MECHANISMS OF SYMPTOM FORMATION IN PSYCHOSIS
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GENERAL INTRODUCTION
The main goal of this thesis was to shed new light on the dynamics underlying symptom formation of one of the most debilitating and heterogeneous mental disorders: schizophrenia. Four studies on two central topics related to persecutory delusions were conducted, based on schizophrenia as a diagnostic category, as well as on symptoms of psychosis, as defined by the current diagnostic criteria of the American Psychiatric Association, the Diagnostic and Statistical Manual, Fifth Edition [DSM-5; 1]. Study 1 examined symptom formation in daily life in a sample of young adolescents, while comparing the subjective and objective experiences of bullying victimization and their relation to subclinical psychotic experiences. Study 2 investigated the neural correlates of trust and cooperation from a developmental perspective by comparing healthy adolescents with adults. Study 3 and 4 were directed at the underlying behavioural and neural mechanisms of the lack of trust evident in psychosis, in patients (i.e. study 3) and their first-degree relatives (i.e. study 4).

PHENOMENOLOGY AND EPIDEMIOLOGY
According to the DSM-5, schizophrenia is a non-affective form of psychosis that lasts for at least 6 months, with a severely deteriorated level of functioning [1]. Psychosis itself might be best described as an aberrant mental state that is characterized by thought distortions and reality loss. This is associated with profound impairments in the ability to perceive, understand and interpret the environment. Psychosis can occur in different mental disorders, such as depression or bipolar disorder. The most severe forms of psychosis typically emerge in schizophrenia, which can be regarded as a non-affective form of psychosis, with a lifetime prevalence of 0.3% to 0.66% [2].

Schizophrenia can be classified into three symptom dimensions (i.e. positive symptoms, negative symptoms and cognitive impairments). The core symptoms of both schizophrenia and psychosis are delusions (i.e. fixed false beliefs that are bizarre and/or implausible), and hallucinations (i.e. sensory perception in the absence of external stimuli), and fall under the positive symptom dimension. Moreover, disorganized thinking, speech or behaviour are also prominent features of psychosis, which can either be classified as positive or as disorganized symptoms. In general, positive symptoms are characterized by distortions of normal functioning, whereas negative symptoms refer to the absence of functions which are present in healthy individuals, i.e. alterations in drive and volition such as affective flattening, lack of motivation, and social withdrawal [3, 4]. Negative symptoms, in combination with long illness duration, are associated with a poor outcome [4]. Nevertheless, positive symptoms are often perceived as far more distressing by the patient. Persecutory delusions, one of the most common positive symptoms, generally lead to profound levels of panic and anxiety, which is experienced as an extremely distressing state of mind. These delusions are the ones that are most likely to be acted upon [5]. The third symptom dimension of cognitive impairments refers to alterations in neurocognition, such as attention and memory deficits, or difficulties with planning and organization [4]. These impairments are highly prevalent in patients with schizophrenia, and tend to be present even before the onset of the first episode of acute psychosis [5, 7].
This phenomenology imposes an immense burden on the overall social functioning of patients. This becomes more evident when considering the social character inherent to a number of main symptoms, such as social withdrawal or social isolation of the negative symptom cluster, but also persecutory delusions or hallucinations. Experiencing an acute psychotic episode with its profound loss of reality may lead to feelings of being different, which in turn is likely to result in alienation from the social surroundings. Specifically, persecutory delusions are fuelled by a determined conviction that the world is dangerous and life-threatening. This state of constant suspicion and general lack of trust in others changes ordinary social encounters into tremendous challenges, which has severe negative consequences for the quality of life of patients. The dynamics underlying the development and maintenance of paranoia forms one of the main foci of this thesis.

Diagnostic criteria
Overall, schizophrenia can be best described as a loose cluster of symptoms, rather than a well-defined disorder. This is supported by the fact that the two current main diagnostic handbooks differ in their diagnostic criteria. First, the Tenth Revision of the International Classification of Diseases (ICD-10) [8] requires a duration of one month of acute symptoms for a diagnosis of schizophrenia, whereas in the DSM-5 [1] acute symptoms have to be present for a minimum period of 6 months. Secondly, in order to diagnose schizophrenia, the DSM-5 requires the presence of social or occupational dysfunction, which is not the case for an ICD-10 diagnosis. These diagnostic differences result in broader illness boundaries for the ICD-10 compared to the more narrow criteria of the DSM-5. Taken together, the symptoms of schizophrenia are very diverse, and are characterized by large individual differences in terms of severity, frequency, illness onset and duration. However, schizophrenia tends to take a chronic course in a significant amount of patients, leading to profound individual and economic costs [4]. Considering the heterogeneity of schizophrenia, it is essential to conduct research not only on the entire diagnostic category, but also on the development of individual symptoms.

The first acute psychosis in schizophrenia typically has an onset in late adolescence or early adulthood. Females and males are approximately equally affected by the disorder; however, females tend to have a later illness onset [9], better social functioning and an enhanced functional outcome compared to males [2].

The psychosis continuum
Epidemiological studies have demonstrated that subclinical psychotic experiences (i.e. less severe forms of psychotic symptoms) can also manifest themselves in healthy individuals from the general population and in persons with an increased psychosis risk [10-12]. These findings contradict the classical categorical view of the illness, suggesting that a dimensional conceptualization integrating the continuous nature of psychosis may be preferable [13]. Moreover, psychotic experiences seem to fall on the same continuous line as psychotic disorders in terms of familial clustering and shared aetiological factors [10-12], which is often referred to as the psychosis continuum. In order to determine which factors drive the transition from mild psychotic-like experiences into a full-blown psychotic disorder, it seems essential to also include groups who are at a (genetically) higher risk of developing psychosis, such as first-degree relatives and individuals from the community with mild or subclinical psychotic experiences, into research on symptom formation.

AETIOLOGY
The heterogeneity and complexity of psychotic disorders such as schizophrenia is reflected in its aetiology: No single cause can explain how one individual makes the transition from mild psychotic-like experiences into the state of the actual clinical disorder. In order to understand how psychotic disorders develops, one can best picture numerous trails consisting of several individual risk factors, whose interaction leads to a full-blown psychosis. To make this picture even more complex, there are various inter-individual differences that determine the exact nature of the clinical outcome.

Foremost, there is a strong genetic component, exemplified by the finding that first-degree relatives of patients with schizophrenia show a ten times higher risk of developing the disorder compared to individuals from the general population [14]. This is further supported by a substantial heritability factor of 80 % [4] as well as findings from twin studies yielding a concordance rate of up to 50% for monozygotic twins and 10% for dizygotic twins [15]. Nevertheless, genes on its own may not be sufficient to explain the heterogeneous nature of schizophrenia. It has been argued that the heritability factor includes gene-environment interaction [16], suggesting that actual illness expression may be driven by the interplay between a given environmental risk factor and an individual’s inherent genetic predisposition towards developing psychosis. Hence, the concept of gene-environment interactions implies that environmental factors also have a strong impact on illness expression. For schizophrenia, among the most common environmental risk factors are obstetric complications [17-19], urbanicity, i.e. living in a city rather than a rural area [20-22], migration (i.e. being an immigrant from an ethnic minority group compared to being native-born) and discrimination [23-25], social deprivation and isolation [26-28], cannabis use [29], and childhood trauma [30, 31].

Vulnerability-stress conceptualization of schizophrenia
Any given vulnerability can be present at birth but never expressed during lifetime. Hence, the question arises as to which factors determine the transition from a pre-existing vulnerability towards actual illness expression. The vulnerability-stress view of schizophrenia was first postulated in 1977 [32]. Both the magnitude of induced stress and the individual’s vulnerability level are assumed to determine whether progression towards an illness episode occurs. In this model, vulnerability is interpreted as an individual’s inherent threshold to tolerate stress. According to the model, cases of low induced stress and high stress tolerability should be restrained internally, whereas the combination of highly stressful events and a diminished ability to tolerate stress (i.e. enhanced vulnerability) would lead to an illness episode. Hence,
vulnerability can be regarded as a stable within-person trait, whereas the episodes seem to be time-restrained.

This model has been further expanded [33], stating that the interplay between pre-existing vulnerability traits and environmental stressors results in transitional states of processing capacity overload and autonomic hyperarousal and reduced processing of social stimuli. This in turn leads to an increase in frequency and level of stress, which has a disturbing effect on the individual's social environment. Consequently, a vicious circle arises: any increase in these overload and arousal states will lead to more intense stress levels, until the individual's threshold for symptom formation is exceeded and specific symptoms such as persecutory delusions will arise.

In line with these models, the neural diathesis-stress-model is based on the concept that the interaction between vulnerability and stress is the crucial element in determining illness expression [34]. In turn, stress exposure has an effect on the function of the brain and can lead to malfunction of the human stress response system, the hypothalamic-pituitary-adrenal (HPA)-axis. Specifically, enhanced release of the human stress hormone cortisol from the HPA-axis can trigger the transition from psychosis vulnerability to actual symptom manifestation by increasing the activity of the neurotransmitter dopamine activity [35]. This suggests that the HPA-axis might function as a mediator of the relation between stress and the extent of illness expression [35]. Hence, patients suffering from psychosis become hypersensitive to stress as a result of DA receptor abnormality and hippocampal damage. This provides a neural framework for the interplay between stress and pre-existing vulnerability towards symptom expression. In sum, the vulnerability-stress and the diathesis-stress models show substantial overlap in clearly emphasizing the tremendous effect of stressful events early on in life on symptom manifestation in psychosis.

**Childhood trauma and psychosis risk**

Childhood trauma is an early life adversity associated with tremendous levels of stress. Several studies support the notion of childhood trauma as a strong environmental risk factor for developing (sub)clinical psychosis [30-31; 37-39]. A recent meta-analysis yielded additional evidence for the strength of the relationship between exposure to childhood trauma and a higher risk of developing psychosis across different study designs [40]. Noteworthy, this finding was established regardless of the nature of the experienced adverse event, emphasizing the general adversity of being subjected to traumatic childhood experiences. Furthermore, childhood trauma has been specifically linked to positive symptoms like paranoid ideation, thought insertions and hallucinations [41-43]. This means that having been subjected to trauma in childhood may lead to a more dangerous and life-threatening interpretation of one's social surroundings, and consequently foster persecutory delusions in severe cases. It has been argued that experiencing trauma may result in alterations in the HPA-axis, through enhanced cortisol levels [30], which is in line with the neural diathesis-stress model.

Bullying victimization constitutes a major form of childhood trauma, having a severe impact on the victim's general and social functioning. Worldwide, approximately 13% of children and adolescents are affected by bullying victimization [44]. Previous studies have provided substantial evidence for a link between bullying victimization and subclinical psychotic symptoms [45-50], meaning that bullying victimization can lead to an enhanced risk for developing psychosis. Specifically, bullying victimization in childhood has been linked to a 2-4-fold increased risk of psychotic experiences [49; 51-52]. This effect seems to be maintained independent of the time point the bullying took place (i.e. early vs. later in childhood), and after controlling for potential confounders, such as gender, socioeconomic status, IQ, and even genetic liability towards psychosis [51]. Furthermore, patients with first-episode psychosis were found to be two times more likely to have experienced bullying victimization compared to controls [53]. Interestingly, victimized controls in the same study were two times as likely to exhibit at least one psychotic-like symptom. Recently, bullying victimization was shown to have a moderating effect on paranoid reactivity to social stressors [50]. Considering that bullied individuals reacted with greater paranoia in response to social forms of stress in particular in this study, this further highlights the notion of marked social difficulties associated with persecutory delusions.

Taken together, these findings indicate that bullying victimization is a prevalent form of childhood trauma that seems to act as a powerful social risk factor for developing (sub)clinical psychosis in many cases. However, not all children who were bullied will go on to develop psychotic-like experiences. Hence, the question arises as to which factors may drive the relationship between bullying victimization and psychosis, and thereby determine when and if an individual with an enhanced psychosis vulnerability, after being subjected to bullying, will make the transition towards symptom expression. Examining the social contributors of developing mild symptoms of psychosis in a more general setting such as in the community might be an important first step towards gaining new insights on overall symptom formation towards a full-blown psychosis. This is in line with a dimensional approach towards illness conceptualization, which forms the basis of the psychosis continuum. So far, mostly self-report measures of victimization have been implemented when studying the link to psychosis. Such measures might be more susceptible to biases such as social desirability or individual interpretations, which could possibly result in over-reporting. Hence, it is important to include other more objectives means of assessing bullying victimization into future research on psychosis.

**MODELS OF SYMPTOM FORMATION – THE CASE OF PARANOIA**

For decades, clinical researchers have tried to understand the underlying dynamics of the onset and maintenance of psychotic symptoms. Several explanatory models have been postulated incorporating different perspectives, ranging from the initial view of schizophrenia as a consequence of an ambivalent, emotionally unavailable mother, towards schizophrenia as a purely genetic disorder in the first decade of this century [54]. For the scope of this thesis, two main theoretical models will be briefly reviewed which are aimed at explaining symptom formation and manifestation of persecutory delusions in psychosis.
The cognitive model of persecutory delusions [55-56] postulates that several dynamics are in play regarding the onset and persistent nature of paranoid thinking. Delusions are depicted as explanations of particular experiences, which in the case of paranoia mainly consist of internal states (i.e. beliefs about the self and others, feelings of arousal or depersonalization, perceptual anomalies or hallucinations) and external events containing ambiguous social information of non-verbal (i.e. facial expressions, eye gaze, gestures) and verbal nature (i.e. conversation details, shouting). Cognitive reasoning biases typically linked to psychotic illnesses (i.e. such as belief confirmation or jumping to conclusions) are assumed to reinforce this effect. Hence, a person with paranoid predispositions who experiences unusual internal feelings in combination with an external ambiguous event (e.g. a stranger staring at him) will try to make sense of this event by misinterpreting the stranger’s neutral gazes as suspicious or even harmful. According to this model, distrustful thinking often co-occurs with emotional distress. In turn, this is linked to early life adversities, such as bullying victimization, that foster paranoid thinking and lead to strongly held beliefs such as seeing oneself as vulnerable, other people as potential sources of danger and the world as an overall negative place. Noteworthy, bullying victimization may result in the development of dysfunctional appraisals such as hostile interpretation of other people’s objectives, which in turn may be linked to the emergence and maintenance of psychotic-like experiences [46; 57].

The aberrant salience hypothesis [58-59] is directed at connecting the phenomenology, biology and pharmacology of the positive symptoms of schizophrenia. Considering that persecutory delusions are one of the most prominent positive symptoms, this model deserves to be further illustrated. Specifically, it states that disturbed dopamine transmission (i.e. dopamine being released independently of the actual context) creates abnormal salience for external and internal events in patients. Hence, high amounts of dopamine are being released out of context prior to the onset of an acute psychosis, leading to an inappropriate salience that will be experienced as a novel state in which specific ideas gain great importance. Within this framework, delusions are regarded as a cognitive effort aimed at making sense of the inappropriate salience. Consequently, persecutory delusions will act as an explanation providing meaning and bringing relief, and will drive thoughts and actions. Hallucinations are depicted as a direct reflection of the disturbed salience of internal representations. At the pharmacological level, antipsychotics are assumed to block abnormal dopamine transmission, and salience will be normalized by the slow, gradual process of attenuation.

In sum, these explanatory models are aimed at explaining symptom formation in schizophrenia. Yet, they should not be seen as contrasting hypotheses, but rather as co-existing hypotheses that account for different levels of the disorder. Interestingly, the cognitive account of delusions as a search for meaning [55-56] is in line with the aberrant salience model [58-59].

THE SOCIAL BRAIN – A NEURAL MECHANISM OF PARANOID SYMPTOM FORMATION?

Social neuroscience constitutes an emerging research field aimed at determining how social functions and social interactions are processed within the human brain. This has led to the concept that a distinct numbers of brain regions – the so-called social brain - is linked to the specific social functions that humans need to implement in order to understand each other in a social context. Noteworthy, psychotic disorders have been described as “disorders of adaptation to social context” [16], and several studies have yielded evidence for severe deficits in social cognitive functioning in patients with psychosis [60-63]. The experience of persecutory delusions is characterised by an extensive level of suspiciousness and a profound lack of trust in others. Trust is a necessary component of successful social interactions and is commonly experienced as inherently rewarding. Therefore, investigating the underlying behavioural and neural mechanisms of (dis)trust in patients with psychosis seems essential for a better understanding of the true nature of paranoia. Yet, an important prerequisite for this is to enhance the knowledge of normal development of trust. One needs to learn how trust tends to progress in healthy individuals first in order to establish an adequate basis for comparison for the investigation of abnormal development, or specifically to study the lack of trust characteristic of persecutory delusions.

The social brain network mainly consists of two regions in the prefrontal cortex - the dorsolateral (DLPFC) and the medial prefrontal cortex (mPFC) – as well as the orbitofrontal cortex (OFC), and the temporal lobe (i.e. the temporal poles (TP), and posterior superior temporal sulcus (pSTS)), and prominent regions in the parietal cortex (i.e. temporo-parietal junction (TPJ)), inferior parietal lobule, precuneus) [64-65]. In addition, a number of smaller structures in the limbic system of the brain are implicated in the social brain: the amygdala, the ventral striatum (i.e. nucleus accumbens) and the dorsal striatum, which consists of the caudate tail and caudate nucleus. Each of these parts play an essential role in everyday social functioning. The prefrontal parts of the brain, especially the medial prefrontal cortex (mPFC), have been linked to making inferences about other people’s mental states, meaning that the mPFC helps with grasping other’s persons’ opinions and thought processes. The TPJ has been described as the importance of perspective taking of other persons; and the striatum, insula and amygdala have been linked to emotional processing and social reward learning [66-73]. Noteworthy, it has been argued that a distinction can be made between two roads of theory of mind (ToM) inferences, with one automatic route by means of empathy or simulation, involving the premotor cortex and insula; and one controlled route of deliberate ToM skills based on mPFC and TPJ functioning [64]. Altogether, it can be summed up that social neuroscience research has led to relevant insights into the healthy social brain and its specific parts and functions. Yet, little is known about the social brain in individuals with psychotic disorders. Consequently, it is now timely to investigate the social brain in relation to psychosis in order to gain new insights on the underlying mechanisms of its devastating symptoms, in particular persecutory delusions with their characteristic levels of distrust.

Up till recently, the dynamics of trust - or the lack thereof - have not been studied properly in an interactive and more ecologically sound manner in relation to psychosis. The recently emerged field of neuro-economics provides promising tools for studying behavioural and neural dynamics underlying social impairments in various psychopathologies [74]. In fact, economic exchange games have been successfully applied to a variety of psychiatric disorders,
such as borderline personality disorder [75], psychopathy [76] and social phobia [77]. This can be translated to psychosis, meaning that the social nature of its core symptoms, especially persecutory delusions, can be investigated in an experimental and interactive way.

In line with the psychosis continuum, it seems essential to include subjects at an enhanced genetic risk, such as first-degree relatives, into research on symptom formation at a neural level. This is particularly relevant for studies focused on brain functions of clinical samples, since anti-psychotic medication are known to act on the dopamine receptors in the brain, which could possibly lead to confounding results. Consequently, investigating different levels of the psychosis continuum is indispensable in order to examine the aetiological dynamics at play, without the confounding effects of anti-psychotic medications.

**AIM AND OUTLINE OF THIS THESIS**

The overall aim of this thesis was to investigate mechanisms of paranoid symptom formation at different levels of the psychosis continuum. Specifically, there were two central topics of this thesis: examining the relationship between bullying victimization and common non-clinical psychotic experiences in the general population, and illustrating the dynamics underlying the profound lack of trust, both at a behavioural and neural level, in patients and first-degree relatives.

Chapter 2a constituted a brief introductory comparison to the following chapter (i.e. 2b), by evaluating the two main methods of assessing bullying victimization: self-reports vs. peer nominations, in terms of their similarities and differences.

Chapter 2b examined symptom formation in daily life and focuses on the questions how the well-established environmental risk factor of bullying victimization is linked to mild psychotic symptoms in the community. A relevant distinction is being made between the subjective or objective experience in order to determine which of the two is a key factor in the expression of non-clinical psychotic experiences in a sample of 724 young adolescents aged between 10 and 14 years.

Chapter 3 aimed to illustrate age-related changes in the neural correlates of trust and cooperation in a sample of 45 adolescents and adults between 13 and 49 years, by means of an interactive, multi-round social neuroscience paradigm, the so-called trust game.

Chapter 4 was devoted to studying the neural mechanisms of dysfunctional trust. For that purpose, 20 patients with non-affective psychosis and 20 healthy controls aged between 18-50 years were tested in an fMRI scanner performing the same trust game paradigm as in Chapter 2.

Chapter 5 was directed at investigating disturbed social reward mechanisms in 50 healthy siblings of patients with psychosis, in comparison to 33 healthy control subjects, with an age range of 18-60 years, by using the same trust game paradigm as in Chapter 3 and 4 in an fMRI setting.

Chapter 6 constitutes a general discussion of the results described in Chapters 2 to 5.

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Chapter 2a

Comments on “Bullying victimization in youths and mental health problems: Much ado about nothing?”

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Arseneault, Bowes and Shakoor's paper [1] examines whether bullying victimization is an essential risk factor for mental health problems, and hence should be targeted by treatment and prevention programs. This is a highly relevant topic, and the authors provide an excellent overview of up-to-date research. Their conclusion that (a) bullying victimization is associated with severe mental health consequences, and (b) efforts should be focused on reducing bullying victimization, is highly convincing.

An important issue in bullying research is the assessment of bullying victimization. The authors critically discuss methods based on self-reports versus peer nominations. We feel that it is important to take this discussion forward by focusing more on the complementary nature of each method, rather than on the supposed superiority of either method. Thus, both approaches are valid, and both are also susceptible to certain biases [2-3]. Self-reports provide a unique, individual source of information, tapping behaviours, which could easily go unnoticed by others. At the same time, this subjective view is susceptible to social desirability, and consequently might result in over- or under-reporting. Peer nominations, on the other hand, are less susceptible to this subjectivity, as multiple observers are used. However, peer nominations are flawed in that relevant behaviours or gestures can be missed in some cases, and nominations may be based on wrong or insufficient information.

Because self-reports and peer nominations measure different constructs (i.e. individual versus group perceptions), they present complementary information. Comparing the data collected with both methods will lead to either converging or diverging results. Whatever the outcomes, we can then potentially employ three research strategies for identifying bullies and victims. In the case of converging results, we get victims (or bullies) identified as such by both methods (minimum strategy, leading to some false negatives). However, we can also employ a maximum strategy by accepting victims (or bullies) as such because they were identified by at least one method (leading to some false positives). Finally, we could use a differential strategy, distinguishing between exclusively self-reported victims (bullies), exclusively peer-reported victims (bullies) and converging victims (bullies). Alternatively, one could use peer reports to identify bullies, but self-reports to identify victims. However, it would still be necessary to employ both measurement methods.

Peer-reported victimization has been associated with more rejection and less acceptance in the group, whereas self-reported victimization has been associated with self-reported adjustment outcomes (i.e. depressed mood, anxiety, loneliness, and negative self-views) [4]. Overall, self-report methods are more strongly linked to internalising problems, whereas peer nominations are better at predicting the status of the victims and the bullies in interpersonal relationships. Using both methods (peer- and self-reports) with the possibility of employing different strategies will advance our knowledge of bullying and victimization more than simply employing either one or the other method.
REFERENCES


Self-perception but not peer reputation of bullying victimization is associated with non-clinical psychotic experiences in adolescents

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ABSTRACT

Background

Bullying victimization may be linked to psychosis, but only self-report measures of victimization have been used so far. This study was aimed at (a) investigating the differential associations of peer nominated vs. self-reported victim status with non-clinical psychotic experiences in a sample of young adolescents, and (b) examining whether different types of self-reported victimization predict non-clinical psychotic experiences in these adolescents.

Methods

A combination of standard self-report and peer nomination procedures was used to assess victimization. The sample (N=724) was divided into four groups (exclusively self-reported victims, self- and peer-reported victims, exclusively peer-reported victims, and non-victims) to test for a group effect on non-clinical psychotic experiences. The relation between types of victimization and non-clinical psychotic experiences was examined by a regression analysis.

Results

Self-reported victims, as well as self- and peer-reported victims scored higher than peer-reported victims and non-victims on non-clinical psychotic experiences. Self-reports of direct relational, indirect relational and physical victimization significantly improved the prediction of non-clinical psychotic experiences, whereas verbal and possession-directed victimization did not have a significant predictive value.

Conclusions

The relationship between victimization and non-clinical psychotic experiences is only present for self-reported victimization, possibly indicative of an interpretation bias. The observed discrepancy between self-report and peer-report highlights the importance of implementing a combination of both measures for future research.

Keywords

psychosis, bullying victimization, adolescents, self-report, peer nomination

INTRODUCTION

Recent studies have demonstrated a link between bullying victimization and subclinical or clinical psychotic symptoms [1-4]. This is in accordance with a large body of evidence describing the adverse effects of being victimized on mental health problems, such as depression and anxiety [5], and self-harm behaviours and suicidal ideations [6-9]. This has highlighted victimization as a major social risk factor, which through its putative effect on cognitive and biological processes may induce a lasting psychological vulnerability [10].

However, so far all studies investigating the association with psychosis have used self-report measures of bullying victimization. This is problematic for two reasons. First, self-report potentially introduces biases due to the subjective quality of the appraisal of bullying. Since the presence of psychotic experiences may plausibly impact on this subjective appraisal, there is a risk of over-reporting of victimization. Longitudinal and prospective studies [4, 11] have been partly able to counter this bias, by showing that the victimization experiences preceded the psychotic symptoms. Still, it cannot be excluded that subtle alterations associated with the vulnerability for psychosis lead to over-reporting of victimization experiences, even before the onset of the psychotic experiences. Secondly, if victimization and psychosis outcome are both based on self-reports, a spurious correlation may arise due to common method variance. Such a correlation may be partly due to the same assessment method being used, thereby overestimating the real relationship between victimization and psychosis.

Elsewhere we have argued that it is essential to include methods using peer reports in studies investigating the adverse effects of victimization [12]. The advantage of peer reports is that they are based on a considerable number of observers who are familiar with and present in a given environment [13]. In addition, while self-reports may be coloured by a possible pre-existing psychotic vulnerability, this risk is absent in peer reports. This does not fully exclude the risk of over-reporting in peer reports, as these may be influenced by a tendency to report as victims the children who behave oddly, but peer report is plausibly less susceptible to this risk than self-report. While both peer nomination and self-report have been established as valid methods [14-15], it is important to realize that they tap different constructs: self-report measures individual perception and peer nominations measure group perceptions [16]. Thus, peer reports are suitable to investigate the reputation of a child, whereas self-reports are useful for tapping the way children view themselves in a given environment. Peer-reported victimization has been associated with more rejection and less acceptance in the group [16]. In turn, social exclusion has been linked to mental health problems in general [17], and psychosis specifically [18]. Self-reported victimization, on the other hand, has been associated with self-reported adjustment outcomes such as depressed mood, anxiety, loneliness, and negative self-views [16]. Comparing self-reports and peer reports of victim status may thus yield essential information, especially with regard to their putative impact on the development of psychotic experiences.

The purpose of this study was to investigate the relation between bullying victimization as assessed with self-reports and peer reports on the one hand and non-clinical psychotic experiences in a general population sample of young adolescents on the other hand. The general
population approach has proven useful because it allows investigating the mechanisms of psychosis at the non-clinical level, where the expression of the phenotype is much more common than at the level of the clinical disorder [19]. Many previous studies have supported this approach, providing evidence for longitudinal continuity [4, 11], shared risk factors [20-22], shared demographic characteristics [23], symptom dimensions [24-25] and neuropsychological correlates [26-27]. To assess victimization, we used standard self-report and peer report measures of victimization. Subsequently, we divided the sample into four subgroups to examine their link to non-clinical psychotic experiences: exclusively self-reported victims, exclusively peer-reported victims, victims according to both self-reports and peer reports, and non-victims.

Considering the established link between self-reported victimization and psychosis, all self-reported victim groups should differ from the non-victims. However, assuming that this relation is due to an interpretation bias, peer reports should not be associated with non-clinical psychotic experiences. Specifically, we expected both exclusively self-reported victims and victims according to both self- and peer reports to report more psychotic experiences than the exclusively peer-reported victims and non-victims. Our secondary aim was to disentangle the relation between self-reported victimization and psychosis by investigating whether the main types of self-reported victimization (i.e. physical, possession-directed, verbal, direct relational, and indirect relational) differentially predict non-clinical psychotic experiences. Examining whether different types of self-reported victimization influence psychosis differently may further our understanding of the risk-increasing effect of bullying and may inform possible interventions.

**METHODS**

**Subjects**

In total, 818 children were asked to participate in this study. Out of those, 19 children did not get parental permission to participate, 22 children were not present at the time of data collection due to illness, 17 did not completely fill in the questionnaires, and 36 subjects could not be classified into one of the bullying roles. Specifically, those 36 subjects received the same scores for multiple and incompatible roles (e.g. bully and outsider) and could thus not be classified to one role. This left us with 724 children, 374 boys (51.7 %) and 350 girls (48.3%). There were no significant difference in terms of age between boys and girls (F=0.006, p>.9). The mean age was 11.9 years (SD 0.76, range 10-14 years), 684 subjects (94.5 %) were born in the Netherlands.

**Procedure**

The data collection took place in April and May 2010. Subjects were recruited in collaboration with their primary schools. In total, 17 primary schools participated, from different villages and cities in the Netherlands. The children were tested at their own schools. At least two research assistants were present during every experimental session. The parents of all children received a consent letter in which the aim and procedures of the study were described. They could return an attached objection note if they did not want their child to participate. Children themselves were also given the opportunity to decline participation, but none did. At the beginning of the session, children were informed that all data would be treated confidentially, and that their names would be removed in the dataset. On average, the testing took thirty minutes per subject.

**Assessment**

*Non-clinical psychotic experiences.* Non-clinical psychotic experiences were assessed by four yes/no questions: (1) “Some children believe in mind reading or being psychic. Have other people ever read your mind?” (2) “Have you ever had messages sent just to you through radio or TV?” (3) “Have you ever thought that people are following you or spying on you?” (4) “Have you ever heard voices other people cannot hear?” These questions were obtained from the Diagnostic Interview Schedule for Children (DISC-C), which is a widely used structured diagnostic instrument aimed at discovering more than 30 different disorders in children and adolescents [28]. The validity and reliability of the DISC-C has been established, indicating that it is a suitable tool for diagnosing children and adolescents. For this study, the four questions tapping psychosis were translated into Dutch. Previous research has shown their high validity in terms of predicting adult psychotic disorder [11], and in terms of assessing psychotic experiences in children [1]. All answers to the psychosis questions were combined into one continuous psychosis outcome measure.

*Peer reputation of victim status.* The Bullying Role Nomination Procedure (BRNP), a standard peer nomination procedure, was used to determine the victims in the class. Previous research has established the validity of this nomination procedure [29]. Further details of the procedure can be found elsewhere [30]. Two questions were asked to obtain victim vs. bully nominations: (a) “Do you know anyone in your classroom who is being victimized in this particular way? If so, could you give us the name(s)?” and (b) “Do you know which classmates carry out that particular form of bullying?” To obtain a general measure for peer nomination of victim status, continuous scores were computed per class by dividing the number of received nominations by the number of nominators (i.e. children who participated in the nomination procedure and were asked to nominate other children – excluding themselves – for bullying roles). Children were assigned the role of victim if their victim nomination score was at least .1 and exceeded all other bullying role scores (i.e., ringleader bully, assistant, reinforcer, outsider, and defender) with at least .01. All other children were classified as non-victims. Hence, the non-victims consisted of all other bullying roles and all non-involved children (i.e. the remaining children who were not involved in bullying).

*Self-perception of victim status.* The self-perception of being victimized was measured by means of the Revised Olweus Bullying Questionnaire [31], which is a standard self-report procedure. First, children received a definition of bullying. We used the general question “How many times have you been the victim of bullying in the past three months?” as an index of self-perceived victim status. Five additional items were used to assess the different forms of bullying victimization: (1) “How many times in the past three months did it happen that you were sworn at, laughed at or ridiculed at school?” (i.e. verbal); (2) “How many times in the past three months
did it happen that classmates did not allow you to participate in group activities even though you wanted to?" (i.e. direct relational); (3) "How many times in the last three months did it happen at school that you were kicked, hit, pushed, or intentionally hurt in a different way?" (i.e. physical); (4) "How many times in the past three months did it happen that classmates told lies or annoying things about you?" (i.e. indirect relational); (5) "How many times in the past three months did it happen that something was stolen from you, hidden or destroyed on purpose?" (i.e. possession-directed). In line with previous research [15], we used a cut-off score of 3 or higher. Thus, whenever a subject reported incidents of victimization occurring two or three times a month (i.e. score 3), once per week (i.e. score 4), or several times per week (i.e. score 5), he or she was classified as a self-reported victim. 

### Statistical analyses

The SPSS software, version 17, was used to analyze the results. First, all cases were selected and recoded into one group variable, consisting of the following four subgroups: exclusively self-reported victims (only victims on the basis of their self-reports), both self- and peer-reported victims (self- and peer reports in agreement), exclusively peer-reported victims (only identified as victims on the basis of peer reports) and non-victims. The continuous psychosis variable was transformed into normalized scores, using Rankit's procedure. This standard SPSS method uses the formula \((r-1/2) / w\), with \(w\) equaling the number of observations, and \(r\) being the rank, ranging from 1 to \(w\). An Analysis of Variance (ANOVA) was performed with group (4 types of victimization) as the independent variable and the normalized psychosis outcome measure as the dependent variable. Post-hoc pairwise comparisons were corrected for multiple comparisons (i.e. Bonferroni correction). Subsequently, a linear regression analysis was conducted to examine the relationship between different victimization types and psychosis, with the different types of self-reported bullying (i.e. physical, possession-directed, verbal, direct relational, and indirect relational) as predictors and the continuous psychosis outcome measure as the dependent variable. All analyses were controlled for gender and age. All statistical tests were evaluated at a significance level of \(\alpha=0.05\).

### RESULTS

#### Frequencies

The sample consisted of 79 exclusively self-reported victims (10.9%), 33 exclusively peer-reported victims (4.6%), 37 both self- and peer-reported victims (5.1%) and 575 non-victims (79.4%). Table 1 depicts the frequencies of each type of self-reported bullying victimization.

In total, 303 subjects (41.9%) answered 'no' to all four psychosis questions, indicating that they had no psychotic-like experience at all, and 421 subjects (58.1%) reported at least one psychotic-like experience. Out of those, 200 subjects (27.6%) reported at least two psychotic-like experiences, 68 subjects (9.4%) reported at least three experiences, and 8 subjects (1.1%) answered 'yes' to all four psychosis questions.

#### Is there a group effect on the psychosis outcome measure?

There was a significant effect of group on non-clinical psychotic experiences (\(F=11.14, p < 0.0001\)). Post-hoc pairwise comparisons (Table 2, Figure 1) showed that self-reported victims scored significantly higher than peer-reported victims and higher than the 'non-victims' subgroup. Both self- and peer-reported victims scored significantly higher than 'non-victims'. There were no significant differences between self-reported victims and both self- and peer-reported victims. Peer-reported victims did not differ significantly from non-victims or both self- and peer-reported victims.

#### Is there a relationship between the different types of self-reported bullying and the psychosis outcome measure?

The model with the self-reported victimization types (i.e. physical, possession-directed, verbal, direct relational, and indirect relational) explained a significant proportion of variance in non-clinical psychotic experiences, \(\Delta R^2 = .089, F=10.91, p < .001\). Direct relational victimization significantly predicted psychosis scores, \(b=.08, t=1.98, p < .05\), as did indirect relational victimization, \(b=.16, t=3.53, p < .001\), and physical victimization, \(b=.12, t=3.11, p < .005\).

<table>
<thead>
<tr>
<th>Table 1. Frequencies and percentages for each type of self-reported victimization.</th>
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<tbody>
<tr>
<td><strong>Type of victimization</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Verbal</td>
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<tr>
<td>Indirect relational</td>
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<td>Relational</td>
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<tr>
<td>Physical</td>
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<tr>
<td>Possession-directed</td>
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<td><strong>Table 2. Test statistics for the pairwise comparisons between the four subgroups.</strong></td>
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<td>-----------------------------------------------</td>
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<tr>
<td><strong>Mean difference</strong></td>
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<tr>
<td>Self-reported vs. non-victims</td>
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<tr>
<td>Self- vs. peer-reported victims</td>
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<td>Self-reported vs. both self- and peer-reported victims</td>
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<td>Both self- and peer-reported victims vs. non-victims</td>
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<td>Both self- and peer-reported victims vs. peer-reported victims</td>
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<tr>
<td>Peer-reported victims vs. non-victims</td>
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</table>

*Significant at an adjusted alpha of .01 after Bonferroni correction.
The prediction of non-clinical psychotic experiences was not significantly improved by verbal victimization, $b = .06, t=1.25, p > .2$, or by possession-directed victimization, $b = -.02, t= -.51, p > .5$.

**DISCUSSION**

This study is the first to investigate the relationship between non-clinical psychotic experiences and both peer reports and self-reports of victimization. The results show that peer-reported victimization is not associated with a higher frequency of non-clinical psychotic experiences. In contrast, there was a strong link between self-reported victimization and non-clinical psychotic experiences. The risk-increasing effect of victimization was exclusively related to the subjective appraisal of victimization experiences. The lack of an association between peer reports and non-clinical psychotic experiences further suggests that children who report psychotic-like experiences do not have an increased risk to become nominated as a victim by their peers. Considering that children are not considered victims because they act differently due to their psychotic-like experiences, the concept of reverse causality may not apply here. These findings underscore the relevance of the use of peer reports in addition to self-reports of victimization.

The finding that self-reported victimization is related to the risk for psychotic-like experiences is in line with previous research [1, 4], supporting the validity of our study. Our results add to this by showing that the different types of self-reported victimization have different associations with psychosis: significant associations were found with direct relational, indirect relational and physical victimization, but not with verbal or possession-directed victimization. The link of both direct and indirect relational victimization with psychotic-like experiences is plausible, given the social nature of the core features of psychosis, such as social withdrawal and paranoia, and suggests that social processes also play a role in the development of non-clinical psychotic experiences. Considering the more subjective social nature of indirect relational victimization, this finding highlights the idea that the individual interpretation may play a role in the association between self-reported victimization and psychotic experiences. Physical victimization, however, is one of the more direct and observable victimization types, and thus less likely to be missed by peer reports. However, even physical interactions may be prone to different interpretations.

The association between self-reported victimization and psychotic-like experiences can be explained by two mechanisms, which are not necessarily mutually exclusive. The first presupposes a causal role for victimization, either through cognitive or biological changes or both. The experience of social adversity in childhood may lead to negative cognitive schemas related to social humiliation, thereby creating a cognitive vulnerability that forms the basis for psychotic-like experiences [32]. Biological models indicate that early trauma may result in long-term changes in the brain. The densities of dopamine receptors and subsequent dopamine release have been shown to rise due to stress-related dysregulation of the HPA-axis [33]. In turn, dopamine sensitization has been proposed as a major mediator for the expression of psychosis [34].

The second mechanism assumes that self-reported victimization is due to an interpretation bias in children with a pre-existing psychosis vulnerability. Accordingly, reports of victimization are considered a consequence rather than a cause. The latter explanation has credibility because peer reports, arguably the more objective measure of victimization, were not associated with increased psychotic-like experiences in this study. However, several precautionary notes are relevant here. First, longitudinal and prospective data exist showing that victimization preceded the onset of psychotic-like experiences [4, 11]. Second, it has been argued that psychosis is associated more strongly with under- than over-reporting of victimization [35-36], which goes against the explanation of self-reported victimization as a consequence of an interpretation bias. Third, peer reports rely on multiple observers and are likely less sensitive to subtle signs of victimization. In this regard, it is important to consider that in general, self-reported victim status was more frequent than peer-reported victim status, showing that children were more likely to perceive themselves as victims than peers do. Although peer reports may seem more objective, they are also susceptible to bias. Considering that bullying sometimes occurs in private, relevant behaviours or gestures can be missed in some cases, and some peer reports may be based on wrong or insufficient information. Hence, combining self- and peer reports allows to examine a higher frequency of victims, supporting the importance of including both measures in the assessment of victimization.

The current findings are limited by a few methodological issues. First, a self-report measure based on four single questions was used to assess non-clinical psychotic experiences. This only allows for a limited, general assessment of psychosis, and precludes distinguishing in terms of symptom frequency or level of conviction. However, the psychosis questions have been derived from a standard clinical interview, and the results are comparable to previous studies using a similar instrument [1, 11]. Secondly, the cross-sectional nature of the study precludes drawing any conclusions about causality. The need to disentangle the temporal order of victimization experiences and development of psychotic-like experiences in longitudinal studies has only become more relevant given the current finding that the association is limited to self-reported
Bullying victimization in youths and mental health problems can both act as a precursor and as a consequence of victimization. The question remains whether this also holds for psychosis.

In conclusion, the current findings suggest that the perception of being victimized is a sufficient condition for the presence of a higher rate of psychotic-like experiences. Peer-reported victimization status does not contribute to an increased frequency of psychotic-like experiences, either because self-reported victimization is due to an interpretation bias of perceptions [16]. That peer nominations and self-reports measure two different constructs: group vs. individual psychosis should refer to children with experiences, either because self-reported victimization is due to an interpretation bias of reported victimization status does not contribute to an increased frequency of psychotic-like experiences.

The mental health problems can both act as a precursor and as a consequence of victimization. Recently it has been shown that depressed children are at a higher risk of being bullied, but also show stronger symptoms after being bullied [37], suggesting that mental health problems can both act as a precursor and as a consequence of victimization. The relationship between bullying, psychotic-like experiences and adult schizophreniform disorder: A 15-year longitudinal study. Archives of General Psychiatry, 2000. 57: p. 1053-1058.

The current literature on assessment of victimization, which suggests the important question is not which measure is superior, but rather which current findings suggest that peer nominations and self-reports measure two different constructs: group vs. individual perceptions [16]. The important question is not which measure is superior, but rather which construct is the key to understanding the association between victimization and psychosis.

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Chapter 3

Default Distrust?
An fMRI investigation of the neural development of trust and cooperation

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**ABSTRACT**

The tendency to trust and to cooperate increases from adolescence to adulthood. This social development has been associated with improved mentalising and age-related changes in brain function. Thus far, there is limited imaging data investigating these associations. We used two trust games with a trustworthy and an unfair partner to explore the brain mechanisms underlying trust and cooperation in subjects ranging from adolescence to mid-adulthood. Increasing age was associated with higher trust at the onset of social interactions, increased levels of trust during interactions with a trustworthy partner and a stronger decline in trust during interactions with an unfair partner. Our findings demonstrate a behavioural shift towards higher trust and an age-related increase in the sensitivity to others’ negative social signals. Increased brain activation in mentalising regions, i.e. temporo-parietal junction, posterior cingulate and precuneus, supported the behavioural change. Additionally, age was associated with reduced activation in the reward related orbitofrontal cortex and caudate nucleus during interactions with a trustworthy partner, possibly reflecting stronger expectations of trustworthiness. During unfair interactions age-related increases in anterior cingulate activation, an area implicated in conflict monitoring, may mirror the necessity to inhibit pro-social tendencies in the face of the partner’s actual levels of cooperation.

**Keywords**

fMRI, perspective-taking, theory of mind, trust game, development

**INTRODUCTION**

Although humans are social by nature, the cognitive abilities that form the basis for successful social interactions are not fully developed at birth, but evolve gradually over time [1,2]. During the transition from adolescence to adulthood, social behaviour becomes increasingly oriented towards others [3-5]. Improved mentalising, the sensitivity to the perspective of others, has been suggested to drive increases in trust and cooperation [6-9]. The changes in social cognition and behaviour occur in parallel with structural and functional maturation of the brain. Several studies have investigated the neural correlates of social interactions, but research has only just begun to investigate the brain-behaviour association from a developmental perspective [9].

Over the last decade, combining approaches from neuroscience and economic research has led to an interest in the neural mechanisms underlying trust and cooperation in adults [6, 10, 11]. Social cognition in action has been investigated with economic exchange paradigms, such as the trust game [12]. The trust game requires mentalising in order to infer intentions from behavioural cues of the other player and to appreciate how own behaviour (e.g. lowering trust in response to trustworthiness) leads to a reputation with others. During the trust game, the first player (investor) receives an amount of money from the experimenter and can choose to cooperate (i.e. share any part of the money) with the second player (trustee) or to defect (i.e. keep the money). The shared amount is multiplied and the trustee decides whether to return any part of this amount or whether to keep the money. The best pay-offs for both players occur when they cooperate. However, the trustee yields the highest pay-off by defecting. Thus, to share money the investor needs to trust in the good intentions of the trustee. Despite different predictions from classic economic theory, investors typically send a share of 50% or more of their initial endowment; this signal of trust is generally reciprocated by the trustee [11,13,14]. In multi-round versions of the trust game the degree of trustee reciprocity is a strong predictor for subsequent decreases or increases in investor trust [6], showing that trust, or the expectation about future behaviour is modulated by the actual behaviour of the game partner.

Previous functional magnetic resonance imaging (fMRI) research with the trust game demonstrated activation in brain regions important for mentalising, reward learning, cognitive control and emotional processing [6, 9, 11, 15-17]. It has been postulated that the reward network, extending from the striatum and specific frontal regions, is involved in the motivation to cooperate and that brain networks of cognitive control and social cognition modulate this motivation in response to contextual information [18]. Cognitive control is important for the adaptation of behavioural patterns in response to new evidence, e.g. behavioural feedback from interaction partners [19, 20]. The social cognitive network supports mentalising, the process of interpreting others’ social signals and is important to minimize betrayal [18, 21].

While cooperation seems to be the preference of adults, developmental studies using trust games suggest a tendency to invest lower amounts and to have less reciprocal interactions in adolescents [7, 9, 22]. This changing quality of social interactions has been attributed to the lower propensity of adolescents to mentalise and a subsequently reduced sensitivity to others’ social signals [5, 9]. Studies have begun to elucidate how these differences in social behaviour and
cognition are reflected in differential activation of networks subserving social interactions [9]. In the study by van den Bos et al. [9], a sample of 62 participants between 12 and 22 years took the trustee role in a two-choice trust game with a generally trustworthy investor. Within this sample, age was unrelated to the degree of reciprocity towards the investor. Yet, indicative of increased mentalising, the sensitivity to the degree of risk that the investor took during decision making significantly increased with age. The neuroimaging results showed age-related increases in brain activation in the left temporo-parietal junction (TPJ) and the right dorsolateral prefrontal cortex in response to investor trust. The TPJ has been suggested to play a role in identifying goals and intentions behind others’ behavior [21, 23]. Previous research showed age to be associated with higher TPJ activity during simple mentalising tasks [24] and self-referential processing [25]. The involvement of the dorsolateral prefrontal cortex was hypothesized to reflect the age-related regulation of selfish responding. Age was also associated with decreases in activation in the anterior medial prefrontal cortex during defection, as compared to reciprocation of investor trust. This area has also been hypothesized to underlie mentalising processes [11], specifically those that include thinking about how oneself is perceived by others [26, 27]. However, previous developmental research also found this area more active during self-related processing as compared to social processing [24, 25].

The previously described study presents initial behavioural evidence in support of age-related increases in the sensitivity to others’ perspectives, as indicated by an increased degree of reciprocity when the interaction partner made high-risk investment decisions. However, it remains unclear whether the sensitivity to the other person’s behavioural cues also increases with age and whether this underlies the age-related development towards a behavioural default of trust and cooperation. To elucidate this question, the current study investigated age-related changes in investor behaviour as a function of partner reciprocity. Participants played two multi-round trust games with anonymous hypothetical game partners, one with a cooperative and one with an unfair decision making style. If sensitivity to the other person’s behavioural cues increases with age, more pronounced increases or decreases in the levels of trust with age should occur in response to cooperation or unfair behaviour by the trustee, respectively.

There is limited research examining social cognitive and behavioural changes during social interactions across broader age ranges. However, previous research indicates that social (cognitive) processes continue to change into adulthood [5, 9]. Therefore, the current study included a sample of participants ranging from adolescence to mid-adulthood. We hypothesised that age would be associated with higher trust and an increased sensitivity to social signals of others and that this would be reflected in (i) higher initial investments and (ii) higher investments throughout interactions with a cooperative, but (iii) lower investments towards an unfair game partner, as any increased sensitivity to the behavioural cues of the other person will likely involve better mentalising skills and/or better social reward learning. We expected at the neural level (i) age-related increases in brain activation within frontal and temporo-parietal brain areas implicated in mentalising (e.g. medial prefrontal cortex, TPJ, precuneus) and (ii) age-related decreases in activation in social reward related areas (e.g. ventromedial prefrontal and orbitofrontal cortex, caudate nucleus) during interactions with a cooperative trustee as a consequence of age-related increases in expectations of the trustworthiness of others. During interactions with an unfair trustee, we similarly expected increases in brain areas implicated in mentalising, but in addition (iii) age-related increases in activation in cognitive control regions (e.g. anterior cingulate cortex, dorsolateral prefrontal cortex) because of the need to suppress the default intention to invest.

**METHOD**

**Participants**

Forty-five healthy right-handed males between the age of 13 and 49 (mean age = 23.6, SD = 9.76) participated in this study. Participants were recruited at local schools, via colleagues and through a community volunteer database ‘Mindsearch’ (http://mindsearch.iop.kcl.ac.uk). All participants had a good command of the English language. There was no history of neurological disorder, current psychiatric diagnosis or psychotropic medication. Informed consent was obtained from all participants and their parents/guardians if they were under the age of 16. The study was approved by the local research ethics committees (London-Surrey Borders (10/H0806/38) and Barking and Havering REC (08/H0702/83)).

**Design**

**Measures.** The vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (WASI) was used as an indicator of general cognitive ability in adolescents (13-18 years) [28]. The vocabulary subtest of the Wechsler Adult Intelligence Scale (WAI) was used in adults (19-49 years) [29]. To exclude systematic differences in IQ between the two samples T-scores of the WASI were converted to WAI scaled scores for comparability [30]. The mean scaled score was 11.56 (SD = 2.9). There was no significant age effect on the WAIS/WASI scores \( b = -0.71 \), \( p = 0.11 \), 95% CI = -0.16/ 0.02).

**Trust game.** Participants were told that they would play two trust games with anonymous human counterparts. However, in reality two probabilistic computer algorithms were used to model the game partners’ behaviour, one reflecting a trustworthy, cooperative and one reflecting an unfair decision making style. Participants were in the investor role throughout the games. In each round, they were asked to transfer an (integer) amount between £0 and £10 to the trustee. The transferred amount was tripled. The subsequent trustee repayment depended on the previous investments of the investor and on the computer algorithm (see Supplementary Material 1). At the beginning of a new round, they received £10 again, i.e. there were no cumulative totals. The order of the trustees (cooperative/unfair) was counterbalanced between subjects. Each trust game consisted of 20 trust game rounds and 20 randomly interspersed control rounds. Each round started with an investment cue of £10 (2 sec). The following investment period required the subject to move a cursor with their index fingers in order to select a number from 0-10 (max. 4 sec). The invested amount was shown (2 sec), followed by a waiting period with a bar slowly filling itself with dots (2-4 secs), and a fixation cross (500 ms). The trustee’s response was then displayed (3 secs), followed by the totals (3-5 sec, depending on the trustee’s...
response). The trial ended with a fixation cross (500 ms). In total, each trial lasted 18.5 sec (Supplementary Figure 1). Control rounds consisted of the same timings but during the investment phase, subjects moved the cursor to a randomly placed target, which was displayed below one of the numbers. During the repayment and outcome phase participants saw two columns as in the real trials.

**Procedure**

All participants/primary caregivers read the information material and gave written informed consent before the testing procedure. The testing sessions were held individually in a quiet room at the Institute of Psychiatry/Centre of Neuroimaging Sciences. First, participants were assessed with the WASI/WAIS vocabulary subtest. Then they completed ten practice trust game rounds on a laptop before the MRI scan. Participants were told that their game partners were in a different location and that they were connected via the internet. After the session, the participants answered a short questionnaire, which was used as a manipulation check and examined their individual perceptions of the games and their game partners. The earnings from one randomly selected round of the trust game were paid to each participant in addition to a fixed payment for the participation.

**fMRI Image acquisition**

Imaging data were acquired using a 3 Tesla GE Signa Neuro-optimised MR System. A quadrature birdcage head coil was used for radio frequency transmission and reception. For each game, 370 T2*-weighted whole-brain echo-planar images depicting the blood oxygen level-dependent (BOLD) contrast were acquired with the following parameters: slice thickness = 2.4 mm; interslice-gap = 1 mm; TR = 2000 ms; TE = 25 ms; flip angle = 75°; in-plane voxel dimension = 3.4 mm, number of slices = 38; dummy acquisitions = 4; matrix = 64 x 64. For anatomical reference, a whole brain high-resolution gradient-echo image of 43 slices was acquired with the following parameters: Slice thickness = 3 mm; interslice-gap = 0.3 mm; TR = 3000 ms; TE = 30 ms; flip angle = 90°; in-plane voxel size = 1.9 mm matrix = 128 x 128. Foam padding was placed around the head in the coil to minimize head movement and the participants were provided with ear protectors.

**Data analysis**

The statistical analysis of the behavioural data was conducted in STATA 11.0 (Statacorp, 2009). For the trust game we used regression analysis to examine (i) the effect of condition (cooperative vs. unfair behaviour) on the mean investments across the whole game and (ii) the associations between age and the first investments in the two games (basic trust). To control for multiple observations within subjects multi-level random regression was used to investigate the associations between age and the evolution of investments towards the two game partners (relation specific trust) across four sequential blocks of five game rounds. For details on the fMRI image analysis see Supplementary Material 2.

**RESULTS**

**Behavioural data**

Participants made significantly higher investments in the cooperative than in the unfair condition (b = -3.09, p < 0.01, 95% CI = -3.35/-2.83, Table 1). Age was significantly and positively associated with the initial investments (b = 0.06, p = 0.05, 95% CI = 0.001/0.12), i.e. basic trust towards an anonymous interaction partner increased with age. To investigate the development of investments over interactions with the two game partners, we analysed the change in investments across four blocks of five game rounds. During cooperative interactions there was a significant effect of age (b = 0.08, p < 0.01, 95% CI = 0.02/0.13) and block (b = 0.26, p < 0.01, 95% CI = 0.09/0.43). The interaction between age and block was not significant (b = -0.18, p = 0.14, 95% CI = -0.43/0.06). Thus, while all participants increased their investments in response to cooperation, older people continued to make higher investments throughout the course of repeated cooperative interactions. In the unfair condition, there was no significant main effect of age (b = 0.04, p = 0.18, 95% CI = -0.02/0.10). A higher block number was significantly associated with lower investments (b = -0.50, p < 0.01, 95% CI = -0.75/-0.23), i.e. all participants decreased their levels of trust in response to unfair behaviour. The interaction was marginally significant (b = -0.27, p = 0.07, 95% CI = -0.57/0.03). In the first block there was a significant positive association between age and investments (b = 0.06, p = 0.04, 95% CI = 0.002/0.12; all other p > 0.53) showing that this effect was driven by a stronger decline in initial trust in older individuals (Figure 1). Regression analyses show that the degree of the decline in investments over the first block (round 1-5) is significantly associated with the first investment b = 0.52, p < 0.01, 95% CI = 0.15/0.90. The higher the initial trust, the stronger the decline in trust. This pattern may reflect stronger tendencies to punish unfair behaviour by the game partner.

**Imaging data**

Correlations between age and BOLD signal during investments were analysed by condition (Table 2). In the cooperative condition, age was positively associated with increasing brain activation in foci in the left TPJ, extending into the inferior parietal lobule. There was also activation evident in the bilateral middle frontal gyri and right precentral gyri (Figure 2a). A negative correlation between brain activation and age was present in the orbitofrontal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Block 1 Investment £ M (SD)</th>
<th>Block 2 Investment £ M (SD)</th>
<th>Block 3 Investment £ M (SD)</th>
<th>Block 4 Investment £ M (SD)</th>
<th>Overall Investment £ M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooperative</td>
<td>5.99 (2.77)</td>
<td>6.38 (2.99)</td>
<td>6.56 (3.03)</td>
<td>6.70 (2.82)</td>
<td>7.34 (2.73)</td>
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<tr>
<td>Unfair</td>
<td>4.66 (2.92)</td>
<td>3.72 (2.96)</td>
<td>3.12 (2.76)</td>
<td>2.51 (2.34)</td>
<td>4.35 (3.35)</td>
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cortex (Figure 2b), the left and right caudate nucleus (Figure 2c) and the bilateral dorsomedial prefrontal cortex. In the unfair condition, increasing age was correlated with increasing activation in the left TPJ including the inferior parietal lobule (Figure 2d) and the mid-cingulate gyrus. Increasing age was also associated with decreasing signal in the left posterior cingulate gyrus, thalamus and the bilateral dorsomedial prefrontal cortex.

An interaction between age and condition was present in the posterior cingulate gyrus and precuneus (Figure 3a) and within foci in the lingual gyrus. With increasing age, these structures were more sensitive to cooperation. An opposite activation pattern was present for the anterior cingulate gyrus (Figure 2e and 3b), i.e. with increasing age the anterior cingulate became more active in response to unfair behaviour.

DISCUSSION

This study examined age-related changes in the neural correlates of trust and cooperation during social interactions. Participants played trust games with two hypothetical partners with a cooperative and an unfair decision making style. Age was associated with higher levels of trust at the onset of social interactions and throughout interactions with a cooperative partner, but also with a steeper decline in the levels of trust throughout interactions with an unfair partner. Associations between age and increased activation in the left TPJ were present during investment decisions towards both game partners. During cooperative interactions, activity in

Table 2. Correlations between age and brain activation

<table>
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<tr>
<th>Cerebral region</th>
<th>BA</th>
<th>Cluster size</th>
<th>P-value</th>
<th>Hemisphere</th>
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Note. *Talairach Coordinates where x = left (-) vs. right (+), y = anterior (+) vs. posterior (-) and z = ventral (-) vs. dorsal (+). Maps are indexed by mean SSQ ratio (sum of squares ratio) and thresholded to less than 1 false positive cluster. BA = Brodmann area.*
also with higher trust during interactions with a cooperative partner and with a steeper decline in trust during interactions with an unfair partner. Still, all participants showed a learning effect regardless of age. They increased their levels of trust in response to cooperation and decreased their levels of trust in response to unfair behaviour. The current imaging findings are in line with hypothesized increases in mentalising. A better understanding of how the game partner will react and interpret one's own behaviour may support and initially higher investment, a move that signals the intention to cooperate. Age-related increases in activity in the left TPJ were present regardless of the nature of the game partner. The TPJ has been described as part of the ‘mentalising system’ [21, 32-34] and trust game research found this area activated when the investor’s decision was revealed to the trustee [9]. We found increased activation within the TPJ during investment decisions. Possibly, this area plays a role in mentalising during decisions about how much to trust that are made while predicting the game partner’s behaviour. The current data also showed a specific age-related activation during cooperation in the right posterior cingulate/precuneus region which also has been described as part of the mentalising network [21, 35]. Our results show that different areas of the mentalising network are differentially activated during social interactions. The TPJ is involved regardless of the nature of the social interaction and its activation increases with age. However, the posterior cingulate/precuneus region shows specific activation in response to trustworthiness. In contrast to van den Bos et al. [9], current age-related changes in the mentalising network were predominantly located in the posterior and not the medial prefrontal brain areas. This discrepancy could be explained by the differential nature of the tasks, the specified contrasts or age differences in the samples (i.e. 12-22 vs. 13-49 years).

In order to make sensible decisions to trust, humans need to learn the associations between their behaviour and the feedback that they receive from others in response. For example, if a certain person answers trust with betrayal we are less likely to trust that person a second time. However, if the person proves to be trustworthy we are more likely to trust this person in future [6]. Thus, reward learning shapes behaviour towards optimal decision-making. In
the current study, age was associated with higher levels of trust at the onset of anonymous social interactions. This suggests an increased expectation of benevolence of others and offers a suitable explanation for why feedback learning during cooperation becomes less important as individuals get older. Where cooperation is anticipated, experiencing cooperative behavioural feedback from the trustee matches the prediction. Therefore, learning of new behaviour-outcome associations is unnecessary. fMRI research showed that the orbitofrontal cortex is important for feedback learning and subsequent goal directed behaviour. It is thought to signal reward value during decision making and is sensitive to value changes, i.e. becomes less responsive when stimuli are less novel or expected [36-38]. The caudate also plays a role in the anticipation and reception of rewards and has been found to decrease signalling when certain predictions match an outcome [16, 39]. Accordingly, we expected that with increasing age brain areas that are important for reward learning (e.g. ventromedial prefrontal and orbitofrontal cortex and the striatum) would be recruited to a lesser extent. During cooperative interactions, we found age-related decreases in orbitofrontal cortex and caudate nucleus activation. We did not find the reverse pattern during interactions with an unfair partner. This is in line with previous trust game research of Phan et al. who found that only positive reciprocity by the partner engages the ventral striatum and orbitofrontal cortex [40]. Also, King-Casas et al. [6] found the caudate specifically active during cooperation.

As indicated by increased levels of trust the anticipation of benevolent behaviour by others increases with age and responding to deviations of trust requires a stronger correction in response to an unfair interaction partner. Hence, the interaction is more demanding for older individuals, as it requires them to adapt their beliefs and behaviour. Younger people need to make fewer adjustments to their investments because of their more distrusting mindset. In line with this reasoning, we found age to be associated with a stronger decrease in trust during the interactions with an unfair partner. During these interactions, expectations of cooperation will have resulted in cognitive conflict in the face of the actual returns. The need to reduce the levels of trust was not reflected in increases in brain areas associated with reward learning, but activation in the dorsal anterior cingulate was modulated by age and the nature of the game partner. This area of the anterior cingulate is known to play a role in conflict monitoring [41-45] and there is evidence that it is important for behavioural adjustments [19, 20]. With age, participants increasingly recruited the anterior cingulate during unfair as compared to cooperative interactions. This may reflect the conflict between expectations of cooperation and experienced social feedback and shows a possible explanation of how feedback shapes future decisions towards more optimal levels of trust [46].

Finally, we found age-related changes in brain areas that were not part of our hypotheses, but that previously have been associated with social cognitive processes. During cooperative interactions, age was also associated with activation in the precentral and bilateral middle frontal gyri. These areas have been described as parts of the ‘mirror system’ [47], a network which is thought to enable humans to understand the goals of observed (physical) actions of others in an intuitive way by internal simulation. Some evidence indicates that this brain network also engages in more abstract forms of social cognition, such as mentalising [35, 48] and empathy [49]. Previous trust game research found this area to be activated during decisions to trust [16] and age-related increases of activation have been found during social perception [50]. During unfair interactions, the middle cingulate gyrus was increasingly active with age. This area has been suggested to function as a relay node between negative emotions and motor action and has been reported to be strongly active during decisions to trust in earlier trust game research [6]. With age, activation in the dorsomedial prefrontal cortex decreased during cooperative interactions. Earlier research showed this area to be involved in the management of uncertainty in decision-making, whereby more uncertainty was associated with increased activation [51].

Limitations

The current results have to be interpreted in the light of some limitations. First, it might be possible that the differences in trust that we see with increasing age could be due to age differences in risk aversion. While a higher risk aversion may influence the degree of trust, there is extensive literature, which shows that age is typically positively associated with increased risk aversion [52-57]. This implies that teenagers should invest more money if risk aversion would be an important motive in the trust game. Furthermore, the concern over whether behaviour in the trust game actually measures trust or risk attitudes has frequently been raised. Eckel and Wilson [58] provide a comprehensive analysis of the way behaviour in two-person sequential trust games correlates with a variety of behavioural and survey-based risk measures [58]. They did not find evidence that any of their risk measures predicts the decision to trust. Also, Houser et al. [59] found that in a risk game with a computer as counterpart, the probability of investing more was significantly higher for risk seeking subjects than for subjects in the risk averse group but risk aversion did not predict investments towards a human counterpart [59]. Second, our manipulation check showed that 6 individuals of the adolescent (n = 25) and 1 of the adult group (n = 20) did have doubts that they were playing with a real human. The fact that fewer adolescents believed that they were playing a human may have reduced their mentalising operations. Yet, the current behavioural results show increases in trust with age that are in line with those of other research and do not support such concerns [7]. Third, it is important to note that age related effects may also be caused by differences in neurovasculature [60]. Yet, research by Kang et al. [61] showed that in voxelwise group comparison of images of visual and motor cortex regions only minimal differences were found between children of 7-8 years and adults [61]. The small differences in time courses and locations of activation foci between child and adult brains do support the feasibility of direct statistical comparison of these groups within a common space. Fourth, it should be noted that other cognitive factors which may offer an alternative explanation for age-related changes in trust game performance to increases in mentalising, such as executive functioning or IQ have not been included as confounders in the current study. While evidence from other research of van den Bos et al. [9] supports that non-social cognitive factors such as intelligence and executive functioning have a modest influence on social decision-making, it would be valuable if future studies would include additional measures of theory of mind and other cognitive functions to validate the interpretation in terms of mentalising. Fifth, subjects
knew that they were taking part in a study with participants between 13 and 18 and 19 and 49, respectively. It is therefore likely that the current effects pertain to trusting behaviour regarding individuals within these age ranges. Trusting behaviour towards other age-groups may differ from the current results. It would therefore be interesting for future research to systematically examine age effects with respect to the age of the trustee. Sixth, in the current paradigm we did not directly control for aspects of monetary reward in the trust game. However, as a means to control that age-related differences in brain activation are not merely due to differences in the investments that were made we, did analyse the association between the invested amounts and brain activation (Supplementary Material Table 2). Age-related in- and decreases in brain activation in certain areas did not overlap with the foci that were associated with higher and lower investments. The associations between brain activation and age do not seem to be caused by differences in investments. Finally, EMRI allows for the investigation of the role of certain brain regions and brain activation (Supplementary Material Table 2). Age-related in- and decreases in brain activation are inferred from activation in specific brain regions [62]. Within the brain it is unlikely that a particular region is activated solely by one cognitive process. The current interpretations are in line with the growing literature about the social brain systems and should be regarded as a guide for future inquiries rather than direct explanations of certain findings.

Conclusion
Our findings render preliminary support to our working hypothesis of improved mentalising as an underlying mechanism of age-related behavioural preferences of trust and cooperation. Initial trust increased with age. During interactions with a cooperative partner age was associated with higher investments. However, when playing with an unfair game partner older people quickly reduced their levels of trust to those of younger ones. The neuroimaging data showed age to be associated with increased recruitment of brain areas that seem to be important for mentalising. In line with a stronger preference for cooperation, age was associated with decreased activation in areas involved in reward learning in response to cooperative behaviour by the partner and increased activation in areas associated with cognitive control in response to an unfair game partner.

REFERENCES
Chapter 3

Chapter 4

Trust versus paranoia: Abnormal response to social reward in psychotic illness

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ABSTRACT

Psychosis is characterized by an elementary lack of trust in others. Trust is an inherently rewarding aspect of successful social interactions and can be examined using neuroeconomic paradigms. This study was aimed at investigating the underlying neural basis of diminished trust in psychosis. Functional magnetic resonance imaging data was acquired from 20 patients with psychosis and 20 healthy controls during two multiple-round trust games, one with a cooperative and the other with a deceptive counterpart. An a priori region-of-interest analysis of the right caudate nucleus, right temporo-parietal junction (TPJ) and medial prefrontal cortex (mPFC) was performed focusing on the repayment phase of the games. For regions with group differences, correlations were calculated between the hemodynamic signal change, behavioral outcomes and patients’ symptoms. Patients demonstrated reduced levels of baseline trust, indicated by smaller initial investments. For the caudate nucleus, there was a significant game x group interaction, with controls showing stronger activation for the cooperative game than patients, and no differences for the deceptive game. The TPJ was significantly more activated in controls than in patients during cooperative and deceptive repayments. There were no significant group differences for the mPFC. Patients’ reduced activation within the caudate nucleus correlated negatively with paranoia scores. The TPJ signal was positively correlated with positive symptom scores during deceptive repayments. Reduced sensitivity to social reward may explain the basic loss of trust in psychosis, mediated by aberrant activation of the caudate nucleus and the TPJ.

Keywords
psychosis, social cognition, trust, neuroeconomics, fMRI

INTRODUCTION

Psychosis is a disorder which manifests itself in social interactions. This is most evident in the core symptoms of psychosis, especially paranoid delusions, which are characterized by a fundamental lack of trust. Trust is an essential and inherently rewarding aspect of successful social interactions. A fundamental lack of trust has long been regarded as a primary process underlying paranoid delusions [1]. However, trust has not been incorporated into cognitive models of psychosis, due to the difficulty in probing the interactive nature of social processes experimentally [2].

Different approaches have been implemented to study socially relevant stimuli, ranging from passive watching [3] and active associative learning [4] towards actual social interactions [5]. The current development of neuroeconomics has shown that complex social interactions, such as trust, can be operationalised in economic exchange games [6-10]. Recent reviews suggest that neuroeconomics offers objective and suitable paradigms to investigate the underlying mechanisms of social dysfunction in psychiatric disorders [11-12].

The classical trust game involves the interaction of two anonymous players, based upon simple investment and repayment decisions [13]. The first player decides how much money to share with the second player. This shared amount is tripled, and the second player has to decide upon how much to repay to the first player. If both players cooperate, mutually beneficial outcomes become more likely, however, the second player could benefit at the expense of the other. Thus, it allows the examination of trust quantified by the amount of money being invested. Previous studies showed that healthy controls invest at least some of their money, and that this sign of trust is strongly reinforced by the reciprocity of the interacting partner [14-17].

Recent imaging studies showed that economic exchange games are associated with cortical regions associated with both social cognition [18-20] and reward networks [8, 21-22]. Mentalizing is essential for successful social interactions, and deficits in mentalizing have been linked to poor social functioning in psychosis [23]. Recent imaging data support the notion that reduced activation in the temporo-parietal junction (TPJ) and the medial prefrontal cortex (mPFC) may underlie the mentalizing impairments in psychosis [24]. Consequently, those brain regions may play an important role for the development of disturbed social interactions and diminished trust in psychosis.

Trust has been linked with activation in brain reward systems; the caudate nucleus was specifically linked to mutually positive interactions between healthy individuals [8]. This suggests a possible mechanism underlying disturbed social interactions in psychosis, bringing into play contemporary theories of dopamine function. Mesolimbic dopamine has a central role in reward, learning and motivation [25], and is also thought to be crucial to the pathophysiology of psychotic symptoms [26-27]. Abnormalities of dopaminergic function may lead to aberrant salience signals, possibly underlying the development of psychotic symptoms [28]. This leads to the hypothesis that aberrant sensitivity to social reward may underlie the basic lack of trust in psychosis. Using a multiround trust game, we have recently shown that patients with psychosis engage in fewer mutually trusting interactions than healthy controls [5].
The purpose of this study was to investigate the lack of trust manifest in psychosis at the neural level. Functional magnetic resonance imaging data was acquired from 20 patients with non-affective psychosis and 20 healthy controls, while participating in two multiple-round trust games. One game was played with a counterpart designed to respond with a cooperative playing style, the other game was based on a deceptive playing style. We expected to find in patients with psychosis as compared to healthy controls (i) reduced baseline trust; (ii) reduced activation in the caudate nucleus in response to cooperative repayments, and (iii) reduced TPJ and mPFC signals during cooperation and deception. As a secondary aim, we examined the link between hemodynamic signal change and symptoms as well as investment behavior to identify if observed brain activation is related to specific symptoms. For the caudate, we focused on the link with baseline trust, measured by initial investments. Examining the mean investments seemed more relevant for the mPFC and the TPJ, considering that mentalizing plays a role throughout the entire interactions, rather than the first rounds. The specific hypotheses were (iv) the magnitude of the brain response in the caudate nucleus is negatively correlated to the level of paranoia scores in patients; (v) the initial investment is positively correlated to the caudate signal in controls, but not in patients; and (vi) the mean investments are positively correlated to the TPJ and mPFC signals in controls, but not in patients.

**Methods and materials**

**Subjects**

Two groups of dextral male subjects aged between 18 and 50 years participated in the study: 20 patients with lifetime presence of non-affective psychosis according to RDC criteria, with illness duration of less than 15 years, and currently treated with atypical antipsychotics, and 20 control individuals without a personal history of psychosis or a family history of psychosis. The recruitment of participants took place via the South London and Maudsley (SLAM) NHS Trust. The SLAM PICuP research register was consulted to identify suitable patients, which is a research database for patients undergoing psychological treatment at the Maudsley Hospital, London. In order to select control subjects, a database of healthy volunteers was used, which has been created for this purpose at the Institute of Psychiatry, King’s College London. Exclusion criteria included: Current treatment with typical antipsychotics, current drug or alcohol abuse, a history of neurological disorder, and serious intellectual impairment. Individuals were also screened with the imaging safety questionnaire and were excluded if they showed any contraindications to magnetic resonance imaging, such as metal in the body or claustrophobia. For the control group, a lifetime or a family history of psychosis was used as an additional exclusion criterion. After complete description of the study to the subjects, written informed consent was obtained. The study received ethical approval by the Barking and Havering Local Research Ethics Committee.

**Assessment**

**Psychotic symptoms.** The Positive, negative and general subscales of the Positive and Negative Syndromes Scale (PANSS) [29] were used to assess the extent of psychotic symptoms. The persecution item of the PANSS was used as an additional index for patients’ paranoid symptoms.

**Depressive symptoms.** The Beck’s Depression Inventory [30] was used as a measure of co-morbid depression to ensure that patients were not suffering from severe depression.

**General cognition.** Two additional cognitive measures were used to control for the potential impact of general cognitive impairment on trust game behaviour. The Vocabulary subtest of the WAIS III [31] was used as an index for general cognitive ability. Working memory was estimated by the Letter Number Span of the WAIS III.

**Experimental design**

The trust game was a modified version of a previous multi-round trust game [8]. Subjects played the role of the first player. They played against the computer, but were led to believe that they would play with two different human partners. Subjects were asked to decide how much money to share with the other player. At the beginning of each round, subjects received the same starting budget consisting of £10. Any amount between zero and ten pounds could be shared. The shared amount was tripled, and the second player had to decide upon how much to repay to the first player.

The computer algorithm consisted of two versions programmed in a probabilistic way, which reflected a cooperative and a deceptive style of playing. The decision on how much money should be returned depended on the previous investments of the investor. Specifically, in the cooperative strategy, the first repayment was either 100% or 150% or 200% of the amount invested. Each of these possible first repayments occurred with a probability of 33%. Subsequent repayment increased in a probabilistic way if the current investment reflected an increase in trust relative to the previous investment, but remained stable in all other situations. Hence, with each increase in trust from the side of the investor, the chance of a repayment of 200% increased with 10%. In the deceptive strategy, the first repayment was 50% or 75% or 100% of the amount invested. Each of these possible first repayments occurred with a probability of 33%. Subsequent repayments decreased in a probabilistic way if the current investment reflected an increase in trust relative to the previous investment, but remained stable in all other situations. Hence, with each increase in trust from the side of the investor, the chance of a repayment of 50% invested increased with 10%.

In total, all participants played two trust games, each consisting of 20 game trials and 20 null trials. The null trials were included as a baseline condition for the fMRI analysis. The design and duration of each event within the null trials was identical to the game trials. Participants were told that the null trials were not related to the investment decisions. In one game, the computer playing style was cooperative, and in the second it was deceptive. The order of the games was counterbalanced across subjects.

A single round was set up as follows. Every trial started with an investment cue of £10 and the investment period of the subject (maximum 6 seconds). The invested amount was shown (2
Scanning parameters
Imaging data were acquired using a 3T GE Signa Neuro-optimised MR System (GE, Milwaukee, Wisconsin, USA) at the Centre of Neuroimaging Science of the Institute of Psychiatry, King’s College London. A quadrature birdcage head coil was used for radio frequency transmission and reception. Foam padding was placed around the subject’s head in the coil to minimize head movement. Three hundred and seventy T2*-weighted whole-brain echo-planar images sensitive to the blood oxygen level-dependent (BOLD) contrast were acquired with the following parameters: Slice thickness = 2.4 mm; gap = 1 mm; TR = 2 s; TE = 25 ms; flip angle = 75°; in-plane resolution = 3.4 mm; number of slices = 38; DDA = 4; matrix = 64 x 64. For anatomical reference, a coronal FSPGR image of the whole brain was obtained for each subject, which consisted of 196 slices acquired with the following parameters: Slice thickness = 1.1 mm; gap = 0; TR = 7 s; TE = 2.8 ms; flip angle = 20°; matrix = 256 x 256.

Statistical Analyses
The SPSS software, version 17, was used to analyze the behavioral data. The average of the initial investments of the first round of both games was used as an index for baseline trust. The average of all investments was calculated for each game separately as an index for overall trusting behavior.

The imaging data was analyzed using Brainvoyager QX, version 2.3 (Brain Innovation, Maastricht, The Netherlands). The functional scans were coregistered to each individual anatomical scan and converted to Talairach space. Preprocessing consisted of slice scan-time correction, 3D motion correction, temporal highpass filtering (0.01 Hz), and modest temporal Gaussian smoothing (3 s). Finally, spatial smoothing using a 3D Gaussian kernel (FWHM = 6 mm) was performed. The preprocessed functional data were then resampled in standard space, resulting in normalized 4D volume time-course data. For each subject, a protocol was created defining the onsets and offsets of the events (real vs. control investments with an onset at 2 seconds with duration of 4 seconds; real vs. control repayments with an onset of 10.5 seconds after trial start and a duration of 5 seconds) for the different games. Using these protocols, design matrices were computed by convolving each event with a standard hemodynamic response function. A priori regions-of-interest (ROIs) were defined based on the Talairach coordinates from previous research, identifying robust reward- and mentalizing-related activation in independent samples for the right caudate nucleus (TA1, 10, 9, 4) [32], the right TPJ (TA1, 51, -54, 27) [33], and the mPFC (TA1, -3, 64, 20) [34]. ROIs were created with a 5 mm sphere centered around the published coordinates. Random-effects General Linear Model analyses were run, based on the individual design matrices and 4D volume time-course data, but restricted to the voxels contained by the ROIs, after correction for serial correlations. For ROIs with a significant group difference, Beta weights were extracted and subjected to further post-hoc analyses in relation to symptoms (i.e. paranoid, positive, negative and general scores) and behavioral outcomes (i.e. initial investment for the caudate and mean investments for the TPJ). These correlation analyses were conducted using adjusted alpha levels of .01 per test.

Furthermore, any effect of repayment magnitude on caudate activation was analyzed using repeated measures ANOVA with repayment magnitude as the within-subjects variable, and group as the between-subjects factor.

An exploratory whole-brain, voxel-wise analysis focusing on the repayment phase of the cooperative and the deceptive game was conducted to investigate if there were group wise differences in regions outside the a priori defined ROIs.

RESULTS
Demographics
Table 1 displays the means and standard deviations for the participant characteristics within each group. To ensure that age and indices of cognitive ability were distributed equally across the two groups, ANOVAs were run, comparing the demographical information obtained from patients and controls. There were no significant differences between patients and controls in terms of age (F(1,38) = .29, n.s.), WAIS vocabulary scores (F(1,38) = .6, n.s.), and WAIS letter-number span (F(1,38) = 2.7, n.s.).

Behavioral results
The variance of the individual investments was examined because the algorithms for the two games were programmed such that an investment of 10 pounds sustained throughout the game would lead to similar repayments. There was no single subject who invested the maximum of 10 pounds throughout all trust game rounds of the two games. Table 2 provides an overview of the means and standard deviations for the behavioral analyses. There was an effect of initial investments: patients invested significantly less during the first round than controls (F(1,38) = 8.071, p < .01), indicating reduced levels of baseline trust in patients. Patients invested significantly less during the cooperative game (F(1,38) = 14.431, p < .01). No group differences were found for the deceptive game (F(1,38) = .033, n.s.).

Table 1. Participant characteristics

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<td>43.9 (10.7)</td>
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<tr>
<td>WAIS letter-number</td>
<td>0-21</td>
<td>11.2 (2.3)</td>
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1Wechsler Adult Intelligence Scale-Revised
fMRI results

For the right caudate nucleus (Figure 1), there was a significant game x group interaction ($F(1,38) = 4.834, p < .04$), with stronger activation in controls than patients during cooperative repayments ($t(38) = 2.144, p < .04$) and no significant differences for deceptive repayments ($t(38) = -0.541, n.s.$). The strength of the caudate signal during cooperative repayments correlated negatively with patients’ paranoia scores (Pearson’s $r = -0.555, p < .01$; Figure 3), but not with negative (Pearson’s $r = -0.117, n.s.$), positive (Pearson’s $r = 0.168, n.s.$) or general symptom scores (Pearson’s $r = 0.094, n.s.$). When tested with a non-parametric measure, the correlation between caudate activation and paranoia scores revealed the same trend, but was not significant at the adjusted alpha level of 0.01 (Spearman’s $\rho = -0.409, p < .05$).

In controls the caudate signal correlated positively with the magnitude of the initial investment (Pearson’s $r = 0.522, p < .01$), linking healthy baseline trust with the brain reward response in controls. The correlation between caudate signal strength and initial investment was not significant for patients (Pearson’s $r = 0.011, n.s.$).

There was a significant group effect for the right TPJ ($F(1,38) = 5.642, p < .03$; Figure 2), with stronger activation in controls than patients during cooperative repayments ($t(38) = 2.064, p < .05$) as well as during deceptive repayments ($t(38) = 2.099, p < .05$). The strength of the TPJ signal during deceptive repayments correlated positively with patients’ positive symptom scores (Pearson’s $r = 0.516, p < .01$; Figure 4), but not with negative (Pearson’s $r = 0.391, n.s.$), general (Pearson’s $r = 0.449, n.s.$), and paranoia symptom scores (Pearson’s $r = 0.292, n.s.$). There were no significant correlations between the TPJ signal during cooperative repayments and any of the PANSS symptom scores. To assess whether the observed association between TPJ signal and positive symptoms was stronger for the deceptive than for the cooperative game, a repeated measures ANOVA was ran for the patient group, yielding a trend-level significant TPJ x positive symptoms interaction ($F(1,37) = 3.583, p < .1$).

The TPJ signal did not correlate significantly with the magnitude of the mean investment during the deceptive game (Pearson’s $r = 0.378, n.s.$).

For the mPFC, there was a significant main effect of game ($F(1,38) = 7.297, p < .02$), with stronger activation for cooperative repayments than for deceptive repayments in both groups ($t(38) = 2.730, p < .01$). There were no significant group differences for the mPFC ($F(1,38) = 1.105, n.s.$). Figure 1 and 2 illustrate the size of the hemodynamic responses during cooperative vs. deceptive repayments for the areas with significant group differences, i.e. the caudate nucleus and the TPJ.

Table 2. Behavioral measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean Patients (SD)</th>
<th>Mean Controls (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First investment</td>
<td>6.1 (2.2)</td>
<td>7.8 (1.4)</td>
</tr>
<tr>
<td>Mean investment during cooperative game</td>
<td>5.8 (2.3)</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td>Mean investment during deceptive game</td>
<td>4.5 (1.7)</td>
<td>4.4 (1.2)</td>
</tr>
</tbody>
</table>

Figure 1. Location and percent signal change of the right caudate nucleus (NC) based on mean beta weights.

Figure 2. Location and percent signal change of the right temporo-parietal junction (TPJ) based on mean beta weights.

Figure 3. Scatterplot of the negative association between caudate signal strength and PANSS persecution scores in patients.
Consequently, this different activation pattern might suggest that patients have a reduced investment during the first round of games compared to controls. During this initial investment, subjects have no information on baseline trust in patients. This is in line with previous research and theories on the role of trust in psychosis [1, 6]. Explicit social information has also been shown to modulate traditional reward learning with evaluation of standard risk and reward. Recently, it has been shown that risk attitudes do not predict trust decisions during trust game interactions [39-40]. The lack of TPJ abnormalities in our study contradicts this notion. One explanation of this discrepancy might be that the TPJ is a better functioning region of the mentalizing network during social decision-making than the mPFC. This would explain why patients exhibited similar mPFC activation as the healthy control subjects in our study, with a stronger signal for beneficial than non-beneficial social encounters. Alternatively, it is also possible that subtle mPFC impairments might be present in patients, which could not be detected in our study due to insufficient sample sizes.

The exploratory whole-brain analysis revealed reduced activation in patients in the inferior parietal lobule during cooperative and deceptive repayments, and additionally in the middle temporal gyrus during cooperative repayments. Abnormal activation in the inferior parietal lobule in schizophrenia has been linked to difficulties in self/other distinction and agency attribution [36-38], but given the exploratory nature of this analysis, the significance of this finding in the context of the trust game should be investigated in future studies.

The current study had a relatively moderate sample size (N=40). Consequently, the results should be regarded as preliminary evidence and have to be interpreted with caution. Replication in a larger sample is required to obtain a more reliable account of the neural correlates of the lack of trust in patients with psychosis. Moreover, the generalizability of the current results is limited due to the strict inclusion criteria (i.e. only right-handed males, illness onset of less than 15 years, only atypical medication). However, these criteria were necessary in order to avoid potential confounding problems due to handedness, gender or medication.

One major drawback is that the design of our task does not allow to clearly differentiate between social reward and more generic reward. Previous studies suggest that social reward during social interaction in the trust game can be distinguished from utilitarian decision making with evaluation of standard risk and reward. Recently, it has been shown that risk attitudes do not predict trust decisions during trust game interactions [39-40]. The neuropeptide oxytocin demonstrates specific effects on social learning, and not on learning in non-social risk games [41]. Explicit social information has also been shown to modulate traditional reward learning systems in the striatum [42], indicating a clear distinction between social learning and reward learning. These studies support the notion that trust games tap into social rather than generic reward learning.

Patients also showed a reduced TPJ signal in response to both cooperation and deception. This is in line with previous imaging data, showing impaired TPJ activation during an on-line mentalizing task [35]. Noteworthy, the TPJ has been specifically linked to mental state reasoning in a social context [33], in line with the notion that our subjects believed that they were interacting with real persons. In the current study, the TPJ signal change was associated with the severity of positive psychotic symptoms during deceptive repayments only, suggestive of a link between enhanced mentalizing activity during unfair social encounters and positive psychotic symptoms. However, this interpretation is based on a suggestive, but non-significant, interaction and hence requires replication in a larger sample.

Surprisingly, no group differences were established for the mPFC. Previous research suggests that mPFC impairments are directly linked to the mentalizing deficits observed in psychosis [24]. The lack of mPFC abnormalities in our study contradicts this notion. One explanation of this discrepancy might be that the mPFC is a better functioning region of the mentalizing network during social decision-making than the TPJ. This would explain why patients exhibited similar mPFC activation as the healthy control subjects in our study, with a stronger signal for beneficial than non-beneficial social encounters. Alternatively, it is also possible that subtle mPFC impairments might be present in patients, which could not be detected in our study due to insufficient sample sizes.

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REFERENCES


Further research in this field should focus on risk groups such as individuals from the general population with subclinical psychotic symptoms or first-degree relatives of patients with psychosis. Previous research on first-degree relatives has revealed similar findings in the relatives as in the patients in terms of dopaminergic abnormalities [45-46]. Recent evidence has been found for reduced trust in relatives at baseline, but trust levels similar to controls in the feedback condition, suggesting that cognitive flexibility may be a protective mechanism against transition from subclinical to clinical symptoms [5]. The neural basis of this transition still needs to be explored.

To conclude, we demonstrate for the first time that reduced sensitivity to social reward in psychosis is accompanied by attenuated caudate activation and this correlates with levels of paranoia. Moreover, there seems to be an impaired TPJ signal in patients, which is linked to positive symptoms for situations of unfair social encounters. Overall, this points to aberrant reward and mentalizing mechanisms disturbed social interactions in psychosis and contributing to paranoid delusions and overall symptomatology. Although speculative, this offers a new account of the origins of social cognition disturbances in psychosis. Further research on paranoia and its manifestations during social interactions is needed to gain more insight into one of the most devastating symptoms of psychosis.


Reduced brain reward response during cooperation in first-degree relatives of patients with psychosis: an fMRI study

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ABSTRACT

The neural underpinnings of psychotic illness remain uncertain, confounded by changes secondary to the disease process, social isolation and antipsychotic medication effects. Recent data revealed analogous deficits across a range of neuropsychological measures, including social cognition tasks, in first-degree relatives of patients with psychosis. This study aimed to clarify the neural mechanisms underlying trust in siblings of patients during an interactive trust task. The hypotheses were: (i) siblings will invest less at the beginning of the trust game; and (ii) siblings will show reduced activation of the brain reward and mentalizing systems compared to controls.

Functional magnetic resonance imaging data was acquired on 50 healthy siblings of patients with psychosis and 33 healthy controls during a multiple-round trust game with a cooperative counterpart. An a priori region-of-interest (ROI) analysis of the caudate, temporoparietal junction (TPJ), superior temporal sulcus (STS), insula and the medial prefrontal cortex (mPFC) was performed focusing on the investment and repayment phases. An exploratory whole-brain analysis was run to test for group-wise differences outside these ROIs.

The siblings’ behaviour during the trust game did not differ significantly from the behaviour of the controls. At the neural level, siblings showed reduced activation of the right caudate during investments, and the left insula during repayments. In addition, the whole-brain analysis revealed reduced putamen activation in siblings during investments. This suggests that siblings show aberrant functioning of regions traditionally involved in reward processing in response to cooperation, which may be associated with the social reward deficits observed in psychosis.

Keywords
functional MRI, schizophrenia, siblings, trust, caudate.

INTRODUCTION

Persecutory beliefs and hallucinations are characteristic features of psychotic illness; their functional implications are evident in the devastating impact on social functioning and levels of trust in others. Social interactions pose a major challenge to patients. The poor social functioning evident in psychosis has been linked to impaired mentalizing [1], i.e. the ability to understand the intentions of others. Mentalizing is highly relevant for engaging in social interactions, but the interactive nature of social encounters is difficult to probe experimentally. The recent development of neuro-economics now allows to investigate complex social interactions by means of interactive paradigms [2-6].

The classical trust game [7] is based on the interaction between two players. The first player (i.e. investor) decides how much money to invest out of a certain starting budget. The invested amount gets multiplied, and the second player (i.e. trustee) then chooses the amount of money to repay to the investor. Mutually beneficial outcomes are most likely if both players cooperate. However, investing involves a certain risk as the trustee gains the highest payoff by keeping all the money to himself. Hence, trust is required for the investor to make an investment. Previous research showed that healthy individuals invest at least some of their money, and that this sign of trust is strongly reinforced by the reciprocity of the interacting partner [8-11]. Recently, we demonstrated that patients with psychosis participate in fewer mutually trusting interactions than healthy individuals [12].

Interactive paradigms from the neuro-economics field have been linked to activation in mentalizing regions [13-14] and the brain reward circuit [4, 15-16]. Benevolent reciprocity (i.e. a higher than expected return) during trust game interactions was associated with significant activation of the caudate nucleus, with a change in the timing of the activation from the outcome to the decision phase indexing the development of trust between interacting persons [4]. Activation of the mPFC and TPJ was associated with mentalizing, and activation of the insula indicated reward and arousal [17]. We have recently shown that patients with psychosis had reduced levels of baseline trust, and reduced activation within the caudate nucleus and the TPJ in response to cooperative repayments [18]. Moreover, we found a negative correlation between the attenuated caudate signal and paranoia levels, but no other symptoms. In line with the King-Casas study [4], this suggests a prominent role of the caudate nucleus in processes related to trust and social reward.

However, imaging studies on psychosis are limited by the potentially confounding effects induced by the antipsychotic medication, which has been shown to act upon the brain reward response [19-20]. Investigating individuals with a familial risk to develop psychosis is a promising solution to this dilemma. Having a first-degree relative with psychosis has been proven to be a risk factor for developing the disorder [21-23]. Recent studies have revealed mentalizing deficits in unaffected relatives of patients with psychosis [24-28]. These impairments seem to be more severe in first-degree than in second-degree relatives [29]. Using a multi-round trust game, we found evidence for lower basic trust in first-degree relatives compared to controls [12]. Unlike patients, relatives increased their investments when receiving positive information about the trustworthiness of the trustee.
In a typical one-shot trust game, the investment phase involves mentalizing (i.e. trying to predict the trustee’s intentions), and the repayment phase involves social reward (or lack thereof, dependent on the magnitude of the repayment). In contrast, in a multi-round trust game, the mentalizing and social reward components become intermingled in both phases of the game. In the investment phase, anticipation of a positive repayment by the trustee may lead to activation of brain areas involved in social reward [4]. Likewise, in the repayment phase, mentalizing activity may occur when subjects start reflecting upon the intentions of the other player, as well as planning the optimal next investment choice. Thus, in the multiround game used in the current study, reward and mentalizing-related activation can occur during both the investment and the repayment phases of the trust game.

The current study aimed to investigate the underlying neural mechanisms of the lack of trust linked to psychosis, without the typical confounders such as hospitalization, medication and symptoms. Functional magnetic resonance imaging (fMRI) data was acquired on 50 healthy siblings of patients with psychosis and 33 healthy controls while participating in a multi-round trust game with a preprogrammed cooperative counterpart. Based on previous research [4, 12], we expected to find: (i) lower baseline trust in siblings than in controls; (ii) no group difference between overall trusting behavior (i.e. mean investments) throughout the trust game, in line with the previous behavioral finding in siblings of intact ability to adapt to the reciprocity of the trustee [12]; and (iii) reduced activation of the caudate, TPJ, STS, insula and the mPFC in siblings compared to controls.

**METHODS**

**Subjects**

Two groups of subjects were tested for this study: 50 healthy siblings of patients with psychosis, and 33 healthy control subjects. The subjects were recruited from the Dutch Genetic Risk and Outcome in Psychosis (GROUP) study [30] (https://www.group-project.nl). The age range was 18-60 years. The main exclusion criteria were: a personal and family history of any psychiatric or neurological disorders for psychosis or any psychiatric or neurological disorders, and personal and family history of any psychiatric disorder other than psychosis. Further exclusion criteria consisted of MRI contraindications such as metal implants, prostheses, pregnancy, history of claustrophobia or epilepsy. The study was approved by a local ethics committee and conducted with strict compliance to ethical standards.

**Experimental design**

We used a modified version of previously implemented multiround trust games [4-5]. Subjects were scanned while playing one trust game against a computer. They received the information that they would play with an anonymous human partner in a different location. Subjects played the role of the investor throughout the whole game, and hence always made the first move. Each round started with the same starting budget consisting of €10. The main task of the subject was to decide how much money he or she wanted to share with the anonymous partner. Any whole amount between zero and €10 could be shared. Shared money was tripled and the subject received an amount repaid by the partner.

The computer algorithm was programmed in a probabilistic way, reflecting a cooperative playing style. The amount of the repays depended on the previous investments of the investor. The repayment of the first round was either 100% or 150% or 200% of the amount invested, each occurring with a probability of 33 %. Subsequent repayment increased in a probabilistic way if the current investment reflected an increase in trust relative to the previous investment, but remained stable in all other situations. Hence, with each increase in trust from the side of the investor, the chance of a repayment of 200% increased with 10%.

The game consisted of 20 game trials and 20 null trials. The null trials were included as a baseline condition for the fMRI analysis. The design and duration of each event within the null trials was identical to the game trials. Participants were told that the null trials were not related to the investment decisions.

A single round was set up as follows. Every trial started with a short statement shown for two seconds asking the participant to make an investment choice. Next, the numbers zero to ten appeared on the screen for up to four seconds, requiring participants to make an investment choice. Responses were made with a MRI-compatible two-button box. The invested amount was shown as a histogram and in numbers. The participant waited between two to four seconds for the response of the partner, viewing a bar slowly filling itself with dots, followed by a fixation cross shown for 500 milliseconds. The partner’s response was displayed on the screen in both graphical and numerical form for three seconds. The totals were presented next, for three to five seconds (i.e. depending on the length of the partner’s response) by means of two bars graph with the corresponding numbers. At the end of each trial, a fixation cross was shown for 500 milliseconds. In total, one trial lasted 18.5 seconds. At the beginning of a new trial, participants always received €10 again. The trials were independent of each other, thus there were no cumulative totals.

**Scanning parameters**

Imaging data were acquired using a 3.0 Tesla whole body scanner (Philips Intera, Best, NL) at the Academic Medical Centre in Amsterdam. A quadrature birdcage head coil was used for radio frequency transmission and reception. Foam padding was placed around the subject’s head in the coil to minimize head movement. The functional images were acquired by a T2-weighted echo producing 37 slices of 3.5 mm thick with no gap, providing complete brain coverage. The functional scans were made in the axial plane (TR = 2.00 s; TE = 30; FOV = 224.0, 129.5, 224.0; Voxel size: 3.5 x 3.5 x 3.5 mm). For anatomical reference, a T1-weighted image (170 slices; isotropic voxels of 1 mm; TR 9 ms; TE 3.54 ms; α 8°; FOV 256 mm) was acquired in the bicommissural plane, covering the whole brain. For safety reasons, ECG measurements were monitored to make sure the participant’s pulse remained stable throughout the entire scanning session.

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Chapter 5

Reduced brain reward response during cooperation in relatives
Statistical Analyses

The SPSS software, version 19, was used to analyze the demographics and the behavioral data of the participants. The first investment made during the first trial of the game was used as an index for baseline trust, as in our earlier fMRI study [18]. Since this measure was based upon the investments from the very first round, subjects did not have any indication as to how the partner will respond. Hence, a higher first investment indicated higher baseline trust. This analysis was conducted by means of a standard one-way Analysis of Variance (ANOVA) with group as the independent variable and the first investment as the dependent variable. The average of all investments was calculated as an index for overall trusting behavior, and analyzed by a one-way ANOVA with group as the independent variable and mean investment as the dependent variable.

The imaging data was analyzed using Brainvoyager QX, version 2.3 (Brain Innovation, Maastricht, The Netherlands). The functional scans were coregistered to each individual anatomical scan and converted to Talairach space. Preprocessing consisted of slice scan-time correction, 3D motion correction, temporal highpass filtering (0.01 Hz), and modest temporal Gaussian smoothing (3 s). Finally, spatial smoothing using a 3D Gaussian kernel (FWHM = 6mm) was performed. The preprocessed functional data were then resampled in standard space, resulting in normalized 4D volume time-course data. For each subject, a protocol was created defining the onsets and offsets of the events (real vs. control investment with an onset of 0 seconds from trial onset and a duration until the last button press, with a maximum duration of 6 seconds; real vs. control repayments with an onset of 10.5-12.5 seconds after trial start -depending on the length of the waiting for partner’s response period- and a duration of 3 seconds). Using these protocols, design matrices were computed by convolving each event with a standard hemodynamic response function.

A priori ROIs were defined based on the Tailarach coordinates from previous research, identifying robust activation in independent samples. The caudate (TAL 16, 17, 6) [31] and the insula (TAL -33, 14, -1) [6] were used as reward-related regions-of-interest. To tap mentalizing-related activation, the TPJ (TAL 51, -54, 27) [32], the STS (TAL 61, -56, 7) [33], and the mPFC (TAL -3, 64, 20) [33] were implemented. ROIs were created with a 5 mm sphere centered around the published coordinates. Random-effects General Linear Model analyses were run, based on the individual design matrices and 4D volume time-course data, but restricted to the voxels contained by the ROIs, after correction for serial correlations. The ROI analyses were conducted using Bonferroni adjusted alpha levels of .01 per test (.05/5).

An exploratory whole-brain, voxel-wise analysis focusing on the investment and repayment phase of the trust game was conducted to investigate if there were group wise differences in regions outside the a priori defined ROIs. To correct for multiple comparisons, a cluster extent threshold determined by Monte Carlo simulations was applied [34], which corresponded to a corrected threshold of $p < 0.05$ across the whole brain volume.

RESULTS

Demographics

The control group consisted of 19 men (57.6%) and 14 women (42.4%), with a mean age of 33.4 years (SD 10.17, range 23-55 years). The majority of the sample was right-handed (28 subjects, 84.8%), only 5 subjects were left-handed (15.2%). In total, 13 subjects had a university education level (39.4%), the remaining 20 subjects had lower educational degrees (60.6%).

The relatives group consisted of 21 men (42%) and 29 women (58%), with a mean age of 33.9 years (SD 8.74, range 20-59 years). The majority of the sample was right-handed (40 subjects, 80%), only 9 subjects were left-handed (18%) and one subject did not have a handedness preference (2%). In total, 13 subjects had a university education level (26%), the remaining 37 subjects had lower educational degrees (74%).

There were no significant differences between siblings and controls in terms of age ($F(1,81) = 0.06, n.s.$), gender ($F(1,81) = 1.93, n.s.$), education ($F(1,81) = 0.74, n.s.$), and handedness ($F(1,81) = 0.01, n.s.$).

Behavioural data

The investing behavior during the trust game was not different for the two groups. Siblings had a mean investment of 8.1 euros (SD 1.3) and a first investment of 6.3 euros (SD 2.5). For the controls, the mean investment was 8 euros (SD 1.5) and the first investment was 6.2 euros (SD 2.2). There were no significant differences between siblings and controls in terms of the mean investments ($F(1,81) = 0.25, n.s.$) or the first investment ($F(1,81) = 0.04, n.s.$).

fMRI data

ROI analyses

For the right caudate (Figure 1), there was a significant group effect ($t(81) = -2.93, p < .01$), with stronger activation in controls than siblings during the investment phase of the trust game.

During the repayment phase of the game, there was a significant group effect for the left insula ($t(81) = -3.83, p < .001$), with stronger activation in controls than in patients (Figure 2). There were no significant group differences for the right TPJ ($t(81) = -2.23, p > .01$), the right STS ($t(81) = -1.99, p > .01$) and the mPFC ($t(81) = -2.17, p > .01$) for both phases of the game.

Whole brain analysis

Making investments was associated with stronger activation of the right putamen, right caudate body and right superior frontal gyrus in controls compared to siblings (Table 1). Receiving repayments was associated with stronger activation of the left insula, the left superior frontal gyrus, and the left subcallosal gyrus in controls than siblings (Table 2).
DISCUSSION

This study investigated the neural correlates of social reward processing during beneficial social interaction in healthy first-degree relatives of patients with psychosis using a neuro-economic game approach. We found no support for behavioral differences between relatives and controls in terms of initial and mean investments.

The imaging analyses revealed reduced caudate activation in siblings during investments, and reduced insula activation during repayments. The caudate has been linked to greater activation in the generous condition of the trust game in healthy controls [4], and might constitute a neural correlate of social reward processing. Our finding of reduced caudate activation in siblings is in line with our previous imaging study showing reduced caudate activation during trust game interactions in patients [18]. Just like patients, siblings showed a reduced brain reward response to beneficial social interactions, indicating an underlying familial substrate to this deficit.

Prior studies have linked the insular cortex to the processing of positive rewarding stimuli [35] and social cognition [16, 36-37], both processes assumed to be impaired in psychosis. Recently, insula activation during the trust game has been associated with reward and arousal [17]. Moreover, the anterior insula has been postulated to form part of the brain salience network [38-39]. Combined with our finding of reduced insula activation in siblings, this may suggest that reduced attention to social stimuli might be due to ineffective salience processing in the anterior insula.

Our results from the exploratory whole-brain analysis are in line with these ROI results: Controls showed stronger activation than siblings of the caudate during investments and stronger activation of the insula during repayments. Additionally, we found stronger activation of the putamen during investments, the superior frontal gyrus during investments and repayments, and the subcallosal gyrus during repayments. We did not have an explicit hypothesis regarding the subcallosal gyrus, but it has an established role in controlling hedonic tone and is observed to be impaired in depressive illness [40]. The putamen has been linked to reward processing [6], and may hence contribute to impaired reward–related activation in response to cooperation. This strengthens the caudate finding from the ROI analyses, suggesting that siblings show a reduced activation of regions of the brain reward circuit in response to beneficial social interactions. Our imaging data are in line with the findings of previous studies showing that reward-related brain activation is linked to engaging in economic exchange games in healthy controls [4, 15, 41], and further strengthens the hypothesis that aberrant social reward mechanisms may underlie disturbed social interactions in psychosis [18].

In spite of our expectations, we did not find any group differences in terms of TPJ, STS or mPFC activation. Considering that these are traditional mentalizing regions, this suggests that the neural basis for making inferences about the partner’s next moves and intentions might work equally well in siblings as in the control individuals during beneficial social interactions. This is also in line with the previous behavioral finding of intact feedback responsiveness in relatives during trust game interactions [12], implying that their ability to respond flexibly may be linked to a more intact mentalizing system. Abnormal mentalizing activation seems to occur
in patients during the trust game [18], but not in their healthy relatives. This may suggest that
the observed mentalizing 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 basic trust
was demonstrated in relatives previously [12], reflecting lower levels of reward during trusting
behaviour, which can be related to our new finding of reduced neural reward processing. This
implies that impaired reward-related activation seems to be present in both patients and healthy
siblings, suggesting a potential role as a vulnerability marker for psychosis.

Our finding of no behavioral differences between the groups in terms of mean investments
is in line with our hypothesis and our previous behavioral study, showing that first-degree
relatives were able to adapt their trusting behavior when receiving feedback on the partner’s
cooperativeness [12]. In general, this finding is also supported by previous studies, showing
that investment behavior in healthy individuals is strongly reinforced by the reciprocity of
the interacting partner [8-11]. Surprisingly, we did not find evidence for reduced basic trust
in siblings. This is at odds with our previous studies showing lower basic trust in patients
[18] and first-degree relatives [12]. However, the current study only included one round of
initial investment, whereas the earlier study was set up with 10 rounds of initial investment,
allowing for a more thorough investigation of basic trust. Future fMRI studies should focus
on a more elaborated assessment of basic trust, by including a condition of subsequent non-
feedback rounds, as described in our previous behavioural study [12]. Alternatively, there may
be differences in characteristics associated with basic trust of the relatives tested in the current
study compared to the relatives from our earlier study.

Finally, the extent to which the trust game indexes social reward as distinct from generic
reward processing is unknown, as well as whether individual attitudes towards risk-taking may
have an impact on the behavior during the trust game interaction. Although several authors have
argued that attitudes towards risk influence behavior in a trust game [42-44], recent empirical
studies point towards a fundamental distinction between those components. First, it has been
shown that risk attitudes did not predict trust decisions [45]. Secondly, behaviour in a task not
involving trust decisions was unrelated to behaviour in a standard trust game [46]. Moreover,
social interactions measured by the trust game have been linked to mentalizing [47], and providing
social information had an impact on traditional reward learning systems in the striatum [41],
pointing towards a clear distinction between social learning and reward learning. However,
recent data on healthy individuals playing the trust game during hyperscanning showed a clear
shift in the trust signal from the repayment towards the investment phase, in line with traditional
reinforcement learning [4]. Combined with the finding of aberrant reward prediction error in
psychosis [48], this suggests a prominent role of neural reward processing in the mechanisms
underlying social interactions. Our findings with regard to relatives may suggest that impaired
reward processing might constitute a vulnerability factor for social deficits commonly observed
in psychosis. However, the design of the study does not allow to differentiate social from generic
reward. Further research is needed to disentangle the relationship between social learning,
reward processing and risk sensitivity during social interactions.

Our findings are further limited by the use of a computer algorithm for the role of the trustee,
rather than a real human partner. The manipulation check showed that there were individuals
in both groups who had doubts as to whether they were playing with a real human partner.
This might have affected the mentalizing operations during the game. However, we chose not to
exclude these subjects from our sample, in order to avoid data loss. Future studies should focus
on trust game fMRI paradigms with real human partners.

In conclusion, this study provides new evidence for diminished caudate, insula and putamen
signals in response to beneficial social interaction in siblings of patients with psychosis. This may
be related to the reward and salience deficits commonly observed in psychosis, and indicates
that aberrant neural social reward processing reflects, at least in part, vulnerability for psychosis.
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Chapter 6
General discussion
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 2a 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 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 a 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 is 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
REFERENCES

SUMMARY

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

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

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

Chapter 2b compares the associations of peer nominated vs. self-reported victim status with non-clinical psychotic experiences in young adolescents. Secondly, the relationship between the five types of self-reported bullying victimization (i.e. direct relational, indirect relational, physical, verbal and possession-directed victimization) and non-clinical psychotic experiences is also investigated in these adolescents. Previous research suggests that bullying victimization is related to psychosis, but only self-report measures of victimization have been used up to now. We were the first to implement a combination of standard self-report and peer nomination procedures in the assessment of victimization. In order to test for a group effect on non-clinical psychotic experiences, the sample (N=724) was split into four groups: exclusively self-reported victims, self- and peer-reported victims, exclusively peer-reported victims, and non-victims. Secondly, the relation between the different types of victimization and non-clinical psychotic experiences was examined by a regression analysis. Self-reports of direct relational, indirect relational and physical victimization significantly improved the prediction of non-clinical psychotic experiences. Verbal and possession-directed victimization did not have a significant
predictive value. In our main analysis, we found that self-reported victims, as well as self- and peer-reported victims, scored higher than peer-reported victims and non-victims on non-clinical psychotic experiences. This implies that the association between victimization and non-clinical psychotic experiences is only present for self-reported victimization, possibly indicative of an interpretation bias. The observed discrepancy between self-report and peer-report highlights the importance of implementing a combination of both measures for future research.

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

Chapter 4 investigates the underlying neural basis of diminished trust in psychosis. Trust is an inherently rewarding aspect of successful social interactions, and has not been investigated in real-time interactions in a sample of patients with psychosis up to now. Functional magnetic resonance imaging data was acquired from 20 patients with non-affective psychosis and 20 healthy individuals during two multi-round trust games with anonymous counterparts. The participants played the part of the investor, and their counterparts were designed to appear cooperative in one game and unfair in the other game. At the behavioural level, age was found to be linked to higher trust at the beginning and enhanced trust levels during cooperative social encounters. There was also a connection with unfairness: The higher the age, the more trusting behaviour declined during unfair social encounters. The whole-brain correlational analyses revealed three important findings. First, there was increased age-related activation in three brain regions implicated in mentalising, i.e. the temporo-parietal junction and the posterior cingulate gyrus and precuneus. Secondly, the orbitofrontal cortex and caudate nucleus, both reward-related brain regions, showed decreased activation with age during cooperative interactions. Third, age-related increases were found in terms of activation in the anterior cingulate, which is implicated in conflict monitoring, in response to deception. This provides evidence for age-related increases in trust and cooperation, possibly driven by increased activation in mentalising related brain areas. The link between reduced reward-related brain activation and higher age might be interpreted as a general tendency to expect trust from the social environment. Age-related increases in neural conflict monitoring might be required to adapt such pro-social tendencies to the partner’s real cooperativeness.

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

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

Paula Marie Gromann was born on September 28th 1983 in Berlin, Germany. In 2003, she graduated from secondary school (Abitur). In 2004, she moved to the Netherlands to study Psychology at Maastricht University where she received a Bachelor of Arts in Cognitive Psychology in 2007. Next, she started the Research Master 'Cognitive and Clinical Neuroscience, Specialization Psychopathology'. During her master studies she spent eight months conducting her master and minor thesis research at the Cognition, Schizophrenia and Imaging Lab at the Institute of Psychiatry at King’s College London, U.K. During that time, she also conducted a clinical internship at the National Psychosis Unit “Fitzmary II” of the Bethlem Royal Hospital, London. In September 2009, she received her Master’s degree (cum laude). She spent the following six months continuing to work with her co-promotor Dr. Sukhi Shergill at the Cognition, Schizophrenia and Imaging Lab at the Institute of Psychiatry. In April 2010, she transferred to Amsterdam to officially start her PhD and work with her promotor prof. dr. Lydia Krabbendam at the department of Educational Neuroscience of the VU University Amsterdam. From September 2011 until September 2013, Paula was a member of the Research Master Educational Committee, which is aimed at improving the research master education of the Faculty of Psychology and Education of the VU. In 2012 and 2013, she discovered her passion for teaching during her work as a co-organizer of the VU honours course “Current Issues in Psychopathology”. From 2016 to 2018, Paula developed her teaching skills further during her work as a research method and statistics teacher for the Psychology bachelor programme of the VU. Additionally, Paula has been working as a freelance researcher since 2016.
PUBLICATIONS


