Chapter 8

General discussion

Objectives

The work presented in this dissertation aimed to contribute to the understanding of social interactions in health and psychosis, by investigating (impairments in) social interactions, using interactive neuroeconomic games and neuroimaging. Mechanisms of social interactions were investigated before and after conversion to psychosis, in first-episode psychosis patients and in patients at clinical high-risk and compared with healthy controls. Participants performed a social mindfulness paradigm and the trust game during fMRI scanning. In the social mindfulness paradigm participants chose one item out of four, reflecting low-cost cooperation and decision-making, and in the trust game baseline trust towards unknown others and development of trust in response to social feedback were investigated. Furthermore, trust outcomes in patients with a psychotic disorder were investigated in relation to urban upbringing, and in a review of the existing literature, associations were investigated between brain structure and function and urbanicity, an epidemiologically well-documented risk factor for psychosis.

This chapter starts with a summary of the main findings of the chapters presented in this dissertation. The results for healthy subjects are discussed, separately for the two paradigms. In the second section, social interactions in psychosis will be discussed, and findings obtained with these paradigms will be integrated into the broader perspective of pro-social cooperation and the underlying neural mechanisms, risk factors, and markers for psychosis, drawing a picture of development of social interactions before and after illness onset. Lastly, urbanicity as an additional risk factor for psychosis will be discussed. This chapter will conclude with an overview of the strengths and weaknesses of this research, clinical implications and directions for future research.

Summary of the main findings

Chapter 1 provides an overview of the topics addressed and methods used in this dissertation. Social mindfulness (SoMi) and trust are closely linked, both play an important role in social interactions and in building close relationships (Van Doesum et al., 2013). Social mindfulness is likely promoting trust and cooperation (Van Lange & Van Doesum, 2015), by protecting the other's autonomy of decision in interpersonal interactions (Declerck et al., 2013; Dou et al., 2018). The ability and willingness (the *skill* and *will*) to think about preferences of others and benefits for them are two core requirements for SoMi and for trust in particular, and for positive social interactions in general. Mentalising is a core mechanism underlying the ability to recognise the needs and wishes of others and to judge the other's trustworthiness and intentions; social motivation, the sensitivity to the intrinsic pleasurable effects of positive social interactions (to act socially mindful or to trust) reflects the willingness to use mentalising abilities in a pro-social, cooperative manner (Declerck et al., 2013; Lemmers-Jansen, Krabbendam, et al., 2018). In the SoMi task, four items were presented, identical (in value) but for one detail that made an item unique: for example three yellow baseball caps and one blue baseball cap; three mugs with stripes, one with dots. Participants were to choose an item first, which would not be replaced. After them, a second person had to choose. Choosing an identical item, and thereby leaving the second person a choice, was considered as socially mindful; taking away the unique item, and thus limiting this other person's choice, was considered as socially unmindful. In the trust game, the participant played the role of investor, and received € 10. He/she could give any amount between € 0 and 10 to the second player, the trustee. The given amount was tripled and the trustee then could return any part of this amount to the investor. The task distinguishes between baseline trust, the first investment made (to an unknown other), and changes of trust in response to social feedback during repeated interactions. The SoMi task involves low costs, thus there is little to lose for the first player, and decisions involve low levels of risk. In the trust game, the stakes are higher (i.e. money can be lost) and decisions therefore involve a certain amount of risk. Repeated interactions with the same game partner involve the building of a model about the other player and adjustment of participants' own behaviour in response to the other player's feedback. Thus, SoMi can be seen as basic and low-cost cooperation, whereas trust in the trust game is more complex, entails a risk, and requires higher order social processes.

In chapters 2 and 3 the neural correlates of social mindfulness in health and psychosis were investigated. Using a within-subject design, **chapter 2** presents the first neural data underlying socially mindful behaviour. Three main findings were highlighted: (1) SoMi activated brain regions previously found during social decision-making (Declerck et al., 2013; Rilling & Sanfey, 2011), involving medial prefrontal and (medial) parietal cortex. (2) Furthermore two different networks were activated: the fronto-parietal network (FPN) during mindful, and the default mode network (DMN) during unmindful decision-making. Choosing the unique item seemed to depend more on self-reflective activity than making socially mindful decisions. (3) Neural activation patterns were partly moderated by SoMi index, the mean proportion of mindful decisions. Activation of the caudate was associated with a higher proportion of mindful decisions, suggesting that in participants who spontaneously tended to choose mindfully, this decision is associated with a greater involvement of reward-related activation.

In **chapter 3,** first-episode psychosis patients (FEP), patients at clinical high-risk for psychosis (CHR), and controls were studied with respect to SoMi. The behaviour of CHR on the SoMi task was similar to healthy controls, but FEP made spontaneously more unmindful decisions. After instruction, all groups increased the number of mindful decisions, but the difference between FEP and controls remained. ROI analyses showed reduced activation of the mPFC and caudate in FEP during mindful decisions, and reduced mPFC, dlPFC and ACC in FEP during unmindful decisions. CHR also showed reduced ACC activation compared to controls. Possibly the low number of mindful decisions in FEP originated in reduced sensitivity for the rewarding aspects of social mindfulness, and reduced consideration for the consequences of their decisions for the other player. Furthermore, reduced prefrontal activity during unmindful decisions suggests that FEP, and to a lesser degree CHR, might perceive unmindful decisions as less incongruent than controls for whom mindful decisions seemed to be the more automatic, natural response.

Chapters 4 and 5 discuss the development of trust in health and early psychosis. Investigating age and gender related changes in trust, **chapter 4** addresses late adolescent (16-27 years) development of trust. Baseline trust in unknown others was stable during this developmental period. Males trusted unknown others more than females, but both genders increased trust similarly during cooperative interactions. During unfair interactions males decreased their trust more with age than females. These findings suggested relatively mature processes of trust and reciprocity in the investigated age range. Gender differences in behaviour only occurred in unfair contexts, and became more pronounced with age. With increasing age, the reward related caudate was increasingly activated during repayments, and the temporo-parietal junction (TPJ) and dorso-lateral prefrontal cortex (dlPFC) were increasingly activated during investing in a cooperative other, suggesting ongoing neural development, despite constant behaviour. During cooperation, males showed more TPJ, whereas females showed more caudate activation, suggesting that males and females adopt slightly different cognitive strategies in response to cooperative repayments. In **chapter 5** the same task was administered to FEP and CHR. Baseline trust was reduced in FEP and CHR compared to controls, but not associated with symptom severity. Reduced baseline trust may be associated with risk for psychotic illness, or generally with poor mental health. Learning from the social feedback was still intact in CHR and FEP, and no differences between groups were found in brain activation, except for hyper-activation of the temporo-parietal junction in CHR.

Chapters 6 and 7 investigate the association between urbanicity (urban birth, upbringing or current city living) and psychosis at the neural level. In **chapter 6**, trust game outcomes were associated with urban upbringing in patients with a psychotic disorder, combining the FEP and CHR sample on the basis of similar levels of psychotic symptoms. 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 lower compared to higher urban patients. On the neural level, during cooperative interactions, higher urbanicity exposure was associated with differential activation of both amygdalae in patients compared to controls. During unfair interactions, no associations with urbanicity were found. Urbanicity seemed to have a stronger influence on patients than 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. 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 are difficult to establish, but there is indirect evidence for the notion that urbanicity increases the sensitivity to stress, impacting dopamine pathways.

Discussion

Social mindfulness in health

Social mindful behaviour depends on the *skill* to recognise the needs and wishes of the other player, and the *will* to act accordingly. SoMi seems to be independent of age (range 18-86 years) and gender, although females scored slightly more mindful than males (Van Doesum et al., 2013). People typically tend to make socially mindful decisions in 60% of the trials. However, these decisions depend on the pro-social orientation of the participant, the trustworthiness of the other player's face, whether the other player is an in-/out-group member or someone (dis)liked, and the social class of the other player, but not of the participant him/herself (Van Doesum et al., 2017; Van Doesum et al., 2013; Van Doesum et al., 2016; Van Lange & Van Doesum, 2015). Social mindfulness has already exhibited reliable associations with self-reports of empathy, perspective-taking, honesty, and pro-social orientation (Mischkowski et al., 2017; Van Doesum et al., 2013; Van Doesum et al., 2016).

Chapter 2 describes the neural correlates of social mindfulness for the first time. Whole brain family-wise error (FWE) corrected analyses showed that socially relevant decisions in the SoMi task (choosing an item presented in the 1:3 ratio, regardless of the decision made), compared with responses that did not have implications for social mindfulness (2:2 ratio), involved medial prefrontal and (medial) parietal activity, areas also activated in other neuroeconomic games. Contrary to our predictions, no insular and ventral striatal activation was found, possibly caused by the low costs of the items involved in these decisions. Low-cost decisions seemed not to elicit reward and emotion related neural responses. Larger gains, or giving up more valuable items might elicit stronger neural activation in these regions [cf. (Knutson, Fong, Bennett, Adams, & Hommer, 2003; Waltz et al., 2010)]. Following these initial analyses, social relevant choices were divided in socially mindful and unmindful decisions in order to specify overlap between the two decisions, and decisions specific activation. Analyses of overlap in neural activation between both decision types showed that mindful and unmindful decisions activated the medial prefrontal cortex (mPFC), the anterior cingulate cortex (ACC), and the temporo-parietal junction (TPJ), suggesting the involvement of mentalising processes and deliberate decision-making throughout the game (Frith & Frith, 2006; Schurz et al., 2014; Van Overwalle, 2011). How these processes were involved, however, remains unclear. Inferences on the basis of found neural activity remain speculative and need to be tested in future research. Deliberately considering the outcomes of both parties does not necessarily result in decisions that are beneficial for the other (Derks et al., 2015). Depending on motivation, considering the outcome for both parties may result in the deliberate choice for the benefits of the other player, or despite these considerations, in the choice for one's own benefit. Condition specific neural activation revealed that mindful decisions activated the TPJ, and unmindful decisions the mPFC. The TPJ is associated with mentalising processes that focus more on the other person, whereas the mPFC is associated with more self-referential mentalising processes (Amodio & Frith, 2006; Frith & Frith, 2006). Adding questionnaires or tasks tapping into motivations underlying the choices might help to elucidate this question. Therefore, associations between neural results and measures of pro-sociality (the *will*) and the Reading the Mind in the Eyes Task (the *skill*) were investigated, to strengthen inferences regarding underlying mechanisms. The proportion mindful decisions was associated with activation of the caudate. Moreover, the better participants were at performing the Reading the Mind in the Eyes task, the more dorso-lateral prefrontal cortex (dlPFC) activation was observed. These associations with the operationalisations of the *skill* and *will* suggested increased consideration of the consequences for the other person during mindful decisions (*skill*), and that for those inclined to choose mindfully, this choice brought about gratifying emotions (*will)*. In combination with the fronto-parietal network (FPN) found during mindful, and the default mode network (DMN) during unmindful decisions, these results suggested that when choosing mindfully, participants were more outwardly oriented, more focused on the other player. In contrast, based on the activation of the DMN, and decision-specific prefrontal activation, processes during unmindful decisions seemed to be more self-oriented, deliberate, and effortful. The number of mindful decisions was associated with caudate activity, suggesting that participants were possibly experiencing feelings of reward when choosing mindfully. It is plausible that doing good, being considerate of the other person, brings about a sense of reward (Higgins & Scholer, 2009). However, choosing the unique (and therefore more valuable item) might be rewarding too (Higgins & Scholer, 2009).

Development of trust

Only few developmental studies have focused on age-related changes in trust and social reciprocity. Sutter and Kocher (2007) found that trust increases linearly until 22 years of age, showing stability in adulthood and a slight decrease thereafter. Similarly, younger individuals showed increasing trust from childhood to mid-adolescence and a slight decrease towards early adulthood (Van den Bos et al., 2010). However, others did not find decreases in adulthood (Fett, Gromann, et al., 2014). With age, first investments and learning over trials increased (Van den Bos et al., 2012). In parallel with behavioural changes, brain activation in mentalising regions, i.e. temporo-parietal junction (TPJ), posterior cingulate and precuneus also increased with age (Fett, Gromann, et al., 2014). Furthermore, age-related reductions in activation were present in the reward-related orbitofrontal cortex and caudate during interactions with a trustworthy, cooperative partner. It is often believed that women are superior at mentalising and therefore more trusting, pro-social and cooperative than men. Research, however, shows that even though women frequently outperform men on mentalising tasks (Baron-Cohen et al., 2001; Rutherford et al., 2012), this does not necessarily translate into higher trust, pro-sociality or social reciprocity. Evidence indicates that men are more trusting than women, both in single (Buchan et al., 2008; Croson & Gneezy, 2009) and repeated social interactions in the trust game (Balliet et al., 2011; Croson & Gneezy, 2009). However, when trust is violated, females are more likely to stay trusting and restore trust (Haselhuhn et al., 2015). Furthermore, increased mentalising abilities do not necessarily drive pro-other oriented behaviour, but can also be used to manipulate others for one's own advantage (Derks et al., 2015). Only little is known about gender differences in trust and social reciprocity during late adolescence and early adulthood. One early study on trust in adolescence reported no gender differences in trust (Van den Bos et al., 2010), while a more recent study found that boys show higher trust towards others than girls (Derks et al., 2014), as often reported in adults.

In chapter 4 we investigated gender differences in the neural development of trust and reciprocity in 43 late-adolescents and young adults (aged 16-27, 21 female, M_{age}= 21.51;

22 male, M_{age}= 20.64). We found that baseline trust towards unknown others was higher in males than females. Baseline trust, however, was unrelated to age, a finding that is at odds with the existing literature. Other studies investigated the development of trust including younger adolescents and children (Sutter & Kocher, 2007; Van den Bos et al., 2010). The absence of age-related changes in trust behaviour in late adolescence suggested that trust develops early in adolescence and has reached adult levels around the age of 16 [see also (Crone & Dahl, 2012)], despite ongoing neural development. A larger, continuous sample from age 12 to 28 may further clarify the critical developmental period for trust. During cooperative interactions increases of trust were independent of age and gender, further strengthening the idea that trust and the development of trust have reached adult levels earlier in development. Gender specific changes in trust were only apparent in unfair interactions, with males adapting their behaviour more strongly towards an unfair partner than females. These findings are in concordance with the idea that females engage in more coaxing attempts to re-establish cooperation; they are more likely to stay trusting and to restore trust when trust is violated, possibly motivated by wanting to maintain relationships (Haselhuhn et al., 2015). Behavioural differences in response to an unfair partner became more pronounced between the genders with age. Despite the absence of age related changes in behaviour, activation of the TPJ and the dorsolateral prefrontal cortex (dlPFC) increased with age. This is in concordance with earlier trust game and developmental findings, suggesting changes in cognitive strategies and continued brain development (Blakemore et al., 2007; Van den Bos et al., 2011). Gender related differences, with males showing more TPJ activation than females, and females showing more caudate activation than males, suggested slightly different cognitive strategies in response to processing repayments. Males might optimise decision-making by increased mentalising (Cahill, 2006; Riedl et al., 2010), whereas increased caudate activity in in females might reflect increased feedback learning, resulting in similar levels of trust as males towards the end of the game. These results indicated the need for additional data assessing the underlying motives of decision-making, including self-report questionnaires and behavioural tasks that tap onto pro-social or competitive tendencies.

Social interactions and the psychotic illness continuum

Social impairments are a critical aspect of the psychosis spectrum. Even before illness onset and in individuals at high-risk for psychosis, lower social functioning is already present (Ballon et al., 2007; Corcoran et al., 2011; Cornblatt et al., 2007; Velthorst, Fett, et al., 2016; Velthorst, Reichenberg, et al., 2016; Yung et al., 2003). Social functioning relies on neurocognitive and social cognitive skills (Addington & Addington, 2008; Couture et al., 2006; Fett et al., 2011; Green & Leitman, 2008) that are impaired in patients with psychosis (Brüne, 2005; Green et al., 2005; Penn et al., 2008; Thompson, Bartholomeusz, & Yung, 2011). Similar social cognitive impairments, albeit to a lesser degree, are found in patients at clinical high-risk for psychosis (CHR) and in unaffected siblings of patients, suggesting milder impairments in high-risk populations, and a major decline with the first episode (Bora & Pantelis, 2013; Lavoie et al., 2013; McCleery et al., 2014; Pinkham et al., 2007). During the course of the illness, from first-episode patients to a chronic stage, social cognitive impairments seem to be relatively stable (Bora & Pantelis, 2013; Green et al., 2011; Pinkham et al., 2007).

The studies described in chapters 3 and 5 are largely based on the same subset of the total sample. Several similarities and differences in outcome are discussed.

Dynamics of social decisions

In chapters 3 and 5 initial spontaneous impairments in social interactions with an unknown counterpart were found in FEP: They spontaneously exhibited less socially mindful behaviour, and initially trusted unknown others less than controls. In the more straightforward, low-cost SoMi task, CHR performed at the same level as controls, whereas in the more complex, higher-cost trust game, initial behaviour resembled the FEP group. The results suggested that basic forms of pro-social cooperative behaviour, e.g., SoMi, only deteriorate as a consequence of the illness, after the first psychotic episode, whereas deficits in more complex and riskier forms of cooperation, e.g., baseline trust, are linked to the risk for psychosis trait, and are already present before onset. Whether the same is true for individuals at genetic risk remains open, data on relatives of patients are not conclusive about reductions in baseline trust (Fett et al., 2012; Gromann et al., 2014).

Social behaviour is flexible: people can adjust their social decisions the specific characteristics of the situation or their counterpart. In the early stages of psychosis, initial impairment in social interactions, such as distrust or reduced SoMi, can still be overcome, by making the patients aware of the perspective of the other person in the SoMi task, and by cooperative feedback from the trustee in the trust game. The studies described in chapter 3 and 5 further elucidated how the adaptation of cooperative behaviour differed between patients with psychosis or at-risk for psychosis, dependent on the specific paradigm used. In the trust game FEP showed larger increases of trust than controls, resulting in a compensation of their reduced initial trust, with similar levels of trust as controls towards the end of the game, suggesting normal levels of trust have been reached. This finding is in line with earlier findings in adolescents with early psychosis (Fett et al., 2016). CHR showed a similar pattern of compensation, resulting in trust levels comparable to controls at the end of the game. An earlier study suggested that in chronic stages of the illness patients responded less to positive feedback, compared to controls (Gromann et al., 2013). Several possible explanations might underlie this difference in early and chronic stages of the illness. It is possible that this reduced responsiveness to positive feedback is associated with the experience of having a chronic psychotic disorder. Negative social experiences might function like a self-fulfilling prophecy, resulting in less engagement in interactions and desensitization for positive feedback. It is noteworthy in this regard, that responses to negative social feedback were unimpaired in chronic patients (Gromann et al., 2013). This decline might also be associated with increasing cognitive and mentalising deficits over the illness course, which may not yet be apparent in CHR and FEP.

In the SoMi task, FEP, CHR, and controls showed similar abilities to increase the number of mindful decisions after instruction. This equal increase resulted in the persistence of the initial difference between FEP and the other two groups after instruction. FEP showed socially mindful behaviour when prompted, but spontaneously chose the unmindful option more often than the other groups. Less frequent spontaneous socially mindful behaviour might be due to reduced consideration for the other player, as reflected in reduced activation of mPFC, dlPFC and ACC (Frith & Frith, 2006). Alternatively, reduced activation of dlPFC and ACC could also suggest that FEP (and CHR to a lesser extent) might perceive unmindful decisions as less incongruent with the automatic mindful responses than controls. It might be that negative social experiences due to their illness have already altered the way patients perceive interactions with others, and thereby their expectations of and norms for these interactions. The possible explanation of reduced sensitivity to the rewarding aspects of SoMi will be discussed below.

Neural mechanisms: mentalising and reward processing

The ability and willingness to think about preferences of and benefits for others are two core requirements for social mindfulness and for trust. The ability, the *skill*, reflects social cognitive processes, especially mentalising, to recognise the needs and wishes of others, to judge the other's trustworthiness and intentions; the willingness, the *will*, reflects social motivation, the sensitivity to the intrinsic pleasurable effects of positive social interactions, to act socially mindful or to trust. Neither FEP nor CHR showed significant reductions in activation of mentalising areas compared to controls in either paradigm. On the contrary, during unfair interactions in the trust game, CHR showed increased activation of the TPJ, and compared to cooperative interactions also increases in the mPFC, compared to controls. CHR adapted well to negative social feedback, possibly caused by the compensatory mentalising activity. Other social cognitive skills than mentalising might underlie the behavioural differences, but it may be possible that the differences do not originate in impairments in social cognitive skills, but rather in the way they are used, the motivation for pro-social cooperation.

When behaviour is rewarding to us, motivation to repeat the experience increases, and we will more frequently engage in such behaviour. Motivation can be intrinsic, when the rewarding aspect is in the behaviour itself, or extrinsic, when rewards come from outside (Ryan & Deci, 2000). In chapter 2 we argued that in the SoMi task pro-social, mindful decisions might be inherently rewarding, due to benefits of social ties to the individual. Chapter 3 demonstrated that FEP showed differential activation of reward processing areas, which might possibly be related to the fact that they chose the mindful option less frequently. We hypothesised that pro-sociality might not be the natural first inclination for FEP, possibly due to reduced sensitivity to the rewarding aspects of social mindfulness. Reduced reward sensitivity has previously been reported in psychosis (Fett et al., 2012; Gold, Waltz, Prentice, Morris, & Heerey, 2008; Gromann et al., 2013; Gromann et al., 2014; Strauss et al., 2013). In contrast to FEP, CHR showed no impairments in reward processing, possibly explaining the intact spontaneous socially mindful behaviour.

In the trust game, no differences in reward processing were found between the groups, indicating that FEP, CHR and controls perceived the positive returns of the trustee as rewarding. Possibly, the rewards in the trust game are more obvious, and larger. It might be that these bigger incentives are still processed normally in FEP, and that reward processing declines in chronic illness stages. Inherently to the SoMi task, where low-cost items are presented, rewards are more subtle, therefore might be less recognised by FEP, or not activate neural regions strongly enough. In a monetary incentive delay task, increasing the rewards increases neural responses (Knutson et al., 2003; Waltz et al., 2010), suggesting larger neural differences when higher rewards are presented. Furthermore, the differences between FEP and CHR in activation of reward related areas might be explained by the fact that SoMi measured reward when doing something good to others, whereas the trust game measured reward processing, when receiving something positive from others.

The continuum of social impairments in psychotic illness, a résumé

Basic forms of pro-social cooperative behaviour were still intact in CHR and only impaired after the first psychotic episode. Possibly, since only one CHR transitioned to psychosis, these patients were not in the prodromal psychosis state. Alterations in more complex forms of cooperation, however, were already present in CHR. Both CHR and FEP were still able to overcome, or even compensate for the initial deficit. CHR showed behavioural adaptations similar to controls, resulting in similar 'endpoints'. Following instructions (in the SoMi task) FEP also showed a similar increase in mindful decisions, but in the more feedback oriented complex trust game, they even compensated their initial lack of trust by steeper increases compared to controls.

Reduced spontaneous mindful behaviour seemed to be only apparent after a first psychotic episode, whereas reduced trust was likely to be associated with the risk for psychosis, based on the presence of psychotic symptoms. Responding to social feedback was still intact in CHR and FEP, suggesting a decline over the years with longer illness duration, in chronic stages. Reward processing, however, already showed some deficits in FEP, but not in CHR. It is likely that the processing of more subtle rewards is affected after first illness onset, and that during the course of the illness this deficit also spreads to more obvious, bigger rewards. Mentalising and reward processing mechanisms might differ between patients with psychotic symptoms with and without the conversion to psychosis. Whether responding to instructions to behave socially mindful in the SoMi paradigm also is affected by illness duration remains to be investigated.

Urbanicity and psychosis

As discussed in chapter 7, the association between urbanicity and non-affective psychosis has been supported by many epidemiological studies, showing elevated incidence rates of psychosis in densely populated urban areas. The effects of the population density in the living area seem particularly pronounced during upbringing (Heinz et al., 2013; Pedersen & Mortensen, 2001). Many mechanisms have been suggested to explain this association, both environmental (e.g., pollution, noise, lack of green space) and social in nature (e.g., decreased social capital and cohesion, social deprivation, and social fragmentation). Every mechanism could explain a small proportion of the association, yet a comprehensive model is still lacking. In recent years, explanations have also been sought at the biological and neural level, associating urbanicity with genetics, brain structure and function. Given the complexity of the urban environment and the plethora of possible explaining factors, isolated factors will not likely yield the answer. Investigating the effect of a combination of possible influential factors in social interactions and real life situations might be the next step to take. In combination with neuroimaging, these can help to elucidate the underlying mechanisms and offer new directions of research.

Interpretation of study findings is complicated by several factors. For example, the measure of urbanicity differs greatly between studies: divisions of urban-rural (DeVylder et al., 2018), rural-town-large city (Haddad et al., 2014; Mortensen et al., 1999), and divisions on the basis of population density per postal code have been used (Frissen et al., 2017; Peeters, Gronenschild, et al., 2015; Peeters, Van de Ven, et al., 2015). Furthermore, the concept of urbanicity may refer to urban birth (Laursen et al., 2007; Mortensen et al., 1999), urban upbringing (Frissen et al., 2017; Haddad et al., 2014; Krabbendam & Van Os, 2005; Pedersen & Mortensen, 2001; Peeters, Van de Ven, et al., 2015), and current city living (Colodro-Conde et al., 2018; Krämer et al., 2017; McKenzie et al., 2013; Sundquist et al., 2004). These operationalisations are used to test different hypotheses: birth factors, developmental influences, and possibly selective migration, respectively. This diversity in methods and definitions makes comparisons between studies difficult. Furthermore, urban environments have different meanings, depending on the wealth and prosperity of the country, where urban living may differ between greater access to resources or greater exposure to social adversity (DeVylder et al., 2018).

Chapter 6 investigated the association between urbanicity and trust, examining urbanicity as a possible explanatory candidate of divergent social behaviour, in healthy individuals and patients with psychotic symptoms, capturing a combination of social factors in a social interactive paradigm. Reduced baseline trust was unrelated to urbanicity. In patients, urbanicity exposure was associated with differential learning from positive social feedback, with a steeper increase in investments in lower compared to higher urban patients. Lower urban patients compensated for their reduced baseline trust, but this was not present in higher urban patients. Functional brain analyses suggested that mentalising and reward learning processes were unaffected by urbanicity and did not explain any of these differences. Furthermore, patients brought up in higher urban areas showed differential activation of the amygdalae in cooperative interactions, which could reflect reduced feedback learning. Accordingly, this finding could suggest that higher urbanicity impacts on feedback learning in FEP and CHR, even though for the group as a whole feedback learning is still intact. The possible underlying mechanism could be altered stress processing, as suggested by Lederbogen et al. (2011), or impaired reward processing, which also seems to be related to stress mechanisms and is also based on the dopamine system, which is thought to play a fundamental role in the aetiology of psychosis (Krämer et al., 2017). The results of these studies, conducted in healthy individuals, do not translate directly to patients with a psychotic disorder. More functional neuroimaging studies in patients are needed to unravel the urbanicity-psychosis association.

Implications for clinical practice

We found impaired baseline trust in early psychosis and in patients at clinical high-risk, indicating that reduced trust in unknown others might be a marker for psychotic illness. Trust is an essential first step for positive social interactions. Facilitating this step might pave the way for better social interactions, and therewith for better functional outcomes (Velthorst, Fett, et al., 2016). Both patient groups were still responsive to positive feedback, and only FEP displayed different reactivity to unfair social feedback. Possibly, the first psychotic episode, and the label of the diagnosis could have been a traumatic experience to them (Brohan, Elgie, Sartorius, Thornicroft, & Group, 2010; Jackson, Knott, Skeate, & Birchwood, 2004; Lysaker, Roe, & Yanos, 2006; Tarrier, Khan, Cater, & Picken, 2007). Combined with repeated negative associations in social interactions, FEP might be desensitised for negative feedback, resulting in reduced responses. CHR do not display these problems yet, and many of them probably never will. Furthermore, treatment reinforcing positive interactions, strengthening social ties and personal beliefs in their capacities will facilitate better functional outcome. When asked, patients valued treatment for affective problems (e.g., depression, low self-esteem) and neuropsychological problems (e.g., memory and attention) as more important than treating positive symptoms (Moritz, Berna, Jaeger, Westermann, & Nagel, 2017). Recovery therefore can be seen as empowerment of the patient, to engage in social interactions, in other words as functional outcome (Jacobson & Greenley, 2001). At the same time targeting and breaking the downward spiral of negative feedback, and reinforcing positive interactions will be crucial in this process.

Facing the end - considering limitations

> *"If you could do it all over, would you do the same again,*
> *or would you take a different turn?"*

First of all, I will not do it all over again! But if I may continue, I will gladly follow a similar track, heading in the same direction. However, I would make several adjustments to the route, based on the pitfalls and limitations I encountered during the research and write-up of this dissertation. First of all, the sample of healthy controls was large, heterogeneous in terms of gender, age, and education level, making it suitable for comparison and generalization. However, for stratified analysis on the basis of gender and for the performance of regression analyses examining age (see chapter 4), the sample was still relatively small. In addition, the FEP sample was very diverse, consisting of acute in-patients and recovering out-patients who were partly re-entering school and working life. A homogeneous sample would have delivered more straight forward findings and interpretations thereof. Alternatively, a much larger heterogeneous sample, allowing for sub-samples could have uncovered specific mechanisms associated e.g., with conversion vs. non-conversion. However, one could also argue that the current sample reflects the clinical reality and cases as they are, complex rather than homogeneous, which increases generalisability and ecological validity of the results. The present FEP sample consisted of adolescents who had experienced a first psychotic episode and who now were at various stages of treatment and recovery, from hospitalised to out-patient care. Despite the diversity, they represent a large group of first-episode patients. As discussed in chapter 5, the concept of CHR raises more questions. Strictly speaking, whether these patients were at high-risk for developing psychosis can only be determined with hindsight. It is debated whether the group is really at increased risk for developing psychosis, or rather a patient group with generally poor mental health that also reports positive psychotic symptoms, which are secondary to other problems such as severe anxiety and depression (Van Os & Linscott, 2012; Van Os & Reininghaus, 2016). The addition of psychotic symptoms renders these patients at-risk for developing any psychopathology, without necessarily developing a psychotic disorder (Fusar-Poli et al., 2013; Yung et al., 2012). Furthermore, the presence of psychotic symptoms is possibly more important in the assessment of clinical high-risk than the transition to psychosis (Van Os & Reininghaus, 2016). Many patients in care for anxiety and depression report psychotic symptoms (Van Os & Linscott, 2012; Van Os & Reininghaus, 2016; Velthorst et al., 2009; Wigman et al., 2012; Woods et al., 2009), but do not transition to psychosis, leaving to debate whether clinical high-risk for psychopathology might better describe this group than clinical high-risk for psychosis.

It has been argued that the presence of these symptoms is associated with a poorer prognosis in general, showing that these patients are certainly in need of special care (McGorry & Van Os, 2013; Ruhrmann et al., 2010; Valmaggia et al., 2013; Van Os & Linscott, 2012; Van Os & Reininghaus, 2016). Thus, identifying patients who are at increased risk due to the presence of psychotic symptoms, and understanding the influence of these symptoms is crucial for adequate treatment. Considering the limitations stated above, in future research I would opt for a large heterogeneous sample of patients, allowing for subdivisions.

Furthermore, no restrictions were made regarding medication, making it difficult to firmly draw conclusions as to what extent the differences in behaviour or neural activation were driven by medication. The sample size was too small to perform statistically relevant analyses based on a division of medicated and non-medicated FEP. However, exploratory neural analyses suggested that medication influenced other brain regions than the ones reported in the studies (data not shown). Furthermore, medication naïve patients are extremely hard to recruit and do not represent the patient population, where the majority is under pharmacological treatment. Similar considerations should be made for the CHR sample. All participants were recruited from one care giving institution. Out of 18 CHR participants, only one made a transition to psychosis, which is lower than the generally reported transition rates.

Furthermore, in most analyses I controlled for the IQ proxy, the WAIS Vocabulary score. In comparisons with patients with psychotic disorder this might cause problems, since one of the defining characteristics of the illness are deficits in cognitive performance. By including WAIS Vocabulary as a covariate, some inter group variance is filtered out, reducing the strength of the results (as reported in chapter 3). However, this conservative approach results in findings that are still significant, adding value to the results. Additionally, comparing three groups in the same model requires large inter-group differences to yield significant results. Possibly, using pair-wise group comparisons would have resulted in more significant outcomes, since the groups were quite similar in many aspects.

Investigating the influence of urban upbringing in patient groups requires large samples of evenly distributed levels of urbanicity. Our sample did not meet these requirements, so that we used a binary division of urbanicity, thereby losing sensitivity for more nuanced urbanicity effects. We compensated for the modest sample size by also including CHR in the patient sample, which we justified based on the presence of equally severe psychotic symptoms as observed in the FEP only sample. Binary divisions (DeVylder et al., 2018; Marcelis et al., 1999), or roughly defined ternary divisions have been used by others (Haddad et al., 2014; Krämer et al., 2017; Lederbogen et al., 2011).

The current sample is representative of the distribution of population density in the Netherlands, which is moderate, even in large cities.

Using neuroeconomic paradigms like the trust game and SoMi task, we found differences in behaviour, for which we could only hypothesise the underlying reasons or mechanisms. Questionnaires or other tasks that tap onto social orientation and the motivations for the targeted behaviour are needed to explain what these behavioural differences mean. Neural activation can hint in a certain direction, but all suggestions are based on reversed inferences, and remain to be tested empirically (Poldrack, 2006; Poldrack et al., 2016). I would include motivational questionnaires in future studies, which can strengthen these inferences.

Research settings are artificial surroundings, where situations are simulated to measure the topic of interest in its most pure form. And for this goal they serve their purpose. But considering the ecological validity of these paradigms, how *social* are interactions with a computer? What we have measured is the theoretical ability to perform such interactions in a hypothetical environment. However, situations might turn out quite differently when facing a real person in real life. Additionally, many psychological mechanisms may underlie these interactions, which are not easy to disentangle. Inferring processes from observed neural activation is speculative (Amodio, 2010; Poldrack, 2006; Poldrack et al., 2016). Without active manipulation of factors of interest, fMRI cannot give conclusive answers about the underlying mechanisms. The complexity of social interactions, and the multiple functions brain regions are involved in, make reverse inferences about these mechanisms uncertain. Furthermore, fMRI measurements are based on haemodynamic changes, an indirect measure for neural activity that does not distinguish between inhibitory and excitatory neural processes. Important questions remain about how to interpret this neural activity. For example, reduced activity might be explained as less effort for a given task, due to automatised processes; or as less recruitment of the specific brain area due to malfunctioning of that area or network.

Thinking about an elevator pitch about my work, I tried to summarise the goals, findings and implications for someone completely unfamiliar to the present work: "*I wanted to measure social interactions in health, clinical high-risk and first-episode psychosis, at the behavioural and neural level. In short, initial problems within the social mindfulness paradigm and trust game encountered by CHR and FEP can be overcome by instruction and positive social feedback. Altered brain activation in mentalising and reward related areas suggests different underlying mechanisms in FEP and CHR compared to controls*." But how representative are the two patient groups and how valid are the used methods when it comes to indicating mechanisms of real social interaction? Can the complex mechanisms of social interactions really be measured using a computerised paradigm inside an MRI scanner? Despite these uncertainties and imperfections, results from laboratory experiments and fMRI research open a window that allows us to capture aspects of social interactions (if not the full complex picture) that can provide evidence for hypotheses about social dysfunction that can be tested in further research. Integrating diary technologies like experience sampling method (ESM) can provide further insight in mechanisms underlying daily life decisions and social interactions. They might not answer the full question now, and many more questions even arise from these results, but a small step is taken, that others can build upon.

The million-dollar question

> *"What would I do if I had not to worry about financial resources or time restrictions?"*

Provided "unlimited" access to patients, I would set up a longitudinal study including three cohorts: CHR, FEP and chronic patients. Following CHR over a period of time will provide insights in traits associated with conversion to psychosis of resilience and will allow for direct comparison between converters and non-converters. The inclusion of FEP will add information on the impact of a transition to psychosis and the development over time. In this group, some will experience several episodes, developing a chronic illness, but others might stabilise or even recover. This group will provide insight in traits associated with these developmental paths. Contrasting these with chronic patients, will cover the complete trajectory from premorbid to chronic. Ideally, these groups are all presented in a large longitudinal study, where individuals are followed from prodromal to chronic stages. For comparisons between stages in this dissertation I had to draw from different studies, with similar but not identical test settings and analyses. Creating uniformity in methodology will increase the power of comparison.

Given the patient population, I would want to do three things with the trust game. First, use a more naturalistic algorithm that includes breaches of the dominant trustee behaviour towards the patient. In real life, people are not always nice, or always unfriendly, and behaviour can change. I would be interested in how they react to a sudden change (and maybe change back) of behaviour; what happens when the building of trust is violated by unfair feedback, and what if an unfair partner suddenly becomes trustworthy and cooperative. But especially I would include many more measures to relate trusting behaviour to: different measures of mentalising and reward (also in the fMRI scanner, for direct comparison), personality questionnaires (e.g., Macchiavellianism), and questionnaires informing about strategies used, underlying the recorded behaviour, investigating coaxing, tit-for-tat strategies etc. Lastly, for the analysis of brain data, predominantly region of interest (ROI) analyses were used. This method has the advantage of analysing activity within specific regions that are thought to be active during the given process. Brain regions, however, do not function in isolation, and I would be interested to perform network or connectivity analyses.

The SoMi paradigm is novel and still presents many unanswered question to be investigated by social psychology. During this PhD process, I have become curious of what would happen when we reversed roles of the two players. If I were not the player choosing first, but were confronted with the choice of the other, safeguarding or limiting my options of choice, would I start to like the socially mindful other, trust more? In parallel, would I dislike the unmindful player, would I do the same or try to restore cooperation by displaying pro-social behaviour? Probably I would do the latter, but being female and not too young anymore (see chapter 4), would socially mindful behaviour be rewarding or would taking the unique item, and frustrating the other make me feel good? Combining SoMi in the reversed version with the Cyberball paradigm, a paradigm measuring social exclusion (Williams, Cheung, & Choi, 2000), could elucidate if being deprived of the option of choice resembles feelings of exclusion. The paradigm was specifically designed for low-cost cooperation, but would the neural signature change (similar to the higher cost trust game), if valuable items were at stake?

In my search for underlying mechanisms, wanting to know why patients with a psychotic disorder behave differently and why some individuals are more resilient than others, urbanicity was an interesting aspect. In the search for mechanisms explaining the association between psychotic disorder and urbanicity, I was particularly interested in the gating deficit hypothesis. I would gladly do research on information processing, social interactions, with different degrees of "added noise", challenging sensory gating abilities. Using interactive paradigms in "rest", and with different disturbing auditory, visual and/or olfactory inputs may reveal different thresholds for patients compared to controls. And if so, the common denominator could still be aberrant stress processing. To be investigated!