Social interactions in health and psychosis

Lemmers-Jansen, I.L.J.

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Chapter 9

Summary

Background

Every day we engage in social interactions, at work with colleagues, at home with family members and with friends. Many perceive these interactions as pleasurable and know how to act. Patients with a psychotic disorder, however, encounter problems in social interactions, or even withdraw from them. Understanding the development of the social cognitive processes underlying the skill and will to engage in social interactions, i.e., mentalising and reward processing, in health and psychosis, can help to elucidate the developmental pathway of psychosis.

Objectives

This dissertation consists of one review study and five fMRI studies, based on a large dataset, including first-episode psychosis patients (FEP), patients at clinical high-risk for psychosis (CHR), and healthy controls. Participants were in late adolescence and early adulthood (aged 16-29). They performed two interactive neuroeconomic paradigms, where participants invested money or chose for objects, in the magnetic resonance imaging (MRI) scanner. Part I (chapters 2 and 3) discusses the social mindfulness paradigm, and part II (chapters 4 and 5) concerns the trust game. For both paradigms we present one paper in healthy individuals and one paper including FEP and CHR patients. Part III (chapters 6 and 7) investigates the association between urbanicity and psychosis at the neural level, with a review on neural correlates of urban risk environments, and a study linking urbanicity to the trust game.

Following **chapter 1,** a general introduction to the contents of this dissertation, Part I examined the neural correlates of social mindfulness in health and psychosis. This form of low-cost cooperation requires participants to see the consequences of their choices for the second player and to act accordingly. In the social mindfulness paradigm (SoMi task) four items are presented, of which three are identical and one is unique (e.g., three green apples and one red apple). Choosing the unique item removes the option of choice for the second player, and is labelled as unmindful, whereas choosing one of the identical items safeguards the option of choice for the other, and is labelled as mindful. **Chapter 2** presents the first neural data underlying socially mindful behaviour. Using a within-subject design, 47 healthy adolescents and young adults, aged 16-27, performed the task twice during functional magnetic resonance imaging (fMRI) scanning. The first time participants received the general task information that did not prompt a particular behaviour, and the second time they were instructed "to keep the best interest of the other player in mind". Performing this task was associated with activity in brain areas previously found during neuroeconomic paradigms, showing that also low-cost cooperation activates similar brain areas as paradigms that require more complex social decisions. Mindful decisions (choosing one of the three items) showed activity in the right parietal cortex, a region associated with taking the perspective of the other person. Unmindful decisions (choosing the unique item) were associated with activity in the left prefrontal cortex, which is associated with deliberate planning and thinking. Exploratory whole brain analyses showed that mindful decisions activated the fronto-parietal network (FPN), a network associated with various cognitive processes, such as planning, attention, cognitive control, and integrating information from the external environment with stored internal representations. Unmindful decisions activated the default mode network (DMN), associated with spontaneous internal cognition, self-referential thoughts, and processing of self-promotion goals. The proportion mindful decisions was associated with the activation of the reward related caudate, possibly indicating that choosing the socially mindful option brings about gratifying emotions in those inclined to choose mindfully. Moreover, the better participants were at performing the Reading the Mind in the Eyes task, the more dorso-lateral prefrontal cortex (dlPFC) activation during mindful choices they showed, suggesting increased consideration of the consequences for the other person during mindful decision-making. The neural findings combined with the behavioural preference for mindful choices suggests that socially mindful decisions are the basic inclination, whereas socially unmindful responses may be more deliberate and self-reflective.

In **chapter 3**, 20 first episode psychosis patients (FEP) and 17 patients at clinical high-risk for psychosis (CHR), aged 16-31, were compared with healthy control participants in social mindfulness. The behaviour of CHR on the SoMi task was similar to healthy controls, but FEP tended to make spontaneously more unmindful decisions. A similar increase of mindful decisions after instruction in all three groups indicated an unimpaired ability for social mindfulness when prompted in patients with psychosis. Investigating brain activity in specific regions of interest (ROIs) showed in FEP reduced activation of the reward related caudate and medial prefrontal cortex (mPFC) during mindful- and of regions associated with cognitive control and planning, e.g., the anterior cingulate cortex (ACC), mPFC, and left dlPFC during unmindful choices. These results suggest that most likely the low number of mindful decisions made by FEP originated in reduced sensitivity for the rewarding aspects (feelings of pleasure) of social mindfulness, and reduced consideration for the consequences of their decisions for the other player. Furthermore, FEP, and to a lesser degree CHR, seem to perceive unmindful choices as less incongruent and effortful than controls, for whom mindful choices seem to be the automatic, natural response.

Part II of this dissertation discusses the development of trust in health and early psychosis. Trust is an essential element for social interactions. Using two iterative trust games, one with a cooperative and one with an unfair partner allows for the investigation of baseline trust in unknown others (the first investment made), and the development of (dis)trust, in response to the social feedback received. The cooperative partner is trustworthy, and will always return the same amount of money as invested or more, whereas the unfair partner will return less than invested, thus not reciprocate trust. Investigating age and gender related changes in trust, **chapter 4** addressed behavioural and neural development of trust in 43 late-adolescents and young adults (aged 16-27, 21 female, M_{age}= 21.51; 22 male, M_{age}= 20.64). Baseline trust was stable during this developmental period, suggesting development at an earlier age than the presented sample. Males trusted unknown others more than females, but both genders increased trust similarly during cooperative interactions, with no differences in average trust. During unfair interactions males decreased their trust more with age than females. Gender differences in behaviour only occurred in unfair contexts, and became more pronounced with age. Looking into specific brain regions of interest, ROI analysis showed age-related increases in activation in the mentalising related temporo-parietal junction (TPJ) and dlPFC, which is implicated in cognitive control, during cooperative investments. Increased age-related caudate activation, associated with reward processing and reward learning, was found during both cooperative and unfair repayments. Gender differences in brain activation were only observed during cooperative repayments, with males activating the TPJ more than females, and females activating the caudate more than males. The findings suggest relatively mature processes of trust and reciprocity in the investigated age range in males and females and that major changes of trust occur earlier in development. It seems that males and females adopt slightly different cognitive strategies in response to processing the social feedback, however, resulting in similar behavioural outcomes.

In **chapter 5** the same subset of 43 healthy controls from the previous sample was compared to 26 FEP with non-affective psychosis, aged 16-21, and 17 CHR, aged 16-31. Region of interest analyses were performed on mentalising and reward processing areas, during the investment and outcome phases of the games. Compared to healthy controls, FEP and CHR displayed reduced baseline trust, however, symptom severity did not explain this reduction. Since both patient groups displayed reduced baseline trust, this may be associated with the risk for psychotic illness, or generally with poor mental health, rather than reduced trust being a consequence of a first psychosis. Learning from cooperative and unfair feedback was still intact in CHR and FEP. In FEP higher negative symptoms were associated with reduced response to cooperative feedback. No differences between groups in brain activation were found, except for a hyper-activation of the TPJ in CHR during investments in the unfair condition. This hyper-activation in CHR was associated with greater symptom severity, suggesting increased effort in mentalising areas with stronger symptoms. FEP did not show this compensatory mechanism. Overall, feedback learning seems to be still intact in CHR and FEP, as opposed to chronic patients, who display reduced learning from positive feedback. However, CHR showed distinct neural activation patterns of the TPJ, suggesting increased effort or compensatory mechanisms.

Part III investigated the association between urbanicity and psychosis at the neural level. The association between urbanicity and non-affective psychosis, psychotic symptoms and experiences has been established by many epidemiological studies, showing elevated incidence rates in densely populated urban areas. Increased incidence rates have been linked with urban birth, urban upbringing, and current city living. Many mechanisms have been proposed as possible explaining mechanisms, but none of them could explain the association. Neural research in patients, associating urbanicity with brain structure or function is scarce. The majority of (f)MRI research on urbanicity is conducted in healthy individuals. In **chapter 6**, trust game outcomes were associated with urban upbringing in patients with psychotic symptoms and controls. In this patient group, both CHR and FEP were included, based on similar levels of psychotic symptoms. We investigated if reduced trust, a component of impaired social functioning in patients with psychotic disorder, which is associated with the risk for psychotic illness, was associated with urban upbringing. Thirty-nine patients (22 first-episode and 17 clinical high-risk patients) and 30 healthy controls, aged 16 – 29 performed two multi-round trust games. Urban exposure during upbringing (0-15 years) was defined as higher-urban (>2500 inhabitants/km^2) or lower-urban (<2500 inhabitants/km^2). Contrary to our expectation, urbanicity was not associated with reduced baseline trust in patients. However, urbanicity exposure was associated with differential learning from positive social feedback in patients, with a steeper increase in investments in patients raised in lower urban areas, compared to less increase in patients raised in higher urban areas. On the neural level, during cooperative interactions, higher urbanicity exposure during upbringing was associated with differential activation of both amygdalae in patients compared to controls. The amygdala is associated with (negative) emotions, fear, and stress processing. During unfair interactions, no associations with urbanicity were found. Impaired learning from positive social feedback suggests that urbanicity is a proxy for social stress, possibly resulting in distrust. Urbanicity seems to have a stronger influence on patients than on controls, especially during positive social interactions and trust building.

Chapter 7 reviews the existing literature on neural correlates of urban risk environments in psychosis. Associations with brain function and structure were discussed. Given the scarcity of research on this topic, additionally neural urban literature in healthy subjects, and possibly urbanicity related environmental and social mechanisms were discussed. Direct associations between urban risk-attributes and brain function or structure in psychosis are difficult to establish, yet there is indirect evidence for the notion that urbanicity increases the sensitivity to stress, impacting on dopamine pathways. Two studies investigated neural responses in relation with urbanicity, during stress processing and reward processing. Although the authors suggested that these findings would translate to psychosis, these studies were conduct in healthy subjects. The research discussed in chapter 6 was also reviewed, as it is the only study linking urbanicity to functional neuroimaging in patients.

In short, the main conclusions of this dissertation, presented in **chapter 8** can be summarised as follows: (a) socially mindful decisions recruit a more outward focused neural network, considering the other person more, elicit feelings of reward, and seem to be more automatic than socially unmindful decisions; (b) males trust more than females, based on different underlying motivations and trust seems to have reached adult levels before the age of 16; (c) initial pro-social cooperation, both basic and more complex, is impaired in FEP and CHR, except the preserved socially mindful behaviour in CHR. This initial lack of pro-social behaviour can be overcome by instruction and feedback; (d) these studies suggest that mentalising is still intact in CHR and FEP, and reward processing might be intact in CHR, whereas FEP already show some deficits; (e) urbanicity is associated with reduced learning from positive social feedback. The underlying mechanism however, remains unclear. Limitations, clinical implications and suggestions for future research are discussed.