Navigating Social Life: On Social Cognition in Health and Psychosis

General Introduction
Navigating the Social World

Humans are inherently social. Every day we naturally engage in countless social interactions such as negotiating with strangers when boarding crowded metros, discussing issues with colleagues or spending time with our partners, friends and family. Although a matter of course for most people, our social environment is highly complex and navigating the social world we live in requires a set of sophisticated social skills [1].

Cognition is the compass that humans use in order to understand and make sense of the world. It refers to a set of mental processes such as perception, memory, visual processing, attention, reasoning and problem solving. These processes are commonly referred to as ‘cold’, basic or neurocognition while ‘hot’ or social cognition refers to information processing within social and emotional contexts [2]. Social cognition comprises of processes such as emotion perception, mentalising or empathy, that we use to understand social stimuli and interpersonal cues. These functions enable us to act appropriately in response to our social environment. Social signals of others such as facial expressions or gaze direction can convey valuable information about danger in the environment or can indicate pleasant or desirable events [3]. The ability to correctly perceive and interpret a range of emotions is required to allow us to decode these social signals and give them meaning. Other higher-level social cognitive skills such as mentalising or theory of mind (ToM) are the foundation of smooth social interactions and enable humans to form long lasting relationships and to function in the social community [4-5]. ToM is the ability to take the perspective of another person and to make attributions about their intentions, desires and beliefs. While this process comes naturally to most human adults, it is not a skill that is present at birth (for a review see [6-7]).

The Development of Social Cognition

The automatic and self-evident way with which adults employ social cognitive abilities belies the long-lasting developmental process. Although some basic social cognitive functions are present during early childhood, most cognitive functions become increasingly sophisticated throughout life. Simple emotional responses are present within a few months after birth [8]. In their first year children start to understand intentional and goal directed behaviour. Also, the first signs of cooperation, such as handing objects to another person, are present well before language develops [9-10]. Around their second year children become aware of the fact that different people can have different attitudes towards the same objects [11]. Between four and five years of age they typically pass false belief paradigms,
such as the Sally and Anne test (Figure 1), which require them to understand that a person has a belief that actually contradicts reality [12-13]. When they reach school age most children are able to understand the intentions and beliefs of others and to manage their own social signals [14]. Gradually, the fairly egocentric world of infant’s shifts towards a more other-oriented one [15]. A higher perspective-taking tendency (i.e. the sensitivity to viewpoints of others) has been found to be associated with increased pro-social behaviour, i.e. voluntary behaviour intended to benefit another such as helping, sharing or comforting [16]. While of great importance to the understanding of normative and abnormal social cognitive development during adolescence, most research to date focused on the development of social cognition during infancy and childhood [6-7, 17].

![Figure 1 | The Sally and Anne test](image)

Adolescence, the transition from childhood to adulthood, is a highly interesting period of social change during which young people attain a new role in society [19]. The onset of adolescence is typically manifested by the beginning of puberty. Relationships with others reach a higher level of social complexity, peer groups become more important and parents less influential and young people begin engaging in romantic relationships [19]. These changes in social behaviour are often viewed in conjunction with a continuous development in social cognition. A handful of studies have presented initial evidence for increased perspective-taking and more sophisticated social behaviour in late adolescence [20-22].

**The Social Brain**

Social cognitive development occurs in parallel to maturational processes in the brain. Maturation takes place in the form of increased myelination of fibre tracts that connect different brain regions, synaptic pruning, i.e. the reduction of neurons
and synapses to well-organized, efficient configurations and changes in connectivity, the interregional brain organization [23-24]. These processes are thought to result from an interaction of genetic and environmental factors [25-27]. It is appealing to assume that brain maturation is complete once the rest of the body has reached its adult state; however, there is evidence for continuous cortical changes that last well beyond this time point [28-29]. Plausibly, the changes in social cognition across the lifespan reflect developmental progress and enduring experience dependent changes of socially relevant brain areas [30]. This ‘social brain’ network (Figure 2) comprises prefrontal cortex (PFC) areas including the dorsolateral (DLPFC), the anterior medial (amPFC), the ventral (vmPFC) and the orbitofrontal (OFC) aspects and the temporal lobe (temporal poles (TP), posterior superior temporal sulcus (pSTS)). The frontal areas, which are the last to develop in ontogenesis, have been associated with the ability to infer the intentions and viewpoints of others. The temporal poles and OFC play a role the processing of (social) reward related information and their integration with social conceptual knowledge [31-33]. In addition, the social brain network includes parts of the parietal cortex (e.g. temporo-parietal junction, inferior parietal lobule, precuneus) that have been implicated in perspective switches from self to other and several deeper brain structures (i.e., striatum, insula and amygdale) that have been associated with emotional processing and social reward learning [30, 34-40]. It is important to note that changes in social behaviour and cognition are not merely associated with changes in brain organization and structure, but also with changes brain function [27]. To date, research about developmental changes in social brain function is still scarce. Previous studies that used mentalising related paradigms showed an age related shift in brain activation from anterior (medial PFC) to posterior regions (pSTS; [41-42]). Others have observed shifts in brain activation (i.e. age related increases in TPJ, DLPFC and decreases in the amPFC) and interpreted these as reflection of the perspective shift from more self to other oriented processing [22].
Adolescence is a period of change in many respects. The biological processes of puberty cause remarkable physical changes and substantial changes take place in social settings, behaviour and cognition. Teenagers are challenged to coordinate various novel aspects of their lives (e.g. relationships, finishing school, moving out of their parental home) with increasing independence from their guardians [44]. These challenges can lead to personal growth, but also render adolescents particularly vulnerable to the development of psychopathology [45-46], as indicated by an increased incidence of a range of psychiatric disorders, such as psychosis and schizophrenia [47-48].

The Phenomenology

Psychosis refers to an abnormal mental state characterized by distortions in perception and thought and a profound loss of reality. Its core symptoms include hallucinations (i.e. sensory perception in the absence of external stimuli) and delusions (i.e. firmly held, false beliefs that are bizarre and/or implausible). These core symptoms are also known as positive symptoms because they reflect an excess of normal function. Psychosis occurs in a range of affective and non-affective mental illnesses (e.g. depression and schizophrenia), the most severe of which is probably schizophrenia [49]. Schizophrenia belongs to the non-affective psychoses and has a lifetime prevalence between 0.3%-0.66% [50]. There are large inter-individual variations in pathogenesis and phenomenology, yet in a substantial number of cases...
the illness becomes chronic and causes immense human and economic costs [48]. With a peak incidence during adolescence and early adulthood, schizophrenia severely disrupts normal developmental trajectories in social and vocational life. Individuals who are affected by schizophrenia frequently experience other symptoms in addition to psychosis. The inability to experience pleasure (anhedonia), a lack of emotion, motivation, poverty of speech and social dysfunction refer to the lack of a range of functions that are normally present in healthy people and are therefore described as negative symptoms. Furthermore, patients may present with disorganized thinking, speech or behaviour, which traditionally have been grouped under the umbrella of positive symptoms. Although currently not part of the official disease classification of schizophrenia, the illness is in many cases associated with cognitive symptoms such as attention and memory problems or difficulties with planning and organization [51]. Cognitive dysfunctions have been shown to be a better predictor of the daily life functioning of patients than symptoms [52-53]. This led to aspiring research efforts into new treatment interventions to improve cognition in schizophrenia [54].

Social Cognition and Schizophrenia

Recently these research efforts have started considering social cognition [55-56]. This interest grew out of a number of observations. Firstly, one of the most disabling aspects of schizophrenia is the accompanying deficit in social functioning. This is reflected in the current diagnostic criteria of the Diagnostic and statistical manual [57]. To be diagnosed with schizophrenia, one must experience social or occupational dysfunction. Secondly, various symptoms of schizophrenia have a social character [58]. Paranoid delusions, for example, reflect a profound distrust in others and negative symptoms include social withdrawal. Finally, extensive evidence has shown impaired social cognitive functioning in schizophrenia [59-62]. The increased recognition of the social character of schizophrenia set the stage for research into social cognitive deficits as underlying mechanisms of symptoms and social functioning. While many of the exact mechanisms are still unknown, social cognitive impairments have been associated with psychotic, negative and disorganized symptoms [63-66]. Social cognitive impairment also has been associated with worse functional outcome of patients [67]. These findings highlight the specific clinical importance of social cognition as a potential target for interventions in schizophrenia.
The Psychosis Continuum

Current schizophrenia illness classification systems follow a categorical approach; however there is extensive evidence from epidemiological research showing that subclinical psychotic experiences also occur in the general population and in individuals at heightened risk for the illness [48, 61, 68-69]. This indicates that the illness may actually be better described by a continuous, rather than a dichotomous ‘absent or present’ approach. In support of the continuum hypothesis, subclinical psychotic experiences share many epidemiological and phenomenological aspects of clinical psychosis. Research about symptomatic expression in ‘at risk’ populations, such as first-degree relatives, has the potential to elucidate transitions from subclinical symptoms to full-blown psychotic illness. Furthermore, it may enhance knowledge about the underlying mechanisms of psychosis whilst avoiding the influence of confounders, such as the treatment with antipsychotic medication or illness duration.

The Aetiology of Schizophrenia

Despite extensive research efforts, the aetiology of what we know as schizophrenia remains largely unknown more than a hundred years after its official entry into psychiatric history. Today the prevailing view of the aetiology of schizophrenia is a complex interplay of genetic and environmental factors [48, 58]. Schizophrenia occurs at a higher rate in families, e.g. first-degree relatives of affected people have a ten times higher risk of developing schizophrenia than individuals in the general population. Twin studies showed a concordance rate of up to 50% for monozygotic twins and 10% for dizygotic twins [70]. Environmental risk factors associated with the illness include pre- and perinatal complications, daily life stressors and other factors that could be a proxy of stress, such as minority status and urbanicity, and cannabis abuse [71-76].

The search for genetic factors is in full swing but is still in its infancy. Schizophrenia has been associated with several susceptibility genes that play a role in brain development and dopamine regulation [77-78], however inheritance patterns are complex with likely interactions between susceptibility genes, epigenetic and environmental factors. Affected people differ in the genetic patterns that predispose them to the illness. This makes the quest for genes that are associated with the phenomenology of the disease challenging. Meanwhile research is also investigating intermediate phenotypes, which are measurable heritable traits that are genetically less complex and closer to the genotype than the symptoms of the illness [48]. These characteristics are thought to reflect the liability to a disorder without the expression
of the diagnostic phenotype. Intermediate phenotypes have to 1) be associated with the illness, 2) be heritable and co-segregate within families, 3) be state independent and finally 4) occur in unaffected relatives of patients to a higher degree than in the general population [79]. As core features of schizophrenia that fulfil these criteria, cognitive impairments are promising intermediary phenotypes [51, 67].

**Dopamine versus Neurodevelopment**

Various explanatory models try to account for the symptoms of schizophrenia. Currently the two leading frameworks are the neurodevelopmental hypothesis and the dopamine hypothesis. The neurodevelopmental hypothesis suggests that abnormal developmental processes in the brain lead to pathologic neural circuits, which during adolescence or young adulthood lead to an increased risk of clinical symptoms [80-82]. The dopamine hypothesis suggests a ‘final common pathway’ of abnormal mesolimbic dopamine as a result of various genetic and environmental risk factors [83]. Abnormal stimulus independent dopamine signalling is thought to lead to aberrant salience, the association of stimuli, which in reality are not meaningfully connected. Psychotic symptoms may reflect a top-down attempt to explain these experiences. Both hypotheses account for different aspects of schizophrenia symptoms. They are not mutually exclusive and may explain deficits in (social) cognitive functioning via structural and functional abnormalities [84].

**Schizophrenia and Problems with Adaptation to Social Context**

Schizophrenia has been described as a disorder of functional and structural connectivity of social brain areas [84-86]. Environmental risk factors are thought to impact brain development during sensitive periods [58] and cause abnormalities in brain structure, connectivity or neurotransmitter signalling [82-83, 87]. These aberrations may account for changes in social perception (e.g. low experience of reward during social interactions) and subsequently disturb social behaviour and the adaptation to social context. Although theoretically appealing, little is known about how abnormalities in brain function and structure translate into social cognition and behaviour. Previous research on social cognitive abilities in healthy populations and populations with psychopathology has mainly been conducted by means of ‘offline’ measures, in which participants had to interpret stories, cartoons or pictures. While this research yielded valuable insights into social cognitive functions, such as emotion perception and processing or mentalising, it could not capture the most intrinsic, interactive aspect of social behaviour [88-89].
Studying Social Interactions ‘Online’

Social interactions can be defined as the co-regulated coupling between at least two autonomous agents [88]. In the last decade, growing knowledge about the role of social cognition in social interactions came from neuroeconomics, an interdisciplinary field that emerged from the fusion of neuroscience and experimental economics. Neuroeconomics uses game theoretical exchange paradigms to investigate social constructs such as trust, reciprocity or fairness within social interactions [90-94]. Game theoretical paradigms bring experimental research on social cognition and behaviour closer to real life interactions. They require participants to use ToM to interpret and predict others’ social cues and intentions and, at the same time, to evaluate their own social signals [40]. The trust game is a reciprocal exchange paradigm of specific interest in the study of dysfunctional social behaviour and psychosis [93]. In the trust game the first player (investor) receives an endowment and then has to decide how much of this money he would like to share with the second player. The transferred amount is multiplied during the transaction. Subsequently, the second player (trustee) has to decide how much of this amount he wants to give back to the first player (Figure 3). Cooperation yields the best pay-off for both players. However, for the second player the best pay-off is reached through defection. Therefore, investing money in the first place requires trust in the benevolence of player two. Healthy people tend to trust and to reciprocate trust to a higher degree than would be expected on the basis of economic theories [41, 95]. Social behaviour is in fact influenced by many other factors than the highest pay-off, such as inequality aversion, social reward through cooperation, altruistic punishment in the case of non-cooperation and previous knowledge about the interaction partners [95-99]. Neuroimaging studies linked social decision-making in the trust game to brain areas that previously have been found to show activation during mentalising operations [22, 92-93, 100]. The outcome phase, during which cooperation or non-cooperation of the game partner are revealed, has been associated with activity in dopamine-governed areas of reward learning. This is of particular relevance to research on the dynamics of social interactions in schizophrenia, where an abnormal sensitivity to social reward could account for the reduced inclination to engage in (pro-)social behaviour. In conclusion, neuroeconomic paradigms have a high potential to bridge the gap between social cognition, social behaviour and their underlying neural substrates in health and psychosis.
Aims and Outline of this Thesis

The objective of the research presented in this thesis was two-fold. The first part focused on the typical development of social cognition and function, and its neural correlates in the healthy population (Chapters 2 and 3). The second part aimed to examine the impact of social cognitive dysfunctions on functional outcome and quality of life (QoL) of patients with non-affective psychosis (Chapters 4 and 5), and explored the association between social cognition, symptoms and social functioning across the psychosis continuum (Chapters 6 and 7). More specifically, the studies presented in this doctoral thesis focused on the following topics:

Part 1: Social Cognition in Health

Adolescence is characterized by substantial changes in social behaviour that were suggested to be associated with an increased sensitivity to the perspective of others. However, the associations between perspective-taking and social processes, such as trust and reciprocity, have rarely been investigated. The study described in Chapter 2 aims to enhance current knowledge regarding the relationship between social cognition and social behaviour in adolescence. We used an ‘online’ perspective-taking task and the trust game to investigate the association between perspective-taking and trust and cooperation in a sample of 50 adolescents between 13-18 years of age. Cooperation and trust towards others seem to increase with age [21, 101]. During adolescence and early adulthood, the developmental changes in social behaviour are in parallel with maturation processes in the ‘social brain’ network. Yet, indicative of further experience dependent alterations in the brain, social behaviour becomes more sophisticated during adulthood [20, 101]. Chapter 3 describes an fMRI investigation that utilizes the trust game to study age-related changes in the
neural correlates of trust and cooperation in a sample of 45 adolescents and adults between 13 and 49 years.

**Part 2: Social Cognition in Psychosis**

Numerous studies have indicated associations between impairments in different neuro- and social cognitive domains and functional outcome in schizophrenia and other non-affective psychoses. The issue of differential associations between social cognition and neurocognition and functional outcome is important for the identification of specific cognitive domains as possible targets for treatment intervention [102]. Chapter 4 describes a systematic review and meta-analysis of 52 studies on the associations between social cognition, neurocognition and functional outcome in non-affective psychosis. Typically, the illness is not only associated with a worse functional outcome but also with a poorer QoL. While the effects of neurocognitive functioning and symptoms on the QoL of schizophrenia patients have recently been studied, little is known about the influence of social cognitive deficits on QoL. The study described in Chapter 5 investigates the association between social cognitive deficits and QoL in a large sample of 1032 patients with non-affective psychosis, 1017 of their healthy siblings and 579 control subjects that were recruited within the Genetic Risk and Outcome in Psychosis (GROUP) study. Chapters 6 and 7 focus on the relationship between social cognitive impairment and positive, negative and disorganized symptoms and the impact of social cognitive impairment on social behaviour. Chapter 6 uses a genetically sensitive cross-trait cross-sibling design in a large sample of the GROUP study to investigate whether the overlap between symptoms and social cognitive deficits that is seen in patients is due to shared familial factors. Finally, the research described in Chapter 7 examines the underlying mechanisms of 'online' social functioning and its associations with (subclinical) symptoms across the psychosis continuum. In order to study these processes a modified version of trust game was used in a sample of 29 patients, 24 healthy first-degree relatives and 35 healthy controls as player one and 176 students who took on the role of player two.

Chapter 8 provides a general discussion of the findings from Chapters 2 to 7.
# REFERENCES

Chapter 1


