SUMMARY

Psychosis is a highly heterogeneous disorder, consisting of loose clusters of various symptoms, which differ in terms of severity, frequency and course. Hence, it may also be regarded as a syndrome without clear boundaries. This poses a challenge for psychosis research. This thesis entitled 'Mechanisms of Symptom Formation in Psychosis' was aimed at examining mechanisms of symptom formation at different levels of the psychosis continuum. Specifically, there were two central topics of this thesis: the relationship between bullying victimization and common non-clinical psychotic experiences in the general population, and illustrating the dynamics underlying the profound lack of trust, both at a behavioural and neural level, in healthy adolescents vs. adults, in patients and in first-degree relatives.

Chapter 1 provides a general introduction to this thesis. First, the terminology of schizophrenia vs. psychosis is being illuminated, as well as the corresponding phenomenology and epidemiology, and current diagnostic criteria. The concept of the psychosis continuum is tapped, along with relevant research findings, highlighting the importance of including different groups with varying symptom severity into research on psychosis. The aetiology of psychotic disorders, including the relevance of environmental risk factors, is described. Explanatory models such as the vulnerability-stress and neural diathesis-stress-models are taken into account next. Relevant research findings with regard to the link between bullying victimization and psychosis, as well as social cognition are critically evaluated. The concepts of social neuroscience, the social brain and neuro-economics are explained, along with their potential to investigate the social nature of psychosis and its core symptoms, especially persecutory delusions, in an experimental and interactive way.

Chapter 2 a can be regarded as a brief introduction to the following chapter (i.e. 2b), since it provides a comparison the two current main methods for assessing bullying victimization: self-reports vs. peer nominations, along with a critical evaluation in terms of their similarities and differences.

Chapter 2b compares the associations of peer nominated vs. self-reported victim status with non-clinical psychotic experiences in young adolescents. Secondly, the relationship between the five types of self-reported bullying victimization (i.e. direct relational, indirect relational, physical, verbal and possession-directed victimization) and non-clinical psychotic experiences is also investigated in these adolescents. Previous research suggests that bullying victimization is related to psychosis, but only self-report measures of victimization have been used up to now. We were the first to implement a combination of standard self-report and peer nomination procedures in the assessment of victimization. In order to test for a group effect on non-clinical psychotic experiences, the sample (N=724) was split into four groups: exclusively self-reported victims, self- and peer-reported victims, exclusively peer-reported victims, and non-victims. Secondly, the relation between the different types of victimization and non-clinical psychotic experiences was examined by a regression analysis. Self-reports of direct relational, indirect relational and physical victimization significantly improved the prediction of non-clinical psychotic experiences. Verbal and possession-directed victimization did not have a significant

predictive value. In our main analysis, we found that self-reported victims, as well as self- and peer-reported victims, scored higher than peer-reported victims and non-victims on non-clinical psychotic experiences. This implies that the association between victimization and non-clinical psychotic experiences is only present for self-reported victimization, possibly indicative of an interpretation bias. The observed discrepancy between self-report and peer-report highlights the importance of implementing a combination of both measures for future research.

Chapter 3 is directed at examining the neural mechanisms of trust and cooperation and whether related changes occur between early adolescence and adulthood. 45 healthy males between 13 and 49 years were tested in the fMRI scanner while playing two multi-round trust games with anonymous counterparts. The participants played the part of the investor, and their counterparts were designed to appear cooperative in one game and unfair in the other game. At the behavioural level, age was found to be linked to higher trust at the beginning and enhanced trust levels during cooperative social encounters. There was also a connection with unfairness: The higher the age, the more trusting behaviour declined during unfair social encounters. The whole-brain correlational analyses revealed three important findings. First, there was increased age-related activation in three brain regions implicated in mentalising, i.e. the temporo-parietal junction and the posterior cingulate gyrus and precuneus. Secondly, the orbitofrontal cortex and caudate nucleus, both reward-related brain regions, showed decreased activation with age during cooperative interactions. Third, age-related increases were found in terms of activation in the anterior cingulate, which is implicated in conflict monitoring, in response to deception. This provides evidence for age-related increases in trust and cooperation, possibly driven by increased activation in mentalising related brain areas. The link between reduced reward-related brain activation and higher age might be interpreted as a general tendency to expect trust from the social environment. Age-related increases in neural conflict monitoring might be required to adapt such pro-social tendencies to the partner's real cooperativeness.

Chapter 4 investigates the underlying neural basis of diminished trust in psychosis. Trust is an inherently rewarding aspect of successful social interactions, and has not been investigated in real-time interactions in a sample of patients with psychosis up to now. Functional magnetic resonance imaging data was acquired from 20 patients with non-affective psychosis and 20 healthy individuals during two multiple-round trust games, one with a cooperative and the other with an unfair counterpart. In both games, the participants played the role of the investor, requiring them to decide how much money they wanted to share with their counterpart. We focused our analyses on three brain regions, which are known to play a role in the neural processing of reward or social cognition. Specifically, an a priori region-of-interest analysis of the right caudate nucleus, right temporo-parietal junction (TPJ) and medial prefrontal cortex (mPFC) was performed focusing on the repayment phase of the games, i.e. the time point when participants saw how much money they got back from their counterpart. For regions with group differences, correlations were calculated between the strength of the brain signal, behavioral outcomes and patients' symptoms. At a behavioural level, patients showed reduced levels of baseline trust, indicated by smaller investments at the beginning of the games. At a neural level, we found a significant game x group interaction for the caudate nucleus, with

healthy individuals showing stronger activation for the cooperative game than patients, and no differences for the unfair game. The TPJ was significantly more activated in healthy individuals than in patients during both cooperative and unfair repayments. For the mPFC, no significant group differences were found. Patients' reduced activation within the caudate nucleus correlated negatively with paranoia scores. The TPJ signal was positively correlated with positive symptom scores during unfair repayments. This provides promising evidence for the hypothesis that reduced sensitivity to social reward may explain the basic loss of trust in psychosis. Aberrant activation of the caudate nucleus and the TPJ seems to act as a mediator on the diminished social reward sensitivity, leading to higher levels of distrust or paranoia.

Chapter 5 aims to further elucidate the neural mechanisms underlying diminished trust in psychosis. Investigating the neural underpinnings of loss of trust in psychotic illness remains a challenge, due to the confounding effects of the disease process, social isolation and antipsychotic medication. First-degree relatives have shown analogous deficits across a range of neuropsychological measures, including social cognition tasks than patients, albeit to a lesser degree. We acquired fMRI data on 50 healthy siblings of patients with psychosis and 33 healthy control participants during a multiple-round trust game with a cooperative counterpart. A priori region-of-interest (ROI) analyses were performed on brain regions known to play a role in reward processing or social cognition: the caudate, temporo-parietal junction (TPJ), superior temporal sulcus (STS), insula and the medial prefrontal cortex (mPFC). An exploratory whole-brain analysis was run to test for group-wise differences outside these ROIs. All analyses focused on both the investment and repayment phase of the game. Compared to the healthy control participants, the siblings did not behave significantly different during the trust game interaction, thus both first and mean investments were similar for the two groups. At the neural level, siblings showed reduced activation of the right caudate during the investment phase, and the left insula during the repayment phase. Additionally, the whole-brain analysis revealed reduced putamen activation in siblings during the investment phase. These findings indicate that in response to cooperation, first-degree relatives of patients with psychosis show aberrant functioning of brain regions which are traditionally involved in reward processing. This may be associated with the social reward deficits observed in psychosis.

Chapter 6 summarizes and critically examines the main findings from Chapters 2 to 5. These results from different angles of psychosis research are being discussed and integrated. Potential practical and clinical implications are evaluated and directions for future research are given.