General introduction
Displays of emotion are important elements of everyday social interactions. Trouble understanding the emotions of other people can lead to great difficulties in social functioning as can be seen in autism, but also in schizophrenia (Boraston, Blakemore, Chivers, & Skuse, 2007; Chan, Li, Cheung, & Gong, 2010; Harms, Martin, & Wallace, 2010; Kee, Green, Mintz, & Brekke, 2003; Law Smith, Montagne, Perrett, Gill, & Gallagher, 2010). Emotion perception involves a complex interplay between various brain regions that is still poorly understood. In this thesis, we will examine the neural underpinnings of emotion processing with an emphasis on simulation or mirror mechanisms. We will study autism in combination with schizophrenia to gain more insight into the similarities and differences between these patient groups in terms of (social) behavior, social functioning, social cognition, and neural responses during emotion perception. Combined study of these patient groups will provide more information about the underlying neural mechanisms of social (cognitive) dysfunction and give more insight into what makes each disorder unique. These insights could provide important pointers for the development of more effective therapies. In this general introduction, we will provide the reader with the necessary background information to set the stage for the subsequent chapters.

The social arena

Human beings are intrinsically social. We are not the fastest species, nor the strongest, but we have survived because we know how to cooperate to fulfill our needs and those of our conspecifics. The demands placed on our social abilities have increased tremendously since the days of group hunting. Nowadays we are generally part of societies that are governed by complex social rules and cultural values. To navigate smoothly through this environment, we need social cognitive skills that help us manage social relationships effectively (Burns, 2006). These skills are studied in the field of social cognition, which refers to the domain of cognition that involves the perception, interpretation and processing of social information or phrased more simply: to the way we make sense of other people and ourselves (Fiske & Taylor, 1991).

A fundamental part of social cognition is the ability to understand the emotions of other people (for a scientific definition of emotion see textbox 1.1). When a person storms up at us we want to know, for instance, whether that person is angry or happy in order to respond adaptively; should we open our arms to embrace the person or use our arms to cover our face? Bodily expressions, and facial expressions in particular, provide essential information about another person’s emotional state (Ekman, Friesen, & Ancoli, 1980). Through transient changes in the configuration of facial muscles, humans both consciously and unconsciously transmit messages that can help others grasp what is going on in their minds and in their environment (Russell, Bachorowski, & Fernandez-Dols, 2003). This information is essential for maintaining good interpersonal relationships and for learning about, for instance, potential dangers in our environment (Darwin, 1998/1872; Ekman, 1992a; Ekman et al., 1980). Due to the central role of emotional signals in communicating to and influencing others, difficulties in emotion processing can lead to severe impairments in social functioning (Feldman, Philippot, & Custrini, 1991).
1.1 What is an emotion?
During the course of a normal day many of us experience a multitude of emotions, ranging from very basic ones such as happiness and disgust to complex emotions such as guilt (Ekman, 1992a). Emotions color our lives, which makes them most interesting to study. Their scientific scrutiny is, however, complicated by difficulties in defining what an emotion actually entails. In everyday conversations, emotions are often equated with feelings: we feel angry at the person cutting in line in front of us. However, emotions are not mere subjective experiences or intangible mental qualities (Damasio, 1994): when we are angry we can often feel our temperature and heartbeat rise and we might experience a tendency to approach the other person to confront him with his behavior. In addition, we probably (unconsciously) express our feeling of anger by contracting our facial muscles into a frown or by clenching our fists. This example illustrates that the domain of emotion not only comprises subjective experiences, but also expressive reactions of the face and the body, physiological reactions, and (tendencies towards) instrumental and coping behavior (Cornelius, 1996). Thus, emotions are not single mental entities, but complex psychophysiological experiences that can be studied from many different perspectives, including neurobiology.

Simulation theory of social cognition
Historically, theories of social cognition have emphasized theoretical processes involved in identifying the mental states of others. These Theory theories suggest that we attribute a mental state to another individual based on deliberate explicit inferences about that person’s behavior, environment, and other mental states (Gallese & Goldman, 1998; Goldman & Sripada, 2005). Imagine there is a lady sitting in front of you, who bites into her sandwich and shows the most horrifying grimace. According to Theory theory, you would process many percepts of this scene: the sandwich with perhaps a tiny maggot peaking out, a foul smell, the woman’s wrinkled face upon ingestion, and the sound of her gagging. You would then integrate these elements and use your prior knowledge about the meaning of facial expressions, the hygiene in the restaurant and so forth to infer that this woman is experiencing disgust. Cognitive elaborations on sensory representations are an important tool in social cognition, but can only provide a detached account of the experiences of others, while we often have instantaneous ‘gut’ feelings of what is going on in other individuals (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Adolphs, Tranel, & Damasio, 2003). These gut feelings are better accounted for by Simulation theory.

Simulation theories claim that humans (also) use their personal mental mechanism to come to an understanding of the mental life of another individual (Goldman & Sripada, 2005; Keysers & Gazzola, 2006). Here, simulation does not refer to mentalizing by imagining oneself in the same situation as a target. Rather, it refers to an unconscious process by which we directly link first-person (I act) and third-person (he/she acts) experiences, thereby creating a meaningful interpersonal space (Gallese, 2003). As our brain-body system is similar to that of other people, the linkage between the first and third person experiences of actions, sensations and emotions may be established by embodied simulation (Gallese, Keysers, & Rizzolatti, 2004; Keysers & Gazzola, 2006). Embodied simulation is a form of neural processing of social information that involves activating neural states during observation -in representation codes that are specific to the body- that match those that the observer would experience in a similar situation. Motor simulation, for instance, occurs when seeing other people’s actions activates a pattern of motor activity in the observer that
corresponds to the pattern when the observer would perform the same action.

The entwining of action and perception is evident at the behavioral level: the execution of an action can be facilitated by simultaneously watching an action that is similar, and hindered by watching dissimilar actions (Brass, Bekkering, Wohlschlager, & Prinz, 2000; Craighero, Bello, Fadiga, & Rizzolatti, 2002). When seeing emotions, people (unconsciously) mimic the emotional expressions they see in a muscle-specific manner; a process referred to as facial mimicry (Dimberg, Thunberg, & Elmehed, 2000). Seeing a smiling face, for instance, triggers activity in the zygomaticus major muscles that make our mouth corners curl upwards. Besides these motor responses, seeing emotions in another person can also cause the emotional state to (unconsciously) spill over to the observer; a process named emotional contagion (Wild, Erb, & Bartels, 2001). A brief look at the woman’s horrified face might, for instance, make you feel nauseous yourself, which helps you realize what she is going through in an instant. The motor simulation of other people’s facial configuration seems to interact with these affective processes. Adopting emotion-specific postures can, for instance, trigger the corresponding emotion (Ekman, 1992b; Strack, Martin, & Stepper, 1988). Additionally, motor interference can modify the subjective experience of observed emotions (Effron, Niedenthal, Gil, & Droit-Volet, 2006). Several studies demonstrate that congruent mimicry of facial expressions can facilitate emotion recognition, while blocking facial movements can interfere with it (Niedenthal, 2007; Niedenthal, Brauer, Halberstadt, & Innes-Ker, 2001; Oberman, Winkielman, & Ramachandran, 2007). Thus, motor simulation may play a role in emotional contagion and emotion understanding. Facial mimicry and emotional contagion both involve an automatic coupling of information from the self and the other, which already occurs early in life (Hatfield, Cacioppo, & Rapson, 1993; Hess, Philippot, & Blairy, 1999). This direct link between self and other could facilitate attachment, provide a source of information on another person’s emotional state, and help establish empathy.

**Mirror mechanisms**

Simulation theories were greatly stimulated by the discovery of mirror neurons in premotor (F5) and inferior parietal (PF) regions of the macaque monkey’s brain. Single-cell recordings demonstrated that these motor neurons have a special property; they not only respond to the execution of hand-object interactions, but also to the sight of similar actions (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Fogassi et al., 2005; Fujii, Hihara, & Iriki, 2008; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). A subset of ventral premotor neurons triggering mouth actions also fire to the observation of similar mouth actions, including communicative gestures (Ferrari, Gallese, Rizzolatti, & Fogassi, 2003). The discovery of this mirroring property provided neurobiological support for common coding theory, which challenges the distinction between action and perception, and inspired the core idea of embodied simulation theory, namely that our own motor programs may play a role in understanding the actions performed by others (Prinz, 1990; Rizzolatti, Fogassi, & Gallese, 2001). Single-cell (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried), fMRI (Buccino et al., 2001; Filimon, Nelson, Hagler, & Sereno, 2007; Gazzola, Rizzolatti, Wicker, & Keysers, 2007; Grèzes, Armony, Rowe, & Passingham, 2003) and TMS (Avenanti, Bolognini, Maravita, & Aglioti, 2007) studies show that a similar system involving the premotor and posterior parietal cortex exists in humans: the **Mirror Neuron System** (MNS). The facilitation of the execution of actions by the sight of similar
actions (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995) is, for instance, impaired when the premotor cortex is transiently impaired by magnetic stimulation (Avenanti et al., 2007). The motor simulation mechanism implemented in the human MNS may contribute to understanding the intentions behind the actions of others (Rizzolatti & Craighero, 2004).

In addition to an entwining of action perception and execution in the premotor and parietal cortex, there is evidence for a shared circuit in the somatosensory cortex that maps the perception and experience of tactile sensations (Blakemore, Bristow, Bird, Frith, & Ward, 2005; Bufalari, Aprile, Avenanti, Di Russo, & Aglioti, 2007; Keysers et al., 2004). Recently it has been proposed that beyond actions and tactile perceptions, our brain also readily simulates the emotions of others (Decety & Jackson, 2004; Keysers & Gazzola, 2006; Niedenthal, 2007). As further detailed in textbox 1.2, emotions have a complex neurobiological basis. Therefore, simulation of other’s emotions likely involves many different regions. Emotional states often become visible to others through motor acts, namely our bodily and in particular our facial expressions. Recent studies show that the MNS is indeed also activated when humans perceive these facial actions of others (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Hennenlotter et al., 2005; Leslie, Johnson-Frey, & Grafton, 2004; van der Gaag, Minderaa, & Keysers, 2007; Wicker et al., 2003; Wild, Erb, Eyb, Bartels, & Grodd, 2003). Interestingly, activity in the frontal part of the MNS, in pars opercularis of the inferior frontal gyrus, is associated with the participant’s tendency to empathize with other individuals (Gazzola, Aziz-Zadeh, & Keysers, 2006; Jabbri et al., 2007; Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008; Saarela et al., 2007; Schulte-Rüther, Markowitsch, Fink, & Piefke, 2007). In addition, lesions to this area are associated with deficits in emotional empathy and emotion recognition (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). This suggests that motor simulation of facial expressions may help decode the internal state of another person and provide a means to empathize with other people. In chapter 2, we further investigate the role of motor simulation and examine whether during emotion perception somatosensory and affective aspects of other’s emotions are also mirrored.

Due to the alleged role of the MNS in emotion recognition, empathy, and other social skills, such as imitation (Iacoboni et al., 1999) and joint action (Kokal, Gazzola, & Keysers, 2009), various researchers have suggested that a dysfunctional MNS is at the heart of social impairments in autism (Iacoboni & Dapretto, 2006; Oberman & Ramachandran, 2007; Rizzolatti & Fabbrì-Destro, 2008; Rizzolatti, Fabbrì-Destro, & Cattaneo, 2009; Williams, Whiten, Suddendorf, & Perrett, 2001). The mirror neuron hypothesis of autism is grounded in the idea that mirror neurons are involved in the formation of self-other representations, which provide the basis for low level imitation and goal understanding, from which cognitively more sophisticated processes such as the ability to understand other people’s state of mind can develop. Therefore, early developmental impairments in the MNS of children with autism may lead to a cascade of impairments ranging from impaired imitation and goal inference to poor mentalizing and other social abilities. The mirror neuron theory of autism has an intuitive appeal, because the alleged functions of the MNS seem to correspond with the social cognitive deficits seen in autism. We will investigate the role of the MNS in autism in chapters 4 and 5 of this thesis.
1.2 The neurobiology of emotion

Early attempts to identify and understand the neural systems underlying emotion searched for one specific circuit accommodating emotions, “The Emotional Brain”, which resulted in the concept of the limbic system (MacLean, 1949). Although the concept has been widely used in scientific research, it has not been supported by empirical facts (Kotter & Meyer, 1992). Classic limbic areas such as the cingulate gyrus and amygdala have indeed been proven important for emotional processes, but they are also important for non-emotional processes (Devinsky, Morrell, & Vogt, 1995; LeDoux, 2007). Additionally, non-limbic regions such as the insular and somatosensory cortices fulfill important emotional functions as well (Damasio, 1994). In effect, emotions have a multifaceted neurobiological basis. One aspect is the production of affective states (e.g. the subjective experience of feeling happy), which involves structures such as the amygdala and anterior insula (Phillips, Drevets, Rauch, & Lane, 2003a). Another aspect constitutes the bodily responses in reaction to an emotional event, which are continuously represented in the somatosensory cortices (Damasio, 1994). Furthermore, the striatum may, in concert with other areas, serve to coordinate motor responses to emotive stimuli in order to guide the organism towards a desired goal (e.g. approach or withdrawal, Phan, Wager, Taylor, & Liberson, 2002). Expressive reactions of the face are represented in two major adjacent ventrolateral frontal areas (i.e. primary motor cortex, M1, ventral premotor cortex, vPMC), the medial Supplementary Motor Area (SMA) and the cingulate motor cortices (Morecraft, Stilwell-Morecraft, & Rossing, 2004). The precise contribution of the participating areas in emotion experience and the way these widely distributed networks interact is still largely unknown. What we know is that the experience of emotions entails a complex interplay between regions supporting different functions including affective, somatosensory and motor processes.

Autism, Schizophrenia, and Social Dysfunction

Autism Spectrum Disorder

Autism is a severe and lifelong neurodevelopmental disorder, which already manifests itself in the first three years of life by fundamental impairments in reciprocal social interaction and communication, and by stereotyped behaviors and interests (American Psychiatric Association, APA, 2000). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), autism is the core syndrome of the Pervasive Developmental Disorders (PDD), which also include Asperger’s syndrome, PDD-Not Otherwise Specified (PDD-NOS), Childhood Disintegrative Disorder, and Rett’s Disorder. The latter two disorders are less prevalent and presumably of different etiology. Prevalence of all PDDs is estimated to be 60 per 10,000 with an elevated incidence rate in boys compared to girls (4:1, Fombonne, 2005). Because autistic disorders are defined by a common set of behaviors, recent developments of the DSM head towards eliminating separate categories and considering autism as a single spectrum disorder (www.dsm5.org). In this thesis, we will use Autism Spectrum Disorder (ASD) as an umbrella term to refer to autism, Asperger’s syndrome, as well as PDD-NOS. In some cases we will abbreviate this to autism (e.g. title of this thesis). Our focus is on high-functioning individuals; individuals with average or above-average general abilities (i.e. IQ).

The clinical presentation of ASD is heterogeneous depending on clinical specifiers (e.g. severity), associated features (e.g. intellectual disability), and comorbid conditions (e.g. depression). Besides this heterogeneity, impaired social functioning is central to all forms of ASD and persists across the lifespan (Shattuck et al., 2007). Even the most high-functioning adults with
ASD experience difficulties in social interaction and participate less in various social arenas such as work and (social) recreation (Howlin, Mawhood, & Rutter, 2000). These impairments are not unique to ASD, but also exist in other psychiatric disorders such as schizophrenia.

**Schizophrenia**

Schizophrenia is a severe neurodevelopmental disorder with great diversity in symptoms. It typically develops in adolescence and early adulthood, with half to one percent of the population affected and a higher prevalence in men (McGrath et al., 2004). Schizophrenia, which literally means "split mind", is often confused by the general public with the presence of multiple personalities (i.e. dissociative identity disorder). In truth, split mind refers to the dissociation from reality that is typical of the disorder. During psychotic episodes, individuals may display disorganized speech or behaviors, may have unfounded and irrational beliefs (e.g. delusions of persecution), or experience sensory perceptions of things that are not present (e.g. auditory hallucinations of voices). These distortions of normal functions are commonly referred to as positive symptoms. Negative symptoms of schizophrenia entail a loss or absence of normal traits or abilities, such as affective flattening, inability to experience pleasure (anhedonia), lack of motivation (avolition), and a lack of desire to form relationships (asociality). Eugen Bleuler (1911), who coined the term schizophrenia, thought that these latter symptoms are even more fundamental to the disorder than the psychotic symptoms, but current diagnostic manuals give equal weight to both types of symptoms. Schizophrenia is a mixture of symptoms that can manifest itself in many ways, but commonly involves social and occupational dysfunction (DSM-IV-TR, APA, 2000). Disturbances in social interaction are already seen at the prepsychotic phase of the illness, suggesting that they are not simply the consequence of the social isolation and hospitalization that individuals with schizophrenia face (Abdi & Sharma, 2004; Addington, Penn, Woods, Addington, & Perkins, 2008a; Bearden et al., 2000).

**Where ASD and schizophrenia meet**

As previously discussed, ASD and schizophrenia both have unique features and their own developmental course, but severe difficulties in social functioning exist in both (DSM-IV-TR, 2000; Frith, 2003; Goldstein, Minshew, Allen, & Seaton, 2002; Kanner, 1943). Social behaviors of individuals with schizophrenia can resemble autistic symptoms, especially when psychotic symptoms are in remission and negative symptoms become more prominent (Frith, 2003; Sheitman, Kraus, Bodfish, & Carmel, 2004). Common to both is a withdrawal from social contact, which is illustrated by the origin of the term autism: to first describe the developmental disorder, Kanner (1943) borrowed the term autism from Eugen Bleuler (1911), who used it to describe one of the negative symptoms associated with schizophrenia: a withdrawal from contact with the outside world. Due to behavioral similarities between autistic and negative symptoms, a co-diagnosis of autism and schizophrenia can only be established when prominent hallucinations or delusions occur in the presence of a pervasive developmental disorder (DSM-IV-TR, APA, 2000). The presence of negative symptoms does not suffice.

In this thesis, we will focus on the two disorders when they are most similar. We recruit
high-functioning adult men with ASD and non-psychotic adult men with schizophrenia with (mild) negative symptomatology in a similar age and IQ range. We verify clinical diagnoses in the ASD group with the Autism Diagnostic Observation Schedule (ADOS), one of the golden standards for diagnostics in autism research (Lord et al., 2000). The ADOS is a standardized instrument that assesses social interaction, communication, and imagination during a semi-structured interaction with an examiner. To investigate whether our patient groups indeed show similar social behaviors, we apply the ADOS to the schizophrenia group as well. Of particular interest is whether this observational instrument can distinguish ASD from schizophrenia and whether there is an association of autistic symptoms as measured by the ADOS with negative symptomatology in the schizophrenia group (chapter 6). To see whether the patient groups resemble each other in terms of social functioning, we administer the Social Functioning Scale (SFS, Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990, see chapters 4 and 7). The SFS taps those areas that are crucial to community maintenance (e.g. employment, pro-social activities) and is specifically designed for people with known social difficulties.

ASD and schizophrenia can resemble each other in terms of social behavior, but also in terms of the underlying social cognitive skills. In fact, in both disorders social dysfunction is related to impairments in social cognitive skills such as difficulties in recognizing other’s emotions (Couture, Penn, & Roberts, 2006; Fett et al., 2011; Hughes, Soares-Boucaud, Hochmann, & Frith, 1997; Kee et al., 2003; Klin, Jones, Schultz, Volkmar, & Cohen, 2002). Important for our study is that social cognitive deficits in schizophrenia may be more severe and resemble the deficits in ASD more when negative symptoms are prominent (Couture et al., 2010; Edwards, Jackson, & Pattison, 2002; Frith, 1994; Kohler et al., 2003; Schneider, Gur, Gur, & Shtasel, 1995; van ’t Wout et al., 2007). To investigate whether our patient groups resemble each other in terms of social cognition (chapter 7), we administer the Ekman 60 Faces Test (FEEST), a measure of emotion recognition in which the subject has to indicate which of six named basic emotions was expressed in pictures of actors displaying prototypical emotional expressions (Young, Perrett, Calder, Spergelmeier, & Ekman, 2002). Additionally, we use the Interpersonal Reactivity Index (IRI, Davis, 1983) as a measure of empathy.

### Studying Neural Correlates of Emotion Processing

In both schizophrenia and ASD abnormalities have been found in brain regions associated with a deficit in emotion processing. Structural and functional abnormalities have been found, for instance, in regions involved in face processing such as the fusiform gyrus (Abdi & Sharma, 2004) and in regions important for the coding of the emotional significance of the stimulus such as the amygdala, anterior insula, and ventral striatum (Phillips, Drevets, Rauch, & Lane, 2003b). The MNS has also been implicated in both disorders (Gallese, 2003; Salvatore, Dimaggio, & Lysaker, 2007). Although social difficulties overlap in autism and schizophrenia and similar brain regions have been implicated, the two disorders have mainly been studied separately. A combined study will provide more information about the underlying neural mechanisms of social dysfunction and give insight into what makes each disorder unique. To study in vivo how the brain processes information, we will use functional Magnetic Resonance Imaging (fMRI).
Chapter 1

Magnetic Resonance Imaging

MRI is an example of a non-invasive technique that allows researchers to study the living human brain. An MRI scanner can be found in any modern medical hospital and is used to visualize various inner parts of the human body. An MRI scanner can, for instance, create high-resolution pictures of the knee’s bones, tendons, and menisci, but is also perfectly suited to create structural images of the human brain by providing sharp contrasts between the different brain tissues. The technique cleverly takes advantage of the fact that the human body is mainly composed of water molecules. A powerful magnetic field aligns these hydrogen atoms and when this field is perturbed by radio frequencies, the cores of the atoms generate a rotating magnetic field that is detectable by the scanner. Different manipulations of the magnetic field can provide researchers and clinicians with different kinds of information. Important to the field of neuroscience, an MRI scanner not only allows the visualization of brain structures, but also provides the opportunity to study ongoing neural processes. Functional MRI measures neural activity through changes in the MR signal caused by so-called blood-oxygen-level dependent (BOLD) effects. An active brain region consumes oxygen, which leads to an increase in deoxygenated hemoglobin. This would have diminished the MR signal from that region, were it not for the vascular system that responds by sending a disproportionate amount of oxygenated hemoglobin. Because the amount of oxygenated hemoglobin outnumbers the deoxygenated hemoglobin, the MR signal increases in active regions. This information is used to create images that reflect neural activity. MRI is a wonderful technique to study the structure and the workings of the human brain, because it is harmless for the participant, has good spatial resolution, and can create an image of the brain once every 1-3 seconds. The technique, however, also poses some constraints. MRI scans, for instance, have a low signal-to-noise ratio, which means images can appear grainy. Many repetitions of a certain task and as many participants as possible are needed to increase the signal intensity relative to the noise in order to obtain enough power to detect effects. Another constraint is that a subject needs to lay as still as possible in the tube of the scanner to obtain clear images. These factors play an important role when designing fMRI experiments in general and experiments on emotion processing in particular.

Main Paradigm

In this thesis, we will study both motor mirror mechanisms and affective mirror mechanisms. The experimental study of motor mirror mechanisms in emotions requires a condition in which subjects perceive facial expressions and generate facial expressions themselves (chapter 4). The study of affective mirror mechanisms or shared circuits requires a condition in which subjects experience emotions themselves in addition to a condition in which subjects perceive emotions (chapter 3, 4, 7). Emotion perception can be relatively easily studied inside the MRI environment. The most common method is to present pictures of emotional facial expressions, which the subjects then have to label. The emotional expressions we are confronted with in daily life are, however, dynamic and usually do not come with an explicit task. As a first step in the direction of more naturalistic paradigms, we use passive observation of movies of emotional facial expressions throughout this thesis (chapters 3, 4, 7). Inducing emotions is a more daunting task, which is complicated by ethical considerations (imagine inducing fear) and the constraints imposed by the MRI environment (e.g. restricted motion, need for repetitions). In this thesis, we have chosen disgust for the emotion
experience condition, because it can be triggered in a reliable and repeatable way that is ethically sound through the administration of unpleasant flavors (chapters 3, 4, 7) and the use of scripts (chapter 3).

Thesis outline
This thesis examines the neural underpinnings of emotion processing with an emphasis on simulation or mirror mechanisms. In chapter 2 we will first review studies to investigate whether the observation of emotions directly triggers activation of matching neural substrates in the observer that extend beyond the original MNS as defined for actions into regions involved in somatosensory and affective processes. In chapter 3 we dive deeper into the emotion disgust to examine whether social perception and mental imagery of disgust share common neural substrates and what functional circuits are involved in typically developing subjects. In chapters 4 and 5 we turn to the role of motor simulation in the MNS in autism. Hypoactivation of the inferior frontal gyrus during the perception of emotional facial expressions has been interpreted as evidence for a deficit of the MNS in children with autism. Chapter 4 examines whether this dysfunction persists in adulthood, and how brain activity in the MNS relates to social functioning outside the laboratory. In chapter 5 we review evidence from various studies to evaluate the claim that ASD may result from an impairment of the MNS. Social abnormalities are not unique to ASD, but also occur in schizophrenia. In chapter 6 we investigate whether adults with ASD can be distinguished from individuals with schizophrenia on the basis of behavioral observation. Similarities between ASD and schizophrenia in their social profile raise the question in what aspects neural impairments are similar and different in these two disorders. Therefore, we compare the findings on the link between the MNS and social functioning in ASD to individuals with schizophrenia that have comparable social deficits in the second part of chapter 4. In chapter 7 we compare the groups on measures of social cognition and use a whole-brain approach to examine similarities and differences in their neural signature during emotion perception. Chapter 8 concludes this thesis with a summary of the chapters and a general discussion.