Social interactions and reward in the schizophrenia spectrum

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Summary

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In our daily lives we have to navigate the complex social world by engaging in social interactions. Social cognitive abilities, trust and social reward underlie successful social functioning in healthy individuals and a disturbance could contribute to problems in social behaviour. According to diagnostic manuals (i.e. the DSM-5 and the ICD-10), schizophrenia spectrum disorders have some important social consequences, for instance social and occupational dysfunction, social withdrawal and difficulties in developing and maintaining social relationships, stressing the key role of social functioning in the schizophrenia spectrum. Gaining more insight in social interactions and the underlying mechanisms can help understand the mechanisms of social dysfunction in patients' daily lives.

The objective of the research presented in this dissertation was threefold: a) to advance the knowledge on the causal (neural) mechanisms that underlie social interactions, specifically focussing on trust, social context processing and social reward in schizophrenia spectrum disorders; b) to elucidate social reward and non-social reward learning in schizophrenia spectrum disorders and to assess the impact of a familial liability; and c) to ameliorate symptoms and improve social functioning in daily life in patients by means of an ecological momentary smartphone intervention.

Summary

In **chapter 1** an introduction is given into the topics of this dissertation. In this chapter, schizophrenia spectrum disorders are introduced, including phenomenology and aetiology. Schizophrenia spectrum disorders are mostly known for positive symptoms, such as hallucinations and delusions, and negative symptoms, such as flattened affect and lack of pleasure, however, the disorder is frequently accompanied by social cognitive impairments. Social cognitive abilities are essential to engage successfully in interactions with other people and to guide social behaviour. In addition, the rewarding nature of social interactions underlies goal-directed and socially motivated behaviour. Studying the mechanisms of social interactions and reward in the schizophrenia spectrum provides further insight in social dysfunction seen in patients' everyday lives. Moreover, examining social interactions in real time provides the opportunity to investigate the more complex nature of interpersonal interactions. Chapter 1 describes the two paradigms used in this dissertation to study social interactions, i.e. the trust game to study pair-wise interactions and the public goods game to elucidate the more complex dynamics in social groups.

Notably, to examine whether impairments seen in (social) reward learning are a possible endophenotype of the disorder, it is important to study healthy first-degree relatives of patients, because they offer the chance to elucidate the familial risk. Chapter 1 describes the current insights in trust, cooperation and reward processing in the schizophrenia spectrum. Social impairments seen in the schizophrenia spectrum remain a challenge to treat successfully. A brief overview is given the promising possibilities of ecological momentary interventions to improve functioning in schizophrenia spectrum disorders.

In **chapter 2** the literature review clearly shows that schizophrenia spectrum disorders are accompanied by impairments in cognition. Research findings to date paint a fairly consistent picture. Neurocognitive mechanisms, such as executive functioning, memory, attention and processing speed, are impaired. Next to neurocognitive dysfunction, social cognitive abilities are diminished, such as mentalizing difficulties and problems with interpreting social cues and emotion. Like neurocognition, impairments in social cognitive abilities are seen before the disorder is fully manifest and are also present in first-degree relatives, albeit in a less severe form. Suggesting that they are both a characteristic of the disorder, meaning that they represent a trait rather than a state and a possible endophenotype. Social cognitive impairments may underly social dysfunction seen in daily life in the schizophrenia spectrum and literature shows that social cognition may be an even better predictor for problems in everyday functioning than neurocognition. Chapter 2 also describes metacognitive problems that may accompany a diagnosis in the schizophrenia spectrum. The term metacognition refers to high-order cognitive processes that concern beliefs and attitudes with regard to one's own cognitive functions. In schizophrenia spectrum disorders, metacognitive skills are often impaired, for instance in jumping to conclusions (i.e. reasoning bias), monitoring of self-generated actions, and illness insight. Last, the chapter provides an overview of how (social) cognitive mechanisms may underlie psychotic symptoms.

In **chapter 3** the neural underpinnings of reward processing in first-degree relatives (siblings) of patients with a schizophrenia spectrum disorder were investigated. During functional magnetic resonance imaging (fMRI), 94 healthy siblings of patients and 57 healthy controls completed the monetary incentive delay (MID) task. Both reward anticipation and reward consumption were examined. On the behavioural level, siblings performed at a similar level as healthy controls. Region-of-interest (ROI) analyses did not point to altered brain activity in classical reward related brain areas, such as the ventral striatum. Whole-brain analyses did reveal group differences; during reward anticipation,

siblings showed higher activation in the insula, posterior cingulate cortex (PCC) and medial frontal gyrus (MFG) than controls. During reward consumption, siblings engaged the PCC, precuneus and the bilateral MFG more compared to controls. These areas are typically associated with the default mode network (DMN). This may point to reduced task-related suppression during a reward processing task of the DMN. The insula is part of a cognitive task control network, which is thought to play a pivotal role in the disengagement of the DMN and engagement of task-related networks. These results may reflect increased processing demands on reward-related tasks, even though this is not yet manifest at the behavioural level. These abnormal neural responses during reward processing in first-degree relatives of patients may suggest that reward processing deficits are at least partly caused by a familial risk in schizophrenia spectrum disorders.

In **chapter 4** social and non-social reward learning was examined in a sample of 50 patients with a diagnosis in the schizophrenia spectrum, 20 first-degree relatives and 49 healthy controls. Two interactive investment paradigms probing social decision-making during 20 trials (i.e. the trust game) and non-social decision-making during 20 trials (i.e. a lottery game) were used. In both paradigms, the repayments were pre-programmed to subtlety reward trusting behaviour, i.e. increases in repayment followed after increases in investments. Findings reveal that healthy volunteers learned from this feedback equally well in social and non-social contexts, as reflected by an increase of investments over game rounds in both paradigms. In contrast, patients and relatives showed reduced reward learning, regardless of the social or non-social nature, reflected by flatter or decreasing slopes over game rounds in both paradigms. These results suggest a general insensitivity to reward with no aggravating effect of social rewards in the schizophrenia spectrum. No effects of symptoms on learning were found, indicating that all patients, regardless of symptom severity, were unable to elicit or pick up on the subtle rewards. Given that the same pattern was observed in patients and first-degree relatives, the general insensitivity to rewards seems to reflect a familial vulnerability to schizophrenia spectrum disorders rather than illness-related mechanisms.

In **chapter 5** cooperation and sensitivity to social feedback in a public goods game (PGG) were examined in patients with a schizophrenia spectrum diagnosis, to elucidate the dynamics of social group interactions. The sample consisted of 27 patients with a diagnosis in the schizophrenia spectrum and 27 healthy control subjects. Findings indicate that patients have a lower initial inclination to cooperate in social groups, as indicated by a lower level of baseline investments into the public good compared to

healthy controls. In addition, patients seem to be sensitive to social enforcement in social groups, indicated by an increase in cooperation in patients and controls when social feedback, i.e. a punishment, was allowed compared to the condition where fining was not allowed. The same change in behaviour was observed after direct negative social feedback, i.e. receiving a punishment from another player. The findings also suggest that patients are sensitive to social rules and willing to altruistically punish other players to reinforce social norms at the same level as healthy control subjects. To engage in social interactions, one has to trust the other person's willingness to cooperate, which seems to be a key precursor in the development of cooperation in a public goods dilemma. Patients tend to approach social group interactions with less trusting and cooperative behaviour, which could contribute to social dysfunction in daily life. However, an intact sensitivity to social enforcement and negative feedback may indicate that patients can adjust their behaviour accordingly in social groups.

In **chapter 6** the neural correlates and the impact of prior social contextual information on social interactions, trust and social reward learning were investigated in patients with a disorder in the schizophrenia spectrum and healthy controls, using an interactive trust game while measuring brain activity with fMRI. The trust game was played three times, with either no, positive or negative information about the counterpart's trustworthiness, while in fact all partners behaved trustworthy. In addition, the experience sampling method (ESM) was used to measure social engagement in real life and to examine the association with the neural processes underlying social interactions, because little is known about how neural findings translate to real-world functioning. Patients did not show a differential effect of social context on baseline trust (i.e. the first investment where partner feedback has not yet been received), suggesting a general insensitivity to social context. Healthy controls did show a distinct context effect, reflected in a linear increase of baseline trust from negative, to no, to positive contextual information. In addition, patients did not increase trust in response to benevolent behavioural feedback in the no context and negative context condition, whereas controls did increase trust after prior given negative information. On the neural level, lower activation in the left dorsolateral prefrontal cortex (dlPFC) during context presentation was found, with no effect of context, suggesting a social context processing deficit on the neural level as well as on the behavioural level. Less engagement of the right caudate during repayments in patients compared to controls coincides with absence reward learning on the behavioural level. These results suggest that schizophrenia spectrum disorders are associated with a general insensitivity to social contexts and with a reduced sensitivity to social reward. Both

mechanisms can crucially disturb social functioning. In daily life patients spent more time alone than healthy controls. However, there was no association between real-life social engagement and aberrant brain activity in patients.

In **chapter 7** a randomized controlled trial investigating an ecological momentary smartphone intervention was presented. This study assessed whether an interactive smartphone application providing personalised feedback was feasible and whether it would improve symptoms and social functioning in patients with a schizophrenia spectrum disorder. The ESM was built into an application to map thoughts, feelings, and behaviour in everyday life, ensuring a high ecological validity. Two groups were included, one group of 27 patients, received personalised feedback prompts according to their ESM entries and the other group of 23 patients, completed the ESM questionnaires, but did not receive feedback prompts. The application provided feedback in the following categories: a) psychotic symptoms, b) social engagement, c) health behaviour (i.e. sleep, eating), d) physical activity, and e) mood and emotion. Participants used the applications for a period of three weeks. Results showed that compliance to the application was high and that the application was rated as user-friendly and understandable. Regardless of receiving feedback or not, feelings of loneliness decreased and lab-based measured psychotic symptoms declined. In addition, providing personalised feedback can help ameliorate momentary psychotic symptoms, measured in daily life, in comparison to the ESM control group. These results suggest that smartphone-based modalities with and without ESM-derived personalised feedback offer opportunities for simple and accessible interventions. They also offer a way to empower patients to take an active role in their mental health management as a key element of their recovery. The given feedback was non-specific, i.e. targeting different modalities, such as physical activity, mood and sleep next to social functioning. Future studies incorporating more specific social feedback may be more effective in improving social functioning in daily life.

In **chapter 8** the main findings are summarised and integrated. Here, a critical discussion of the main conclusions is provided and results are put into a broader perspective. Possible clinical implications, limitations of the work presented in this dissertation and directions for future research are given.