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"The Opioid System and the Recognition of Emotional Facial Expressions"

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Outline

# 1 Theoretical Part

## 1.1 Introduction

The endogenous opioid system has been associated with the emotional system in humans because it influences almost every basic emotion (Nummenmaa & Tuominen, 2018). Moreover, especially the mu-opioid receptor (MOR) system is central to reward and pain regulation across species (Fields, 2004; Van Ree et al., 2000), and its function is associated with the evaluation of social cues in humans, as MOR activation not only increases visual exploration of faces showing neutral expressions and overt attention to the eye region (Chelnokova et al., 2016), but also increases ratings of attractiveness for neutral faces (Chelnokova et al., 2014). According to Hsu et al. (2013), social rejection leads to an increased MOR activation. Therefore, the opioid system has a crucial role in socialization and day-to-day functioning (Ballantyne & Sullivan, 2017).

An important component for social functioning across the lifespan is the ability to interpret emotions in facial expressions of others (Thomas et al., 2007). In 1872, Darwin already emphasized the importance of the interpretation of emotional facial expressions for social communication between humans and pointed out its evolutionary advantage. Human faces are important visual stimuli and an essential source of information because they convey social signals which indicate the emotional state of other individuals (Hunnius et al., 2011). This information is helpful for both expressers and observers to regulate their adaptive behavior in social interactions as it allows decisions about what to approach and what to avoid (Calvo & Beltrán, 2013).

Some studies have already investigated the relationship between the MOR system and facial expression recognition and suggest a lower sensitivity for negative emotional facial expressions (Bershad et al., 2016; Ipser et al., 2013; Løseth et al., 2018) and a higher sensitivity for positive social stimuli (Bershad et al., 2016) during MOR activation. However, questions remain unanswered regarding the exact role of MOR in the recognition of happy, angry, and fearful faces, which the present study addresses by examining the effects of morphine – a mu-opioid receptor agonist and one of the most used pain killers (Le Merrer et al., 2009) – on the recognition of these emotional facial expressions.

## 1.2 Emotion Recognition

### 1.2.1 Explanation of emotion recognition in distinction to identity recognition

Facial emotion recognition is defined as the correct interpretation of other people's facial expressions in order to draw conclusions about their emotional state (Unoka et al.,

2011). When looking into the face of a person, we concentrate mainly on the eye and the mouth area (Smith et al., 2005). Schurgin et al. (2014) even suggest five more precisely divided facial regions to be most critical in emotion recognition: the eyes, the upper nose, the lower nose, the upper lip, and the nasion. Some emotions, such as anger, fear, and sadness, are recognized best from the eyes, while other emotions, such as happiness and disgust, are recognized best from the mouth (Sullivan et al., 2007).

Facial expressions arise through muscle movements: A cheerful face is created by the zygomaticus major pulling the upper lips up and backwards and the orbicularis oculi simultaneously altering the eye region, so that the eyes are squeezed together, and small wrinkles appear around the outer corners of the eyes (Ekman & Friesen, 1978). In an angry face, the corrugator supercilii muscle causes the eyebrows to contract (Hansen & Hansen, 1988). Fearful or surprised faces usually have wide open eyes, which is due to the medial frontalis muscle lifting the eyebrows (Ekman & Friesen, 1978), whereby in fearful faces the corrugator supercilii muscle is also active (Van Boxtel, 2010). In all emotional facial expressions, not only the individual parts of the face change but also the configuration of the parts, such as the distances between them (Leppänen & Nelson, 2006).

Obviously, the face of a person does not only indicate the emotional state, but also transmits information about the gender, the age, and thus about the identity of the person (Fox et al., 2000). Several studies addressed the question of whether emotional facial expressions are processed differently from facial identity. A model established by Bruce and Young in 1986 provided the basis for the assumption of two separate functional routes for the recognition of facial identity and facial expression. Haxby et al. (2000) agreed to this, suggesting two functionally and neurologically distinct pathways for the visual analysis of faces. Fox et al. (2000) also pointed to some studies suggesting that the human brain processes information regarding a person's identity and emotional state using different neural systems. Although Calder and Young (2005), after reviewing the evidence in this matter, emphasized that the idea of fully separate pathways is not strongly supported, they still acknowledged that the two systems for processing emotional state and identity are to some extent separate from each other.

A recent study by Connolly et al. (2020) investigated individual differences in emotion recognition ability across the face, body, and voice, and the connection between emotion recognition ability and affective and cognitive traits. They found evidence for a superordinate emotion recognition factor processing emotional information conveyed by both visual and

auditory signals (i.e., by the face, body, or voice). Importantly, they suggest that this superior emotion recognition ability is independent of the ability to recognize facial identity, although these two systems are closely related. Moreover, according to this study, general intelligence is a significant predictor of the ability to recognize emotions, but not of the ability to recognize face identity. Summarizing the research literature, a distinction can thus be made between systems for emotion and identity recognition.

### 1.2.2 Development in childhood and adolescence

A comprehensive review of several studies regarding the development of emotion recognition is provided by Leppänen and Nelson (2006). According to this, an innate preparedness and the further development of the brain based on experience interact in the development of the recognition of facial expressions. Although it has been shown that even very young infants can distinguish between different facial expressions (Field et al., 1982), Leppänen and Nelson (2006) emphasize that it is not certain whether this is actually due to facial emotional expression changes or to other concomitant feature changes between the faces displayed, such as an open versus a closed mouth. However, according to Hertenstein and Campos (2004), infants can recognize emotion from faces in the first year of life. This is consistent with a study by Hunnius et al. (2011) which found that although both adults and 4-month-old and 7-month-old infants showed shorter dwell times in response to threat-related compared to non-threat-related faces, only adults avoided the eye region of the faces, suggesting that the avoidance of the eyes might be a mechanism shaped by experiences with facial expressions.

Various studies have examined internal and external influences on the ability to recognize emotions in childhood. For example, Bennett et al. (2005) found that children's cognitive ability is a strong predictor of their emotional knowledge (which includes emotion facial expression recognition). In their study, children with a relatively high cognitive ability at age 2, had greater emotion knowledge at age 4. Apart from this, maternal verbal intelligence and environmental risk factors also predicted a correspondingly different emotional recognition. On the other hand, other examined factors such as parenting or maternal depressive symptoms had no influence on the ability to recognize emotions at the age of 4 years. However, another study found that the supportive presence of parents at the age of 4 can improve the ability to recognize emotions at the age of 6 (Berzenski & Yates, 2017). In a study by English et al. (2018) adult women who had experienced emotional maltreatment as children recognized fearful faces more quickly under conditions of high

cognitive stress, suggesting that external circumstances in childhood may influence emotion recognition into adulthood.

Although there is agreement in the research literature that emotion recognition develops at different velocities depending on the specific emotion, there are still differences in the individual research results. Also, regarding the age at which the recognition of emotions is completed, studies come to different conclusions. According to Herba et al. (2006), who conducted a study with 4- to 15-year-old participants, facial emotion processing continues to evolve through preschool age, middle childhood and adolescence, with particularly the recognition of fear and disgust improving significantly with age. Thomas et al. (2007) suggested that changes in the recognition of emotions still occur in adolescence, at least for negative emotions, as they found that adults showed higher sensitivity to small differences in facial expressions compared to both children (7-13 years) and adolescents (14-18 years), who did not differ from each other. In contrast to this, Mancini et al. (2013) found adult levels of emotion recognition at the age of 11 years, with the ability to recognize neutral and sad facial expressions increasing rapidly between the ages of 8 and 11, and a slow increasement during this time period for recognizing expressions of anger, disgust, and fear, but no age effect on the recognition of happy faces. Durand et al. (2007) found that although happiness and sadness were recognized almost as well at the age of 5 or 6 as in adulthood, fear, anger and neutral expressions were recognized at an adult level only at the age of 10, and the recognition of disgust reached the adult level at 11 or 12 years of age. Lawrence et al. (2015) partly agree with this, showing that the recognition of fear, disgust, and surprise improved significantly with age in 6- to 16-year-old participants, while for happiness, sadness, and anger, levels of recognition did not differ significantly for 6-year-old and 16-year-old participants. Chronaki et al. (2015) examined facial and vocal emotion recognition in 4- to 11-year-old children compared to adults. They found that the ability to recognize emotions improves in children with age, reaching adult levels at the age of 11 years.

In summary, despite some differences in the results regarding the development of recognition of individual emotions, most studies agree that the ability to recognize happy facial expressions develops early while the ability to recognize negative expressions takes longer to develop. Furthermore, most studies agree that the development of emotion recognition is generally completed at around 11 years of age.

### 1.2.3 Emotion recognition in higher age

According to most research reports, the ability to recognize emotions from faces declines at an older age, but again there is no agreement on the specific emotions that cause age-related difficulties in recognition. For instance, one study found a decline in the emotional recognition of happiness, fear, disgust, and anger associated with age, but no differences in the recognition of sadness and surprise (Isaacowitz et al., 2007). In contrast, a meta-analysis of various studies on that matter reported an age-related decline in the recognition of facial expressions of all emotions except disgust, where even an age-related improvement was found (Ruffmann et al., 2008). According to Richter et al. (2011), emotion recognition is not only emotion-specific but also context-dependent. In this study, older compared to younger participants were worse at recognizing anger and sadness in both context-rich and context-poor emotion recognition tasks. However, in recognizing happiness, age differences were minimized by context-rich tasks.

The decrease in the ability to recognize emotions is attributed to age-related differences in the brain, but in parts of the brain that are independent of a general decrease in cognitive capacity (Sullivan & Ruffmann, 2004). However, according to Sullivan et al. (2007), the reason for the decreased emotion recognition ability could also be due to age-related reduced processing speed, since older people compared to younger people focus longer at the mouth of the presented faces when performing emotion recognition tasks, perhaps because they must focus on a region of the face for a longer period of time in order to correctly assign the emotion.

### 1.2.4 Differences in gender

Regarding the question of whether women and men differ in the recognition of emotions, there are different conclusions in the research literature, but a clear direction can still be identified. A meta-analytic review of literature on sex differences in facial expression processing conducted by McClure (2000) indicates a significant female advantage in the processing of facial expressions both in infants and in children and adolescents. The results found by Mancini et al. (2013) and Lawrence et al. (2015) are consistent with this, as they indicate a higher accuracy of girls in childhood and adolescence in recognizing emotions. In adult life, too, according to some studies (Anderson et al., 2011; Biele & Grabowska, 2006), the ability to recognize emotions in faces seems to be better developed in women. However, Herba et al. (2006) emphasize that gender differences in emotion recognition may also be due to differences in the respective tasks within a study, as boys have a higher spatial understanding and girls have higher verbal skills. In their study, the male participants scored

slightly better, which could be due to visuo-spatial parts of the tasks. Grimshaw et al. (2004), who did not find any gender differences, also point out that possible differences in emotion recognition between women and men may be caused by procedural variables strongly influencing task performance. Another study (Hoffmann et al., 2010) found that women recognized subtle emotions in facial expressions with greater accuracy, but there was no difference between men and women in the recognition of highly expressed facial expressions. In contrast, a more recent study (Wingenbach et al., 2018) showed that women are faster and more accurate in emotion recognition than men, regardless of the intensity of the facial expression presented, while no gender difference was found in the recognition of neutral facial expressions. Importantly, Løseth et al. (2018), on whose work the present study is partly based, and which will be discussed in more detail later, found a significant difference in participant gender, as facial expressions were considered happier by male than by female participants. In summary, despite a few exceptions, the literature points to a female advantage in the recognition of emotions in facial expressions.

### 1.2.5 Clinical conditions associated with impairments in emotion recognition

The connection between facial emotion recognition and different clinical conditions has been investigated many times. An impairment in emotion recognition can be seen in several neuropsychiatric and psychopathological disorders (Connolly et al., 2020). In order to point out the relevance of emotion recognition in the clinical-psychological context, an overview of the current state of research in this area regarding some clinical conditions is given below.

Individuals with major depression or anxiety disorders show deficits in recognizing facial emotion expressions, with the impairment being greater in major depression (Demenescu et al., 2010). Machado-de-Sousa et al. (2010) compared several studies on the connection between social anxiety and emotion recognition and concluded that socially anxious individuals process emotional facial expressions differently than healthy controls. More precisely, individuals with social anxiety display heightened sensitivity to subtle threat cues such as masked facial expressions of anger (Mogg & Bradley, 2002). Another study also found an enhanced recognition of negative emotional expressions among people with social anxiety (Gilboa-Schlechtman et al., 2008). This is consistent with the results of a study by Joormann and Gotlib (2006), in which people with social phobia, people with depressive disorders, and healthy people were compared to each other regarding their ability to recognize emotional facial expressions of varying intensity: The socially anxious participants recognized angry facial expressions at lower intensity than the healthy and depressed

participants. Oh et al. (2018) compared socially anxious individuals with healthy subjects in terms of accuracy and response time in the recognition of emotional facial expressions and found a lower accuracy rate in the socially anxious individuals for surprised and happy faces, i.e. emotions with positive valence.

It has been shown several times that depressive disorders can be accompanied by an impairment in the recognition of emotional facial expressions (e.g., Asthana et al., 1998; Mikhailova et al., 1996). Anderson et al. (2011) found a general impairment of emotion recognition in depressive disorders, regardless of the specific emotion: For all examined emotions, there was found lower recognition accuracy in currently depressed participants and increased accuracy in those with a history of depression who were currently well. However, Surguladze et al. (2004) mainly found a difference in the recognition of happy facial expressions: Compared to healthy controls, participants with depression showed a significantly lower tendency to recognize happy faces of 50% intensity and neutral expressions as happy. Results of the above-mentioned study by Joormann and Gotlib (2006) agree with this, because depressive participants needed a higher intensity of emotional facial expression to recognize happy faces compared to healthy controls and persons with social phobia. Depressed people unknowingly pay more attention to sad faces, noticing them more quickly and focusing their attention on them longer than on happy faces (Gotlib et al., 2004). Also, for angry faces, depressed people show maintained attention compared to neutral faces, while non-depressed people turn their gaze away from them sooner (Leyman et al., 2007). These results are not surprising in the context of depression, as they indicate increased attention to negative social information and difficulties in identifying positive social information in depressive disorders.

Individuals with autism spectrum disorder (ASD), which is generally characterized by problems in the social field, display an impairment in emotion recognition, although there are discrepant research results due to inconsistencies between studies (Harms et al., 2010). Nevertheless, several study results agree that individuals with ASD show specific deficits in recognizing negative emotions like anger and disgust (Enticott et al., 2014; Philip et al., 2010). But it has been pointed out that these impairments only occur for lower intensity presentations, suggesting that people with ASD mainly have difficulties in recognizing subtle facial emotional expressions (Law Smith et al., 2010).

The borderline personality disorder (BPD) is also related to differences in the recognition of emotions: While Lynch et al. (2006) reported a general heightened sensitivity

to facial expressions in individuals with BPD, Domes et al. (2008) did not find a general impairment in BPD patients in accurately processing facial emotional expressions. However, they did report a bias towards the recognition of anger in highly ambiguous faces showing mixed emotions. This is also consistent with the results of a meta-analysis indicating that individuals with BPD show impairments in correctly identifying neutral facial expressions and in recognizing facial expressions of anger and disgust (Daros et al., 2013).

Schizophrenia is associated with an impaired identification and emotional recognition of facial stimuli, with the difficulty being greater in emotional recognition (Martin et al., 2005). Affected persons recognize all emotional expressions, but especially fearful, disgusted, and neutral faces, worse than healthy controls, with neutral faces more often being mistaken for negative emotional expressions (Kohler et al., 2003). There is a greater impairment in the recognition of negative expressions, while better recognition of happy faces correlates with less pronounced negative symptoms (Turetsky et al., 2007).

The purpose of this overview was to demonstrate that many clinical conditions are related to impairments in emotion recognition. It should be noted that some clinical conditions are in turn associated with changes in the opioid system. Since, as mentioned above, the opioid system – especially the MOR – plays such a crucial role in social experience and behavior, it is not surprising that social anxiety disorders can be related to changes in the opioid system (Bowers et al., 2012; Hsu, et al., 2013). The experience of harmful social interactions can lead to dysregulations in the opioid system, which in turn are involved in the development of depressive disorders (Carlezon & Krystal, 2016). Critical factors in depression include decreased sensitivity to socially rewarding stimuli and hypersensitivity to social pain (Lutz et al., 2018), both of which are closely related to the opioid system, as will be explained in more detail later. In addition to depression and anxiety disorders, changes in the opioid system also occur in other clinical conditions mentioned above, such as schizophrenia (Alfimova et al., 2019), ASD (Pellissier et al., 2018), and BPD (Bandelow et al., 2010). This is to illustrate the relevance of further research into the relationship between emotion recognition and the opioid system.

### 1.2.6 Recognition of happy, angry, and fearful faces

Ekman and Friesen (1976) identified six basic emotions which seem to be recognized similarly by different cultures as they allow rapid responses to biologically relevant stimuli. These basic emotions are happiness, sadness, anger, disgust, fear, and surprise. Later, contempt was added as the seventh basic emotion (Ekman, 1992). As some of these

expressions inform about potential harm respectively potential benefit, the observer must recognize the shown expression quickly and accurately in order to react in the most appropriate way (Calvo & Beltrán, 2013). Since this thesis focuses on the recognition of happy, angry, and fearful facial expressions, a brief overview of the current state of research on the recognition of these three facial expressions in general is given below.

From a biological or evolutionary point of view, it is advantageous to detect threatening stimuli faster than non-threatening stimuli in order to ensure survival and personal safety (Williams, 2006). Because negative emotional facial expressions like those of anger and fear can signal a threat, an impairment in the accurate recognition of negative emotional expressions may lead to greater problems than an impairment in recognizing positive emotions (Enticott et al., 2014). As already mentioned above, Hunnius et al. (2011) examined visual scanning patterns in response to threat-related (i.e., angry or fearful) compared to non-threat-related facial expressions. They found that participants (both adults and infants), when seeing threat-related faces, concentrated less on the inner features of the face but rather distributed their fixation over the whole face, suggesting a vigilant looking behavior when exposed to threat-related expressions.

In line with that is the anger superiority hypothesis which, according to Hansen and Hansen (1988), states that angry faces are detected more efficiently than friendly faces. In their experiments, angry faces were found more efficiently in happy crowds than vice versa, which led the authors to believe that the search for signals of threat happens in a preattentive way. The anger superiority effect has been confirmed by several studies, some of which used schematized line drawings of facial expressions as stimuli (Fox et al., 2000; Öhman et al., 2001), and another used photographs (Horstmann & Bauland, 2006).

Fearful facial expressions also indicate a possible threat, however more indirectly than angry facial expressions (Calvo & Beltrán, 2013). Yet, in some studies, fearful expressions were less easily recognized than other emotions (Rapcsak et al., 2000; Zhao et al, 2013). According to a study by Calvo and Lundquist (2008), fearful faces are recognized the least accurate and the slowest compared to the other basic emotions and neutral facial expressions. Importantly, Adolphs (2002) points out that fear is not the most difficult to identify emotional expression per se but rather easy to discriminate from neutral expressions; it is only recognized less accurate in forced-choice tasks with the six basic emotions as possible answer choices because fear is often confused with surprise.

Although it is biologically or evolutionary beneficial to process threat-related expressions faster than non-threat expressions, Calvo and Beltrán (2013) suggest a recognition advantage for happy expressions in categorization tasks in which an expression must be consciously identified. In the study mentioned above (Calvo & Lundquist, 2008), participants identified happy and neutral faces with greater accuracy and shorter reaction times than all the other expressions. Tottenam et al. (2009) evaluated a set of face stimuli showing facial expressions. Within this set of facial expressions, happy expressions had high recognition rates, while other expressions (in particular, sad, fear, and surprised) had poor recognition rates. Grimshaw et al. (2004) found happy faces to be more discriminable than either angry or sad faces. In Kosonogov's and Titova's study (2018), which examined hit rates and verbal responses to various emotions, happiness was also best recognized.

In the literature there are different explanations for the easier recognition of happy faces. According to Adolphs (2002), people initially divide facial expressions into two categories: happy and non-happy. The smile in happy faces is a unique facial feature which distinguishes them from unhappy expressions. Although Leppänen and Nelson (2006) state that configural information is more important for recognizing an emotional facial expression than individual facial features (i.e., a smile), another study (Calvo et al., 2012) in which pictures of eye regions and mouths showing different expressions were morphed together showed that a face with a smiling mouth was more probable to be judged as happy, regardless of its congruence or incongruence with the eye region expression. Unhappy (e.g., sad, angry, or fearful) faces have more overlapping features and are therefore more easily confused with one another (Adolphs, 2002). Another explanation for greater accuracy in recognizing happy faces could be a greater familiarity with happy faces or rewarding aspects of happy faces (Hare et al., 2005). According to Spreckelmeyer et al. (2009), just looking at pictures of happy faces can be rewarding in itself. The perception and processing of reward is in turn closely related to the opioid system, which will be discussed in more detail in the next section.

In summary, on the one hand threatening faces are recognized faster, but in categorization tasks there is an advantage for happy facial expressions. According to Calvo and Beltrán (2013), that is no contradiction, but the two systems are compatible with one another: Threat detection takes place at early stages in a non-conscious way while a more elaborate distinction is required in explicit expression categorization.

## 1.3 The Opioid System

### 1.3.1 Structure and functions of the opioid system

The discovery of the opioid system began in early history in connection with the use of opium, which is extracted from poppy seeds and has analgesic and euphoric effects. (Le Merrer et al., 2009). Opiates are substances containing opium or opium alkaloids, primarily morphine, whereas the term opioid refers to all morphine-like active substances (Lutz et al., 2018). Morphine is the most active ingredient of opium and was named after Morpheus, the god of dreams in Greek mythology. It has been used medically for centuries, and today it is one of the most commonly used painkillers, although it can have several serious side effects such as respiratory depression, constipation, and drowsiness, and a prolonged use of morphine can lead to tolerance and dependence (Le Merrer et al., 2009; Waldhoer et al., 2004).

The existence of opioid receptors (i.e., binding points for opioids) in the human organism was only discovered in the 1970s (Kuhar et al., 1973). There are three main opioid receptors: the mu-opioid receptor (MOR), the kappa-opioid receptor (KOR), and the delta-opioid receptor (DOR), which are in the central and peripheral nervous system and all belong to the super family of G-protein coupled receptors (Bowers et al., 2012). The body's own opioid peptides – the endorphins, the enkephalins, the dynorphins, and the endomorphins – serve as natural ligands (i.e., binding partners) which can dock to the opioid receptors (Lutz et al., 2018). But the opioid receptors can also be activated exogenously by drugs like heroin or analgesics like morphine which is a MOR agonist (Waldhoer et al., 2004).

Having already given a first insight into the functions of the opioid system in the introduction to this paper while emphasizing its connection with social experience and behavior, this will be discussed in more detail below to provide a more complete overview. Waldhoer et al. (2004) summarize the different effects which can occur when opioid receptors are activated: analgesia, respiratory depression, euphoria, feeding, the release of hormones, inhibition of gastrointestinal transit, and effects on anxiety. The opioid system plays a crucial role in nociception (i.e., the perception of a pain stimulus) and it is also involved in several physiological responses such as the regulation of stress (Le Merrer et al., 2009). When the organism is exposed to a stressful situation, endogenous opioids are released, which have a defensive effect by helping to dampen the stress response (Drolet et al., 2001). The opioid system is therefore related to mood regulation (Ribeiro et al., 2005).

An important function of the opioid system is the regulation of the reward system: Agonists selective for MOR and DOR are analgesic and rewarding (Waldhoer et al., 2004),

and opioids produce reward independently of dopamine, which is often considered the most important neurotransmitter in processing reward but is not necessary for morphine-induced reward (Hnasko et al., 2005). Nummenmaa and Tuominen (2018) also suggest the release of endogenous opioids during reward consumptions and positive moods. Le Merrer et al. (2009) summarize several studies indicating the involvement of the opioid system in the modulation of food and sexual reinforcement and the contribution of mu-opioid receptors to the reinforcing properties of drugs of abuse.

### 1.3.2 The opioid system and social perception and behavior

The connection of the opioid system to the response to stress is consistent with the finding that the MOR system plays a protective or adaptive role under conditions of social pain, because the mu-opioid receptors are activated when experiencing social rejection, correlating with a decrease in the level of sadness and the feeling of being rejected (Hsu et al., 2013; Hsu et al., 2015), and exogenous activation of the MOR system during a social rejection task also results in decreased perception of rejection (Bershad et al., 2016).

In situations of social comfort, however, MOR activation facilitates social behavior (Pellissier et al., 2018), and differences in MOR availability are associated with the individuals' social relationships and psychosocial well-being (Nummenmaa et al., 2015). Syal et al. (2015) found that activation of the MOR system led to a significant improvement in short-term memory when remembering happy faces, but not fearful or angry faces. Another study mentioned at the beginning of this paper (Chelnokova et al., 2014) found that activation of mu receptors increases attractive ratings for neutral facial expressions. The reason for the interaction between positive social experiences and the opioid system might be its above-mentioned connection to the perception of reward (Lutz et al., 2018; Petrovic et al., 2008). While primary rewards such as food, water, and sex, are necessary for the survival of the species, secondary rewards tend to involve social stimuli, such as pleasant touch and perceiving respect and attention (Bandelow et al., 2010).

In summary, the presented studies allow the assumption that the opioid system is associated with a decrease in sensitivity to negative social stimuli and an increase in sensitivity to positive social stimuli or a generally more positive assessment of social stimuli.

### 1.3.3 Approaching the relationship between the opioid system and emotion recognition: Brain areas involved

Opioid receptors are mainly located in the cortex, limbic system, and brain stem (Le Merrer et al., 2009; Berridge & Kringelbach, 2013). Mu-opioid receptors are mainly found in

brain areas involved in social cognition, emotional processing, motivation and reward (Colasanti et al., 2012; Kroll et al., 2018; Le Merrer et al., 2009; Liberzon et al, 2002; Nummenmaa & Tuominen, 2018), such as the limbic system consisting of several structures which may be located apart from each other but belong together functionally (Rajmohan & Mohandas, 2007). In the literature there is particular emphasis on the high density of mu-opioid receptors in the amygdala (Adolphs, 2002; Jacobsen et al., 2006), an almond-shaped group of nuclei in the medial part of the respective temporal lobe and part of the limbic system (LeDoux, 2003; Swanson & Petrovic, 1998). The amygdala plays an important role in cognitive functions, such as learning, memory, attention, and perception, but also in emotion (Baxter & Murray, 2002). During emotional stimulation, limbic components of the emotion-motivation circuit show opioidergic responses (Nummenmaa & Tuominen, 2018). Under conditions of sustained pain, the MOR system is activated in several brain regions, including the amygdala (Ribeiro et al., 2005). But also, during the experience of positive emotions there is a release of endogenous opioids in the amygdala (Koepp et al., 2009).

Since the amygdala has an important role in social learning (Rosenberger & Van Honk, 2019) and is involved in the emotional evaluation and assessment of a situation and in the processing of emotional information (Baxter & Croxson, 2012), it seems consistent that several studies have also found a connection between the amygdala and emotion recognition in facial expressions (see Adolphs, 2002, for a review). The amygdala is particularly involved when emotions are automatically recognized without involvement of the cortex, allowing a rapid reflex-like reaction, which is especially useful in situations of threat (Adolphs, 2002). Already in 1994, a study by Adolphs et al. showed that bilateral amygdala damage causes impairments in recognizing fear from the face. According to Morris et al. (1996), neuronal activity in the left amygdala is significantly higher when looking at fearful faces than when looking at happy faces. This is consistent with study results described above, which showed that threatening facial expressions are recognized faster than happy facial expressions (Calvo & Beltrán, 2013; Hansen & Hansen, 1988; Hunnius et al., 2011). Further studies then extended the role of the amygdala from the recognition of fear to the recognition of other negative emotions such as anger and sadness (see Adolphs & Tranel, 2003, for a summary). Adolphs and Tranel (2003), whose study also replicated this result, emphasize that the amygdala seems to be extremely specialized in recognizing negative facial expressions. However, the amygdala also appears to be active in processing positive emotions (Baxter & Murray, 2002) and to be sensitive to variations in the intensity of positive emotions (Bonnet et al., 2015). According to Costafreda et al. (2008), although negative emotional facial

expressions such as disgust or anger are more probable to activate the amygdala than happiness, the probability of activation is higher for all emotional expressions compared to neutral faces.

The hippocampus, located in the temporal lobe, also has a high density of mu-opioid receptors (Rowbotham, 2001). Injection of opioid agonists into the hippocampus – as well as into the amygdala – leads to a decrease in unconditioned fear (Zarrindast et al., 2008). Since the hippocampus is responsible for memory formation, it is involved in emotion recognition by establishing a connection to existing knowledge about the perceived emotional facial expression (Adolphs, 2002). There has also been found a connection between impairment in the recognition of emotional facial expressions with damage of the hippocampus (Hlobil et al., 2008).

Mu-opioid receptors are also found in prefrontal cortical structures (Ribeiro et al., 2005; Volk et al., 2012). Cortical structures, especially the prefrontal cortex, play a role in emotion recognition by being particularly responsible for differentiating more precisely between emotional facial expressions after an initial recognition of emotional valence has taken place in the amygdala (Adolphs, 2002; Daros et al., 2013). The prefrontal cortex can respond very rapidly to faces and facial expressions (Kawasaki et al., 2001). According to Adolphs (2002), especially those parts of the prefrontal cortex are involved in emotion recognition which have a connection to the amygdala or are also responsible for emotion processing, i.e. mainly ventral and medial sectors.

The thalamus, a subcortical structure involved in pain regulation and strongly connected to the cortex, also has a high density of mu-opioid receptors (Le Merrer et al., 2009; Colasanti et al., 2012). Sustained pain leads to a release of endogenous opioids, interacting with mu-opioid receptors, in various subcortical and cortical brain regions, including the thalamus (Zubieta et al., 2016). According to Cheung et al. (2006), a damaged thalamus leads to impairments in the recognition of emotional – more precisely, sad – facial expressions.

A complete summary of the brain areas in which mu-opioid receptors are present can be found in Le Merrer et al. (2009). Adolphs (2002) provided a detailed description of the brain areas involved in emotion processing and recognition. Here, the aim was to demonstrate that certain brain areas with a high density of mu-opioid receptors are involved in emotion recognition, which further confirms a connection between the opioid system and emotion recognition.

## 1.4 The Opioid System and Emotion Recognition

### 1.4.1 Opioid dependence/abuse and emotion recognition

The association between the opioid system and emotion recognition has already been investigated a few times, but so far there is only a small number of studies with healthy participants – which will be discussed later –, so definite conclusions regarding the role of the opioid system in emotion recognition cannot be reached until now (Nummenmaa & Tuominen, 2018). However, several studies suggest a link between opioid dependence/abuse and emotion recognition. Kornreich et al. (2002) found that opiate dependence is associated with an impairment in emotional facial expression decoding, although this impairment is smaller than in alcoholism. Martin et al. (2006) investigated facial expression recognition in chronic opiate users by comparing them to ex-opiate users and healthy controls. Interestingly, they found that opiate users were more accurate than ex-users in recognizing expressions of disgust. However, they were generally slower than controls in recognizing all expressions. In another study (McDonald et al., 2013), participants on opioid maintenance regimens were much poorer than abstinent users or controls when asked to recognize emotions in others. Kroll et al. (2018) showed that chronic opioid users reveal inferior performance primarily in recognizing emotions from faces. Zhou et al. (2012) found that heroin addicted people are especially impaired in recognizing expressions of negative emotions.

Although it is suggested that opioid abuse impairs facial expression recognition (Nummenmaa & Tuominen, 2018), it should be noted that substance abuse in general is associated with a reduction in emotion recognition accuracy (Fernandez-Serrano et al., 2010). Moreover, emotion-decoding impairments may be present *before* the development of substance dependence since populations at risk for developing a dependence (e.g., children of substance-misusing parents) show greater emotional disturbances and communication difficulties (Foisy et al., 2005). Therefore, research with healthy participants may be more informative.

Importantly, results of a study by Craparo et al. (2016) suggest that alexithymia may be partly responsible for impaired emotion recognition in opioid-dependent people. Alexithymia is defined as a personal trait characterized by the subclinical inability to identify and describe emotions experienced by one's self or others (Sifneos, 1973), and it has a higher prevalence in opioid addicts than in non-addicted people (Giynas Ayhan et al., 2018; Torrado et al., 2013). Craparo et al. (2016) compared heroin addicts and healthy controls in terms of reaction times and accuracy in recognizing emotional facial expressions. Heroin addicts

detected emotions more slowly and with less accuracy, but the higher reaction times could be explained by alexithymia. The authors also suggest that prolonged opioid dependence further increases the severity of alexithymia.

### 1.4.2 State of the art: Current research with healthy participants

As mentioned earlier, there are a few studies which examined the connection between emotion recognition and the opioid system in healthy volunteers and can be therefore seen as the state of the art in this matter. In 2013, Ipser et al. examined the effects of buprenorphine on the recognition of fearful facial expressions. Buprenorphine, which is used as a painkiller and to treat opioid dependence, is a partial mu-opioid agonist and a kappa-opioid antagonist. The authors hypothesized that the administration of a small dose of buprenorphine would reduce the sensitivity for recognizing fearful faces in an emotion recognition task. They conducted a within-subject design study in which the participants were given either 0.2 mg of buprenorphine or a placebo at different testing days. Two hours after drug administration, participants were presented on a computer screen with images of neutral facial expressions and had to press the 'enter' key to have the images transformed into an emotional facial expression in 2%-steps. After 1-3 seconds, an emotional facial expression of 10%, 20%, 30% … or 100% intensity was shown, which the participants had to categorize as happy, sad, angry, or fearful by pressing the appropriate key. As hypothesized, the intake of buprenorphine compared to placebo resulted in a reduced sensitivity for the recognition of fearful facial expressions. In contrast, buprenorphine had no effect on the recognition of happy, sad, or angry facial expressions.

In 2016, Bershad et al. tested the effects of buprenorphine on different dimensions of social processing. This study was mentioned earlier in this paper because it also showed that the activation of the MOR system during a social rejection task leads to a lower subjective perception of rejection. At this point, however, the focus is on the investigated effects of buprenorphine on attention to emotional facial expressions and on emotional responses to images with or without social content. It was hypothesized that buprenorphine would reduce initial attention to negative emotional expressions and decrease affective responses to negative social stimuli. Like the study by Ipser et al. (2013), this study was also conducted in a within-subject design, and here, too, the participants were given either 0.2 mg of buprenorphine or a placebo at separate testing days. Ninety minutes after drug administration, participants were presented with two images side by side on a computer screen, one of them showing a person with a neutral facial expression and the other one showing the same person with an either angry, fearful, sad, or happy facial expression. The participants' attention was

measured based on the number of times they looked toward the image of the emotional expression first, as compared to the neutral one. In another task, participants saw different pictures which were either neutral, positive, or negative and either social (containing people interacting with each other) or non-social (not containing any persons). Participants had to rate each image on an evaluating space grid from 0 to 4 regarding perceived positivity and negativity. The results showed that administration of buprenorphine lead to decreased attention to fearful facial expressions – in line with the result found by Ipser et al. (2013) – and increased ratings of positivity for images with social content, suggesting that buprenorphine may enhance reaction to positive social stimuli.

Surprisingly, Wardle et al. (2016) showed that naltrexone also leads to a reduced recognition of fear. Importantly, naltrexone is a mu- and kappa-opioid antagonist, so one would not expect the same effect as with buprenorphine, a mu-opioid agonist. According to Wardle et al. (2016), there are different possible explanations for this apparent contradiction: The recognition of negative faces may relate to mu-opioid functioning in a way that either increased or decreased mu-opioid functioning disrupts this ability. On the other hand, this effect may be due to the anxiolytic effects of kappa-opioid antagonism, since both buprenorphine and naltrexone are KOR antagonists.

So far, only one study addressed this matter by investigating the effects of morphine on the perception of anger and happiness (Løseth et al., 2018). The hypothesis put forward was that morphine would dampen perception of anger and increase perception of happiness in the faces of others. This was also a study in within-subject design with two test dates, whereby the participants were administered 10 mg morphine on one test day and a placebo on the other day. The emotion recognition task – or here called emotional perception task – took place 135 min after administration of the drug. Here, the participants were shown images of happy, neutral and angry facial expressions in one of three intensities each, resulting in five different alternatives: explicitly happy, implicitly happy, neutral, implicitly angry, and explicitly angry. On two visual analogue scales, the participants were then asked to rate the images according to how happy and how angry they thought the person in the image was. Different than expected, morphine did not enhance the perception of happiness. But as hypothesized, morphine lead to a decreased perception of anger. However, this effect was present for implicitly angry, neutral, and implicitly happy facial expressions but there were no differences in ratings of faces expressing explicit anger or happiness.

### 1.4.3 Gaps and differences in previous studies

The studies presented provide an important theoretical basis for the present work. However, questions remain open, partly because the topic was approached in different ways. Importantly, both Ipser et al. (2013) and Bershad et al. (2016) investigated the effects of buprenorphine on emotion recognition, while the present work aims to examine the effects of morphine. The main difference between these two drugs is that morphine only binds to the mu-opioid receptor, while buprenorphine is a MOR agonist and KOR antagonist (Huang et al., 2001; Le Merrer et al., 2009). Buprenorphine has been shown to reduce the sensitivity to fearful facial expressions (Ipser et al., 2013; Bershad et al., 2016). However, this has not been assessed with morphine yet, and buprenorphine's antagonistic effects in the KOR system may be the reason for this effect. Hence, the relationship between the mu-opioid receptor and the recognition of fear may not be fully investigated so far.

The studies differ from each other and from the present study also regarding the measurements taken. Bershad et al. (2016) examined the participants' attention toward emotional facial expressions and ratings regarding perceived positivity and negativity, and Løseth et al. (2018) asked the participants to rate the perceived happiness and anger in the presented faces, the latter emphasizing in their discussion that this might not be the most appropriate approach to this matter. The present work is the closest to Ipser's study (2013) in terms of approach, since here, too, the accuracy of emotion recognition is determined. In addition, however, here the reaction time is also examined.

Apart from that, Bershad et al. (2013) only used full facial expressions as stimuli in their studies. But, as was shown by Løseth et al. (2018), the ambiguous or implicit expressions seem to be of relevance. That is why, in the current study, there are assessed different levels of emotional intensity.

In the studies described, as done here, possible influences of symptoms of mood of the participants, and in one study (Løseth et al., 2018) also possible influences of symptoms of ASD on emotion recognition were taken into account. However, the possible influence of alexithymia on emotional recognition was not controlled. Since alexithymia is associated with impairments in emotion recognition (Taylor & Bagby, 2013) and there even seems to be a connection with the opioid system (Craparo 2016; Giynas Ayhan et al., 2018; Torrado et al., 2013), this study investigated whether the participants were affected by alexithymia and possible influences on the recognition of emotions were taken into account.

## 1.5 Research Questions and Hypotheses

The first research question concerns changes in the perception and evaluation of positive stimuli, here happy facial expressions, through activation of the MOR system. That other studies have found no change in the perception of happy faces after MOR activation (Bershad et al., 2016; Ipser et al., 2013; Løseth et al., 2018) may be due to the differences in approach or limitations described above. Nevertheless, as already mentioned, looking at happy faces can be rewarding (Spreckelmeyer et al., 2009). The opioid system is related to the perception of positive stimuli such as social rewards (Nummenmaa & Tuominen, 2018; Syal et al., 2015). Moreover, MOR activation leads to a more positive evaluation of images with social content (Bershad et al., 2016). Based on these considerations, the first hypothesis is as follows:

**H1: Morphine will increase the ability to recognize happy faces (especially in case of ambiguity).**

The second research question focuses on changes in the perception and evaluation of negative social stimuli, caused by MOR activation. Both angry and fearful faces can indicate a threat (Calvo & Beltrán, 2013; Enticott et al., 2014; Hunnius et al., 2011). The MOR system has been proven to dampen the perception of negative social stimuli (Bershad et al., 2016; Hsu et al., 2013; Hsu et al., 2015). Brain areas which have a particularly high density of mu-opioid receptors, such as the amygdala (Adolphs, 2002; Jacobsen et al., 2006), are involved in the recognition of fearful and angry faces (Adolphs & Tranel, 2003). Previous studies indicate that activation of the MOR system results in decreased attention towards angry faces (Løseth et al., 2018) respectively reduced sensitivity (Ipser et al., 2013) and decreased attention (Bershad et al., 2016) towards fearful faces. Based on current literature and considering the gaps in research, the second hypothesis is as follows:

**H2: Morphine will reduce the ability to recognize fearful and angry facial expressions (especially in case of ambiguity).**

# 2 Methods

## 2.1 Participants

### 2.1.1 Sample characterization

Forty healthy women aged between 19 and 31 years participated in the study. Table 1 provides information on the characteristic of the sample.

Table 1

*Characteristic of the Sample*

| Variable | N | *M (SD)* | Minimum | Maximum |
|---|---|---|---|---|
| Age | 40 | 24.30 (3.54) | 19 | 31 |
| BMI | 40 | 22.62 (3.34) | 17.36 | 32.11 |
| Education | 40 | 5.73 (1.34) | 2 | 7 |
| AQ | 40 | 6.42 (3.89) | 0 | 18 |
| Alexithymia | 39 | 40.00 (8.88) | 26 | 59 |

*Note.* Here the mean values (M) and standard deviations (SD) as well as the respective minimum and maximum values of the individual variables are shown for the complete sample (N). The educational level was determined using the following selection options: 1 = no education, 2 = compulsory school, 3 = apprenticeship, 4 = specialized school, 5 = general secondary school, 6 = professional secondary school, 7 = university. The autism spectrum quotient (AQ) was assessed with the German short version of the Autism Spectrum Quotient questionnaire (AQ-k; Freitag et al., 2007). Alexithymia was assessed with the German version of the Toronto Alexithymia Scale (TAS; Kupfer et al., 2001), which one participant did not fill out due to technical problems.

### 2.1.2 Recruitment

Recruitment began in October 2019 and continued parallel to the study. A flyer (appendix A) was repeatedly hung up at different locations of the University of Vienna and distributed at some entrances of the university. It was also uploaded once a week to several Facebook groups. The flyers contained brief notes on the individual parts of the study, a note on the financial compensation, the inclusion and exclusion criteria, and the advice to contact the e-mail address provided if interested in participating in the study.

All persons who expressed their interest in participating in the study at the e-mail address provided were sent a document containing more detailed information on the study and a link to online questionnaires, which they were asked to complete in order to determine their

eligibility to participate in the study. In case of eligibility regarding the online questionnaires, an appointment for the medical and psychological screening was made by phone.

The medical and psychological screening took place at the department of psychiatry and psychotherapy at the Vienna General Hospital (Allgemeines Krankenhaus, AKH). First the participants were given the information document they had already received by e-mail in printed form and were asked to sign it. Hereafter, the examination was conducted which consisted of an electrocardiogram, a blood sample, and the Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998).

Participants were informed of the results of the examination by phone a few days later and in case of eligibility a study appointment was scheduled. To avoid differences due to hormonal variations, the luteal phase of each participant was calculated by requesting cycle-related information (usual duration of the cycle, day of the beginning of the last period, usual number of days of the period), so that all participants were in the luteal phase at the time of study participation. The cycle phase may have an impact on emotion recognition, since women in the follicular phase recognize emotions of faces better than women in the luteal phase, which is attributed to the current progesterone level (Derntl et al., 2008). During this telephone conversation and by e-mail, they were informed about what they should consider before the study regarding food intake, exercise, smoking and alcohol consumption. The testing session took place at the same location within 8 weeks after the screening.

### 2.1.3 Exclusion and inclusion criteria

The participants should be healthy and not at risk for possible side effects of the drug. To avoid bias of the results due to gender differences, only female participants were admitted to the study. In Løseth et al. (2018) significant gender differences were found, as males compared to females rated presented faces as happier. A certain age range was defined to increase the comparability of the participants, since the ability to recognize emotions can change with age, as described above (see 1.2.3 Emotion recognition in higher age). The effect of the drug should be the same for all participants, therefore participants with regular/recent drug use or dependence were excluded and a restriction of the BMI was specified. In order to avoid prior knowledge of individual participants regarding the content and purpose of the study, master students of psychology and former participants of similar studies were excluded from participation. Table 2 provides a detailed list of the inclusion and exclusion criteria for study participation.

Table 2

*Inclusion and Exclusion Criteria for Study Participation*

| Inclusion and exclusion criteria |
| --- |
| Demographic criteria:<br>– Female gender<br>– Age between 18 and 35 years<br>– German level > C1<br>Physical criteria:<br>– BMI of 17–35<br>– Regular cycle<br>– No pregnancy or breast feeding<br>– No hormonal contraceptives<br>Drug related criteria:<br>– No addiction of any kind<br>– No regular drug consumption<br>– No strong opioid use in the last 2 years before study participation<br>Other criteria:<br>– No master students of psychology<br>– No past participation in a similar study<br>– Consent to physical recordings<br>– Right-handedness |

## 2.2 Study Design

The emotion recognition task was part of a larger study investigating the relationship between the opioid system and social behavior and the analyses reported here are preliminary. The study used a between-subject design in which healthy participants (after a medical and psychological screening) received either placebo or 10 mg per oral morphine in a counterbalanced order under double-blind conditions before completing several tasks regarding risk and trust behavior, reward responses, and emotion perception. The duration of one testing session was 3.5 hours.

## 2.3 Drug Administration

Morphine is a MOR agonist and one of the most used analgesics (Le Merrer et al., 2009). Participants received a capsule filled with either 10 mg of morphine (Morapid®) or 650 mg of mannitol (sugar) from the study doctor. The same dose of morphine was used by Løseth et al. (2018) to mimic endogenous MOR activation while minimizing subjective effects. Peak

concentration in blood and maximal effect of oral morphine is reached 1-2 hours after administration (Lugo & Kern, 2002). As done by Løseth et al. (2018), participants were led to believe that they would receive either an opioid agonist (morphine), or a placebo, or an opioid antagonist (naltrexone) to reduce expectancy about the drug's effect.

## 2.4 Procedure of the Entire Study

After arrival of the participant, a urine test was carried out to rule out drug use and pregnancy. Then the participants were seated in front of a computer with an LCD monitor with a resolution of 1280 x 1024 pixels, where they remained for the entire testing session. After a relaxation period in which participants received instructions for a later task, they were given the pill by the study doctor (see 2.3 Drug Administration). The participants then engaged in an economic trust game (Berg et al., 1995; Schweiger et al., 2014). After conducting the motor coordination control tasks described below (see 2.6 Motor Coordination Tasks), the EMG preparation took place in which the participants were given electrodes on the left half of their face to measure the activity of certain facial muscles. Next, in the facial mimicry task, the participants were presented with short video clips of morphed faces adopting different emotional expressions (see Meier et al., 2016). After this, the emotion recognition task took place (see 2.5 Emotion Recognition Task). The Trier Social Stress Test (TSST; Kirschbaum et al., 1993), which followed hereafter, is a stress-inducing task containing a simulated job interview and the solving of a mathematical problem. The last task of the study was the social reward task, in which the participants were given touch stimuli at different velocities. At the end of the testing session, the study doctor took a blood sample and the participants were informed about the purpose of the study.

EMG measurements of facial muscles were performed during the facial mimicry task and during the social reward task. With a polar belt worn by the participants during the entire testing session and connected to an app on the test supervisor's mobile phone, the heart rate of the participants was measured during the relaxation phase, during the TSST, and during the social reward task. Saliva samples were collected a total of six times during the study. The mood of the participants was assessed at 7 points in the study using visual analogue scales (see 2.7.3 Mood).

## 2.5 Emotion Recognition Task

### 2.5.1 Stimuli

From three male and three female persons one picture with a neutral facial expression and one with a happy, a fearful, and an angry facial expression were taken from the

NimStimSet of Facial Expressions (Tottenam et al., 2009). These were morphed in 10%-steps to create different intensities of facial expression using the software Fantamorph (version 5.4.7). Three levels of intensity were used in the task: 20% (level 1), 40% (level 2), and 80% (level 3). An intensity of 20% is the most ambiguous level (almost neutral), an intensity of 40% is a medium level. In previous pilot studies, facial expressions of an emotion were as well recognized at 80% intensity as at 100% intensity, and the intensity of 80% was chosen, so that a level was always twice as high as the previous. This resulted in a total of 54 stimuli (appendix B). The individual steps of such a morphing process are shown in figure 1.

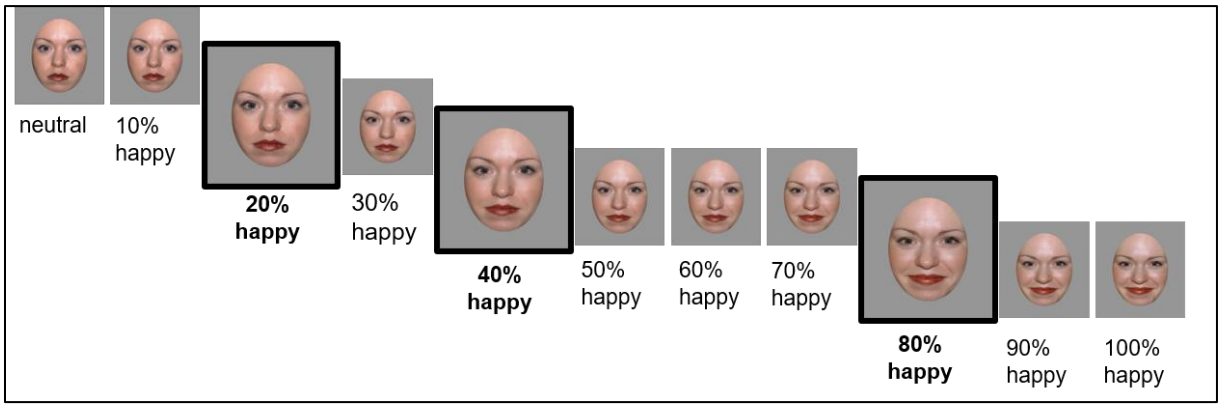


*Figure 1.* Individual steps of the morphing process of a female face from a neutral facial expression to a happy face in full intensity. The framed and enlarged images represent the levels used in the study.

### 2.5.2 Procedure

The emotion recognition task took place 80 minutes after drug administration. First, the participants were instructed that they would see pictures of faces showing either happy, angry, or fearful expressions, to which they should assign the corresponding emotion as quickly as possible by pressing the correct key on the keyboard of the computer. To do so, they were shown how to hold their right hand, with the index finger on the arrow key pointing to the left, the middle finger on the arrow key pointing up, and the ring finger on the arrow key pointing to the right. Each key was assigned the meaning of one emotion, whereby the assignment was randomized for the participants.

In order to memorize the meaning of the keys and practice their use, the participants first conducted two training rounds. First, in 21 trials, they had to respond to the words "happy", "angry", or "fearful" (in German: “fröhlich”, “wütend”, “ängstlich”) presented on the screen by correctly pressing the respective key. In the second training round, they were shown nine pictures of facial expressions (happy, angry, or fearful) in a row – but of different people

than later in the actual task – and had to use the keys to correctly recognize the presented emotion. Each word or picture was shown for a maximum of 1.5 seconds. In contrast to the actual task, they were given feedback during the training trials about whether their answers were correct or not correct or if they missed the time to respond.

In the actual task, the presentation of the pictures occurred in a semi-randomized order with no more than two pictures of the same emotion appearing consecutively. Every picture was shown for a maximum of 1.5 seconds, followed by a fixation cross presented for 1.5-2.5 seconds. Participants had to indicate the presented emotional expression immediately by pressing the correspondent key on the keyboard. If the participants answered faster than within 1.5 seconds, the image disappeared immediately, and the fixation cross appeared. The fixation cross was not always presented for the same duration to prevent the participants from getting used to a pattern and always reacting after a certain time. As every picture was presented twice within the task, it was a total of 108 trials and the task took 8 minutes. Figure 2 illustrates the scheme of an exemplary sequence of the task.

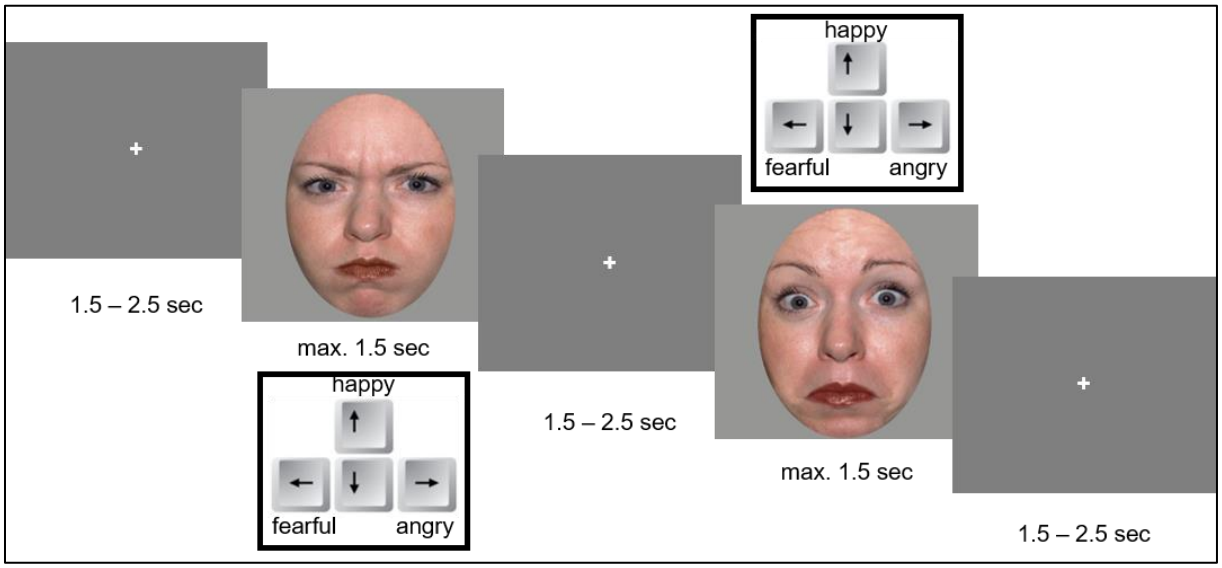


*Figure 2.* An exemplary sequence of the emotion recognition task. Alternating with fixation crosses, an image of an angry face in 80% intensity and a fearful face in 80% intensity is presented. The arrow keys with the assigned meanings illustrate that the emotion should be assigned correctly during the presentation of the facial expression.

### 2.5.3 Measurements and operationalization

As independent variables, group (drug vs. placebo condition), emotion (happy, angry, fearful), and level (20%, 40%, 80% expression) were determined. The variable group is the between-subject factor and emotion and level are within-subject factors, since all participants

were presented with each emotion and level. Dependent variables are reaction time (RT) and accuracy in recognizing the presented emotion. Reaction time is expressed in the number of milliseconds needed to respond to a presented image. Accuracy is expressed as a percentage of the correct answer given for each combination of emotion and level. For example, an accuracy value of 60 means that the participant responded correctly 60% of the total amount of this condition (e.g., happy faces with an expression of 20% intensity).

## 2.6 Motor Coordination Tasks

Potential drug effects on motor function and alertness were assessed using the Trial Making Task (TMT; Reitan, 1995) and the Digit Symbol Substitution Test (DSST; Wechsler, 1958) at approximately 55 minutes post drug administration. The TMT is to connect letters in alphabetical order and numbers in ascending order as quickly as possible, with the experimenter measuring the time required. In the DSST, participants see an assignment of symbols to digits in front of them and must draw the corresponding symbol under as many displayed digits as possible within a fixed time of 90 seconds. The purpose of these two tasks was to exclude the possibility that any slower reactions to the stimuli in the emotion recognition task could be attributed to a general slowdown in motor activity caused by taking morphine.

## 2.7 Questionnaires

### 2.7.1 Toronto Alexithymia Scale

Alexithymia, the subclinical inability to identify and describe emotions experienced by one's self or others (Sifneos, 1973), was assessed with the German version of the Toronto Alexithymia Scale (TAS; Kupfer et al., 2001; appendix C) which every participant except one filled out online before the first appointment. The German version of the TAS consists of 18 items in three scales. The scales measure difficulties in identifying feelings, difficulties in describing feelings, and an externally oriented style of thinking. Examples for items are “It is often not clear to me what I am feeling” (scale 1), “Other people tell me to show my feelings more” (scale 2), and “I use my imagination a lot” (scale 3). The answers are given on a five-level rating scale, with level 1 meaning "does not apply at all" and level 5 meaning "applies completely”. The cut off in this questionnaire is at a score of 61, i.e. people with values above that are considered to have alexithymia. Values between 51 and 60 mean "possible alexithymia". This questionnaire was used in order to rule out that any difficulties in recognizing emotional expressions could be due to symptoms of alexithymia, which would distort the results of the study.

### 2.7.2 Autism Spectrum Quotient

The German short version of the Autism Spectrum Quotient (AQ-k; Freitag et al., 2007; appendix D) was used to investigate whether the participants had symptoms of autism spectrum conditions which can include deficits in nonverbal communicative behaviors used for social interaction (American Psychiatric Association, 2013). The questionnaire consists of 33 statements with the respective answer options "definitely agree", "slightly agree", "slightly disagree", or "definitely disagree", whereby the wording of one half of the statements is aimed at agreement and the other half at disagreement from a neurotypical person. Examples for items are “I find it difficult to empathize with other people” and “I find it easy to figure out what someone is thinking when I just look at her/his face”. The cut off for this questionnaire is at a score of 17. This questionnaire was used in order to rule out that any difficulties in recognizing emotional expressions could be due to problems regarding social competencies, which would distort the results of the study.

### 2.7.3 Mood

Participants’ mood was evaluated several times using visual analogue scales to assess individual emotional states at particular points of the study (appendix E). The participants should indicate their respective mood states regarding four positive (happy’, ‘relaxed’, ‘calm’, and “good”) and four negative moods (‘stressed’, ‘anxious’, ‘bad’, and ‘tense’). An elevated mood can lead to a more positive evaluation of neutral and negative facial expressions, i.e. a positive bias, while a bad mood can cause the opposite, i.e. a more negative evaluation of happy and neutral faces (Schmid & Schmid Mast, 2010). On the other hand, a worse internal mood state can lead to impairments in emotion recognition in general (Demenescu et al., 2010). Therefore, it seemed necessary to survey the mood in which the participants were in during the performance of the emotion recognition task.

## 3 Statistical Analysis

The statistical analysis was performed using the statistics software SPSS Statistics 26 for Windows. The significance level for hypothesis testing was set at $\alpha = 5\%$ (two-sided). Consequently, a result with $p \leq .05$ is considered significant and with $p \leq .001$ highly significant (Bühner & Ziegler, 2009).

The equal distribution of age, BMI, education, autism spectrum quotient, and alexithymia in the two groups (i.e., the two drug conditions morphine vs. placebo) was investigated using the *t* test for independent samples. A *t* test for independent samples was also used to compare the mood and the values in the motor coordination tasks between the

two groups. The homogeneity of variances required for this was assessed with the Levene's test. Regarding mood, only those data were analyzed which were made 60 minutes after taking the pill, i.e. at the shortest time before the emotion recognition task. A positive mood score was calculated by averaging the scores of the VAS items 'happy', 'relaxed', 'calm', and 'good', and a negative mood score was calculated by averaging the scores of the VAS items 'stressed', 'anxious', 'bad', and 'tense'.

Neither the RT nor the accuracy dataset contained outliers (i.e. values with standard deviations above or below 2.5). The Shapiro-Wilk-test used to determine the normal distribution of the dependent variables showed complete normal distribution for the RTs, but not for accuracy. However, according to the central limit theorem (Bühner & Ziegler, 2009), normal distribution was still taken as given, since the sample size was larger than 30. Sphericity was assessed with the Mauchly-test. In case of no sphericity, a Greenhouse-Geisser correction was made.

Emotion and level of emotional intensity are the within subject factors, group is the between subject factor. The influence of these factors on RT and on accuracy was investigated with repeated measures ANOVAs. Furthermore, to exclude possible influences of alexithymia, symptoms of autism spectrum disorders, and mood of the participants on the results, ANCOVAs with the TAS-score, the score in the AQ-k, positive mood and negative mood were performed for RT and for accuracy. Significant main and interaction effects were further investigated using *t* tests corrected with the Bonferroni-method. Effect sizes were reported using partial Eta squares ($\eta_p^2$).

# 4 Results

## 4.1 Descriptive Analyses

As can be seen from Table 3, the sample characteristics were equally distributed across the two groups.

Table 3

*Distribution of Sample Characteristics and Mood Values Across the Groups*

| | Group | n | *M (SD)* | Significance (2-sided) |
|---|---|---|---|---|
| Age | 1 | 21 | 24.81 (3.80) | |
| | 2 | 19 | 21.74 (3.23) | .345 |
| BMI | 1 | 21 | 23.242 (2.61) | |
| | 2 | 19 | 21.934 (3.95) | .220 |
| Education | 1 | 21 | 6.00 (1.14) | |
| | 2 | 19 | 5.42 (1.50) | .175 |
| AQ | 1 | 21 | 6.19 (3.78) | |
| | 2 | 19 | 6.68 (4.10) | .694 |
| TAS | 1 | 21 | 40.14 (9.11) | |
| | 2 | 18 | 39.83 (8.86) | .915 |
| Positive Mood | 1 | 21 | 74.27 (17.02) | |
| | 2 | 19 | 64.80 (22.00) | .134 |
| Negative Mood | 1 | 21 | 7.62 (7.51) | |
| | 2 | 19 | 13.29 (15.86) | .168 |

*Note.* Distribution regarding individual variables for the two groups or partial samples (n). Because of technical problems, one participant did not fill out the TAS (Kupfer et al., 2001). The positive mood score indicates an average of the items ‘happy’, “relaxed”, ‘calm’, and ‘good’. The negative mood score indicates an average of the items ‘stressed’, ‘anxious’, ‘bad’, and ‘tense’.

## 4.2 Inferential Statistical Analyses

### 4.2.1 Motor coordination tasks

Due to technical problems, the data regarding TMT A and TMT B of one participant is not included in this analysis. There was no statistically significant difference between the two groups regarding DSST, $t(38) = 0.8$, $p = .937$. There was no significant difference between the two groups regarding TMT A, $t(36) = -0.62$, $p = .539$, and TMT B, $t(36) = -1.41$, $p = .166$.

### 4.2.2 Reaction time

For reaction time, the ANOVA revealed a highly significant main effect of emotion ($F(1.55, 58.87) = 23.57$; $p < .001$; $\eta_p^2 = .38$), a highly significant main effect of level ($F(1.54, 58.47) = 89.92$; $p < .001$; $\eta_p^2 = .70$), and a highly significant interaction effect of emotion by level ($F(4, 152) = 23.25$, $p < .001$; $\eta_p^2 = .38$). The ANOVA did not reveal a significant main effect of group ($F(1, 38) = 2.08$; $p = .158$).

Regarding the main effect of emotion, RTs for fearful faces were highly significantly higher than for both happy faces ($p < .001$) and angry faces ($p < .001$). Figure 3 shows the mean values of reaction times for each emotion.

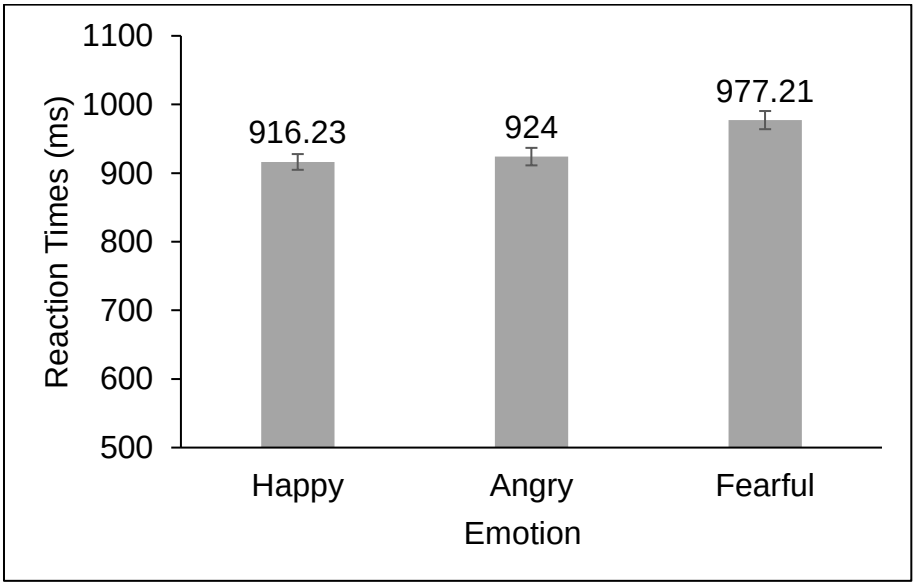


*Figure 3.* Reaction time mean values separated by emotions. Error bars represent standard errors.

Regarding the main effect of level, RTs for faces at level 1 were highly significantly higher than for both faces at level 2 ($p < .001$) and faces at level 3 ($p < .001$). RTs for faces at level 2 were highly significantly higher than for faces at level 3 ($p < .001$). Figure 4 shows the mean values of reaction times at every level.

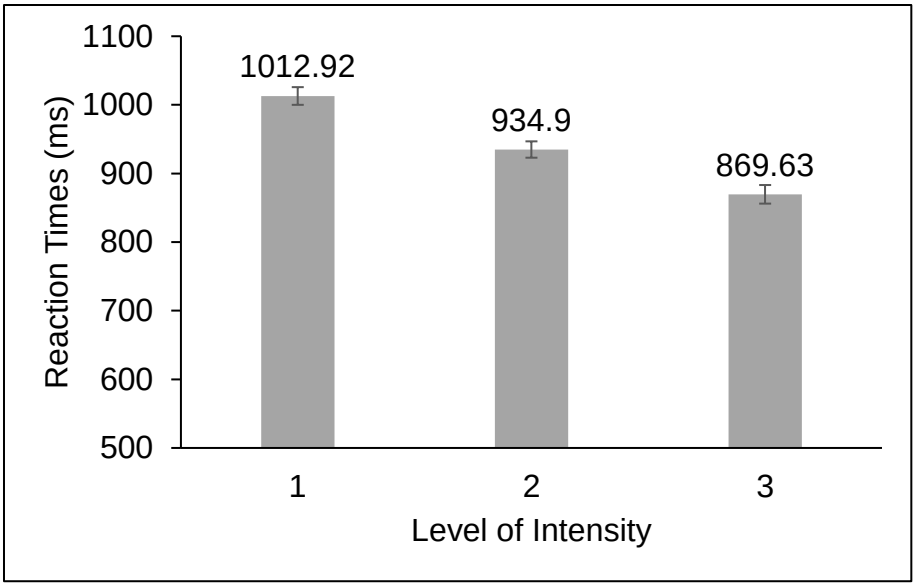


*Figure 4.* Reaction time mean values separated by levels of intensity. Error bars represent standard errors.

Regarding the interaction effect of emotion by level, RTs for fearful faces at level 2 were significantly higher than both happy faces ($p = .016$) and angry faces ($p > .001$) at level 2. RTs for fearful faces at level 3 were highly significantly higher than for happy faces ($p < .001$) and angry faces ($p < .001$) at level 3, and RTs for angry faces at level 3 were highly significantly higher than for angry faces at level 3 ($p < .001$). Figure 5 shows the mean values of reaction times for each emotion, for each level separately.

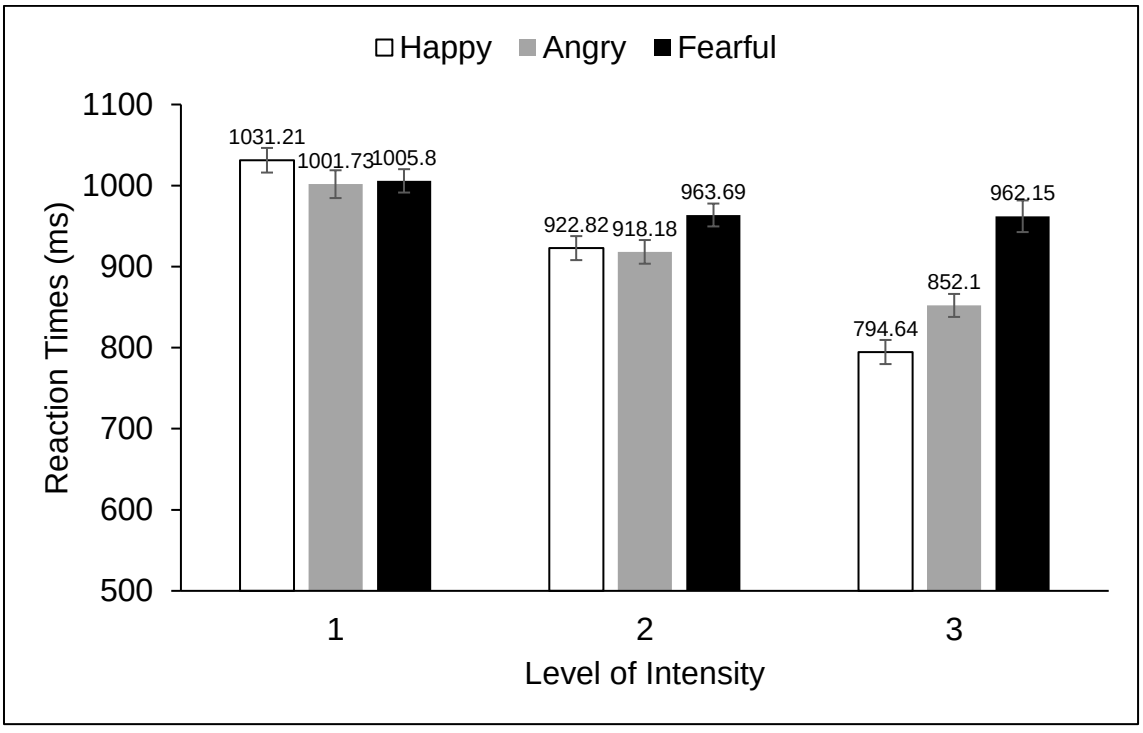


*Figure 5.* Reaction time mean values for each emotion, separated by levels of intensity. Error bars represent standard errors.

The ANCOVA with the TAS-score, the score in the AQ-k, positive mood and negative mood as defined covariates revealed no significant effects.

### 4.2.3 Accuracy

Regarding accuracy, the ANOVA revealed a highly significant main effect of emotion ($F(1.87, 71.02) = 8.55$; $p < .001$; $\eta_p^2 = .18$), a highly significant main effect of level ($F(2, 76) = 326.85$; $p < .001$; $\eta_p^2 = .90$), and a highly significant interaction effect of emotion by level ($F(2.99, 113.59) = 17.91$; $p < .001$; $\eta_p^2 = .32$). The ANOVA did not reveal a significant main effect of group ($F(1, 35) = 0.07$; $p = .158$).

Regarding the main effect of emotion, compared to angry faces, both happy faces ($p = .004$) and fearful faces ($p = .005$) were recognized with greater accuracy. Figure 7 shows the mean values of accuracy for each emotion separately.

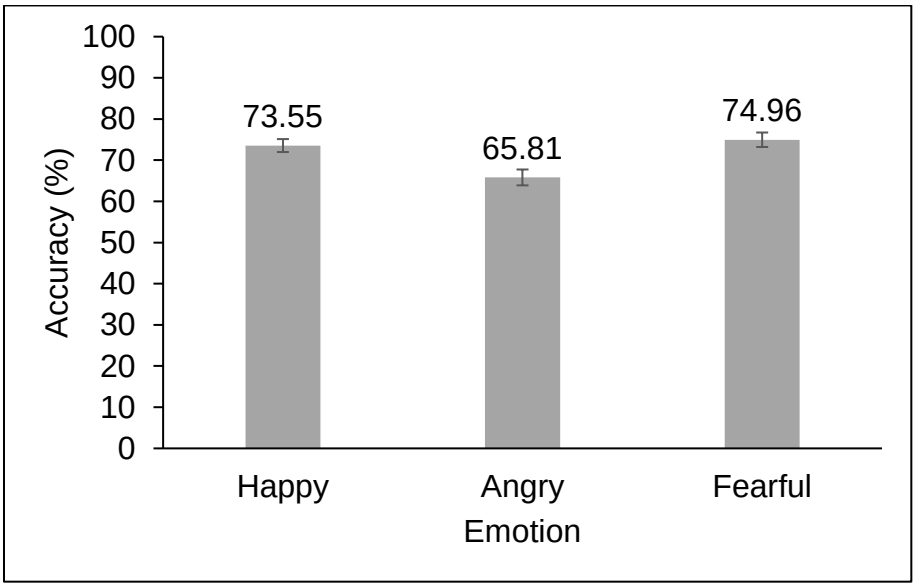


*Figure 6.* Accuracy mean values separated by emotions. Error bars represent standard errors.

Regarding the main effect of level, accuracy for faces at level 3 was significantly higher than for faces at level 1 ($p < .001$) and faces at level 2 ($p < .001$). Accuracy for faces at level 2 was significantly higher than for faces at level 1 ($p < .001$). Figure 8 shows the mean values of accuracy for each level separately.

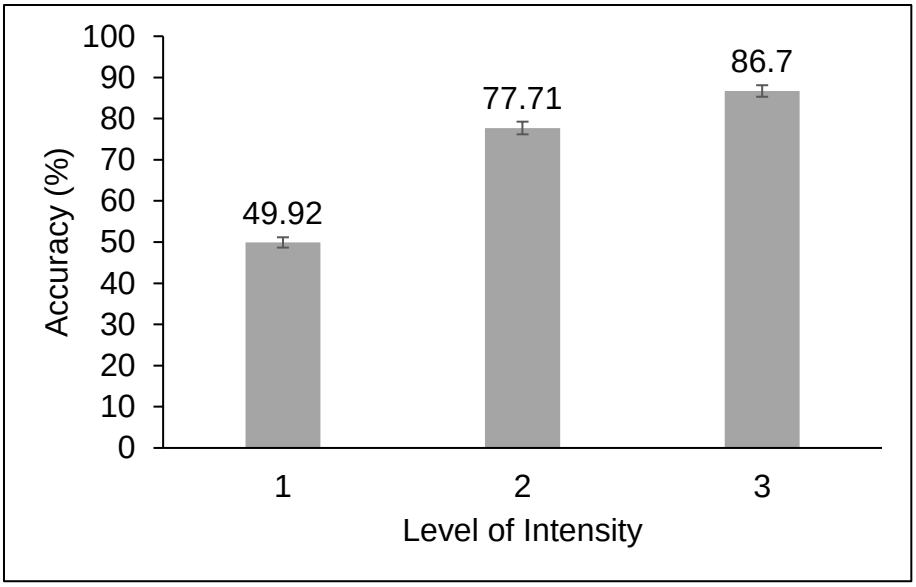


*Figure 7.* Accuracy mean values separated by levels of intensity. Error bars represent standard errors.

Regarding the interaction effect of emotion by level, accuracy for fearful faces at level 1 was highly significantly higher than for happy faces ($p < .001$) and angry faces ($p < .001$) at level 1. Accuracy for both happy faces ($p < .001$) and fearful faces ($p < .001$) at level 2 were highly significantly higher than for angry faces at level 2. Accuracy for happy faces at level 3 was highly significantly higher than for angry faces ($p < .001$) and fearful faces ($p < .001$). Figure 9 shows the mean values of accuracy for each emotion, for each level separately.

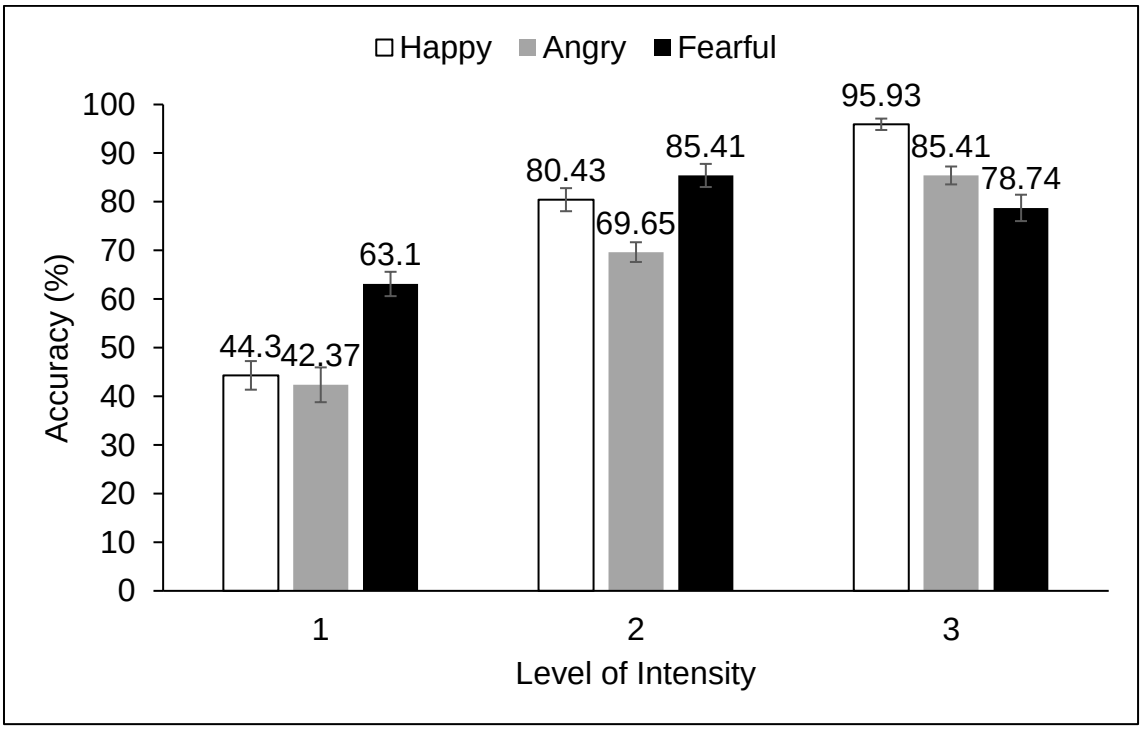


*Figure 8.* Accuracy mean levels for each emotion, separated by levels of intensity. Error bars represent standard errors.

The ANCOVA with the TAS-score, the score in the AQ-k, positive mood and negative mood as defined covariates revealed a significant main effect of level ($F(2, 66) = 5.43$; $p = .007$; $\eta_p^2 = .14$).

# 5 Discussion

## 5.1 Summary and Discussion of Results

### 5.1.1 Addressing the research questions

The aim of this study was to investigate effects of mu-opioid receptor activation on healthy volunteers' recognition of happy, angry, and fearful facial expressions with different levels of intensity. For this purpose, the participants were administered either morphine or a placebo and these two groups were compared in terms of reaction time and accuracy in the recognition of emotion in facial expressions.

The first hypothesis was that happy faces would be recognized faster and more accurately under the influence of morphine. This hypothesis could not be confirmed since there could not be found any significant difference between the two groups regarding reaction time or accuracy in the recognition of happy faces. This result is not in line with study results suggesting a more positive evaluation of social stimuli under activation of the MOR system (Bershad et al., 2016), and the assumed connection between the rewarding perception of happy faces (Spreckelmeyer et al., 2009) and the important role of the MOR system in the perception of social rewards (Nummenmaa & Tuominen, 2018; Syal et al., 2015) could not be demonstrated here. However, the result is consistent with earlier work which also found no effect caused by activation of the MOR system on the recognition of happy faces (Bershad et al., 2016; Ipser et al., 2013; Løseth et al., 2018). As the present work differs from these studies in terms of methodology and the measurements taken, this nevertheless consistent result can be considered as a further confirmation or extension of their findings. While previous studies had examined the influence of buprenorphine on emotion recognition, the present study examined the effects of morphine. Thus, activation of the MOR system does not seem to lead to a higher ability to recognize happy faces, regardless of whether the drug under investigation also binds to kappa-opioid receptors (like buprenorphine) or exclusively to mu-opioid receptors (like morphine). Furthermore, morphine seems to have no influence on the accuracy in the recognition of happy expressions, as already observed by Ipser et al. (2013), nor on the reaction time required for the recognition of happy expressions, which in the present study was measured in addition to accuracy.

The second hypothesis was that angry and fearful faces would be recognized more slowly and less accurately under the influence of morphine. This hypothesis could not be

confirmed either since there could not be found any significant difference between the two groups regarding reaction time or accuracy in the recognition of angry and fearful faces. Regarding angry faces, this result is partly consistent with previous research, as neither Ipser et al. (2013) nor Bershad et al. (2016) found an effect on the recognition of angry faces after administration of buprenorphine. However, the result contrasts with the study conducted by Løseth et al. (2018) which showed a reduced attention to angry faces after administration of morphine. Here, the different approach in this study in comparison to the present work should be considered again. There, the participants were asked to rate emotional facial expressions on visual analogue scales according to how happy and how angry they appeared. Here, on the other hand, the task was the correct assignment of emotions. The different approach – subjective assessment versus categorization task – may have contributed to the fact that different results were found.

The influence of morphine on the recognition of fearful faces had not been investigated before, since the only study examining possible effects of morphine on emotion recognition (Løseth et al., 2018) did not include fearful faces. However, the lack of effect seems to be in contradiction to earlier studies, which found reduced sensitivity (Ipser et al., 2013) or decreased attention (Bershad et al., 2016) on fearful faces after administration of buprenorphine, which is why similar effects were expected in the present study using morphine. But the fact that no morphine-induced effect on the recognition of fearful faces was found here may be due exactly to the difference between buprenorphine and morphine regarding opioid receptor binding. Wardle et al. (2016) found similar effects on the recognition of fear as Ipser et al. (2013) and Bershad et al. (2016) with naltrexone, which is a KOR antagonist like buprenorphine, but also a MOR antagonist. That both drugs are KOR antagonists was considered as a possible explanation for the same effect of buprenorphine and naltrexone on the recognition of fear. Bershad et al. (2016) suggest that the combination of binding at the KOR and the MOR occurring in buprenorphine contributed to the effects found in their study. However, from the joint consideration of the results of Bershad et al. (2016) and Wardle et al. (2016) it could be concluded that the MOR system has no influence on the recognition of fearful faces. This may again be confirmed by the absence of a corresponding effect in the present work, since a drug (morphine) was used here that only binds to mu-opioid receptors and the effect can therefore be considered independently of the KOR system. The present study therefore contributes to a considerable gain in knowledge in this area.

To exclude possible influences of alexithymia, symptoms of autism spectrum conditions, and mood, covariance analyses were performed with these variables. Even under

control of these possible influencing factors, the two hypotheses cannot be confirmed, since the morphine group showed no better recognition of happy faces or worse recognition of angry or fearful faces in the ANCOVAs.

### 5.1.2 Interpretation of hypothesis-independent effects

Both ANOVAs and the ANCOVA for accuracy revealed a significant effect of level. Images with the lowest intensity of emotional facial expression (i.e. 20% or level 1) had the highest reaction times and the lowest accuracy. These were therefore the slowest and least accurate images recognized by the participants. Images with medium intensity (i.e. 40% or level 2) were in the middle in terms of both reaction times and accuracy. Images with the highest intensity (i.e. 80% or level 3) were recognized with the lowest reaction times and the highest accuracy. These clear differences represent a desirable result, as they confirm that the selected levels were sufficiently distinguishable. However, this trend is less clear for fearful faces compared to the other two emotions, as the reaction times and accuracy between level 2 and level 3 are only slightly different for fearful faces. Thus, for fearful faces, a higher level seemed hardly to contribute to an easier recognition. Regarding reaction times, under control of the covariates the effect of level is not significant anymore whereby the exact reason for this could be investigated in further research.

When comparing the recognition of the three emotions, happy faces were recognized with rather low reaction times and high accuracy. This difference becomes even stronger when comparing the reaction times and accuracy in the recognition of the three emotions at 80% intensity. Here, happy faces have the lowest reaction times, but the highest accuracy, and were therefore recognized fastest and most accurately compared to angry and fearful faces. This is clearly in line with the current state of research, as it has been repeatedly shown that happy faces are recognized faster and more accurately than other emotional expressions in categorization tasks (Calvo & Beltrán, 2013; Calvo & Lundquist, 2008; Grimshaw et al., 2004; Kosonogov & Titova, 2018).

Fearful faces have the highest reaction times, but also, like happy faces, a high accuracy. This is only partially consistent with the current state of research indicating that in categorization tasks fearful faces are recognized both the slowest and the least accurate (Calvo & Lundquist, 2008; Rapcsak et al., 2000; Zhao et al., 2013). One possible explanation for the high degree of accuracy found here could be that fear is often confused with surprise (Adolphs, 2002), which was not an answer choice in the current study. The result found here suggests that the participants took longer to answer when presented to a fearful face, but then

often made the right decision. However, at 80% intensity, fearful faces still have high reaction times, but in comparison to happy and angry faces, they have the lowest accuracy rates, which again fits well with previous study results mentioned above.

On closer examination of the values for angry faces, it is noticeable that they have low reaction times and the lowest accuracy compared to the other emotions. This indicates that the participants reacted quickly to angry faces without being sure about the answer (in contrast to fearful faces, where the participants apparently took longer to respond, but then showed a relatively high accuracy), perhaps because they wanted to remove angry faces as soon as possible which may be related to the perception of angry faces as possible threat cues in the environment (Enticott et al., 2014; Williams, 2006). In this case, the participants would have recognized the angry faces at a rather unconscious level and would have responded by any quick reaction that was not necessarily correct. This is consistent with the findings of studies showing that angry faces are perceived more quickly than other facial expressions, sometimes in a non-conscious way (Calvo & Beltrán, 2013; Fox et al., 2000; Hansen & Hansen, 1988; Horstmann & Bauland, 2006; Öhman et al., 2001). Regarding angry faces, the present work was thus able to achieve a gain in knowledge by measuring both reaction times and accuracy.

Under control of the TAS-score, the score in the AQ-k, positive mood, and negative mood, the main effect of emotion which was significant in the ANOVA – higher RTs for fearful faces and a lower accuracy for angry faces – was no longer significant. Various studies indicate that people with alexithymia have particular difficulties in recognizing negative facial expressions. For example, they are slower in labeling fearful and angry faces compared to happy and neutral faces (Ihme et al., 2014). Moreover, in alexithymia the automatic processing and the detection of change and novelty in expressions is disturbed especially for angry faces (Vermeulen et al., 2006; Vermeulen et al., 2008). Taking this into account, it may have been the case here that alexithymia worsened the recognition of fearful and angry faces even more, resulting in significant differences between the emotions, which disappear when the influence of alexithymia is removed. Regarding ASD, the same assumptions can be made, because persons with ASD have specific problems with the recognition of negative facial expressions such as anger (Enticott et al., 2014; Philip et al., 2010). However, it must be noted that the TAS has a cut off at a score of 61 and only above this value actual alexithymia is assumed. The sample examined here contained five participants with values between 51 and 60, which indicate "possible alexithymia". Also, only one participant had a score above the cut off in the AQ, so final conclusions cannot be drawn here. As explained above, the perception or assessment of positive and negative stimuli can vary according to mood

(Schmid & Schmid Mast, 2010), which may also have contributed to the fact that the difference between the emotions is no longer significant in the ANCOVA.

It was not intended that significant differences between the emotions would appear at all, but the stimuli were chosen in a way that should give a similar degree of difficulty in recognizing all three emotions. However, this significant difference disappears under control of various possible influencing factors, suggesting that the difference was caused by these factors.

### 5.2 Limitations and Future Directions

As the survey of the study had to be interrupted for a longer period of time due to the COVID-19 regulations, the sample whose data were analyzed for the present work was relatively small which is particularly problematic since the study has a between-subject design.

Only women could participate in the study, which was decided primarily based on influences which might affect the results in other parts of the study, such as stress levels, which may differ between the sexes. But according to several studies, differences between women and men can also occur in the recognition of emotions (Anderson et al., 2011; Biele & Grabowska, 2006; McClure, 2000). Therefore, the findings obtained here are not representative of both genders. Further research could examine this in more detail and include men in a repetition of the present study to determine whether different results are found between women and men.

The educational level of the participants was quite high, since a large part of the participants had high school or university degrees, which was probably due to the recruitment mostly taking place in different buildings of the university and via several Facebook groups of different study programs. Therefore, the results of this study are not representative for all educational levels in society, also because general intelligence can be a possible predictor for emotion recognition (Connolly et al., 2020). Further studies in the future with a more heterogeneous sample could provide more accurate results.

### 5.3 Conclusion

In the present study, no improved perception of positive stimuli or worsened perception of negative stimuli through activation of the MOR system could be found. Especially in the context of fearful facial expressions, however, the present work could provide new insights, since the influence of morphine on the recognition of these facial expressions had not been investigated before. The present work is also the first among comparable studies in which the

influence of alexithymia on the recognition of emotions in healthy subjects in connection with opioid system activation was considered. Future research may start here and provide further findings. Investigating the relationship between the mu-opioid system and emotion recognition is of high clinical relevance, since, as described in the theoretical part of this work, several clinical conditions are associated with impairments in emotion recognition and with changes in the opioid system. Further knowledge in this area could therefore be of importance in the clinical psychological field, especially in the pharmacological context.

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## 7 Abstract

The mu-opioid receptor (MOR) system has an important role in social behavior. According to the current state of research, an activation of this system increases receptivity to positive social stimuli and decreases receptivity to negative social stimuli. This study investigated possible influences of an opioid system activation by the MOR agonist morphine on the recognition of emotional facial expressions. It was assumed that morphine would facilitate the recognition of happy faces and impair the recognition of angry and fearful faces. For this purpose, 40 healthy participants were divided into two groups, one of which was given a low dose of morphine and the other a placebo. The participants were then asked to assign the right emotion to faces presented on a screen with happy, angry, or fearful facial expressions in different intensities. The two groups were compared regarding the reaction times required for the recognition of the individual emotions and the accuracy achieved. The hypotheses could not be confirmed, as no difference was found between the two groups regarding the recognition of the individual emotions. Regarding fearful faces, these findings are new, since the influence of morphine on the recognition of fearful faces had not been investigated in this form before.

*Key words:* Opioid System, Mu-Opioid Receptor, Morphine, Emotion Recognition, Happy, Angry, Fearful, Facial Expression

## 8 Zusammenfassung

Das Mu-Opioid-Rezeptor-System (MOR-System) hat eine entscheidende Rolle im Sozialverhalten inne. Aktuelle Studienergebnisse legen nahe, dass eine Aktivierung dieses Systems die Empfänglichkeit für positive soziale Reize erleichtert und für negative soziale Reize beeinträchtigt. Die vorliegende Arbeit untersuchte mögliche Einflüsse einer Opioidsystem-Aktivierung durch den MOR-Agonisten Morphin auf die Erkennung emotionaler Gesichtsausdrücke. Dabei wurde angenommen, dass Morphin die Fähigkeit zur Erkennung fröhlicher Gesichter erhöhen und die Erkennung wütender und ängstlicher Gesichter erschweren würde. Zu diesem Zweck wurden 40 gesunde Teilnehmerinnen in zwei Gruppen unterteilt, wobei der einen Gruppe eine niedrige Dosis des Wirkstoffs Morphin und der anderen Gruppe ein Placebo verabreicht wurde. Daraufhin sollten die Teilnehmerinnen auf einem Bildschirm präsentierten Gesichtern mit fröhlichen, wütenden bzw. ängstlichen Gesichtsausdrücken in unterschiedlichen Intensitäten die jeweils richtige Emotion zuordnen. Die beiden Gruppen wurden bezüglich der für die Erkennung der einzelnen Emotionen benötigten Reaktionszeiten und der dabei erreichten Genauigkeit miteinander verglichen. Die

Hypothesen konnten nicht bestätigt werden, da kein Unterschied zwischen den beiden Gruppen hinsichtlich der verglichenen Werte gefunden wurde. Bezüglich ängstlicher Gesichter bringt diese Studie neue Erkenntnisse, da Einflüsse von Morphin auf die Erkennung ängstlicher Gesichter zuvor noch nicht in dieser Form untersucht worden waren.

*Schlüsselbegriffe:* Opioidsystem, Mu-Opioid-Rezeptor, Morphin, Emotionserkennung, fröhlich, wütend, ängstlich, Gesichtsausdruck

## 9 List of Figures



## 10 List of Tables



## 11 List of Abbreviations

| | |
|---|---|
| ASD | Autism spectrum disorder |
| AQ | Autism Spectrum Quotient |
| AQ-k | Autism Spectrum Quotient questionnaire, German short version |
| BPD | Borderline personality disorder |
| DSST | Digit Symbol Substitution Test |
| KOR | Kappa-opioid receptor |
| M | Mean |

| | |
|---|---|
| MOR | Mu-opioid receptor |
| N | Complete sample |
| n | Partial sample |
| p | Significance |
| RT | Reaction time |
| SD | Standard deviation |
| TMT | Trial Making Task |
| α | Measure of internal consistency |
| $\eta_p^2$ | Measure of the effect power of partial Eta² |

## 12 List of Appendices

Appendix A

Flyer for Recruitment

# TEILNEHMERINNEN für Studie GESUCHT

Sie sind...

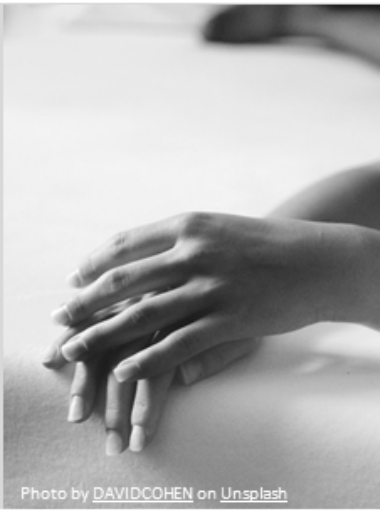
- Weiblich
- Zwischen 18–35 Jahre jung
- Gesund
- Nutzen keine hormonelle Empfängnisverhütung

Dann melden Sie sich, um an unserer Studie teilzunehmen und dafür eine **finanzielle Entschädigung** zu erhalten!

Wir untersuchen die Funktionsweise gewisser Rezeptoren bei der Beeinflussung von sozialer Kognition, Motivation und Entscheidungsfindung.

Nachdem wir mit Onlinefragebögen und ersten Tests geprüft haben, dass Sie für die Teilnahme geeignet sind, erhalten Sie einmalig einen von zwei zugelassenen **Arzneistoffen** oder ein Scheinpräparat (Placebo).

Dann werden Sie Fragebögen ausfüllen, führen ein Schein-Vorstellungsgespräch durch und erledigen andere Aufgaben, die Berührungsreize am Unterarm und die Beurteilung emotionaler Bilder beinhalten.



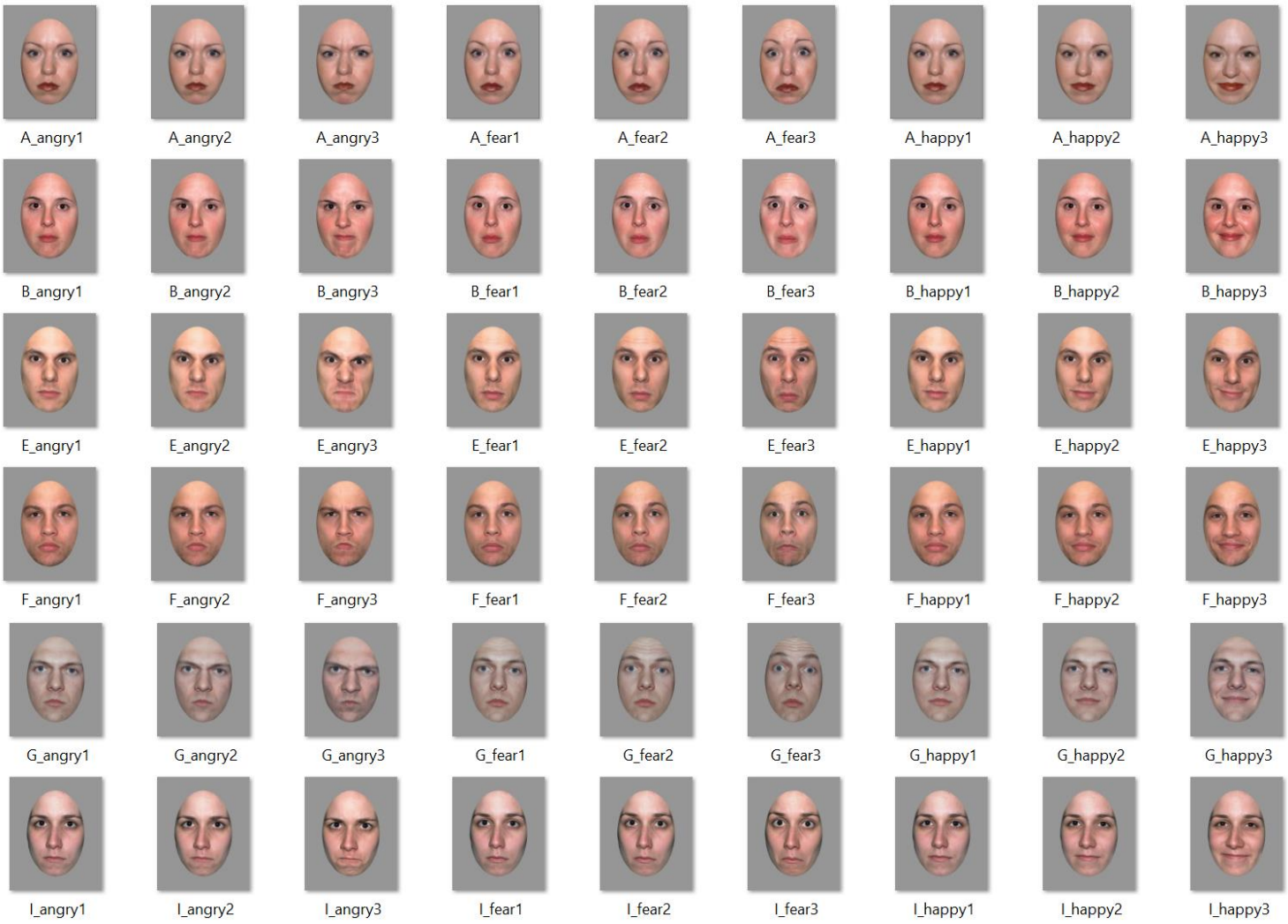

**Dauer**
Die Studie dauert **4,5 Stunden** und findet an **2 Tagen** statt. Zwischen den beiden Laborbesuchen dürfen maximal 8 Wochen liegen.

**Ort**
Die Studie findet an der **Univ. Klinik für Psychiatrie und Psychotherapie**, **Allgemeines Krankenhaus (AKH)**, Währinger Gürtel 18-20, 1090 Wien statt.

Bei Interesse schreiben Sie bitte eine E-Mail mit Angabe Ihrer Telefonnummer an **csn.unit.2018@univie.ac.at**

# Appendix B

## Stimuli



# Appendix C

## Toronto Alexithymia Scale

Im Folgenden geht es um den Umgang mit Gefühlen. Bitte geben Sie an, wie sehr die folgenden Aussagen auf Sie zutreffen oder nicht zutreffen. Kreuzen Sie bitte diejenige Antwort an, die am besten auf Sie persönlich zutrifft.

| | Trifft gar nicht zu | Trifft eher nicht zu | Teils/teils | Trifft eher zu | Trifft völlig zu |
|---|---|---|---|---|---|
| Mir ist oft unklar, welche Gefühle ich gerade habe. | ○ | ○ | ○ | ○ | ○ |
| Es fällt mir schwer, die richtigen Worte für meine Gefühle zu finden. | ○ | ○ | ○ | ○ | ○ |
| Ich habe körperliche Empfindungen, die sogar die Ärzte nicht verstehen. | ○ | ○ | ○ | ○ | ○ |
| Es fällt mir leicht, meine Gefühle zu beschreiben. | ○ | ○ | ○ | ○ | ○ |
| Ich gehe Problemen lieber auf den Grund, als sie nur zu beschreiben. | ○ | ○ | ○ | ○ | ○ |
| Wenn mich etwas aus der Fassung gebracht hat, weiß ich oft nicht, ob ich traurig, ängstlich oder wütend bin. | ○ | ○ | ○ | ○ | ○ |
| Ich bin oft über Vorgänge in meinem Körper verwirrt. | ○ | ○ | ○ | ○ | ○ |
| Ich lasse die Dinge lieber einfach geschehen und versuche nicht herauszufinden, warum sie gerade so passiert sind. | ○ | ○ | ○ | ○ | ○ |
| Einige meiner Gefühle kann ich gar nicht richtig benennen. | ○ | ○ | ○ | ○ | ○ |
| Sich mit Gefühlen zu beschäftigen, finde ich sehr wichtig. | ○ | ○ | ○ | ○ | ○ |

| | Trifft gar nicht zu | Trifft eher nicht zu | Teils/teils | Trifft eher zu | Trifft völlig zu |
|---|---|---|---|---|---|
| Ich finde es schwierig zu beschreiben, was ich für andere Menschen empfinde. | ○ | ○ | ○ | ○ | ○ |
| Andere fordern mich auf, meine Gefühle zu beschreiben. | ○ | ○ | ○ | ○ | ○ |
| Ich weiß nicht, was in mir vorgeht. | ○ | ○ | ○ | ○ | ○ |
| Ich weiß oft nicht, warum ich wütend bin. | ○ | ○ | ○ | ○ | ○ |
| Ich unterhalte mich mit anderen nicht gerne über ihre Gefühle, sondern lieber darüber, womit sie sich täglich beschäftigen. | ○ | ○ | ○ | ○ | ○ |
| Ich sehe mir lieber „leichte“ Unterhaltungssendungen als psychologische Problemfilme an. | ○ | ○ | ○ | ○ | ○ |
| Es fällt mir schwer, selbst engen Freunden gegenüber meine innersten Gefühle mitzuteilen. | ○ | ○ | ○ | ○ | ○ |
| Ich kann mich jemandem sogar in Augenblicken des Schweigens sehr nahe fühlen. | ○ | ○ | ○ | ○ | ○ |
| Ich finde, dass “mir-klar-werden” über meine persönlichen Gefühle wichtig ist, wenn ich persönliche Probleme lösen muss. | ○ | ○ | ○ | ○ | ○ |
| Durch die Suche nach verborgenen Bedeutungen nimmt man sich das Vergnügen an Filmen oder Theaterstücken. | ○ | ○ | ○ | ○ | ○ |

# Appendix D

## Autism Spectrum Quotient – Short Version

### AUTISMUS SPEKTRUM QUOTIENT-KURZVERSION AQ-K

*Sämtliche Informationen werden vertraulich behandelt und unterliegen dem Datenschutz und der ärztlichen Schweigepflicht.*

Name: _____ Geschlecht: 0 männlich 0 weiblich

Geburtsdatum: ____.____._____ Das heutige Datum: ____.____._____

***Zum Ausfüllen des Fragebogens:***

*Der Fragebogen besteht aus einer Liste von Sätzen. Bitte, lesen Sie jeden Satz sehr aufmerksam durch und überlegen Sie, ob und wie stark Sie dem Satz zustimmen können. Kreuzen Sie dann die entsprechende Antwort an. Die Antworten reichen von ganz starker Zustimmung („ich stimme eindeutig zu") über leichte Zustimmung („ich stimme ein wenig zu") und leichte Ablehnung („ich stimme eher nicht zu") zu ganz starker Ablehnung („ich stimme überhaupt nicht zu").*

***Bitte, lassen Sie keinen Satz aus.***

*Beispiele:*

| | ich stimme eindeutig zu | ich stimme ein wenig zu | ich stimme eher nicht zu | ich stimme überhaupt nicht zu |
|---|---|---|---|---|
| E1: Ich nehme gerne Risiken auf mich. | ☐ | ☒ | ☐ | ☐ |
| E2: Ich spiele gerne Brettspiele. | ☒ | ☐ | ☐ | ☐ |
| E3: Ich finde es leicht, ein Instrument spielen zu lernen | ☐ | ☐ | ☐ | ☒ |
| E4: Andere Kulturen faszinieren mich. | ☐ | ☐ | ☒ | ☐ |

*Fragebogen:*

| | ich stimme eindeutig zu | ich stimme ein wenig zu | ich stimme eher nicht zu | ich stimme überhaupt nicht zu |
|---|---|---|---|---|
| 1. Ich mache lieber Sachen mit anderen als alleine. | ☐ | ☐ | ☐ | ☐ |
| 2. Ich mache bestimmte Sachen gerne immer wieder auf dieselbe Art und Weise. | ☐ | ☐ | ☐ | ☐ |
| 3. Wenn ich mir etwas vorzustellen versuche, fällt es mir sehr leicht, ein Bild im Kopf entstehen zu lassen. | ☐ | ☐ | ☐ | ☐ |
| 4. Andere Menschen sagen mir häufig, dass das, was ich gesagt habe, unhöflich war, obwohl ich denke, es sei höflich gewesen. | ☐ | ☐ | ☐ | ☐ |

| | ich stimme eindeutig zu | ich stimme ein wenig zu | ich stimme eher nicht zu | ich stimme überhaupt nicht zu |
|---|---|---|---|---|
| 5. Wenn ich eine Geschichte lese, kann ich mir leicht vorstellen, wie die Figuren in der Geschichte aussehen könnten. | ☐ | ☐ | ☐ | ☐ |
| 6. Ich kann in einer Gruppe leicht den Gesprächen von mehreren unterschiedlichen Menschen folgen. | ☐ | ☐ | ☐ | ☐ |
| 7. In sozialen Situationen fühle ich mich wohl. | ☐ | ☐ | ☐ | ☐ |
| 8. Ich würde lieber in die Bibliothek als zu einer Party gehen. | ☐ | ☐ | ☐ | ☐ |
| 9. Mir fällt es leicht, Geschichten zu erfinden. | ☐ | ☐ | ☐ | ☐ |
| 10. Ich fühle mich eher von Menschen als von Gegenständen angezogen. | ☐ | ☐ | ☐ | ☐ |
| 11. Ich genieße Gespräche über Land und Leute. | ☐ | ☐ | ☐ | ☐ |
| 12. Wenn ich eine Geschichte lese, fällt es mir schwer, mir die Absichten der Figuren auszumalen. | ☐ | ☐ | ☐ | ☐ |
| 13. Mir fällt es schwer, neue Freunde kennen zu lernen. | ☐ | ☐ | ☐ | ☐ |
| 14. Es macht mir nichts aus, wenn sich mein Tagesablauf verändert. | ☐ | ☐ | ☐ | ☐ |
| 15. Ich stelle oft fest, dass ich nicht weiß, wie ich ein Gespräch aufrechterhalten kann. | ☐ | ☐ | ☐ | ☐ |
| 16. Es fällt mir leicht, Zwischentöne zu verstehen, wenn sich jemand mit mir unterhält. | ☐ | ☐ | ☐ | ☐ |
| 17. Wenn ich mit jemandem rede, merke ich, wenn es ihm/ihr langweilig wird. | ☐ | ☐ | ☐ | ☐ |
| 18. Mir fällt es leicht, mehrere Sachen gleichzeitig zu machen. | ☐ | ☐ | ☐ | ☐ |
| 19. Wenn ich mit jemandem telefoniere, weiß ich nicht genau, wann ich an der Reihe bin. | ☐ | ☐ | ☐ | ☐ |
| 20. Ich bin gerne spontan. | ☐ | ☐ | ☐ | ☐ |
| 21. Ich verstehe Pointen bei einem Witz oft als allerletzte/r. | ☐ | ☐ | ☐ | ☐ |
| 22. Mir fällt es leicht herauszufinden, was jemand denkt, wenn ich nur auf ihr/sein Gesicht schaue. | ☐ | ☐ | ☐ | ☐ |
| 23. Wenn ich unterbrochen worden bin, kann ich schnell mit meiner vorherigen Tätigkeit weitermachen. | ☐ | ☐ | ☐ | ☐ |

| | ich stimme eindeutig zu | ich stimme ein wenig zu | ich stimme eher nicht zu | ich stimme überhaupt nicht zu |
|---|---|---|---|---|
| 24. Mir macht es Spaß, mich mit Leuten zu unterhalten. | ☐ | ☐ | ☐ | ☐ |
| 25. Oft wird mir erzählt, dass ich ständig über dieselben Dinge spreche. | ☐ | ☐ | ☐ | ☐ |
| 26. Als ich klein war, habe ich gerne Rollenspiele mit anderen Kindern gespielt. | ☐ | ☐ | ☐ | ☐ |
| 27. Mir fällt es schwer, mich in andere Personen hineinzuversetzen. | ☐ | ☐ | ☐ | ☐ |
| 28. Ich genieße soziale Ereignisse. | ☐ | ☐ | ☐ | ☐ |
| 29. Mir fällt es schwer zu erkennen, was andere Menschen vorhaben. | ☐ | ☐ | ☐ | ☐ |
| 30. Unbekannte Situationen ängstigen mich. | ☐ | ☐ | ☐ | ☐ |
| 31. Ich lerne gerne neue Leute kennen. | ☐ | ☐ | ☐ | ☐ |
| 32. Ich bin sehr diplomatisch. | ☐ | ☐ | ☐ | ☐ |
| 33. Mit fällt es leicht, Rollen- oder Phantasiespiele mit Kindern zu spielen. | ☐ | ☐ | ☐ | ☐ |

*Vielen Dank für das Ausfüllen des Fragebogens!*

Originalveröffentlichung: Baron-Cohen et al., Journal of Autism and Developmental Disorders, 2001 und im Buch: The Essential Difference, 2003. Übersetzung und Copyright der deutschen Version: Christine Freitag

## Appendix E

## Visual Analogue Scales to Assess Mood

**Im Moment fühle ich mich...**

Glücklich

gar nicht_____sehr

Gestresst

gar nicht_____sehr

Ängstlich

gar nicht_____sehr

Entspannt

gar nicht_____sehr

Schlecht

gar nicht_____sehr

Ruhig

gar nicht_____sehr

Gut

gar nicht_____sehr

Angespannt

gar nicht_____sehr