2: Smile execution

Anatomical Description	Hem	MNI			TAL			Size	*t*
		x	*y*	*z*	*x*	*y*	*z*		
Move - Rest									
Superior frontal gyrus (pre-SMA)	R	2	14	62	2	16	56	1161	6.27
Medial frontal gyrus (ACC)	L	-4	4	52	-4	6	48		6.40
Precentral gyrus (PMd)	L	-46	-2	56	-46	1	52	1421	9.06
Precentral gyrus (PMv/PMd)	L	-54	0	44	-53	2	40		7.24
Precentral gyrus (M1/S1)	L	-44	-10	34	-44	-8	32		5.67
Precentral gyrus (PMv)/*pars opercularis*	L	-58	6	8	-57	6	7		7.71
Precentral gyrus (PMd)	R	46	-4	54	46	-1	50	1748	4.94
Precentral gyrus (PMv/PMd)	R	56	2	48	55	4	44		5.20
Precentral gyrus (M1/S1)	R	46	-10	36	46	-8	34		7.75
Precentral gyrus (PMv)/*pars opercularis*	R	62	8	12	61	8	11		7.68
Parietal operculum (SII)	R	68	-28	22	67	-26	22	45	3.55
Superior temporal gyrus	L	-60	-38	20	-59	-36	20	25	3.68
Putamen	L	-22	0	18	-22	1	17	64	6.72
Posterior cingulate (PCC)	R	20	-66	10	20	-63	12	53	4.68
Posterior cingulate (PCC)	L	-10	-70	8	-10	-67	11	52	8.71
Insula/inferior frontal gyrus	L	-46	-4	2	-46	-4	2	198	6.35
Thalamus	L	-12	-18	-2	-12	-18	-1	45	6.10
Thalamus	R	10	-24	-2	10	-23	-1	25	3.70
Globus pallidus/dorsal amygdala	R	20	-4	-10	20	-4	-8	283	8.72
Globus pallidus/dorsal amygdala	L	-24	-4	-12	-24	-4	-10	123	5.61
Insula/inferior frontal gyrus	R	40	10	-12	40	9	-11	231	5.77
Cerebellum (hemisphere, vermis)	L	-10	-60	-28	-10	-59	-21	1326	6.93
Cerebellum (hemisphere, vermis)	R	12	-56	-28	12	-55	-21	1243	7.31

Local maxima of activated foci expressed in Montreal Neurological Institute Standard Brain (MNI) and Talairach space (TAL) ($P < 0.005$, $k = 20$). Only the most significant local maximum is given for the left and right cerebellum respectively. Hem =Hemisphere.

5.4.3 Overlap between observation and execution of smiles

To identify areas implicated in a shared representation network for observation and execution of emotional facial action, overlaps were determined by creating the intersection of the thresholded three-dimensional statistical maps of the smile observation (smile-neutral) and execution (move-rest) contrasts. Regions implicated in the conjoint activation map are shown in Figure 5.2 (yellow colour) and local maxima of activated foci are given in Table 5.3. Significant overlaps were located exclusively in premotor and somatosensory-related cortices. The premotor sites included the right ventral premotor cortex and *pars opercularis* of the inferior frontal gyrus (area 44/PMv) and the dorsal part of the right ventral premotor cortex plus the adjacent rostral section of the dorsal premotor cortex (PMv/PMd) (see Figure 5.2a). Overlaps within somatosensory-related regions were noted in the parietal operculum (area

40/SII) (Figure 5.2a) and left anterior insula extending into area 47 of the inferior frontal lobe (Figure 5.2b).

Table 5.3: Overlap between smile observation and execution

	Hem	MNI			TAL			Size	*t*
Anatomical Description		*x*	*y*	*z*	*x*	*y*	*z*		
Smile - Neutral AND Move - Rest									
Precentral gyrus (PMv/PMd)	R	56	8	40	55	10	36	58	4.51
Parietal operculum (SII)	R	60	-32	18	59	-30	18	18	3.33
Precentral gyrus (PMv)/pars opercularis	R	60	8	6	59	8	5	46	4.43
Anterior insula/inferior frontal gyrus	L	-40	14	-10	-40	13	-9	38	4.61

Local maxima of significant overlaps between the 'smile-neutral' and 'move-rest' contrasts expressed in MNI and Talairach space. Overlaps were determined by creating the intersection of the thresholded (P < 0.005 uncorrected, k = 20) three-dimensional contrast images. This method provides a valid test for an AND conjunction even under dependence between the tests (see Methods section). Hem =Hemisphere.

5.5 Discussion

The results of the present study provide evidence for a common neural basis of perceiving and expressing pleasant facial affect. Regions involved in this shared representation network were located in the right premotor cortex and *pars opercularis* of the inferior frontal gyrus, right parietal operculum (SII) and left anterior insula. Observation of smile expressions further yielded signal increases within the posterior STS, fusiform gyrus and ventral amygdala. We will first examine the areas implicated in the mirroring system for pleasant facial affect and then discuss some of the regions involved in smile observation that were not part of the shared representation network.

5.5.1 Shared representation network

Brain imaging experiments suggest that the region lining the inferior part of the precentral sulcus is implicated in a human mirror matching system (Binkofski et al., 1999; Buccino et al., 2001; Buccino et al., 2004; Decety, Chaminade, Grezes, & Meltzoff, 2002; Decety et al., 1997; Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Grezes, Armony, Rowe, & Passingham, 2003; Grezes, Costes, & Decety, 1998; Grezes & Decety, 2001; Iacoboni et al., 1999; Perani et al., 2001; Rizzolatti, Fadiga, Matelli et al., 1996) that maps the observed action onto the observer's motor representation of the same action (Rizzolatti & Craighero, 2004). In humans, the mirror system is not restricted to object-related hand actions, but

includes various body actions that activate the premotor system in a somatotopic manner (Buccino et al., 2001). Buccino et al. (2001) have shown that observation of non-object-related mouth actions activates the lower part of the bilateral precentral gyrus and *pars opercularis* of the inferior frontal gyrus with larger and stronger activation in the right hemisphere. Accordingly, we show significant overlaps between the brain activation associated with observation and execution of emotional facial action within the right ventral precentral gyrus and *pars opercularis* of the inferior frontal gyrus. This finding provides direct evidence for the bimodal properties of this area in humans and suggests that a mirroring mechanism is also involved in the perception of facial action expressing pleasant affect.

Two recent functional imaging studies have addressed the neural correlates involved in imitation of static (Carr et al., 2003) and dynamic facial expressions (Leslie et al., 2004). Unlike the findings derived from the execution task in the present study, the neural correlates of imitative actions represent an interaction between motor performance and visual perception that cannot be resolved by subtracting the effects of a separate observation condition. It is therefore problematic to compare the neural sites associated with imitation of emotional facial expressions with those implicated in non-imitative execution of emotional facial action found in our study. However, the study of Leslie et al. (2004) included a condition where subjects passively observed dynamic facial expressions similar to the observation condition of the present study. Consistent with the results of our observation task they found right lateralised activation of ventral premotor cortex when subjects observed video sequences showing happy and sad facial expressions. The authors suggest that left hemisphere *pars opercularis* might rather be implicated in conscious goal-directed movements such as imitation of facial expressions, whereas, in agreement with evidence for right hemisphere dominance in emotional processing, empathic mirroring involved in the perception of emotionally expressive faces may be mediated by the right hemisphere ventral premotor cortex.

Furthermore, Leslie et al. (2004) suggest that the right hemisphere ventral premotor cortex may contain mirror neurons and may also be related to unconscious facial mimicry. The finding that subjects spontaneously, rapidly and covertly imitate visually presented facial expressions (‘facial mimicry’) is well established (e.g., Dimberg & Petterson, 2000; Dimberg et al., 2000). In fact, subtle involuntary activation of facial musculature corresponding to visually presented facial expressions is suggested to represent an instance of a mirroring phenomenon that obtains for somatic musculature more generally (Goldman & Sripada, 2005). Using TMS, Fadiga et al. found that observation of various actions (e.g., grasping an object, tracing a figure in the air) produced electromyographically detectable activation in the

corresponding muscle groups of the observer (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995). Activation of the shared representation network during observation of facial expressions and covert activation of corresponding facial muscles are therefore intimately related (Goldman & Sripada, 2005) and conceived as an expression of the same mirroring mechanism on a neural and behavioural level, respectively (Leslie et al., 2004).

A further site of shared neural activation was located in the dorsal part of the right ventral premotor cortex with an extension into the rostral section of the dorsal premotor cortex (PMv/PMd) slightly invading the posterior-most part of the middle frontal gyrus. Visually provoked signal increases within this area are well in line with several reports of mid-premotor activity during passive observation of static (Carr et al., 2003) and dynamic (Leslie et al., 2004; Wicker et al., 2003) facial expressions. Recruitment of the dorsal premotor cortex during action observation has been suggested to represent motor preparation or activation of a dorsal sector of the mirror neuron system (Buccino et al., 2004; Grezes et al., 2003).

Using a valid test for conjunction effects to identify overlaps between the activations determined by observation and execution of facial affect, we show that empathic mirroring is not confined to the right premotor cortex but also includes somatosensory-related areas, that is, the parietal operculum (SII) and anterior insula. Activations within the right parietal operculum (SII) and adjacent somatosensory fields have previously been reported during observation of hand/finger (Grezes et al., 2003; Iacoboni et al., 1999) and emotionally expressive face actions (Leslie et al., 2004). During action observation, activation of SII is suggested to reflect the somatosensory consequences of a retrieved motor representation (Grezes et al., 2003) analogous to the proprioceptive feedback, which normally accompanies overt actions. Using MEG Avikainen et al. have recently demonstrated that manipulative hand actions and their observation have parallel effects on responses recorded from SI and SII (Avikainen, Forss, & Hari, 2002). Such an involvement is not unexpected because SII has strong reciprocal connections with the ventral premotor area F5 (Cipolloni & Pandya, 1999; Matelli, Camarda, Glickstein, & Rizzolatti, 1986) known to contain mirror neurons (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti, Fadiga, Gallese et al., 1996). This connection could provide neurons in the parietal operculum with the property to respond to both observation and execution of emotional facial action.

Execution of smile expressions yielded signal increases within the bilateral insula. Activation within this area during smile observation was restricted to the left anterior insula. Left anterior insula has frequently been related to perception of mainly negative facial

expressions such as fearful (Morris et al., 1998) and disgusted faces (Calder, Keane, Manes et al., 2000; Hennenlotter et al., 2004; Sprengelmeyer et al., 1998; Wicker et al., 2003). Though there is evidence for a role of the anterior insula in the experience of pleasant emotion (Damasio et al., 2000) and the perception of pleasant touch (Olausson et al., 2002), the present study is the first demonstration of left anterior insula activation associated with the perception of dynamic expressions of pleasant emotion. Most importantly, the visual representation of smile expression within this area clearly overlapped with activations determined by smile execution.

Neuroanatomical data suggest that information concerning all manner of changes in the physiological state of the body reach the insula, including its anterior sector, via a lamina-1 spinothalamocortical pathway (Craig, 2002). The insula, as the limbic sensory cortex (Craig, 2002), supports interoceptive representations and is therefore conceived as distinct from extero- or proprioceptive parietal somatosensory cortices such as SII. Accordingly, insula activations have been associated with feeling states and feedback representations from peripheral autonomic arousal (Craig, 2002; Critchley, Mathias, & Dolan, 2001; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Damasio et al., 2000) that is mediated by structures involved in the translation of sensory processing into automatic emotional responses, such as the amygdala (Critchley, Mathias, & Dolan, 2002; Morris, 2002). Interestingly, the voluntary production of emotionally expressive face gestures has been linked to the induction of autonomic arousal and changes in feeling states (Adelmann & Zajonc, 1989; Levenson, Ekman, & Friesen, 1990). We therefore suggest that the sensory effects that accompany the production of emotional facial expressions are stored in somato- and limbic sensory centers such as SII and the anterior insula respectively and that these representations are reactivated during the observation of similar movements. According to simulationist models of face-based emotion recognition, the observer would then classify the face as being expressive of the same state produced in herself (Goldman & Sripada, 2005). Such a somatosensory representation of the feeling state may be caused by the covert activation of the corresponding facial muscles in the observer (‘reverse simulation model’, Goldman & Sripada, 2005) and/or its associated motor representation. Alternatively, a somatosensory representation associated with the observed facial expression may directly be triggered from the visual representation of the target’s facial expression, corresponding to a reverse simulation model with ‘as if’ loop (‘as if loop’, Damasio, 1994; Damasio, 1999; Goldman & Sripada, 2005). In either case, a somatosensory image of the body state associated with an emotional facial expression is supposed to be important for recognising emotions

expressed by others (Adolphs, 2002b). This has been demonstrated by lesion studies showing that damage to somatosensory-related structures, including the insular cortex (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Calder, Keane, Manes et al., 2000) and SII (Adolphs, 2002b), impairs the recognition of emotionally expressive faces.

It is interesting to note that a recent study found the same sites in the left anterior insula activated when subjects were observing facial expressions of disgust and when they inhaled disgusting odorants (Wicker et al., 2003). The authors argue that understanding of emotions expressed by others involves the activation of somatosensory structures directly associated with the experience of the same emotion ('unmediated resonance model', Goldman & Sripada, 2005). Our findings do not contradict this notion, however, they clearly demonstrate that recognition of facial affect also involves premotor and somatosensory-related networks associated with the production of these expression. Thereby, the ventral premotor cortex may subserve the function of mapping the visually coded action onto the observer's motor representation of the same action (Rizzolatti & Craighero, 2004), whereas activation of somatosensory-related structures such as the parietal operculum (SII) and anterior insular cortex could provide a somatosensory description of what the expression would feel like if produced in the observer (Adolphs, 2002b).

Notably, our subjects passively observed the stimuli, that is, no instruction was given to explicitly recognise the emotion expressed by the faces. Activation of the shared representation networks in response to the perception of a highly overlearned social signal such as a smile may therefore occur automatically and largely independent of conscious processing. It is currently unclear to what degree such *implicit* recruitment of premotor and somatosensory-related structures associated with the production of a perceived expression is involved in *explicit* emotion recognition. Case studies of three people with Möbius syndrome (Calder, Keane, Cole et al., 2000) which is a rare congenital disorder that causes paralysis of the facial muscles, that is, inability to produce facial expressions, revealed only mild impairments on (explicit) facial expression processing tasks in these patients. Another single case study reported complete inability of a person with Möbius syndrome to interpret facial expressions (Giannini, Tamulonis, Giannini, Loiselle, & Spirtos, 1984). It seems, however, plausible that the precise mechanisms and neural structures implicated in the process of emotion recognition depend on the demands made by the recognition task. Explicit recognition tasks are likely to engage additional neural circuitries implicated in the detailed perceptual analysis of the stimuli and the generation of associated knowledge, whereas

implicit emotion recognition may rather proceed via the automatic retrieval of premotor and somatosensory representations associated with the execution of the facial action pattern.

5.5.2 Activations in other regions

We also found evidence for visual analysis of facial expressive features within occipital and temporal regions including posterior STS, fusiform gyrus and ventral amygdala that were not part of the shared representation network. In the monkey's STS, neurons have been described that respond to the visual perception of moving biological stimuli such as hands, faces and bodies (Perrett et al., 1989; Perrett, Hietanen, Oram, & Benson, 1992; Perrett, Rolls, & Caan, 1982). In humans, activation of the STS has been related to the perception of biologically and socially salient visual motion stimuli (Allison et al., 2000), including the perception of dynamic facial expressions (Kilts, Egan, Gideon, Ely, & Hoffman, 2003). Modulation of activity within the STS caused by imitative behaviour has been reported for hand (Iacoboni et al., 2001) and face actions (Carr et al., 2003). Increased activation of this area during action imitation has been suggested to reflect an interaction between the observed action and the reafferent motor-related copies of actions made by the imitator (Iacoboni et al., 2001), since neural responses in the STS seem not to be associated with motor behaviour itself (Iacoboni, 2003). Our functional imaging results are in line with this notion since the signal increases within the right posterior STS during visual processing of facial expressions were not part of the shared representation network.

Consistent with previous reports using static (Carr et al., 2003; Phillips et al., 1997; Vuilleumier et al., 2001) and dynamic (Leslie et al., 2004; Wicker et al., 2003) face stimuli, activity of the fusiform face area and early visual areas (area 18) was enhanced during the emotional compared to the neutral face condition. Increased activation of these areas during perception of emotional facial expressions probably represents top-down modulatory effects of the amygdala onto the visual processing stream (Morris et al., 1998) reflecting allocation of attentional resources to emotionally salient stimuli (Pessoa et al., 2002; Vuilleumier et al., 2001). Concerning the present data, this interpretation is supported by the finding of bilateral amygdala activation during processing of pleasant compared to neutral faces.

Amygdala activation during processing of facial action patterns of pleasant emotion is well in line with findings from recent functional imaging studies reporting signal increases within the amygdala during perception of static displays depicting happy facial expressions (Somerville, Kim, Johnstone, Alexander, & Whalen, 2004; Winston et al., 2003; Yang et al., 2002). Beyond its well-known role in processing of negative facial affect (for review see A.J.

Calder et al., 2001), the amygdala has been supposed to play a generalized role in the decoding of various emotions from the face including happiness (Winston et al., 2003).

Execution of smiles also revealed significant activation of the bilateral amygdala. In contrast to observation of smiles, yielding signal increases in the ventral sector of the bilateral amygdala and adjacent parahippocampal gyrus, this activation was located in the dorsal amygdala and substantia innominata (SI) region extending into the bilateral pallidum. Activation of the dorsal amygdala/SI region may reflect autonomic arousal induced by voluntary contraction of facial muscles. This notion, although tentative, is reinforced by the finding that activity within the human dorsal amygdala/SI region including the central nucleus of the amygdala has been related to arousal and overall state of vigilance, whereas the ventral amygdala comprising the basolateral amygdala is probably tuned to the detection of stimuli with emotional valence (Somerville et al., 2004; Whalen, Kapp, & Pascoe, 1994; Whalen et al., 1998). However, in line with recent imaging studies that aimed to investigate overlapping neural activations across different experimental conditions (e.g. Wicker et al., 2003), the present experiment was run in separate sessions and developed to identify shared neural representations between observation and execution conditions. Further studies are therefore needed, with paradigms designed to test for differential effects of the observation and execution task in order to verify the different amygdala locations.

5.5.3 Conclusion

The results of the present study provide evidence for a common neural basis of perceiving and expressing pleasant facial affect. This network includes areas concerned with motor as well as somato- and limbic-sensory processing, that is, premotor cortex and SII/anterior insula. Together with temporal regions serving the visual analysis of facial expressive features, a mechanism that maps the observed expressions onto neural circuitries associated with the production of these expressions and its somatosensory consequences may contribute to empathic understanding of others' feelings. It might further provide a neural basis for the link between the sender and receiver of a message that has been postulated as the necessary prerequisite for all forms of communication[2].

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6 CONCLUSION AND PERSPECTIVE

Humans are probably unique in the extent of their reliance on socially transmitted information in coping with physical and social environments (Tomasello, 1999). The face is a visible signal both of others' intentions and internal states, and facial expression continues to be a critical variable in social interaction. The exploration of the neural basis that underlies the perception of such facial signals was the main subject of this thesis. Our findings provide some new insights concerning neural substrates involved in the perception of specific emotional expressions as well as neural mechanisms that mediate the extraction of meaning during facial expression processing.

The first experiment (chapter 3) addressed the question of whether the perception of surprise in others is associated with a specific neural substrate. The results reveal that the perception of surprised facial expressions consistently recruits structures within the medial temporal lobes that have previously been associated with novelty detection. Our findings therefore suggest a close relation between perceiving surprise in others and the response to novel events.

The first evidence that perception of disgusted facial expressions might be associated with a particular neural substrate came from investigations of people with Huntington's disease who show a disproportionately severe impairment in recognising facial expressions of disgust. To explore which brain regions are associated with this deficit was the goal of the second study (chapter 4). Our finding of dysfunctionally decreased insula activation in pre-symptomatic Huntington's disease provides an explanation for the clinical deficit in recognising facial expression of disgust and underscores the role of the insula in the emotion of disgust.

With the detection of mirror mechanisms in monkeys and humans, simulation theories of emotion recognition have become increasingly popular. Do we understand what others feel by putting ourselves into the shoes of the other via a neural mechanism that simulates the observed expression? This question was addressed in the third experiment (chapter 5). The results show that we map the observed expressions onto neural circuitries associated with the production of these expressions and its somatosensory consequences, thereby providing a description of what the expression would feel like if produced in the observer.

To return to the issue of whether emotions are best described in terms of category-based frameworks or unifying dimensional accounts outlined in the introduction (chapter 2.2), the idea that individual emotions are represented as distinct psychological categories is clearly consistent with the findings derived from the first two experiments (chapter 3 and 4). Both studies support the notion that there are distinct neural substrates dedicated to processing emotions as displayed by different facial expressions. Insula involvement in impaired disgust processing (chapter 4) is particularly interesting given its identified role in gustatory function (Frey & Petrides, 1999; Small et al., 1999). This finding further converges with the proposal of Rozin et al. that disgust has developed from a phylogenetically more primitive system involved in distaste (Rozin & Fallon, 1987; Rozin, Lowery, & Ebert, 1994). The adaptive significance of disgust has been related to a specific form of threat response associated with an internal defence system, as opposed to an external defence system related to fear (A.J. Calder et al., 2001). The results of the experiment described in chapter 3 provide evidence for a disproportionately severe involvement of the medial temporal lobes, namely the parahippocampal gyrus, in the perception of surprised facial expressions. Based on the well established role of the parahippocampal formation in the detection of contextually novel stimuli (see chapter 3.5), we suggest that the perception of others' surprise subserves a specific adaptive function, related to the evaluation of unexpected events in order to update knowledge for successful individual-environmental transaction (Schutzwohl, 1998).

It is important, however, to clarify that we are not claiming that disgust and surprise are represented exclusively by specialized neural systems. Instead, the emotion-specific circuits act in concert with various neural systems more generally involved in the analysis of facial gestures. According to the model of Haxby et al. (2000) described in chapter 2.1, a first general analysis of facial expressive features is served by superior temporal regions subsequently projecting to various limbic and paralimbic structures, some of which are involved in the processing of specific basic emotions. In agreement with this model, our findings also provide evidence for a general involvement of several occipito-temporal regions, including the superior temporal sulcus, in the perception of facial expressions of disgust and surprise as well as happiness (see chapter 5). Moreover, compared to disgust processing, there have been no patient-based or lesion studies reporting a selective impairment in recognising facial expressions of surprise so far. Though the parahippocampal formation might be disproportionately involved in the processing of surprise expressions, it is not yet clear whether this region is essential for recognising surprise in others. Investigations of facial expression recognition in patients with circumscribed lesions in the described areas are

needed to address this question.

The 'basic emotions' approach underlying the first two experiments was useful to gain some interesting insights into the neural basis of processing specific emotions and to speculate about their unique survival value. However, since this approach is primarily based on descriptive taxonomies, that is a number of discrete emotions that differ from one another in several fundamental ways, it does not provide any predictions concerning the mechanisms that mediate facial emotion processing. In the third experiment we therefore aimed to explore the neural basis of expression processing from a different perspective, namely the perspective of intersubjectivity that has recently gained considerable interest (Gallese, 2003; Gallese, Keysers, & Rizzolatti, 2004). What makes the recognition of facial expressions so different from that of facial identity is that we not only witness expressions in other people's faces, but we also generate them ourselves. Motivated by the detection of neural 'mirror systems' in animals and humans, a mechanism that attempts to simulate in the observer components of the emotional response shown in the face of the sender has therefore been suggested to be involved in the understanding of others' facial expressions (see chapter 2.4 and 5). In the third experiment (chapter 5) we provide direct evidence for the existence of neural structures with bimodal properties implicated in both observation and generation of specific facial expressions. The results show that we map the observed expressions onto premotor and somatosensory-related structures associated with the production of these expressions and its sensory consequences, thereby providing a description of what the expression would feel like if produced in the observer. In the introduction (chapter 2.4) we mentioned two different views of simulation, that is a 'cold' hypothesis holding that observation of the facial expression of another person triggers a similar neural motor representation and its associated somatosensory consequences in the observer, and a 'hot' hypothesis postulating that in order to understand the facial expressions displayed by others, a feeling of the emotion must also occur in the observer. Although some of our subjects might also have experienced happiness during perception of facial expressions (hot hypothesis) our findings suggest that a motor representation of the perceived expression and its associated somatosensory consequences may be enough to trigger an implicit grasp of what is expressed by the face (cold hypothesis). This notion is supported by findings that show that facial expressions, especially smiles, are primarily social signals, in that they are produced with greater frequency and intensity in social situations (Fridlund, 1991; Jancke & Kaufmann, 1994; Kraut & Johnston, 1979) and are therefore not necessarily associated with emotional experience (Fridlund, 1994), as implied by the hot hypothesis.

However, the extent to which hot experience is resonated in the observer probably depends on various situational and personal factors such as, for example, the degree of involvement or whether or not the observer knows the person signalling an emotion. Though our findings support a simulationist account of face-based emotion recognition, it is important to stress that simulation is only one among several other possible mechanisms that may mediate the understanding of emotions (see chapter 2.4) and that the neural circuitries implicated in the process of emotion recognition depend on the demands made by the recognition task, such as for example explicit or implicit emotion recognition (Critchley et al., 2000; Gorno-Tempini et al., 2001).

Although these aspects and many other important questions related to the field of facial expression processing remain untouched, our findings provide some interesting new insights into the neurobiology of what has sometimes been called the ‘language of emotion’.

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