

University of Groningen

Mirror images

Bastiaansen, J. A. C. J. (2011). *Mirror images: neural correlates of emotion processing in autism, schizophrenia, and mental health*. s.n.

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2011

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Bastiaansen, J. A. C. J. (2011). *Mirror images: neural correlates of emotion processing in autism, schizophrenia, and mental health*. s.n.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

General discussion

8

By providing a direct link between ourselves and others, mirror mechanisms may play an important role in understanding the actions and emotions of other people. These mechanisms have been implicated in Autism Spectrum Disorder (ASD); a neurodevelopmental disorder characterized by impaired social functioning and difficulties in many important social cognitive skills such as the ability to understand and feel with the emotions of other people. In this thesis, we investigated the workings of mirror mechanisms during emotion perception in typically developing (TD) individuals and individuals with ASD. We believe this endeavor will help improve our understanding of the neurobiology of ASD and provide pointers for the development of more effective therapies. Merely comparing individuals with ASD to TDs cannot, however, establish whether neural abnormalities are specifically associated with ASD or with social dysfunction in general. Therefore, we included a second psychiatric group with marked social deficits: schizophrenia. Social deficits are the most reliable predictor of long-term prognosis in schizophrenia, and are especially profound when negative symptoms are on the foreground. In this thesis, we presented the first studies that compare the two disorders where they resemble each other most, that is in high-functioning individuals with ASD and non-psychotic individuals with chronic schizophrenia. To this end, we used behavioral observation, measures of social cognition and social function, and functional magnetic resonance imaging (fMRI) mainly focused on the perception of dynamic displays of emotion. The combined study of ASD and schizophrenia provides a unique opportunity to gain more information about the underlying neural mechanisms of social (cognitive) dysfunction and the differences between the disorders. In this concluding chapter, we will integrate our findings to form new directions for research and the clinic.

Mirror mechanisms in emotion processing

Historically, theories of social cognition have emphasized cognitive processes in identifying the mental states of others. In **chapter 2** we reviewed evidence that shows that seeing someone else experiencing an emotion triggers much more in us than a purely theoretical, disembodied interpretation of other people's mental states. Humans activate premotor and parietal cortical areas involved in action execution when they see someone perform a goal-directed action, but also when they see facial expressions (Carr et al., 2003; Hennenlotter et al., 2005; Leslie et al., 2004; van der Gaag et al., 2007; Wicker et al., 2003; Wild, Erb, Eyb, Bartels, & Grodd, 2003). This motor simulation in what became known as the Mirror Neuron System (MNS) is involved in action understanding and may also contribute to understanding the intentions of others (Rizzolatti & Craighero, 2004). Emotion simulation extends beyond the ventral premotor cortex and inferior frontal gyrus (IFG) to somatosensory and affective regions, such as the ACC, anterior insula, and amygdala, all of which are crucial for emotion recognition (Adolphs et al., 2000; Adolphs et al., 2003; Broks et al., 1998; Calder et al., 2000; Sprengelmeyer et al., 1999; Tranel et al., 2006). Embodied simulation thus seems to be a general endowment of the brain, which involves motor, somatosensory, and affective components (Keysers & Gazzola, 2006). There is, however, no one-to-one mapping of particular emotions onto particular brain regions. Rather, emotion simulation seems to involve a network of regions, whose activation strengths depend on the quality of the emotion and its associated output. Signals of fear, for instance, possibly enhance amygdala activity (in particular in stressful situations), because they indicate a potential threat, which increases visual

attention to the outside world. Similarly, visceral responses mediated by the anterior insula are probably more important for disgust, and the anterior middle cingulate cortex (aMCC) with its strong motor connections might be particularly relevant for pain. The precise interaction between the various components and how they relate to more cognitive systems still remains unclear. There are probably many routes to equally many types of emotions, which are processed in various regions of the brain. One route could lead from motor simulation, in the frontal component of the MNS, to trigger emotion simulation in emotional centers of the brain, such as the insular cortex and amygdala (Carr et al., 2003; Jabbi & Keysers, 2008; Keysers & Gazzola, 2006; Niedenthal, 2007). This motor route found some support from findings in the next chapter.

Seeing, feeling, and imagining disgust

Chapter 3 illustrated that simulation is a highly integrated process, which is likely to depend on different networks in different conditions. For this study, we scanned healthy control subjects while they experienced, viewed someone else experiencing, and imagined experiencing gustatory emotions through script-driven imagery. We showed that social perception, mental imagery, and personal experience of disgust commonly involve the anterior insula and frontal operculum (IFO), which confirms the role of this structure in the embodiment of feeling states. The IFO involvement in the imagery condition might help explain why reading books and imagining hypothetical experiences can make you experience vivid emotions. This finding is promising for the use of script-driven imagery as an easy and more comfortable way of inducing emotions in experimental settings. Most importantly, effective connectivity analysis demonstrated that, although the IFO is commonly recruited when observing, feeling and even imagining disgust, the involved networks are quite different. During disgust experience, the IFO is embedded into a network composed of somatosensory, gustatory/motivational and motor output regions. During observation, the IFO receives its strongest input from the right inferior frontal gyrus (BA45), which supports the idea presented in **chapter 2** that motor simulation of facial expressions could trigger emotion simulation in the anterior insula. During script-driven mental imagery, the IFO is embedded in a network of language processing and semantic memory areas, which is suggestive of a more cognitive route to emotion simulation. The differences in the networks in which shared circuits are engaged may play an important role in distinguishing self and other during social interactions and in the different phenomenology of seeing, feeling, and imagining an emotional event.

Motor simulation of emotional facial expressions in autism

As discussed in **chapter 2**, motor simulation in the frontal part of the MNS may play an important role in many social skills such as imitation and emotion understanding. Hypoactivation of the inferior frontal gyrus (IFG) during the perception of facial expressions has been interpreted as evidence for a deficit of the mirror neuron system in children with autism (Bookheimer et al., 2008; Dapretto et al., 2006; Uddin et al., 2008). In **chapter 4**, we zoomed in on this structure to examine whether its dysfunction persists in adulthood, and how brain activity in the MNS relates to social functioning outside the laboratory. To this end, we measured brain activity during the observation of dynamic facial expressions in a group of adults with ASD compared to pair-matched controls.

Contrary to findings of IFG hypoactivity in children, on average, we did not find evidence for an underactivated MNS, even when the analysis was restricted to the region of hypoactivity in children. This discrepancy between findings in children and adults is intriguing. Our study demonstrated that age may be a critical factor: IFG activity during the observation of facial expressions increased with age in ASD, but not in controls. In addition, the within-subject variance decreased with age in the ASD group, suggesting that neural ‘noise’ in the IFG decreases and functioning of the MNS improves. The age-related increase in activity was associated with changes in gaze behavior and improvements in social functioning. These age-related neurocognitive improvements were not found in the group of individuals with schizophrenia, who had comparable levels of social functioning. Our cross-sectional study instigates an interesting hypothesis that is important for future (longitudinal) studies on autism to assess: individuals with ASD might have a unique developmental pattern of improving facial simulation abilities during adolescence and early adulthood, which positively impacts social relationships. These results are consistent with the clinical impression of improvements in social functioning and responsiveness to other’s distress in adolescents and adults with ASD (Farley et al., 2009; McGovern & Sigman, 2005; Piven et al., 1996; Seltzer et al., 2003; Shattuck et al., 2007). Here, it is important to note that these findings should not be taken to suggest that with age all will be normal: even in our older individuals with ASD the levels of social functioning were still below those of the TDs. There might, however, be unexpected room for improvement later in life. We hope that our findings will generate new research on this possibility and will give an impulse to the investigation of interventions directed at emotion simulation or directly targeted at the MNS. Given the plasticity of the MNS and its connections to visual regions, especially early imitation training of facial expressions and explicit training to change gaze behavior might be beneficial (Calvo-Merino et al., 2005; Catmur et al., 2007; Cross et al., 2006; Haslinger et al., 2005; Lahav et al., 2007; Wright et al., 2008). Training methods for individuals with ASD, however, often cope with limited generalization from training material to daily life situations (Golan et al., 2009; Golan & Baron-Cohen, 2006). Possibly, imitation training effects could be enhanced by modifying cortical plasticity in the inferior frontal cortex through Transcranial Magnetic Stimulation (TMS) or transcranial Direct Current Stimulation (tDCS) in those children with ASD, who show abnormal mu wave suppression, theta burst abnormalities, or diminished BOLD responses when perceiving other’s actions or emotions (see **chapter 5**, Dapretto et al., 2006; Martineau et al., 2008; Oberman et al., 2005). The effects of these noninvasive brain stimulation techniques on cortical plasticity and excitability in ASD (Oberman et al., 2010) and their clinical benefits will be important topics for future research (Fregni & Pascual-Leone, 2007).

Autism and the mirror neuron system

The mirror neuron hypothesis of autism is grounded in the idea that a pervasive impairment of the MNS in individuals with autism may lead to a cascade of impairments ranging from impaired imitation and goal inference to poor mentalizing and social abilities (Iacoboni & Dapretto, 2006; Oberman & Ramachandran, 2007; Rizzolatti & Fabbri-Destro, 2008; Rizzolatti et al., 2009; Williams et al., 2001). The fact that IFG activity was not disrupted in (older) adults with ASD during emotion perception (**chapter 4**), indicates that the role of the MNS in ASD is not that straightforward. Therefore, we further evaluated the MNS hypothesis of ASD in **chapter 5** by reviewing studies on

simulation of observed actions and facial expressions.

In the past five years many studies have been conducted in this domain, but overall they have come up with very inconsistent results. The available evidence in the hand action domain suggests that individuals with ASD do not seem to have great difficulty imitating and understanding the goal of other's actions. Instead, they seem to experience more difficulties when imitation requires understanding the beliefs of someone else (Hamilton et al., 2007) and when the exact imitation of style is required (Hobson & Hobson, 2008; Hobson & Lee, 1999). Moreover, action perception *can* trigger motor responses in individuals with ASD even though responses are not reported as consistently as in typically developing individuals. The relatively intact basic imitation mechanisms in combination with the comparatively greater theory of mind difficulties form an interesting paradox. It means that, if higher forms of social cognition are underpinned by imitation (Rogers & Pennington, 1991), mind-reading impairments in ASD cannot be reduced to basic abnormalities in MNS functioning (Hamilton et al., 2007). Understanding emotions and other mental states of others also engages structures outside the MNS, among which the medial prefrontal cortex (MPFC), the superior temporal sulcus (STS), the temporal poles, and the temporo-parietal junction (TPJ, Amodio & Frith, 2006; Gallagher & Frith, 2003; Saxe, 2006), which may (also) be affected in ASD (Castelli et al., 2002; Happe et al., 1996).

However, the fact that abnormal MNS functioning cannot on its own explain the whole constellation of clinical features that constitute ASD does not mean that the MNS is unrelated to the social cognitive problems in ASD. In fact, many studies did point to abnormalities in motor simulation, which may be more profound for emotional faces (Beall et al., 2008; Dapretto et al., 2006; McIntosh et al., 2006) than for goal-directed meaningful hand actions (Avikainen et al., 1999; Bernier et al., 2007; Bird et al., 2007; Dinstein et al., 2010; Fan et al., 2010; Raymaekers et al., 2009). Additionally, activity in the IFG during emotion perception has been linked to social competence in both typically developing individuals (Pfeifer et al., 2008) and individuals with ASD (Bastiaansen et al., 2011a; Dapretto et al., 2006).

The involvement of the MNS in ASD depends on several factors, which we are now beginning to uncover (e.g. nature of the stimuli, degree of identification with the actor, heterogeneity in ASD groups within and between studies). Of particular interest is the role of age, because its link to motor simulation and social functioning could mean that promoting the simulation of facial and bodily expressions at an early age improves social functioning in ASD. On the one hand, inconsistencies between studies thus inform us about important factors. On the other hand, they make it difficult to draw firm conclusions about the role of the MNS in the social cognitive difficulties and etiology of ASD and call for further research. One aspect that deserves further attention is the nature of imitation difficulties in ASD. The dissociation between imitation of goal and style (Hobson & Hobson, 2008) and the finding of diffuse facial mimicry in ASD (McIntosh et al., 2006) instigate an interesting yet speculative hypothesis. Possibly, the broadly congruent mirror neurons function sufficiently well to successfully match the goal of observed actions, but the strictly congruent mirror neurons do not function well enough (early in development) for the more vulnerable reproduction of style.

Behavioral similarities in autism and schizophrenia

In **chapter 4** we reported that our ASD and schizophrenia groups have similar levels of general social dysfunction. This means that both groups participate less than their typically developing peers in various areas that are crucial to community maintenance, including employment and prosocial activities. In **chapter 6** we investigated whether these patients also show similar social behaviors by investigating the psychometric properties of the Autism Diagnostic Observation Schedule (ADOS, Lord et al., 2000). The ADOS is a standardized instrument that assesses social interaction, communication, imagination, and restricted and repetitive behaviors during a semi-structured interaction with an examiner. The instrument has been widely used in clinical as well as research settings to assess the presence of ASD. It has been extensively validated in children, but not yet in adolescents and adults with fluent speech (module 4). Here, we investigated the psychometric properties of module 4 in (a subsample of) four groups of adults that signed up for neuroimaging experiments conducted in our lab and for whom ADOS was administered: ASD¹ and schizophrenia, but also psychopathy and typical development.

In general, our findings show that ADOS module 4 is a reliable instrument that has good predictive value for ASD. We found high specificity (0.82), which means that a high proportion of non-autistic individuals was correctly classified as ‘nonspectrum’. Therefore, if an individual does receive an ADOS classification it is a strong lead for a clinician to at least consider an ASD diagnosis. Specificity is tightly linked to sensitivity, which in this context refers to the proportion of actual clinical cases of ASD that the instrument correctly classified. We found rather low sensitivity (0.61), which indicates that ADOS module 4 failed to classify ASD in a significant proportion of our high-functioning and more mildly affected ASD group. This could be due to compensatory strategies during the semi-structured setting of the interview. As an unfortunate consequence, various motivated individuals that signed up for our fMRI studies could not participate. The aim of the assessment determines whether sensitivity or specificity is most important. High specificity of module 4 is particularly important for research purposes such as ours, because researchers need to be certain that their ASD group comprises only individuals with ASD. When the aim of the assessment is to screen for ASD, high sensitivity is more crucial in order not to miss any potential case. For this purpose, lower thresholds could be considered at the expense of specificity. To prevent overinclusiveness, developmental history and current daily functioning should then be carefully reviewed.

Concerning group differences, we showed that ADOS module 4 can adequately discriminate ASD from psychopathy and typical development in an adult population. The distinction between psychopathy and ASD remained when we only took forensic individuals with ASD into account (although the group size was rather small to perform such an analysis). The finding that ASD and psychopathy are so well-discriminated by means of ADOS scores is promising for forensic psychiatric settings. As expected, discrimination was more difficult with respect to schizophrenia due to behavioral overlap. In the group with schizophrenia the degree of negative symptomatology was positively associated with ADOS scores, especially on items resembling negative symptoms such as

¹ The ASD group in chapter 6 consisted of 38 individuals. Only 21 of them were eligible for participation in the reported fMRI studies, which was primarily based on ADOS classification and the absence of MRI contraindications.

(lack of) directed facial expressions and expressions of shared enjoyment. The ASD and schizophrenia group can be distinguished on some core items, and the revised algorithm of the ADOS seems promising for better discrimination of the two groups. In sum, these findings confirm that there can be overlap in the social behaviors seen in ASD and schizophrenia, which extends the finding of comparable levels of social dysfunction presented in **chapter 4**.

Neural similarities and differences in autism and schizophrenia during emotional facial expression processing

Despite these similarities, the region of interest fMRI analysis in **chapter 4** showed that only in the ASD group improvements in social functioning were associated with increased activity in the inferior frontal gyrus. In **chapter 7**, we zoomed out of the IFG and presented the first whole-brain fMRI study that investigates the similarities and differences in neural dysfunctions in these two groups with a shared social profile. First, we showed that both groups tend to withdraw from social participation in daily life and have similar difficulties with empathy and emotion recognition. Then, we probed social dysfunctions in an ecologically valid fashion, by presenting all subjects with movies of facial expressions that vary in valence (positive, neutral, negative) and social directedness without an explicit task. Based on learning theory, we hypothesized that two processes may play a role in the social withdrawal seen in both disorders. First, increased social *avoidance* may occur because of increased sensitivity to negative social stimuli or a general bias towards perceiving social stimuli as more negative or excluding. Second, reduced social engagement or *approach* may occur due to reduced sensitivity/reinforcement by positive social stimuli. The core findings of this chapter are two-fold. First, although the patient groups differed in their overall level of activation -with hyperactivity in the ASD group and a tendency towards hypoactivity in the schizophrenia group- both groups rated the faces more negatively and showed a relative bias towards negative facial expressions in visual brain regions and regions involved in the embodied processing of emotions. Excessive sensitivity to and vicarious sharing of negative emotions of other people may lead to the reported higher levels of personal distress and social withdrawal seen in both ASD and schizophrenia. Second, only the schizophrenia group showed a reduced sensitivity for pleased faces in regions involved in approach behavior and reward processing, which might further reduce social engagement in schizophrenia. Neural responses during emotion processing in patients with ASD and schizophrenia are thus biased in a way that might provide a learning theoretical explanation for their social isolation.

Our findings suggest that therapies aimed at normalizing the balance between sensitivity for positive and negative social information may help both patient groups to re-establish an adaptive equilibrium between social approach and withdrawal. The groups should, however, be approached in different ways. Due to the differences in overall sensitivity, individuals with ASD might benefit most from desensitization to social stimuli in general and negative stimuli in particular (e.g. by reappraisal strategies). Individuals with schizophrenia might benefit most from findings ways to make social interactions more rewarding or perhaps from techniques that directly target brain regions that are hypoactivated. A recent meta-analysis suggests that individuals with schizophrenia and negative symptoms might benefit from repetitive TMS (rTMS) of frontal brain regions (Dlabac-de Lange, Knegtering, & Aleman, 2009). RTMS of the (left) prefrontal cortex can increase prefrontal

cortical excitability and may modulate mesolimbic and mesostriatal dopamine release (Pogarell et al., 2007; Strafella, Paus, Barrett, & Dagher, 2001; Strafella, Paus, Fraraccio, & Dagher, 2003). This suggests that TMS might be able to enhance activity in those areas that we found were hypoactive when seeing positive facial expressions (i.e. left frontal cortex, striatum and insula). Improving the negative symptoms by rTMS might, however, worsen positive symptoms (Hajak et al., 2004). Current findings warrant further study of rTMS as a potential treatment for negative symptoms and call for studies combining rTMS with neuroimaging techniques (Dlabac-de Lange et al., 2009; Sparing & Mottaghy, 2008).

Taking a developmental perspective

Although most obvious abnormalities of ASD are already present in early childhood, our findings suggest that important developmental processes may continue throughout the lifespan. We reported age-related neurocognitive changes in high-functioning adults with ASD ranging from 18 to 54 years of age. The incremental activity of the IFG could mean that, although in ASD motor simulation of facial expressions is suboptimal in childhood (Dapretto et al., 2006), it improves during adolescence and early adulthood. Premotor activity can be reflected in facial muscle reactions in response to the perception of facial expressions (Schilbach et al., 2008). Together, three cross-sectional studies on facial mimicry provide support for an abnormal developmental pattern of face simulation in ASD. First, in contrast to their typically developing peers, children with ASD between 7 and 12 years of age did not show any muscle-specific reactions to happy and angry facial expressions and showed undifferentiated responses to fearful expressions (Beall et al., 2008). Second, undifferentiated facial muscle responses of normal intensity were found in an ASD group that consisted of older children and adults in a wide age range (13-64 years, McIntosh et al., 2006). Finally, in a study involving only adults, Magnée et al. (2007) found stronger facial muscle responses in the ASD group that were congruent with the displayed happy and fearful emotions. These findings suggest that ASD might be characterized by a delayed developmental trajectory, which moves from a complete absence of simulation in children (Beall et al., 2008; Dapretto et al., 2006), to a pattern of normal overall intensity coupled with a lack of specificity, to normal or even enhanced simulation of facial expressions in adults (Bastiaansen et al., 2011a; Magnée, De Gelder et al., 2007). Importantly, our findings suggest that these changes may have a significant impact on social functioning. Interpretations of cross-sectional findings should be made cautiously, but these studies might provide the dots that longitudinal studies may be able to connect.

Although we did not find age-related changes in our group of individuals with schizophrenia, a developmental perspective seems equally important for the study of schizophrenia. Central to this thesis were the remitted phases of the illness, which are dominated by social impairments. Social impairments and neurodevelopmental abnormalities have, however, also been widely reported before the onset of symptoms in the prodrome period and even in early childhood (Addington, Penn, Woods, Addington, & Perkins, 2008b; Asarnow, 1988; Ballon, Kaur, Marks, & Cadenhead, 2007; Cannon et al., 2008; Feinberg, 1982; Jones, 1997; Mednick & McNeil, 1968; Mirsky, Kugelmass, Ingraham, Frenkel, & Nathan, 1995; Rapoport, Addington, Frangou, & Psych, 2005). Social dysfunction thus seems to be an early-emerging, defining, and persistent characteristic of schizophrenia (Sasson, Pinkham, Carpenter, & Belger, 2011). To better understand the nature and

course of these deficits, longitudinal studies are necessary that follow the development of individuals from childhood to prodrome to chronic schizophrenia.

Keeping an eye on visual processing

Another or perhaps complementary explanation for the observed age-related increase in IFG activity could be a change in the way older individuals with ASD look at facial expressions. We analyzed the subjects' points of regard during the experiment and found that with age the time spent looking at the lower half of the face increased. The associated increases in IFG activity and social functioning suggest that this gaze pattern could be a beneficial strategy. In fact, the lower half of the face contained much relevant information about the emotion displayed in the movie clips (i.e. disgust, neutral, pleasure). Similar to our findings, Klin et al. (2002) have also found that time spent looking at the mouth region is significantly correlated with social competence in adolescents with ASD. Even though our eye tracking analyses were rather rough, they point to the important role of gaze behavior during social perception. Future neuroimaging studies should take into account visual processing in more detail to investigate how differential gaze patterns influence activity throughout the brain.

While looking at the lower face region may be a compensatory strategy later in life, a failure to look at the eyes of others during critical windows of development may have cascading effects on socialization (Jones & Klin, 2009). From early on, children with ASD do not show the normal preferential attention to the eyes of other people (Jones et al., 2008) and they do not automatically orient towards biological motion, but tend to orient towards non-social contingencies instead (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Klin et al., 2009). An early deficit in attention allocation to socially relevant signals likely has negative consequences on the maturation of the posterior STS circuits supporting the processing of biological motion (Blake et al., 2003; Boddart et al., 2004), and consecutively on the development of the mirror neuron system. More research is needed on the developmental trajectory of abnormal social skills in ASD, especially on how early abnormalities in basic mechanisms such as preferential attention to the eyes and biological motion might give rise to problems in more complex social skills such as the ability to understand the intentions of others (Jones & Klin, 2009).

Face to face: autism and schizophrenia

There are sizeable *independent* literatures on social functioning, social cognition, and implicated neural substrates in both ASD and schizophrenia (e.g. see Abdi & Sharma, 2004), which makes it difficult to draw conclusions on where these disorders are similar and different. Studies have, for instance, used a wide range of experimental tasks, different methodologies, and used samples with different characteristics (Sasson et al., 2011). Knowledge on the disorder specific and social cognitive impairment specific pathways and mechanisms will be essential for developing new interventions. Direct comparisons between autism and schizophrenia that can help illuminate what aspects are disorder-specific and what aspects are related to social deficits per se are, however, scarce.

In this thesis, we presented two of the first fMRI studies that compare two relatively large

and homogeneous groups with a shared presentation of social isolation while using the same experimental designs. The unique combination of these groups allowed us to demonstrate behavioral (**chapter 6**) and neurobiological (**chapter 4 & 7**) similarities and differences between ASD and schizophrenia. One important finding was that the groups were comparable in terms of social dysfunction, but during emotion perception the degree of social function was only related to activity strength in the MNS in the ASD group. By contrasting the two groups, we may have found evidence for a specific developmental trajectory of motor simulation of facial expressions in ASD. Another finding was that, although both groups were more sensitive to negative social stimuli, only the schizophrenia group showed reduced responses to positive social stimuli in regions related to reward processing. This suggests reward processing may be a particularly important area of disturbance in schizophrenia (Ziauddeen & Murray, 2010).

There is currently only one other study that has directly compared the neural substrates of social cognition in autism and schizophrenia. Using gray-scale pictures of unemotional faces during a trustworthiness task, Pinkham et al. (2008) found similar abnormalities in predefined regions implicated in social cognitive processing (e.g. amygdala, fusiform face area) in individuals with ASD and paranoid schizophrenia. Interestingly, they found a specific impairment in the posterior STS for individuals with ASD compared to both paranoid and non-paranoid individuals with schizophrenia. Another rare study that directly compared gaze behavior in autism and schizophrenia adds to this that while both patient groups pay less attention to faces, only individuals with ASD fail to orient more rapidly to faces when facial information is present (Sasson et al., 2007). Together with the findings presented in the previous paragraph, this suggests that circuits supporting attention orienting to socially relevant signals, including the posterior STS, are specifically disturbed in individuals with ASD. These and our studies are illustrative of the knowledge that can be gained from studying autism and schizophrenia in combination.

Moving across borders

As discussed in the previous paragraph, contrasting two diagnostic categories can provide important information about the convergence and divergence between disorders. Using diagnostic categories as a starting point does, however, raise two important issues.

First, the current DSM-defined psychiatric categories are very heterogeneous and therefore likely involve multiple brain systems instead of reflecting neurologically discrete phenomena (Gillihan & Parens, 2011; Insel et al., 2010). In case of schizophrenia, for instance, two individuals with the same classification do not necessarily share one similar symptom (DSM-IV-TR). In our studies, we have tried to reduce this heterogeneity by selecting non-psychotic individuals with schizophrenia on the basis of negative symptomatology and high-functioning individuals with ASD with above cut-off scores on the ADOS. These groups were comparable on important factors as age, sex and general cognitive abilities. As discussed previously, the comparison of two different patient groups with common behavioral characteristics helps illuminate what neurobiological aspects are disorder-specific and what aspects are related to the common characteristics. Selecting subgroups on the basis of behavioral characteristics naturally reduces heterogeneity at the expense of generalizability. Therefore, our findings will be difficult to generalize to, for instance, mentally retarded individuals with ASD and psychotic individuals with schizophrenia. Another important open

question is to what extent our findings apply to women.

The second issue is that the current state of the literature suggests that the genetic and neural correlates of psychopathology are generally not unique to specific diagnoses (Gillihan & Parens, 2011). Similar genes have, for instance, been implicated in ASD and schizophrenia, but also in schizophrenia and bipolar disorder (e.g. Cuthbert & Insel, 2010; Marx, 2007). In **chapter 7**, we showed that both individuals with ASD and individuals with schizophrenia may have a negative bias, which was reflected in increased activity for negative social stimuli in visual and somatosensory regions. The additional reduced sensitivity to positive social stimuli in the schizophrenia group may also not be disorder specific. In fact, anxiety and depression have also been linked to an attentional bias for negative information and a reduced sensitivity for positive information (Baert, De Raedt, Schacht, & Koster, 2010; Bourke et al., 2010; Winton et al., 1995). This suggests that the neural circuits underlying negative affect and reward processing may be two important brain-behavior domains in the study of psychiatric disorders in general. Therefore, another fruitful approach could be to identify the neural circuitry underlying mental domains such as negative emotionality and reward and then examine how variation relates to behavior. This approach would be in line with a new strategic plan developed by the US National Institute of Mental Health (NIMH), which emphasizes the need to study mental domains across current diagnostic boundaries (www.nimh.nih.gov/research-funding/rdoc.shtml). This could entail a dimensional approach that investigates mental domains such as reward processing and negative affect across diagnostic borders of ASD, schizophrenia, bipolar disorder, major depressive disorder, and social anxiety disorder. The hope is that when behavior-brain relationships (e.g. reward circuitry) can be linked to clinical phenomena (e.g. anhedonia), more specific therapies can be developed to target them. The new strategic plan might eventually lead to a new classification of mental disorders that is based on identifiable neural circuits instead of a constellation of various symptoms.

Concluding remarks

In short, we have shown that motor, affective, and somatosensory representations play a role in the embodied simulation of the emotional expressions of other people. The interaction between these components during emotion perception is still largely unknown, but motor simulation may play an important role in triggering activity in emotional centers of the brain. Abnormal motor simulation in the MNS seems to be related to the social problems in ASD, but cannot explain the whole constellation of clinical features. Additionally, findings on the MNS are too inconsistent to provide for a reliable biological diagnostic marker, but there may be an abnormal developmental trajectory of simulation abilities specific to ASD that needs further investigation. We have also reported that social behaviors of individuals with deficit schizophrenia can resemble those individuals with ASD. In addition, these groups were comparable in terms of social dysfunction, social withdrawal and social cognitive impairments. However, with respect to the underlying neural pathology there seem to be more differences than similarities. We need to pursue a more thorough understanding of the neurobiology of ASD and schizophrenia by taking a developmental and comparative approach, for instance by simultaneously mapping social cognitive development in ASD and schizophrenia starting in early childhood. More detailed knowledge about the similarities and differences is necessary in order to develop more tailored therapies for these patient groups. At present, interventions are

especially lacking for the two patient groups studied throughout this thesis: adults with ASD and individuals with schizophrenia presenting with negative symptoms. As discussed previously, imitation training or TMS treatment might be useful to target core problems of these disorders. Further research into other treatments that can help alleviate comorbid symptoms of distress and depression, such as mindfulness-based stress reduction (MBSR), is also warranted (Bögels, Hoogstad, van Dun, de Schutter, & Restifo, 2008; Spek, van Ham, & van Lieshout, 2010).

Moving on...

The studies discussed in this thesis were conducted in the Social Brain Lab headed by Christian Keysers. In the next years, the autism line of the lab will be further developed by Leonardo Cerliani and Marc Thioux. They will be working on a highly multimodal study that combines fMRI, structural imaging, and connectivity analyses. Of special interest will be how the structures involved in low-level embodied processes are integrated with regions involved in higher-level inference-based processes (Keysers & Gazzola, 2006), such as the TPJ and MPFC (Amodio & Frith, 2006; Gallagher & Frith, 2003; Saxe, 2006). Recent studies indicate that regions involved in mental state attribution and shared sensorimotor representations influence each other and are equally important to come to a complete understanding of the mental states of another person (Cheng et al., 2007; Schippers, Roebroek, Renken, Nanetti, & Keysers, 2010; Simon et al., 2006; Singer et al., 2006; Zaki et al., 2007). Given the fact that individuals with ASD often experience great difficulties with mentalizing tasks and have shown MPFC abnormalities in a couple of independent fMRI studies (Castelli et al., 2002; Happe et al., 1996), we believe it is time to evaluate the functioning of both the MNS and ToM systems in one experimental design (Thioux & Keysers, in preparation). The strength of the new project is that it will combine measures of *functional* connectivity within and between these systems with measures of *structural* connectivity of the white matter structures that interconnect gray matter regions and form neural circuits underlying important (social) cognitive functions.

