Chapter 1

General introduction

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 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's 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 being 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 strangers' 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 the important role 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 psychopathogies [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 a 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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