NAVIGATING SOCIAL LIFE:
ON SOCIAL COGNITION IN HEALTH AND PSYCHOSIS

GENERAL DISCUSSION
**Objectives and Main Findings**

The research presented in this thesis had two main objectives: first, to increase the current knowledge on developmental aspects of social cognition and social behaviour in the healthy population and second, to investigate social cognitive impairment and its impact on outcome and social functioning across the psychosis continuum. Experimental game theoretical paradigms, neuroimaging, meta-analytic and epidemiological methods were applied as a means.

The findings from part one showed that higher sensitivity to the perspective of others is associated with higher trust and better mental model building within social interactions. Trust and the responsiveness to others' social cues increased with age, in particular during the transition from adolescence to adulthood. Specifically, in healthy people a higher tendency to consider another person's viewpoint leads to more cooperation and a lower tolerance for deceptive behaviour. The older we are, the better we get in using others' behavioural cues to estimate their intentions and to predict their future behaviour. The developmental changes in the sensitivity to others' social cues are associated with differential patterns of brain activation in areas that play a role in mentalising, conflict monitoring and reward learning.

The findings from part two consistently showed impaired social cognitive functioning in patients with non-affective psychosis. Patients' social cognitive impairments, particularly in the domain of theory of mind (ToM), were found to be associated with a worse outcome in terms of community functioning. Conversely, impairments in ToM and emotion perception were not associated with a lower subjective quality of life, showing the importance of specific definitions of outcome in schizophrenia research. Social cognitive impairment is associated with symptoms of schizophrenia. Suggestive of an at least partly familial aetiology of social cognition, social cognitive functioning clustered between siblings. We investigated whether the associations between symptoms and social cognition that are seen in patients are due to common familial factors. Our findings suggest that the associations with ToM are due to non-shared factors, i.e. that they are specific to the affected person, whereas associations with emotion perception showed familial overlap. Within patients, the associations between symptoms and social cognition varied considerably between the respective symptom domains and between the social cognitive measures and domains. 'Offline' measures of social cognition showed the strongest association with disorganized and negative symptoms. 'Online' social cognition, as indicated by performance in the trust game, was most strongly associated with positive symptoms.
Thus, ‘online’ and ‘offline’ measures seem to capture different aspects of the social cognitive mechanisms associated with psychotic psychopathology. Finally, in ‘online’ social interactions, vulnerability for psychosis was associated with less trust towards others. First-degree relatives, but not patients, were able to increase their levels of trust and cooperation when they knew that their counterpart was trustworthy and in response to the counterpart’s positive behavioural feedback. This shows the direct, negative impact of uncorrected negative beliefs about others on the quality of social interactions in patients.

How do the current findings advance our understanding of social cognition, its typical and atypical development and functioning and its neural basis and what are the implications for clinical practice and future research? This final chapter aims to put the main findings into a broader perspective.

**The Trust Game – Measuring Social Cognition ‘Online’**

Measuring social cognition is not a simple undertaking. The dynamic cognitive mechanisms of social interactions are difficult to capture in experimental research. Previous research has mainly employed ‘offline’ measures to assess various aspects of social cognition. These measures generally require participants to adopt a third person standpoint, meaning that they have to interpret social stimuli in a passive way. Studies using ‘offline’ measurements of social cognition yielded important information about separate social cognitive functions in isolation of each other and in isolation of social context. However, by their nature interactive social processes involve more than one person. They require humans to use multiple social cognitive functions simultaneously and in a flexible way, because they necessitate a continuous adjustment to behavioural changes of others. For that reason, the investigation of the second person perspective is essential for the understanding of the underlying social cognitive processes of social interactions [1]. The implementation of game theoretical paradigms brought social cognitive research closer to the complexity of real life. Chapters 2, 3 and 7 of this thesis utilized the trust game. During the trust game, participants are required to infer their game partner’s intentions to cooperate or to defect from their behavioural cues. Decisions to trust (or not to trust) are based on subsequent predictions about the other player and these predictions have to be adapted in response to new evidence that emerges during repeated interactions. At the same time, participants are also required to continuously evaluate how the game partner perceives their own moves. The current findings from Chapters 2 and 3 show that trust and cooperation are higher in those with a stronger tendency to consider others’ viewpoints, showing that increased ‘online’ mentalising supports mental model
building during social interactions. Chapter 7 further highlights pre-established beliefs about others, flexible processing of social contextual cues and feedback learning as important determinants of successful social interactions and shows how these processes go awry in patients with psychosis.

**The Development of Social Cognition and its Neural Substrate**

Developmental changes in social cognition and its neural correlates are most pronounced during childhood and adolescence, but there is increasing evidence for prolonged changes that continue well into adulthood [2-3]. Research showed that trust in others and social perspective-taking increase with age [4-6]. According to the current findings, these changes occur in a non-continuous manner. Adolescents between 13 and 18 years showed relatively stable ‘online’ mentalising and social behaviour during the trust game did not change within this age window. Regardless of age, those with a higher sensitivity to others’ perspectives showed more trust and increased cooperation during interactions with a trustworthy counterpart and a steeper decline in trust during interactions with an untrustworthy counterpart. However, in line with earlier research that reported increases in the utilization of ‘online’ mentalising between late adolescence and early adulthood [7], Chapter 3 showed an increasing sensitivity to the social signals generated by others across an age-range from 13 to 49. Age was associated with more initial trust and increased cooperation during interactions with a trustworthy counterpart and a steeper decline in trust during interactions with an untrustworthy counterpart. In general, cooperation appears to be the behavioural preference of adults, teenagers in contrast show a stronger tendency to distrust. Notably, those teenagers with a high perspective-taking tendency showed similar behavioural patterns to those of adults (see Chapters 2 and 3, Figure 2).

Multiple brain regions referred to as the ‘social brain’ network contribute to social behaviour [8-10]. From a maturational perspective, the improvement in social behaviour takes place because of developmental processes within specific social brain areas. Accordingly, brain areas with the most prolonged structural maturation are expected to show the longest functional development. Furthermore, changes in the brain should come to a halt once it has reached its adult state. However, evidence from neuroimaging research shows that development is more than a process in which brain areas come ‘online’ once they reached maturity. For example, some brain regions become less active with increasing age and there are age-related shifts in brain activation from one area to another [11-13]. In addition, the brain is experience dependent and reversely, social context and behaviour can
further shape the brain towards differential patterns in structure, connectivity and function [14]. The study described in Chapter 3 shows that social behaviour and the associated neural processes continue to change beyond adolescence. This is in line with the model of interactive specialization [15], according to which development is a set of highly complex, dynamic processes in which genes and environment interact to shape brain structure, connectivity and function. Along these lines our imaging data showed age-related decreases in activation in brain areas that are important for reward learning (i.e. signalling in these areas is reduced because cooperation is the expected response). Furthermore, with increasing age increased activation was present in brain regions that support mentalising. Besides, a differential age-related responsiveness of brain regions important for cognitive control was present in response to the character of the interaction partner. Specifically, increasing age was associated with a greater responsiveness to deception. The findings suggest that functional brain changes may underlie overt changes in social behaviour. Yet, these changes may not solely be age-dependent. Chapters 2 and 3 showed similar mechanisms of trust in cooperation in adults and teenagers with a high perspective-taking tendency, possibly the latter group might also show mature, ‘adult-like’ neural mechanisms. However, alternatively it is also possible that similar social behaviour could be supported by differential underlying neural mechanisms.

The findings from the first part of this thesis are of particular interest with respect to the development of schizophrenia and other non-affective psychotic disorders. These disorders typically have their onset in late adolescence or early adulthood and coincide with a range of social cognitive and functional problems [16-18]. In healthy individuals, the transition from adolescence to adulthood is characterized by substantial changes in social cognition and behaviour towards a default modus of trust and cooperation. In individuals with non-affective psychosis, this developmental stage could be disrupted by the illness onset, leading to persistence of a more distrusting mindset as default. Alternatively, a disturbed development of trust could contribute to the instantiation of the illness.

**Social Cognition and Schizophrenia**

Social cognitive research in schizophrenia (and other non-affective psychoses) generally has two main aims: first, to understand the role of social cognitive impairments in patients’ functional outcome and second, to understand the role of social cognitive impairment with respect to specific clinical symptoms. The following paragraphs will discuss the implications of this thesis with respect to these research goals.
Social Cognition and Outcome

Social problems are a core feature of schizophrenia and have been described as one of the most rate limiting factors of functional recovery [19-20]. Patients experience social cognitive aberrations in a variety of domains that are important for the understanding and interpretation of others’ social cues and rules of social conduct. It is appealing to assume that these social cognitive problems underlie functional problems. Previous meta-analytic work on non-social cognitive impairment and outcome showed that non-social cognition is more strongly associated with outcomes than other clinical features [21-22]. The question is, whether social cognition can explain additional variance in outcome beyond neurocognition. There is consensus that although overlapping with non-social cognition, social cognition represents a largely distinct construct [23-25]. Hence, it may have an additional value in the prediction of outcomes. Knowledge about the associations between the various social and non-social cognitive functions and outcome is therefore important to determine the value of specific cognitive functions as treatment targets. Chapter 4 set out to determine these associations. The findings strengthen the evidence for social cognitive ability as an important factor in the understanding of functional outcome [26-27]. Specifically, ToM impairment had stronger associations with a reduced functional outcome in terms of community functioning than any other social or non-social cognitive function. This stresses the significance of ToM as a treatment target for interventions that aim to improve outcome. However, the meta-analysis could not clarify the causal pathways underlying this cognition-outcome association.

The study presented in Chapter 7 suggests a possible mechanism for the association between impaired mentalising and other aberrations in cognitive processing and problematic functioning in the interpersonal domain. In the trust game patients showed reduced levels of trust in others. Because of their negative beliefs about the trustworthiness of others, they display less positive social signals at the onset of social interactions. In addition, a reduced sensitivity to others’ social signals renders patients unable to increase their levels of trust in response to information that the interaction partner is trustworthy and in response to cooperative behaviour of the interaction partner. Thus, there is experimental evidence showing that rigid negative beliefs about others continuously disrupt relationship building. Other investigations that modelled the cognition-outcome relationships indeed suggested that social cognition has direct associations with various aspects of outcome, but that it also partially mediates the association between neurocognition and outcome [26, 28-29]. Besides, other factors proximal to social cognition, such a social support and social competence may be important determinants on the path between social cognition and outcome [26, 28]. The current associations between social cognition and
functional outcome varied in strength. Obviously, the underlying link between specific cognition-outcome associations may vary by social cognitive domain and outcome domain or both [28]. Future research is needed to identify the differential underlying mechanisms and to inform future strategies for treatment interventions that aim to enhance functional outcome.

The Definition of Outcome

Despite considerable variation in strength, the meta-analysis described in Chapter 4 showed consistent associations between better social cognitive functioning and improved functional outcome in all domains. The study described in Chapter 5 showed that in a large sample of patients ToM, but not emotion perception (EP), was a significant predictor of quality of life (QoL). Unexpectedly, and in contrast to the findings of the meta-analysis, lower ToM was associated with better QoL. The analyses further indicated an interaction between ToM and symptoms, showing that QoL was the lowest in those with high symptom levels and unimpaired ToM. How can the discrepancy between the two studies be explained? As discussed in Chapter 5, QoL may reflect more subjective life satisfaction, which is thought to be negatively associated with insight [30]. However, this explanation is at odds with findings showing that high symptom levels are typically associated with low insight and a worse social cognitive performance [31]. Could it be that this association pertains to specific symptom dimensions rather than to symptoms in general? The total symptom score of the PANSS which has been used as an indicator of illness severity in Chapter 5 also reflects symptoms, such as depression or anxiety that have been related to a greater insight into the illness [30]. This could explain why a specific subgroup of patients with high symptom levels and good ToM experiences a lower QoL. This hypothesis could be tested by re-analysing the specific associations with regard to the three symptom clusters, rather than the overall symptom score. Another possible explanation for the differential associations between social cognition (ToM and EP) and outcome that has been reported in Chapter 5 could be the definition of QoL that included physical and psychological health and environmental variables, such as financial resources and the satisfaction with transport. These aspects are by nature non-social. The domain of community functioning as used in Chapter 4, on the other hand, emphasized social aspects of outcome and ratings were generally made by observers, rather than by patients themselves. Chapter 4 implies specifically ToM as a promising target for treatment interventions that aim to improve functional outcome. Chapter 5 shows that patients with unimpaired ToM and high (general) symptom levels may rather profit from interventions that aim to raise their QoL. Such interventions may focus on psycho-education, the reduction of stigma and depressive
cognitive schemas and/or the attainment of coping strategies. Taken together, the definitions of social cognition (e.g. ToM, EP, Social knowledge, etc.) and outcome have important consequences for cognition-outcome associations and their subsequent clinical implications. The current findings stress the importance of a comprehensive assessment of outcome and the need to distinguish between subjective and objective perspectives, actual real world functioning and non-social resources, such as local amenities or transport.

Social Cognition and Symptoms

Chapters 5, 6 and 7 demonstrate that social cognitive impairments are present in non-acute stages of the illness and, depending on the utilized measures, to a lower degree in first-degree relatives of patients with non-affective psychosis. This suggests that social cognitive deficits may contribute to the illness instantiation, rather than being a by-product of the illness or its symptoms. In support of a familial basis of social and non-social cognition [32-34], cognitive performance clustered within sibling pairs. Thus, in line with previous findings, the current research designates social cognitive impairment as a possible (trait) marker of psychosis risk [35-36]. A vast amount of research established the link between social cognitive impairments and schizophrenia symptoms and this thesis contributed to this literature [24, 37-38]. Other research rendered evidence in favour of social cognitive impairment as precursor of the illness [39]. Suggestive of a role in the genesis of symptoms, research showed that a poorer ToM predicts the conversion from ultra high risk state to clinical psychosis [40]. However, social cognitive impairment also appears to deteriorate during acute psychosis [41]. This implicates mechanism in which social cognition influences the instantiation of symptoms, but in which acute symptoms further deteriorate social cognitive functioning. In view of that, social cognitive impairment may be understood as a state-mediated trait. Additionally, both symptoms and social cognitive impairments could partly be due to a third underlying mechanism. Chapter 6 addressed the question whether a familial origin underlies the associations between social cognitive functioning in EP and ToM and symptomatic expression. The findings revealed that associations between ToM and the three symptom clusters are due to non-shared factors. Indicative of a shared aetiology, EP in patients was associated with positive and disorganized subclinical symptoms in siblings. A shared aetiology could point to a common genetic basis, but could also be caused by familial factors, for example parental rearing style. The exact nature of the familial origin should be addressed in future research. The underlying mechanisms (i.e. shared vs. non-shared) of the symptom-cognition association varied by social cognitive domain, showing that social cognition does not equal social
cognition. In order to be able to elucidate the different associations between symptoms and social cognition future studies will have to adopt a multi-dimensional approach [29, 42].

The current findings also showed distinctive associations between the respective symptoms clusters and social cognition. Within ‘online’ social interactions, we found the risk for non-affective psychosis to be associated with lower trust and a reduced cooperation towards others. Lower levels of trust were associated with higher (subclinical) positive, but not negative symptoms. Notably, first-degree relatives were able to adapt their behaviour in response to changing social contexts. Our finding matches with results from previous research on real world social interactions and paranoia, which found high but not low or medium trait paranoia to be associated with a reduced sensitivity to social context [43]. Along the lines of Garety et al.’s (2001) cognitive model of positive symptoms, our findings show how rigid belief systems, a reduced sensitivity to social context and the misinterpretation of others’ social cues may influence the instantiation and maintenance of positive symptoms and how these mechanisms disturb social behaviour [44]. The research described in Chapter 6 showed the strongest associations between social cognitive impairment in ToM and EP and disorganized and negative symptoms. The associations between social cognitive functioning and positive symptoms were also significant but considerably weaker. Which mechanisms could account for the discrepancy between the two studies? First, in patients with predominately positive symptoms ToM might be disturbed in the sense of an exaggerated attribution of malevolent intentions and abnormal processing of social context. In those with disorganized symptoms, a reduced performance may be due to neurocognitive problems and deficits in their general understanding. Finally, in those with negative symptoms associations may also stem from neurocognitive problems, and in addition, they may be amplified by a lack of social competence or reduced motivation [29, 45-48]. The different methods that we utilized to measure social cognition have a differential sensitivity to these impairments. The Hinting Task, for example, is sensitive to a reduced understanding of indirect speech and requires neurocognitive skills such as verbal comprehension and memory. Therefore, task performance is likely to be more strongly associated with disorganized and negative symptoms [47]. This idea is supported by the relatively high correlations between Hinting Task performance, EP and IQ that were seen in patients (r = 0.37 and 0.22, respectively). Even if patients with positive symptoms do have a reduced understanding of the social cognitive components in ‘offline’ tasks, they may be able improve their performance with relatively intact neurocognitive abilities. In the trust game, their beliefs about others...
and a cognitive inflexibility are expressed in lower investments. Disorganized and negative symptoms, however, are more likely to be associated with random investment patterns rather than consistent patterns of low investments. Altogether, the current findings highlight the significance of definitions of symptoms and the nature of the specific social cognitive tasks for the detection of specific symptom-cognition associations. In addition, they suggest that interactive paradigms are specifically well suited to assess social cognitive functioning in patients with positive symptoms, while circumventing the effects of neurocognitive capacities.

**Implications for Clinical Practice**

The results of this thesis have a number of implications for clinical practice. The findings support previous evidence showing that problems with social cognition and social functioning remain even in absence of acute symptoms [49-50]. Furthermore, they suggest that social cognition has value in explaining variance in outcome in addition to neurocognitive functioning. Therefore, therapeutic strategies to improve social cognition may enhance social relationships and functional outcome in addition to treatments that target non-social cognition and symptoms. Improvement in social cognition may also contribute to the reduction and prevention of the (social) symptoms of the illness. The latter is of specific interest with respect to patients who present with first signs of psychosis.

The transition from adolescence to adulthood is a period of social change. In healthy individuals it is characterized by an increased sensitivity to others’ perspectives and to social context (Chapters 2 and 3, [11, 51]). However, this period is also associated with an increased incidence of psychosis [16, 52] and early psychosis comes along with social problems [18, 40]. A disrupted development of perspective-taking and a consequently reduced sensitivity to others’ social cues could possibly account for reduced levels of trust and problems in social functioning. Chapter 7 showed that a higher sensitivity to social context and cues enhances functioning within social interactions. Hence, it can be hypothesized that particularly patients in the early stages of the illness may benefit from interventions that seek to increase their awareness of others’ perspectives.

The research described in Chapter 7 will be translated into an intervention module for a group intervention for patients with schizophrenia that is known as meta-cognitive training (MCT). The MCT is based on the cognitive-behavioural model of schizophrenia. It targets common cognitive errors and problem solving biases in schizophrenia, which are thought to contribute to the instantiation and maintenance
of symptoms [53]. Specifically the MCT aims to increase patients’ awareness and critical reflection about their cognitive biases. It utilizes psycho-education to normalize and explain problematic cognitive processes and practical tasks to increase problem solving abilities. Currently, the MCT includes modules on attributional distortions, the jumping to conclusions bias and a bias against disconfirmatory evidence, deficits in ToM, over-confidence in memory errors and depressive cognitive patterns. We will develop an additional training module with the aim to foster trust and to enhance positive social interactions of patients.

Implications for Future Research

Research into social neuroscience and social cognition has been increasing rapidly in the last decade. However, despite significant advances, much remains to be understood regarding the developmental pathways of social cognition and behaviour and the underlying neural substrate in health and psychopathology [54]. Some suggestions for future research have been given in the previous paragraphs. This paragraph highlights the main points. First, one of the difficulties with social cognitive research that was stressed by the last paragraph, and that still warrants more attention from future research, is the definition of social cognition and the development of suitable assessment tools. Social cognition comprises of a wide variety of psychological constructs, e.g. ToM, EP, empathy, social knowledge or attributional style. It is still unclear in how far these domains represent differential abilities with different underlying substrates. Second, many of the measures for social cognition were developed for research in children and are subject to ceiling effects in older populations [55]. Other social cognitive tests are hampered by their low sensitivity to subtle impairments. The Hinting Task, for example, shows ceiling effects in at risk populations [27]. Consequently, these tasks are not well suited to detect subtle deviations or delicate changes in response to cognitive rehabilitation. The selection and psychometric evaluation of measurement tools for social cognition is crucial to enhance the quality and comparability of future studies. Initial attempts to improve the measurement of social cognition are now being made by the social cognition psychometric evaluation study [56]. Third and as previously discussed, research is now aiming to increase the ecological validity of social cognitive measures by designing interactive tasks in which participants are required to adopt a second person perspective [5-6, 11, 57-59]. However, study situations are still somewhat artificial; e.g. anonymity between the interaction partners is often required. To increase ecological validity further, future research with economic paradigms should systematically include contextual information to investigate the influence of variables such as familiarity between the players, age or gender. It is
additionally important to investigate how findings from offline and interactive experimental studies on social cognition translate to real life functioning and functional outcome. Future research should aim to integrate different measures of social cognition and incorporate these with methods, such as experience sampling, a structured diary technique that is able to capture social processes within the context of daily life [60]. Fourth, the findings from this thesis are of interest with respect to the developmental (brain) mechanisms of disturbed social interaction in schizophrenia. In healthy individuals, different levels of trust and cooperation are associated with differential activation patterns in dopamine governed brain areas that are important for reward learning and cognitive control. Schizophrenia and its symptoms have been associated with aberrant dopamine signalling [61]. It can be hypothesized that social reward learning mechanisms operate differently in patients with schizophrenia than in healthy individuals. Evidence in support of this notion comes from research of our group [62], showing that in patients with schizophrenia reduced levels of trust are associated with altered activation patterns within the caudate nucleus. In ongoing projects, we now examine whether reduced trust and cooperation and an aberrant neural response to social reward is present during the early phases of psychotic illness. Finally, it needs to be noted that the results of our cross sectional studies described in part one of this thesis show age-related, but not developmental changes. Likewise, part two cannot clarify whether reduced functional outcome, or increased symptoms are a consequence of social cognitive impairment. Longitudinal research is indispensable to uncover the complex developmental processes that smoulder during childhood and adolescence and to investigate how social cognition and behaviour are influenced by genetic predisposition and environmental factors, such as early traumatic experiences, parental behaviour or siblings. Similarly, longitudinal designs are crucial to unravel the association between psychosis and social cognition and to assess the value of social cognition in the prediction of the illness course and its outcome.

**Conclusion**

Taken together, this thesis increased the knowledge of social cognition, social behaviour and the neural correlates in healthy populations and elucidated the impact of social cognitive impairments on functional outcome, QoL and social interactions across the psychosis continuum. The current findings constitute pieces of a complicated puzzle and highlight the importance of interdisciplinary future research. Developmental, clinical, and social psychology, social neuroscience and other fields, such as neuroeconomics and genetics need to join forces to formulate an integrative model of social cognitive functioning in health and psychosis.
In adolescence, perspective-taking is associated with specific mechanisms of trust and reciprocity. A higher sensitivity to others’ perspectives leads to higher (initial) trust towards others and to a steeper decline in trust if others behave untrustworthy.

The sensitivity to others’ social cues increases with age and as a result social cognition and behaviour change towards a default of trust and cooperation. Notably, these developmental processes are non-continuous, as indicated by a relative stability in adolescence and a significant change thereafter.

Improvements in social cognition and behaviour are associated with functional changes in the ‘social brain’, specifically in areas associated with mentalising, reward learning and cognitive control.

Non-affective psychosis goes hand in hand with impairments in social cognition.

In patients, ToM impairment has stronger associations with a poorer functional outcome than other social and non-social cognitive functions. This stresses the significance of ToM as a treatment target for interventions that aim to improve the outcome of patients.

Subjective quality of life and objective functional outcome are differentially associated with social cognitive functioning of patients with non-affective psychosis.

Social cognitive impairment is associated with schizophrenia symptoms. The associations vary considerable in strength and depend on the different symptom clusters and social cognitive measures.

‘Online’ social cognitive paradigms capture interactive social mechanisms, such as trust and the flexibility in response to social context. They seem to be less confounded by neurocognitive functioning than ‘offline’ measures of social cognition.

Suggestive of a common familial basis, social cognitive functioning clusters between siblings. However, the associations between theory of mind impairment and symptoms that are observed in patients with non-affective psychosis are due to individual factors.

The risk for non-affective psychosis is associated with a more distrusting attitude towards others. In patients, but not first-degree relatives, this attitude is maintained by an impaired sensitivity to social contextual cues. This lack of flexibility in response to socially relevant information may play a role in the progression from subclinical symptoms to a full-blown psychosis.
REFERENCES

Chapter 8


