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## **Mechanisms of symptom formation in psychosis**

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# Chapter

General discussion

# 6



## GENERAL DISCUSSION

### Summary of the main findings

The main objective of this thesis was to gain new insights into the dynamics underlying symptom formation in psychosis, focusing on the cluster of persecutory delusions. Considering the heterogeneous nature of psychotic disorders, it makes most sense to examine the development of individual symptoms, rather than the entire diagnostic category. Two central topics with respect to persecutory delusions were investigated in an observational and experimental manner. First, the connection between bullying victimization and common non-clinical psychotic experiences in the general population was studied by comparing subjective (i.e. self-reports) with more objective (i.e. peer reports) measures of victimization (i.e. chapter 2a and 2b). Secondly, this thesis was directed at illuminating the social nature of psychosis by implementing a combination of game theoretical paradigms and neuroimaging methods. Specifically, three fMRI studies based on the trust game were conducted with different samples to examine the neural foundation of the lack of trust and disturbances in social reward learning in healthy adults and adolescents (i.e. chapter 3), patients (i.e. chapter 4) and first-degree relatives of patients suffering from psychosis (i.e. chapter 5).

The findings from **chapter 2 a and 2b** clearly emphasized the relevance of implementing both self-reports and peer reports as assessment tools for bullying victimization, by revealing different results for the relationship between bullying victimization and non-clinical psychotic experiences in young adolescents. There was a specific link between self-reported victims and non-clinical psychotic experiences, but not between peer-reported victims. Consequently, having the internal representation of being victimized seems to be a sufficient condition for the presence of a higher rate of psychotic-like experiences in young adolescents. This could be indicative of an interpretation bias or a greater sensitivity of children with a pre-existing psychosis vulnerability. Given the complementary nature of peer- and self-report measures, using a combination thereof leads to a more complete picture and more thorough examination of any research question, especially in the case of a heterogeneous disorder such as psychosis.

**Chapter 3** revealed age-related increases in trust and cooperation during social encounters, with corresponding improvements in mentalising as the most likely underlying explanation. Increases in the sensitivity to social signals of the interacting partner seem to drive the transition from adolescence to adulthood, as indicated by the behavioural findings of more cooperation and a lower tolerance for deceptive behaviour in healthy adults. This enhanced social sensitivity in adulthood was linked to differential activation patterns of brain regions that are essential for the mental processes of mentalising, conflict monitoring and reward learning. **Chapter 4** showed that patients with psychosis had a diminished capacity to respond to beneficial social interactions, which became evident at a behavioural level by reduced (baseline) trust at the initial stages of social encounters. This was accompanied by attenuated activation of brain areas traditionally linked to reward learning (i.e. the caudate) and mentalizing (i.e. the TPJ). Noteworthy, the strength of the caudate signal was associated with the patients' paranoia scores. Unlike the control subjects, there was no link between the caudate signal and baseline trust in

patients. This provides a specific link between patients' symptomatology and reduced reward processing. Moreover, **chapter 5** demonstrated diminished neural reward-related processing (i.e. the caudate) during mutually beneficial interactions in first-degree relatives of patients with psychosis when compared to healthy adults without an enhanced genetic risk for psychosis. Noteworthy, no different activation patterns of mentalising brain regions and no behavioural differences were observed between first-degree relatives and the control group in this study.

The final chapter of this thesis is directed at evaluating the main findings of this thesis critically with regard to implications for research and clinical practise.

## IMPLICATIONS FOR RESEARCH ON PSYCHOSIS

### Investigating social exposure

Experiencing social adversity as a child constitutes a severe trauma with far-reaching, negative consequences on one's mental health. The study on bullying victimization described in **chapter 2b** was the first to implement both subjective and objective measures of victimization and revealed valuable insights, by implying that the subjective experience of being bullied may actually drive the relationship between bullying victimization and psychosis. This can be explained by means of an underlying interpretation bias causing children who are susceptible for developing psychotic-like symptoms to interpret their social surroundings as threatening. Noteworthy, any response to trauma can be regarded as the sum of the objective event and the interpretation thereof. This is in line with the cognitive model of persecutory delusions described in **chapter 1** [1].

Additional support for the notion of trauma as the sum of an objective event and its interpretation comes from previous studies that have argued that hostile interpretations of other's people's intentions are related to the onset and maintenance of mild psychotic experiences [2, 3]. The intent to harm seems to be a highly relevant feature: Encounters with harmful intentions show a stronger link to psychotic symptoms than those lacking such intent, and it has even been argued that the component of threat or the just the perception thereof can trigger psychotic symptoms [4, 5]. This could also be related to the secondary findings of **chapter 2b** showing that both self-reported direct relational and indirect relational victimization were more strongly associated with non-clinical psychotic experiences than other types of victimization without a social aspect (i.e. verbal and possession-directed victimization). Considering the social character of psychosis that is inherent to its main symptoms like persecutory delusions or social isolation, this indicates that social processes may have a substantial impact on the onset and maintenance of mild psychotic-like experiences in the general population. This is in line with a recent study [6], revealing a moderating effect of bullying victimization on psychotic-like responsiveness to social stress.

Noteworthy, it has already been postulated earlier on that hypersensitivity might be a trait linked to schizophrenia vulnerability [7], meaning that individuals who are more prone to develop the illness would react stronger and more sensitive to their environment. Accordingly, hypersensitive children could perceive and interpret everyday social encounters as more

harmful than intended by their social surroundings. A recent study supported this notion by showing that both self-reported bullying victimization and the personality trait of interpersonal sensitivity were found to predict paranoia scores, i.e. paranoid ideation and suspiciousness [8]. Specifically, an excessive sensitivity and viewing oneself as vulnerable to threat resulted in an inclination for external attributions of adverse experiences, which in turn fostered paranoid ideation. Taken together, this yields further support for the hypothesis that the subjective experience of victimization may drive the association between bullying victimization and psychosis at least in some children. Additionally, it has been argued that early social adversities result in negative internal representations based on social humiliation and subordination, which in turn may foster voices and paranoia [9].

An open question is whether the findings relating to bullying victimizations can also be extended to trauma in general. In particular, it is possible that the association between trauma and psychosis in part reflects personal interpretations and a greater sensitivity to social events, but this remains a question for future research. The current study was limited by its cross-sectional nature and the rather crude assessment of psychosis by means of four questions; therefore these findings should be regarded as preliminary evidence. Nevertheless, it seems fair to assume that both subjective and objective perceptions can play a role when examining bullying victimization. Considering that Freeman's model suggests that both the adverse event as well as one's interpretation play a role, the distinction between subjective and objective measures of other forms of early social adversity such as neglect or abuse may also be useful for the vast literature on the relationship between trauma and psychosis. Future research should focus on longitudinal, prospective studies implementing a combination of subjective and objective assessment of different kinds of trauma.

## Investigating Social Cognition

Game theoretical paradigms from the neuro-economics research field has offered the intriguing potential to conduct social cognitive research on trust and social interactions in a more complex and ecologically sound manner. Chapters 3, 4 and 5 of this thesis employed the trust game, which in its original form constitutes an one-shot interactive game based on an monetary exchange between two players [10]. Specifically, the first player, the so-called investor, receives a fixed investment amount and is asked how much money he would like to share with the second player (i.e. the trustee). Shared money is being tripled, and the trustee's task is to decide how much money to repay to the investor. Trust is needed to make investment decision and the amount invested by the investor can be regarded as an index of trust. This provides the underlying rationale for choosing the role of the investor in order to investigate the lack of trust in psychotic disorders by means of the trust game. In this thesis, a repeated rounds version of the trust game has been implemented, meaning that participants had to infer their partner's intentions from behavioural cues continuously. The findings of chapter 3, 4 and 5 of this thesis highlight the relevance of intact mentalising and social reward learning for successful social interactions in healthy individuals. This is in line with previous studies showing that mentalising and social

reinforcement learning are important for strategic reasoning about the partner's intentions during the trust game and to infer how the partner perceives one's own behaviour [11, 12]. This thesis further adds to this by showing that impairments in these highly relevant social processes – as in the case of psychoses – have negative consequences on an individual's ability to function and profit optimally during social encounters such as beneficial trust game exchanges.

Chapter 3 provided evidence for default distrust in healthy adolescents, but not in adults, meaning that development of healthy trusting behaviour is characterized by an inclination to distrust in adolescence, which consequently transforms into a more trusting disposition in adulthood. Recent evidence from developmental social neuroscience suggest that adolescence is a key developmental period for the development of the social brain [13]. Adolescence is also the key period of risk for development of schizophrenia. Therefore, it is interesting to consider these findings in light of the psychosis proneness-persistence-impairment model [14], which states that in adolescence specific processes develop and interact with risk factors, resulting in psychotic-like symptoms in a large number of individuals. According to this model, up to 75-90% of psychotic experiences are transient and tend to normalize over time. A small part of these experiences can become persistent and lead to clinical impairment dependent on the amount of environmental risk that a given psychosis-prone individual is submitted to. The findings of chapter 3 showed that healthy adolescents were less trusting and less able to adjust their behaviour to negative social signals of the partner than healthy adults. This suggests that healthy development is characterized by a change from an inclination to distrust towards an inclination to trust, which may be facilitated by an increased understanding of whom to trust. Taken together, these findings may suggest that schizophrenia is the developmental outcome of a pathological persistence in default distrust. Noteworthy, subclinical psychotic experiences are associated with the same risk factors that apply to psychotic disorder, providing evidence for aetiological continuity. One of those factors was trauma, which has been thoroughly investigated and discussed in chapter 2b.

Furthermore, it seems essential to discuss the nature of the implemented paradigm and consider whether the trust game taps into other processes in addition to trust and social reward. It can be argued that the decision to invest also reflects risk-taking behaviour. Any decision to share money with the second player also constitutes a certain amount of risk, since it is uncertain whether one's trust will be reciprocated. If the second player decides to keep all the money to himself, the investor suffers certain loss. However, from a conceptual point of view, risk is inherent to trusting others, due to the uncertain outcome of any social encounter. The design of the trust game paradigm implemented in chapters 3, 4 and 5 does not allow differentiating between risk taking in a social and a non-social context. Several authors have claimed that attitudes towards risk influence behaviour in a trust game, because the decision is made under uncertainty [15-17]. Others have demonstrated that risk attitudes do not predict trust decisions [18], and that there is a fundamental difference between risk-taking in a social vs. non-social context [19]. In support of this view, the neuropeptide oxytocin was found to act solely on improving the effects of social learning, and not on learning in a non-social risk game [20].

A related question is to what extent the trust game reflects general rather than social reward learning. Social context can have a modulating effect on trusting behaviour, by affecting reward learning in the striatum [21]. This does not only support the social nature of trust game paradigms, but also clearly shows that trust games are not only based on monetary reward. The fact that social expectations influence reward-learning in the brain shows that monetary reward by itself cannot explain trusting behaviour. In line with this notion, it has been shown that human social behaviours, in particular the incentive of getting a good reputation, activate the same reward circuitry as monetary rewards [22]. Finally, our own within-group results from chapter 5 showed activation in brain regions that have been implicated as neural substrates of social cognition [23], thereby supporting that social reward, rather than generic reward, is being tapped. Taken together, it seems fair to assume that social reward can be distinguished from generic reward processing and risk-based decision-making during the trust game and that our paradigm tapped into social learning rather than generic reward learning. Nevertheless, future research implementing the trust game could benefit from controlling for sensitivity to generic reward and risk.

## Investigating the Social Brain

Neuroimaging research has become increasingly popular in the last decades. Imaging techniques have become more and more defined and accurate and led to impressive insights into the neural mechanisms underlying various symptoms of psychotic disorders. However, one should bear in mind that there are limitations to the interpretations of such findings. Up to date, no single neural irregularity has been established as being specific to psychosis and underlying all its patients, even though schizophrenia has been described as a brain disease [24]. Specifically, it has been argued that schizophrenia evolves as a result of the interplay between brain vulnerabilities and environmental factors, and is associated with dysfunctional circuits consisting of multiple brain regions, rather than deficit in one specific brain region [24].

Moreover, adequate reporting of functional imaging results can be problematic due to an overabundance of analysis choices, and the impact thereof on the results. It has recently been argued that there is an issue with small sample sizes inherent to most fMRI studies [25]. Specifically, between-group designs with sophisticated contrasts may result in smaller effects sizes, meaning that real effects may be missed due to insufficient power. In line with this, one could argue that some effects could have been missed in chapter 3 of this thesis, which used a rather small sample size of 20 patients compared to 20 healthy individuals, particular in the case of lack of group differences of the mPFC. Power poses a challenge for patient studies, considering that it is difficult to find a large number of patients who fulfil the inclusion criteria, are MRI compatible and willing and able to endure an hour of testing inside of the MRI scanner.

The issue of “reverse inference” has been raised by Poldrack as a considerable critic on the common practise used cognitive neuroscientists whereby the involvement of a certain cognitive process is being inferred based on the activation found in a specific brain region [26-28]. According to Poldrack, this approach is not valid from a deductive point, but can



yield useful information as long as the selectivity is clearly established. This selectivity refers to the notion that activation of a certain brain region should be predictive for the cognitive process that is being investigated. The anterior cingulate is a good example for when making reverse inferences can be problematic, considering that it has a great range of varying proposed functions such as conflict monitoring, interoception, pain, autonomic regulation, effort, and consciousness [28]. Considering this concept of selectivity seems essential for the evaluation of any neuroimaging findings. Chapter 4 and 5 of this thesis highlighted differences in brain activation in two brain regions associated with mentalizing, the TPJ, and reward processing, the caudate. Both these brain areas can be regarded as more selective than the anterior cingulate, but not purely selective considering that the TPJ is not only associated with mentalising, but also with attention [29]. However, one might argue that when it comes to neuroimaging findings, it is hard to establish truly selective findings based on a one on one relationship considering that almost all brain areas seem to be implicated in multiple functions. Therefore, it seems fair to conclude that the imaging results of this thesis still offer valuable insights into the neural mechanisms underlying the social deficits of psychotic disorders.

## Investigating psychosis

Psychosis can be studied at a variety of levels, ranging from subclinical or mild psychotic-like experiences (as in chapter 2b), to first degree-relatives with an enhanced genetic risk of psychosis (as in chapter 5), to first-episode patients, and to full-blown acute clinical psychotic disorders (as in chapter 4). The relevance of including relatives – with an enhanced genetic risk of developing the disorder and similar deficits on neurocognitive tasks, albeit to a lesser degree, as in patients - becomes evident when comparing the findings from chapter 4 and 5. Noteworthy, abnormal activation in brain areas associated with mentalising was found in patients during the trust game (chapter 3), but not in their healthy relatives (chapter 4). This may suggest that the observed mentalising deficits during social encounters in patients are related to the illness itself, and may not constitute a potential risk factor for psychosis. In contrast, reduced reward processing was present in both patients and healthy siblings, suggesting a potential role as a vulnerability marker for psychosis.

Overall, the findings from this thesis showed that examining different levels of the psychosis continuum can lead to valuable insights. Nevertheless, when it comes to specific clinical risk groups, one may wonder about their exact characteristics and how representative they are for drawing conclusions on psychotic disorders. The so-called ultra-high risk group (UHR) has been extensively studied in the past decade, with the promising idea that individuals at risk could be identified early on and properly treated in order to prevent them from developing a psychotic disorder. The underlying assumption was that one could identify at-risk individuals first presenting to care services, who are in a prodromal (i.e. pre-stage) phase before making the transition to the actual psychotic disorder, and that it would constitute a well-defined specific group characterized by early positive symptoms. In spite of the popularity of the ultra-high risk concept, it should be interpreted with caution. Noteworthy, the scientific validity of

the terms ultra-high risk and transition has been questioned recently [30]. The authors raise some convincing points, such as the different sampling methods and wide variety of exclusion criteria being used across studies with ultra-high risk groups. Contrary to the well-defined UHR criteria, those for the term transition are rather vague and represent a dimensional shift, which may increase the risk for false positives accounts of transitions cases. According to the authors, UHR is based on the misleading assumption that almost all early psychotic experiences result in schizophrenia. This stands in contrast with the common characteristic that most UHR individuals across studies suffer from depression, anxiety or substance abuse with only mild psychotic symptoms.

Noteworthy, the concept that psychotic symptoms can occur in other psychopathology without being predictive for psychotic disorders is already being implemented in the DSM5 [31]. Specifically, the DSM5 accounts for psychotic forms of OCS and dysmorphobia in a separate chapter from the one on psychosis. The Australian Headspace initiative [32] might be a promising alternative to the narrow focus of UHR-concept on high-risk cases. Headspace implements both low and high risk cases, with a public health perspective of attempting to reduce risk overall. Considering that most psychological suffering occurs in adolescence, low-threshold access to normalizing and trendy environments that attract young adolescents could be beneficial to deal with both psychotic and non-psychotic symptom onset.

## IMPLICATIONS FOR CLINICAL PRACTICE

The findings of this thesis lead to several implications for clinical practice. Understanding and properly responding to one's social context is essential for one's social life. As shown and discussed in this thesis, severe social deficits are highly prominent in psychotic disorders. Specifically, it has been shown that social deficits occur at various levels of the psychosis continuum, and can be linked to specific abnormalities in the neural social reward circuit. Considering the high social burden of psychosis, it seems fair to conclude that its treatments should also target the social character of psychosis.

Psychological therapies such as cognitive-behavioural therapy and cognitive remediation play an important role in the treatment of psychosis. However, the social impairments have not been properly targeted in the past. The Metacognitive Training (MCT) consists of a group-based intervention targeting common cognitive errors and problem solving biases in schizophrenia that are related to the development and maintenance of psychotic disorders [33], such as attributional distortions, jumping to conclusions bias, bias against disconfirmatory evidence, deficits in ToM, over-confidence in memory errors and depressive cognitive patterns. The basic principle of MCT is the following: making patients aware of and educating them about the main cognitive biases underlying their psychotic symptoms can lead to improvement of not only these biases but also the individual's symptomatology [34]. Hence, the main focus of MCT lies on changing cognitive biases.

Noteworthy, the main findings of this thesis can be linked to this underlying premise of MCT. First, chapter 2b of this thesis suggested that the association between bullying victimization

and psychotic experiences might be at least partly based upon a distorted perception of one's social environment. This illustrates not only the importance of an individual's observation and perception, but also implies that psychotic experiences can be based on small errors in judgment, such as an interpretation bias consisting of a tendency to interpret one's social environment as more harmful than it actually is.

Moreover, our trust studies (i.e. chapters 3 – 5) clearly highlight the devastating consequences of mentalizing impairments as well as the importance to target these in treatment. Based on those findings, our research group has developed two additional MCT modules aimed at improving the lack of trust underlying psychotic disorders. During the first part (i.e. module 9), participants first get familiarized with the concepts of interpersonal trust and distrust, and possible consequences of trust for social relations are discussed. The next level (i.e. module 10), targets trust from the perspective of others. Participants are encouraged to think about how they can be trustworthy, how others may react if they are not trustworthy, how they can increase their credibility and how they feel when they are trusted or not by another person. The trust modules are concluded with a repetition of useful social rules. Pilot data from our research group revealed that both modules have been evaluated as useful and the suitable for all patients with schizophrenia or other psychotic disorder, regardless of symptom severity.

Earlier research has provided evidence for the feasibility, acceptability and efficacy of the MCT [35]. However, more recent findings have raised some doubts regarding the positive effects of MCT. A recent meta-analysis based on 11 studies investigated the effectiveness of MCT on delusions, data-gathering bias and positive symptoms [36]. Only small non-significant effects were revealed by this meta-analysis, indicating that there seems to be no strong evidence for the beneficial effects of MCT on delusions and related symptoms. The authors make several suggestions for improvement that could explain the non-significant results. First, the MCT protocol is based on transferring knowledge, but this is mostly done by means of general and non-individualized examples. It seems advisable to shift the focus by targeting personally relevant appraisals instead, since they might be more accessible for cognitive modification than general examples. Secondly, implementing coping strategies rather than trying to change cognitive biases might yield more beneficial effects, considering that some biases might be too persistent to change. Thirdly, promoting the accessibility of positive memories could prove beneficial in particular in cases of comorbid depression. Lastly, including mindfulness-based strategies such as self-distancing and decentering to the MCT could facilitate more beneficial treatment outcomes for emotionally involved patients by helping them to get the necessary distance from their delusions.

## CONCLUSIONS

Overall, this thesis yielded new insights into symptom formation in psychosis, both at a neural level and a behavioural level. Regarding research on the association between bullying victimization and psychosis, it is advisable to consider and combine the complementary nature of self-report and peer nomination measures of bullying in order to get a complete picture of

both individual and group perception of adverse experiences. The neuro-economics approach of investigating trust or the lack thereof provided an innovative approach towards a more ecologically valid measure as compared to former approaches based on offline questionnaires. Studying the underlying neural mechanisms of the severe social deficits of psychotic disorders by means of neuroimaging can yield highly valuable insights both for research as well as for the clinical practice. Considering the severity and heterogeneity of psychotic disorders, it seems essential to investigate individual symptoms at different levels of the psychosis continuum in order to gain more in-depth knowledge of the multiple facets of the underlying mechanisms of symptom formation in psychosis.

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