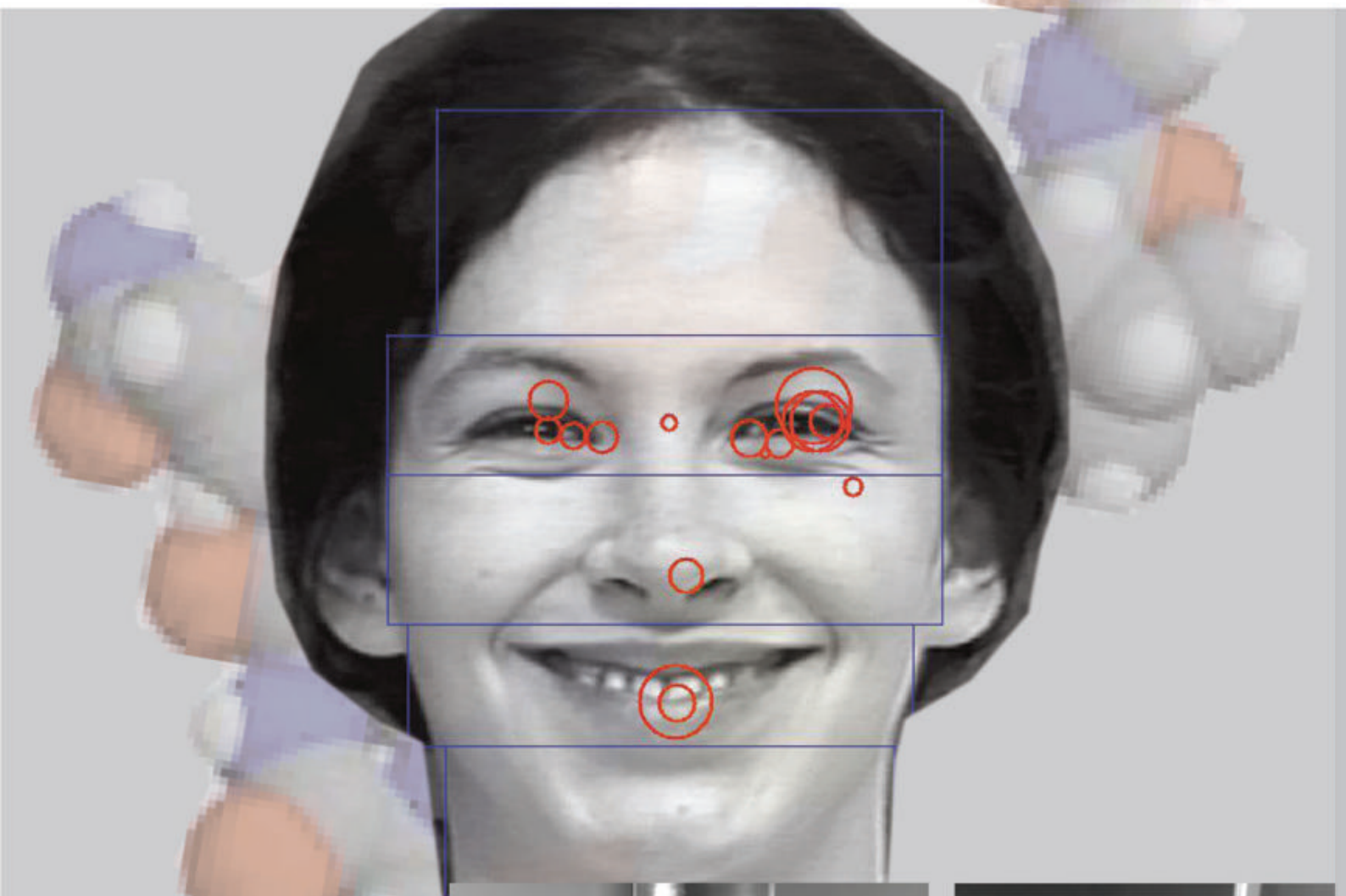
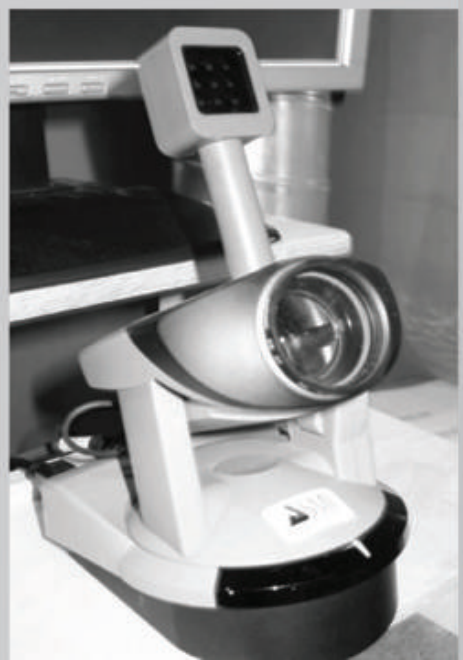
Effects of Oxytocin on Emotion Recognition and Eye Gaze

Angela Steiner





Cuvillier Verlag Göttingen
Internationaler wissenschaftlicher Fachverlag

Effects of Oxytocin on Emotion Recognition and Eye Gaze

Angela Steiner

Cuvillier Verlag Göttingen
Internationaler wissenschaftlicher Fachverlag

Bibliografische Information der Deutschen Nationalbibliothek
Die Deutsche Nationalbibliothek verzeichnet diese Publikation in der Deutschen Nationalbibliografie; detaillierte bibliografische Daten sind im Internet über http://dnb.ddb.de abrufbar.
1. Aufl. - Göttingen : Cuvillier, 2008
Zugl.: Zürich, Univ., Diss., 2008

978-3-86727-820-1

Die vorliegende Arbeit wurde von der Philosophischen Fakultät der Universität Zürich im Herbstsemester 2008 auf Antrag von Herrn Prof. Dr. rer. nat. Markus Heinrichs und Herrn Prof. Dr. rer. nat. Lutz Jäncke als Dissertation angenommen.

Nonnenstieg 8, 37075 Göttingen
Telefon: 0551-54724-0
Telefax: 0551-54724-21
www.cuvillier.de

1. Auflage, 2008
Gedruckt auf säurefreiem Papier

978-3-86727-820-1

Acknowledgements

I'm very thankful to so many people for all their support and contribution to finishing this work – I'd like to thank all of them here.

First of all, I would like to explicitly thank Prof. Dr. Markus Heinrichs, who has been my supervisor and mentor since the beginning of this work. I'm deeply grateful to him for guiding me throughout the whole time, and for always supporting me in scientific questions as well as with practical advice.

Further, I also wish to express my thanks to the members of my dissertation steering committee of the Neuroscience Center in Zurich (ZNZ), Prof. Dr. Ulrike Ehlert and Prof. Dr. Lutz Jäncke, who were interested in the progress of my work from the very beginning. Both of them provided me with the opportunity to conduct the studies for this work at their department.

I would like to thank my students, Janine Haldi, Sabine Spoerri, Sina Loretz and Christina Häfliger, for their excellent work and high motivation during these experiments. You have always been a very reliable team and provided me with every kind of support. I enjoyed working with you very much. Thanks also to all the voluntary participants who made these studies possible.

I wish to thank my friends and colleagues for their support whenever I was feeling stressed and ran out of energy. In particular, I would like to express my thanks to Séverine Gerber. You've always found the right words to keep me motivated and were there to lend me an ear whenever I needed you.

My most personal thanks are addressed to Matthias Häne, who provided me with all imaginable kinds of social support during the final months of this work. Therefore, I wish to express my thanks for your love, your enduring emotional and practical support, and for your patience.

Last but not least, I express my deepest gratitude to my family, my parents Carla and Ruedi Steiner and my brother Martin Steiner, to whom this book is dedicated. You've supported me psychologically as well as financially since the beginning of my studies in Zurich. Whenever I needed support, I could count on you. I thank you for always being there, for your never-ending love, support and encouragement throughout this project.

Abstract

Theoretical Background: Appropriately decoding and recognizing facial expressions is a substantial ability that develops very early in infancy and is crucial for the understanding of and adaptation to social interactions (Thomas, De Bellis, Graham, & LaBar, 2007). Furthermore, in humans and other primates, facial expressions serve as important social cues to regulate behavior and for establishing and maintaining social relationships (Kringelbach & Rolls, 2003). Studies with normal adults showed that they direct most of their attention to the core features of the face (i.e. eyes, nose, and mouth) and spend less time on non-feature areas while exploring facial expressions (Pelphrey et al., 2002). Within the core features, the eyes are considered to provide humans with the most information in terms of emotion recognition. Numerous studies confirmed this bias towards inspecting the eyes from very early in ontogeny (Holmes, Richards, & Green, 2006; Walker-Smith, Gale, & Findlay, 1977). Deficits in emotion recognition and eye-to-eye gaze are core symptoms of various disorders with difficulties in social interactions (e.g. autism, schizophrenia, borderline personality disorder, social phobia, etc.). In addition, individuals with a personality trait called alexithymia have distinct difficulties in recognizing emotions. Alexithymia is a non-clinical, psychological concept defined by difficulties in understanding and regulating emotions. The neuropeptide oxytocin (OT) is well known for its physiological functions in milk ejection and during labour. Apart from these functions, OT receptors are distributed in various brain areas associated with social behavior (for a review, see Heinrichs & Domes, 2008). Given that oxytocin is believed to promote social attachment in non-human mammals and approach behavior – such as trust – in humans, we hypothesized that oxytocin might also promote the ability to infer the mental state of others from social cues of the eye region in subjects with particular deficits in recognizing emotions (RMET, Baron-Cohen, 1999; Domes et al., 2007). Moreover, oxytocin was expected to improve the performance in a task

testing the ability to detect subtle changes in human facial expressions (emotion recognition task; Porges et al., in press) and to modulate eye gaze when viewing videos of facial expressions.

Methods: In a placebo-controlled, double-blind design, 65 healthy male participants were randomly assigned to receive a single dose of 24 IU oxytocin intranasally 40 minutes before the experiment. During the experimental phase, participants performed an emotion recognition task. For this task, pictures of the eye region of the six basic emotions (fear, sadness, disgust, happiness, anger, surprise and neutral) were chosen from the “Pictures of Facial Affect” (Ekman & Friesen, 1976). Pictures were presented to the participants on a computer screen with four alternative labels describing what the person displayed might be thinking or feeling at the moment. While we used static stimuli of only the eye region for the first experiment, the second study used the affect recognition test, (ART; Porges et al., in press), which presents videos of faces expressing different emotions. Participants were shown 48 neutral faces in a randomized sequence, which turned into one of the six primary emotions (anger, happiness, surprise, disgust, sadness and fear) over time. Within these experiments, eye movements were assessed during the viewing of the facial expressions.

Results: Results of the first study investigating the effects of oxytocin in persons with selective difficulties in recognizing emotions showed that the single administration of 24 IU oxytocin led to an increased ability to recognize emotions in the high-alexithymic group (t_{30} = 2.23; p = .033), while no such effect occurred in the low-alexithymic group (t_{31} = -.594; p = .557). Furthermore, in the group with high alexithymia, oxytocin administration induced an improvement of emotion recognition particularly in emotions that are difficult to recognize (t_{30} = 2.218; p =.034). The results of the second study revealed that over the whole time sequence, subjects with oxytocin made more fixations towards the eyes ($F_{1;59}$ = 3.23; p = 0.077) and spent significantly more time fixating the eye region ($F_{1;59}$ = 4.42; p = 0.04) than the placebo group for happy facial expressions. In terms of the time sequence of the videos of facial

expressions, we found that particularly in the early time phase during face exploration, subjects with oxytocin spent significantly more time on the eyes ($F_{1;60}$ = 6.37; p = .014) and made significantly more fixations to the eyes ($F_{1;60}$ = 6.73; p = .012). Moreover, subjects of the oxytocin group looked less at ($F_{1;60}$ = 3.94; p = .052) and spent less time fixating on the nose ($F_{1;60}$ = 3.67; p = .06) in the early detection phase.

Conclusion: This is the first study to show that a single dose of intranasal oxytocin is sufficient to improve performance in an emotion recognition task in healthy men with difficulties in identifying and describing emotions. Although alexithymia is a subclinical phenomenon, it is associated with general psychological distress, especially with depression and anxiety, and has been observed in numerous psychiatric and somatic disorders (Bankier, Aigner, & Bach, 2001; Gil et al., 2007; Le, Ramos, & Munoz, 2007; Marchesi, Bertoni, & Maggini, 2008; Saarijärvi, Salminen, Taylor, & Toikka, 2006; Taylor, Bagby, & Parker, 1997). Further, our results show that a single dose of oxytocin enhances the gaze toward the eye region for all basic emotions, and in particular in happy faces. These findings may therefore have several important clinical implications. People with impaired ability to process or regulate emotions have been shown to be at risk of developing mental disorders such as major depression, anxiety disorder, eating disorders, and substance abuse. Moreover, the inability to focus the attention toward the eyes seems to be responsible for emotion recognition deficits, for example in autism or social anxiety disorder, and thus, oxytocin may provide substantial support in the treatment of disorders with social deficits.

Contents

Acknowledgements i

Abstract iii

Figures and Tables xi

1. Introduction 1

2. Theoretical Background 5

2.1. The concept of emotions 5

2.1.1. What is an emotion? 5

2.1.2 Classification of emotions – Are there basic emotions? 8

2.1.3 Emotion, mood and other related affective constructs 10

2.1.4 The function of emotions 12

2.1.5 Summary 13

2.2 Facial expressions of emotion 14

2.2.1 An evolutionary perspective 14

2.2.2 Universality of facial emotional expressions 15

2.2.2.1 Evidence from adult humans across cultures 16

2.2.2.2 Evidence from nonhuman primates 16

2.2.3 Facial expressions covary with distinct physiological responses 17

2.2.4 Summary 18

2.3 Emotion recognition 19

2.3.1 The development of emotion recognition 19

2.3.2 A functional model of emotion recognition 20

2.3.3 Neural systems for recognizing emotion 22

2.3.3.1 Visual cortices 24

2.3.3.2 Amygdala 25

2.3.3.3 Orbitofrontal cortex 26

2.3.3.4 Somatosensory-related cortices and the basal ganglia 27

2.3.3.5 Summary: neural systems for recognizing emotions from faces 28

2.3.4 Moderating variables of emotion recognition 29

2.3.4.1 The issue of task difficulty 29

2.3.4.2 Age 30

2.3.4.3 Gender 32

2.3.4.4 Static versus dynamic stimuli 32

2.3.4.5 The role of eye gaze in emotion recognition 33

2.3.5 Psychopathology and emotion recognition 34

2.3.5.1 Autism 35

2.3.5.2 Schizophrenia 39

2.3.5.3 Social Phobia 42

2.3.5.4 The construct of alexithymia 46

2.3.6 Summary 49

2.4 Oxytocin and behavior 50

2.4.1 The peripheral oxytocin system: Synthesis, receptor distribution and mechanisms of action 50

2.4.2 The central oxytocin system 52

2.4.2.1 Oxytocin and the blood-brain barrier 53

2.4.2.2 Central nervous system actions of oxytocin 54

2.4.2.3 Oxytocin, anxiety and stress 55

2.4.2.4 Oxytocin, social approach and social cognition 57

2.4.3 Clinical implications 59

2.4.3.1 Oxytocin and autism 59

2.4.3.2 Oxytocin and other axis I disorders: OCD and social phobia 61

2.4.3.3 Oxytocin and axis II disorders: borderline personality disorder 62

2.4.4 Summary 63

3. Oxytocin improves emotion recognition in individuals with difficulties in recognizing, describing and regulating emotions 66

3.1 Introduction 66

3.2 Methods 68

3.2.1 Subjects 68

3.2.2 Experimental Protocol 69

3.2.2.1 Procedure 69

3.2.2.2 Substance administration 70

3.2.3 Emotion Recognition Task 70

3.2.4 Psychological Measures 71

3.2.5 Autonomic Measures 72

3.2.6 Statistical Analyses 73

3.3 Results 74

3.3.1 Description of the study groups 74

3.3.2 Emotion recognition task 76

3.3.2.1. Answer Correctness 76

3.3.2.2. Reaction time 79

3.3.3 Mood 80

3.3.4 Heart Rate 82

3.4 Discussion 84

4. Effects of Oxytocin on Affect Recognition and Eye Movements while Viewing Movies of Facial Emotion Expressions 89

4.1 Introduction 89

4.2 Methods 91
4.2.1 Subjects 91
4.2.2 Experimental Protocol 92
4.2.2.1 Procedure 92
4.2.2.2 Substance administration 94
4.2.3 Affect Recognition Task and Face Ratings 95
4.2.3 Psychological Measures 95
4.2.4 Autonomic Measures 97
4.2.5 Eye Movement Recordings and Analysis 97
4.2.5.1 Eye Tracking Apparatus 97
4.2.5.2 Regions of Interest and Process Measures 98
4.2.6 Statistical Analyses 99
4.3 Results 100
4.3.1 Description of the study groups 100
4.3.2 Affect recognition task 101
4.3.2.1 Answer correctness 101
4.3.2.2 Reaction time 102
4.3.2.4 Face ratings 103
4.3.2.5 Mood 105
4.3.2.6 Heart rate 106
4.3.3 Eye tracking analyses 107
4.3.3.1 Fixations to and viewing time within the face 107
4.3.3.2 Fixations to the regions of interest 108
4.3.3.3 Fixations across the time span of the videos 117
4.3.3.4 Fixations and fixation time within the early phase of face exploration 117

4.3.3.5 Fixations and fixation time within the middle phase of face exploration 121

4.3.3.6 Fixations and fixation time within the late phase of face exploration 122

4.4 Discussion 126

5. General Discussion 129

5.1 Summary of the Results 130

5.1.1 Oxytocin promotes emotion recognition in individuals with difficulties in recognizing and describing feelings 130

5.1.2 Oxytocin increases eye gaze toward the eye region in happy faces 131

5.2 Methodological Considerations and Limitations 133

5.3 Discussion of the results 136

5.4 Conclusions, Clinical Relevance and Outlook 139

6. Bibliography 142

Figures and Tables

Figure 1: Facial expression of fear (Ekman, 1973) and physiological fear responses. 6

Figure 2: The dimensional structure of emotion categories (Ekman, 1992; Russel, 1980). 8

Figure 3: Six basic emotions according to Ekman & Friesen (1982): from top left: anger, fear, disgust, surprise, happiness and sadness 10

Figure 4: Facial expressions of Macaca arctoides according to intensity and emotion (Darwin, 1973). 15

Figure 5: Model of face processing (Bruce & Young, 1986). 21

Figure 6: Processing of emotional facial expressions as a function of time (R. Adolphs, 2002a; R. Adolphs, 2002b). 23

Figure 7: Schematic model for the neural basis of deficits in schizophrenia (Philips et al., 2003)..... 41

Figure 8: Scanpaths of social phobics compared to healthy controls (Horley et al. 2004). 44

Figure 9: Synthesis of oxytocin in the paraventricular and supraoptic nuclei. 51

Figure 10: Interactions between anxiety and stress, social approach behavior, and the oxytocinergic system (Heinrichs & Domes, 2008). 64

Figure 11: Experimental procedure empirical study 1. 70

Figure 12: Mean Answers for high-alexithymia group in the emotion recognition task for all emotions, easy emotions and difficult emotions. Error bars are standard error of the mean (SEM). 76

Figure 13: Mean answers for low-alexithymia group in the emotion recognition task for all emotions, easy emotions and difficult emotions. Error bars are standard errors of the mean (SEM). 77

Figure 14: Mean answers for high-alexithymia group for the emotions fear, anger, happiness, sadness, surprise, disgust and neutral. *p < .05. Error bars are standard errors of the mean (SEM). 78

Figure 15: Mean answers for low-alexithymia group for the emotions fear, anger, happiness, sadness, surprise, disgust and neutral. Error bars are standard errors of the mean (SEM). 79

Figure 16: Experimental procedure empirical study 2. 94

Figure 17: Happiness: Proportion of fixation count at the forehead, eyes, nose, mouth and chin. Error bars are standard errors of the mean (SEM). 111

Figure 18: Happiness: Proportion of fixation time at the forehead, eyes, nose, mouth and chin. Error bars are standard errors of the mean (SEM). 112

Figure 19: Participants with oxytocin spent more time and made more fixations at the eyes in happy faces..... 113

Figure 20: Participants with placebo made fewer fixations at the eyes and spent less time at the eyes in happy facial expressions. 113

Figure 21: Early phase 1: Proportion of the number of fixations to the forehead, eyes, nose, mouth and chin over all emotions. Error bars are standard errors of the mean (SEM). 119

Figure 22: Early phase 1: Proportion of the fixation time on the forehead, eyes, nose, mouth and chin over all emotions. Error bars are standard errors of the mean (SEM). 119

Figure 23: Early phase 1: Proportion of the fixation count on the forehead, eyes, nose, mouth and chin for happiness. Error bars are standard errors of the mean (SEM). 121

Figure 24: Late phase 3: Proportion of the fixation count on the forehead, eyes, nose, mouth and chin for fear. Error bars are standard errors of the mean (SEM). 124

Figure 25: Late phase 3: Proportion of the fixation time on the forehead, eyes, nose, mouth and chin for fear. Error bars are standard errors of the mean (SEM). 124

Figure 26: Late phase 3: Proportion of the fixation count on the forehead, eyes, nose, mouth and chin for happiness. Error bars are standard errors of the mean (SEM). 125

Figure 27: Late phase 3: Proportion of the fixation time on the forehead, eyes, nose, mouth and chin for happiness. Error bars are standard errors of the mean (SEM). 125

Table 1: Characteristics of the study groups. 75

Table 2: Mean reaction time emotion recognition task. 80

Table 3: Mood over the time course of the experiment. 81

Table 4: Heart rate during the experiment. 82

Table 5: ART characteristics of the study groups. 101

Table 6: Mean percentage of answer correctness in the ART. 102

Table 7: Mean reaction time (in sec) during the ART. 103

Table 8: Mean face rating on trustworthiness (range from -3 to + 3). 104

Table 9: Proportion of fixations and fixation time within the face related to the screen. 108

Table 10: MANOVA for fixations (%) and fixation time (%) over all emotions. 109

Table 11: Positive and negative emotions: MANOVAs for fixations (%) and fixation time (%). 110

Table 12: MANOVA for happiness with group as between-subject factor. 112

Table 13: MANOVAs for each emotion with group as between-subject factor. 114

1. Introduction

The aim of the presented research project was to combine knowledge on emotions, facial expressions of emotions, their role in mediating social interactions and the neuropeptide oxytocin, which is known for its beneficial effects on human social behavior such as trust, “mind-reading” and social support. The project consisted of the following two parts: first, we examined the possible clinical relevance of the beneficial effects of a single dose of intranasal oxytocin in individuals with selective difficulties in recognizing and describing emotions in an emotion recognition task. The second part comprised the effects of oxytocin on fixations and the duration of these fixations when viewing videos of emotional facial expressions.

Emotions have been studied with great interest for decades. This attention has been given to emotions for good reason: There is no doubt that emotions serve numerous functions, such as an evolutionary function, a decision-making function and a social and communicative function, among others (Amstadter, 2008). Facial expressions are important visual signals, which provide information about an individual’s gender, age, and familiarity, and more importantly, they offer significant cues as to the intentions and mental states of others. Therefore, the ability to recognize these cues and to respond accordingly plays a crucial role in human social life. Deficits in face perception and a consequent deficit in facial affect recognition are apparent in many disorders with social deficits (autism, schizophrenia, social phobia, etc). To understand these difficulties, the most direct method is to record the visual scanpaths, the pattern of eye movements that occur when an individual processes facial expressions.

In particular, individuals with alexithymia have distinct difficulties in recognizing emotions. Alexithymia is a psychological concept defined by difficulties in understanding and regulating emotions. These include difficulties in recognizing,

identifying, distinguishing, and describing emotions. In the literature, alexithymia is thought of as a personality trait that differs among people, and about 10% of the normal population show poor expressiveness of emotional states (Berthoz et al., 2002). The current project focused on healthy participants, who were divided into a subclinical “high”- and “low”-alexithymia group using a median split with the sum score of the TAS-20 (Toronto alexithymia scale; Bach et al., 1996) in order to avoid influences of comorbid psychological disorders on the ability to recognize facial expressions (Taylor, 2000). The four groups, consisting of 19 subjects with OT and 13 subjects with PL in the “high”-alexithymia group and 14 subjects with OT and 19 subjects with PL in the “low”-alexithymia group, did not differ significantly in any relevant baseline measurements, such as psychopathological symptoms or trait characteristics. General well-being, and mood as well as heart rate were repeatedly measured. Subjects were required to be non-smokers, who were medically healthy and not receiving any pharmacological treatment in order to exclude possible interruption in the emotion recognition task. The results within the “high”-alexithymia group revealed that 24 IU oxytocin before the emotion recognition task was sufficient to enhance answer correctness in all emotional stimuli and especially in those emotions that were difficult to detect. In the “low”-alexithymia group, no such effect was found. Further, no group differences were observed regarding the reaction time.

Previous studies on the recognition of emotion from facial expressions have shown that the viewing of faces is associated with longer fixations compared with natural scenes and is typically accompanied by a stereotypical eye scanning pattern (Guo, 2007). Specifically, the eye region in neutral or expressive faces is often the first destination of the saccade and attracts the highest proportion of fixations compared with other facial features (Guo, Mahmoodi, Robertson, & Young, 2006).

Given that the eyes are often inspected first and for a longer time during face exploration, and in light of the results of a previous study by Guastella and colleagues (2007) showing that intranasal oxytocin increased fixations towards the eyes and the fixation duration towards the eyes when viewing neutral human faces, the second study examined the effects of a single dose of intranasal oxytocin on the ability to recognize facial expressions from video stimulus material (answer correctness and reaction time). Moreover, it also examined the effect on fixations as well as fixation time towards facial features such as eyes, nose, mouth, chin and front. Subjects had to fulfill the same criteria as in study one: They were required to be non-smokers, who were medically healthy and not receiving any pharmacological treatment in order to exclude possible interruption in the affect recognition task and in their visual scanpaths. The two groups, consisting of 30 subjects with oxytocin (OT) and 32 subjects with placebo (PL) did not differ in any baseline measurement assessing personality traits or psychopathologies. During the whole experiment, psychological (mood) and physiological (heart rate) parameters were repeatedly measured. The affect recognition task consisted of 36 video stimuli of facial expressions comprising 6 videos for each basic emotion (happiness, surprise, disgust, anger, fear, sadness). To assess eye movements non-invasively during the facial videos, an eye-tracking system was used during the experiment.

The results of the second study revealed that a single dose of oxytocin before viewing facial expressions led to more and longer fixations to the eyes independently of the valence of the emotion. Further, and again independently of the emotional valence, subjects with oxytocin spent less time on and gazed less towards the nose than the subjects of the placebo group. When analyzing each emotion category separately, we found that oxytocin significantly enhanced the number of fixations and the time spent fixating the eye region, in particular in happy facial expressions. When we considered the time sequence of the video stimuli and divided each of the 36 videos into three equal phases (early, middle and late face exploration), and doing so for each individual

participant, we found that in the early detection phase, oxytocin changes visual scanpaths of subjects significantly in that subjects with oxytocin made fewer fixations to the nose, but more into the eyes, and spent less time fixating to the nose but more to the eyes over all emotions. Again, this effect was highly significant for happy faces. Taken together, we were able to show that a single dose of oxytocin enhances the ability to recognize basic emotions in individuals with difficulties in recognizing emotions and that subjects with oxytocin gazed more at and spent more time fixating to the eyes, which provide us with the most socially relevant information within the face. Therefore, our results may have important clinical implications for patients with social deficits.

2. Theoretical Background

2.1. The concept of emotions

This chapter includes the basic constructs of the present work. They are structured into the concept of emotions, including a definition of emotion and its classification, the function of emotion expression and emotion recognition in humans, and the elucidation of behavioral effects of oxytocin and its modulation of emotion recognition.

2.1.1. What is an emotion?

"What is an emotion?"

This question was posed by William James, as the title of an essay he wrote 100 years ago (James, 1984; Solomon, 2008). As with many of the terms used in psychology, "emotion" was originally lifted from everyday discourse. For this reason, it has fuzzy boundaries rather than classical edges, and it refers to an astonishing array of happenings – from the mild to the intense, the brief to the complex, and the private to the public. This incredible diversity has led many theorists to despair of ever deriving a tidy classical definition of emotion. Instead, they have begun to think of emotion in prototype terms, and have identified key features.

One commonly described feature has to do with what gives rise to emotions (J. J. Gross, 2008; Lazarus, 1991). Emotions are thought to arise when an individual attends to a situation and understands it as being relevant to his or her current goals. Therefore, each emotion leads to a characteristic form of adaptive behavior. A second commonly described feature of emotion has to do with its constituent elements. According to Izard (Izard, 1977), an emotion generally contains three differentiable components:

1. A prototypic form of expression (typically facial),
2. A pattern of consistent autonomic changes (peripheral physiology), and
3. A distinct subjective feeling state.

For instance, the emotion fear is characterized by a distinctive facial expression in which the eyebrows are raised and drawn together, the eyes are opened widely, the lower lip tensed, and the lips are stretched back (Watson & Clark, 1994; Mauss et al., 2005; (R. Adolphs, 2002a; J. J. Gross, 2008). At the same time, fear is also associated with marked autonomic changes, including rapid increases in heart rate and skin conductance. Finally, fear involves a characteristic state in which the individual feels scared, frightened, nervous, and apprehensive (see Figure 1).

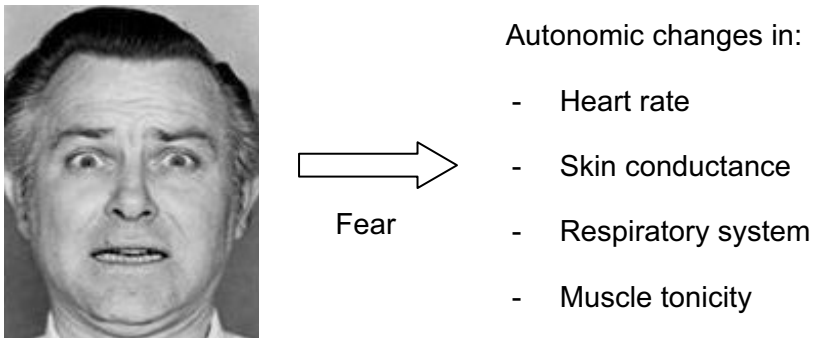


Figure 1: Facial expression of fear (Ekman, 1973) and physiological fear responses.

An important issue that is often overlooked concerns the distinction between the emotional reaction (the physiological emotional response) and the feeling of the emotion (relies on a central representation of this physiological emotional response) (Damasio, 1999). It is also essential to keep in mind that an emotional response typically involves concerted changes in a very large number of somatic parameters, including endocrine, visceral, autonomic, and

musculoskeletal changes including facial expressions, all of which unfold in a complex fashion over time.

2.1.2 Classification of emotions – Are there basic emotions?

In the literature, there is an ongoing debate on whether emotions should be thought of as discrete states (such as the ones we have names for in language and which subjects assign as labels to facial expressions) (Ekman, 1992), as regions falling in a low-dimensional space (for instance, a two-dimensional space with axes of arousal and valence) (Russel, 1980), or as assembled dynamically from a large possibility of component processes, depending on the appraisal of the situation (R. Adolphs, 2002a; Scherrer, 1988).

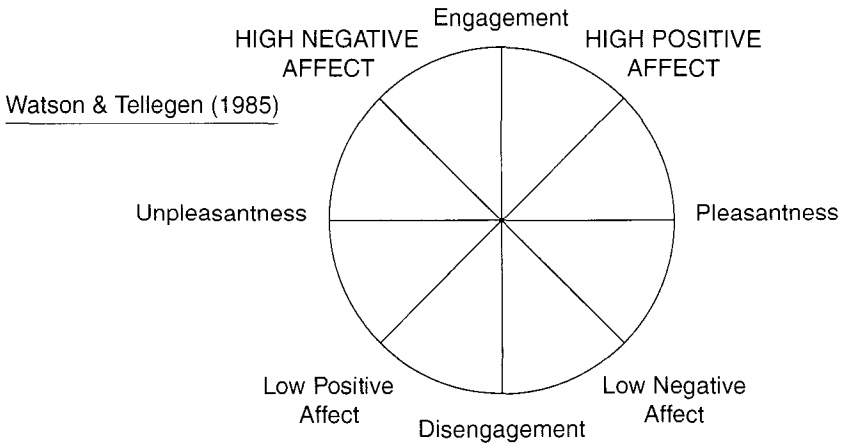


Figure 2: The dimensional structure of emotion categories (Ekman, 1992; Russel, 1980).

As mentioned, one way to determine how emotions are conceptualized is to find out the basic dimensions underlying the ways in which individuals make judgments about different aspects of emotions (Niedenthal, 2008). Researchers taking this approach have endorsed a two-dimensional account of emotion knowledge (Barrett & Russel, 1999; Larsen & Diener, 1992; Watson & Tellegen, 1985) (Figure 2). The two dimensions, with some differences in how they are believed to be related to each other, correspond to the degree to which a state is “pleasant” versus “unpleasant” and the degree to which a state is

experienced as “activated” versus “deactivated”. The evidence in favor of a two-dimensional structure of emotion concepts is interpreted as meaning that states that are labeled as “fear” or “anger” are understood in terms of the degree of pleasure and activation that typically characterizes them. For example, “anger” is conceptualized as highly unpleasant and moderately activated (Niedenthal, 2008; Russel & Barrett, 1999). Although relevant research has repeatedly revealed a two-dimensional structure, the meaning of the dimensions and the relationships between them have not been interpreted in precisely the same way by different theorists. Although Watson and Tellegen (1985) also found a two-dimensional structure, these researchers proposed that a rotation of the axis of the observed factors by 45 degrees constitutes the best characterization of it, because they proposed that the dimensions of interest lie between those two axes, and should be labeled “negative affect” (high and low) and “positive affect” (high and low).

Hence, there are multiple schemes for categorizing emotions. The present work focuses on a classification into so-called *basic emotions*. This basic emotion hypothesis finds support in indications for the existence of dedicated brain circuits and neurohumors, apart from the evidence for label-specific facial expressions (Frijda, 2008). The latter was shown in several studies on the recognition of facial expressions, in which Ekman and colleagues identified *six basic emotions* (Ekman & Friesen, 1982; Ekman, Matsumoto, & Friesen, 1997): happiness, surprise, fear, anger, disgust, and sadness (see Figure 3).

Figure 3: Six basic emotions according to Ekman & Friesen (1982): from top left: anger, fear, disgust, surprise, happiness and sadness

In their earliest works, Ekman (Ekman, 1972; Ekman & Friesen, 1971) and Izard (1971) conducted judgment studies, in which observers of different cultures viewed facial stimuli and judged the emotions portrayed to them. Results of both studies identified the six universal expressions mentioned above in all cultures. Since the original studies by Ekman and Izard, 27 studies examining judgments of recognition of facial expressions of emotions have replicated these findings (Matsumoto & Kupperbusch, 2001). Since then, research has focused on the investigation of differences between these six basic emotions.

2.1.3 Emotion, mood and other related affective constructs

Mood and emotion are two concepts in psychology that are often used similarly to refer to a certain aspect of affect. Moods can be distinguished from emotions in terms of time duration. There is no general agreement regarding how long an

emotion typically lasts for, but according to Ekman (1984, 1994), emotions can be very brief, lasting a matter of seconds or at most minutes. In contrast, moods last for hours, and sometimes days. If the state endures for weeks or months, however, it is not a mood, but is more properly identified as an affective disorder (Ekman & Davidson, 1994).

Although it is the most obvious difference, duration is not the only criterion for differentiating moods from emotions. Moods seem to lower the threshold for arousing the emotions, which occur most frequently during a particular mood. When a person is in an irritable mood, for example, that person becomes angry more easily than usual.

Furthermore, these two constructs differ along another dimension: reference to a particular object or to a more general or undefined class of objects (Frijda, 1994). It is a basic fact that most emotional states involve a relationship of a subject with an object: One is afraid of something, angry at someone, happy about something, and so on. The feature of intentionality not only applies to emotional experience but also to emotional behavior: angry behavior is directed at someone or something, etc. But, there exist affective states that are not intentional, such as moods. According to Frijda (1994), moods normally have causes, and the cause of a particular mood may be a particular emotionally charged event; nevertheless, this event or the person focal to it does not constitute its object. Depressed mood can be understood as diffuse negative affect, a generalized absence of goals for striving, and generalized low inclination to undertake action, or to relate to the environment (Ekman & Davidson, 1994).

In the literature, another substantial overlap can be found with the construct of sentiments. Human beings possess dispositions to respond affectively to particular objects or events (Frijda, 1994). Such dispositions are called sentiments or emotional attitudes, because they consist of an appraisal of an object. They are usually referred to as “likes” or “dislikes”. Sentiments are

acquired on the basis of previous experience or social learning and some sentiments may have an innate basis and be fairly common among human beings (dislike for seeing blood). Sentiments differ from emotions in that emotions consist of feelings, perceptions and motor responses with temporal specification, while this is not the case with sentiments.

The relationships between motivation and emotion constitute a further problem. Many emotions form motivational states, but many motivational states (e.g. need for food) are not emotions. Although emotions overlap with the broader category of motivational states, they differ from motivational states in a number of respects. Emotions (unlike motivational states like pain, hunger or thirst) feature prominently in social communication and the regulation of social behavior (like shame, pride, guilt, etc.) and seem therefore to possess a unique facial expression (Ekman, 1984).

2.1.4 The function of emotions

From an evolutionary point of view, emotions are largely seen as adaptively useful. Thus, anger, shame, feeling guilty, and sympathy are powerful regulators of social interactions (Frederickson & Cohn, 2008). Moreover, sadness, for example, may serve purposes of disengagement from attachment after personal loss. Considering the evidence for phylogenetic origin and continuity, this functional perspective of emotions is plausible. Many emotions are, moreover, functional in a somewhat different sense. A primary function noted previously was that they supply information to others through distinctive facial and vocal expressions and to oneself through distinctive thoughts and feelings (G. C. Clore, 1994). According to the so-called affect-as-information view (Schwarz & Clore, 1983), a primary function of emotion is to provide information about how a situation has been appraised. This information is conveyed internally by emotional experience and it serves as data for judgment and decision-making processes (G. L. Clore & Ortony, 2008). Furthermore,

according to Clore & Huntsinger (G. L. Clore & Huntsinger, 2007), the information leads to an extensive reordering process of priorities and therefore has effects on cognitive functions such as memory.

In short, emotions represent efficient modes of adaptations to changing environmental demands. Psychologically, they alter attention, shift certain behaviors upward in response hierarchies, and activate relevant associative networks in memory (Levenson, 2008; Amstadter, 2008). Physiologically, emotions rapidly organize the responses of different biological systems including facial expression, muscular tonus, voice, autonomic nervous system activity, and endocrine activity to produce a bodily milieu that is optimal for effective response.

2.1.5 Summary

Taken together, psychologists and neurobiologists have conceptualized an emotion as a concerted, generally adaptive, phasic change in multiple physiological systems (including both somatic and neural components) in response to a stimulus. In humans, many physiological and endocrine responses have been observed in emotions. There is still a debate regarding whether specific emotions have unique physiological characteristics, and despite a century of research in human emotion, no definite conclusion has yet been reached. Furthermore, different psychological theories argue that emotions should be thought of as discrete states, or as regions falling in a low-dimensional space, for example a two-dimensional space with axes of arousal and valence (see Figure 2).

Faces constitute perhaps the most important stimuli in social interactions. Moreover, facial expressions of emotions can be considered as aspects of an emotional response and of social communication. Facial expressions and their evolutionary functions in non-human primates and humans will be elucidated in the following sections.

2.2 Facial expressions of emotion

Within the field of emotion, the study of facial expressions has been notable both for empirical advances and for theoretical controversy. In this chapter, an "evolutionist" approach to emotion, inspired by Charles Darwin, is discussed in order to draw together recent studies of facial expression.

2.2.1 An evolutionary perspective

An evolutionist approach to facial expression has its roots in the work of Darwin (Darwin, 1972); 1998) and of those who have refined and elaborated upon his evolutionist claims (Ekman, 1992); Izard, 1971; Chevalier-Skolnikoff, 1973; Matsumoto et al., 2008). According to Darwin, as part of our evolutionary heritage, all people, regardless of race or culture, should express emotions in the face and body in a similar fashion (Matsumoto et al., 2008). Darwin wrote "The Expression of the Emotions in Man and Animals" and engaged in a detailed study of the muscle actions involved in emotion. He concluded that the muscle actions are universal, and their precursors can be seen in the expressive behaviors of nonhuman primates and other mammals (see Figure 4).

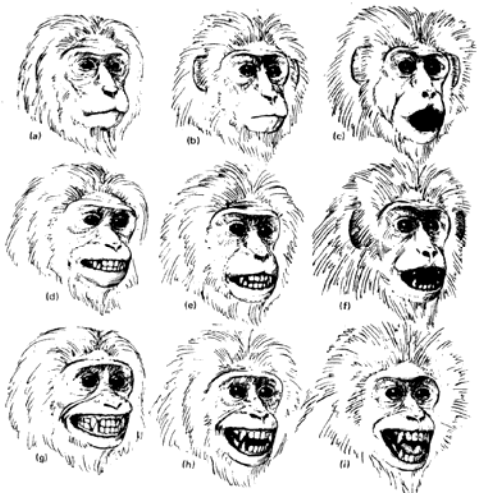


Figure 4: Facial expressions of Macaca arctoides according to intensity and emotion (Darwin, 1973).

2.2.2 Universality of facial emotional expressions

"Are facial expressions of emotion the same for all men?"

"When someone is surprised, for example, will we see the same facial appearance no matter what his country, race or culture?"

Darwin (1972) believed the answer to these questions was yes. Furthermore, he believed not only that facial expressions are universal but also that they are innate. The strongest evidence for the universality of facial expressions of emotion comes from studies that directly measure facial behaviors when emotions are elicited (Matsumoto et al., 2008). In the two chapters that follow, recent evidence from human and primate studies that bears upon these claims are brought together.

2.2.2.1 Evidence from adult humans across cultures

The first of these was Ekman's (1972) well-known study involving American and Japanese participants who viewed neutral and stressful films, and whose facial behaviors were recorded throughout the experiment (Ekman, 1973). Ekman coded the last 3 minutes of facial behavior during the neutral films, and the entire 3 minutes of the last stress film clip, using a modified version of the "Facial Affect Scoring Technique" (FAST), a precursor to the "Facial Action Coding System" (FACS; Ekman & Friesen, 1987). The FAST identified facial configurations of the six basic emotions in different regions of the face. Two sets of analyses were performed: one involving separate facial areas, and one involving the whole face. The rank-order correlations on the facial behavior codes from separate areas between American and Japanese participants ranged between .86 in the brows-forehead regions to .96 in the lower face (Matsumoto et al., 2008; Ekman, 1973). Subsequent research has yielded further evidence that universal facial expressions are elicited by specific emotionally evocative stimuli. There have been at least 25 published studies in which facial behaviors of individuals who participated in emotionally arousing conditions were coded reliably with the FACS and matched to the universal facial configurations of emotion (Bonnano et al., 2002; Bonnano & Keltner, 1997, , 2004; J. J. Gross & Levenson, 1993; Harris & Alvarardo, 2005; Lerner, Gonzalez, Dahl, Hariri, & Taylor, 2005; Matsumoto & Willingham, 2006; Mauss, Levenson, McCarter, Wilhelm, & Gross, 2005; Ruch, 1993, , 1995; Soto, Levenson, & Ebling, 2005).

2.2.2.2 Evidence from nonhuman primates

Morphological similarities between human expressions of emotion and nonhuman primate expressions have been discussed for many years (Chevalier-Skolnikoff, 1973; Geen, 1992; Snowdon, 2003). Ueno and colleagues (2004) demonstrated in their study that both infant rhesus macaques

and infant chimpanzees showed different facial expressions to sweet and bitter tastes (Ueno, Ueno, & Tomonaga, 2004).

The newest research in this area goes beyond demonstrating equivalence in morphological descriptions. According to Waller and colleagues (2006), the forehead musculature of chimps is less well developed than that of humans, but many other facial muscles and expressions have homologues and analogues comparable to those defined by the human FACS (Matsumoto, Keltner, Shiota, O'Sullivan, & Frank, 2008; Waller, Vick, Parr, Pasqualini, & Bard, 2006).

2.2.3 Facial expressions covary with distinct physiological responses

Numerous studies show that facial expressions are coordinated with physiology (Davidson, 2003; Ekman, Davidson, & Friesen, 1990; Levenson & Ekman, 2002; Mauss, Levenson, McCarter, Wilhelm, & Gross, 2005). The question of whether different emotional states are accompanied by unique patterns of physiological activity goes back to William James' feedback hypothesis (Davidson, 1994; LeDoux, 1994). James implied that different emotions are accompanied by unique patterns of skeletal muscle and physiological changes and that our experience of emotion is a direct function of feedback from the periphery (James, 1984).

However, there is still a debate regarding whether specific emotions have unique physiological characteristics (Belzung & Philippot, 2007). Recent studies have shown that when facial expressions are used as markers for emotions, discrete changes can be observed in the autonomic nervous systems (ANS) as well as in the brain. For example, anger leads to a reddening of the face and this is ANS-mediated through vasodilation (increased contractability) (Levenson, 2003). Furthermore, fear exhibits several changes in facial

expressions: blanching (vasoconstriction), sweating (sweat glands) and piloerection (muscle fibers at base of hair follicles).

Most recently, Lerner and colleagues (2005) demonstrated that discrete facial expressions of fear, anger and disgust were reliably linked not only to cardiovascular responses, but also to neuroendocrine activity. Participants were exposed to three different types of stressors during which they were videotaped and their cardiovascular and cortisol responses were measured. Lerner et al. (Lerner, Gonzalez, Dahl, Hariri, & Taylor, 2005) showed that fear expressions were associated with elevated cardiovascular and cortisol levels. In contrast, anger and disgust were linked with reduced responses.

In humans, many physiological responses have been observed in emotion expression, and despite a century-long tradition of physiological research in human emotion and first hints of emotion-specific physiological responses, no definite conclusion has yet been reached (Belzung & Philippot, 2007). One reason may be that physiological responses in human emotions seem to result from a complex interaction between the demands of the situation, personality characteristics, and the type of regulation strategy used in that situation (for an overview, see Pauls, 2004).

2.2.4 Summary

Facial expressions that covary with emotion have certain properties, including brief duration, symmetry of muscle actions, and the presence of involuntary muscle actions (Ekman & Friesen, 1989; Matsumoto, 2008). Facial expressions act as commitment devices to likely courses of action that are momentarily beyond the individual's volitional control (Gonzaga et al. 2001). The evolutionist perspective also suggests that facial expressions are more than simple readouts of internal states; they coordinate social interactions through their informative, evocative, and incentive functions. They provide information to

perceivers about the individual's emotional state, behavioral intentions, relational status vis-à-vis the target of the expression and objects and events in the social environment (Matsumoto, 2008; Ekman & Rosenberg, 2005). Therefore, the ability to recognize emotion from facial expressions is of great importance for human beings, and disturbances in emotion recognition may be one of the most pervasive and serious aspects in a variety of psychopathological disorders.

2.3 Emotion recognition

The recognition of emotion from facial expression has been the focus of a large number of psychological studies over the past several decades, complemented more recently by a wealth of neurobiological findings. These findings will be discussed in the next sections.

2.3.1 The development of emotion recognition

The ability to discriminate and to recognize emotion from facial expression develops in a complex fashion in infancy (McClure, 2000; Saarni, Mumme, & Campos, 1997) and matures somewhat earlier in females than in males (Thomas, De Bellis, Graham, & LaBar, 2007). Infants already orient themelves to face-like stimuli at birth, and there is some evidence that this may depend primarily on subcortical pathways, as indicated by the fact that they appear to process faces preferentially in temporal visual fields (Bushnell, Sai, & Mullin, 1989; Simion, Valenza, Umilta, & DallaBarba, 1998; Valenza, Simion, Machhi-Cassioa, & Umilta, 1996).

Nelson and colleagues (Nelson, Morse, & Leavitt, 1979; Soken & Pick, 1992) showed that some basic emotions can be discriminated by 7-month-olds, and

responses in temporal visual cortices show some selectivity to the sight of faces in 2-month-old monkeys (Rodman, O Scalaidhe, & Gross, 1993). Furthermore, according to Izard (Izard et al., 2001) the ability to recognize facial expressions at age 5 has been found to predict later social and academic competence, although it remains unclear to what extent this correlation reflects a causal relationship. Given that emotion recognition has been observed already in infancy, in the next section, relevant structures for perceiving emotion from faces will be elucidated.

2.3.2 A functional model of emotion recognition

As reported in a previous chapter, there are multiple schemes for categorizing emotions. This section focuses on the recognition of the six basic emotions that can be most reliably recognized from facial expressions: happiness, surprise, fear, anger, disgust and sadness. Most brain structures that participate in the recognition of basic emotions involve both

1. Perceptual processing – identifying the geometric configuration of facial features in order to discriminate among different stimuli on the basis of their appearance, and

2. Recognition of the emotional meaning of a stimulus – knowing that a certain expression signals a discrete emotion.

According to Adolphs (R. Adolphs, 2002a; R. Adolphs, 2002b; R. Adolphs, Tranel, & Damasio, 2003), recognition relies on disparate strategies. For example, to recognize fear from a facial expression, a linking of the perceptual properties of the facial stimulus to various knowledge-based processes is needed. These include the knowledge components of the concept of fear, the lexical label “fear”, the perception of the emotional fear response that the stimulus triggers in the subject, or knowledge about the motor representations required to produce the expression shown in the stimulus.

A first explicit model of face processing by Bruce and Young (1986) emphasized distinct psychological processes for identifying facial expression or facial identity (see Figure 5).

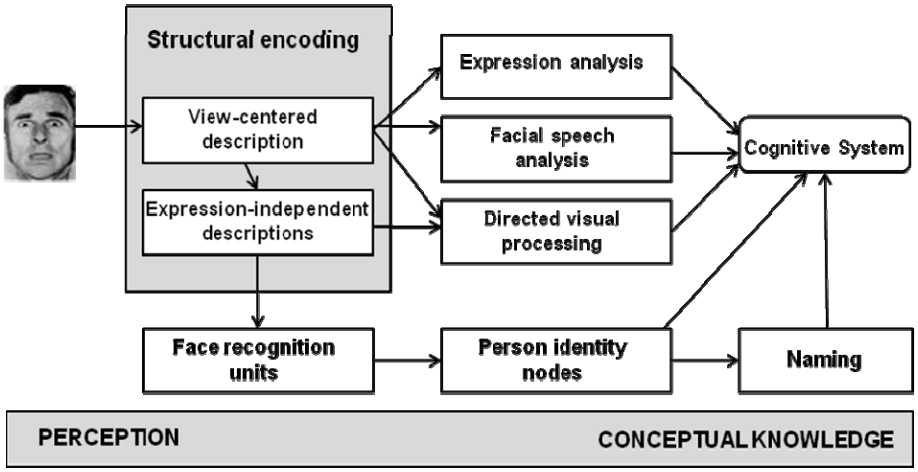


Figure 5: Model of face processing (Bruce & Young, 1986).

The model begins with perceptual processing of the features of faces and their configural relations (structural encoding), and progresses through relatively specialized functional modules for recognizing specific types of information from the face, culminating in naming the information that is recognized and in modulating other aspects of cognition on the basis of such information (R. Adolphs, 2002a; Posamentier & Abdi, 2003). This model is intended to provide a description of the computational aspects of face processing in the brain. One possibility to link this model with brain structures according to Adolphs (2002b) is that different types of information are processed by subsystems that are already distinct at the level of perception – perhaps at the level corresponding to Bruce and Young's (1986) structural encoding. The neuronal structures as well as neuronal systems underlying emotion recognition will be elucidated in the next section.

2.3.3 Neural systems for recognizing emotion

A large number of different structures participate in recognizing the emotion shown in a face (R. Adolphs, 2002b; Calder & Young, 2005; Eimer & Holmes, 2007; Haxby, Hoffman, & Gobbini, 2002; Johnson, 2005; M. L. Phillips, Drevets, Rauch, & Lane, 2003a; Posamentier & Abdi, 2003):

- the occipito-temporal cortices
- amygdala
- orbitofrontal cortex
- basal ganglia
- right parietal cortices, among others

These structures are engaged in multiple processes and at various points in time, making it difficult to assign a single function to a structure (see Figure 6). In Figure 6, some of the structures shown on the views of a brain are indicated on the left-hand side; on the right-hand side, some of the processes that are occurring and the processing stages outlined in the model of Bruce & Young (1986) (Figure 6), to which they roughly correspond, are indicated.

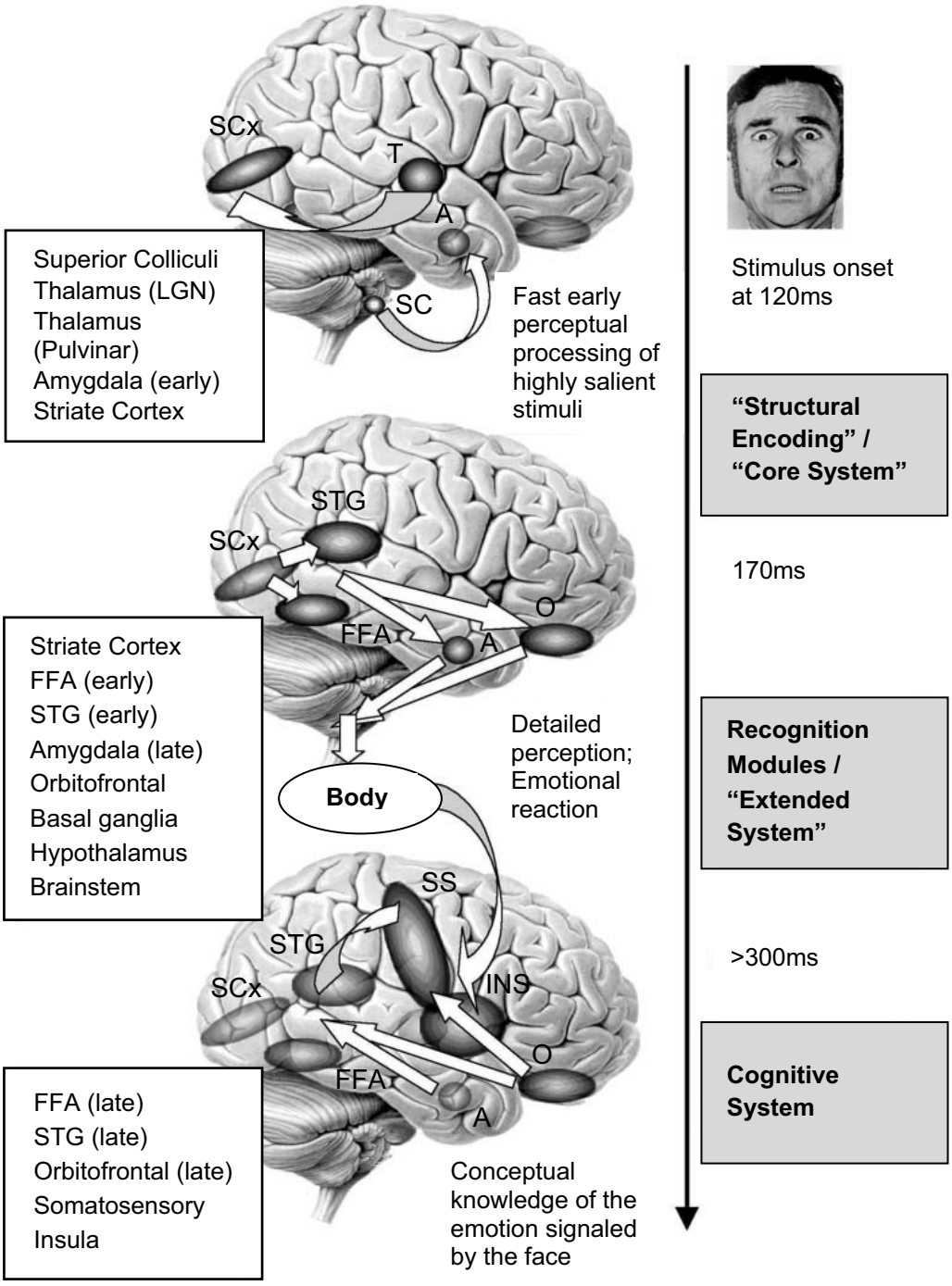


Figure 6: Processing of emotional facial expressions as a function of time (R. Adolphs, 2002a; R. Adolphs, 2002b).

Note: A = amygdala; O = orbitofrontal cortex; INS = insula; SC = superior colliculus; SCx = striate cortex; T = thalamus; LGN = lateral geniculate nucleus; FFA = fusiform face area; STG = superior temporal gyrus.

The process starts with the onset of a stimulus, a facial expression at the top, and progresses through perception to final recognition of the emotion at the bottom. Certain brain structures are preferentially engaged in processing structural information of the stimulus (early perception), whereas others participate more in retrieving conceptual knowledge or linking the perceptual representations to the modulation of other cognitive processes or to the elicitation of physiological states (e.g. an emotional somatic reaction to the stimulus).

2.3.3.1 Visual cortices

It is well known that the regions of the occipital and posterior temporal visual cortices play a critical role in perceptual processing of socially and emotionally relevant visual stimuli (R. Adolphs et al., 2005; Calder & Young, 2005; Furl, van Rijsbergen, Treves, Friston, & Dolan, 2007; Haxby, Hoffman, & Gobbini, 2002). Major evidence that cortical areas in the lateral parts of the inferior occipital gyrus, fusiform gyrus, and superior temporal gyrus are important in face processing come from single-unit studies in monkeys, intracranial field potential studies in neurosurgical human patients and functional imaging studies (Furl, van Rijsbergen, Treves, Friston, & Dolan, 2007; Haxby et al., 2001; Johnson, 2005; M. L. Phillips, Drevets, Rauch, & Lane, 2003a).

Moreover, studies from Kanwisher and colleagues (Kanwisher, 2000; Kanwisher, McDermott, & Chun, 1997) showed that the cortex around the fusiform gyrus is activated more by the sight of faces than by the sight of other objects or scrambled faces, and has therefore been called the “fusiform face area (FFA)”. In more detail, there is further evidence that the fusiform gyrus is especially involved in representing the static features of faces, and consequently in contributing to encoding identity, whereas the superior temporal gyrus is especially involved in representing the dynamic, changeable features of

faces, and therefore in contributing to encoding facial expression and directions of gaze (Haxby, Hoffman, & Gobbini, 2000, , 2002; Hoffman & Haxby, 2000).

Monkey single-unit recordings showed that although information sufficient to distinguish faces from other objects is encoded in ~120ms, responses encoding fine-grained, subordinate information sufficient to distinguish different emotional expression only appear at ~170ms (see Figure 6) (Sugase, Yamane, Ueno, & Kawano, 1999). These findings suggest the possibility that feedback from structures such as the amygdala and the orbitofrontal cortex modulate the responses to emotional stimuli in visual cortices.

2.3.3.2 Amygdala

The role of the amygdala in detecting and responding to emotional stimuli such as facial expressions has been extensively studied (R. Adolphs, 2002b; R. Adolphs, Tranel, & Damasio, 1998; R. Adolphs, Tranel, Damasio, & Damasio, 1994; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004; A. W. Young, 1995). According to Morris (Morris et al., 1998; Morris, Ohman, & Dolan, 1999), the amygdala participates in the recognition of emotional signals through two distinct input mechanisms (see Figure 6):

- A subcortical route via the superior colliculus and the pulvinar thalamus, and
- A cortical route via the visual neocortex

When healthy subjects are shown subliminal facial expressions of fear or when subjects with blindsight discriminate facial expressions of fear, both structures in the subcortical route are activated (Morris, Ohman, & Dolan, 1999). These findings are in line with animal and human lesion studies, which suggest that the amygdala plays a crucial role in the acquisition of fear responses (R. Adolphs et al., 2005; Berntson, Bechara, Damasio, Tranel, & Cacioppo, 2007).

In humans, amygdalar lesions can produce a general impairment of emotional responses and a disproportional deficit in the recognition of fearful facial expressions (R. Adolphs, Tranel, Damasio, & Damasio, 1994; R. Adolphs, Tranel, Damasio, & Damasio, 1995; Anderson & Phelps, 2000; Broks et al., 1998; Schmolck & Squire, 2001).

Lesion studies further show that unilateral damage to the amygdala generally results in more subtle impairments (R. Adolphs, 2002b).

Results from functional imaging studies are in line with the previous findings and have shown that the amygdala is activated disproportionately by facial expressions (Morris et al., 1996; Whalen et al., 2001).

2.3.3.3 Orbitofrontal cortex

An additional key structure in emotion processing, with which the amygdala is intimately connected, is the orbifrontal cortex. Damages, especially on the right orbitofrontal cortex, can result in impaired emotion recognition (R. Adolphs, 2002a; Hornak, Rolls, & Wade, 1996). In accordance with such findings, Vuilleumier and colleagues showed an activation in the right orbitofrontal cortex when comparing presentations of fearful and neutral faces (Vuilleumier, Armony, Driver, & Dolan, 2001).

Further, prefrontal regions may be activated when subjects are engaged in a cognitive task requiring identification of an emotion (Nakamura et al., 1999), which is in contrast to the amygdala's activation in response to passive viewing of emotional faces.

So far, there is clear evidence for some regions of the prefrontal cortex in processing emotional facial expressions. Studies from electrophysiological recordings in patients suggest a disproportionate role for medial and ventral sectors in processing highly arousing emotions (fear, anger) and further suggest

that this function may be lateralized to the right hemisphere. Additional findings from single-unit responses from a patient in the right ventro-medial prefrontal cortex in response to presentation of facial expressions of fear and happiness revealed that a neuronal discrimination between the two emotions first appeared after 120ms (Kawasaki et al., 2001).

These findings implicate that sectors of the orbitofrontal cortex, like the amygdala, can exhibit very rapid responses to emotionally salient stimuli, and that they are consequently in a position to modulate even relatively early aspects of perceptual processing (R. Adolphs, 2002a) (see Figure 6).

2.3.3.4 Somatosensory-related cortices and the basal ganglia

Evidence for the role of the right somatosensory cortex in emotion recognition come from a lesion study from Adolphs and colleagues (R. Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000). For all emotions, this study revealed a consistent pattern: lesions in the right ventral primary and secondary somatosensory areas, and, to a lesser extent in the insula and anterior supramarginal gyrus, comprised emotion recognition. According to Wild (2001), one interpretation of these findings is that viewing facial emotion expressions triggers an emotional response in the perceiver that mirrors the emotion shown in the stimulus (Wild, Erb, & Bartels, 2001), and that representing this emotional response in somatosensory cortices in turn provides information about the emotion. This idea that knowledge of other people's emotions may rely on a simulation of the observed emotion is in line with numerous studies in humans and monkeys (for more details see R. Adolphs, 2002a).

Functional imaging studies provided further evidence that the insular cortex is activated when subjects process facial expressions of disgust (Calder, Keane, Manes, Antoun, & young, 2000; Philips et al., 1997; Sprengelmeyer, Rauch, Eysel, & Przuntek, 1998). Regarding the recognition of disgust, there is also

good evidence that it requires the integrity of the basal ganglia as well as of other somatosensory-related cortices in the right hemisphere (for more details, see Adolphs et al., 2000), indicating a distributed neural network for processing this emotion.

2.3.3.5 Summary: neural systems for recognizing emotions from faces

Taken together, upon a presentation of an emotionally meaningful stimuli, such as facial expressions, a first feed-forward sweep of information processing is proceeded along occipital and temporal neocortices, and the extraction of perceptual information of faces, after ~100ms in humans, would categorize the stimulus as expressing an emotion or not, on the basis of the structural properties of the image (R. Adolphs, 2002b). Amygdala and orbitofrontal cortices could participate in at least three ways in the processes of emotion recognition from the face:

1. They may modulate perceptual representations via feedback (fine-tuning of the categorization of facial expression),
2. By modulation of visual attention by emotional stimuli, which requires the amygdala (Anderson & Phelps, 2000). This mechanism might contribute especially to retrieval of conceptual knowledge about the emotion.
3. Third, they may generate an emotional response in the subject, through connections to motor structures, hypothalamus, and brainstem nuclei, where components of an emotional response of the facial expression can be activated (via the process of simulation).

2.3.4 Moderating variables of emotion recognition

When reporting about impairments in emotion recognition that are specific to certain domains, it is of great importance to ensure that the specificity observed could not be attributed to other factors that also influence the subjects' performance in emotion recognition tasks such as task difficulty, age, gender, static vs. moving stimuli and the role of eye gaze. These factors will be discussed in the following sections.

2.3.4.1 The issue of task difficulty

In a review article, Adolphs et al. (2002a) suggests two factors that could give rise to relatively selective impairments in the recognition of facial expressions:

1. Certain emotional expressions might be more difficult to discriminate than others, perhaps because they are configurally more ambiguous, or more complex, or place special demands on perceptual systems.

2. Recognition of some expressions might be impaired because of different demands on the retrieval of knowledge. It is possible that the categorization of certain expressions requires a subject to classify those expressions at a more subordinate level than other expressions; in this case, subjects could categorize expressions at superordinate levels (e.g. happy versus unhappy) but not at more subordinate levels (e.g., a fearful surprise versus a happy surprise).

A recent study on this issue was conducted by Rapcsak and colleagues (2000). This study found that recognition of fear was less accurate than recognition of the other basic emotions even in normal subjects. In addition, Rapcsak and colleagues showed that if general difficulty is accounted for in the analysis, subjects with damage to amygdala or to the right parietal cortex are, in fact, not disproportionately impaired in recognizing fear (Rapcsak et al., 2000).

In contrast, according to Adolphs (2002a), fear is not more difficult than any of the other emotions to discriminate from neutral expressions. Data from morphing studies showed that fear, together with surprise and happiness, is quite easy to discriminate from neutral expressions, whereas sadness and especially disgust are more difficult (R. Adolphs, 2002a). Moreover, fear does indeed turn out to be relatively more ambiguous to match to a label when offered a choice between the labels for the six basic emotions; critically, this ambiguity depends on there being a choice between the labels fear and surprise.

For Adolphs (2002a), the problem with this particular forced-choice task is that it does not control for the different confusability between the six choices: not all choices are equally distinct. One could think of happiness as a superordinate category and all the basic negatively valenced emotions as more subordinate categories of the superordinate category unhappy. This may partly explain why impairments are observed more commonly on negatively valenced emotions than on happiness: the negative emotions are more subordinate and more confusable with one another than with happiness.

To get around this problem, Adolphs (2002a) suggests either controlling for the different label confusability in terms of how data from this matching task are analyzed, or using a different task.

2.3.4.2 Age

Research suggests that a person's emotion recognition declines with advancing years (Sullivan, Ruffman, & Hutton, 2007). For instance, subtle age differences have been found in emotion recognition skills, with older adults demonstrating relatively consistent deficits in identifying anger, fear and sadness over a number of studies (Sullivan & Ruffman, 2004). Findings also indicate that older adults do not identify emotions and cognitive states in the same way as younger

adults do when they are presented with just the eye region of faces (L. H. Phillips, MacLean, & Allen, 2002). One explanation could lie in age-related changes in the way in which younger and older subjects look at the eyes in emotional faces (e.g. viewing time at the eye region, amount of fixations to the eyes), as research suggests that the eyes are a particularly important source of emotional information for people when they are reading the mental states of others (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Sullivan, Ruffman, & Hutton, 2007). In line with these findings are the results of an eye-tracking study by Sullivan and colleagues (2007). Given that the emotions that older adults have the most difficulties in recognizing are those that are better identified from eye information than from other facial features (Bassili, 1979; Calder, Keane, Manes, Antoun, & young, 2000), Sullivan et al. (2007) examined whether older adults were less likely than younger adults to look at the eyes when presented with pictures of full faces. A critical difference was found for each emotion type, in that older adults spent about 700 ms longer looking at the mouth, whereas they tended to spend less time looking at the eyes. One interpretation is that older adults may need more time to process face stimuli because of age-related decline in processing speed (Salthouse, 1992; Sullivan & Ruffman, 2004). In contrast, there is also evidence for the consistent recognition of facial emotion across the life span (Moreno, Borod, Welkowitz, & Alpert, 1993), and thus it remains unclear whether less eye-looking might cause worse emotion recognition in older adults. To conclude, the current experiments indicate both similarities and differences between young and older adults in their ability to determine facial expression of emotions. However, compared with young adults, older adults show subtly worse emotion recognition, and a pattern of relatively more mouth-looking and less eye-looking. How subtle differences in emotion recognition might affect real-life adaptation in older adults remains to be addressed.

2.3.4.3 Gender

There is evidence that women are better at identifying facial expressions of emotion (Biele & Grabowska, 2006; Thayer & Johnsen, 2000). Furthermore, these differences seem to depend on the type of perceived emotion, with women showing better recognition abilities for fear and sadness, and men being superior in identifying expressions of anger. As reported above, sex differences are noticeable very early in development and girls are more accurate in identifying emotion than boys (Biele & Grabowska, 2006). Although gender differences in processing facial emotion do emerge in functional imaging studies as well, these findings imply that these effects seem to be relatively small (Kesler-West et al., 2001). Furthermore, it should be noted that in some studies, no sex differences were observed, suggesting that sex effects are dependent upon procedural variables that influence subjects' performance (Grimshaw, Bulman-Fleming, & Ngo, 2004) . One possible variable is the use of static versus moving stimuli, which will be discussed in the following section.

2.3.4.4 Static versus dynamic stimuli

A large number of neuropsychological studies have demonstrated a clear dissociation with regard to processing information related to recognition of static visual stimuli, and to the processing of visual motion (R. Adolphs, Tranel, & Damasio, 2003). Evidence is mostly provided by non-human primate studies showing two so-called visual streams: a ventral stream leading into the temporal lobe that is critical for object recognition, and a dorsal stream leading into the parietal lobe that is critical for localizing objects in space and for visually guided reaching (R. Adolphs, Tranel, & Damasio, 2003; Felleman & Van Essen, 1991; Ungerleider & Mishkin, 1982). In humans, there is good evidence that cortices in the temporal lobe subserve the processing of visual information (object recognition versus reaching for objects under visual guidance), while cortices in the parietal and frontal lobe subserve the processing of lexical information (knowledge of nouns versus verbs) (Caramazza & Hillis, 1991; Gainotti, Silveri, Daniele, & Giustolisi, 1995; Tranel, Adolphs, Damasio, & Damasio, 2001;

Tranel, Damasio, & Damasio, 1997). Most of the research on the perception of emotion is conducted using static faces as stimuli. According to Caron (1985), facial display of emotion, however, is a highly dynamic phenomenon and a static picture is very unnatural (Caron, Caron, & Myers, 1985). Consistent with such findings are results showing that the speed of emotion unfolding is an important factor influencing perception of emotional expressions (Sato & Yoshikawa, 2004). These studies show that some expressions are recognized better when presented quickly (i.e. happiness) and some when presented slowly (i.e. sadness) (Sato & Yoshikawa, 2004). Several investigations using different kinds of stimuli (natural movies, computer-generated schematic movies, subtle displays of emotions) pointed to the importance of dynamics in the perception of emotional expression (Ambadar, Schooler, & Cohn, 2005; Bassili, 1979; Kilts, Egan, Gideon, Ely, & Hoffman, 2003; Wehrle, Kaiser, Schmidt, & Scherer, 2000). The conclusion of these studies is that dynamics of expression is a factor that facilitates recognition.

2.3.4.5 The role of eye gaze in emotion recognition

From as early as 2 months old, neonates show a preference for looking at the eyes over other facial features, and young adults spend significantly more time looking at pictures of a person in which the eyes are open than at one with closed eyes (Batki, Baron-Cohen, Wheelwright, Connellan, & Ahluwalia, 2000; Hood, Willen, & Driver, 1998; Langton, Watt, & Bruce, 2000). By 3 months, infants look at targets more rapidly if an adult has gazed in that direction and 4-month-olds discriminate between direct and averted gaze. Such evidence suggests that a preference for looking at the eyes over other facial features develops early in infancy (Langton, Watt, & Bruce, 2000). Findings also indicate that this preference for looking at the eyes extends into adulthood. In addition, when viewing a face stimulus, normal adults devote the vast majority of fixations to the eyes, nose, and mouth, with nearly 70% of these fixations directed to the eyes (Walker-Smith, Gale, & Findlay, 1977). Eye contact also appears to be important in social encounters. For instance, when complex emotions are

judged, the eyes have been found to be just as informative as the whole face (Baron-Cohen, Wheelwright, & Jolliffe, 1997).

Research examining the visual scanpaths and the ability to recognize facial expressions of clinical populations with difficulties in social behavior lends further weight to the notion that looking at the eyes is important for social reasoning. The emotion recognition deficits often found in autistic spectrum disorders, for instance, may be attributable to the tendency of people with autism to ignore information from the eyes (Baron-Cohen, Wheelwright, & Jolliffe, 1997). Therefore, the following sections will give a review of psychopathological disorders with impaired emotion recognition such as autism, schizophrenia, social phobia and a construct called alexithymia.

2.3.5 Psychopathology and emotion recognition

Since it is known that faces are highly salient and biologically meaningful visual stimuli that provide a wealth of information that is crucial for social communication and for adaptation as social humans, research is interested in looking at disturbances of recognizing emotions in facial expressions and face processing. Impaired face processing is one of the most commonly cited aspects of various psychopathological disorders or symptoms with difficulties in social behavior such as autism and schizophrenia.

Furthermore, faces constitute one of the most complex classes of stimuli encountered by the visual system (Jemel, Mottron, & Dawson, 2006). As reported above, evidence that face recognition in humans may be qualitatively different and anatomically segregated from the recognition of objects emerged from brain lesion, behavioral and neuroimaging studies. Another characteristic of the perceptual processing of faces in humans is the face inversion effect, which is defined as a larger decrease in recognition performance for faces than for other mono-oriented objects when they are presented upside-down (Guo,

Robertson, Mahmoodi, Tadmor, & Young, 2003). However, not all humans are proficient at face processing. In the following chapters, impairments of face processing and emotion recognition are elucidated in psychopathological disorders which are characterized by marked impairments in social behavior.

2.3.5.1 Autism

Autism is a severe and pervasive neurodevelopmental disorder characterized by impairments in verbal and nonverbal communication, deficits in social interaction, and stereotypic behaviors (DSM-IV;(APA, 1994). Individuals with autism often present stereotyped patterns of behavior, most notably the persistent preoccupation with parts of objects and the prolonged display of repetitive, self-stimulating behavior. They also exhibit a chronic impairment in the processing of social and emotional information, including abnormalities in the use of eye-to-eye gaze and in the expression and comprehension of facial affect (Sasson, 2006). Some characteristics, such as preference for inanimate objects and a lack of interest in others, are often evident very early in infancy (Osterling, Dawson, & Munson, 2002). Children and adults with autism exhibit irregularities in a wide variety of face-processing tasks (Behrmann, Thomas, & K., 2006; Grelotti, Gauthier, & Schultz, 2002; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007; Jemel, Mottron, & Dawson, 2006; Marcus & Nelson, 2001; Pelphrey et al., 2002), including visual scanning, memory for faces and affect recognition. The presence of these behavioral abnormalities is mainly supported by a growing body of evidence that individuals with autism process faces in a different manner to others (Pierce, Miller, Ambrose, Allen, & Courchesne, 2001; Schultz et al., 2000).

Individuals with autism

- employ disorganized visual scanning
- rely to a greater degree on the mouth region and to a lesser degree on the eye region for identity recognition
- do not exhibit a mnemonic advantage for faces over objects
- tend to rely on a more feature-based style in processing faces (in contrast to a more holistic style in controls)

Results are conflicting with regard to these differences in face processing in autism. While overall face recognition performance on upright faces indicates that individuals with autism may sometimes perform similarly to controls, the process by which they reach their judgments may be vastly different (Sasson, 2006). These findings indicate that individuals with autism are abnormal in their encoding and representation of faces and suggest a failure to treat the face as a special stimulus, regardless of their actual performance in an emotion recognition task. Thus, results concerning emotional expression processing have been inconsistent. Some studies have demonstrated that people with autism show difficulties on tasks with complex mental states (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Baron-Cohen, Wheelwright, & Jolliffe, 1997), whereas their accuracy in recognizing basic emotions may be intact (R. Adolphs, Sears, & Piven, 2000; Grossman, Klin, Carter, & Volkmar, 2000; Volkmar, Sparrow, Rende, & Cohen, 1989). However, other studies have reported deficits in people with autism in processing basic emotions (Bolte & Poustka, 2003; Celani, Battacchi, & Arcidiacono, 1999; Howard et al., 2000).

An abnormality in facial encoding and representation in the sense that individuals with autism use a cognitive style characterized by enhanced local feature detection over holistic processing is most evident in the reduced tendency to demonstrate an inversion effect for faces (Frith, 2003; Happe,

1999; Jemel, Mottron, & Dawson, 2006). Studies have demonstrated that this previously reported facial inversion effect is not present to the same degree in autism, and that compared to controls, individuals with autism often perform better at the recognition of inverted faces (Sasson, 2006).

Several neuroimaging studies suggest that the brains of individuals with autism process faces in a fashion more typically found in object processing (Pierce, Miller, Ambrose, Allen, & Courchesne, 2001; Schultz et al., 2000). This research indicates that the fusiform gyrus exhibits reduced activation in persons with autism in response to the viewing of unfamiliar faces (Critchley et al., 2000; Dalton, Nacewicz, Alexander, & Davidson, 2007; Ogai et al., 2003). Activation patterns for object stimuli, however, appear normal.

Whereas the fusiform gyrus is important for the perception of facial identity, the amygdala has been shown to play a critical role in the early-stage processing of facial expressions (Calder & Young, 2005; Morris et al., 1998). Therefore, the amygdala has attracted great interest among autism researchers. Results from a number of fMRI studies have shown the amygdala to be hypoactive during a face perceptual task (Critchley et al., 2000; Pierce, Miller, Ambrose, Allen, & Courchesne, 2001). These findings are thought to be strongly related to the known deficits in emotion perception (Celani, Battacchi, & Arcidiacono, 1999). Complementing these results is a growing catalogue of differences in brain structure. There is further evidence from lesion and imaging reports pointing to abnormal development of the amygdale in autism. In summary, individuals with very mild autistic deficits tend to exhibit normal to enlarged amygdala during adolescence and young adulthood, while those with more substantial impairment in social behavior have smaller amygdale than typically developing control subjects (Dalton, Nacewicz, Alexander, & Davidson, 2007).

Results are also conflicting with regard to atypical face scanning patterns. Whereas Joseph et al. (Joseph & Tanaka, 2003) and Klin et al. (Klin, Jones, Schultz, Volkmar, & Cohen, 2002) concluded that autistic individuals attend

significantly more to the lower part of faces than do non-autistics, other studies fail to support this conclusion. In a study by Pelphrey et al. (2002), for instance, autistic participants spent a greater proportion of their inspection time viewing non-feature areas of the faces and spent a smaller percentage of time examining core features such as the nose, mouth, and, in particular, the eyes (Pelphrey et al., 2002).

In general, the scan paths of the participants with autism seemed undirected and disorganized and often as reflecting the processing of only one or two relatively unimportant feature such as an ear or the chin. In contrast, the scanpath of controls seemed strategic and controlled, generally tracing a triangle that subtended the eyes, nose and mouth (Pelphrey et al., 2002). Interestingly, scan paths did not differ as a function of the instructions given to the participants (i.e., “Please look at the faces in any manner you wish.” vs. “Please identify the emotion portrayed in these faces”.). These results are consistent with previous research and may rely on individual parts of the face for identification rather than the overall configuration.

The current edition of the Diagnostic and Statistical Manual of Mental Disorders (APA, 1994), however, does not list abnormal face processing as a defining feature of autism. Nevertheless, because faces provide humans with a pivotal source of social information, the study of impaired face processing in autism may help explain the origins and maintenance of the disorder’s deficits in reciprocal social interaction and non-verbal communication. Indeed, abnormal face processing may operate as both a cause and an effect of various social deficits inherent to autism and may therefore offer a window into the disorder’s basic affective irregularities (Sasson, 2006).

2.3.5.2 Schizophrenia

Bleuler (1959) defined schizophrenia as essentially a splitting of thoughts (cognition) from feelings (emotion). Further, a “flattening of affect” and anhedonia have been recognized since its first description (Bleuler, 1950). Schizophrenia has traditionally been viewed as a psychiatric illness with prominent clinical features of psychosis, negative symptoms and cognitive dysfunction. Individuals with schizophrenia are further impaired in aspects of interpersonal communication, and disturbances in affect recognition may be one of the most pervasive and serious aspects of the schizophrenic patient’s interpersonal problems (Kohler & Martin, 2006; Schartz, Rosse, Johri, & Deutsch, 1999). The possibility that individuals with schizophrenia may be disturbed not only in their experience and/or expression of affect, but also in their ability to perceive emotion expressed by others, has received increasing attention over the past few decades (Edwards, Jackson, & Pattison, 2002). There is substantial evidence that schizophrenics show severe deficits in face processing. As compared to unaffected individuals, patients with schizophrenia often demonstrate a significant impairment in their ability to identify and accurately interpret emotions from facial expressions (Edwards, Jackson, & Pattison, 2002; Kohler & Martin, 2006; Shayegan & Stahl, 2005). According to Kline et al., such deficits do not appear to be related to antipsychotic treatment selection or dose, nor do they appear to be correlated to age or gender (Shayegan & Stahl, 2005).

Although not all studies of affect recognition in schizophrenia report significant differences between affected individuals and controls, it has been suggested that the inconsistency of such findings may be explained by the diversity of symptom profiles observed to be manifest in patients with psychotic illness (Abdi & Sharma, 2004). Other findings have suggested a greater differential impairment in negative affect recognition, the superior ability of paranoid compared to nonparanoid patients in negative affect identification (M. L. Phillips, Drevets, Rauch, & Lane, 2003b).

In addition, patients with schizophrenia have problems in emotion processing as well as a tendency to recognize ambiguous stimuli as being harmful or threatening (Philips, Senior, & David, 2000). Accordingly, impairments in emotion perception and processing have been closely associated with the inability of many schizophrenics to interpret various social cues appropriately and in proper context with respect to a given situation. Interestingly, in the absence of pronounced paranoia, persecutory delusions, and hallucinations, patients with schizophrenia appear to show considerably better performance in their ability to more accurately recognize and make social judgments from facial expressions as compared to individuals predominantly experiencing such symptoms (Hall et al., 2004).

Although no universal emotional identification deficits have been demonstrated in schizophrenic patients, emotions thought to rely on intact amygdala function (particularly fear) have been found to be most consistently affected (Evangeli & Broks, 2000). Studies employing neuroimaging techniques have demonstrated structural and functional abnormalities within the ventral and dorsal neural systems important for emotion processing, although inconsistent findings have been noted (M. L. Phillips, Drevets, Rauch, & Lane, 2003b).

How are the reported emotion processing and structural and functional neurobiological abnormalities associated with symptoms in schizophrenic patients? Philips and colleagues (2003b) proposed a schematic model for the neural basis of the observed deficits in emotion perception and behavior in schizophrenics (see Figure 7). The structural and functional abnormalities within the ventral system, including the amygdala, anterior insula, and ventral striatum, may result in a restriction of the range of emotions identifiable, a decreased range of subsequent affective states and behaviors, and a misinterpretation as threatening of nonthreatening and ambiguous stimuli. These phenomena may be perpetuated by impairments in reasoning, contextual processing, and effortful regulation of affective states, resulting from structural and functional

abnormalities within the hippocampus and dorsal prefrontal cortical regions. This reported pattern of abnormalities may be associated with specific symptoms, including emotional flattening, anhedonia, and persecutory delusions (see Figure 7).

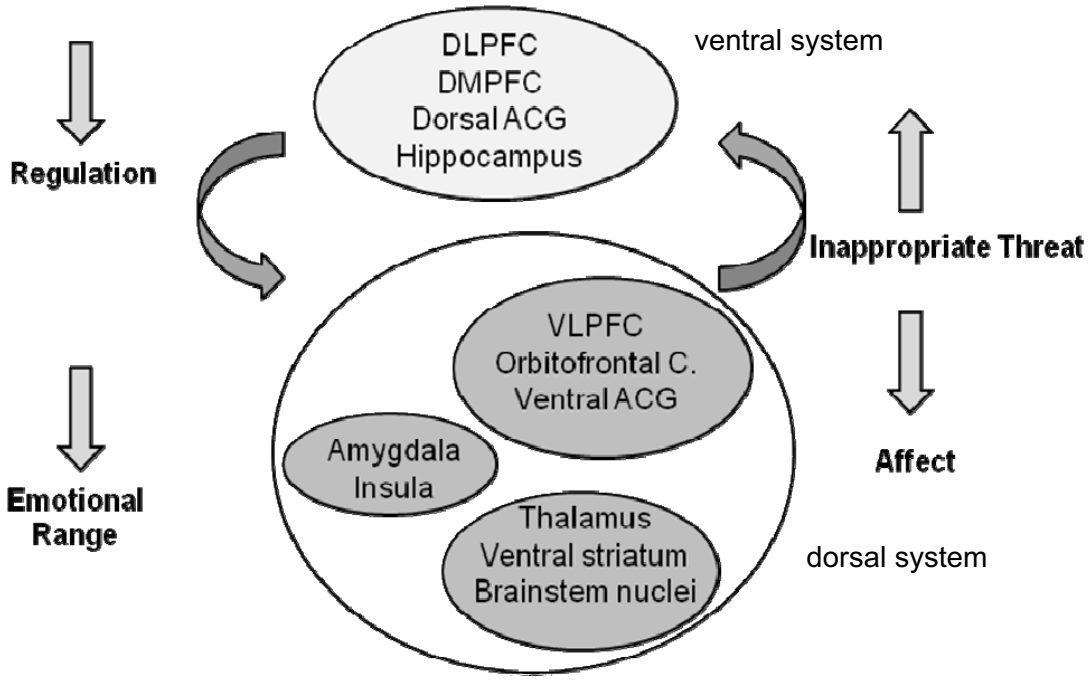


Figure 7: Schematic model for the neural basis of deficits in schizophrenia (Philips et al., 2003).

Note: DLPFC = dorsolateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; ACG = anterior cingulated gyrus; VLPFC = ventrolateral prefrontal cortex.

In line with predictions of the hypothetical model according to Philips et al. (2003b), clinical findings of altered functioning of mediotemporal structures (the amygdala in particular) present in schizophrenia appear to support the hypothesized relationship between such functional abnormalities and the emotion perception and processing deficits described previously (Shayegan & Stahl, 2005). Patients with schizophrenia demonstrate marked functional

anomalies, failing to activate their amygdala in response to sad, aversive, or threatening stimuli (Williams et al., 2004). In addition, there is evidence for structural abnormalities such as a either decreased or increased amygdala volume as compared to normal controls (Shenton, Dickey, Frumin, & McCarley, 2001).

The impact that emotion processing deficits have on outcome in schizophrenia is not yet known. Nevertheless, insights into the relationship between impaired emotion perception, social knowledge and functioning, and patient quality of life continue to grow through accumulating experimental evidence and clinical recognition.

2.3.5.3 Social Phobia

Social Phobia is an anxiety disorder, characterized by a marked and persistent fear in social situations, with excessive concern that others may evaluate the person's behavior negatively (APA, 1994). Since fear of negative evaluation is the key feature of social phobia, cognitive models of social phobia propose that individuals with social phobia are hypervigilant for social threat cues such as angry, disapproving facial expressions (de Jong & Martens, 2007; Hermans & van Honk, 2006). Evidence from cognitive studies are in line with the proposal of Beck and Emery (1985) that the fear of social evaluation in social phobia produces "hyperattention" to social threat cues and these cognitive findings suggest that there may be an excessive automatic engagement by signals of social threat in individuals with social phobia (Hirsch & Clark, 2004).

Clinical observations further indicate that social phobics avoid looking at the faces of others, which may be an important indicator of social fears. In particular, social phobia has been associated clinically with the avoidance of eye contact, which is an important signal in social interactions as reported previously (Darwin, 1972; Emery, 2000). According to Öhman (1986), eyes are

also considered to be the most-fear inducing feature in situations of social appraisal by others (Öhman, 1986). The apparent contradiction between evidence of an attentional bias towards social threat cues and the active avoidance of salient stimuli such as eyes might be resolved in terms of early and late attentional processes. For instance, the vigilance-avoidance hypothesis proposes that hypervigilance ("hyperattention") is associated with automatic processing, while avoidance reflects the strategic (later) allocation of attentional processes (Beck & Clark, 1997). In this regard, the avoidance of eye contact in social phobia may represent a defensive strategy for coping with a hyperattention to perceived threat in social situations (Horley, Williams, Gonsalvez, & Gordon, 2004).

Regarding emotion recognition from facial expressions, social phobic individuals show an enhanced recognition of negative compared with positive facial expressions (Foa, Gilboa-Schechtman, Amir, & Freshman, 2000). A study by Gilboa-Schechtman (1999) showed in particular an enhanced recognition accuracy for angry faces.

Horley and colleagues (2003) were the first to examine visual scanpaths to neutral face stimuli in social phobics (Horley, Williams, Gonsalvez, & Gordon, 2003). While the visual scanpath of healthy subjects tends to follow a triangular pattern, in which fixations are directed mainly at the salient features that define facial expressions, the mouth and the eyes, social phobics showed a pattern of hyperscanning for face stimuli but also a marked avoidance of the eyes when making foveal fixations. In a second study, Horley et al. (2004) examined the scanpaths of social phobics including threat-related facial expressions (anger) in comparison to less explicitly threatening negative (sad), positive (happy) and neutral control faces (see Figure 8).

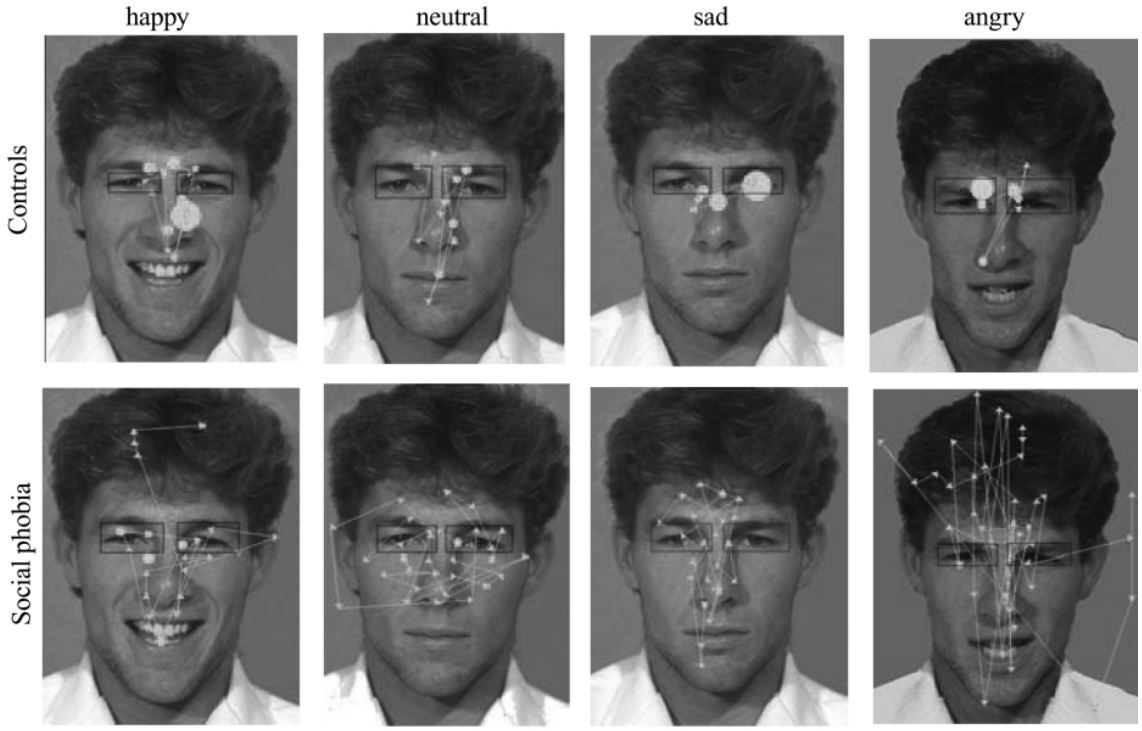


Figure 8: Scanpaths of social phobics compared to healthy controls (Horley et al. 2004).

While control subjects showed an increasing fixation towards eyes across happy, neutral, sad and angry faces, social phobics showed an increasing avoidance of eyes across these emotions. With regard to attention to the eyes in particular, social phobics displayed the hypothesized avoidance of the eyes, and this was most prominent for the angry faces. In addition, social phobics also showed an extensive scanning of non-features (Horley, Williams, Gonsalvez, & Gordon, 2004) and this too was especially dominant in negative faces, but not for the happy faces. Therefore, hyperscanning may be a measure of phobic concern regarding negative social evaluation.

In summary, these findings confirm initial evidence for face processing disturbances in social phobia and provide additional specific evidence that explicitly threat-related faces provoke marked increases in hypervigilance and

avoidance of eyes. These disturbed behavioral responses are likely to be part of a defensive strategy of avoidance behavior, associated with fear of negative evaluation thought to underlie the disorder.

Recently, investigators have begun to examine the neurobiological bases of the processing of social stimuli in social phobia and have found that individuals with social phobia exhibit elevated activation to negative faces (especially anger and disgust) in the anterior cingulate cortex, insula, parahippocampal gyrus, and amygdala when their responses are contrasted to neutral faces (Cooney, Atlas, Joormann, Eugene, & Gotlib, 2006). In interpreting these findings, researchers have suggested that in particular, amygdala activation to threatening social stimuli plays an important role in social anxiety (Phan, Fitzgerald, Nathan, & Tancer, 2006). Phan and colleagues (2006) showed that relative to happy faces, activation of the amygdala in response to harsh (angry, disgusted and fearful) faces was greater in social phobics than in controls, and the extent of amygdala activation was positively correlated with the severity of social anxiety symptoms. It is important to note, however, that behavioral studies have suggested that social phobics are likely to interpret neutral facial expressions negatively. This is in line with brain imaging studies which demonstrate that social phobics exhibit different patterns of amygdala activation compared with controls when presented with neutral faces that are paired with an aversive stimulus (Cooney, Atlas, Joormann, Eugene, & Gotlib, 2006).

Furthermore, an fMRI study by Cooney and colleagues (2006) demonstrated that social phobics showed a different pattern of amygdala activation in response to neutral faces, suggesting a neural basis for the biased processing of ambiguous social information.

2.3.5.4 The construct of alexithymia

The ability to identify and communicate one's feelings is a personality trait that differs among people. About 10% of the normal population are characterized by poor expressiveness of emotional states, i.e. alexithymia, a term denoting the absence of words for feelings (Sifneos, 1973). Alexithymia is a subclinical phenomenon which is most commonly measured using the 20-item Toronto Alexithymia Scale (Bagby, Parker, & Taylor, 1994; Bagby, Taylor, & Parker, 1994) and involves the following three components (Berthoz et al., 2002; J. D. A. Parker, Taylor, & Bagby, 1993a; P. D. Parker, Prkachin, & Prkachin, 2005):

- Difficulty in identifying and describing feelings
- Difficulty in distinguishing feelings from the bodily sensations of emotional arousal
- A tendency to focus on external events rather than inner experience (externally oriented thinking)

Notably, alexithymia has also been implicated in problems in the recognition of facial expressions. A number of studies have reported impaired emotion recognition in individuals meeting criteria for alexithymia on the TAS-20. These findings lead to the suggestion that the commonly found problems in putting emotions into words in alexithymia might represent a more general impairment in emotional information processing (Lane et al., 2000). Aspects of affective information processing that have been investigated include differences in the manner in which emotional experiences are registered and elaborated verbally, differences in the manner in which emotion is expressed and differences in processing the emotional behavior of others.

In a first study, McDonald and Prkachin (1990) found no differences between high- and low-scoring people on the TAS in their abilities to label and judge pictures of facial expression of emotions (McDonald & Prkachin, 1990). However, there might be a difference in the way in which alexithymics attend to

emotional stimuli. Therefore, Parker et al. (1993b) compared responses on a non-emotional Stroop task and an emotional task involving identification colors of emotional words. They found that alexithymics responded more slowly to emotional words than non-alexithymics, while the responses regarding the non-emotional words did not differ (J. D. A. Parker, Taylor, & Bagby, 1993b). In terms of recognizing facial expressions, Parker et al. (1993b) reported further that subjects with high scores in alexithymia were significantly less accurate than low-scoring subjects. More recently, Lane and colleagues (Lane et al., 1996; Lane, Sechrest, Riedel, Shapiro, & Kasniak, 2000) have provided further evidence of a pervasive deficit in the recognition of emotional expression in alexithymia.

Parker et al. (2005) examined whether alexithymia involves a deficit in the efficiency of emotional processing and suggested that deficits may appear when excessive demands are made on emotion-processing capacity, for instance by limiting the amount of time available to encode and transform emotional stimuli. They found that when alexithymics had a time of 3 sec to observe and judge, there were no performance differences compared to the controls. By contrast, when challenged by having to observe and make judgments within 1 sec, participants higher in alexithymia, showed reduced ability to detect expressions of negative emotions (P. D. Parker, Prkachin, & Prkachin, 2005).

Several studies examining the neurobiological basis of alexithymia found evidence for dysfunction of the corpus callosum, whereas other studies observed a relationship between alexithymic features and dysfunction of the right cerebral hemisphere, anterior cingulate cortex or the mediofrontal and orbitofrontal cortex (Berthoz et al., 2002; Kugel et al., 2008). Furthermore, in a recent fMRI study, Kugel and colleagues (2008) investigated automatic amygdala reactivity to negative (sad) and positive (happy) emotion faces as a function of alexithymic features in a sample of normal young adults. They found a reduced automatic response of the amygdala to negative faces and the

authors suggested that automatic amygdala hyporesponsiveness to negative emotion stimuli may contribute to the problems in recognizing one's emotions in everyday life (Kugel et al., 2008).

Furthermore, elevated levels of alexithymia have been reported in several clinical disorders, including depression (Dannlowski et al., 2006; Gaebel & Wolwer, 2004; Leppanen, Milders, Bell, Terriere, & Hietanen, 2004), eating disorders (Bydlowski et al., 2005), somatoform disorders (Gil et al., 2007), and obsessive-compulsive disorder (Aigner et al., 2007; De Berardis et al., 2005), that have also been shown to exhibit deficits in emotion recognition from faces (Bankier, Aigner, & Bach, 2001). It is therefore plausible that the presence of alexithymia in these clinical groups might have contributed to their problems in recognizing emotion from facial expressions. Moreover, about 25% of all patients seeking psychotherapeutic treatment are considered to be alexithymic (Grabe et al., 2008) and by contrast, it is still unclear to what extent alexithymia itself may be modified by psychotherapeutic intervention.

2.3.6 Summary

Several studies suggest that the brain has specific neural circuits involved in processing social information rather than nonsocial stimuli. For example, the lateral fusiform gyrus is activated to a greater degree when subjects view faces than when viewing nonface objects (Haxby, Hoffman, & Gobbini, 2000). Taken together, these findings suggest that abnormalities in the functioning of either or both of the two neural systems involved in face processing – the ventral system which is important for the rapid appraisal of emotional stimuli, the production of affective states and autonomic response regulation, and the dorsal system, important for effortful regulation of resulting affective states – may therefore be associated with abnormalities in emotional behavior and regulation and result in the generation of symptomatology characteristic of different psychiatric disorders, as described in the previous sections.

2.4 Oxytocin and behavior

The peptide hormone oxytocin (OT) has been implicated in the regulation of mammalian social behavior. Oxytocin is a nine-amino acid peptide that has been identified in all classes of vertebrates and many invertebrate species. Oxytocin and the structurally similar peptide arginine vasopressin (AVP), which differs from OT in two of the nine amino acid residues, are the only members of this family of peptides that are identified in mammals (Kiss & Mikkelsen, 2005).

OT has long been considered to be limited to its peripheral effects on stimulating uterine contractions during labor and milk ejection during lactation. However, OT exerts a wide spectrum of central and peripheral effects (Gimpl & Fahrenholz, 2001). In the early 1970s, de Wied brought neuropeptides back to the site of their origin, the brain. However, oxytocin is widely distributed throughout the central nervous system, where it acts as a neuromodulator. Over the past decade, the central actions of OT in particular have been intensively studied. The actions of OT range from the modulation of neuroendocrine reflexes to the establishment of social and bonding behaviors.

2.4.1 The peripheral oxytocin system: Synthesis, receptor distribution and mechanisms of action

Peripherally acting OT may originate in the brain or peripheral tissues. In this case, the brain OT functions as a typical hormone and is a product of the classical hypothalamo-neurohypophysial system. OT is synthesized in magnocellular neurons of the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus, which project to the posterior pituitary and release OT into the bloodstream, where it acts on distant target organs including the mammary glands and kidneys (Bale, Davis, Auger, Dorsa, & McCarthy, 2001; Gimpl & Fahrenholz, 2001; Kiss & Mikkelsen, 2005) (see Figure 9).

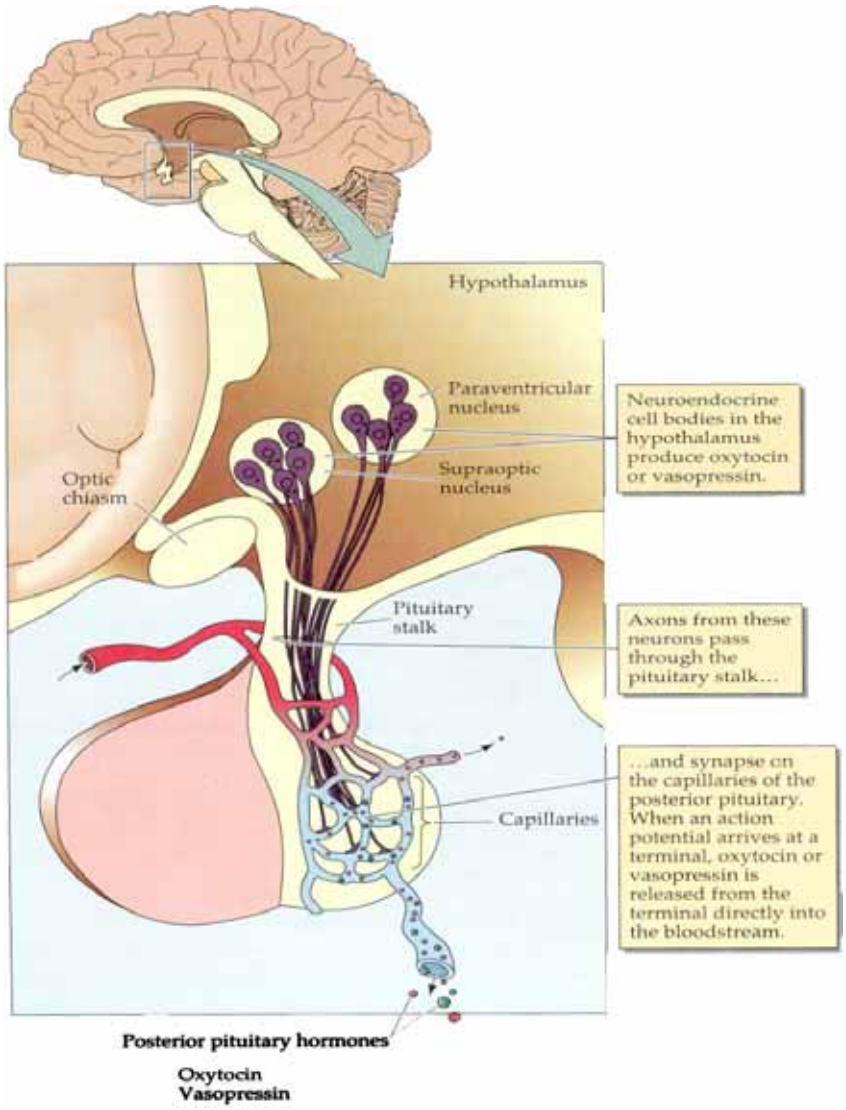


Figure 9: Synthesis of oxytocin in the paraventricular and supraoptic nuclei.

Peripheral tissues also synthesize OT, e.g. uterus, placenta, amnion, corpus luteum, testis, and heart. The multiple hormonal and neurotransmitter functions of OT are mediated by the specific OT receptors. There is only one OT receptor gene, and therefore the same receptor protein is expressed in brain and peripheral organs (Kiss & Mikkelsen, 2005) (for a review of OT receptor structure and receptor regulation, see Gimpl & Fahrenholz, 2001). Within the periphery, OT receptors have been demonstrated in many different tissues,

including the kidney, heart, thymus, pancreas and adipocytes (Blanks & Thornton, 2003). This peripherally acting OT is well known in female reproduction, where it is critical for the processes of initiating lactation and maintenance of parturition (Blanks, Shmygol, & Thornton, 2007; Blanks & Thornton, 2003; Ivell et al., 2001). OT secretion from the neurohypophysis is increased during parturition stimulated by the uterine contractions, which in turn induce further contractions of the uterus leading to the development of a positive feedback loop at the end of the pregnancy. The neural pathway that drives OT neurons via the brainstem involves A2 noradrenergic cells in the brainstem (Russel, Leng, & Douglas, 2003). More specifically, OT acts on the endometrium smooth muscle during labor to increase the intensity of the uterine contractions, and on the myoepithelial cells of mammary glands, which provoke milk ejection in response to suckling.

Oxytocin has many other effects besides uterine contraction and milk ejection. Most of them are exerted within the central nervous system (CNS).

2.4.2 The central oxytocin system

Centrally released OT is known to be involved in a wide range of behavioral regulation. It is synthesized, as described above, in the parvocellular neurons of the hypothalamic paraventricular nuclei, which projects to limbic sites (hippocampus, amygdala, striatum, hypothalamus, nucleus accumbens) and to mid- and hind-brain nuclei.

The methodological approaches used to shed light on this involvement differ and need consideration, particularly to justify comparability among different findings. While animal studies use the administration of synthetic OT, its receptor agonists, knockout mice and transgenic strategies, researchers investigating the role of OT in humans have had to rely on more indirect measures like assaying plasma OT. Moreover, even as an indirect measure,

plasma OT has limited value because the relationship between central and peripheral OT is not well understood, and because of the correlational nature of the findings, it is not possible to clarify issues regarding causality (Bartz & Hollander, 2006). When administered systemically, the compounds of OT do not readily pass the blood-brain barrier, and additionally, they evoke potent hormone-like side effects when circulating in the blood (Born et al., 2002; Fehm, Perras, Smolnik, Kern, & Born, 2000). In humans, a major approach in this context focuses therefore on the administration of synthetic OT via intranasal application (Born et al., 2002; Landgraf & Neumann, 2004).

2.4.2.1 Oxytocin and the blood-brain barrier

There is evidence that after intranasal administration, peptides such as OT and AVP have direct access to the cerebrospinal fluid (CSF) (Fehm, Perras, Smolnik, Kern, & Born, 2000) and to their respective brain receptors within 45-90 minutes (Pietrowsky, Strüben, Mölle, Fehm, & Born, 1996; Pietrowsky, Thieman, Kern, Fehm, & Born, 1996). Born and colleagues (2002) have shown that neuropeptides cross the blood-brain barrier after intranasal administration, thus providing a useful method for studying the central nervous system effects of OT in humans. Born et al. (2002) administered three peptides (melanocortin, vasopressin and insulin) intranasally to healthy humans and measured the concentrations of each peptide within 80 minutes after administration in samples of cerebrospinal fluid (CSF) and systemic blood obtained through intraspinal and intravenous catheters. For all three peptides, mean CSF concentrations began to rise within 10 min of intranasal administration, and for vasopressin, CSF concentrations continued to rise for up to 80 min after administration.

Two possible routes have been suggested for the direct passage of peptides from the nose to the brain: an intraneural and an extraneuronal pathway (Pietrowsky, Strüben, Mölle, Fehm, & Born, 1996). While the intraneural pathway involves the internalization of the peptide into olfactory neurons,

followed by axonal transport, and would therefore require hours to reach the olfactory bulb, traveling by extracellular route seems more plausible by passing through patent intercellular clefts in the olfactory epithelium to diffuse into the subarachnoidal space (Born et al., 2002).

Although the exact extent of peptide uptake from CSF into human brain tissue is not known, animal studies have shown significant uptake even in more interior brain regions such as the amygdale. Nevertheless, the potential usefulness of nasal administration derives from the fact that biologically effective concentrations of neuropeptides can be achieved in the human brain without strong, systemic, hormone-like side effects (Born et al., 2002; Fehm, Perras, Smolnik, Kern, & Born, 2000).

2.4.2.2 Central nervous system actions of oxytocin

As described previously, oxytocin is a nine-amino-acid peptide. Neuropeptides are biologically active sequences of three or more amino acid residues, which are produced in and released from distinct populations of neurons and are capable of influencing functional parameters of target neurons (Landgraf & Neumann, 2004). Once released in the brain, neuropeptides act in multiple ways in interneural communication, such as neuromodulators and / or neurotransmitters; additionally, as reported in chapter 2.4.1, when secreted into the systemic circulation, neuropeptides may act as hormones.

As transmitters, neuropeptides contribute to the synaptic mode of information transfer, which refers to fast point-to-point signaling. Furthermore, as neuromodulators, peptides are non-synaptically released from multiple sites of the neuronal membrane and act on relatively distant targets (for review see Landgraf & Neumann, 2004). Combining these activities is likely to bring about a high level of regulatory capacity, including all advantages from precise point-to-point signaling up to diffusely spread neuromodulation.

Thus, oxytocin receptors are distributed in various brain areas associated with the central nervous system control of stress and anxiety and with social behavior including pair-bonding, parental care, social memory and aggression (Landgraf & Neumann, 2004). Literature on the effects of OT in human social behavior will be reviewed in the next section.

2.4.2.3 Oxytocin, anxiety and stress

A number of animal studies suggest that OT is involved in the stress response. In particular, it is thought to play a role in reducing stress by dampening the hypothalamic-pituitary-adrenal (HPA) activity (Neumann, 2002). Much of the research has focused on lactation because OT is released during lactation in response to suckling in order to cause milk ejection (Uvnas-Moberg, Widstrom, Nissen, & Bjorvell, 1990). It has been found that suckling in the postpartum period is linked to decreased HPA axis activity (Carter & Altemus, 1997; Windle et al., 1997), and moreover, that lactating rats show blunted adrenocorticotropic hormone (ACTH) and cortisol secretion to physical and psychosocial stress (Uvnas-Moberg, Ahlenius, Hillegaart, & Alster, 1994). There is additional evidence that OT injections have anxiolytic and sedative effects in male rats and reduce reactivity to painful stimuli (Bartz & Hollander, 2006). A study by Huber and colleagues (Huber, Veinante, & Stoop, 2005) showed that intracerebral OT reduces the activity of the amygdala in the modulation of the autonomic fear response via OT receptors in the amygdala.

Furthermore, Neumann and colleagues found in several studies (Neumann, Kromer, Toschi, & Ebner, 2000a; Neumann, Wigger, Torner, Holsboer, & Landgraf, 2000b) a peripheral OT release and a release within the brain in response to both physical and psychological stress and fearful situations.

Lactation in humans also appears to dampen stress responsivity (Heinrichs et al., 2001). Lactating woman were found to show attenuated ACTH, cortisol and

glucose response to physical stressors and, postpartum lactating woman showed reduced pituitary-adrenal reactivity to a psychosocial stressor after endogenous oxytocin stimulation (Altemus, Deuster, Galliven, Carter, & Gold, 1995; Heinrichs et al., 2001). Further evidence was provided by Light and colleagues, who showed that breast-feeding woman with increased plasma oxytocin have decreased blood pressure in response to a psychosocial stressor (speech task) after holding their baby, an event thought to enhance the effects of OT (Light et al., 2000).

With regard to stress, a more recent study by Ditzen and colleagues showed that woman receiving standardized physical contact (neck and shoulder massage) from their partner before stress exposure exhibited reduced cortisol and lower heart rate responses to stress in comparison with woman who received verbal social support or no social interaction from their partner (Ditzen et al., 2007).

Altogether, these findings from human studies point to a direct protective effect of endogenous OT stimulation. However, it should be noted that there are a number of confounding factors, in particular the release of other hormones (e.g., prolactin or opioid peptides), making it difficult to ascertain the specific role of OT in stress reduction. Moreover, plasma OT concentrations do not seem to reflect the availability of the neuropeptide in the central nervous system (Landgraf & Neumann, 2004). Thus, to address the investigation of OT as an underlying biological mechanism for the reduction of stress and anxiety in humans, more recently, procedure methodologies involving OT administration in double-blind, placebo-controlled designs have been used.

Heinrichs et al. (2003) investigated the effects of exogenously administered OT on cortisol and subjective responses to a psychosocial stressor. Moreover, they were interested in examining the interactive effects of OT and social support on stress response. In a double-blind, placebo-controlled design, all participants were randomly assigned to receive either 24 IU oxytocin intranasally or placebo

50 min before the stress task, and either social support from their best friend during the preparation phase or no social support (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). Results clearly showed that subjects who received both social support and OT exhibited the lowest cortisol concentrations during stress exposure, whereas subjects who received no social support demonstrated the highest cortisol response. Furthermore, those who received both reported decreased anxiety from pre- to post-stress, supporting the hypothesized anxiolytic effect of OT.

Thus, research to date strongly suggests that OT reduces stress response and may also play an important role as an underlying biological mechanism for the well-known stress-protective effects of positive social interaction.

Regarding the effects of OT on the human amygdala, an initial fMRI study by Kirsch and colleagues found that 27 IU intranasal OT markedly reduced activation of the amygdala and, moreover, reduced coupling of the amygdale to brainstem regions implicated in autonomic and behavioral manifestations of fear when fear-inducing stimuli were presented to the subjects (Kirsch et al., 2005). In a more recent fMRI study by Domes et al. (2007a) using a double-blind, placebo-controlled within-subject design, intranasal OT was found to reduce right-sided amygdala responses to all categories of face valences: fearful, happy and angry (Domes et al., 2007a).

In conclusion, these initial neuroimaging studies strongly suggest a modulatory role of OT on amygdala responsiveness irrespective of the emotional valence of stimuli.

2.4.2.4 Oxytocin, social approach and social cognition

In addition to its role in stress response, OT is involved in the regulation of social affiliation, social approach and attachment. A host of animal studies have implicated OT in mating, pair-bonding, and adult-infant attachment (Bartz &

Hollander, 2006; Lim & Young, 2006). For instance, it is well known that OT regulates pair-bonding in prairie voles and that differences in OT receptors may underlie individual differences in social behavior and differences between species (Campbell, 2008; L. J. Young, 2002). In contrast to the animal literature, very few studies have examined OT and social affiliation and the associated cognitive processes in humans.

Recently, however, Kosfeld and colleagues (2005) reported intriguing findings suggesting that intranasal OT promotes trust, a prerequisite of social affiliation and social approach. Results indicated that a single dose of 24 IU intranasal OT caused a substantial increase in trust among humans, thereby greatly increasing the benefits from social interaction in a trust game (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Most importantly, these findings show that the effect of OT on trust was not due to a general increase in the readiness to bear risk. Rather, OT particularly increases an individual's willingness to accept social risks within social interactions.

Concentrating more on the modulation of social cognitive processes, a recent study by Domes and colleagues (2007b) examined the effects of OT on the ability to infer the affective state of another individual from facial cues such as the eye region (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007b). Participants were given a set of pictures showing the eye region of emotional faces, and were asked to infer the internal state of the depicted person. This test was originally developed to assess social deficits in patients with autism spectrum disorders (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Domes et al. showed that a single dose of OT enhanced performance in this test compared to placebo. Even though the causal mechanisms are still unclear, OT-induced facilitation of certain social cognitive functions might be associated with social approach behavior.

A recent study by Guastella and colleagues (2007) indicated a key role of OT in facial processing. The authors reported an increased number and a prolonged

duration of gazes towards the eye region of neutral human faces following an intranasal OT administration as compared to placebo.

In summary, overall, these findings from studies of healthy humans parallel those from animal studies and point to the role of OT in social perception and social cognition, thereby possibly promoting social approach and affiliation. Besides the role of OT in stress response and its anxiolytic effect, OT seems to be involved in social cognitive functions such as emotion recognition.

2.4.3 Clinical implications

Since deficits in social behavior belong to the core characteristics of several psychological disorders, such as social anxiety, autism spectrum disorders, obsessive-compulsive disorder and borderline personality disorder, research has been focusing on examining the role of OT in these mental disorders. An overview will be given in the next sections.

2.4.3.1 Oxytocin and autism

As described in a previous chapter, autism is a developmental disorder defined by abnormalities in speech and communication, impaired social functioning, and repetitive behaviors and restricted interests (APA, 1994). A number of researchers have suggested that OT may be implicated in the etiology of autism since deficits in social interaction and affiliation are core features of autism and these neuropeptides are involved in the regulation of affiliative behaviors (Bartz & Hollander, 2006; Hollander et al., 2007; Hollander et al., 2003). In addition, results from nonhuman animal studies have suggested that OT influences behaviors that are abnormal in autism, including cognitive and communicative behaviors as well as motor stereotypes (T. R. Insel, O'Brian, & Leckman, 1999).

First evidence came from studies investigating plasma OT levels in individuals with autism (Green et al., 2001; Modahl et al., 1998). Modahl and colleagues found significantly lower plasma OT levels in children with autism compared to

age-matched controls. Furthermore, these researchers showed a significant correlation between OT blood levels and social impairment (Modahl et al., 1998). A subsequent study by Green et al. (2001) found that not only were plasma samples obtained from the autistic children associated with lower OT levels but they were also associated with higher OT precursor levels, as well as an increased ratio of OT precursor to OT, implicating alterations in OT metabolism in autism.

The second line of evidence highlights the possible role of the OT receptor gene in autism (McCauley et al., 2005; Wu et al., 2005). For instance, Wu et al. (2005) found evidence in a sample of Chinese Han families for two single nucleotide polymorphisms, indicating that these two loci may be associated with autism. Support for these results came from studies in a Caucasian sample (Jacob et al., 2007; Lerer et al., 2007) and was extended in a family-based association study by Lerer at al. (2007) showing interactions with social cognitive skills.

Finally, recent studies by Hollander and colleagues (Hollander et al., 2007; Hollander et al., 2003) suggest that systemic infusions of OT may reduce repetitive behavior and improve emotion recognition in autism.

Taken together, a number of studies implied that the availability of OT is associated with socio-cognitive functioning in autism, and there is further evidence that the OT gene might be involved in the development of autism. Therefore, OT may have therapeutic benefits for the treatment of autism spectrum disorders, especially with respect to addressing repetitive behaviors and deficits in social functioning.

2.4.3.2 Oxytocin and other axis I disorders: OCD and social phobia

Obsessive-compulsive disorder (OCD) was one of the first psychiatric disorders to be linked to OT (McDougle, Barr, Goodman, & Price, 1999). According to the DSM-IV (APA, 1994), OCD is defined by recurrent, intrusive thoughts and fears of danger or contamination, and compulsive behaviors or cognitions for relieving anxiety.

A number of findings support the possible role of OT in OCD: animal studies found a marked increase in stereotyped behaviors following the central administration of OT (McDougle, Barr, Goodman, & Price, 1999); female patients with OCD often report the onset of the disorder during pregnancy; and a study by Leckman (1994b) found increased CSF OT levels in an adult OCD group (Leckman et al., 1994b). However, Altemus and colleagues (1999) were not able to confirm the finding of enhanced OT levels in OCD (Altemus et al., 1999).

A very early case study by Ansseau et al. (1987) showed a symptomatic improvement in OCD patients after an intranasal treatment with OT (Ansseau et al., 1987). Despite these positive findings, subsequent controlled studies did not confirm therapeutic effects of systemic or intranasal administration (Epperson, McDougle, & Price, 1996; Salzberg & Swedo, 1992).

To summarize, the role of OT in OCD is still unclear. Thus, further research is needed to elucidate the potential role of OT in compulsive behavior.

OT may have therapeutic benefits for other anxiety disorders in which social withdrawal is a prominent feature, such as social phobia. Social phobia (SP) is an anxiety disorder marked by persistent and excessive fear of social interaction and/or performance situations (DSM-IV) (APA, 1994). Individuals with SP are worried that they will be negatively evaluated by others and are plagued by fears that they will do or say something to humiliate or embarrass themselves. SP is the most common anxiety disorder, but in spite of this, very

little is known about its etiology or about effective treatment. OT is an ideal candidate for the involvement in and potential treatment of SP (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005).

2.4.3.3 Oxytocin and axis II disorders: borderline personality disorder

Finally, OT may be implicated in some personality disorders marked by disrupted social interactions and attachments. Borderline personality disorder (BPD) is characterized by affective instability, anger, impulsivity, and identity confusion (APA, 1994; Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004). Regarding the pathogenesis of BPD, the interpersonal relationships which are marked by mental and / or physical abuse, as well as neglect are believed to play a central role. Furthermore, individuals with BPD have profound fear of abandonment, which leads to intense interpersonal relationships, and desperate attempts to avoid being left alone.

Given the link between OT and trust and prosocial behavior, OT may have beneficial effects in targeting the disordered attachment and mistrust associated with BPD. Indeed, a number of researchers speculate that early stress has important implications for adult affiliative behaviors and, moreover, that OT might be involved in this process. Carter (2003) suggested that early stress interferes with the developing neuropeptide system and alters receptor binding of OT, thereby promoting the developmental of attachment disorders such as in BPD (Carter, 2003)

2.4.4 Summary

In conclusion, most studies over the last decades investigating the neurobiology of social behavior and affiliation have used animal models. So far, there is a growing body body of evidence from human studies that indicate that some of the basic effects of OT on social behavior from animal research may also play an important role in human social interaction. The findings to date are encouraging in terms of providing a better understanding of the neuroendocrine mechanisms of human social behavior. Moreover, these translational findings suggest that OT may play a key role in the etiology and treatment of various clinical disorders with social deficits and disturbed attachments.

Concerning the role of OT in human social behavior, according to Heinrichs and Domes (2008), the following findings can be summarized:

1. OT is thought to regulate the behavioral and endocrine stress response.
2. Positive social interactions, such as social support or social proximity, lead to an OT release, thus representing a possible mediator for the well-known stress-protective effects of social support.
3. The limbic areas, particularly the amygdala, have been suggested as a neural correlate for the anxiolytic effect of OT. Moreover, it has been shown that OT attenuates the amygdala reactivity to emotional and social stimuli and reduces brain stem activity, which is associated with autonomic arousal.
4. OT promotes social cognition and the interpretation of social signals.
5. Finally, an altered OT system possibly underlies several mental disorders with social deficits, such as autism, OCD, social phobia and personality disorders.

With regard to a therapeutic use of OT in mental disorders, the currently most promising approach seems to be to increase the availability of OT in the central nervous system by exogenous administration (Heinrichs & Domes, 2008). Figure 10 shows an integrative model of the interactions of anxiety, stress, social approach behavior, and the oxytocinergic system, which leads to a new approach of a psychobiological therapy in psychopathological illnesses.

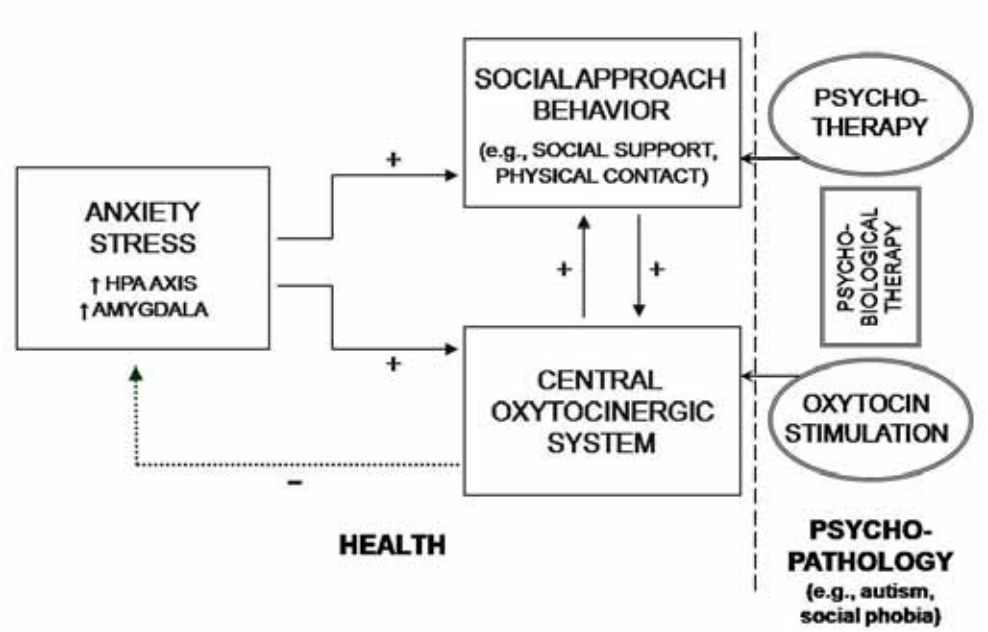


Figure 10: Interactions between anxiety and stress, social approach behavior, and the oxytocinergic system (Heinrichs & Domes, 2008).

According to the authors, anxiety and stress promote social approach behavior and stimulate OT release in healthy humans. Positive social interactions, such as physical contact, are associated with OT release, and in turn, OT induces social approach behavior. As OT inhibits hypothalamic-pituitary-adrenal (HPA) axis responses and limbic reactivity to stress, the neuropeptide plays a key role as an underlying neurobiological mechanism for the anxiolytic/stress-protective effect of positive social interaction. Heinrichs and Domes (2008) suggest that in mental and developmental disorders with severe social deficits, novel

therapeutic approaches combining effective psychotherapy methods with OT administration offer a great opportunity to develop a “psychobiological therapy”.

3. Oxytocin improves emotion recognition in individuals with difficulties in recognizing, describing and regulating emotions

3.1 Introduction

The ability to perceive and understand facial expressions from others play a key role in nonverbal human communication, which substantially modulates and codetermines social interactions and interpersonal relationships (Spitzer, Siebel-Jürges, Barnow, Grabe, & Freyberger, 2005). Therefore, humans have to infer internal states (emotions) from external cues such as facial expressions in order to make sense of or predict another person's behavior ("mind-reading").

In particular, persons with alexithymia have distinct difficulties in recognizing emotions. Alexithymia represents a multifaceted personality construct defined by marked deficits in the cognitive processing and regulation of emotions (Spitzer, Siebel-Jürges, Barnow, Grabe, & Freyberger, 2005). It encompasses the core features of difficulties in understanding, identifying feelings and distinguishing them from the bodily sensations of emotional arousal, the difficulty in describing feelings to other people and an externally oriented cognitive style (Taylor, Bagby, & Parker, 1997). Alexithymia is thought of as a personality trait that differs among people. About 10% of the normal population are characterized by poor expressiveness of emotional states, i.e., alexithymia (Berthoz et al., 2002). Furthermore, alexithymia has also been implicated in problems in the recognition of emotion in facial expressions (Lane et al., 1996; Lane, Sechrest, Riedel, Shapiro, & Kasniak, 2000; J. D. A. Parker, Taylor, & Bagby, 1993a). High-alexithymic individuals were found to identify facial expressions of emotions less accurately than low-alexithymic individuals (Jessimer & Markham, 1997; Lane, Sechrest, Riedel, Shapiro, & Kasniak, 2000; J. D. A. Parker, Taylor, & Bagby, 1993a).

Although alexithymia is a subclinical phenomenon, it is associated with general psychological distress, especially with depression and anxiety, and has been

observed in numerous psychiatric and somatic disorders (Bankier, Aigner, & Bach, 2001; Gil et al., 2007; Le, Ramos, & Munoz, 2007; Marchesi, Bertoni, & Maggini, 2008; Saarijärvi, Salminen, Taylor, & Toikka, 2006; Taylor, Bagby, & Parker, 1997).

In non-human mammals, the neuropeptide oxytocin (OT) has a central role in the regulation of social behavior and particularly in positive social interactions. Aside from its well-known physiological functions in milk ejection and during labor, OT receptors are distributed in various brain areas associated with social behavior, including affiliative behavior, pair-bonding and social attachments (Carter & Altemus, 1997; T. T. Insel & Young, 2000; L. J. Young, 2002). Moreover, results from animal studies show that oxytocin facilitates approach behavior by overcoming their natural avoidance of proximity.

Recent studies in humans report similar direct effects of OT on human social behavior such as trust, social support and “mind-reading” (for a review, see Heinrichs & Domes, 2008). For instance, OT was found to decrease anxiety to psychosocial stress (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Heinrichs et al., 2001) and to induce a significant increase in trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). In a recent study, Domes and colleagues (2007) showed that a single dose of OT improved the ability to infer the mental states of others from subtle facial cues such as the eye region. Domes et al. (2007) argued that one possible mechanism underlying this effect was an enhancement of eye gaze towards the eye region during the emotion recognition task. Since face processing is a basic process in interpersonal communication and critical information is taken from the eyes and to a lesser extent the mouth, Guastella and colleagues (2007) examined the effects of a single dose of OT in eye gaze to facial stimuli. In this study, participants given OT showed an increase in the number of fixations and total gaze time toward the eye region when viewing neutral faces (Guastella, Mitchell, & Dadds, 2007).

Therefore, the aim of this study was to investigate the effects of a single dose of OT on emotion recognition in high- versus low-alexithymic persons. It was hypothesized that intranasal oxytocin improves the ability to recognize emotions from social cues of the eye region. Specifically, oxytocin was expected to improve the performance in participants with symptoms of high alexithymia.

3.2 Methods

3.2.1 Subjects

Sixty-five non-smoking healthy male volunteers (mean age ± SD: 24.06 ± 2.33 years) participated in this study. They were recruited by advertisements and by the use of e-mail lists at the University of Zurich and the Federal Technical University (ETH) of Zurich. All men who expressed an interest in participating were first screened by telephone and then through psychological questionnaires with regard to the exclusion criteria. Subjects were ineligible if they were using medication or reported mental or medical illness (acute or chronic). Further exclusion criteria were smoking more than 5 cigarettes per day, substance abuse and being a psychology student. Fifteen of the original 87 were excluded after completing the screening questionnaires: ten who met criteria for a mental health disorder based on the Brief Symptom Inventory (BSI; Franke, 2000) and five who scored above the cut-off score for alexithymia on the Toronto Alexithymia Scale (TAS-20; Bach, Bach, deZwaan, Serim & Bohmer, 1996). Subjects were instructed to abstain from alcohol, smoking, caffeinated beverages, and medication the day prior to the experiment. Seven subjects were excluded post-hoc from data analyses because they reported alcohol consumption or smoking marijuana the day before the experiment. The study was approved by the ethics committee of the University of Zurich and all volunteers gave written informed consent for participation in the study. After the experiment, subjects were paid with 50 Swiss francs for participation.

3.2.2 Experimental Protocol

Participants were instructed to eat breakfast and lunch during the day before the experiment and were then asked to refrain from eating, drinking anything but water, and intense physical exercise for at least two hours prior to the experiment. All experimental sessions lasted approx. 1.5 hours and were conducted between 4:00 PM and 9:00 PM at the laboratory of the department of Clinical Psychology and Psychobiology at the University of Zurich.

3.2.2.1 Procedure

The study protocol consisted of four consecutive phases (Fig. 11): introduction and demographics (10 min), substance administration and waiting time (40 min), emotion recognition task (approx. 8-10 min) and debriefing (15 min).

Participants arrived at the laboratory in the late afternoon (between 4 and 5 PM). The experimental procedure was explained and they were given a demonstration on how to use the nose spray. Furthermore, participants were instructed to wear the heart rate monitor and told how to set heart rate markers during the experiment. Following this, questionnaires on demographic characteristics and mood (MDBF, SAM) were completed.

Next, subjects were given the substance (Oxytocin or Placebo) and a 40-minute waiting phase followed, in which participants filled out more questionnaires (BDI, TAS, etc).

Shortly before and after the emotion recognition task, subjects again completed questionnaires on their mood. They were then prepared with instructions for the emotion recognition task. The final 10 to 15 minutes were used to debrief the participants and to pay out the compensation.

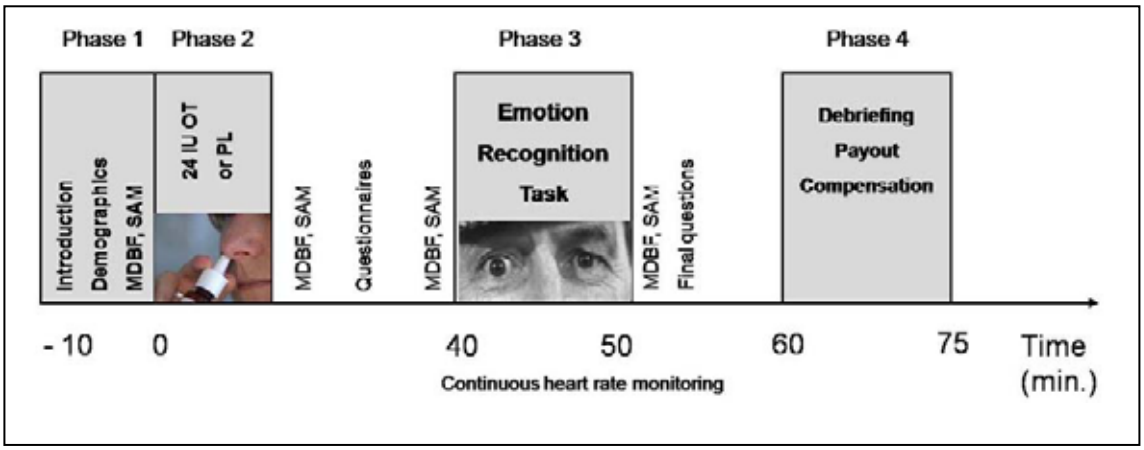


Figure 11: Experimental procedure empirical study 1.

3.2.2.2 Substance administration

In a placebo-controlled double-blind study design, all 65 volunteers were randomly assigned either to receive an intranasal dose of 24 IU oxytocin (Syntocinon® Spray; Novartis, Basel, Switzerland; each puff with 4 IU oxytocin) or placebo (containing all ingredients except for the peptide). Intranasal administration took place 40 minutes before the emotion recognition task in order to make sure that the peptide achieved the cerebrospinal fluid (CSF) (Born et al., 2002).

3.2.3 Emotion Recognition Task

For this task, pictures of the six basic emotions (fear, sadness, disgust, happiness, anger, surprise) were chosen from the “Pictures of Facial Affect” (Ekman & Friesen, 1976). Using a computer program, they were reduced to the eye region, resulting in a set of 21 pictures of the eye region of different persons (6 emotions x 3 and 3 neutral eye regions). These stimuli were presented to the participant on a computer screen with four alternative labels describing what the person displayed might be thinking or feeling at the moment. Pictures and labels were presented in a randomized order. Participants were instructed to

choose the correct label. As dependent variables, we recorded the correctness of the answer and also the reaction time. All emotions were divided into two subsets of easy and difficult emotions. These two subsets were generated based on the median of item difficulty derived from data of the PL group.

3.2.4 Psychological Measures

Subjects received questionnaires on personality characteristics two weeks before the experiment. On the day of the experiment, shortly before the emotion recognition task, they completed further questionnaires designed to measure demographic items, personality characteristics and psychopathological symptoms. Before and after the emotion recognition task, mood was repeatedly assessed.

The validated German versions of the following questionnaires were included:

Brief Symptom Inventory (BSI; Franke, 2000) for screening of symptoms of psychopathology, the Trait Version of the *State-Trait Anxiety Inventory* (STAI; Spielberger et al., 1970) for measuring trait anxiety, the *Beck Depression Inventory* (BDI; Hautzinger, Bailer, Worall & Keller, 1995) to assess severity of depression, the *Toronto Alexithymia Scale 20* (TAS 20; Bach et al., 1996) to measure alexithymia and its components: difficulty identifying feelings, difficulty describing feelings and externally oriented thinking, the *Adult Attachment Scale* (AAS; Collins & Reads, 1990) for testing attachment behavior with its subscales of: Secure, Fearful, Preoccupied, and Dismissing, the *Close Relationship questionnaire* (CRQ; Brennan, Clark & Philipp, 1998) for assessing individual differences with respect to attachment-related anxiety (i.e., the extent to which people are insecure vs. secure about the extent of their partner's availability and responsiveness) and attachment-related avoidance (i.e., the extent to which people are uncomfortable being close to others vs. secure

towards others), the *Sensation Seeking Scale V* (SSS-V; Beauducel, Brocke, Strobel & Strobel, 1999) for the assessment of sensation seeking and its four subscales thrill and adventure seeking, experience seeking, disinhibition and boredom susceptibility, the Neo-FFI Inventory (Borkenau & Ostendorf, 1993) to measure the Five Factor Model: extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience, the *State-Trait Anger Inventory* (STAXI; Schwenkmetzger, Hodapp & Spielberger, 1992), which measures the intensity of anger as an emotional state (State Anger) and the disposition to experience angry feelings as a personality trait (Trait Anger).

Mood responses before and after the emotion recognition task were repeatedly assessed with the *Multidimensional Mood Questionnaire* (MDBF; Steyer, Schwenkmetzger, Notz & Eid, 1997) (three components good-bad, awake-tired, calm-nervous) and the *Self-Assessment-Manikin* (SAM; Lang, 1985), which is a culture- and language-free measurement for mood, which depicts the three dimensions pleasure, arousal and dominance with a graphic character arrayed along a continuous nine-point scale (pleasure: from smiling, happy to frowning, unhappy; arousal: sleepy to excited; dominance: very small figure, being controlled, to very large figure representing a powerful feeling).

3.2.5 Autonomic Measures

Heart rate was monitored at beat-to-beat intervals throughout the experiment using a wireless chest heart rate transmitter and a wrist monitor recorder (Polar S810i^{TM}, Polar Electro, Finland). For analysis, one-minute intervals were computed from 5 minutes before until 5 minutes after cessation of the emotion recognition task. Baseline measures were assessed before substance administration and 40 minutes after substance administration.

3.2.6 Statistical Analyses

Baseline differences between the four groups were examined using two-way analysis of variance (ANOVA) with substance (OT or PL) and group (high-alexithymia or low-alexithymia) as between-subject factors. The main hypothesis concerning the effects of oxytocin on emotion recognition in high- versus low-alexithymia subjects was examined with Student's t-tests for independent groups and Bonferroni-corrected data were interpreted. Data were tested for normal distribution and homogeneity of variance using Kolmogorov-Smirnov and Levene's test before statistical procedures were applied. All reported results were corrected by the Greenhouse-Geisser procedure where appropriate (violation of sphericity assumption).

To determine changes in heart rate and mood, two-way ANOVAs with repeated measures were calculated with substance (OT vs. PL) and group (high-alexithymia vs. low-alexithymia) as the between-subject factor and time as the within-subject factor

All analyses were two-tailed, with the level of significance set at $p < .05$. All statistical analyses were assessed using SPSS 14.0, German version. Unless otherwise indicated, all results shown are means ± standard error of means (s.e.).

3.3 Results

3.3.1 Description of the study groups

The four groups, consisting of 19 subjects with OT and 13 subjects with PL in the high-alexithymia group, and 14 subjects with OT and 19 subjects with PL in the low-alexithymia-group did not differ significantly in any relevant baseline measurements, such as psychopathological symptoms or trait characteristics (table 1). In order to divide the participants into high- and low-alexithymia subjects, a median split was conducted with the sum score of the Toronto Alexithymia Inventory (TAS-20). The median lay at a total score of 41. All subjects who scored above this were assigned to the high-alexithymia group (n = 32), and all subjects scoring below 41 to the low-alexithymia group (n = 33).

Table 1: Characteristics of the study groups.

	High-Alexithymia		Low-Alexithymia		ANOVA p
	Oxytocin (n = 19)	Placebo (n = 13)	Oxytocin (n = 14)	Placebo (n = 19)	
Age	23.84 ± 0.45	23.69 ± 0.66	23.93 ± 0.62	24.63 ± 0.61	.48
Global severity (BSI)	0.30 ± 0.04	0.31 ± 0.05	0.29 ± 0.04	0.21 ± 0.40	.25
Trait Anxiety (STAI)	35.83 ± 1.62	34.46 ± 1.56	36.36 ± 2.75	31.16 ± 1.57	.32
Depression (BDI)	2.74 ± 0.53	3.08 ± 0.87	2.79 ± 0.77	2.84 ± 0.78	.85
Trait-Aggression (STAXI)	15.72 ± 0.96	17.23 ± 1.16	18.57 ± 1.30	15.68 ± 2.45	.06
Sensation Seeking (SSS)	22.53 ± 1.02	23.39 ± 1.31	22.79 ± 1.39	25.58 ± 1.05	.42
Neuroticism (Neo-FFI)	17.44 ± 1.39	16.62 ± 1.47	16.50 ± 1.72	12.37 ± 1.21	.26
Openness (Neo-FFI)	30.11 ± 1.39	30.39 ± 1.79	34.00 ± 1.61	33.79 ± 1.46	.88
Extraversion (Neo-FFI)	29.00 ± 0.86	27.70 ± 1.35	28.00 ± 1.71	30.89 ± 1.33	.11
Agreeableness (Neo-FFI)	29.28 ± 0.99	29.77 ± 1.25	30.00 ± 1.33	30.53 ± 1.29	.99
Conscientiousness (Neo-FFI)	33.78 ± 1.34	31.92 ± 1.82	30.00 ± 1.80	31.79 ± 1.46	.26
Alexithymia (TAS)	47.47 ± 1.2	45.54 ± 1.08	36.43 ± 1.12	35.26 ± 0.81	.72
Attachment (AAS)	35.50 ± 1.1	35.46 ± 1.41	34.79 ± 2.06	31.21 ± 1.34	.24

Data given as mean +/- s.e.

3.3.2 Emotion recognition task

3.3.2.1. Answer Correctness

Results showed that the single administration of 24 IU oxytocin led to an increased ability to recognize emotions in the high-alexithymia group (t_{30} = 2.23; p = .033), while no such effect occurred in the low-alexithymia group (t_{31} = -.594; p = .557) (Fig. 12).

In the group with high alexithymia, oxytocin administration further induced an improvement of emotion recognition particularly in emotions that are difficult to recognize (t_{30} = 2.218, p =.034). No significant increase was found in either group for the subscores of easy emotions (high-alexithymia: t_{30} = .972, p = .339; low-alexithymia: t_{31} = -.944, p = .352) (Fig. 13).

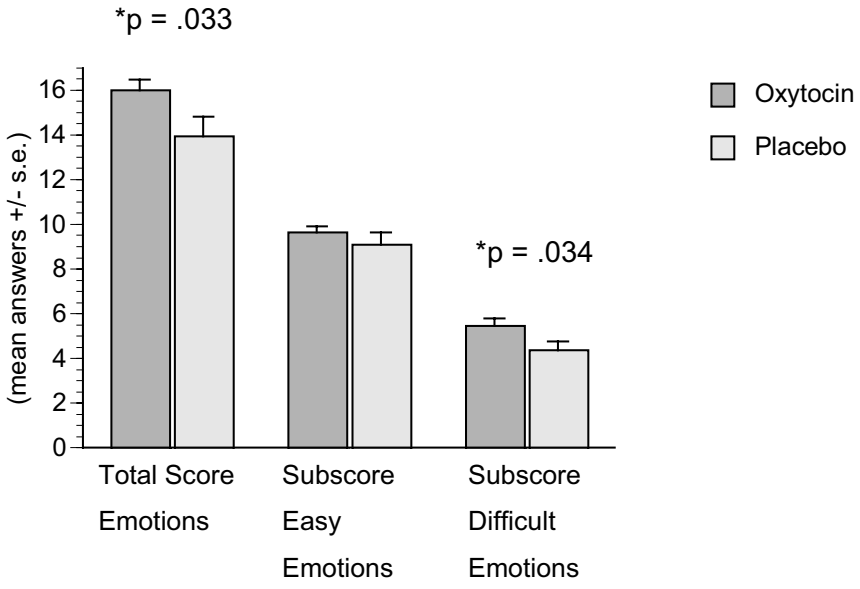


Figure 12: Mean Answers for high-alexithymia group in the emotion recognition task for all emotions, easy emotions and difficult emotions. Error bars are standard error of the mean (SEM).

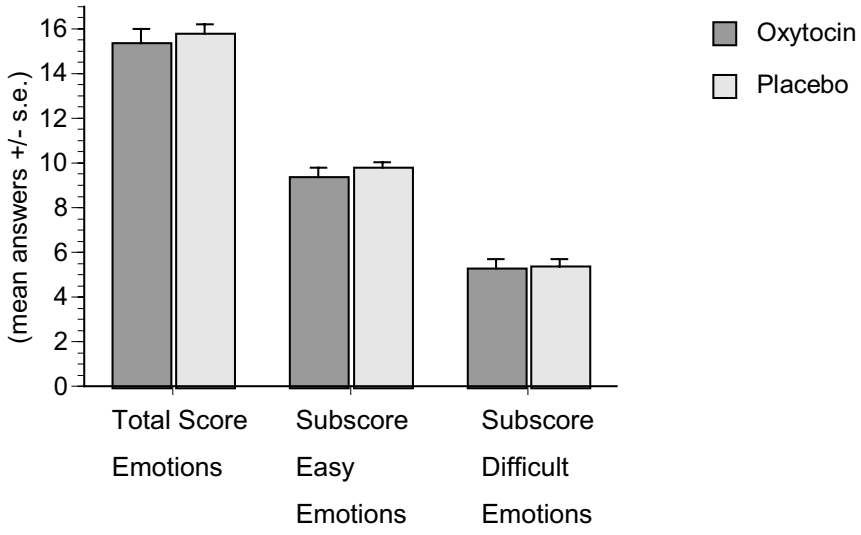


Figure 13: Mean answers for low-alexithymia group in the emotion recognition task for all emotions, easy emotions and difficult emotions. Error bars are standard errors of the mean (SEM).

Student's t-tests showed that there were no significant differences between the substances in the low-alexithymia group (Fig. 15), while there was a significant increase in correct answers in the high-alexithymia-group for anger ($t_{1;30} = 2.32$; $p = .027$) and surprise ($t_{1;30} = 2.12$; $p = .043$) (Fig. 14).

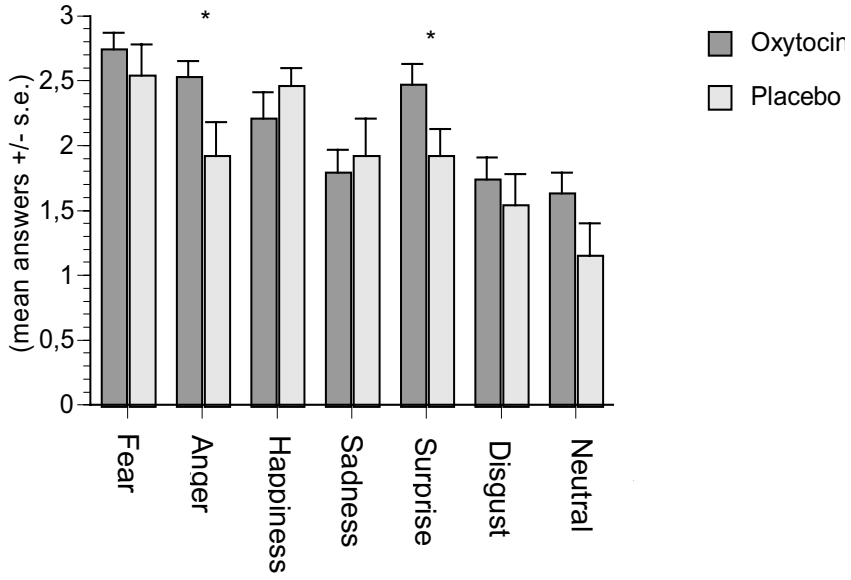


Figure 14: Mean answers for high-alexithymia group for the emotions fear, anger, happiness, sadness, surprise, disgust and neutral. *p < .05. Error bars are standard errors of the mean (SEM).

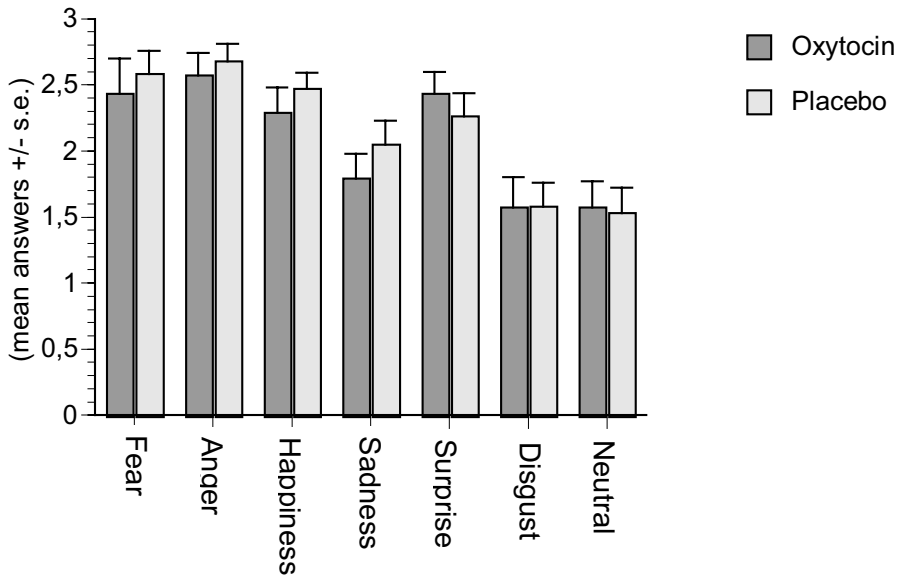


Figure 15: Mean answers for low-alexithymia group for the emotions fear, anger, happiness, sadness, surprise, disgust and neutral. Error bars are standard errors of the mean (SEM).

3.3.2.2. Reaction time

When comparing the substances within each group (table 2), the results of the Student's t-tests showed no significant differences for all emotions in total. Furthermore, no significant difference in reaction time was observed either for easy and difficult emotions or for each emotion individually (fear, anger, happiness, sadness, surprise, disgust, neutral) (table 2).

Table 2: Mean reaction time emotion recognition task.

	High-Alexithymia			**Low-Alexithymia**		
	Oxytocin (n = 19)	Placebo (n = 13)	t-test p	Oxytocin (n = 14)	Placebo (n = 19)	t-test p
Total Emotion	**7.69 ± 0.68**	**6.67 ± 0.43**	**.26**	**7.62 ± 0.61**	**7.07 ± 0.34**	**.41**
Easy Emotions	**6.80 ± 0.66**	**5.88 ± 0.44**	**.24**	**6.57 ± 0.51**	**6.18 ± 0.31**	**.51**
Difficult Emotions	**7.85 ± 0.68**	**6.62 ± 0.41**	**.50**	**8.05 ± 0.77**	**7.29 ± 0.39**	**.28**
Fear	7.04 ± 0.60	5.99 ± 0.61	.64	6.16 ± 0.50	6.72 ± 0.62	.31
Anger	6.68 ± 0.67	6.08 ± 0.40	.17	6.79 ± 0.66	6.03 ± 0.35	.25
Happiness	7.69 ± 1.29	5.42 ± 0.57	.64	5.81 ± 0.32	6.46 ± 0.42	.96
Sadness	7.48 ± 0.94	6.12 ± 0.45	.27	8.84 ± 0.97	7.12 ± 0.48	.09
Surprise	6.00 ± 0.49	6.34 ± 0.48	.09	6.43 ± 0.76	6.50 ± 0.36	.10
Disgust	7.66 ± 0.61	7.22 ± 0.64	.18	8.39 ± 1.37	7.07 ± 0.43	.35
Neutral	8.55 ± 0.93	6.45 ± 0.52	.30	8.52 ± 0.88	7.09 ± 0.34	.49

Data given as mean ± s.e.

3.3.3 Mood

To control for nonspecific effects of oxytocin on arousal, wakefulness and mood, we assessed these variables directly before and after the emotion recognition task by means of a suitable questionnaire (Steyer et al., 2004).

Two-way analyses of variance (ANOVA) (substance x group) showed no significant main effect of group for mood ($F_{1;64}$ = .02; p = .13), arousal ($F_{1;64}$ = .10; p = .88) or wakefulness ($F_{1;64}$ = 2.01; p = .16) and no significant main effect

of substance for mood ($F_{1;64}$ = 2.32; p = .13), arousal ($F_{1;64}$ = .10; p = .75), or wakefulness ($F_{1;64}$ = .83; p = .37) shortly before the emotion recognition task. Furthermore, no significant substance by group interactions were observed before the emotion recognition task for mood ($F_{1;64}$ = .18; p = .67), arousal ($F_{1;64}$ = .39; p = .53) or wakefulness ($F_{1;64}$ = 1.59; p = .21).

Three-way analyses of variance (ANOVA) with repeated measurement (substance x group x time) (repeated factor 2) revealed a significant main effect of group for arousal (see table 3). However, no further significant main effects of time, group or substance (table 3) were observed. Substance by group by time analyses were non-significant for all three measurements for mood (table 3).

Table 3: Mood over the time course of the experiment.

	Time (df = 1; 64)		**Substance** (df = 1; 64)		**Group** (df = 1; 64)		**Interaction** (time x substance x group) df = 1; 64	
	F	p-value	F	p-value	F	p-value	F	p-value
Mood	.46	.50	.69	.41	1.40	.24	1.76	.19
Arousal	.84	.36	.04	.83	.63	.015	.81	.37
Wakefulness	.17	.69	.40	.53	1.90	.17	3.57	.06

3.3.4 Heart Rate

Two-way analyses of variance showed that there were no statistical differences among the four groups when comparing heart rates at baseline before substance administration or during the emotion recognition phase (baseline: arrival; after introduction; during emotion recognition task: 40 min after substance administration, 5 to 1 min before the emotion recognition task, after emotion recognition task: 1 to 5 min after) (table 4).

Table 4: Heart rate during the experiment.

	High-Alexithymia		**Low-Alexithymia**		**ANOVA p**
	Oxytocin (n = 15)	Placebo (n = 10)	Oxytocin (n = 13)	Placebo (n = 19)	
Arrival Baseline	79.80 ± 2.86	74.80 ± 3.33	77.38 ± 3.03	75.53 ± 2.79	.61
After Introduction (without substance)	80.33 ± 3.19	76.90 ± 3.79	75.85 ± 2.52	76.95 ± 2.69	.47
40min after substance admin.	73.80 ± 2.73	68.70 ± 2.39	72.69 ± 3.04	70.89 ± 2.11	.54
5 min before task	67.00 ± 1.47	70.40 ± 3.19	65.15 ± 2.56	71.16 ± 2.55	.61
4 min before task	67.33 ± 1.95	70.30 ± 3.25	66.38 ± 3.04	69.05 ± 2.71	.96
3 min before task	64.80 ± 1.53	67.10 ± 2.58	62.54 ± 2.80	66.74 ± 2.95	.73
2 min before task	64.93 ± 1.69	66.30 ± 2.91	63.38 ± 2.82	66.11 ± 2.61	.80
1 min before task	68.27 ± 1.99	66.90 ± 8.70	63.31 ± 2.31	67.21 ± 2.27	.28
1st min during task	70.13 ± 2.53	66.00 ± 3.25	62.54 ± 2.41	67.53 ± 2.37	.09

1 min before end	69.40 ± 1.52	68.50 ± 3.56	65.08 ± 2.53	69.79 ± 2.36	.27
1 min after task	71.93 ± 2.05	69.10 ± 3.46	67.92 ± 2.22	74.00 ± 2.95	.12
2 min after task	71.07 ± 2.30	71.00 ± 2.89	67.54 ± 2.53	71.26 ± 2.51	.48
3 min after task	68.60 ± 1.84	68.00 ± 3.09	63.23 ± 2.13	68.58 ± 2.25	.22
4 min after task	68.27 ± 2.23	69.30 ± 3.15	64.23 ± 2.74	71.29 ± 3.14	.72
5 min after task	69.86 ± 2.24	68.40 ± 3.53	64.42 ± 2.74	71.29 ± 3.14	.14

Data given as mean +/- s.e.

Results obtained by three-way ANOVA with repeated measures including substance and group as between-subject factors and time as a within-subject factor were then performed to assess differences in the course of the emotion recognition task (mean heart rates from 5 min before, during the average duration (8min) and 5 min after the emotion recognition task). As reported previously, the groups did not differ in heart rate 5 min before the experiment (main effect of substance: $F_{1;53}$ = 3.44; p = . 069; main effect of group: $F_{1;53}$ = .046, p = .831; substance by group interaction: $F_{1;53}$ = .26; p = .610). There was a significant main effect of time ($F_{7.02;343.84}$ = 6.16; p = .000). Comparisons for time by group interactions ($F_{7.02;343.84}$ = 1.05; p = .393), time by substance interactions ($F_{7.02;343.84}$ = .94; p = .478) and time by group by substance interactions ($F_{7.02;343.84}$ = 1.52; p = .159) were non-significant.

However, between-subjects analyses showed that there was no main effect of substance ($F_{1;49}$ = 1.10; p = .299), no main effect of group ($F_{1;49}$ = .268; p = .299) and no substance by group interaction effect ($F_{1;49}$ = .1.02; p = .317).

3.4 Discussion

This is the first study to show that a single dose of intranasal oxytocin is sufficient to improve performance in an emotion recognition task in healthy men with symptoms of high alexithymia.

The ability to attribute mental states to oneself and others is referred to as social cognition or theory of mind. Making social cognitive inferences is crucial for successful social interactions because they mediate an understanding of the dispositions and intentions of others and lead to the correct prediction of behavior (Dziobek et al., 2006). Furthermore, in humans and other primates, facial expressions serve as important social cues to regulate behavior (Darwin, 1972; Ekman & Friesen, 1971). Changes in social behavior based on facial expression come so naturally to humans and are in place so early in child development that some might argue that this functionality is essentially innate.

However, human social behavior is sufficiently flexible that we can easily learn to adapt our behavior to most facial expressions (Kringelbach & Rolls, 2003). This flexibility is an important aspect of much human behavior, as it allows us to learn to adapt to different behaviors of both individuals and groups. In particular, individuals with symptoms of alexithymia often have selective deficits in inferring others' mental states such as facial expressions (Gil et al., 2007; Taylor, Bagby, & Parker, 1997).

It is notable that a number of studies reported a significantly impaired emotion recognition from facial stimuli in subjects meeting the criteria for alexithymia compared to non-alexithymic participants (Lane, Sechrest, Riedel, Shapiro, & Kasniak, 2000; J. D. A. Parker, Taylor, & Bagby, 1993a, , 1993b; P. D. Parker, Prkachin, & Prkachin, 2005). Moreover, the ability to identify and communicate one's feelings is thought to be a personality trait that differs among individuals. It is well established that about 10% of the normal population suffers from

alexithymia, which is defined by difficulties in identifying and describing feelings, difficulties in discriminating feelings from bodily sensations of emotional arousal, and a marked impairment in imaginative processes with a cognitive style that is concrete and reality-based (tendency to focus on external events rather than inner experience) (Bankier, Aigner, & Bach, 2001; Berthoz et al., 2002; Spitzer, Siebel-Jürges, Barnow, Grabe, & Freyberger, 2005). Although alexithymia was initially used as a syndrome for clinical patients with psychopathological disorders, more recently, alexithymic characteristics have been shown to be prominent in people in nonclinical populations (Jessimer & Markham, 1997). Even though alexithymia is thought of as a relative stable personality trait, there is still an ongoing debate regarding the changeability of alexithymic traits by psychotherapy (Honkalimpi, Hintikka, Saarinen, Lehtonen, & Viinamaki, 2000; Luminet, Bagby, & Taylor, 2001; Saarijärvi, Salminen, Taylor, & Toikka, 2006). It is noteworthy that this is the first study to provide evidence that a single exogenous oxytocin administration improves the ability to recognize emotions from the eye region in high-alexithymic subjects.

The neurohypophyseal peptide oxytocin is well known for its physiological functions in milk ejection and during labor. Apart from these functions, OT receptors are distributed in various brain areas associated with social behavior, including reproductive and parenting behavior, affiliation and attachment, social memory and reactivity to stress in nonhuman mammals (Carter et al., 1998, Ferguson et al., 2000, Young & Wang, 2004). Taken together, these results from animal studies imply that oxytocin seems to facilitate approach behavior. Another line of evidence comes from several recent studies suggesting that the social impairments found in autistic disorders are possibly associated with changes in plasma oxytocin (OT) levels (Modahl et al., 1998; Green et al., 2001).

As reported previously, oxytocin receptors are distributed in various brain regions associated with social behavior, including the amygdala (Huber,

Veinante, & Stoop, 2005; Landgraf & Neumann, 2004). Recent human studies found evidence that exogenously administered OT suppresses amygdala responses to emotional faces irrespective of their valence (Domes et al., 2007a).

Moreover, alexithymia has been associated with hyperarousal to emotional stimuli or situational stressors (Berthoz et al., 2002; Infrarsca, 1997; Rabavilas, 1987). In a study in which the participants viewed an emotional film, alexithymia was associated with increased sympathetic arousal, resulting in a higher skin conductance (Taylor, 2000). Most studies, however, found either hypoarousal or no alexithymia effect during exposure to stressors. Heart rates in these studies are in line with the previous results, showing no baseline differences in heart rate or differences in heart rate reactivity during the emotion recognition task.

Furthermore, it is well established that the amygdala is critical for the processing of emotional stimuli. It is therefore surprising that only a small number of studies have investigated amygdala responsivity to emotional stimuli in alexithymics. A recent fMRI study by Leweke and colleagues showed a lower activation of the right amygdala in response to negative visual stimuli (i.e. anxiety, disgust-inducing scenarios) in high alexithymia compared with individuals scoring low on alexithymia (Leweke et al., 2004). More recently, Kugel et al. (2008) examined the automatic amygdala reactivity to facial emotions on alexithymic features in a sample of healthy young adults. They found an association between the alexithymia feature difficulty in identifying feelings and a reduced automatic response of the amygdala to negative faces, and the authors suggested that a reduced automatic amygdala responsivity may contribute to problems in identifying emotions. It is important to note that both of the above-mentioned studies used a non-clinical sample and subjects did not meet the cut-off score of the TAS-20 for alexithymia.

Taken together, these findings may therefore have several important clinical implications. People with an impaired ability to process or regulate emotions

(alexithymia) have been shown to be at risk of developing mental disorders such as major depression, anxiety disorder, eating disorders, and substance abuse (Aigner et al., 2007; Bach & Bach, 1995; Gil et al., 2007). Furthermore, approximately 25% of all patients asking for psychotherapeutic treatment are considered to be alexithymic. Given that personality and the ability to regulate emotions are believed to play a key role in modulating one's capacity to deal with stressful life events, interpersonal conflicts, and are also believed to influence one's ability to respond to psychotherapeutic treatment, alexithymia is assumed to be negatively associated with therapeutic outcome (Grabe et al., 2008).

This is the first study to show that a single administration of oxytocin improves the ability to identify emotions from social cues of the eye regions in healthy men with features of high alexithymia compared to the low-alexithymic subjects. As oxytocin was found to enhance performance of emotion recognition especially in those emotions that are difficult to detect, it might play a particularly important role in recognizing insecure, difficult emotions. In contrast, oxytocin did not improve performance in easy emotions. These results are consistent with earlier studies demonstrating that deficits in emotional processing in alexithymia particularly occur when excessive demands are made on emotion-processing capacity, for example by limiting the amount of time available to encode and transform emotional stimuli or, as in this study, by viewing facial expressions that are difficult to recognize. These results confirm the hypothesis of Parker and colleagues (2005) that alexithymics do not exhibit an overall impairment in recognizing emotions from facial expressions and that alexithymia rather involves a deficit in the efficiency of emotional processing.

In terms of the six basic emotions, oxytocin particularly improved recognition of anger and surprise in the high-alexithymia group. Furthermore, in the low-alexithymia group, no enhancing effect of oxytocin was observed either over all emotions or within the group of difficult emotions. These findings imply that the

exogenous oxytocin administration improved emotion recognition in subjects with difficulties in recognizing, describing and regulating emotions such that they were able to show a performance level that was almost comparable with the healthy non-alexithymic subjects.

Recent studies in humans imply a modulating role of oxytocin in social perception, cognition and behavior (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007b; Heinrichs & Domes, 2008; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). This study supports the evidence of a possible involvement of oxytocin in social cognitive functions such as emotion recognition. Clearly, more research is needed to examine the underlying neural mechanism of this behavioral effect and with subjects meeting the criteria for alexithymia.

4. Effects of Oxytocin on Affect Recognition and Eye Movements while Viewing Movies of Facial Emotion Expressions

4.1 Introduction

The ability to judge facial expressions accurately and derive other socially relevant information from faces has been shown to play a key role in establishing and maintaining reciprocal social interactions and interpersonal communication (Pelphrey et al., 2002). For instance, the use of nonverbal social communicative behaviors such as eye-to-eye gaze and facial expressions shows a distinct developmental course appearing very early in ontogeny (Baron-Cohen, Wheelwright, & Jolliffe, 1997). In adulthood, faces represent an exceptional class of stimuli (Haxby, Hoffman, & Gobbini, 2002). Thus, face perception is usually holistic or configural rather than elemental or piecemeal. For example, to identify a particular face or facial expression, individuals generally rely on the spatial configuration of the major features of the face, including the eyes, nose and mouth (Farah, Wilson, Drain, & Tanaka, 1998; Pelphrey et al., 2002).

Numerous studies investigating the underlying neurological mechanisms of processing emotional stimuli such as facial expressions have consistently found a crucial role of the amygdala. Amygdala activity has been shown to be associated with facial fear and anger, as well as with happy faces, even when facial emotions were processed without conscious awareness (Glaescher, Tuescher, Weiller, & Buechel, 2004; Morris et al., 1998; Phan, Fitzgerald, Nathan, & Tancer, 2006).

Underlying processes can also be inferred through the analysis of eye movement patterns. Eye movement investigations might reveal useful insights into the way people process faces and might provide further information on brain processes (Heisz & Shore, 2008). Studies which recorded visual scanpaths in normal adults as they viewed face stimuli showed that subjects

devoted the vast majority of their fixations to the eyes, nose and mouth, with nearly 70% of these fixations directed to the eyes (Sullivan, Ruffman, & Hutton, 2007; Walker-Smith, Gale, & Findlay, 1977; Yarbus, 1967). Baron-Cohen and colleagues (2001) found that this preference for looking at the eyes over other facial features develops very early in infancy (Langton, Watt, & Bruce, 2000).

In addition, findings also indicate that eye contact appears to be important in social encounters. Research with clinical populations that suffer from deficits in social interactions (e.g. autism, social phobia, schizophrenia) noted qualitative differences in their visual scanpaths when viewing facial expressions (Horley, Williams, Gonsalvez, & Gordon, 2003; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Pelphrey et al., 2002; Streit, Wolwer, & Gaebel, 1997; Williams, Loughland, Green, Harris, & Gordon, 2003). According to Baron-Cohen et al. (1997), these emotion recognition deficits often found in autistic spectrum disorders may be attributable to the tendency of individuals with autism to ignore information of the eyes. Individuals with autism look less at eyes and more at mouths when viewing persons in social situations (Klin, Jones, Schultz, Volkmar, & Cohen, 2002). Moreover, social phobics tend to avoid fixating the eye region, particularly for angry faces (Horley, Williams, Gonsalvez, & Gordon, 2003, , 2004), and patients with schizophrenia have restricted scanpaths that do not focus on the most salient features of the face (Streit, Wolwer, & Gaebel, 1997).

It is well known from studies with rodents that the neuropeptide oxytocin is an important mediator of complex social behaviors such as attachment, affiliative behavior and pair bonding (Carter & Altemus, 1997; Uvnas-Moberg, 1996; L. J. Young, 2002). In line with these results, oxytocin receptors are distributed in brain areas that are associated with social behavior, the limbic system including the amygdale (Bale, Davis, Auger, Dorsa, & McCarthy, 2001) (Huber, Veinante, & Stoop, 2005; Landgraf & Neumann, 2004). In humans, oxytocin has been found to reduce physiological and psychological stress responses (Heinrichs,

Baumgartner, Kirschbaum, & Ehlert, 2003; Heinrichs et al., 2001), to increase trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), and also to promote the ability to infer the mental state of another person known as mind-reading (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007b). In a first eye tracking study, Guastella and colleagues found that oxytocin increases eye gaze to the eye region when viewing pictures of neutral human faces (Guastella, Mitchell, & Dadds, 2007).

Considering the importance of recognizing facial expressions for all human social interactions, we sought to answer the question of whether oxytocin might promote emotion recognition when viewing facial movies. These facial videos consisted of faces of male and female actresses, which began with a neutral facial expression and slowly developed into emotional facial expressions (anger, sadness, disgust, happiness, surprise and fear). Moreover, it was tested whether oxytocin modulates the visual scanpath when subjects were viewing these facial videos.

4.2 Methods

4.2.1 Subjects

Sixty-seven non-smoking male volunteers (mean age ± SD: 24.03 ± 2.51 years), all recruited by advertisements, participated in this study. Potential subjects were screened by telephone and additionally through psychological questionnaires to determine suitability for the study procedure. Subjects were required to be medically healthy without any pharmacological treatment. Further exclusion criteria were the inability to wear contact lenses when suffering from visual defects, substance abuse, reported mental or neurological illness (chronic as well as acute) and being a psychology student. Subjects who remained eligible at the end of the screening phase were randomly assigned to a double-blind, placebo-controlled design.

Subjects were asked to wear contact lenses if needed for the day of the experiment and were instructed to abstain from alcohol, smoking, caffeinated beverages, excessive sports and medication on the day prior to the experiment.

The study was approved by the ethics committee of the University of Zurich and all subjects gave written informed consent for participation in the study. After the experiment, subjects were paid with 50 Swiss francs for their participation.

4.2.2 Experimental Protocol

All subjects were instructed to eat breakfast and lunch during the day of their experiment and were then asked to refrain from eating, drinking anything but water, and intense physical exercise for at least two hours before their experiment. The experiments took place in the laboratory of the Department of Clinical Psychology and Psychobiology at the University of Zurich between 4:00 PM and 9:00 PM and lasted for approximately 1.5 hours.

4.2.2.1 Procedure

The study consisted of five consecutive phases (Fig. 17): introduction and demographics (10min), substance administration and waiting time (45 min), affect recognition task (10-20 min), face rating task (10-15min) and debriefing (15min).

After arriving at the laboratory in the late afternoon (between 4 and 5 PM), the experimental procedure was explained to the subjects and they were shown how to use the nose-spray. Moreover, participants were instructed to wear the heart rate monitor and told how to set heart rate markers during the experiment. Following this, questionnaires on demographic characteristics and mood (MDBF, SAM) were completed.

Next, subjects received the substance via nose-spray (Oxytocin or Placebo) and a 40-minute waiting phase followed in which subjects filled out more questionnaires. After this waiting phase, subjects were given instructions for the assessment of the visual scanpath during the affect recognition task, in which movies of faces expressing an emotion were shown. Shortly after this instruction, the calibration process started (for more details, see section 4.2.5) (see Fig. 16).

Before the affect recognition test started, subjects again rated their current mood on two separate questionnaires (MDBF, SAM) and were then given explanations of the affect recognition task. Thereafter, an individual rating of trustworthiness and social approachability followed for each of the faces, which had been presented in advance in the affect recognition test (for details about face rating, see chapter 4.2.5). The final 10 to 15 minutes were used to debrief the participants and to pay out compensations.

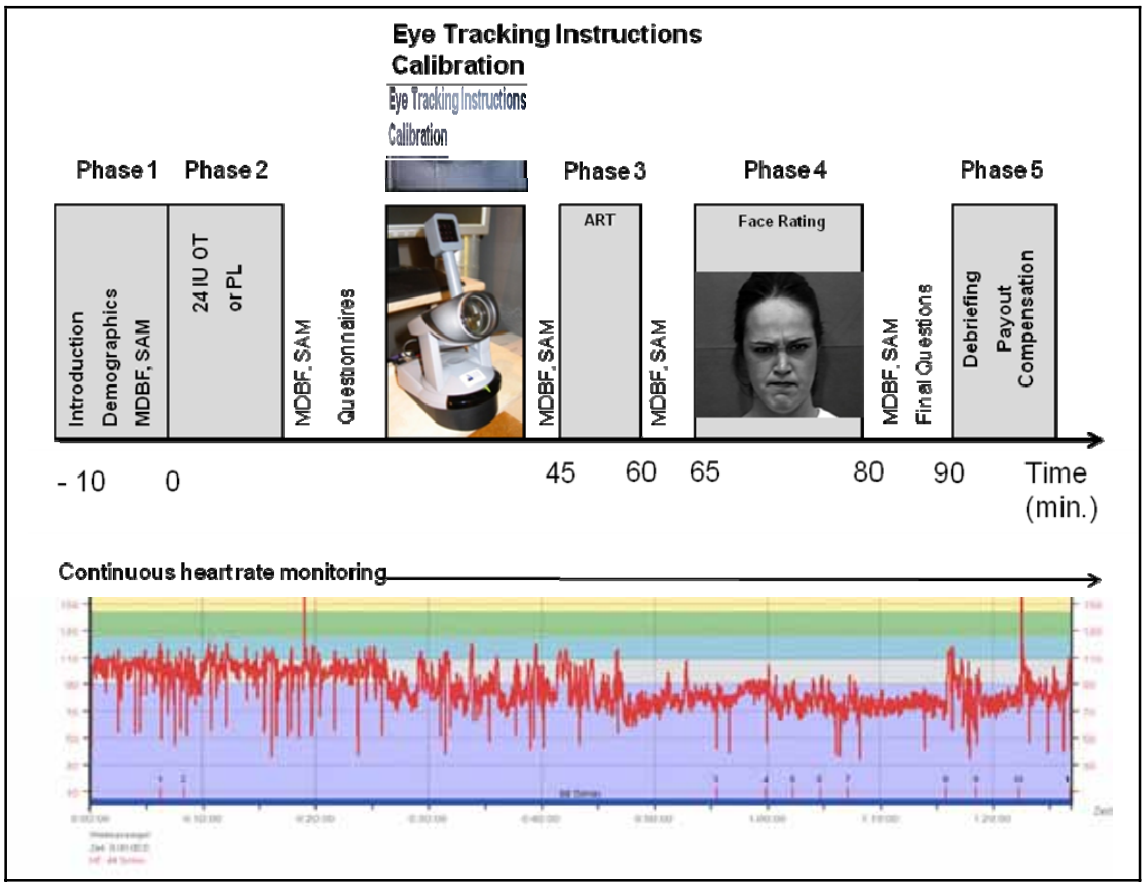


Figure 16: Experimental procedure empirical study 2.

4.2.2.2 Substance administration

In a placebo-controlled double-blind study design, all 67 subjects were randomly assigned either to receive an intranasal dose of 24 IU oxytocin (Syntocinon® Spray; Novartis, Basel, Switzerland; each puff with 4 IU oxytocin) or placebo (containing all ingredients except for the peptide). Intranasal administration took place 40 minutes before the affect recognition task in order to ensure that the peptide reached the cerebrospinal fluid (CSF) (Born et al., 2002).

4.2.3 Affect Recognition Task and Face Ratings

In the affect recognition task (ART; Porges et al., in press), several short videos of people's faces are shown. The faces start out with a neutral expression and then slowly change to show a specific emotion. There are six target emotions: fear, sadness, disgust, happiness, anger and surprise.

The task comprises three phases: a first practice phase, in which the subjects just watch the videos. When this phase is complete, a second practice phase follows. In this second phase, subjects have to press a button as soon as they know what emotion the face is expressing. Participants are instructed to be as quick as they can, but also to be as accurate as possible. As soon as they press the button, the face will disappear and the six different choices of emotion will appear on the computer screen. At this point, subjects have to choose what emotion they think the person's face is expressing. The third phase is the actual affect recognition task, where the answers given and the reaction times are assessed.

After the affect recognition task, subjects are asked to rate each face of the ART on a 7-point scale (-3 to +3) with respect to either approachability or trustworthiness according to Adolphs and colleagues (R. Adolphs, Tranel, & Damasio, 1998). For approachability, subjects are asked to imagine meeting the person on the street, and to indicate how much they would want to walk up to that person and begin a conversation. To rate for trustworthiness, subjects imagine trusting that person with all their money.

4.2.3 Psychological Measures

Two weeks before the experiment, subjects received questionnaires on personality characteristics. On the day of the experiment, shortly before the affect recognition task, subjects completed further questionnaires designed to measure demographic items, personality characteristics and psychopathological

symptoms. Before and after the affect recognition task, mood was repeatedly assessed.

We included the validated German versions of the following questionnaires:

Brief Symptom Inventory (BSI; Franke, 2000) for screening symptoms of psychopathology, the Trait Version of the *State-Trait Anxiety Inventory* (STAI; Spielberger et al., 1970) for measuring trait anxiety, the *Beck Depression Inventory* (BDI; Hautzinger, Bailer, Worall & Keller, 1995) to assess severity of depression, the *Toronto Alexithymia Scale 20* (TAS 20; Bach et al., 1996) to measure alexithymia and its components: difficulty identifying feelings, difficulty describing feelings and externally oriented thinking, the *Adult Attachment Scale* (AAS; Collins & Reads, 1990) for testing attachment behavior with its subscales of: Secure, Fearful, Preoccupied, and Dismissing, the *Close Relationship Questionnaire* (CRQ; Brennan, Clark & Philipp, 1998) for assessing individual differences with respect to attachment-related anxiety (i.e., the extent to which people are insecure vs. secure about the degree of their partner's availability and responsiveness) and attachment-related avoidance (i.e., the extent to which people are uncomfortable being close to others vs. secure towards others), the *Sensation Seeking Scale V* (SSS-V; Beauducel, Brocke, Strobel & Strobel, 1999) for the assessment of sensation seeking and its four subscales thrill and adventure seeking, experience seeking, disinhibition and boredom susceptibility, the Neo-FFI Inventory (Borkenau & Ostendorf, 1993) to measure the Five Factor Model: extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience, the *State-Trait Anger Inventory* (STAXI; Schwenkmetzger, Hodapp & Spielberger, 1992), which measures the intensity of anger as an emotional state (State Anger) and the disposition to experience angry feelings as a personality trait (Trait Anger).

Mood responses before and after the emotion recognition task were repeatedly assessed with the *Multidimensional Mood Questionnaire* (MDBF; Steyer,

Schwenkmetzger, Notz & Eid, 1997) (three components good-bad, awake-tired, calm-nervous) and the *Self-Assessment Manikin* (SAM; Lang, 1985), which is a culture- and language-free measurement of mood, which depicts the three dimensions pleasure, arousal and dominance in a graph arrayed along a continuous nine-point scale (pleasure: from smiling, happy to frowning, unhappy; arousal: sleepy to excited; dominance: very small figure, being controlled, to very large figure representing a powerful feeling).

4.2.4 Autonomic Measures

Subjects were connected to a heart rate monitor (Polar S810i™, Polar Electro, Finland) during the experiment using a wireless chest heart rate transmitter and a wrist monitor recorder. One-minute intervals were computed for the analyses from 5 minutes before the affect recognition task until 5 minutes after cessation of the affect recognition task.

4.2.5 Eye Movement Recordings and Analysis

4.2.5.1 Eye Tracking Apparatus

To assess eye movements non-invasively during the facial videos, an iView X™ RED (Remote Device) infra-red camera from SensoMotoric Instruments (SMI GmbH, Berlin) was used. To define pupil position, the dark-pupil tracking mode was applied). The presentation of the facial videos was preceded by a thirteen-point grid calibration task. Eye movements were recorded at 50 Hz sampling rate at a spatial resolution of < 0.1 degrees for tracking resolution and < 0.5 degrees for gaze position accuracy.

The ART videos were presented on a 17” screen with an eye-to-screen distance of ~ 62 cm at a stimulus-screen resolution of 1280 (horizontal) X 1024 (vertical) pixels. Videos were presented at 30 frames per second (640pixel with X 480pixel height; VideostimInstaller.msi, Windows). Subjects sat with their chin

on a chin rest and the video stimuli were viewed with both eyes, although only the left eye was analyzed. Before the affect recognition task, a 13-point calibration task took place for each participant, which corrected for individual differences in head and seating position.

4.2.5.2 Regions of Interest and Process Measures

Any trials showing a loss of tracking integrity were excluded from subsequent data analysis for the whole subject. Five regions of interest (ROIs) were defined for the eyes, nose, mouth, chin, and the forehead for each single facial stimulus with an in-house program using matlab.

The following metrics were collected during the ART:

- Total number of fixations in the whole face
- Total fixation (gaze) duration in the whole face
- Gaze % (proportion of time) per ROI
- Number of fixations per ROI
- Gaze duration mean per ROI

The minimum fixation duration (ms) was set at 80ms, which defines the minimum time window in which gaze data are analyzed. Fixations smaller than this time window were not caught. Further, for all gaze positions in this window, a minimum bounding rectangle was calculated. If the sum of the rectangle's width and height did not exceed the Maximum Dispertion Value of 200 pixels, the time window was assumed to be part of the window. The first gaze sample causing the bounding rectangle to exceed the maximum dispersion value of the 200 pixels ended the fixation.

The fixations and fixation times on the regions of interest were calculated as a percentage of the total fixations made to the face for each stimulus. Moreover,

the average duration of fixations and the mean number of fixations per stimulus face were calculated for each subject.

4.2.6 Statistical Analyses

All data were analyzed using SPSS Inc. (Version 14.0). Before the application of the statistical procedures, the data were tested for normal distribution and homogeneity of variance using the Kolmogorov-Smirnov and Levene's test. One-way multivariate ANOVAs (MANOVAs) were used for group comparisons within each emotion category in terms of the proportion of fixation count and the proportion of fixation time. Group (2) by valence (6) by region of interest (ROI; 5) interactions were analyzed with ANOVAs with repeated measurements with group as the between-subject factor and valence (happiness, surprise, sadness, disgust, anger, fear) and ROI (forehead, eyes, nose, mouth and chin) as within-subject factor. All reported ANOVA results were corrected by the Greenhouse-Geisser procedure where appropriate (violation of sphericity assumption). For assessment of influences of mood and heart rate, ANOVAs for repeated measurements with group as between-subject factor (OT vs. PL) and time as the within subject factor were calculated. Degrees of freedom may vary across analyses because data were occasionally missing due to technical problems. All analyses were two-tailed, with the level of significance set at $p \leq .05$ and trends were defined at the 10% level. Unless otherwise indicated, all results shown are means ± standard error of means (SEM).

4.3 Results

4.3.1 Description of the study groups

The two groups, consisting of 33 subjects with OT and 34 subjects with PL, did not differ significantly in any relevant baseline measurements, such as psychopathological symptoms or trait characteristics (table 5). There was only one significant difference between the groups regarding the neuroticism scale of the Neo-FFI ($F_{1;63}$ = 5.42; p = .023) in that OT subjects showed significantly higher values (see table 5).

At the end of the experiment, subjects were asked whether they felt physiological changes due to the substance and which substance they had been given. There were no significant differences between the physiological symptoms ($F_{1;63}$ = 0.06; p = .81) and neither of the groups was able to tell which substance they had received ($F_{1;63}$ = .63, p = .43).

Table 5: ART characteristics of the study groups.

	Oxytocin (n = 33)	Placebo (n = 34)	ANOVA p
Age	23.85 ± 0.44	24.21 ± 0.43	.56
Global severity (BSI)	0.29 ± 0.03	0.26 ± 0.03	.36
Trait Anxiety (STAI)	35.65 ±1.35	32.56 ± 1.29	.11
Depression (BDI)	2.68 ± 0.52	2.91 ± 0.50	.75
Trait Aggression (STAXI)	17.09 ± 0.70	16.06 ± 0.67	.29
Sensation Seeking (SSS)	22.65 ± 0.85	24.91 ± 0.81	.06
Neuroticism (Neo-FFI)	17.06 ± 1.11	13.50 ± 1.06	.023
Openness (Neo-FFI)	31.61 ± 1.15	33.03 ± 1.09	.38
Extraversion (Neo-FFI)	29.07 ± 0.88	29.91 ± 0.84	.49
Agreeableness (Neo-FFI)	29.80 ± 0.89	29.91 ± 0.85	.93
Conscientiousness (Neo-FFI)	31.97 ± 1.16	32.56 ± 1.11	.71
Alexithymia (TAS)	42.39 ± 1.27	39.35 ± 1.21	.09
Attachment (AAS)	35.16 ± 1.08	33.38 ± 1.03	.24

Data given as mean ± s.e.

4.3.2 Affect recognition task

4.3.2.1 Answer correctness

Two-way multivariate analyses of variance (MANOVA) including the substance (Oxytocin or Placebo) as a between-subject factor were performed to assess differences in the percentage of correct responses. The result of the multivariate test showed a non-significant main effect for group ($F_{1;59}$ = .644; p = .718). Results of the between-subject effects showed that the groups did not differ either in the total percentage of correct responses or in any specific emotion (all

p > .05) (see table 6). Moreover, the analyses regarding positive and negative emotions found no significant group differences regarding answer correctness (see table 6).

Table 6: Mean percentage of answer correctness in the ART.

	Oxytocin (n = 33)	Placebo (n = 34)	ANOVA $F_{1;65}$	ANOVA p
All items	78.19 ± 1.60	79.09 ± 1.58	0.16	.69
Positive emotions	87.63 ± 1.75	90.44 ± 1.72	1.31	.26
Negative emotions	73.49 ± 2.25	73.41 ± 2.22	0.001	.98
Fear	48.49 ± 5.25	47.55 ± 5.17	0.02	.89
Anger	80.30 ± 3.24	80.88 ± 3.19	0.02	.89
Surprise	76.77 ± 3.50	81.86 ± 3.45	1.08	.30
Disgust	74.75 ± 4.50	73.53 ± 4.44	0.04	.85
Happiness	98.49 ± 0.77	99.02 ± 0.76	0.24	.62
Sadness	90.40 ± 2.24	91.67 ± 2.20	0.16	.69

Data given as mean ± s.e.

In order to obtain different subscores for item difficulty, we divided the 36 videos into two subsets of easy and difficult stimuli. These subsets were generated based on the median of item difficulty derived from the data of the Placebo group. The two-way analysis of variance showed no significant group differences for either the easy ($F_{1;65}$ = 3.17; p = .08) or the difficult emotions ($F_{1;65}$ = 0.11; p = .74).

4.3.2.2 Reaction time

Regarding reaction time, two-way multivariate analyses of variance (MANOVA) including the substance (Oxytocin or Placebo) as a between-subject factor were

performed to assess differences between the groups. The result of the multivariate test showed a non-significant main effect for group ($F_{1;54}$ = .1.38; p = .23). Results of the between-subject effects showed that the oxytocin group was significantly slower in the positive emotions ($F_{1;60}$ = 4.46; p = .04), and explicitly in the surprise emotions ($F_{1;60}$ = 6.05; p = .02) (see table 7). For the subscore easy emotions, a trend was found ($F_{1;60}$ = 3.96; p = .051) in that subjects of the oxytocin group answered slower than the placebo group.

Table 7: Mean reaction time (in sec) during the ART.

	Oxytocin	**Placebo**	**ANOVA**	
	(n = 33)	**(n = 34)**	**$F_{1;60}$**	**p**
All items	11.29 ± 0.39	10.45 ± 0.37	2.44	.12
Positive emotions	9.40 ± 0.35	8.38 ± 0.33	4.46	**.04**
Negative emotions	12.23 ± 0.44	11.49 ± 0.41	0.001	.98
Fear	12.74 ± 0.55	12.12 ± 0.52	0.69	.41
Anger	14.55 ± 0.64	13.92 ± 0.59	0.53	.47
Surprise	10.44 ± 0.45	8.92 ± 0.42	6.05	**.02**
Disgust	10.96 ± 0.36	10.17 ± 0.34	2.52	.12
Happiness	8.36 ± 0.33	7.83 ± 0.31	1.34	.25
Sadness	10.66 ± 0.47	9.75 ± 0.44	1.98	.17
Easy	10.00 ± 0.32	9.12 ± 0.30	3.96	**(.051)**
Difficult	12.57 ± 0.48	11.78 ± 0.45	1.43	.24

Data given as mean ± s.e.

4.3.2.4 Face ratings

To examine group differences in ratings regarding the face ratings, we used separate MANOVAs for ratings and response time for social approach and trust. Two subjects were excluded from the original data set due to technical

problems with the presentation software of the face rating. The two groups consisted of 32 subjects with Oxytocin and 33 subjects with Placebo.

Regarding social approach, there was no significant multivariate group effect ($F_{1;58}$ = 0.32; p = .93). Also, no significant main effect of group was found in the between-subject effects of the ANOVAs (all p > .05).

Using MANOVAs to test for group differences in trust ratings, we found a significant multivariate group effect ($F_{1;57}$ = 2.34; p = .036) in that oxytocin subjects trusted significantly more than the placebo subjects, meaning that their ratings were less negative than those of the placebo group. Furthermore, the ANOVAs revealed a significant main effect in of group for trust ratings in angry faces ($F_{1;63}$ = 5.83 ; p = .019) (see Table 8). The results showed that the Oxytocin group trusted more for any emotion, but results were not significant, except for angry faces (see table 8).

Table 8: Mean face rating on trustworthiness (range from -3 to + 3).

	Oxytocin	**Placebo**	**ANOVA**	
	(n = 32)	**(n = 33)**	**$F_{1;63}$**	**p**
All items	-0.64 ± 0.13	-0.88 ± 0.13	1.71	.19
Positive emotions	0.08 ± 0.16	0.02 ± 0.16	0.07	.79
Negative emotions	-1.09 ± 0.13	-1.37 ± 0.12	2.39	.13
Fear	-0.44 ± 0.19	-0.66 ± 0.19	0.63	.43
Anger	**-1.47 ± 0.13**	**-1.92 ± 0.13**	**5.83**	**.019**
Surprise	-0.51 ± 0.17	-0.48 ± 0.17	0.01	.92
Disgust	-1.44 ± 0.14	-1.73 ± 0.13	2.22	.14
Happiness	0.66 ± 0.19	0.51 ± 0.19	0.29	.59
Sadness	-0.64 ± 0.17	-0.99 ± 0.16	2.25	.14

Data given as mean ± s.e.

Results obtained by MANOVAs regarding mean reaction time showed no significant multivariate group effect either for social approach ($F_{1;56}$ = 1.08, p = .39) or for trustworthiness ($F_{1;58}$ = 1.32; p =.26).

Testing for group differences in separate ANOVAs for social approach revealed that subjects with Oxytocin were slower in all emotions, but these results was only significant for sad faces ($F_{1;62}$ = 5.52; p = .02). In addition, there were trends for all negative emotions ($F_{1;62}$ = 3.58; p = .06) and for disgust ($F_{1;62}$ = 2.82; p = .09) showing that the OT group answered slower.

Regarding ratings on trustworthiness, ANOVAs showed significant main effects for group for fearful ($F_{1;64}$ = 4.75; p = .03), angry ($F_{1;64}$ = 7.01; p = .01) and disgusting faces ($F_{1;64}$ = 6.06; p = .017), revealing slower response times for the OT group. In addition, we found a trend in the sub-score over all negative emotions ($F_{1;64}$ = 3.09; p = .08) such that the OT group answered slower than the PL group.

4.3.2.5 Mood

Mood was assessed repeatedly using the MDBF (Steyer et al., 2004) during the experiment to control for nonspecific effects of oxytocin on arousal, wakefulness and mood (Fig. 16). Student's t-tests showed no group differences in the baseline measurements before substance administration for mood (t_{65} = -1.89; p = .064), arousal (t_{65} =-1.61; p = .11) and wakefulness (.t_{65} = -1.11; p = .27).

Two -way analyses of variance with repeated measurements including the group as between-subject factor were then performed to assess differences over the course of time before and after the ART. The results for the three scales did not reveal any main effect of group for mood ($F_{1;64}$ = 0.38, p = .54), arousal ($F_{1;64}$ = 0.45; p = .50) or wakefulness ($F_{1;64}$ = 0.46; p = .50), and no main effect of time for mood ($F_{1;64}$ = 0.29; p = .59), arousal ($F_{1;64}$ = 0.76; p = .39) or wakefulness ($F_{1;64}$ = 0.58; p = .45). Further, no significant group by time

interaction was found for mood ($F_{1;64}$ = 1.32; p = .25), arousal ($F_{1;64}$ = 0.09; p = .92) or wakefulness ($F_{1;64}$ = 0.02; p = .96)

4.3.2.6 Heart rate

The two groups did not differ in their heart rate at baseline (Fig. 16) (t_{64} = 1.09; p = .28), or after the introduction (without substance) (t_{64} = 1.40; p = .17). Forty minutes after substance administration, there was also no significant group difference found in heart rate (t_{64} = 1.0; p = .32). Two-way ANOVA with repeated measures including group as between-subject factor and time as a within-subject factor were then performed to assess differences in the course of the affect recognition task (ART; mean heart rates from 5 minutes before, during the average duration (12 min.) and until 5 minutes after the affect recognition task). There were no significant main effects for group ($F_{1;64}$ = 0.97; p = .33) and no significant group by time interaction ($F_{1;21}$ = 0.55; p = .95). Furthermore, a significant main effect of time was observed ($F_{1;21}$ = 15.27; p = .00).

4.3.3 Eye tracking analyses

For any trials showing a loss of tracking integrity we excluded the whole subject from subsequent data analysis. The final groups consisted of 30 subjects with OT and 32 subjects with PL (total n = 62).

4.3.3.1 Fixations to and viewing time within the face

Eye-movement data were analyzed for the period up to the point when participants responded in the affect recognition test. As participants were likely to take different amounts of time to respond to different faces, analyses of total gaze duration and the total number of fixations up to the button press were uninformative. Instead, a measure of the proportion of the total time spent looking at each region, along with the proportion of the total number of fixations that fell into each region, was taken. First, we calculated the proportion of the total number of fixations to the face related to the screen and then the same procedure was done for the proportion of time spent looking at the face related to the screen. Results of a subsequent MANOVA showed no multivariate effect of group ($F_{1;59}$ = .14; p = .87). Further, results of the between-subject effects showed no main effect of group either for the percentage of the number of fixations or for the total fixation duration within the face related to the total fixation time within the screen (see table 9). Overall, 93.46% of all fixations were made in the face. Subjects with OT made 93.75% of their fixations in the face, while the PL group made 93.19% fixations within the face. The overall proportion of time spent looking at the face was 95.14% (OT: 95.38% and PL: 94.91%) (see table 9).

Table 9: Proportion of fixations and fixation time within the face related to the screen.

	Oxytocin (n = 30)	Placebo (n = 32)	MANOVA $F_{1;60}$	MANOVA p
%. Fixations to the face / Fixations to the screen	93.75 ± 0.9	93.19 ± 0.9	0.21	.65
% Fixation time within the face / Fixation time within the screen	95.38 ± 0.6	94.91 ± 0.6	0.28	.60

Data given as mean ± s.e.

4.3.3.2 Fixations to the regions of interest

In order to determine whether there were differences in the number of fixations between the OT and the PL group when they were viewing emotion expressions, we performed an ANOVA with group as between-subject factor (2) and valence (6: happiness, surprise, fear, anger, sadness and disgust) and region of interest (ROIs 5: forehead, eyes, nose, mouth and chin) as repeated-measured variables. The dependent variable was the percentage of fixations. Results of the within-subject effects showed a main effect of valence ($F_{1;54}$ = 37.42; p = .00) and a non-significant valence x group interaction ($F_{1;54}$ = 3.48; p = .07). Further, results showed a significant main effect for region of interest ($F_{1;54}$ = 165.18; p = .00) and a non-significant ROI x group interaction ($F_{1;54}$ = .86; p = .49). In addition, there was a significant valence x ROI interaction ($F_{1;54}$ = 21.25; p = .00) and a non-significant valence x ROI x group interaction ($F_{1;54}$ = .61; p = .91).

Results regarding fixation time obtained by one-way ANOVA with repeated measures showed a significant main effect of ROI ($F_{1.77;95.72}$ = 132.11; p = .00) and a significant valence x ROI Interaction ($F_{9.19;496.64}$ = 29.60; p = .00). These effects were not influenced by group assignment (group x ROI interaction:

$F_{1.77;95.72}$ = 1.31; p = .27; valence x ROI x group interaction: $F_{9.19;496.64}$ = .79; p = .62).

To investigate the effect of group within all valences and within each valence separately, we conducted one-way MANOVAs for the number of fixations and the total fixation time using the calculated percentage of fixations towards a region related to the total amount of fixations to the face and the percentage of fixation time within one region of interest related to the total fixation time within the face (see table 10). MANOVAs were used because the dependent variables fixation counts and total fixation time correlated significantly for all valences together as well as in each valence itself in that the longer the viewing time towards an ROI, the more fixations were made.

Table 10: MANOVA for fixations (%) and fixation time (%) over all emotions.

	Oxytocin (n = 30)	**Placebo (n = 32)**	**MANOVA**	
			$F_{1;60}$	**p**
Fixations forehead (%)	05.58 ± 1.3	04.39 ± 1.3	0.42	.52
Fixations eyes (%)	56.17 ± 3.3	50.06 ± 3.2	1.76	.19
Fixations nose (%)	18.78 ± 2.1	23.99 ± 2.0	3.23	**(.08)**
Fixations mouth (%)	17.85 ± 1.9	19.73 ± 1.8	0.52	.48
Fixations chin (%)	01.62 ± 0.7	01.83 ± 0.7	0.05	.83
Fixation time forehead (%)	04.7 ± 1.1	03.9 ± 1.1	0.31	.58
Fixation time eyes (%)	56.12 ± 3.6	48.13 ± 3.5	2.57	0.11
Fixation time nose (%)	17.28 ± 2.3	23.40 ± 2.2	3.63	**(0.06)**
Fixation time mouth (%)	20.13 ± 2.3	22.86 ± 2.2	0.75	.39
Fixation time chin (%)	01.72 ± 0.7	01.76 ± 0.6	0.002	.97

Data given as mean ± s.e.

To examine whether there were any group differences in fixations and fixation duration on a level of positive emotions (happiness, surprise) and negative emotions (sadness, disgust, anger, fear), we used MANOVAs for these two emotion categories. As illustrated in table 11, in the category of positive emotions, we found no significant main effect of group for any of the dependent variables. Even though the OT group looked more and longer into the eyes for positive emotions, these differences were non-significant. In the category of negative emotions, a trend at the 10% level was found in that subjects with OT made fewer fixations to the nose and spent less time fixating the nose than the PL group. As in positive emotions, OT subjects looked more and longer into the eyes, but again, there was no significant difference in the proportion of fixations and fixation time spent at the eyes (see table 11).

Table 11: Positive and negative emotions: MANOVAs for fixations (%) and fixation time (%)

	Positive emotions				Negative emotions			
	OT	**PL**	**$F_{1;60}$**	**p**	**OT**	**PL**	**$F_{1;61}$**	**p**
Fixations forehead (%)	4.5 ± 1.3	4.1 ± 1.2	.05	.82	6.0 ± 1.4	4.5 ± 1.4	0.55	.46
Fixations eyes (%)	51.8 ± 3.3	45.7 ± 3.2	1.78	.19	58.0 ± 3.4	52.0 ± 3.3	1.64	.21
Fixations nose (%)	20.8 ± 2.1	25.0 ± 2.1	2.01	.16	17.9 ± 2.2	23.5 ± 2.1	3.43	**(.07)**
Fixations mouth (%)	21.5 ± 2.3	23.6 ± 2.2	0.40	.53	16.4 ± 1.7	18.1 ± 1.7	0.49	.49
Fixations chin (%)	1.3 ± 0.8	1.6 ± 0.7	0.08	.78	1.7 ± 0.7	1.9± 0.6	0.05	.82
Fix. time forehead (%)	3.7 ± 1.1	3.4 ± 1.0	0.04	.84	5.2 ± 1.2	4.1 ± 1.2	0.43	.52
Fix. time eyes (%)	50.2 ± 3.6	42.2 ± 3.5	2.61	.11	58.6 ± 3.7	50.8 ± 3.6	2.31	.13
Fix. time nose (%)	19.3 ± 2.4	24.4 ± 2.3	2.40	.13	16.4 ± 2.4	22.9 ± 2.3	3.76	**(.057)**
Fix. time mouth (%)	25.3 ± 2.9	28.4 ± 2.8	0.62	.43	18.0 ± 2.0	20.4 ± 2.0	0.73	.40
Fix. time chin (%)	1.5 ± 0.8	1.5 ± 0.7	0.00	.95	1.8 ± 0.6	1.8 ± 0.6	0.00	.96

Data given as mean ± s.e.

To single out group differences within each of the six emotion categories, we further conducted MANOVAs for every emotion with group as between-subject factor and the proportion of fixations and time as dependent variables.

Among local facial features, the eye region often receives the highest proportion of fixations during face exploration. In this experiment, we found a significant main effect of group for happy faces, in that subjects with OT spent significantly more time looking at the eyes and made more fixations to the eyes than the PL group (Fixations: $F_{1;59} = 3.23$; $p = 0.077$; Fixation time: $F_{1;59} = 4.42$; $p = 0.04$) (see Fig. 17, Fig. 18; Figure 19, 20). There were no other significant main effects found for happy faces (see table 12).

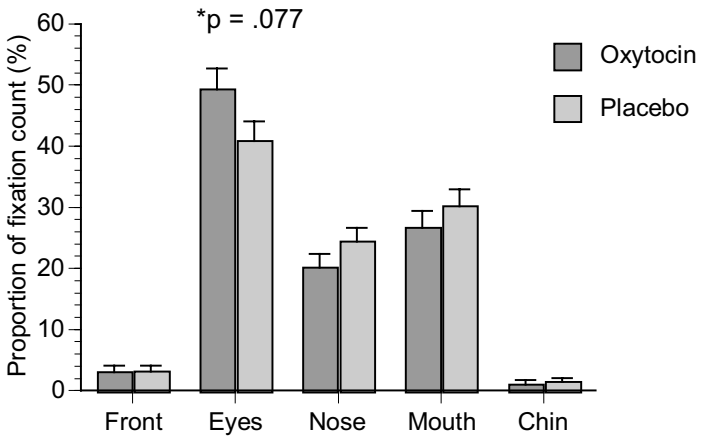


Figure 17: Happiness: Proportion of fixation count at the forehead, eyes, nose, mouth and chin. Error bars are standard errors of the mean (SEM).

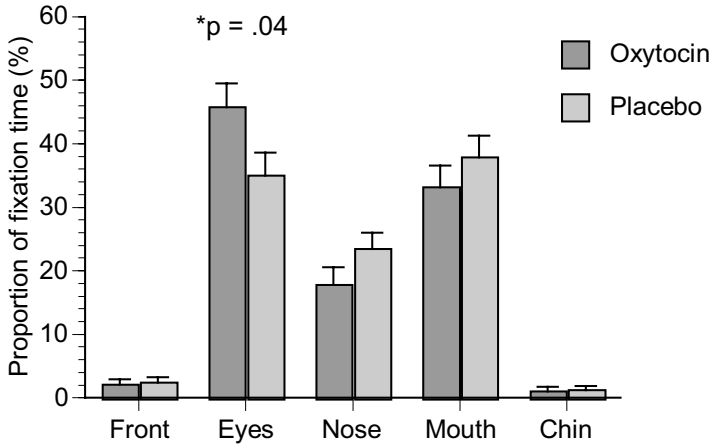


Figure 18: Happiness: Proportion of fixation time at the forehead, eyes, nose, mouth and chin. Error bars are standard errors of the mean (SEM).

Table 12: MANOVA for happiness with group as between-subject factor.

Happiness	Oxytocin (n = 30)	Placebo (n = 32)	MANOVA $F_{1;60}$	MANOVA p
Fixations forehead (%)	03.00 ± 1.1	03.10 ± 1.0	0.01	.93
Fixations eyes (%)	49.3 ± 3.4	40.8 ± 3.3	3.23	**(.077)**
Fixations nose (%)	20.1 ± 2.3	24.4 ± 2.2	1.83	.18
Fixations mouth (%)	26.6 ± 2.8	30.2 ± 2.7	0.86	.36
Fixations chin (%)	01.0 ± 0.7	01.4 ± 0.7	0.19	.66
Fixation time forehead (%)	2.1 ± 0.8	2.4 ± 0.8	0.06	.80
Fixation time eyes (%)	45.8 ± 3.7	35.0 ± 3.6	4.42	**0.04**
Fixation time nose (%)	17.8 ± 2.7	23.40 ± 2.6	2.24	0.14
Fixation time mouth (%)	33.1 ± 3.5	37.9 ± 3.4	0.94	.34
Fixation time chin (%)	01.00 ± 0.7	01.2 ± 0.7	0.03	.86

Data given as mean ± s.e.

Figure 19: Participants with oxytocin spent more time and made more fixations at the eyes in happy faces.

Figure 20: Participants with placebo made fewer fixations at the eyes and spent less time at the eyes in happy facial expressions.

Regarding the other emotions, only trends were found in that OT subjects spent less time fixating at the nose and fewer fixations at the nose than the PL subjects. This was shown for sadness, disgust, fear, and surprise (see table 13). No further main effects of group were detected.

Table 13: MANOVAs for each emotion with group as between-subject factor.

Surprise	**Oxytocin (n = 30)**	**Placebo (n = 32)**	**MANOVA** $F_{1;59}$	**p**
Fixations forehead (%)	6.1 ± 1.6	5.0 ± 1.5	0.27	.61
Fixations eyes (%)	55.7 ± 3.7	49.4 ± 3.5	1.52	.22
Fixations nose (%)	20.4 ± 2.3	25.9 ± 2.2	2.95	**(.09)**
Fixations mouth (%)	16.1 ± 2.2	18.0 ± 2.1	0.40	.53
Fixations chin (%)	01.6 ± 0.9	01.7 ± 0.8	0.00	.98
Fixation time forehead (%)	5.3 ± 1.4	4.2 ± 1.3	0.40	.53
Fixation time eyes (%)	56.2 ± 4.0	48.4 ± 3.8	1.99	.16
Fixation time nose (%)	19.8 ± 2.6	26.2 ± 2.5	3.14	**(.08)**
Fixation time mouth (%)	16.8 ± 2.5	19.5 ± 2.4	0.62	.44
Fixation time chin (%)	01.9 ± 0.9	01.7 ± 0.9	0.01	.93
Sadness	**Oxytocin (n = 30)**	**Placebo (n = 32)**	**MANOVA** $F_{1;60}$	**p**
Fixations forehead (%)	9.00 ± 2.0	6.8 ± 1.9	0.66	.42
Fixations eyes (%)	56.5 ± 3.5	51.3 ± 3.4	1.13	.29
Fixations nose (%)	18.9 ± 2.4	24.2± 2.3	2.52	.12
Fixations mouth (%)	13.7 ± 1.7	15.1 ± 1.7	0.34	.56
Fixations chin (%)	1.8 ± 0.9	2.6 ± 0.7	0.35	.55
Fixation time forehead (%)	7.9 ± 1.8	6.1 ± 1.7	0.52	.47

Fixation time eyes (%)	57.0 ± 3.8	50.3 ± 3.7	1.61	.21
Fixation time nose (%)	17.8 ± 2.7	24.2 ± 2.6	2.87	**(.09)**
Fixation time mouth (%)	15.3 ± 2.0	17.1 ± 1.9	0.43	.52
Fixation time chin (%)	2.0 ± 0.8	2.3 ± 0.8	0.07	.79
Disgust	**Oxytocin (n = 30)**	**Placebo (n = 32)**	**MANOVA $F_{1;60}$**	**p**
Fixations forehead (%)	6.4 ± 1.8	4.5 ± 1.7	0.57	.45
Fixations eyes (%)	63.7 ± 3.6	57.2 ± 3.5	1.67	.20
Fixations nose (%)	16.6 ± 2.4	22.9 ± 2.3	3.6	**(.06)**
Fixations mouth (%)	11.9 ± 1.7	13.5 ± 1.6	0.49	.49
Fixations chin (%)	1.4 ± 0.7	1.8 ± 0.7	0.16	.69
Fixation time forehead (%)	5.9 ± 1.8	4.6 ± 1.8	0.24	.62
Fixation time eyes (%)	65.5 ± 3.9	57.3 ± 3.8	2.28	.14
Fixation time nose (%)	15.5 ± 2.8	22.5 ± 2.7	3.23	**(0.08)**
Fixation time mouth (%)	11.9 ± 1.9	14.2 ± 1.8	0.79	.38
Fixation time chin (%)	1.3 ± 0.5	1.5 ± 0.5	0.11	.75
Anger	**Oxytocin (n = 30)**	**Placebo (n = 32)**	**MANOVA $F_{1;55}$**	**p**
Fixations forehead (%)	4.9 ± 1.1	2.9 ± 1.2	1.5	.22
Fixations eyes (%)	53.5 ± 3.7	50.0 ± 3.9	0.43	.51
Fixations nose (%)	17.5 ± 2.3	20.0 ± 2.4	0.57	.45
Fixations mouth (%)	20.6 ± 2.2	24.4 ± 2.3	1.43	.24
Fixations chin (%)	3.5 ± 1.3	2.8 ± 1.3	0.15	.70
Fixation time forehead (%)	4.4 ± 1.1	1.9 ± 1.1	0.66	.11
Fixation time eyes (%)	51.5 ± 4.1	46.0 ± 4.3	0.87	.36
Fixation time nose (%)	15.3 ± 2.2	17.9 ± 2.3	0.69	.41
Fixation time mouth (%)	24.8 ± 2.7	30.4 ± 2.8	2.16	.15

Fixation time chin (%)	4.0 ± 1.7	3.7 ± 1.8	0.01	.92
Fear	**Oxytocin (n = 30)**	**Placebo (n = 32)**	**MANOVA $F_{1;60}$**	**p**
Fixations forehead (%)	03.00 ± 1.1	03.10 ± 1.0	0.71	.40
Fixations eyes (%)	49.3 ± 3.4	40.8 ± 3.3	1.54	.22
Fixations nose (%)	20.1 ± 2.3	24.4 ± 2.2	2.75	**(.10)**
Fixations mouth (%)	26.6 ± 2.8	30.2 ± 2.7	0.07	.80
Fixations chin (%)	01.0 ± 0.7	01.4 ± 0.7	0.05	.82
Fixation time forehead (%)	2.1 ± 0.8	2.4 ± 0.8	1.17	.68
Fixation time eyes (%)	45.8 ± 3.7	35.0 ± 3.6	1.55	.22
Fixation time nose (%)	17.8 ± 2.7	23.40 ± 2.6	3.64	**(0.06)**
Fixation time mouth (%)	33.1 ± 3.5	37.9 ± 3.4	0.01	.92
Fixation time chin (%)	01.00 ± 0.7	01.2 ± 0.7	0.63	.43

Data given as mean ± s.e.

4.3.3.3 Fixations across the time span of the videos

To investigate eye movements of the participants over the time span, we conducted further analyses, dividing the response time of each single video stimulus of each single participant into 3 equal phases (early, middle, late). Then, we analyzed group differences in the number of fixations and fixation time in each of the three phases separately. The eye region in neutral, expressive or vocalizing faces is often the first destination of the saccade and attracts a disproportionate share of fixations compared with other local facial features. We therefore hypothesized that in the early phase, OT might enhance attention towards the eyes in the affect recognition task, especially for the happy faces. A further hypothesis was that OT might influence eye movements during emotion recognition in the late phase, shortly before a decision is made.

4.3.3.4 Fixations and fixation time within the early phase of face exploration

To investigate interactions between group, valence and region of interest (ROI), these data were entered into a one-way ANOVA with repeated measures with group as between-subject factor and valence and ROI as within-subject factors. The dependent variable was the percentage of fixations over all emotions. For the results of the within-subject factors, Greenhouse-Geisser results were reported due to the violation of the sphericity assumption. Results of the early phase 1 showed a significant main effect of valence (6) ($F_{1;54}$ = 10.31; p = .002) and a significant valence x group interaction ($F_{1;54}$ = .049). In addition, we found a significant main effect of ROI ($F_{1.82;98.24}$ = 161.67; p = .00) and a significant valence x ROI interaction ($F_{9.01;486.58}$ = 8.44; p = .00). However, the ROI x group interaction ($F_{1.82;98.24}$ = 1.59; p = .21) and the valence x ROI x group interaction ($F_{9.01;486.58}$ = .80; p = .62) were non-significant.

The same procedure was calculated for the percentage of fixation time as dependent variable. Again, we found a significant main effect of ROI ($F_{1.87;\ 101.08}$ = 125.24; p = .00) and a significant valence x ROI interaction ($F_{8.69;\ 469.57}$ = 13.48; p = .00). The percentage of time spent examining core features (ROIs) did not differ as a function of group ($F_{1.87;101.08}$ =1.96; p = .15), and the valence x ROI x group interaction ($F_{8.69;\ 469.57}$ = .67; p = .73) was also non-significant.

To further analyze group differences over all emotions, as well as in each emotion category and separately for positive and negative emotions, one-way multivariate ANOVAS (MANOVAs) were used with group (OT or PL) as between-subject factor on fixation count towards and fixation time to the forehead, eyes, nose, mouth, and chin.

The results over all emotions showed significant differences between the groups regarding the amount of fixations towards the nose and eyes and the amount of time spent fixating the nose and the mouth. Subjects with OT made overall more fixations towards the eyes ($F_{1;60}$ = 3.07; p = .085) and significantly fewer fixations towards the nose ($F_{1;60}$ = 5.49; p = .022) than subjects with PL (see Figure 21). Further, the OT group spent more time towards the eyes ($F_{1;60}$ = 3.54; p = .065) and significantly less to the nose ($F_{1;60}$ = 5.34; p = .024) (see Figure 22). No other significant group differences were found.

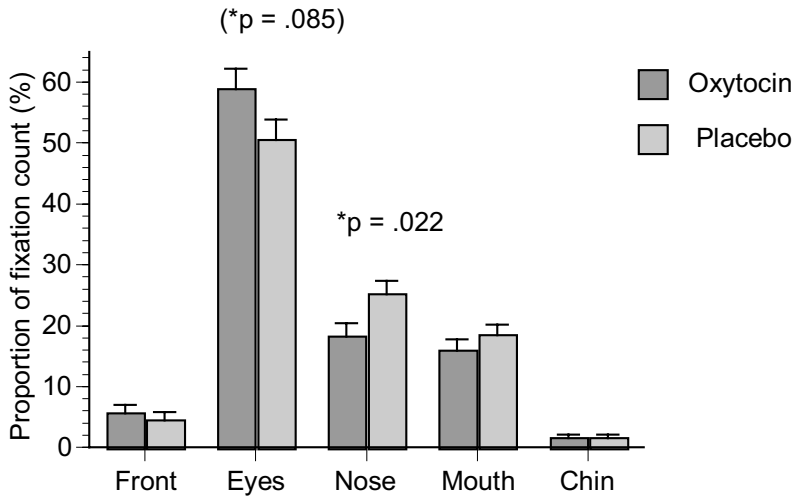


Figure 21: Early phase 1: Proportion of the number of fixations to the forehead, eyes, nose, mouth and chin over all emotions. Error bars are standard errors of the mean (SEM).

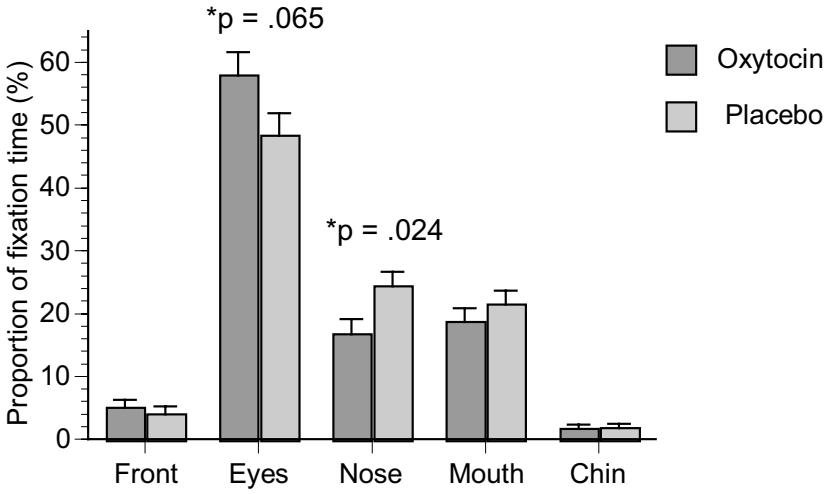


Figure 22: Early phase 1: Proportion of the fixation time on the forehead, eyes, nose, mouth and chin over all emotions. Error bars are standard errors of the mean (SEM).

When investigating in further detail and dividing into the two categories of positive and negative emotions, we observed similar results. For the positive

emotions (surprise and happiness), we found a significant group difference for the time spent towards the eye region ($F_{1;60}$ = 4.49; p = .038) in that the OT group fixated longer to the eyes than the PL group. In addition, results revealed a significant group effect for the amount of fixations towards the eyes ($F_{1;60}$ = 3.99; p = .05), again in that OT subjects made more fixations towards the eyes. They also spent less time towards the nose ($F_{1;60}$; p = 3.48; p = .067), and made fewer fixations to the nose ($F_{1;60}$; p = 3.52; p = .066) than the PL group.

Within the category of negative emotions, subjects with OT gazed significantly less ($F_{1;60}$ = 5.85; p = .019) and spent less time at the nose ($F_{1;60}$ = 5.39; p = .024). Furthermore, they made more fixations toward the eyes and fixated longer on the eyes, although this group difference for fixation time was only a trend (fixation duration: $F_{1;60}$ = 2.97; p = .09).

We also wished to explore for which emotion expression oxytocin particularly influenced the way in which participants scanned faces. To this aim, we conducted analyses for each emotion category.

Regarding the emotion sadness in the early phase, we again found a significant group difference for fixation count and fixation duration for the nose, in that subjects receiving OT made fewer fixations toward the nose ($F_{1;60}$ = 4,92; p = .03), and spent significantly less time fixating the nose ($F_{1;60}$ = 3.28; p = .075). Instead, they made more fixations ($F_{1;60}$ = 2.40; p = .13) and spent more time fixating ($F_{1;60}$ = 2.64; p = .10) towards the eyes. This group effect for the eyes was not significant, but showed a trend for the fixation time towards the eyes at the 10% level. No other group differences were found for the other ROIs.

Results for disgust showed that subjects with OT made significantly fewer fixations to the nose ($F_{1;60}$ = 6.69; p = .012) and more to the eyes (F1;60 = 2.46; p = .12). This effect was the same for the fixation time.

We found no significant group effect for the emotion surprise and anger within the early phase 1, but instead found highly significant results for the other

positive emotion – happiness. Participants with OT looked significantly more ($F_{1;60}$ = 6.73; p = .012) and longer into the eyes ($F_{1;60}$ = 6.37; p = .014) (see Figure 23) and moreover, they looked less at ($F_{1;60}$ = 3.94; p = .052) and spent less time fixating on the nose ($F_{1;60}$ = 3.67; p = .06).

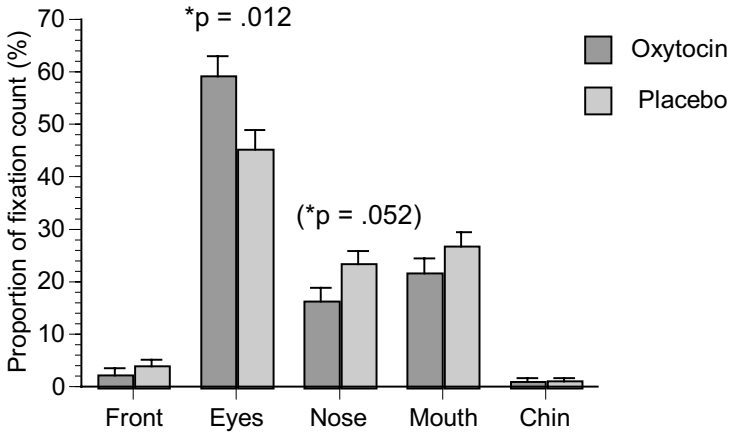


Figure 23: Early phase 1: Proportion of the fixation count on the forehead, eyes, nose, mouth and chin for happiness. Error bars are standard errors of the mean (SEM).

For fearful facial expressions, results showed a significant group effect on fixation time toward the nose, such that subjects with OT spent significantly less time fixating the nose ($F_{1;60}$ = ; p = .048).

4.3.3.5 Fixations and fixation time within the middle phase of face exploration

During the middle phase 2, results of one-way ANOVA with repeated measures for group as between-subject factor and valence and ROI as within-subject factors and proportion of fixation count revealed a significant between-group

effect ($F_{1;54}$ = 9.64; p = .003). Further, results showed a significant main effect for valence ($F_{1;54}$ = 11.22: p = .001), and a significant valence x group interaction ($F_{1;54}$ = 9.64; p = .003). Moreover, we found a significant main effect of ROI ($F_{1;102.07}$ = 140.7; p = .00). The ROI by group interaction was not significant ($F_{1;102.07}$ = .41; p = .66). Further, there was a significant ROI x valence interaction ($F_{8.91;480.99}$ = 20.30; p = .00). The valence x ROI x group interaction showed a non-significant result ($F_{8.91;480.99}$ = 8.9; p = .53).

Regarding the proportion of fixation time as dependent variable, results of one-way ANOVA with repeated measures with group as between subject factor and valence and ROI as within-subject factors, results revealed a significant main effect for ROI ($F_{1.9;102.75}$ = 115.17; p = .00) and a significant valence x ROI interaction ($F_{8.74;\ 472.14}$ = 29.96; p = .00). The ROI x group interaction ($F_{1.9;102.75}$ = .82; p = .44) as well as the valence x ROI x group interaction ($F_{8.74;472.14}$ = 1.32; p = .23) were non-significant.

As there was a significant valence x group interaction for fixation count, we investigated group differences in each emotion category separately. However, results of MANOVAs showed that even though the same relations of fixating more and longer to the eyes and less and for less time to the nose were observed, there were no significant group differences found in any emotion category or within positive and negative emotion categories for fixation count and fixation time.

4.3.3.6 Fixations and fixation time within the late phase of face exploration

In the final third of the emotion recognition phase 3, we investigated interactions between group, valence and region of interest (ROI), again by entering these data into a one-way ANOVA with repeated measures for group as between-subject factor and valence and ROI as within-subject factors. The dependent variable was the percentage of fixations over all emotions. For the results of the within-subject factors, Greenhouse-Geisser results were reported due to the

violation of the sphericity assumption. Results of the late phase 3 showed a significant main effect of ROI (5) ($F_{1.93;104.18}$ = 125.34; p = .00) and a significant valence x ROI interaction ($F_{1;54}$ = 15.78; p = .00). In addition, we found a significant main effect of ROI ($F_{9.33;503.87}$ = 161.67; p = .00). However, the ROI x group interaction ($F_{1.93;104.18}$ = .52; p = .59) and the valence x ROI x group interaction ($F_{9.33;503.87}$ = .84; p = .58) were non-significant.

For the fixation duration, results of the ANOVA with repeated measurement also revealed a significant main effect for ROI ($F_{1.86;100.45}$ = 114.45; p = 00) and a significant valence x ROI ($F_{9.32;503.90}$ = 17.87; p = .00) interaction. No other interaction was significant.

To further analyze group differences over all emotions, as well as in each emotion category and separately for positive and negative emotions, one-way multivariate ANOVAS (MANOVAs) were used with group (OT or PL) as between-subject factor on fixation count towards and fixation time to the forehead, eyes, nose, mouth, and chin.

Results of the MANOVA over all emotions and also divided into the two categories of positive and negative emotions showed no significant group differences between OT and PL. Therefore, we went into greater detail, analyzing each emotion category separately. For this late phase 3, no significant group differences were found in sadness, anger, disgust and surprise.

For fearful faces, we found that subjects with OT gazed more and longer towards the forehead, than PL subjects (fixation count: $F_{1;60}$ = 2.79; p = .10; fixation duration: $F_{1;60}$ = 3.52; p = .066) (see Fig. 24 und Fig. 25).

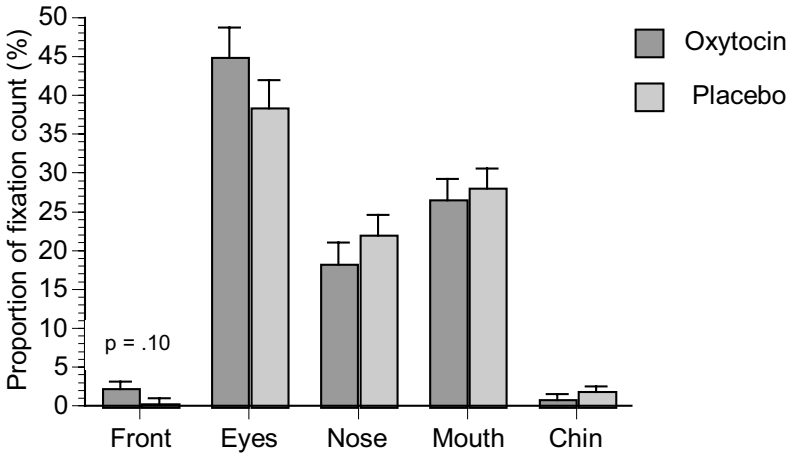


Figure 24: Late phase 3: Proportion of the fixation count on the forehead, eyes, nose, mouth and chin for fear. Error bars are standard errors of the mean (SEM).

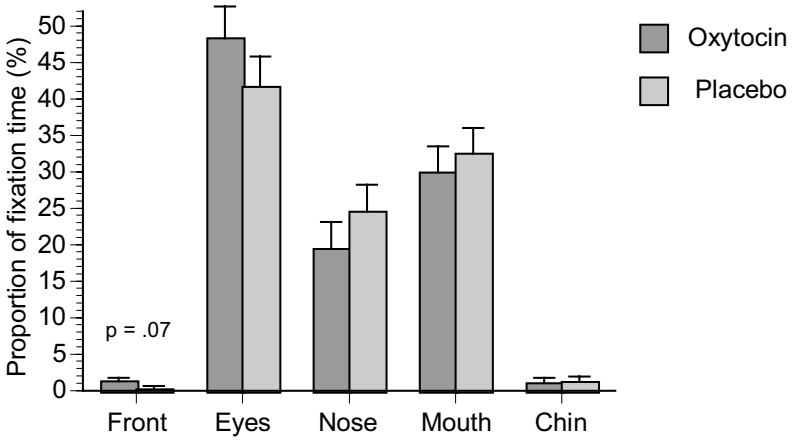


Figure 25: Late phase 3: Proportion of the fixation time on the forehead, eyes, nose, mouth and chin for fear. Error bars are standard errors of the mean (SEM).

For happy facial expressions, results of one-way MANOVA with group as between-subject factor showed that subjects with OT spent highly significant more time fixating the eyes ($F_{1;60} = 6.27$; $p = .015$) and made significantly more fixations to the eyes ($F_{1;60} = 3.73$; $p = .058$) compared to the PL group (Fig. 26,

27). Moreover, they spent less time fixating the mouth than the PL group at a trend level ($F_{1;60} = 3.05$; $p = .086$).

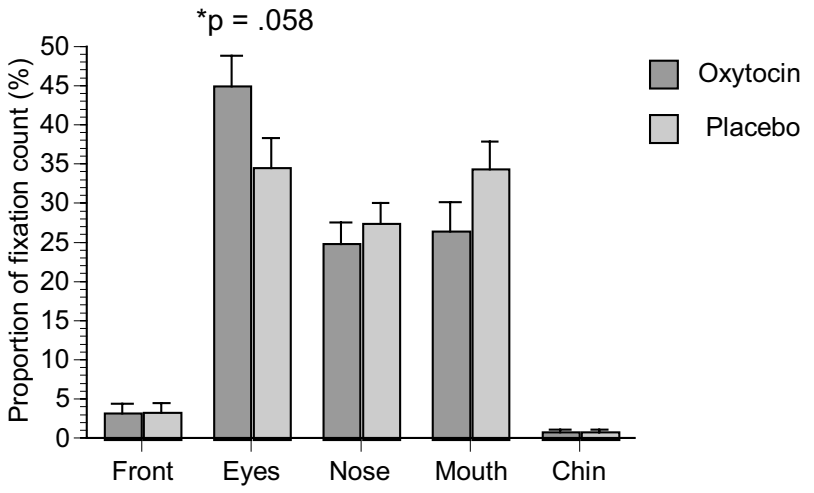


Figure 26: Late phase 3: Proportion of the fixation count on the forehead, eyes, nose, mouth and chin for happiness. Error bars are standard errors of the mean (SEM).

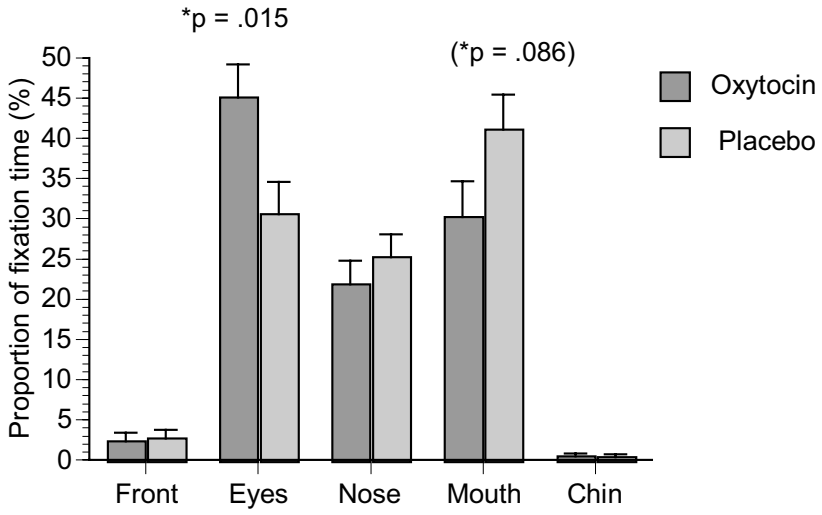


Figure 27: Late phase 3: Proportion of the fixation time on the forehead, eyes, nose, mouth and chin for happiness. Error bars are standard errors of the mean (SEM).

4.4 Discussion

The findings of the present study show that a single dose of intranasally administered oxytocin before viewing videos of facial expressions influences eye movements substantially. When analyzing video sequences as a whole, oxytocin on the one hand enhanced the number of fixations and the fixation time to the eyes and on the other hand significantly reduced the number of fixations and the time spent fixating to the nose. These effects were independent of the valence of the facial expressions. More detailed analyses showed that especially in happy faces, a single dose of oxytocin was able to increase the number of fixations towards the eyes and also lead to a significant increase in the amount of time spent on the eyes. For the category of negative emotions, we found a trend for subjects who received oxytocin to make fewer fixations toward the nose, and they spent significantly less time fixating the nose.

Our stimulus material consisted of animated video sequences of faces, which begin with a neutral face and slowly develop into an emotional facial expression. Therefore, we were especially interested in a time-related analysis of the eye movement data. Response times of the 36 videos of each participant were divided individually into three equal time sequences: an early, a middle, and a late face exploration phase. Results showed that, especially in the early detection phase, oxytocin exerts an influence on fixations and fixation duration toward the eyes and nose independent of the valence of the emotion. Subjects with oxytocin made more fixations to the eyes, spent significantly more time fixating the eye region and made fewer fixations toward the nose and spent significantly less time on the nose. For happy faces in particular, significant effects were detected in this early detection phase. Participants with OT spent significantly more time on the eyes, and, in contrast, showed a trend towards spending less time on the nose. They also made fewer fixations toward the nose, but this group difference was not significant. Interestingly, we did not find

any group differences in the middle phase for any of the emotional valences and also over all emotions. Instead, in the late detection phase, we found an additional effect for happy faces. Again, in the late phase, subjects with OT fixated significantly more and longer toward the eyes, but also, they showed a trend for fixating with less duration on the mouth region. This group difference for the mouth was only a trend at the 10% level.

These findings are consistent with a recent study by Guastella et al. (2007) showing that OT increased gaze to the eye region in neutral faces. The eyes are often inspected first and for a longer time during face detection. Our results show that a single dose of oxytocin is able to enhance this saliency of the eye region at the early stage of face inspection. According to Guo (2007), the eye region, in particular in expressive faces, is often the first destination of the saccade and attracts a disproportional share of fixations compared with other core facial features. Our results are in line with these findings, showing the most fixations and the longest fixation times to the eyes, in every emotion category and over all emotions together.

What neurobiological mechanisms might underlie the observed effects on emotion recognition and on eye gaze? Viewing facial expressions and recognizing emotions comprises face processing, which involves a distributed network of several brain regions, the fusiform gyrus, the superior temporal sulcus, and limbic structures including the amygdala (Haxby, Hoffman, & Gobbini, 2000). Dalton and colleagues (2005) showed in a recent study that an activation of the fusiform face area (FFA) is strongly associated with the amygdala and, moreover, with the amount of time spent fixating on the eye region of emotional faces in autistic patients. Oxytocin receptors are distributed in various brain regions that are associated with social behavior, and therefore also in the amygdala (Huber, Veinante, & Stoop, 2005; Landgraf & Neumann, 2004). In an earlier study by Baron-Cohen and colleagues (1999), an fMRI study showed an amygdala activation in response to the “reading-the-mind-in-

the-eyes test". In addition, a study by Kirsch and colleagues using fMRI indicated that OT reduces amygdala responses to threatening non-social scenes and to angry and fearful faces. In another fMRI study by Domes and colleagues (2007), in which the authors compared the effects of oxytocin on positive compared to negative social cues in humans on the amygdale activation, findings revealed that oxytocin attenuates amygdala responses regardless of valence. These results might be interpreted such that a suppression of the amygdala to happy faces through oxytocin represents a reduced arousal to affective social stimuli in general, rather than a being a specific effect for the detection of threat. These interpretations by Domes et al. contradict studies that argue that the amygdale promotes social cognition by enhancing salience and attention to socially relevant cues (Ferguson, Aldag, Insel, & Young, 2001). So far, our study is in line with previous research indicating a key role of OT in facial processing and thus for interpersonal communication. Specific underlying mechanisms need to be investigated in future research and another interesting question will be whether oxytocin might be relevant for the treatment of psychiatric disorders that involve social dysfunctions and emotion recognition deficits (e.g. autism, social phobia, borderline personality disorder).

5. General Discussion

The aim of this study was to examine possible beneficial effects of a single dose of intranasal oxytocin on the ability to recognize emotions from social cues of the eye region in individuals with defined difficulties in recognizing, describing and feeling emotions (non-clinical form of alexithymia) and further to evaluate the specificity and the extent of this possible effect using an eye-tracking system during an affect recognition task.

A recent study by Domes and colleagues proved an enhancing effect of oxytocin on the ability to infer the mental states of others from cues of the eye region (Domes et al., 2007b). Another study by Domes et al. (2007a) showed that oxytocin attenuated the amygdala responses to positive and negative facial expressions, regardless of their valence. It has not yet been shown yet whether oxytocin might also have beneficial effects on healthy individuals suffering from a personality trait called “alexithymia”. Alexithymia is seen as a personality trait that differs among people. About 10% of the normal population are characterized by poor expressiveness of emotional states (Berthoz et al., 2002). Furthermore, alexithymia has also been implicated in problems in the recognition of emotion in facial expressions (Lane et al., 1996; Lane, Sechrest, Riedel, Shapiro, & Kasniak, 2000; J. D. A. Parker, Taylor, & Bagby, 1993a) and even though alexithymia is a subclinical phenomenon, it is associated with general psychological distress, especially with depression and anxiety, and has been observed in numerous psychiatric and somatic disorders (Bankier, Aigner, & Bach, 2001; Gil et al., 2007; Le, Ramos, & Munoz, 2007; Marchesi, Bertoni, & Maggini, 2008; Saarijärvi, Salminen, Taylor, & Toikka, 2006; Taylor, Bagby, & Parker, 1997).

Furthermore, in the second study, we attempted to evaluate the eye gaze pattern as an underlying mechanism of the above-described effects during an affect recognition task with dynamic stimuli (videos of facial expressions) using eye-tracking. Guastella and colleagues (2007) showed in a recent study that

oxytocin enhanced eye gaze and fixation time toward the eyes in neutral facial expressions. Therefore, we attempted to assess eye gaze during videos of faces expressing one of the six basic emotions (happiness, surprise, anger, sadness, disgust, fear).

This chapter will discuss the results of the two studies and incorporate them into previous research findings. Furthermore, methodological issues and limitations of the studies will be discussed, followed by the clinical relevance of our findings and a consideration of future research steps.

5.1 Summary of the Results

While the first study presented in this book examined the effect of a single dose of oxytocin before an emotion recognition task in individuals with described difficulties in distinguishing emotions, the second study evaluated a possible underlying mechanism of oxytocin through an enhancement of eye gaze towards the eye region during emotion recognition tasks using an eye-tracking system.

5.1.1 Oxytocin promotes emotion recognition in individuals with difficulties in recognizing and describing feelings

Given that oxytocin was found to increase trust and the ability to infer the mental states of others from subtle facial cues such as the eye region, in the first empirical part we were particularly interested in the effects of oxytocin on emotion recognition in individuals with described difficulties in emotion recognition such as alexithymia. Therefore, we divided our healthy participants into a non-clinical high- and low-alexithymic group. For this first emotion recognition task, pictures of the six basic emotions (fear, sadness, disgust, happiness, anger, surprise) were chosen from the “Pictures of Facial Affect” (Ekman & Friesen, 1976). Using a computer program, they were reduced to the

eye region, resulting in a set of 21 pictures of the eye region of different persons (6 emotions x 3 and 3 neutral eye regions).

Results showed that a single dose of oxytocin enhanced emotion recognition ability in the high-alexithymic group regarding the percentage of correct answers, while no such effect occurred in the low-alexithymic group. In additional analyses, all emotions were divided into two subsets of easy and difficult emotions. These two subsets were generated based on the median of item difficulty derived from data of the PL group. We found that oxytocin especially improved emotion recognition in the difficult but not in the easy emotions. Again, this effect was only found in the high-alexithymic group. Regarding reaction times, in both high- and low-alexithymics, oxytocin subjects responded slower, but this effect was not significant.

Furthermore, we found no differences between the four groups regarding mood, wakefulness, arousal or heart rate over the time course of the experiment.

5.1.2 Oxytocin increases eye gaze toward the eye region in happy faces

In the second study, we attempted to elucidate one possible underlying mechanism of oxytocin in its role for emotion recognition and face perception – the eye gaze pattern. Therefore, we assessed eye gaze during a dynamic emotion recognition task “Affect recognition test (ART)”. In the ART, several short video sequences of facial expressions were presented. The faces start from a neutral facial expression and slowly change into a specific emotion (fear, sadness, disgust, happiness, anger and surprise). After the affect recognition task, subjects had to rate each face of the ART on two scales: approachability and trustworthiness according to Adolphs and colleagues (Adolphs et al., 1998). Again, mood and heart rate were assessed repeatedly during the whole experiment.

Results for the emotion recognition task showed no significant group effect for answer correctness. Findings regarding reaction times showed that the oxytocin subjects responded slower, and that this effect was significant for positive emotions, especially for surprise. Furthermore, in the face ratings, we found no significant differences between the groups regarding social approach. Instead, results revealed that subjects with oxytocin trusted more than the placebo subjects (over all emotions), especially in angry faces. No group differences were observed in mood, arousal or wakefulness or in heart rate during the experiment.

Results of the analyses of eye gaze showed that there was no group difference in the proportion of the number of fixations towards the face and the proportion of time spent on the face. Both groups made 94% of their fixations towards the face and spent 95% of their time on the face. Over all emotions, OT subjects made more fixations toward the eye region and spent more time fixating the eyes than the PL group. In contrast, OT subjects made fewer fixations to the nose and spent less time fixating the nose. While the eye effect of oxytocin was not significant over all emotions, results regarding the nose fixations were significant at the 10% level.

Results for each emotion category revealed that OT subjects fixated significantly more and longer on the eye region in happy faces. For the other emotions, we found that with oxytocin, subjects made fewer fixations to the nose and also spent less time fixating the nose; instead, they made more and longer fixations to the eyes. These effects were only trends.

Considering the fixations and fixation times across the time span of the videos, we conducted further analyses dividing the response time of every video of each individual into three equal time phases (early, middle and late phase). Then, we analyzed group differences in each of these phases separately over all emotions and for every category separately. In an early detection phase 1 over all emotions, OT subjects gazed more and longer (both trends < .10) at the

eyes, made significantly fewer fixations and spent less time on the nose. This effect was the same in every emotion category, but was especially significant in happy faces.

In contrast, we found no significant group differences in the middle phase 2 for all emotions together and separately for every emotion alone. Although we observed the same relationships as in phase 1, with OT subjects fixating more and longer to the eyes, and less and for less time to the nose, no such effect was significant.

In the final third of the emotion recognition task, the late phase 3, no significant group differences were found over all emotions. Instead, we only found a significant group effect for happy faces showing that OT subjects gazed significantly more and longer at the eyes shortly before they gave their answers in the ART.

To sum up, in line with previous research, oxytocin increased gaze to the eye region and this effect was especially significant in happy facial expressions. Furthermore, OT was shown to increase eye gaze to the eyes and to reduce eye gaze to the nose in all basic emotions particularly in an early phase of face exploration in which subjects were not completely sure which emotion was being presented. In addition, in the late phase 3, shortly before decision making, subjects with OT spent significantly more time on the eyes and significantly less time on the mouth in happy faces.

5.2 Methodological Considerations and Limitations

In our first study, we examined the effects of oxytocin on emotion recognition in a non-clinical sample of high- and low-alexithymic subjects. Numerous studies investigating the emotion recognition abilities in patients with alexithymia have shown inconsistent findings. While some studies reported significantly impaired emotion recognition from facial stimuli (Lane, Sechrest, Riedel, Shapiro, &

Kasniak, 2000; J. D. A. Parker, Taylor, & Bagby, 1993b; P. D. Parker, Prkachin, & Prkachin, 2005), others did not find these impairments (McDonald & Prkachin, 1990). These inconsistencies might be due to heterogeneous study samples or due to correlational and measurement-based research designs. Many of the early studies on alexithymia and emotion recognition lacked a standardized, reliable measurement of adequate validity (Taylor, 2000). Over the past decade, however, measurement-based and experimental studies have yielded considerable empirical support for the validity of the alexithymia construct and the Toronto Alexithymia Scale (TAS-20) provided a reliable and valid method for measuring the construct. Nevertheless, these developments in the construct definition and in its measurement may explain a part of the inconsistencies found in studies on emotion recognition deficits in alexithymics.

Although alexithymia was initially used as a syndrome for clinical patients with psychopathological disorders, more recently, alexithymic characteristic have been shown to be prominent in people in nonclinical populations (Jessimer & Markham, 1997), and some studies on alexithymia used non-clinical populations, as we did, because this highly selective procedure is indispensable for the development of new therapy approaches. Therefore, a limitation of our study sample is shown in the exclusion of comorbid psychiatric disorders. As studies showed, psychological disorders such as depression, anxiety, and somatoform disorders commonly occur together with alexithymia and therefore we examined only a limited population and cannot generalize our results (Bankier, Aigner, & Bach, 2001; Gil et al., 2007; Le, Ramos, & Munoz, 2007; Marchesi, Bertoni, & Maggini, 2008; Saarijärvi, Salminen, Taylor, & Toikka, 2006; Taylor, Bagby, & Parker, 1997). Another ongoing debate on the stability of the alexithymia construct makes it difficult to interpret our findings (Honkalimpi, Hintikka, Saarinen, Lehtonen, & Viinamaki, 2000; Luminet, Bagby, & Taylor, 2001; Saarijärvi, Salminen, Taylor, & Toikka, 2006). Even though alexithymia is thought of as a relatively stable personality trait, there is still critical discussion on the changeability of alexithymic traits by psychotherapy.

Therefore, it would be important to repeat our experiment, possibly with a combined cross-over design to confirm our results and to investigate the stability of our findings. This did not appear feasible in this study because of learning effects within the emotion recognition task. Therefore, we would have needed two parallel forms of the ART.

Another important source of inconsistencies lies in the differences in the emotion recognition tasks used in previous studies, which are associated with different difficulty levels of the stimulus material. Parker et al. (2005) showed in his study that people with alexithymic characteristics do not show a general impairment in emotional processing, but rather that deficits may appear when excessive demands are made on emotion-processing capacity, for example, by limiting the amount of time available to encode and transform emotional stimuli. We tried to incorporate this issue of task difficulty in our first study by dividing our stimuli into easy and difficult subsets. Nevertheless, since we used social cues from only the eye region of the six basic emotions, our results are only of limited ecological validity. In everyday life, we do not make judgments on static images or about single basic emotions, but rather make complex judgments about dynamic facial signals encountered together with body posture and voice stimuli in a certain situation with a social background.

In the second study, we investigated the effects of a single dose of oxytocin on eye gaze during a dynamic affect recognition task (ART), because research showed that looking at the eyes is important for social reasoning and possible emotion recognition deficits are attributable to differences in visual scanning of faces. Using dynamic video sequences for a greater ecological validity of the results, this method has certain limitations. A first methodological issue points to the eye tracking data, which can only be analyzed for the period of time when each participant viewed the movie and when he pressed the stop button, i.e. when he made his choice. This response time varies in each video for each participant. Various studies investigating emotion recognition and its underlying

mechanisms either allowed subjects only a limited but standardized time to give their responses, or else allowed them to view the facial expressions for as long as they wished. Therefore, we analyzed the data as proportions of the amount of fixations toward a specific face region compared to the total sum of fixations toward the whole face.

Another limitation of our findings is that we were unable to confirm enhancing effects of oxytocin on emotion recognition in terms of correctness of the given answers. We did not find any significant group differences in answer correctness either over all emotions, or in a specific basic emotion category. In contrast, we found longer reaction times for the OT group, pointing to a greater attention especially towards positive emotions.

It is noteworthy that the data of both studies do not allow a specific interpretation of a specific central nervous system action of oxytocin, because we do not know what happened in the specific brain areas involved in face processing and emotion recognition. Therefore, imaging studies or combined imaging and eye tracking studies are needed to examine the effects of oxytocin in the relevant brain structures such as the fusiform face area, the lateral inferior occipital gyri, the posterior superior temporal sulcus and especially the amygdala.

Another issue of both experiments is the limitation of an exclusively male sample. Therefore, we only investigated a limited population. In addition, there are still no dose-response studies on oxytocin, meaning that the exact mechanism of brain penetration and the relationship between plasma and central OT is still unclear.

5.3 Discussion of the results

This is the first study to show that a single administration of oxytocin improves the ability to identify emotions from social cues of the eye regions in healthy

men with features of high alexithymia compared to low-alexithymic subjects. Moreover, the second study elucidates that eye gaze enhancement is one possible mechanism through which oxytocin might be associated with an increased face perception.

Considering that oxytocin enhanced performance of emotion recognition especially in those emotions that were difficult to detect, oxytocin might therefore particularly play an important role in recognizing insecure, difficult emotions. In contrast, oxytocin did not improve performance in easy emotions. These results are consistent with earlier studies demonstrating that deficits in emotional processing in alexithymia particularly occur when excessive demands are made on emotion-processing capacity, for example by limiting the amount of time available to encode and transform emotional stimuli or, like in this study, by viewing eye regions which are difficult to recognize. These results confirm the hypothesis of Parker and colleagues (2005) that alexithymics do not exhibit an overall impairment in recognizing emotions from facial expressions and that alexithymia rather involves a deficit in the efficiency in emotional processing.

Furthermore, in the low-alexithymia group, no enhancing effect of oxytocin was observed either over all emotions or within the group of difficult emotions. These findings indicate that the exogenous oxytocin administration improved emotion recognition in subjects with difficulties in recognizing, describing and regulating emotions, in that they were able to show a performance level almost comparable with the healthy non-alexithymic subjects.

Findings of both studies are in line with previous research from animal and human studies showing that OT is implicated in social behavior, including attachment and affiliative behavior such as pair-bonding. An increasing number of human studies have only just begun to gain insights into the way in which OT modulates social approach behavior and affiliation including its cognitive processes (Heinrichs & Domes, 2008). Our findings are consistent with a recent study by Domes and colleagues (2007) showing that a single dose of oxytocin

enhances the ability to infer the mental state of others by social cues of the eye region. Moreover, our findings confirm results of Guastella and colleagues (2007) showing that OT increased gaze to the eye region in neutral faces. The eyes are often inspected first and for a longer time during face detection. Our results show that a single dose of oxytocin is able to enhance this saliency of the eye region at the early stage of face inspection. According to Guo (2007), the eye region, in particular in expressive faces, is often the first destination of the saccade and attracts a disproportional share of fixations compared with other core facial features. Our results are in line with these findings, showing the most fixations and the longest fixation times to the eyes, in every emotion category and over all emotions together.

A first human fMRI study by Kirsch and colleagues (2005) indicated that OT reduces amygdala responses to threatening non-social scenes and to angry and fearful faces. According to the authors, these effects of OT might reflect a selective suppression to signals of threat. However, a recent imaging study by Domes et al. (2007) investigating the role of the amygdala in mediating the socio-affective effects of oxytocin in an fMRI study showed that OT attenuated amygdala responses to emotionally laden social stimuli regardless of the valence of the face (positive and negative). These results would speak more for a suppression of amygdala activity in terms of oxytocin reducing arousal to affective social stimuli in general. A reduced amygdala activity could be one possible explanation for our findings regarding the improved emotion recognition abilities and the enhancement of eye gaze toward the eye region. Positive as well as negative facial stimuli activate the amygdala, and the administration of OT might have reduced this activity and thereby facilitated participants to have more eye contact. However, the specificity of oxytocin effects has to be more thoroughly investigated with various stimuli (ambiguous and uncertain vs. unambiguous and familiar).

5.4 Conclusions, Clinical Relevance and Outlook

The presented findings have clinical implications for several reasons: About 25% of all patients asking for psychotherapeutic treatment are considered to be alexithymic (Grabe et al., 2008) and furthermore, alexithymia has been assumed to be negatively associated with therapeutic outcome in many psychological disorders. On the other hand, it is still unclear to what extent alexithymia might be modified by psychotherapeutic interventions. Since patients suffering from alexithymia are often socially avoidant, cold, and less emotionally attached to others, this could reduce adherence to psychotherapy despite severe mental distress (Grabe et al., 2001). Therefore, the most pressing need for the future cognitive-behavioral therapy of described psychological disorders associated with alexithymia (e.g. depression, anxiety disorder, eating disorders, obsessive-compulsive disorders and somatoform disorders) is to investigate the efficiency of interdisciplinary therapy approaches. One currently highly promising approach seems to be to increase the availability of OT in the central nervous system by exogenous administration of OT.

In general, OT treatment is thought to enhance the readiness to socially interact and to increase recognition of emotions from facial expressions. This effect could be used in combined biopsychological treatments of psychiatric disorders involving social deficit such as autism, borderline personality disorder and social phobia.

Autism is a developmental disorder defined by abnormalities in speech and communication, impaired social functioning, and repetitive behaviors and restricted interests (APA, 1994). A number of researchers have suggested that OT may be implicated in the etiology of autism since deficits in social interaction and affiliation are core features of autism and these neuropeptides are involved in the regulation of affiliative behaviors (Bartz & Hollander, 2006; Hollander et al., 2007; Hollander et al., 2003). Results from nonhuman animal studies suggested in addition that OT influences behaviors that are abnormal in autism,

including cognitive and communicative behaviors as well as motor stereotypes (T. R. Insel, O'Brian, & Leckman, 1999). Since impaired face processing is one of the most commonly cited aspects of the social cognition deficits observed among persons with autism, our findings indicating that OT enhances eye gaze toward the eye region suggest that OT may have therapeutic benefits for the treatment of autism spectrum disorders, especially with respect to addressing repetitive behaviors and deficits in social functioning.

Presumably, oxytocin may be implicated in some personality disorders marked by disrupted social interactions and attachments. Borderline personality disorder (BPD) is characterized by affective instability, anger, impulsivity, and identity confusion (APA, 1994; Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004). Regarding the pathogenesis of BPD, the interpersonal relationships which are marked by mental and / or physical abuse, as well as neglect are believed to play a central role. Given the link between OT and trust and prosocial behavior, OT may have beneficial effects to target the disordered attachment and mistrust associated with BPD. Indeed, a number of researchers speculate that early stress has important implications for adult affiliative behaviors and, furthermore, that OT might be involved in this process.

OT may also have therapeutic benefits for other anxiety disorders in which social withdrawal is a prominent feature, such as social phobia. Social phobia (SP) is an anxiety disorder marked by persistent and excessive fear of social interaction and/or performance situations (DSM-IV) (APA, 1994). Individuals with social phobia are worried that they will be negatively evaluated by others and are plagued by fears that they will do or say something to humiliate or embarrass themselves. SP is the most common anxiety disorder but despite this fact, very little is known about its etiology or about effective treatment. OT is an ideal candidate for the involvement in and the potential treatment of SP (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Moreover, an eye-tracking study by Horley and colleagues (2003) showed that while the visual

scanpath of healthy subjects tends to follow a triangular pattern, in which fixations are directed mainly to the salient features that define facial expressions, the mouth and the eyes, social phobics showed a pattern of hyperscanning for face stimuli but also a marked avoidance of the eyes when making foveal fixations. In a second study, Horley et al. (2004) examined the scanpaths of social phobics including threat-related facial expressions (anger) in comparison to less explicitly threatening negative (sad), positive (happy) and neutral control faces. While control subjects showed an increasing fixation to eyes across happy, neutral, sad and angry faces, social phobics showed an increasing avoidance of eyes across these emotions. With regard to attention to the eyes in particular, social phobics displayed the hypothesized avoidance of the eyes and this was most prominent for the angry faces.

Our findings indicate beneficial effects of oxytocin in social phobics and stimulate the potential of novel therapeutic approaches aimed at reducing social anxiety and increasing social abilities including eye gaze towards the eye region, thereby enhancing emotion recognition. To date, cognitive-behavioral therapy is known as the most effective therapy for social anxiety disorders but its outcome is still not satisfactory. Future steps should therefore evaluate the efficiency of a combination of cognitive-behavioral therapy with an administration of exogenously administered oxytocin.

6. Bibliography

Abdi, Z., & Sharma, T. (2004). Social cognition and its neural correlates in schizophrenia and autism. *CNS Spectrums, 9*, 335-343.

Adolphs, R. (2002a). Recognizing emotion from facial expressions: psychological and neurological mechanisms. *Behavioral and Cognitive Neuroscience Reviews, 1*(1), 21-61.

Adolphs, R. (2002b). Neural systems for recognizing emotion. *Current Opinion in Neurobiology, 12*, 169-177.

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., & Damasio, A. R. (2000). A role for somatosensory cortices in the visual recognition of emotion as revealed by 3-D lesion mapping. *Journal of Neuroscience, 20*, 2683-2690.

Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P., & Damasio, A. R. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature, 433*(6), 68-72.

Adolphs, R., Sears, L., & Piven, J. (2000). Abnormal processing of social information from faces in autism. *Journal of Cognitive Neuroscience, 13*(2), 232-240.

Adolphs, R., Tranel, D., & Damasio, A. R. (1998). The human amygdala in social judgment. *Nature, 393*(4), 470-472.

Adolphs, R., Tranel, D., & Damasio, A. R. (2003). Dissociable neural systems for recognizing emotions. *Brain and Cognition, 52*, 61-69.

Adolphs, R., Tranel, D., Damasio, A. R., & Damasio, H. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372*, 669-672.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1995). Fear and the human amygdala. *Journal of Neuroscience, 15*(5879-5892).

Aigner, M., Sachs, G., Bruckmuller, E., Winklbaur, B., Zitterl, W., Kryspin-Exner, I., et al. (2007). Cognitive and emotion recognition deficits in obsessive compulsive disorder. *Psychiatry Res, 149*, 121-128.

Altemus, M., Deuster, P. A., Galliven, E., Carter, C. S., & Gold, P. W. (1995). Suppression of hypothalamic-pituitary-adrenal axis responses to stress in lactating woman. *J Clin Endocrinol Metab, 80*(10), 2954-2959.

Altemus, M., Jacobson, K. R., Debellis, M., Kling, M., Pigott, T., Murphy, D. L., et al. (1999). Normal CSF oxytocin and NPY levels in OCD. *Biol Psychiatry, 45*(7), 931-933.

Ambadar, Z., Schooler, J. W., & Cohn, J. F. (2005). Deciphering the enigmatic face: the importance of facial dynamics in interpreting subtle facial expressions. *Psychological Science, 16*, 403-410.

Amstadter, A. (2008). Emotion regulation and anxiety disorders. *Anxiety disorders, 22*, 211-221.

Anderson, A. K., & Phelps, E. A. (2000). Expression without recognition: contributions of the human amygdala to emotional communication. *Psychological Science, 11*, 106-111.

Ansseau, M., Legros, J. J., Mormont, C., Cerfontaine, J. L., Papart, P., Geenen, V., et al. (1987). Intranasal oxytocin in obsessive-compulsive disorder. *Psychoneuroendocrinology, 12*(3), 231-236.

APA. (1994). *DSM-IV-R. Diagnostic and statistical manual of mental disorders* (4th ed. ed.). Washington, DC: American Psychiatric Association.

Bach, M., & Bach, D. (1995). Predictive value of alexithymia: a prospective study in somatizing patients. *Psychotherapy and Psychosomatics, 64*, 43-48.

Bagby, R. M., Parker, J. D. A., & Taylor, G. J. (1994). The twenty-item Toronto Alexithymia scale. I. Item selection and cross validation of the factor structure. *Journal of Psychosomatic Research, 38*, 23-32.

Bagby, R. M., Taylor, G. J., & Parker, J. D. A. (1994). The twenty-item Toronto Alexithymia Scale. II. Convergent, discriminant and concurrent validity. *Journal of Psychosomatic Research, 38*, 33-40.

Bale, T. L., Davis, A. M., Auger, A. P., Dorsa, D. M., & McCarthy, M. M. (2001). CNS region-specific oxytocin receptor expression: importance in regulation of anxiety and sex behavior. *The Journal of Neuroscience, 21*(7), 2546-2552.

Bankier, B., Aigner, M., & Bach, M. (2001). Alexithymia in DSM-IV disorder: comparative evaluation of somatoform disorder, panic disorder, obsessive-compulsive disorder, and depression. *Psychosomatics, 42*, 235-240.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes Task" Test, revised version: A study with normal adults, and adults with Asperger Syndrome or high-functioning Autism. *Journal of Child Psychology and Psychiatry, 42*(241-251).

Baron-Cohen, S., Wheelwright, S., & Jolliffe, T. (1997). Is there a language of the eyes? Evidence from normal adults, and adults with autism or Asperger Syndrome. *Visual Cognition, 4*(311-331).

Barrett, L. F., & Russel, J. A. (1999). Structure of current affect. *Current Directions in Psychological Science, 8*, 28-58.

Bartz, J. A., & Hollander, E. (2006). The neuroscience of affiliation: forging links between basic and clinical research on neuropeptides and social behavior. *Hormones and behavior*, 1-11.

Bassili, J. (1979). Emotion recognition: the role of facial movement and the relative importance of upper and lower areas of the face. *Journal of Personality and Social Psychology, 37*, 2049-2058.

Batki, A., Baron-Cohen, S., Wheelwright, S., Connellan, J., & Ahluwalia, J. (2000). Is there an innate gaze module? Evidence from human neonates. *Infant Behaviour & Development, 23*(223-229).

Beck, A. T., & Clark, D. A. (1997). An information processing model of social anxiety: automatic and strategic processes. *Behaviour Research and Therapy, 35*, 49-58.

Behrmann, M., Thomas, C., & K., H. (2006). Seeing it differently: visual processing in autism. *Trends in Cognitive Science, 10*(6), 258-264.

Belzung, C., & Philippot, P. (2007). Anxiety from philogenetic perspective: Is there a qualitative difference between human and animal anxiety? *Neural Plasticity*, 1-17.

Berntson, G. G., Bechara, A., Damasio, H., Tranel, D., & Cacioppo, J. T. (2007). Amygdala contribution to selective dimensions of emotion. *Soc Cogn Affect Neurosci, 2*, 123-129.

Berthoz, S., Artiges, M. D., Van de Moortele, P. F., Poline, J.-B., Rouquette, S., Consoli, S. M., et al. (2002). Effect of impaired recognition and expression of emotions on frontocingulate cortices: an fMRI study of men with alexithymia. *American Journal of Psychiatry, 159*, 961-967.

Biele, C., & Grabowska, A. (2006). Sex differences in perception of emotion intensity in dynamic and static facial expressions. *Exp Brain Res, 171*, 1-6.

Blanks, A. M., Shmygol, A., & Thornton, S. (2007). Regulation of oxytocin receptors and oxytocin receptor signaling. *Semin Reprod Med, 25*, 52-59.

Blanks, A. M., & Thornton, S. (2003). The role of oxytocin in parturition. *BJOG, 110*, 46-51.

Bleuler, E. (1950). *Dementia Praecox or the Group of Schizophrenias*. New York: International University Press.

Bolte, S., & Poustka, F. (2003). The recognition of facial affect in autistic and schizophrenic subjects and their first-degree relatives. *Psychological Medicine, 33*(5), 907-915.

Bonnano, G. A., Kelner, D., Noll, J., Putman, F. W., Tricket, P. K., & LeJeune, J. (2002). When the face reveals what words do not: Facial expressions of emotion, smiling, and the willingness to disclose childhood sexual abuse. *Journal of Personality and Social Psychology, 83*(1), 94-110.

Bonnano, G. A., & Keltner, D. (1997). Facial expression of emotion and the course of conjugal bereavement

Journal of Abnormal Psychology, 106(126-137).

Bonnano, G. A., & Keltner, D. (2004). The coherence of emotion systems: Comparing "on-line" measures of appraisal and facial expressions, and self-report. *Cognition and Emotion, 18*(3), 431-444.

Born, J., Lange, T., Kern, W., McGregor, G. P., Bickel, U., & Fehm, H. L. (2002). Sniffing neuropeptides: a transnasal approach to the human brain. *Nature Neuroscience, 5*(6), 514-516.

Broks, P., Young, A. W., Maratos, E. J., Coffey, P. J., Calder, A. J., Isaac, C., et al. (1998). Face processing impairments after encephalitis: amygdala damage and recognition of fear. *Neuropsychologia, 36*, 59-70.

Bruce, V., & Young, A. (1986). Understanding face recognition. *British Journal of Psychology, 77*, 305-327.

Bushnell, I. W. R., Sai, F., & Mullin, J. T. (1989). Neonatal recognition of the mother's face. *British Journal of Developmental Psychology, 7*, 3-15.

Bydlowski, S., Corcos, M., Jeammet, P., Paterniti, S., Berthoz, S., Laurier, C., et al. (2005). Emotion-processing deficits in eating disorders. *Int J Eat Disord, 37*, 321-329.

Calder, A. J., Keane, J., Manes, F., Antoun, N., & young, A. W. (2000). Impaired recognition and experience of disgust following brain injury. *Nature Neuroscience, 3*, 1077-1078.

Calder, A. J., & Young, A. W. (2005). Understanding the recognition of facial identity and facial expression. *Nature Reviews, 6*, 641-651.

Campbell, A. (2008). Attachment, aggression and affilitation: the role of oxytocin in female social behavior. *Biological Psychology, 77*, 1-10.

Caramazza, A., & Hillis, A. E. (1991). Lexical organization of nouns and verbs in the brain. *Nature, 349*, 788-790.

Caron, R. F., Caron, A. J., & Myers, R. S. (1985). Do infants see emotional expressions in static faces? *Child Development, 56*, 1552-1560.

Carter, C. S. (2003). Developmental consequences of oxytocin. *Physiology & Behavior*, 383-397.

Carter, C. S., & Altemus, M. (1997). Integrative functions of lactational hormones in social behavior and stress management. *Ann N.Y. Acad. Sci., 807*, 164-174.

Celani, G., Battacchi, M. W., & Arcidiacono, L. (1999). The understanding of the emotional meaning of facial expressions in people with autism. *Journal of Autism and Developmental Disorders, 29*(1), 57-66.

Chevalier-Skolnikoff, S. (1973). Facial expression of emotion in nonhuman primates. In P. Ekman (Ed.), *Darwin and facial expression* (pp. 11-89). New York: Academic Press.

Clore, G. C. (1994). Why emotions are felt. In P. Ekman & J. R. Davidson (Eds.), *The Nature of Emotions* (pp. 103-111.). New York: Oxford University Press.

Clore, G. L., & Huntsinger, J. R. (2007). How emotions inform judgment and regulate thought. *Trends in Cognitive Science, 11*(9), 393-399.

Clore, G. L., & Ortony, A. (2008). Appraisal Theories. How Cognition Shapes Affect into Emotion. In M. Lewis, J. M. Haviland-Jones & L. Feldman Barret (Eds.), *Handbook of Emotions* (pp. 628-644). New York: The Guilford Press.

Cooney, R. E., Atlas, L. Y., Joormann, J., Eugene, F., & Gotlib, I. H. (2006). Amygdala activation in the processing of neutral faces in social anxiety disorder: is neutral really neutral? *Psychiatry Res, 148*(1), 55-59.

Critchley, H. D., Daly, E. M., Bullmore, E. T., Williams, S. C. R., Van Amelsvoort, T., & Robertson, D. M. (2000). The functional neuroanatomy of social behaviour: Changes in cerebral blood flow when people with autistic disorder process faces. *Brain, 123*, 2203-2212.

Dalton, K. M., Nacewicz, B. M., Alexander, A. L., & Davidson, R. J. (2007). Gaze-fixation, brain activation and amygdala volume in unaffected siblings of individuals with autism. *Biol Psychiatry, 61*, 512-520.

Damasio, A. R. (1999). *The feeling of what happens: Body and emotion in the making of consciousness.* New York: Harcourt Brace.

Dannlowski, U., Kersting, A., Donges, U. S., Lalee-Mentzel, J., Arolt, V., & Suslow, T. (2006). Masked facial affect priming is associated with therapy response in clinical depression. *Eur Arch Psychitry Clin Neurosci, 256*, 215-221.

Darwin, C. (1972). *The expression of emotions in man and animals*. Chicago: University of Chicago Press.

Davidson, J. R. (2003). Parsing the subcomponents of emotion and disorders of emotion: Perspectives from affective neuroscience. In J. R. Davidson, K. R. Scherer & H. H. Goldsmith (Eds.), *Handbook of affective science* (pp. 8-24). New York: Oxford University Press.

De Berardis, D., Campanella, L., Gambi, F., Sepede, G., Salini, G., Carano, A., et al. (2005). Insight and alexithymia in adult outpatients with obsessive-compulsive disorder. *Eur Arch Psychitry Clin Neurosci, 255*, 350-358.

de Jong, P. J., & Martens, S. (2007). Detection of emotional expressions in rapidly changing facial displays in high- and low-socially anxious women. *Behaviour Research and Therapy, 45*, 1285-1294.

Ditzen, B., Neumann, I. D., Bodenmann, G., von Dawans, B., Turner, R. A., Ehlert, U., et al. (2007). Effects of different kinds of couple interaction on cortisol and heart rate responses to stress in woman. *Psychoneuroendocrinology, 32*, 565-574.

Domes, G., Heinrichs, M., Glascher, J., Buchel, C., Braus, D. F., & Herpertz, S. C. (2007a). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biol Psychiatry, 62*(10), 1187-1190.

Domes, G., Heinrichs, M., Michel, A., Berger, C., & Herpertz, S. C. (2007b). Oxytocin improves "mind-reading" in humans. *Biol Psychiatry, 61*(6), 731-733.

Edwards, J., Jackson, H. J., & Pattison, P. E. (2002). Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. *Clinical Psychology Review, 22*, 789-832.

Eimer, M., & Holmes, A. (2007). Event-related brain potential correlates of emotional face processing. *Neuropsychologia, 45*, 15-31.

Ekman, P. (1992). An argument for basic emotions. *Cognition and Emotion, 6*, 169-200.

Ekman, P., Davidson, J. R., & Friesen, W. V. (1990). The Duchenne smile: Emotional expression and brain physiology: II. *Journal of Personality and Social Psychology, 58*(2), 342-353.

Ekman, P., & Davidson, R. J. (1994). *The nature of emotions. Fundamental questions*. New York: Oxford University Press.

Ekman, P., & Friesen, W. V. (1982). Felt, false and miserable smiles. *Journal of Nonverbal Behavior, 6*(4), 238-258.

Ekman, P., Matsumoto, D., & Friesen, W. V. (1997). Facial expression in affective disorders. In P. Ekman & E. L. Rosenberg (Eds.), *What the face reveals: Basic and applied studies of spontaneous expression using the Facial Acting Coding System (FACS)* (pp. 331-341). New York: The Guilford Press.

Emery, N. J. (2000). The eyes have it: the neuroethology, function and evolution of social gaze. *Neuroscience and Biobehavioral Reviews*, 581-604.

Epperson, C. N., McDougle, C. J., & Price, L. H. (1996). Intranasal oxytocin in obsessive-compulsive disorder. *Biol Psychiatry, 40*(6), 547-549.

Evangeli, M., & Broks, P. (2000). Face processing in schizophrenia: Parallels with the effects of amygdala damage. *Cognit Neuropsychiatry, 5*, 81-104.

Farah, M. J., Wilson, K. D., Drain, M., & Tanaka, J. (1998). What is special about face perception? *Psychological Review, 105*, 482-498.

Fehm, H. L., Perras, B., Smolnik, R., Kern, W., & Born, J. (2000). Manipulating neuropeptidergic pathways in humans: a novel approach to neuropharmacology. *European Journal of Pharmacology, 405*, 43-54.

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral cortex, 1*, 1-47.

Ferguson, J. N., Aldag, M. J., Insel, T. R., & Young, L. J. (2001). Oxytocin in the medial amygdala is essential for social recognition in the mouse. *The Journal of Neuroscience, 15*, 8278-8285.

Foa, E. B., Gilboa-Schechtman, E., Amir, N., & Freshman, M. (2000). Memory bias in generalized social phobia remembering negative emotional expressions. *Journal of Anxiety Disorders, 14*(5), 501-519.

Frederickson, B. L., & Cohn, M. A. (2008). Positive emotions. In M. Lewis, J. M. Haviland-Jones & L. Feldman Barret (Eds.), *Handbook of Emotions* (pp. 777-796). New York: The Guilford Press.

Freire, A., Lee, K., & Symons, L. A. (2000). The face-inversion effect as a deficit in the encoding of configural information: Direct evidence. *Perception, 29*, 159-170.

Frijda, N. H. (1994). varieties of Affect: Emotions and Episodes, Moods, and Sentiments. In P. Ekman & J. R. Davidson (Eds.), *The Nature of Emotions* (pp. 59-67). New York: Oxford University Press.

Frijda, N. H. (2008). The Psychologists' Point of View. In M. Lewis, J. M. Haviland-Jones & L. Feldman Barret (Eds.), *Handbook of emotions* (3rd ed ed., pp. 68-87). New York: The Guilford Press.

Frith, U. (2003). *Autism. Explaining the enigma* (2nd ed. ed.). Oxford: Blackwell.

Furl, N., van Rijsbergen, N. J., Treves, A., Friston, K. J., & Dolan, R. J. (2007). Experience-dependent coding of facial expression in superior temporal sulcus. *PNAS, 104*(33), 13485-13489.

Gaebel, W., & Wolwer, W. (2004). Facial expressivity in the course of schizophrenia and depression. *Eur Arch Psychitry Clin Neurosci, 254*, 335-342.

Gainotti, G., Silveri, M. C., Daniele, A., & Giustolisi, L. (1995). Neuroanatomical correlates of category-specific semantic disorders: A critical survey. *Memory, 3*, 247-264.

Geen, T. (1992). Facial expressions in socially isolated nonhuman primates: Open and closed programs for expressive behavior. *Journal of Research in Personality, 81*(2), 247-262.

Gil, F. P., Ridout, N., Kessler, H., Neuffer, M., Schoechlin, C., Traue, H. C., et al. (2007). Facial emotion recognition and alexithymia in adults with somatoform disorders. *Depression and Anxiety, 0*, 1-9.

Gimpl, G., & Fahrenholz, F. (2001). The oxytocin receptor system: structure function and regulation. *Physiological Reviews, 81*(2), 629-683.

Glaescher, J., Tuescher, O., Weiller, C., & Buechel, C. (2004). Elevated responses to constant facial emotions in different faces in the human amygdala: an fMRI study of facial identity and expression. *BMC Neuroscience, 5*(45), 1-13.

Grabe, H. J., Frommer, J., Ankerhold, A., Ulrich, C., Gröger, R., Franke, G. H., et al. (2008). Alexithymia and Outcome in Psychotherapy. *Psychotherapy and Psychosomatics, 77*(3), 189-194.

Green, L., Fein, D., Modahl, C., Feinstein, C., Waterhouse, L., & Morris, M. (2001). Oxytocin and autistic disorder: alterations in peptide forms. *Biol Psychiatry, 50*(8), 609-613.

Grelotti, D. J., Gauthier, I., & Schultz, R. T. (2002). Social interest and the development of cortical face specialization: What autism teaches aus about face processing. *Developmental Psychobiology, 40*, 213-225.

Grimshaw, G. M., Bulman-Fleming, M. B., & Ngo, C. (2004). A signal detection analysis of sex differences in the perception of emotional faces. *Brain and Cognition, 54*, 248-250.

Gross, J. J. (2008). Emotion Regulation. In M. Lewis, J. M. Haviland-Jones & L. Feldman Barret (Eds.), *Handbook of Emotions.* (Third Edition ed., pp. 497-512.). New York: The Guilford Press

Gross, J. J., & Levenson, R. W. (1993). Emotinal supression: Physiology, self-report, and expressive behavior. *Journal of Personality and Social Psychology, 64*(6), 970-986.

Grossman, J. B., Klin, A., Carter, A. S., & Volkmar, F. (2000). Verbal bias in recognition of facial emotions in children with Asperger syndrome. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 41*, 369-379.

Guastella, A. J., Mitchell, P. B., & Dadds, M. R. (2007). Oxytocin increases gaze to the eye region of human faces. *Biol Psychiatry*, in press.

Guo, K. (2007). Initial fixation placement in the face images is driven by top-down guidance. *Exp Brain Res, 181*, 673-677.

Guo, K., Mahmoodi, S., Robertson, D. G., & Young, M. P. (2006). Longer fixation duration while viewing face images. *Exp Brain Res, 171*, 91-98.

Guo, K., Robertson, R. G., Mahmoodi, S., Tadmor, Y., & Young, M. P. (2003). How do monkeys view faces?--A study of eye movements. *Exp Brain Res, 150*(3), 363-374.

Hadjikhani, N., Joseph, R. M., Snyder, J., & Tager-Flusberg, H. (2007). Abnormal activation of social brain during face perception in autism. *Human Brain Mapping, 28*, 441-449.

Hall, J. L., Harris, J. M., Sprengelmeyer, R., Sprengelmeyer, A., Young, A. W., Santos, I. M., et al. (2004). Social cognition and face processing in schizophrenia. *British Journal of Psychiatry, 185*(169-170).

Happe, F. (1999). Autism: Cognitive deficit or cognitive style. *Trends in Cognitive Science, 3*, 216-222.

Harris, C. R., & Alvarardo, N. (2005). Facial expressions, smile types, and self-report during humous, tickle and pain. *Cognition and Emotion, 19*(5), 655-669.

Haxby, J. V., Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., & Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science, 293*, 2425-2429.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Science, 4*, 223-233.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2002). Human neural systems for face recognition and social communication. *Biol Psychiatry, 51*, 59-67.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., & Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol Psychiatry, 54*(12), 1389-1398.

Heinrichs, M., & Domes, G. (2008). Neuropeptides and social behavior: effects of oxytocin and vasopressin in humans. *Progress in Brain Research, 170*, 337-350.

Heinrichs, M., Meinlschmidt, G., Neumann, I., Wagner, S., Kirschbaum, C., Ehlert, U., et al. (2001). Effects of suckling on hypothalamic-pituitary-adrenal axis responses to psychosocial stress in postpartum lactating women. *J Clin Endocrinol Metab, 86*(10), 4798-4804.

Heisz, J., & Shore, D. I. (2008). More efficient scanning for familiar faces. *Journal of Vision, 8*(1), 1-10.

Hermans, E. J., & van Honk, J. (2006). Towards a framework of deficit emotion processing in social phobia. *Cognitive Neuropsychiatry, 11*(3), 307-331.

Hirsch, C. R., & Clark, D. M. (2004). Information-processing bias in social phobia. *Clinical Psychology Review, 24*, 799-825.

Hoffman, E. A., & Haxby, J. V. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nature Neuroscience, 3*, 80-84.

Hollander, E., Bartz, J. A., Chaplin, W., Phillips, A., Sumner, J., Soorya, L., et al. (2007). Oxytocin increases retention of social cognition in autism. *Biol Psychiatry, 61*, 498-503.

Hollander, E., Novotny, S., Hanratty, M., Yaffe, R., DeCaria, C. M., Aronowitz, B. R., et al. (2003). Oxytocin infusion reduces repetitive behaviors in adults with autistic and asperger's disorders. *Neuropharmacology and Neurotoxicology, 28*, 193-198.

Holmes, A., Richards, A., & Green, S. (2006). Anxiety and sensitivity to eye gaze in emotional faces. *Brain and Cognition, 60*, 282-294.

Honkalimpi, K., Hintikka, J., Saarinen, P., Lehtonen, J., & Viinamaki, H. (2000). Is alexithymia a permanent feature in depressed patients? Results from a 6-month follow-up study

Psychotherapy and Psychosomatics, 69, 303-308.

Hood, B. M., Willen, J. D., & Driver, J. (1998). Adult's eyes trigger shifts of visual attention in human infants. *Psychological Science, 9*, 131-134.

Horley, K., Williams, L. M., Gonsalvez, C., & Gordon, E. (2003). Social phobics do not see eye to eye: a visual scanpath study of emotional expression processing. *J Anxiety Disord, 17*(1), 33-44.

Horley, K., Williams, L. M., Gonsalvez, C., & Gordon, E. (2004). Face to face: visual scanpath evidence for abnormal processing of facial expressions in social phobia. *Psychiatry Res, 127*(1-2), 43-53.

Hornak, J., Rolls, E. T., & Wade, D. (1996). Face and voice identification in patients with emotional and behavioral changes following ventral frontal lobe damage. *Neuropsychologia, 34*, 247-261.

Howard, M. A., Cowell, P. E., Boucher, J., Broks, P., Mayes, A. R., & Farrant, A. (2000). Convergent neuroanatomical and behavioral evidence of an amgygdala hypothesis of autism. *Neuroreport, 11*(13), 2931-2935.

Huber, D., Veinante, P., & Stoop, R. (2005). Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. *Science, 308*(8), 245-248.

Infrarsca, R. (1997). Alexithymia, neurovegetative arousal and alexithymia: an experimental study. *Psychotherapy and Psychosomatics, 66*, 276-280.

Insel, T. R., O'Brian, D. J., & Leckman, J. F. (1999). Oxytocin, Vasopressin, and Autism: Is there a connection. *Biol Psychiatry, 45*, 145-157.

Insel, T. T., & Young, L. J. (2000). Neuropeptides and the evolution of social behavior. *Current Opinion in Neurobiology, 10*, 784-789.

Ivell, R., Kimura, T., Muller, D., Augustin, K., Abend, N., Bathgate, R., et al. (2001). The structure and regulation of the oxytocin receptor. *Exp Physiol, 86*(2), 289-296.

Izard, C. E. (1977). *Human emotions*. New York: Plenum Press.

Izard, C. E., Fine, S., Schultz, D., Mostow, A., Ackerman, B., & Youngstrom, E. (2001). Emotion knowledge as a predictor of social behavior and academic competence in children at risk. *Psychological Science, 12*, 18-23.

Jacob, S., Brune, C. W., Carter, C. S., Leventhal, B. L., Lord, C., & Cook, E. H. (2007). Association of the oxytocin receptor gene (oxtr) in caucasian children and adolescents with autism. *Neuroscience Letters, 417*, 6-9.

James, W. (1984). What is an emotion? *Mind, 9*, 188-205.

Jemel, B., Mottron, L., & Dawson, M. (2006). Impaired face processing in autism: fact or artifact. *Journal of Autism and Developmental Disorders, 36*(1), 91-106.

Jessimer, M., & Markham, R. (1997). Alexithymia: a right hemisphere dysfunction specific to recognition of certain facial expressions? *Brain and Cognition, 34*, 246-258.

Johnson, M. H. (2005). Subcortical face processing. *Nature Reviews, 6*, 766-774.

Joseph, R. M., & Tanaka, J. (2003). Holistic and part-based face recognition in children with autism. *Journal of Child Psychology and Psychiatry, 44*, 529-542.

Kanwisher, N. (2000). Domain specificity in face perception. *Nature Neuroscience, 3*, 759-763.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience, 17*, 4302-4311.

Kawasaki, H., Adolphs, R., Kaufman, o., Damasio, H., Damasio, A. R., Granner, M., et al. (2001). Single-unit responses to emotional visual stimuli recorded in human ventral prefrontal cortex. *Nature Neuroscience, 4*, 15-16.

Kesler-West, M. L., Andersen, A. H., Smith, C. D., Avison, M. J., Davis, C. E., Kryscio, R. J., et al. (2001). Neural substrates of facial emotion processing using fMRI. *Brain Research: Cognitive Brain Research, 11*, 213-226.

Kilts, C. D., Egan, G., Gideon, D. A., Ely, T. D., & Hoffman, J. M. (2003). Dissociable neural pathways are involved in the recognition of emotion in static and dynamic facial expressions. *NeuroImage, 18*, 156-168.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., et al. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *J Neurosci, 25*(49), 11489-11493.

Kiss, A., & Mikkelsen, J. D. (2005). Oxytocin - Anatomy and functional assignments: A minireview. *Endocrine Regulations, 39*, 97-105.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry, 59*, 809-816.

Kohler, C. G., & Martin, E. A. (2006). Emotional processing in schizophrenia. *Cognitive Neuropsychiatry, 11*(3), 250-271.

Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature, 435*(7042), 673-676.

Kringelbach, M. L., & Rolls, E. T. (2003). Neural correlates of rapid reversal learning in a simple model of human social interaction. *NeuroImage, 20*, 1371-1383.

Kugel, H., Eichmann, M., Dannlowski, U., Ohrmann, P., Bauer, J., Arolt, V., et al. (2008). Alexithymic features and automatic amygdala reactivity to facial emotion. *Neuroscience Letters, 435*(1), 40-44.

Landgraf, R., & Neumann, I. D. (2004). Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. *Frontiers in Neuroendocrinology, 25*, 150-176.

Lane, R., Sechrest, L., Reidel, R. G., Weldon, V., Kasniak, A. W., & Schwartz, G. E. (1996). Impaired verbal and nonverbal emotion recognition in alexithymia. *Psychosomatic Medicine, 58*, 203-210.

Lane, R., Sechrest, L., Riedel, R., Shapiro, D. E., & Kasniak, A. W. (2000). Pervasive emotion recognition deficit common to alexithymia and the repressive coping style. *Psychosomatic Medicine, 62*, 492-501.

Langton, S. R. H., Watt, R., & Bruce, V. (2000). Do the eyes have it? Cues to the direction of social attention. *Trends in Cognitive Science, 4*(50-59).

Larsen, R. J., & Diener, E. (1992). Promises and problems with the circumplex model of emotion. *Review of Personality and Social Psychology, 13*(25-59).

Lazarus, R. S. (1991). *Emotion and adaptation*. New York: Oxford University Press.

Le, H. N., Ramos, M. A., & Munoz, R. F. (2007). The relationship between alexithymia and perinatal depressive symptomatology. *Journal of Psychosomatic Research, 62*, 215-222.

Leckman, J. F., Goodman, W. K., North, W. G., Chappell, P. B., Price, L. H., Pauls, D. L., et al. (1994b). Elevated cerebrospinal fluid levels of oxytocin in obsessive-compulsive disorder. Comparison with Tourette's syndrome and healthy controls. *Arch Gen Psychiatry, 51*(10), 782-792.

Leder, H., & Bruce, V. (2000). When inverted faces are recognized: The role of configural information in face recognition. *Quarterly Journal of Experimental Psychology, 53*(A), 513-536.

Leppanen, J. M., Milders, M., Bell, J. S., Terriere, E., & Hietanen, J. K. (2004). Depression biases the recognition of emotionally neutral faces. *Psychiatry Res, 128*, 123-133.

Lerer, E., Levi, S., Salomon, S., Darvasi, A., Yirmiya, N., & Ebstein, R. P. (2007). Association between the oxytocin receptor (oxtr) gene and autism: relationship to Vineland Adaptive Behavior Scales and cognition. *Mol. Psychiatry*.

Lerner, J. S., Gonzalez, R. M., Dahl, R. E., Hariri, A. R., & Taylor, S. E. (2005). Facial expressions of emotion reveal neuroendocrine and cardiovascular stress responses. *Biol Psychiatry, 58*, 743-750.

Levenson, R. W., & Ekman, P. (2002). Difficulty does not account for emotion-specific heart rate changes in the directed facial action task. *Psychophysiology, 39*(3), 397-405.

Leweke, F., Stark, W., Milch, W., Kurth, R., Schienle, P., Kirsch, P., et al. (2004). Patterns of neuronal activity related to emotional stimulation in alexithymia. *Psychother. Psych. Med. Psychol., 54*, 437-444.

Lieb, K., Zanarini, M. C., Schmahl, C., Linehan, M. M., & Bohus, M. (2004). Borderline Personality Disorder. *Lancet, 364*(9432), 453-461.

Light, K. C., Smith, T. E., Jones, J. M., Brownley, K. A., Hofheimer, J. A., & Amico, J. A. (2000). Oxytocin responsivity in mothers of infants: a preliminary study of relationships with blood pressure during laboratory stress and normal ambulatory activity. *Health Psychology, 19*(6), 560-567.

Lim, M. M., & Young, L. J. (2006). Neuropeptidergic regulation of affiliative behavior and social bonding in animals. *Hormones and behavior, 50*, 506-517.

Luminet, O., Bagby, R. M., & Taylor, G. J. (2001). An evaluation of the absolute and relative stability of alexithymia in patients with major depression. *Psychotherapy and Psychosomatics, 70*, 254-260.

Marchesi, C., Bertoni, A. A., & Maggini, C. (2008). Is alexithymia a personality trait increasing the risk of depression? A prospective study evaluating alexithymia before, during and after a depressive episode. *Psychological Medicine*, 1-6.

Marcus, D. J., & Nelson, C. A. (2001). Neural basis and development of face recognition in autism. *CNS Spectrums, 6*, 36-59.

Matsumoto, D., Keltner, D., Shiota, M. N., O'Sullivan, M., & Frank, M. (2008). Facial Expressions of Emotions. In M. Lewis, J. M. Haviland-Jones & L. Feldman Barret (Eds.), *Handbook of Emotions* (3rd ed ed., pp. 211-234). New York: The Guilford Press.

Matsumoto, D., & Kupperbusch, C. (2001). Idiocentric and allocentric differences in emotional expression and experience. *Asian Journal of Social Psychology, 4*, 113-131.

Matsumoto, D., & Willingham, B. (2006). The thrill of victory and the agony of defeat: Spontaneous expressions of medal winners at the 2004 Athens Olympic Games. *Journal of Personality and Social Psychology, 91*(3), 568-581.

Mauss, I. B., Levenson, R. W., McCarter, L., Wilhelm, F. H., & Gross, J. J. (2005). The tie that binds?: Coherence among emotion experience, behavior, and physiology. *Emotion, 5*, 175-190.

McCauley, J., Li, C., Jiang, L., Olson, J. M., Crockett, G., Gainer, K., et al. (2005). Genome-wide and ordered-subset linkage analyses provide support for autism loci on 17q and 19p with evidence of phenotypic and interlocus genetic correlates. *BMC Medical Genetics, 6*, 1-11.

McClure, E. B. (2000). A meta-analytic review of sex differences in facial expression processing and their development in infants, children, and adolescents. *Psychological Bulletin, 126*, 424-453.

McDonald, P. W., & Prkachin, G. C. (1990). The expression an perception of facial emotion in alexithymia: A pilot study. *Psychosomatic Medicine, 52*, 199-210.

McDougle, C. J., Barr, L. C., Goodman, W. K., & Price, L. H. (1999). Possible role of neuropeptides in obsessive compulsive disorder. *Psychoneuroendocrinology, 24*(1), 1-24.

Modahl, C., Green, L., Fein, D., Morris, M., Waterhouse, L., Feinstein, C., et al. (1998). Plasma oxytocin levels in autistic children. *Biol Psychiatry, 43*(4), 270-277.

Moreno, C., Borod, J. C., Welkowitz, J., & Alpert, M. (1993). The perception of facial emotion across the adult life span. *Developmental Neuropsychology, 9*, 305-314.

Morris, J. S., Friston, K. J., Buechel, C., Frith, C. D., Young, A. W., Calder, A. J., et al. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain 121*, 47-57.

Morris, J. S., Frith, C. D., Perret, D. I., Rowland, D., Young, A. W., Calder, A. J., et al. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature, 383*, 812-815.

Morris, J. S., Ohman, A., & Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *PNAS, 96*, 1680-1685.

Nakamura, K., Kawashima, R., Ito, K., Sugiura, M., Kato, T., Nakamura, A., et al. (1999). Activation of the right inferior frontal cortex during assessment of facial emotion. *Journal of Neurophysiology, 82*, 1610-1614.

Nelson, C. A., Morse, P. A., & Leavitt, L. A. (1979). Recognition of facial expressions by seven-month-old infants. *Child Development, 50*, 1239-1242.

Neumann, I. D. (2002). Involvement of the brain oxytocin system in stress coping: interactions with the hypothalamo-pituitary-adrenal axis. *Progress in Brain Research, 139*, 147-162.

Neumann, I. D., Kromer, S. A., Toschi, N., & Ebner, K. (2000a). Brain oxytocin inhibits the (re)activity of the hypothalamo-pituitary-adrenal axis in male rats: involvement of hypothalamic and limbic brain regions. *Regul. Pept., 96*, 31-38.

Neumann, I. D., Wigger, A., Torner, L., Holsboer, F., & Landgraf, R. (2000b). Brain oxytocin inhibits basal and stress-induced activity of the hypothalamo-pituitary-adrenal axis in male and female rats: partial action within the paraventricular nucleus. *Journal of Neuroendocrinology, 12*, 235-243.

Niedenthal, P. M. (2008). Emotion concepts. In M. Lewis, J. M. Haviland-Jones & L. Feldman Barret (Eds.), *Handbook of emotions* (pp. 687-617). New York: The Guilford Press.

Ogai, M., Matsumoto, H., Suzuki, K., Ozawa, F., Fukuda, R., & Uchiyama, I. (2003). FMRI study of recognition of facial expressions in high-functioning autistic patients. *Neuroreport, 14*, 559-563.

Öhman, A. (1986). Face the beast and fear the face: animal and social fears as prototypes for evolutionary analyses of emotion. *Psychophysiology, 23*, 123-145.

Osterling, J. A., Dawson, G., & Munson, J. A. (2002). Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation. *Development and Psychopathology, 14*, 239-251.

Parker, J. D. A., Taylor, G. J., & Bagby, R. M. (1993a). Alexithymia and the recognition of facial expression of emotions. *Psychotherapy and Psychosomatics, 59*, 197-202.

Parker, J. D. A., Taylor, G. J., & Bagby, R. M. (1993b). Alexithymia and the processing of emotional stimuli: An experimental study. *New Trends in Experimental and Clinical Psychiatry, 9*, 9-14.

Parker, P. D., Prkachin, K. M., & Prkachin, G. C. (2005). Processing of facial expressions of negative emotion in alexithymia: the influence of temporal constraint. *Journal of Personality and Social Psychology, 73*(4), 1087-1107.

Pauls, C. A. (2004). Physiological consequences of emotion regulation: taking into account the effects of strategies, personality and situation. In P. Philippot & R. S. Feldman (Eds.), *The Regulation of Emotion* (pp. 333.358). Mahaw, NJ: Lawrence Erlbaum Associates.

Pelphrey, K. A., Sasson, N. J., Reznick, J. S., Paul, G., Goldman, B. D., & Piven, J. (2002). Visual scanning of faces in autism. *Journal of Autism and Developmental Disorders, 32*(4), 249-261.

Phan, K. L., Fitzgerald, D. A., Nathan, P. J., & Tancer, M. E. (2006). Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biol Psychiatry, 59*, 424-429.

Philips, M. L., Senior, C., & David, A. S. (2000). Perception of threat in schizophrenics with persecutory delusions: an investigation using visual scan paths. *Psychological Medicine, 30*, 157-167.

Philips, M. L., Young, A., Senior, C., Brammer, M., Andrew, C., Calder, A. J., et al. (1997). A specific neural substrate for perceiving facial expressions of disgust. *Nature, 389*, 495-498.

Phillips, L. H., MacLean, R. D. J., & Allen, R. (2002). Age and the understanding of emotions: Neuropsychological and sociocognitive perspectives. *Journal of Gerontology: Psychological Sciences, 57*(B), 525-530.

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003a). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry, 54*(5), 504-514.

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003b). Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry, 54*(5), 515-528.

Pierce, K., Miller, R. A., Ambrose, J., Allen, G., & Courchesne, E. (2001). Face processing occurs outside the fusiform 'face area' in autism: Evidence from functional MRI. *Brain, 124*, 2059-2073.

Pietrowsky, R., Strüben, C., Mölle, M., Fehm, H. L., & Born, J. (1996). Brain potential changes after intranasal vs. intravenous administration of vasopressin: evidence for a direct nose-brain pathway for peptide effects in humans. *Biol Psychiatry, 39*, 332-340.

Pietrowsky, R., Thieman, A., Kern, W., Fehm, H. L., & Born, J. (1996). A nose-brain pathway for psychotropic peptides: evidence from a brain evoked potential study with cholecystokinin. *Psychoneuroendocrinology, 21*(6), 559-572.

Posamentier, M. T., & Abdi, H. (2003). Processing faces and facial expressions. *Neuropsychology Review, 33*(3), 113-143.

Rabavilas, A. D. (1987). Electrodermal activity in low and high alexithymic neurotic patients. *Psychotherapy and Psychosomatics, 47*, 101-104.

Rapcsak, S. Z., Galper, S. R., Comer, J. F., Reminger, S. L., Nielsen, L., Kaszniak, A. W., et al. (2000). Fear recognition deficits after focal brain damage. *Neurology, 54*, 575-581.

Rodman, H. R., O Scalaidhe, S. P., & Gross, C. G. (1993). Response properties of neurons in temporal cortical visual areas of infant monkeys. *Journal of Neurophysiology, 70*, 1115-1136.

Ruch, W. (1993). Extraversion, alcohol, and enjoyment. *Personality and Individual Differences, 16*(89-102).

Ruch, W. (1995). Will the real relationship between facial expression and affective experience stand up? The case of exhilaration. *Cognition and Emotion, 9*(33-58).

Russel, J. A. (1980). A circumplex model of affect. *Journal of Personality and Social Psychology, 39*, 1161-1178.

Russel, J. A., & Barrett, L. F. (1999). Core affect, prototypical emotional episodes, and other things called emotion: Dissecting the elephant. *Journal of Personality and Social Psychology, 76*, 805-819.

Russel, J. A., Leng, G., & Douglas, A. J. (2003). The magnocellular oxytocin system, the fount of maternitiy: adaptions in pregnancy. *Frontiers in Neuroendocrinology, 24*, 27-61.

Saarijärvi, S., Salminen, J. K., Taylor, G. J., & Toikka, T. (2006). Temporal stability of alexithymia over a five-year period in outpatients with major depression. *Psychotherapy and Psychosomatics, 75*, 107-112.

Saarni, C., Mumme, D. L., & Campos, J. J. (1997). Emotional development: Action, communication, and understanding.
. In W. Damon (Ed.), *Handbook of child psychology* (Vol. 3, pp. 237-309). New York: John Wiley.

Salthouse, T. A. (1992). *Mechanisms of age-cognition relations in adulthood*. Hillsdale, NJ: Erlbaum.

Salzberg, A. D., & Swedo, S. E. (1992). Oxytocin and vasopressin in obsessive-compulsive disorder. *Am J Psychiatry, 149*(5), 713-714.

Sasson, N. J. (2006). The development of face processing in autism. *Journal of Autism and Developmental Disorders, 36*(3), 381-394.

Sato, W., & Yoshikawa, S. (2004). The dynamic aspects of emotional facial expressions. *Cognition and Emotion, 18*, 710-710.

Schartz, B. L., Rosse, R. B., Johri, S., & Deutsch, S. I. (1999). Visual scanning of facial expressions in schizophrenia. *J Neuropsychiatry Clin Neurosci, 11*(1), 103-106.

Scherrer, K. R. (1988). Criteria for emotion-antecedent appraisal: A review. In V. Hamilton, G. H. Bower & N. H. Frijda (Eds.), *Cognitive perspectives on emotion and motivation* (pp. 89-126). Dordrecht, Holland: Nijhoff.

Schmolck, H., & Squire, L. R. (2001). Impaired perception of facial emotions following bilateral damage to the anterior temporal lobe. *Neuropsychologia, 15*, 30-38.

Schultz, R. T., Gauthier, I., Klin, A., Fulbright, R., Anderson, A., & Gore, J. C. (2000). Abnormal ventral temporal cortical acitivity during face discrimination among individuals with Autism and Asperger Syndrome. *Archives of General Psychiatry, 57*, 1-23.

Schwarz, N., & Clore, G. L. (1983). Mood, misattribution, and judgments of well-being: informative and directive functions of affective states. *Journal of Personality and Social Psychology, 45*, 513-523.

Shayegan, D. K., & Stahl, S. M. (2005). Emotion processing, the amygdala and outcome in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 29*, 840-845.

Shenton, M. E., Dickey, C. C., Frumin, M., & McCarley, R. W. (2001). A review of MRI findings in schizophrenia. *Schizophr Res, 49*, 1-52.

Sifneos, P. E. (1973). The prevalence of 'alexithymic' characteristics in psychosomatic medicine. *Psychotherapy and Psychosomatics, 22*, 255-262.

Simion, F., Valenza, E., Umilta, C., & DallaBarba, B. (1998). Preferential orienting to faces in newborns: A temporal-nasal asymmetry. *Journal of Experimental Psychology: Human Perception and Performance, 24*, 1399--1405.

Snowdon, C. T. (2003). Expression of emotion in nonhuman animals. In J. R. Davidson, K. R. Scherer & H. H. Goldsmith (Eds.), *Handbook of affective science* (pp. 457-480). New York: Oxford University Press.

Soken, N. H., & Pick, A. D. (1992). Intermodal perception of happy and angry expressive behaviors by seven-month-old infants. *Child Development, 63*(787-795).

Solomon, R. C. (2008). The Philosophy of Emotions. In M. Lewis, J. M. Haviland-Jones & L. Feldman Barret (Eds.), *Handbook of emotions* (3rd ed ed., pp. 3-16). New York: The Guilford Press.

Soto, J. A., Levenson, R. W., & Ebling, R. (2005). Cultures of moderation and expression: Emotional experience, behavior, and physiology in Chinese Americans and Mexican Americans. *Emotion, 5*(2), 154-165.

Spitzer, C., Siebel-Jürges, U., Barnow, S., Grabe, H. J., & Freyberger, H. J. (2005). Alexithymia and Interpersonal Problems. *Psychotherapy and Psychosomatics, 74*(4), 240-246.

Sprengelmeyer, R., Rauch, M., Eysel, U., & Przuntek, H. (1998). Neural structures associated with recognition of facial expressions of basic emotions. *Proc R Soc London Ser B, 265*, 1927-1931.

Streit, M., Wolwer, W., & Gaebel, W. (1997). Facial-affect recognition and visual scaning behaviour in the course of schizophrenia. *Schizophr Res, 24*, 311-317.

Sugase, Y., Yamane, S., Ueno, A., & Kawano, K. (1999). Global and fine information coded by single neurons in the temporal visual cortex. *Nature, 400*, 869-872.

Sullivan, S., & Ruffman, T. (2004). Emotion recognition deficits in the elderly. *International Journal of Neuroscience, 114*, 403-432.

Sullivan, S., Ruffman, T., & Hutton, S. B. (2007). Age differences in emotion recognition skills and the visual scanning of emotion faces. *Journal of Gerontology, 62*(1), 53-60.

Taylor, G. J. (2000). Recent developments in alexithymia theory and research. *Canadian Journal of Psychiatry, 45*, 134-142.

Taylor, G. J., Bagby, R. M., & Parker, J. D. A. (1997). *Disorders of affect regulation: alexithymia in medical and psychiatric illness*. Cambridge: Cambridge University Press.

Thayer, J. F., & Johnsen, B. H. (2000). Sex differences in judgement of facial affect: a multivariate analysis of recognition errors. *Scand J Psych, 41*, 242-246.

Thomas, L. A., De Bellis, M. D., Graham, R., & LaBar, K. S. (2007). Development of emotional facial recognition in late childhood and adolescence. *Developmental Science, 10*(5), 547-558.

Tranel, D., Adolphs, R., Damasio, H., & Damasio, A. R. (2001). A neural basis for the retrieval of words for actions. *Cognitive Neuropsychology, 18*, 655-670.

Tranel, D., Damasio, A. R., & Damasio, H. (1997). A neural basis for the retrieval of conceptual knowledge. *Neuropsychologia, 35*, 1319-1327.

Ueno, A., Ueno, Y., & Tomonaga, M. (2004). Facial responses to four basic tastes in newborn rhesus macaques and chimpanzees. *Behavioral Brain Research, 154*(1), 261-271.

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In D. G. Ingle, M. A. Goodale & R. J. Q. Mansfield (Eds.), *Analysis of visual behavior*. Cambridge, MA: MIT Press.

Uvnas-Moberg, K. (1996). Neuroendocrinology of the mother-child interaction. *Trends Endocrinol. Metab., 7*, 126-131.

Uvnas-Moberg, K., Ahlenius, S., Hillegaart, V., & Alster, P. (1994). High doses of oxytocin cause sedation and low doses cause an anxiolytic-like effect in male rats. *Pharmacol. Biochem. Behav., 49*(1), 101-106.

Uvnas-Moberg, K., Widstrom, A.-M., Nissen, E., & Bjorvell, H. (1990). Personality traits in woman 4 days postpartum and their correlation with plasma levels of oxytocin and prolactin. *J. Psychosom. Obstet. Gynecol., 11*, 261-273.

Valenza, E., Simion, F., Machhi-Cassioa, V., & Umilta, C. (1996). Face preference at birth. *Journal of Experimental Psychology: Human Perception and Performance, 22*, 892-903.

Volkmar, F., Sparrow, S., Rende, R. D., & Cohen, D. J. (1989). Facial perception in autism. *Journal of Child Psychology and Psychiatry, 30*, 591-598

Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2001). Effects of attention and emotion on face processing in the human brain. An event-related fMRI study. *Neuron, 30*, 829-841.

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., & Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nature Neuroscience, 7*, 1271-1278.

Walker-Smith, G. J., Gale, A. G., & Findlay, J. M. (1977). Eye movement strategies involved in face perception. *Perception, 6*, 313-326.

Waller, B. M., Vick, S.-J., Parr, L. A., Pasqualini, M. S., & Bard, K. A. (2006). Intramuscular electrical stimulation of facial muscles in humans and chimpanzees: Duchenne revisited and extended. *Emotion, 6*(3), 367-382.

Watson, D., & Tellegen, A. (1985). Towards a consensual structure of mood. *Psychological Bulletin, 98*, 219-235.

Wehrle, T., Kaiser, S., Schmidt, S., & Scherer, K. R. (2000). Studying the dynamics of emotional expression using synthesized facial muscle movements. *Journal of Personality and Social Psychology, 78*(1), 105-119.

Whalen, P. J., Shin, L. M., McInerney, S. C., Fischer, H., Wright, C. I., & Rauch, S. L. (2001). A functional MRI study on human amygdala responses to facial expressions of fear versus anger. *Emotion, 1*, 70-83.

Wild, B., Erb, M., & Bartels, M. (2001). Are emotions contagious? Evoked emotions while viewing emotionally expressive faces: quality, quantity, time course and gender differences. *Psychiatry Res, 102*, 109-124.

Williams, L. M., Das, P., Harris, A. W., Liddell, B. B., Brammer, M. J., Olivieri, G., et al. (2004). Dysregulation of arousal and amygdala-prefrontal systems in paranoid schizophrenia. *American Journal of Psychiatry, 161*, 499-489.

Williams, L. M., Loughland, C. M., Green, M. J., Harris, A. W., & Gordon, E. (2003). Emotion perception in schizophrenia: an eye movement study comparing the effectiveness of risperidone vs haloperidol. *Psychiatry Res, 120*, 13-27.

Windle, R. J., Wood, S., Shanks, N., Perks, P., Conde, G. L., da Costa, A. P., et al. (1997). Endocrine and behavioural responses to noise stress: comparison of virgin and lactating female rats during nondisrupted maternal activity. *Journal of Neuroendocrinology, 9*(6), 407-414.

Wu, S., J., M., Ruan, Y., Liu, J., Guo, Y., Shuang, M., et al. (2005). Postitive association of the oxytocin receptor gene (oxtr) with autism in the chinese han population. *Biol Psychiatry, 58*, 74-77.

Yarbus, A. L. (1967). *Eye movements and vision*. New York: Plenum Press.
Young, A. W. (1995). Face processing impairments after amygdalotomy. *Brain, 118*, 15-24.
Young, L. J. (2002). The neurobiology of social recognition, approach and avoidance. *Biol Psychiatry, 51*, 18-26.