Exploring pathways to psychosis:

Childhood trauma as the invisible backpack

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Colofon

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Routekaart naar psychose:
trauma in de kindertijd als de onzichtbare rugzak
(met een samenvatting in het Nederlands)

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Promotor: Prof. dr. I.E.C. Sommer

Voor mijn ouders
Voor Tim en Daaf

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Europe

This is where it all began: the Netherlands. Where I was born and raised, and performed my bachelor, master and PhD. All research data described in this dissertation were also collected here. Europe therefore illustrates the introduction of my thesis. From here, we venture out to other continents.

CHAPTER 1

General introduction

Dr. Rosen: You can't reason your way out of this!
Professor Nash: Why not? Why can't I?
Dr. Rosen: Because your mind is where the problem is in the first place.

- A Beautiful Mind -

During my first year of college, there was an assignment about the movie entitled *A Beautiful Mind* (Grazer et al., 2001). This is when I first learned about schizophrenia as a psychiatric disorder. Based on the biography by Sylvia Nasar, this movie depicts the life of mathematician John Nash. He was a professor at Princeton and made several groundbreaking contributions to game theory. At the same time, he struggled with schizophrenia for much of his adult life. The quotation above is from dr. Rosen, John's treating psychiatrist, and illustrates the problem that patients face during a psychotic episode: losing contact with reality. In the case of John Nash, this meant hearing voices that were not there and seeing people that others did not see.

I have asked myself many times what it must be like to have a vivid perception of something that is not present. This has inspired my interest in the topic of psychotic experiences and still motivates me up till this day to investigate which factors are involved. In my research, I have focused on the period that forms an important starting point for the rest of one's life: our childhood. This first chapter will introduce traumatic events during childhood as an important risk factor for the development of psychotic experiences later in life. This theoretical background provides a framework for understanding the aim of this dissertation: exploring the different pathways that link childhood trauma to psychosis.

Schizophrenia

Schizophrenia is a psychiatric disorder that has a severe impact on the lives of patients and the people close to them. The annual incidence of schizophrenia averages 15 per 100,000 and the risk of developing the illness over one's lifetime is around 0.7% (Tandon et al., 2008), with higher incidences in large cities. Men are more likely to develop schizophrenia than women, with a male–female relative risk of 1.4 (Aleman et al., 2003; McGrath et al., 2004). The onset is typically in adolescence or early adulthood, although it is frequently preceded by subclinical symptoms that can already be observed many years before the illness onset (Owen et al., 2016).

Schizophrenia is characterized by the impairment of a person to be in contact with reality, to think clearly, to respond emotionally, and to behave in a

way that is appropriate in society. Diagnosis is made clinically, by following criteria such as described by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, American Psychiatric Association, 1994).

The clinical symptoms can be divided into three clusters: positive, negative and cognitive symptoms. Positive symptoms refer to thoughts, perceptions and behaviors that are ordinarily absent, including hallucinations (hearing, seeing, tasting, feeling, or smelling things that others do not experience) and delusions (false beliefs based on misinterpretations of reality). Negative symptoms, on the other hand, describe the absence of normal emotional function or behaviors. These include reduced motivation, lack of energy, anhedonia, diminished expression of emotions and social avoidance. This classic division into positive and negative symptoms already originates from the 1980s (Andreasen & Olsen, 1982). However, it is now well-established that cognitive dysfunction also constitutes a core component of schizophrenia (Kahn & Keefe, 2013), referring to the loss of intellectual abilities such as thinking, remembering, and reasoning. The positive symptoms are thought to relapse and remit, while the negative and cognitive symptoms are often more chronic and difficult to treat. Importantly, cognitive functioning is found to predict long-term functional outcome (Green et al., 2004; Emsley et al., 2008).

Despite the fact that these three symptom clusters provide a useful framework for structuring the clinical and scientific evaluation of schizophrenia symptoms, it has also been recognized that the term 'schizophrenia' has poor reliability and validity - two individuals can receive the same diagnosis while they do not have a single symptom in common (Read et al., 2004). Patients vary widely in their disease course, response to treatment, and outcome. It can therefore be more informative and productive to investigate specific symptoms, instead of focusing on heterogeneous diagnostic categories such as schizophrenia (Beavan et al., 2011). Importantly, psychotic symptoms also emerge in other psychiatric diagnoses, such as bipolar disorder, borderline personality disorder and post-traumatic stress disorder (PTSS) (Lindley et al., 2000; Sommer et al., 2012). Somatic or neurological disorders can also present with psychotic symptoms, including hearing loss, Parkinson's disease and Alzheimer's dementia (Sommer et al., 2012; Linszen et al., 2016; Schutte et al., submitted). Moreover, the significance of psychotic experiences goes beyond psychopathology as they also occur in the general population, albeit in an attenuated form. Psychotic experiences have therefore been described in terms of a psychosis continuum: ranging from benign and/or transient experiences in non-clinical individuals on one end, to the clinical psychotic symptoms observed in patients on the other end (Van Os et al., 2009).

Psychotic experiences in non-clinical individuals

The popular notion that psychotic experiences are rare and invariably indicative of 'madness' has been often disproven, as it is estimated that they occur in more than 7% of the general population (Beavan et al., 2011; Linscott & van Os, 2013). Some individuals even have these psychotic experiences on a frequent basis. Our research team has studied these non-clinical individuals, as they form an important possibility to evaluate the psychological, social and biological factors of psychotic experiences in the absence of medication effects and comorbidities (Sommer et al., 2010). This non-clinical group is mainly characterized by auditory verbal hallucinations, also described as 'hearing voices': the phenomenon of hearing a voice in the compelling sense of reality, while there is no corresponding external stimulus. These individuals present with additional characteristics that indicate a general increase in schizotypal and delusional tendencies, such as elevated levels of suspicion, a tendency for magical ideation as compared to controls and some degree of formal thought disorder (Sommer et al., 2010). Notably, they do not have a need for treatment and function well on both social and professional levels, thereby not fulfilling criteria for schizotypal personality disorder.

When comparing the phenomenological characteristics of auditory verbal hallucinations between these non-clinical individuals and patients with a psychotic disorder, similarities are found with regard to the perceived location of the voices, volume, personification (attribution to a real, familiar person) and the number of different voices (Daalman et al., 2011). Important differences are also observed, as non-clinical individuals start hearing voices at a younger age and hear voices less frequently. Moreover, patients appraise their voices as more malevolent, powerful, dangerous and uncontrollable and are typically more distressed by their voices (Brett et al., 2014; Honig et al., 1998). It is still a debated issue to what extend these auditory verbal hallucinations indeed confer the same phenomenon in non-psychotic individuals as in patients. However, these non-clinical individuals offer an interesting opportunity to study psychotic experiences in the absence of confounding factors inherently related to psychopathology, as they are not burdened by negative symptomatology, do not use anti-psychotic medication and have no history of hospitalization. Research has shown that these individuals indeed share some vulnerability factors that have been observed in patients, including genetic loading and environmental risk factors such as childhood trauma (Sommer et al., 2010; Kelleher & Canon, 2011). Studying non-clinical individuals alongside patients will not only improve our understanding of the etiology of psychotic experiences, but also provides more insight in the important question why some individuals pass the psychosis threshold while others do not. This may provide leads for protective or compensational factors, such as cognitive talents and social support.

Origins of psychosis

During the past decades, scientific literature has accumulated on the potential causal factors of psychosis. Schizophrenia has long been considered a disease of genetic origin. Genetic and twin studies have shown that genetic liability indeed contributes substantially to the risk of developing schizophrenia, with an estimated heritability rate around 70% (Sullivan et al., 2003; Lichtenstein et al., 2009). However, this estimation also indicates that a significant proportion of the liability for psychosis can be explained by environmental factors, which can add to and interact with genetic factors (gene-environment interactions). During the past twenty years, a growing body of literature has examined the role of social and environmental factors in the etiology of schizophrenia and psychotic experiences. A number of risk factors have been identified, such as immigration, urbanicity, drug abuse, pre- and perinatal infections, and adverse life events (McDonald & Murray, 2000; Begemann et al., 2016). The research described in this dissertation specifically investigated the role of negative events that one may encounter early in life: childhood trauma.

Childhood trauma as the invisible backpack

The word trauma stems from the ancient Greek word for wound (τραῦμα), referring to physical injury. Over time, the term also became used to describe the psychological and physical symptoms characterizing persons who had suffered from intensely distressing experiences. Childhood trauma is now used to capture different types of trauma including physical, sexual, and emotional abuse as well as emotional and physical neglect. There are other forms of childhood adversity, such as parental loss, separation and bullying. However, childhood trauma appears to have a particularly large and long-lasting impact – especially when induced by a perpetrator with an intention to harm (Morgan et al., 2005; Schreier et al., 2009; Van Dam et al., 2015).

Up to 15% of the children growing up in high-income countries worldwide are exposed to a form of childhood trauma (Gilbert et al., 2009). The negative consequences of childhood trauma can have a life-long impact on those who experienced this, the people close to them and society in general. Research shows that childhood trauma is associated with reduced social and professional functioning during childhood and later in life (Nelson et al., 2002). Moreover, it is a risk factor for most psychiatric disorders (MacMillan et al., 2001; Teicher & Samson, 2013; Varese et al., 2012): even when controlling for other psychosocial variables, childhood trauma has been associated with the development of post-traumatic stress disorder (PTSD), depression and anxiety disorders, eating

disorders, dissociative disorders, personality disorders, drug and alcohol abuse and, at the center of this dissertation, psychosis.

It has been estimated that patients with a psychotic disorder are almost three times more likely to have been exposed to childhood trauma than controls (OR 2.7, 95%CI=1.90–3.88) (Varese et al., 2012). Childhood adversity is also more prevalent in individuals with an ultra-high risk for developing psychosis (Kraan et al., 2015). In addition, our group previously showed that non-clinical individuals with frequent psychotic experience also report high rates of trauma exposure which are notably similar to patients with a psychotic disorder (Daalman et al., 2012). Moreover, longitudinal studies have shown that children who were exposed to maltreatment were more likely to report psychotic symptoms at a later age even after adjusting for a wide range of confounding variables, including gender, socioeconomic deprivation, IQ and genetic liability to developing psychosis (Arseneault et al., 2011). These findings indicates that childhood trauma is an important risk factor for the full continuum of psychotic experiences.

The pathways from childhood trauma to psychosis

While much research has been devoted to uncovering the causal nature of childhood trauma in the development of psychotic symptoms, the underlying mechanisms have only partly been illuminated. Notably, only a minority of maltreated children eventually develops psychotic experiences, which may or may not be part of a psychotic disorder. Studying potential mediating factors can lead to valuable progress in our understanding of how childhood trauma increases the risk for developing psychotic experiences later in life, which is necessary for improving prevention and treatment strategies. While previous studies have typically studied patient samples, it is fundamentally important to investigate these potential mechanisms across the continuum. This way, we can address the trivial question of why some individuals pass the psychosis threshold, while others do not.

The research presented in this dissertation aims to investigate the pathways by which childhood trauma is linked to psychotic experiences. We evaluated these associations in a cross-sectional sample covering the proposed continuum of psychosis: patients with a psychotic disorder, non-clinical individuals with frequent psychotic experiences and individuals without these experiences. To explore different pathways, we have used various methods that will be described below.

Childhood Trauma Questionnaire

In all studies, childhood trauma severity was assessed by the Childhood Trauma Questionnaire - Short Form (Bernstein et al., 2003). This 25-item version was derived from the original 70-item CTQ (Bernstein & Fink, 1998; Bernstein et al., 1994).

The self-report questionnaire can be filled in within five minutes. Five different subtypes are measured: sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect. It is important to note that childhood trauma is a subjective experience, and individuals with psychiatric symptoms might recall negative events differently compared to individuals without psychopathology. However, previous studies have established the validity of the CTQ-SF in comparison with psychiatrist-led interviews (Bernstein et al., 1997; Spinhoven et al., 2014; Thombs et al., 2009). Moreover, good internal consistency and reliability has been demonstrated in both clinical (Bernstein et al., 2003) and community samples (Scher et al., 2001). The CTQ-SF therefore constitutes a useful tool for research projects in its simplicity and robustness.

Personality

Neuroticism is one of the five distinguished personality traits, and can be described as a proneness to emotional instability and to experience anxiety, fear, and sadness (McCrae & Costa, 2005). Epidemiological data has shown that neuroticism is an important vulnerability factor for the development and outcome of psychotic experiences (van Os & Jones, 2001; Krabbendam et al., 2002; Goodwin et al., 2003). Patients with a schizophrenia spectrum disorder who display high levels of neuroticism, have more severe positive symptoms and adopt an avoidant coping style when under stress (Lysaker et al., 2003, 2007). Neuroticism has also been linked to psychotic experiences in non-clinical individuals (Wiltink et al., 2015). Importantly, patients with schizophrenia with a history of abuse show higher levels of neuroticism compared to patients without such a history (Lysaker et al., 2001). Neuroticism could therefore be a mediating factor in the association between childhood trauma and psychotic experiences.

This was investigated in **chapter 3**, using the revised NEO Personality Inventory (McCrae et al., 2005). This is a self-report questionnaire with 240-items, evaluating five different personality dimensions: Openness to Experience, Conscientiousness, Extraversion, Agreeableness, Neuroticism (also referred to as OCEAN). It is a reliable and valid instrument for use in non-clinical individuals as well as patients (Costa & McCrae, 2008; Conner et al., 2004; Bohlmeijer et al., 2011).

Cognitive functioning

Patients with a psychotic disorder show moderate-to-large deficits across multiple cognitive domains compared to healthy individuals (Reichenberg & Harvey, 2007), including distractibility, problems with executive functioning, reduced working memory and lower speed of processing. Although smaller in magnitude, reduced cognitive functioning has also been observed among

individuals at high risk for developing a psychotic disorder (Fusar-Poli et al., 2012; Agnew-Blais & Seidman, 2013) and non-clinical individuals with psychotic experiences (Daalman et al., 2011). Childhood trauma has also been linked to reduced cognitive functioning, in both children and adults (Aas et al., 2012). Therefore, cognition may be an important pathway between childhood trauma and psychotic experiences.

In **chapter 4**, we studied the associations between childhood trauma and cognitive functioning in non-clinical individuals with frequent psychotic experiences, to avoid disease-related confounding factors. Various neuropsychological tests were administered in a fixed order, covering different cognitive domains that are often affected in patients with a psychotic disorder, as described in Box 1:

Executive functioning and working memory
Stroop Colour-Word Task (time Card 3 minus time Card 2: Stroop, 1935).
Backward digit span-task (WAIS III subtask: Wechsler, 1997).

Attention
Forward digit-span task.

Memory
California Verbal Learning Test (CVLT: Delis et al., 1987; Dutch VLGT: Mulder et al., 1996). Complex Figure of Rey-Osterrieth (recall: Knight & Kaplan, 2003).

Processing speed
Stroop task (time Card 1, time Card 2).

Spatial ability
Complex Figure of Rey-Osterrieth.

Lexical access and abstract reasoning
Vocabulary test and similarities test (WAIS III subtask: Wechsler, 1997)

Verbal fluency
Controlled Oral Word Association Test (COWAT: Lezak et al., 2004).

Verbal IQ
National Reading Test for Adults (NART: Crawford et al., 1989, Blair & Spreen, 1989; Dutch NLV: Schmand et al., 1992) .

Magnetic Resonance Imaging

Since the advent of modern neuroimaging techniques, the neuroanatomical underpinnings of psychosis are becoming increasingly illuminated. A large meta-analysis showed that patients with schizophrenia show intracranial (2%) and total brain (2.6%) volume reductions (Haijma et al., 2013). The most pronounced reductions were found for gray matter structures, which were associated with longer duration of illness and higher dose of antipsychotic medication. These deviations are already present at disease onset and have even been demonstrated in individuals at ultra high risk (UHR) for psychosis. Notably, childhood trauma has a negative impact on the developing brain, which could subsequently increase the risk for psychiatric illness.

We investigated the neurobiological correlates of childhood trauma by evaluating gray matter volume in **chapter 5**. Structural Magnetic Resonance Imaging (sMRI) is a non-invasive technique to measure brain structure. By making use of magnetic fields, radio waves and field gradients, an MRI scanner can generate structural images (anatomy) of the brain. All participants were scanned on the same 3T Philips Achieva medical scanner, equipped with an 8-chanell SENSE headcoil (Philips, Best, The Netherlands), placed in the University Medical Center Utrecht.

Stressful events later in life

Individuals with a history of childhood trauma have an increased risk for being exposed to additional traumatic events later in life (Acierno et al., 1999; Kim et al., 2014). In patients with schizophrenia, both major life events and subjective experiences of stress have proven to be predictive for poor clinical outcome (Malla and Norman, 1992). We therefore evaluated if stressful events encountered later in life could be a potential pathway linking childhood trauma to psychotic experiences.

In **chapter 6**, the Life Stressor Checklist Revised (LSC-R; Wolfe et al., 1996) was used to evaluate the role of stressful life events that are encountered after childhood. This is a self-report questionnaire that is composed of 26 items (yes/no). For each endorsed event, follow-up questions address the age at which the event took place and to what extend the event still had had impact on the participants life during the past year. When applicable, two additional questions evaluate whether participants had believed they were in danger and whether they had experienced feelings of helplessness.

Itinerary

The general introduction and the methods presented in this first chapter will hopefully encourage readers to further travel the road from childhood trauma to psychosis, by reading the chapters that follow. Conducting this research and writing this dissertation was a personal journey. The end-point was clear: constructing a road map of the different potential pathways by which childhood trauma can be linked to psychotic experiences. This PhD project also provided me the opportunity to literally travel across the world. To give this dissertation a personal note, the individual chapters are therefore depicted as different continents, each with their own background story. Chapters 2 to 6 are research papers and can be read independently. All continents are depicted together on the world map in chapter 7, where the findings resulting from these papers are combined.

Part I of this dissertation addresses the finding that psychotic experiences are not only observed in patients with a psychotic disorder, but also in the general population. In **chapter 2**, we specifically reviewed studies on the **prevalence of auditory hallucinations** and combined their findings in meta-analysis to calculate the mean lifetime prevalence in the general population.
In part II, we explored potential pathways linking childhood trauma to psychotic experiences in clinical and non-clinical individuals. **Chapter 3** evaluated **neuroticism** as a potential pathway between childhood trauma and psychotic experiences. In **chapter 4**, we investigated the role of **cognition** in relation to trauma and psychotic experiences. **Chapter 5** assessed the associations between **brain structure**, childhood trauma and psychopathology. In **chapter 6**, childhood trauma and **stressful events later in life** were linked to psychotic experiences.

There will be different types of readers, including researchers, clinicians, and general readers such as relatives and friends. ***Researchers*** and ***clinical practitioners*** are advised to read the individual research papers as described in chapters 2 to 6. The results of these studies are summarized and discussed in chapter 7, together with methodological considerations and clinical implications. ***General readers*** are suggested to start with the summary in chapter 7, or chapter 8 which is written in Dutch and provides a short introduction to the subject of psychotic experiences trauma together with a summary of our main findings. When time allows, one can explore the individual research chapters that are outlined below to discover what a research paper entails. If anything, choose the continent that is most appealing to you.

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Australia

The program used to conduct the meta-analytic calculations described in this chapter is Comprehensive Meta-Analysis (CMA). I was granted the opportunity to follow an in-depth course on this program, which was held in Melbourne.

CHAPTER 2

Auditory hallucinations across the lifespan: a systematic review and meta-analysis

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Abstract

Background

Auditory hallucinations (AH) are nowadays regarded as symptoms following a continuum; from a (transient) phenomenon in healthy individuals on one end to a symptom of (psychiatric) illnesses at the other. An accumulating number of epidemiological studies focused on the prevalence of AH in the general population, but results vary widely. The current meta-analysis aims to synthesize existing evidence on lifetime prevalence of AH across the lifespan.

Methods

We conducted a quantitative review and meta-analysis according to PRISMA guidelines. Studies were combined to calculate a mean lifetime general population AH prevalence rate. Moreover, prevalences were calculated for four age groups: children (5-12 years), adolescents (13-17 years), adults (18-60 years) and elderly (≥60 years).

Results

We retrieved 25 study samples including 84 711 participants. Mean lifetime prevalence rate of AH was 9.6% (95%CI: 6.7%-13.6%). The mean lifetime prevalence was similar in children (12.7%) and adolescents (12.4%), but these two groups differed significantly from the adults (5.8%) and the elderly (4.5%). Significant heterogeneity indicated that there is still dispersion in true prevalence rates between studies, even within the different age categories.

Conclusions

Current meta-analysis shows that AH are quite common (up to one in ten individuals) in the general population during lifetime, with children and adolescents reporting these experiences significantly more often compared to adults and elderly. Large follow-up studies on the longitudinal course of AH are needed to reveal associated risk and resilience factors.

Introduction

The psychotic experiences that characterize schizophrenia spectrum disorders have previously been described in terms of a psychosis continuum, ranging from benign and/or transient experiences in non-clinical individuals on one end, to psychotic symptoms in patients on the other end (Johns & van Os, 2001; Larøi, 2012). Therefore, the meaning of psychotic experiences goes beyond psychopathology. Research has indeed shown that well-functioning individuals with frequent psychotic experiences share a wide range of risk factors with clinical patients with psychosis, including developmental and environmental factors (Kelleher & Cannon, 2011, Daalman et al., 2012). In turn, presence of psychotic experiences is suggested to be an important risk marker for early psychopathology, as young people with hallucinatory and/or delusional experiences report higher rates of non-psychotic symptomatology, including symptoms of depression (Kelleher et al., 2012b), suicide attempts (Sommer et al., 2010) and higher levels of thought disorder (Sommer et al., 2010). Moreover, well-functioning individuals with frequent non-clinical psychotic experiences also show vulnerability factors including high rates of childhood trauma, reduced brain volume and lower cognitive performance (Sommer et al., 2010; Kelleher & Canon, 2011; van Lutterveld et al., 2013; Begemann et al., 2016) similar to, but to a lesser degree than patients with a psychotic disorder.

Van Os and colleagues conducted a meta-analysis in 2009 to investigate the prevalence of psychotic symptoms in the general population, comprising hallucinations and delusions. They reported a median prevalence of 5.3%, which was mainly based on studies in adults. An update in 2013 by Linscott and van Os included additional studies on children and adolescents, showing a prevalence rate of 7.2%. Importantly, general psychotic experiences were found to be more common among younger individuals. Kelleher and colleagues (2012a) showed a higher median prevalence of 17% in children (9-12 years) compared to 7.5% in adolescents (13-18 years). A systematic review on the longitudinal course of general hallucinatory experiences during childhood and adolescence reported that discontinuation of hallucinatory experiences occurred in approximately 75% of the cases (person–year discontinuation 3% to 40.7% (Rubio et al., 2012). It has therefore been suggested that, while psychotic symptoms may be more commonly experienced during typical development as a child (van Os et al., 2009), these experiences become less frequent and increasingly indicative of pathology with advancing age (Kelleher et al., 2012b).

Next to the prevalence of general psychotic experiences, many epidemiological studies have specifically focused on the occurrence of auditory hallucinations

(AH). The number of studies evaluating the frequency of AH of young and adult populations has been rapidly accumulating during the past years. However, prevalence rates are found to differ greatly between studies (Beavan et al., 2011, de Leede-Smith & Barkus, 2013, Jardri et al., 2014). For example, Beavan and colleagues (2011) found rates varying between 0.6% to 84%, resulting in a median prevalence of 13.2% of AH in the general adult population. The authors reported that comparisons between studies were problematic given the different methodologies used. Several factors may be responsible for this high variance, such as the period over which presence of auditory hallucinations is assessed (last week, last month, last year, or lifetime), the type of questionnaire used (e.g. self-rated vs. interview-based, phrasing of questions), and age of the population studied. Following the high prevalence of psychotic experiences during childhood and adolescence, and the transient course of AH, it can be hypothesized that the prevalence of AH decreases after childhood.

To provide more insight in the occurrence of AH in the general population, aim of the current meta-analysis is to estimate the prevalence of AH across the lifespan by combining population-based samples, from childhood to old age. As age may be an important factor, the prevalence rates are also separately evaluated for different developmental groups: children, adolescents, adults and elderly.

Methods

Search strategy

This quantitative review was conducted following the guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (www.prisma-statement.org; Moher et al., 2009). A systematic search for relevant studies published in English peer-reviewed journals was performed in Pubmed, EMBASE, PsychINFO. The search cut-off date was January 31st, 2016. The following search terms were used: (prevalence OR prevalences OR prevalent OR epidemiology OR epidemiologic OR epidemiological) AND ("voice hearing" OR "hearing voices" OR "voice hearer" OR "AVH" OR "psychotic symptom" OR "psychotic symptoms" OR "psychotic experience" OR "psychotic experiences" OR "hallucination" OR "psychotic like" OR "psychosis like" OR "hallucinatory" OR "hallucinative" OR "hallucinatic" OR "hallucinoid"). In addition, review articles and eligible studies were examined for cross-references.

Eligibility criteria

To be eligible, the articles had to meet the following criteria:

1. Data were provided on the lifetime prevalence of auditory hallucinations, or suggested that this information was available
2. The included cohort was a general population sample

Study selection and data collection

Two reviewers (L.C. and E.T.) independently examined titles and abstracts of all retrieved articles to select potential eligible articles. If consensus was not reached, a third reviewer (K.M.) was consulted. For every eligible article, the corresponding author was contacted by email to ask for original or complementary data, so we were able to recalculate prevalence rates for the different developmental age groups when necessary. In case multiple publications were retrieved that described the same cohort, only the sample with largest overall sample size and/or original data was included. When an article reported data on different cohorts, each cohort was regarded as a separate study sample.

Several decisions were made to optimise uniformity between studies:

1) As the majority of studies provided self-report data, this was preferred over interviewer-rated data when both were reported in the article.

2) When prevalence rates were separately reported for 'conscious' vs. sleep and/or drug related AH, the first option was used.

3) The answering options 'certainly'/'definite'/'yes' were considered as positive for experiences of AH, while 'possible'/'probable'/'maybe' were considered as negative; this, in line with previous prevalence studies. Similarly, 'sometimes' and 'often/always' were both considered as positive for AH and therefore prevalence rates were summed when an article reported both options separately .

In five study samples, the authors designed their own questionnaire to evaluate the experience of AH (Verdoux et al., 1998; Yoshuzimi et al., 2004; Polanczyk et al., 2010; de Loore et al., 2011; Knobel et al., 2012). Four out of five screening questions were rather similar, specifically assessing AVH (Have you heard voices that other people cannot hear? Have you ever heard or are you currently hearing somebody's voice that no one around can hear? Have you ever heard voices other people cannot hear?), while the fifth evaluated auditory hallucinations in general (Do you have any noises in your ears or head?). These questionnaires were all grouped into one category termed 'designed by author'.

Data analysis

First, our aim was to calculate a weighed mean lifetime prevalence rate of AH in the general population. Therefore, we derived sample size and prevalence rate for each study sample. Second, we evaluated the specific prevalence rates within four different developmental age groups: children (≤12 years), adolescents (13-17 years), adults (18-60 years) and elderly (≥60 years) (Kelleher et al., 2012b). When the age range of an included cohort cut across the aforementioned developmental age ranges, original data were used to split the sample accordingly; sample size and prevalence rates were recalculated for each of the proposed age groups.

Studies were combined in meta-analysis to calculate a pooled estimate of general lifetime prevalence of AH in the general population. A random effects model was deemed most appropriate for this research area given the heterogeneity in applied methods (Borenstein et al., 2009). In random-effects meta-analysis, the observed effect size is expected to vary to some extend from study to study. To determine whether the observed variation falls within the range that can be attributed to sampling error or whether the variation reflects differences in true effect sizes, we assessed heterogeneity using the Q-statistic and the I^2-statistic (Borenstein et al., 2009). The Q-statistic tests the null hypothesis, stating that all studies in the analysis share a common effect size. If all studies shared the same effect size, the expected value of Q would be equal to the degrees of freedom (the number of studies minus 1). In addition, I^2 was calculated which indicates the proportion of the observed variance reflecting differences in true effect sizes rather than sampling error. Moreover, it is important to investigate potential outlier studies, defined as standardized residual z-scores of effect sizes exceeding ± 1.96 (p<.05). All calculations were executed using Comprehensive Meta-Analysis version 2.0 (www.meta-analysis.com) (Borenstein et al., 2005; Borenstein et al., 2009).

Results

Twenty-seven articles investigating the prevalence of AH in the general population were retrieved from the literature search. Six of these eligible publications described overlapping cohorts of which three articles with the smallest sample size were excluded (Lataster et al., 2006, Shevlin et al., 2011, Alsawy et al., 2015). One article investigated two different study populations (Wigman et al., 2011), which were entered as separate study samples. Therefore, twenty-five study samples were included with a total number of 84 711 participants. See the PRISMA flowchart (Figure 1) for the study selection process.

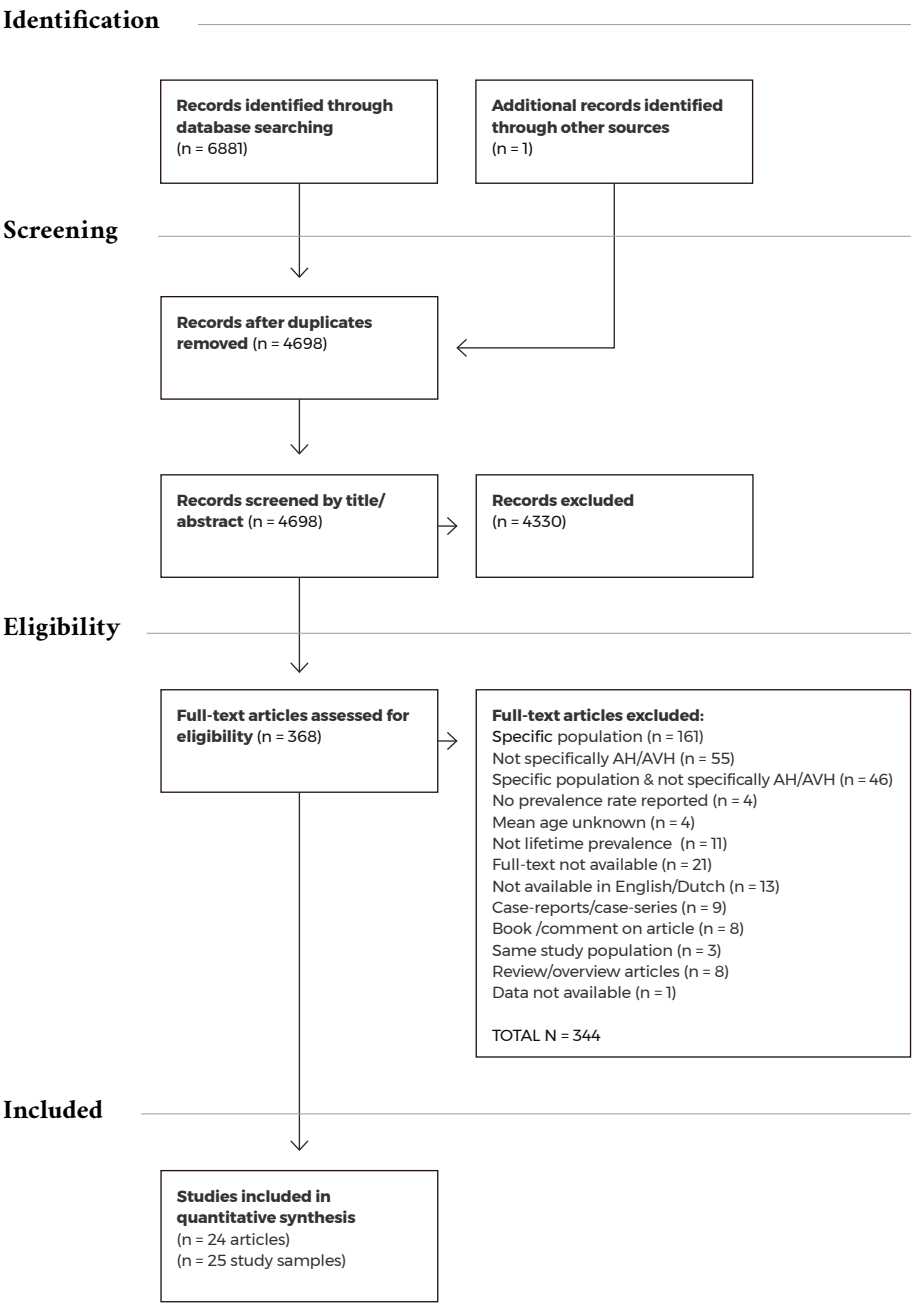

Figure 1. PRISMA Flow Diagram of the performed literature search.

Table 1 shows an overview of all 25 included study samples with calculated lifetime prevalence rates. We received original data from 19 of the 25 included study samples. The age range of four study samples without original data exactly fell within the proposed age groups, while two study samples (Mamah et al., 2012 and 2013) did not. These two samples were designated to one age category based on the mean age of the study sample.

General prevalence of AH

Including the prevalence rates of all 25 study samples, the pooled estimate of prevalence was 9.6%, with the 95% confidence interval (95%CI ranging from 6.7% to 13.6% , n=84 711). The Q and I^2 statistic both showed heterogeneity, $Q(24)=6672.47$, $p<.001$, $I^2=99.64\%$, indicating that the true prevalence will vary between studies. Indeed, the prevalence rates of the individual study samples ranged between 2% and 37.5%. No outliers were detected.

Developmental age categories: children, adolescents, adults and elderly

To evaluate whether prevalence rates differed between different age groups, the study samples were divided into four developmental age categories. This resulted in 36 study subsamples: nine subsamples evaluating AH in children ≤12 years; thirteen adolescent subsamples of 13–17 years; nine subsamples evaluating adults aged 18–60 years and five subsamples on individuals aged ≥60 years.

Prevalence of AH was 12.7% in children (n=14 878; 95%CI: 8.1% to 19.3%; $Q(8)=1142.91$, $p<.001$; $I^2=99.30\%$), 12.4% for adolescents (n=33 033; 95%CI:8.3% to 18.1%; $Q(12)=1333.40$, $p<.001$, $I^2=99.18\%$), 5.8% for adults (n=27 375; 95%CI: 3.6% to 9.2%; $Q(8)=289.91$, $p<.001$; $I^2=97.24\%$) and 4.5% for the elderly (n=9 425; 95%CI: 2.5% to 8.1%; $Q(5)=204.73$ $p<.001$; $I^2=97.56$) (see Figure 2). Within each age subgroup analysis, the Q- and I^2-values remained high. Moreover, the pooled Q-value was evaluated to assess whether this grouping (children vs. adolescents vs. adults vs. elderly) could explain the variance in true effect sizes. The pooled Q-value was significant ($Q(32)=2970.94$; $p<.001$), also indicating that true variance remained even within the developmental age subgroups.

When comparing the prevalence rates between the four age categories, prevalence was found to significantly vary with age ($Q(3)=13.66$, $p=.003$). Post-hoc analysis showed that the prevalence rate in both children (12.7%) and adolescents (12.4%) was significantly higher compared to the adult prevalence of 5.8% ($z=2.39$; $p=.017$ and $z=2.44$; $p=.015$, respectively). Children and adults also experienced more AH compared to the prevalence rate of 4.5% in the elderly ($z=2.76$; $p=.006$ and $z=2.81$; $p=.005$, respectively). The difference in prevalence in children vs. adolescents was not significant ($z=0.08$; $p=.094$), nor in adults vs. elderly ($z=0.66$; $p=.512$).

Table 1. Overview of the included studies and calculated lifetime prevalences

Study sample	Prevalence (%)	Sample size	Continent	Mean age (years)	Age range (years)	Questionnaire	A(V)H
Eaton et al., 1991,*	5.3	3543	Europe	33.7	18-96	DIS(C)/ - interview	AVH
Verdoux et al., 1998*	19.3	457	Europe	56.8	18-93	Designed by author – self-report	AVH
Yoshizumi et al., 2004	15.8	380	Japan	11.6	11-12	Designed by author – self-report	AVH
Kessler et al., 2005*	8.3	2349	North America	44.3	18-95	CIDI 3.0 - interview	A(V)H
Shevlin et al., 2007*	4.8	5907	North America	32.0	15-59	CIDI - interview	A(V)H
Pearson et al., 2008	33.4	500	Europe	14.8	14-15	HQ - self-report	AVH
Scott et al., 2008*	3.5	2534	Australia	19.9	18-23	CIDI - interview	A(V)H
Yung et al., 2009	29.8	875	Australia	15.6	13-18	CAPE - self-report	AVH
Polanczyk et al., 2010	4.2	2127	Europe	12.0	12	Designed by author - self-report	AVH
Barragan et al., 2011	37.5	777	Europe	14.4	13-17	CAPE - self-report	AVH
De Loore et al., 2011	5.3	2100	Europe	14.3	13-16	Designed by author - self-report	AVH
Nakazawa et al., 2011	10.3	4864	Japan	13.8	12-15	DIS(C) - self-report	AVH
Wigman et al., 2011-I	9.0	1643	Europe	10.8	10-12	CAPE - self-report	AVH
Wigman et al., 2011-II*	22.2	4550	North America	13.9	12-16	CAPE - self-report	AVH
Knobel et al., 2012*	2.0	733	South America	9.8	5-16	Designed by author - interview	AH
Laurens et al., 2012	35.1	7780	Europe	9.9	9-11	DIS(C) - self-report	AVH
Mamah et al., 2012	6.9	2627	Africa	18.5	14-29	mPRIME - self-report	A(V)H
Mamah et al., 2013	12.7	1199	Africa	13.0	8-19	CIDI - self-report	A(V)H
Cederlöf et al., 2014	4.3	5343	Europe	15.9	15-18	DIS(C) - interview	AVH
Soares et al., 2014	7.5	1124	South America	70.8	≥ 60	CAMDEX- interview	AH
Adriaanse et al., 2015*	10.3	702	Europe	13.2	9-15	K-SADS - self-report	AVH
Dolphin et al., 2015*	13.7	5867	Europe	15.0	12-19	APSS - self-report	AH
Kompus et al., 2015*	10.6	9646	Europe	16.9	16-19	LSHS - self-report	AVH
Kråkvik et al., 2015*	6.8	2533	Europe	49.6	19-96	LSHS - self-report	AVH
Sharifi et al., 2015*	2.1	14551	North America	49.5	18-92	DIS(C) - interview	AVH

Note. *studies for which prevalence rates were recalculated based on original data. A(V)H=Auditory (verbal) hallucinations; DIS(C)=Diagnostic Interview Schedule (Child); CAPE=Community Assessment of Psychic Experiences; CIDI=Composite International Diagnostic Interview; K-SADS=Kiddie-Schedule for Affective Disorders and Schizophrenia; HQ=Hallucination Questionnaire; LSHS= Launay-Slade Hallucinations Scale; APSS=Adolescent Psychotic-Like Symptom Screener; mPRIME=; CAMDEX=Cambridge Mental Disorders of the Elderly Examination

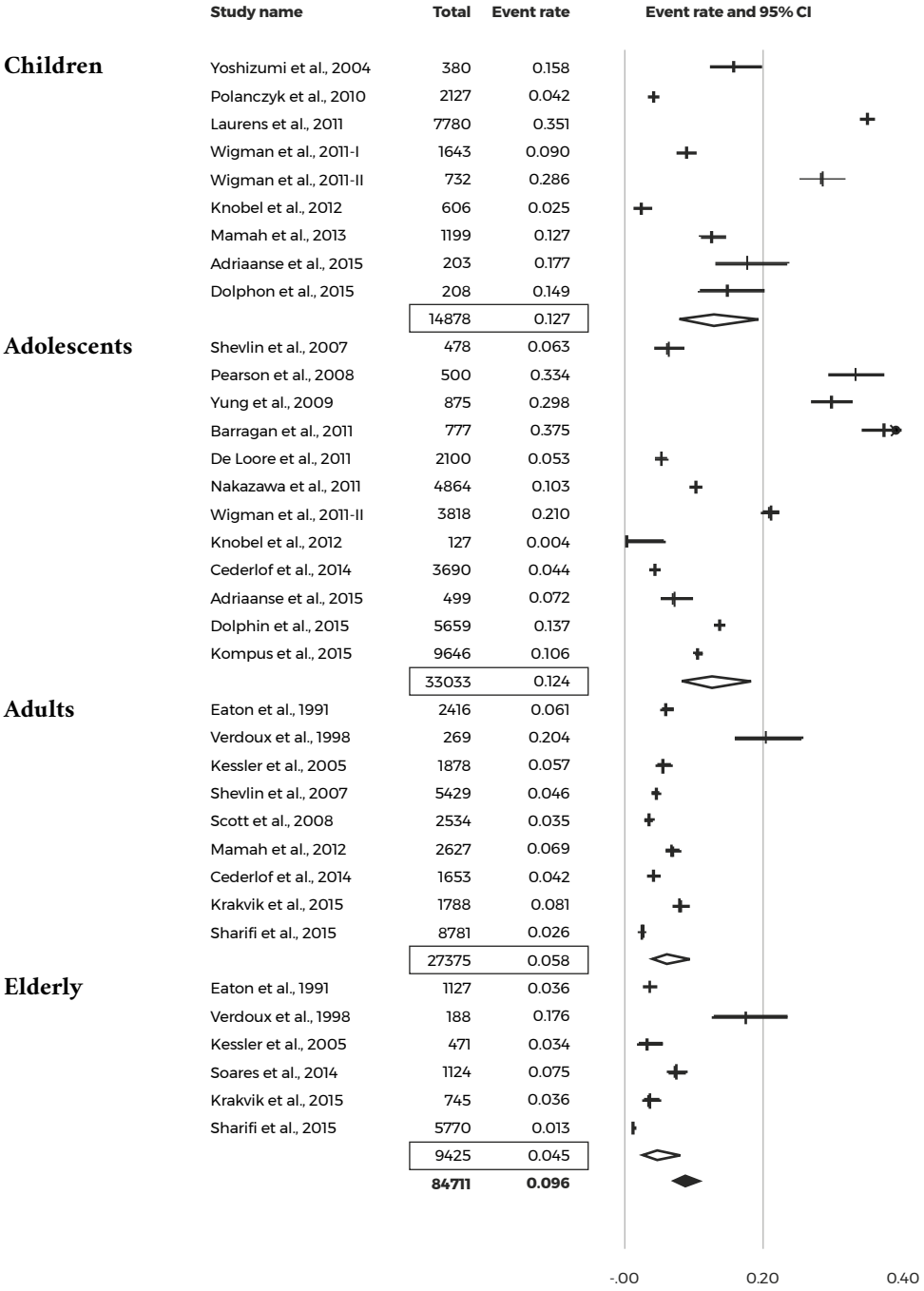

Figure 2. Prevalence of AH in the different developmental age groups.

Discussion

Current meta-analysis included 25 study samples evaluating the prevalence of AH in the general population across the lifespan, with a total of 84 711 participants. We found a mean prevalence rate of 9.6% (95%CI: 6.7% to 13.6%). When evaluating different age groups, the mean lifetime prevalence of AH was similar in children (12.7%) and adolescents (12.4%), but these two groups differed significantly from adults (5.8%) and elderly (4.5%).

Decreasing trend in lifetime prevalence

Our results suggest that AH are quite prevalent in children and adolescents, with more than 1 in every 10 individuals reporting these experiences. After adolescence, this prevalence rate decreases by half. When assessing lifetime prevalence numbers however, one would expect a general increasing trend with older age as a result of cumulative experiences over the years. Our data did not reflect such a trend. It could well be the case that lifetime prevalence estimates are biased downwards due to underreporting (McGrath et al., 2015), implicating the role of memory or recall bias. We speculate that AH at a younger age tend to be forgotten later in life, when infrequent and/or non-distressing. Indeed, AH are sporadic and simple in most cases as McGrath et al. (2015) showed that 64% of the participants with psychotic experiences only had these once to five times in their lives. Regarding distress, while only 15% of young children report suffering (i.e. fear, distress and/or dysfunction) from AH (Bartels-Velthuis et al., 2010), this percentage increases with age, up to 70% in the elderly (Tien., 1991).

It could also be that the common (and mostly transient) character of AH in childhood reflects typical development (van Os et al., 2009). The course of brain maturation starts during fetal development and continues into young adulthood (Toga, Thompson & Sowell, 2006). Gray and white matter studies show that the language areas mature around puberty (11 to 13 years; Gogtay et al., 2004). We hypothesize that immaturity of these areas might lead to a (transient) vulnerability for spontaneous, aberrant activity resulting in AH. The more advanced 'executive' functions, e.g. inhibition and source- and self-monitoring, mature later during late adolescence (Gogtay et al., 2004), and thereby the increasing ability to accurately interpret stimuli and phenomena such as inner speech during adolescence.

Accordingly, patients with a psychotic disorder but also healthy individuals with AH show reduced executive functioning (Aas et al., 2015, Begemann et al., 2015). While the common transient and 'benign' AH experiences in childhood (due to aberrant auditory stimuli or limited executive abilities) may decrease with age, the incidence of psychopathology-related AH is known to increase in adolescence

(Kelleher et al., 2012b; Schimmelmann et al., 2015), which could explain the relatively higher prevalence rates we found in both children and adolescents.

Methodological considerations

The *Q*- and I^2-values showed high heterogeneity within the mean lifetime prevalence estimate. While age was expected to be an explanatory factor, heterogeneity remained high within the different developmental age groups. This indicates that factors other than age are involved. One explanation could be the different questionnaires used in the separate studies. The 25 study samples used 11 different rating scales. When categorized by each of the different questionnaires, the mean prevalence ranged from 3.9 to 33.4%. Retrospectively, we quantitatively compared prevalence rates between scales but found that these differences did not reach significance ($Q(10)=8.850$, $p=.546$), suggesting that type of questionnaire is not an explanatory factor per se. When qualitatively evaluating the different questions used to screen for AH, almost half of the studies used identical phrasing even though different questionnaires were used (namely the DIS(C), KSADS, APSS and four out of the five 'designed by author' questionnaires). Moreover, the variety in definitions of AH does not seem to result in a specifically high or low prevalence.

For example, a broad definition like 'Do you have any noises in your ears or head' as applied by Knobel et al. (2012) yielded one of the lowest prevalence rates (2.0%), while Pearson et al. (2008) asked for specific forms of auditory hallucinations and found one of the highest prevalence rates (33.4%). Importantly, even when studies did use the same questionnaire, prevalence estimates also showed large variety. For example, three studies used the DIS(C) in a young population – while Cederlöf et al. (2014) found an interview-rated prevalence of 4.3%, self-reported prevalences were 10.3% and even 35.1% (Nakazawa et al., 2001; Laurens et al., 2012). This can partly be due to the observation that although the DIS(C) and CIDI are designed as interviews, these were also applied as self-report questionnaires in some studies.

Response rates could therefore be 'confounded' by the incapacity of distinguishing 'true' auditory hallucinations from other aberrant auditory perceptions, especially when using self-report questionnaires instead of interviews. However, self-report does not necessarily lead to higher estimates. A questionnaire such as the CAPE which is solely used as self-report, revealed both relatively low estimates (9.0% for Wigman et al., 2011-I) as well as relatively high estimates (22.2% for Wigman et al., 2011-II, 29.8% for Yung et al., 2009 & 37.5% for Barragan et al., 2011). This would suggest that neither type of questionnaire nor type of assessment (self-report vs. interview) explains the heterogeneity. Other factors than type of questionnaire or type of assessment, for example the setting of testing and the introduction of the test, are more likely to be of influence (Beavan et al., 2011). A

systematic evaluation of these methodological factors was not possible in current meta-analysis, given the large variety of applied methods compared to the relatively low number of studies in each developmental age group.

Future directions and implications for research

Our findings underline previous statements about the relatively common character of AH in the general population and can help in de-stigmatizing and normalizing these experiences in both young, adult and elderly populations (Beavan et al., 2011). Although there is abundant information on the prevalence of AH, only few studies provide longitudinal data, which is of great clinical relevance to AH experiences. Knowledge on which individuals with AH (eventually) warrant clinical care is needed to further develop prevention and early intervention strategies. Future studies should therefore include large follow-up datasets to allow a more detailed view on the course of AH with age and possible associated developmental risk and resilience factors.

Conclusion

The current meta-analysis shows that AH are quite common in the general population, with one in ten individuals reporting these experiences (mean prevalence 9.6%). Children (12.7%) and adolescents (12.4%) report significantly more AH compared to adults (5.8%) as well as elderly (4.5%). In order to support the development of prevention and intervention strategies, future large follow-up studies are needed to provide more details on the longitudinal course of AH and reveal concurrent risk and resilience factors.

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Asia

This chapter resulted from an international collaboration with the University of Hong Kong. I have travelled Asia many times and during the last phase of my PhD it was a great pleasure to actually visit Hong Kong for a Gordon Conference.

CHAPTER 3

Relationship between neuroticism, childhood trauma and cognitive-affective responses to auditory verbal hallucinations

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Abstract

Background

Neuroticism has been shown to adversely influence the development and outcome of psychosis. However, how this personality trait associates with the individual's responses to psychotic symptoms is less well known. Auditory verbal hallucinations (AVHs) have been reported by patients with psychosis and non-clinical individuals. There is evidence that voice-hearers who are more distressed by and resistant against the voices, as well as those who appraise the voices as malevolent and powerful, have poorer outcome. This study aimed to examine the mechanistic association of neuroticism with the cognitive-affective reactions to AVH.

Methods

We assessed 40 psychotic patients experiencing frequent AVHs, 135 non-clinical participants experiencing frequent AVHs, and 126 healthy individuals.

Results

In both clinical and non-clinical voice-hearers alike, a higher level of neuroticism was associated with more distress and behavioral resistance in response to AVHs, as well as a stronger tendency to perceive voices as malevolent and powerful. Neuroticism fully mediated the found associations between childhood trauma and the individuals' cognitive-affective reactions to voices.

Conclusions

Our results supported the role of neurotic personality in shaping maladaptive reactions to voices. Neuroticism may also serve as a putative mechanism linking childhood trauma and psychological reactions to voices. Implications for psychological models of hallucinations are discussed.

Introduction

Neuroticism is a personality trait characterized by emotional instability and proneness to experiencing anxiety, fear, and sadness (McCrae et al., 2005; McCrae & Costa, 1987). The association between neuroticism and mood disorders such as major depression and generalized anxiety disorder has been well established (Ormel et al., 2001; Kendler et al., 2006; Weinstock et al., 2006; Kotov et al., 2010). More recently, there has been an increase in evidence linking neuroticism with psychosis. Wiltink and colleagues (2015) reported a significant association between neuroticism and perceptual abnormalities in non-clinical adolescents, even after taking depression into account. Epidemiological data revealed that individuals with neuroticism are at increased risk of subsequently developing psychosis. This prediction remained significant even after adjusting for levels of anxiety and depression, supporting the argument for neuroticism as one of the vulnerability factors for psychosis (van Os et al., 2001; Krabbendam et al., 2002; Goodwin et al., 2003). Lysaker and colleagues (2003, 2007) found that patients with schizophrenia spectrum disorders who were high on neuroticism tended to have more severe positive symptoms, and to adopt an avoidant coping style when under stress.

Although there is rich evidence that neuroticism contributes to the development and outcome of psychosis in both clinical and non-clinical groups, how this personality trait associates with the individual's responses to specific psychotic symptoms is less well known. Auditory verbal hallucination (AVH) refers to the phenomenon where individuals report hearing voices, with a sufficient sense of reality, but without the presence of corresponding external stimulation (Anthony, 2004). These sensory experiences have been reported in patients with psychotic disorders, as well as other psychiatric disorders such as borderline personality disorder, bipolar disorder and severe mood disorders (Toh et al., 2015; Larøi et al., 2012). AVHs also occur in people without a psychiatric diagnosis, at a median prevalence rate of 13.4% (Beavan et al., 2011). Phenomenological studies have revealed similarities in physical characteristics of AVHs across clinical and non-clinical groups, such as the perceived location of the voices, volume, and number of voices (Daalman et al., 2011). However, there are important differences in both phenomenological characteristics and the individuals' reactions, too. Patients are more likely to attribute their voices to specific people or agencies, and to appraise voices as uncontrollable, malevolent, powerful and dangerous (Daalman et al., 2011; Lovatt et al., 2010; Honig et al., 1998; Brett et al., 2014). Patients are also typically more distressed by the voices than non-clinical voice hearers (Larøi et al., 2012; Daalman et al., 2011; Honig et al., 1998). The present

study aimed at examining the mechanistic association of neuroticism with the cognitive-affective reactions to AVH in clinical and non-clinical voice hearers.

In noise stress research, individuals high on neuroticism have been shown to be more emotionally aroused in noisy and stressful conditions, manifesting more anxiety and worry (Belojevic et al., 2003). When asked to perform mental tasks under a noisy condition, their performance was also more severely impacted than in non-neurotic individuals (Belojevic et al., 2003). This suggests that neuroticism enhances affective reactivity to stressors. Therefore, we hypothesized that neuroticism would predict a higher level of emotional distress and resistance in response to AVH. Furthermore, according to the cognitive model proposed by Birchwood and Chadwick (Birchwood et al., 2000, 2002), hallucinatory distress and behavioral resistance against voices is mediated by appraisal of voices as malevolent and powerful (Andrew et al., 2008). Since neuroticism is also characterized by a pervasive perception that the world is dangerous and threatening, and that one is unable to manage in face of challenges (Eysenck, 1947; Barlow et al., 2004, 2014), our second hypothesis was that neuroticism would predict a stronger tendency to appraise AVHs as malevolent and powerful.

Contrary to the historical view that neuroticism is fixed and genetically based, evidence of gene-environment interactions has raised the possibility that environmental factors, such as childhood trauma, may underlie the development of neuroticism (Jacobs et al., 2011; Li et al., 2014; Roy, 2002). It has been suggested that repeated exposure to aversive experiences may sensitize the individual into becoming more emotionally reactive (Kendler et al., 2004; Lanius et al., 2010; Figueiredo et al., 2003), purportedly by inducing a sense of unpredictability and uncontrollability (Barlow et al., 1991, 2004, 2014). In patients with schizophrenia, Lysaker et al. (2001) found that those who were exposed to childhood sexual abuse exhibited significantly higher levels of neuroticism than those who did not have a history of abuse. According to Birchwood et al. (2000), and Kilcommons and Morrison's cognitive models of AVH (2005), traumatic experiences may render an individual more vulnerable to negative schemas about the self, others, and the world, which may in turn influence his/her appraisals of AVH. In summary, childhood trauma has been shown to be associated with both neuroticism and cognitive-affective reactions to AVH. There is ample evidence supporting an association of childhood trauma with occurrence of psychosis (Varese et al., 2012; Kelleher et al., 2013; Janssen et al., 2004; Bebbington et al., 2004) and AVH (Bentall et al., 2012; McCarthy-Jones 2011; Read et al., 2005; Shevlin et al., 2007; Daalman et al., 2012). However, whether neuroticism mediates the link between childhood trauma and an individual's cognitive-affective reactions to AVH has not been tested directly. As emotional responses to and beliefs about voices are typical targets of cognitive

behavior therapy for psychosis, investigating the factors that maintain these reactions to AVH bears clinical importance.

In the current study, we will test whether there is an association in both clinical and non-clinical voice hearers, between level of neuroticism and level of emotional distress in response to AVH. We will also test the association between level of neuroticism and levels of perceived power and malevolence of AVH, as well as resistance against AVH. Finally, we will test if the level of neuroticism mediates the associations between childhood trauma and these cognitive-affective reactions to voices.

Methods

Research ethics for all methods involved in this study were approved by the Human Ethics Committee of the University Medical Center Utrecht. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Participants

The sample consisted of three groups of participants: psychiatric patients with persistent AVHs, participants from the general community who experienced persistent AVHs, and healthy controls without AVH. Part of this sample was shared with our previous studies (Daalman et al., 2012; Sommer et al., 2010), although analysis in relation to the current research questions has not been previously reported. All participants provided informed written consent for study participation. Clinical participants were recruited from the University Medical Centre Utrecht. Patients who received routine treatment for psychosis or second opinion on refractory psychosis in our clinic were invited to join the study. Inclusion criteria were as follows: age 18-65 years, and regular experience of AVHs for over a year. The Comprehensive Assessment of symptoms and History (CASH; Andreasen et al., 1992) was conducted by an independent psychiatrist to confirm psychiatric diagnoses and assess alcohol and substance use.

Non-clinical voice hearers were included in the study if they were 18-65 years old, experienced AVHs at least once a month, and did not meet criteria for any diagnosis on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; First, 1994) nor for a personality disorder as per SCID-II diagnosis (First, 1995). Healthy controls were included if they were 18-65 years old, reported absence of AVH experience, and did not meet criteria for any DSM-IV (axis 1 or 2)

diagnosis. For all three groups, participants were excluded if they had alcohol or substance dependence.

The two non-clinical groups were recruited and identified according to the following steps. Firstly, individuals who visited a Dutch mental health website "Explore Your mind" (www.verkenuwgeest.nl) were invited to fill out a self-test on AVH. This self-test was based on the Launay and Slade Hallucinations Scale (LSHS; Larøi et al., 2004). Individuals who scored a total of 7 or above on two LSHS items ("In the past, I have had the experience of hearing a person's voice and then found that no one was there" and "I have been troubled by voices in my head"), and those who scored 0 on both items, were identified for further screening by trained psychologists. In the second stage, individuals (both high and low LSHS scorers) were interviewed over the phone to see if they fulfilled the following criteria: (1) no diagnosis or treatment for psychiatric disorders other than depressive or anxiety disorders in complete remission; (2) no alcohol or substance abuse for at least 3 months; and (3) no chronic somatic disorder. Individuals who scored high on the two LSHS items were further inquired whether (4) their voices were distinct from thoughts and had a perceptual quality; and that (5) their voices were experienced at least once a month for over 1 year. At the third stage of selection, participants who fulfilled all the above criteria were invited to attend a clinical interview, which consisted of the CASH interview (Andreasen et al., 1992) and the Structured Clinical Interview for Personality Disorder (SCID-II; First, 1995). Non-clinical individuals were screened for alcohol and substance dependence by self-report, followed by urine tests. Ten non-clinical individuals were declined participation in this study due to positive screening result of alcohol or substance dependence.

Measures

The revised Launay-Slade Hallucination Scale (LSHS).

To screen for hallucinations in the non-clinical groups, the present study adopted a modified, 17-item version of the LSHS (Larøi et al., 2004).

Psychotic Symptom Rating Scale (PSYRATS).

Aspects of hallucinatory experiences were assessed using the 11-item auditory hallucinations scale of the PSYRATS interview (Haddock et al., 1999), which has been used in clinical and non-clinical voice hearers (Hill et al., 2012). The two items on negative content of voices (items 6 "Degree of negative content" and 7 "Amount of negative content") and the two distress items (items 8 "Amount of distress" and 9 "Intensity of distress") were averaged into two combined measures respectively due to high correlations between the component items (Negative content: r=0.766, p<.001; Distress: r=0.787, p<.001).

Beliefs about Voices Questionnaire-Revised (BAVQ-R).
Beliefs about voices and emotional and behavioral response to voices were assessed using the BAVQ-R (Cahdwick et al., 2010). Good internal consistency and test-retest reliability of the scale have been reported in clinical samples (Chadwick et al., 2000) and non-clinical voice hearers (Lawrence et al., 2010).

The revised NEO Personality Inventory (NEO–PI–R).
The revised NEO Personality Inventory is a 240-item questionnaire that assesses five key personality dimensions, including Neuroticism, Extraversion, Openness to Experience, Agreeableness and Conscientiousness (McCrae et al., 2005). Only the Neuroticism subscale was reported in the present study. The Cronbach's α for NEO neuroticism score was previously reported as 0.93 among non-clinical participants, and 0.91 among patients with substance dependence (Costa & McCrae et al., 2008; Conner et al., 2004).

Childhood Trauma Questionnaire-Short Form
Childhood trauma was assessed using a 25-item CTQ-SF (Bernstein et al., 2003). Frequency of five types of trauma was assessed – namely sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect. Good internal consistency reliability has been reported in both clinical (Bernstein et al., 2003) and community samples (Scher et al., 2001).

Statistical Analysis
Group differences were tested by using one-way MANOVAs and ANOVAs. In all group comparison analyses, gender, age and years of education were entered as covariates. In view of the unbalanced group sizes, we conducted bootstrap processes (resampling for 1000 times) to check the robustness of group differences. To examine associations between neuroticism and cognitive-affective reactions to AVH (distress, resistance, perceived malevolence, and perceived power), hierarchical linear regression models were built, with the respective cognitive-affective variable as dependent variable (DV). Gender (dummy recoded), age and years of education as independent variables (as IVs) were entered at the first level (where they were significant predictors), neuroticism and group (dummy recoded) as IVs entered at the second level, and interaction term neuroticism (grand-centred) x group as IV at the third level.
To examine the mediation effect of neuroticism on the relationships between childhood trauma and the cognitive-affective responses to AVH, we adopted the causal steps approach developed by Baron and Kenny (1986). In each mediation model, CTQ-SF total score was entered as IV, neuroticism as mediator, and each

of the following variables as respective DV (distress, resistance, perceived malevolence, and perceived power). Analyses were performed on SPSS 22. Missing values were handled by case-wise deletion.

Results

The final sample consisted of 40 patients with a psychiatric diagnosis, 135 non-clinical voice hearers and 126 healthy individuals.

Demographic and clinical variables

As shown in Table 1, the three groups were matched on age and gender ratio. Healthy individuals completed more education than both voice-hearing groups (*ps*<.05). All patients had a diagnosis of schizophrenia spectrum or other psychotic disorder: schizophrenia (*n*=4), schizoaffective disorder (*n*=1), and psychotic disorder NOS (*n*=35). Some of them had additional (concurrent or past) diagnoses as follows: bipolar I or II disorder (*n*=4), major depressive disorder (*n*=4), personality disorder (*n*=14), dissociative disorder NOS (*n*=2), and religious or spiritual problem (*n*=1).

Table 1. Demographic information across groups

	Patients (*N* = 40)	Non-clinical voice hearers (*N* = 135)	Healthy controls (*N* = 126)	Group comparison
Age	45.43 ± 11.95	50.60 ± 12.70	50.80 ± 14.52	$F(2) = 2.69$, $p = .070$, $\eta^2_p = .02$
Gender	32F[a] (80.0%)	92F (68.1%)	86F (68.3%)	$x^2(2) = 2.29$, $p = .318$, Cramer's $V = .09$
Years of Education	13.15 ± 2.90	13.35 ± 2.12	14.05 ± 2.30	$F(2) = 3.81$, $p = .023$, $\eta^2_p = .03$

Note. [a] F means female.

Table 2 displays the characteristics of AVH reported by patients and non-clinical voice hearers on PSYRATS. One-way MANOVA revealed a significant group difference on PSYRATS scores (Wilks' Lambda $F(9,125)=8.29$, $p<.001$, $\eta^2p=.37$), after adjusting for demographic variables. Follow-up univariate ANOVAs revealed that patients scored significantly higher than non-clinical voice hearers on the following PSYRATS dimensions: duration, negative content, distress and disruption to life (ps<.006, threshold Bonferroni corrected). Results of group differences remained the same before and after bootstrapping.

Table 2 displays appraisals of AVH reported by the two voice hearer groups. One-way MANOVA revealed a significant group difference on BAVQ-R scores

(Wilks' Lambda $F(5,131)=4.47$, $p<.001$, $\eta^2p=.15$), after adjusting for demographic variables. Follow-up univariate ANOVAs revealed that patients scored significantly higher than non-clinical voice hearers on resistance, malevolence and power, while significantly lower on engagement and benevolence ($ps<.01$, threshold Bonferroni corrected). Results of group differences remained the same before and after bootstrapping.

Table 2. Characteristics of and responses to AVH (*M*±*SD*) on PSYRATS and BAVQ-R across groups

	Patients (*N* = 40) *M* ± *SD*	Non-clinical voice hearers (*N* = 135) *M* ± *SD*	*F*-test	
PSYRATS scores				
Frequency	1.92 ± 1.24	1.54 ± 1.22	*F* = 3.77	*p* = .05
Duration	2.15 ± 1.01	1.54 ± 0.73	***F* = 16.98**	***p* < .001**
Location	2.21 ± 1.11	2.21 ± 1.15	*F* = 0.03	*p* = .86
Loudness	1.70 ± 0.72	1.80 ± 0.67	*F* = 0.80	*p* = .37
Belief of origin	2.68 ± 1.19	3.16 ± 1.13	*F* = 6.14	*p* = .01
Negative content	1.74 ± 1.36	0.56 ± 1.03	***F* = 35.91**	***p* < .001**
Distress	1.50 ± 1.25	0.53 ± 0.98	***F* = 26.02**	***p* < .001**
Disruption to life	1.20 ± 1.29	0.23 ± 0.61	***F* = 49.37**	***p* < .001**
Controllability	2.38 ± 1.48	1.82 ± 1.49	*F* = 3.51	*p* = .06
BAVQ-R scores				
Malevolence	5.28 ± 5.86	1.74 ± 3.83	***F* = 16.02**	***p* < .001**
Benevolence	7.20 ± 5.29	10.20 ± 4.51	***F* = 8.37**	***p* = .004**
Power	6.88 ± 4.92	4.75 ± 2.93	***F* = 10.69**	***p* = .001**
Engagement	8.65 ± 7.98	12.34 ± 7.08	*F* = 4.75	*p* = .03
Resistance	10.58 ± 8.56	4.50 ± 6.76	***F* = 20.66**	***p* < .001**

Note. "Negative content" score was the average of PSYRATS items 6 (amount of negative content) and 7 (degree of negative content), whereas "Distress" score was the average of PSYRATS items 8 (amount of distress) and 9 (intensity of distress). Significant findings are indicated in bold.

Level of neuroticism across groups

One-way ANOVA revealed a significant group difference in neuroticism score on NEO-PI-R ($F(2,287)=10.08$, $p<.001$, $\eta^2p=.07$) after adjusting for demographic variables. Post-hoc Bonferroni tests revealed that neuroticism score was higher in patients ($M=3.07$, $SD=0.24$) than non-clinical voice hearers ($M=2.96$, $SD=0.21$; $SE=0.04$, $p=.020$), and higher in non-clinical voice hearers than healthy controls ($M=2.90$, $SD=0.17$; $SE=0.03$, $p=.030$). Bootstrapping yielded a consistent result of group comparisons.

Association between neuroticism and cognitive-affective responses to voices

Hierarchical linear regression models revealed that hallucinatory distress was significantly associated with age (*β*=-0.20, *t*=-2.42, *p*=.017), but not with gender or years of education (*ps*>.05). With the effect of age adjusted for, neuroticism and group significantly predicted the amount of hallucinatory distress (*β*=0.18, *t*=2.29, *p*=.024 and *β*=0.32, *t*=4.15, *p*<.001, respectively; see Table 3). The neuroticism x group interaction effect was non-significant (*p*=.748), suggesting that strength of the association between neuroticism and hallucinatory distress did not differ between clinical and non-clinical voice hearers.

Hierarchical linear regression models revealed a significant age effect on resistance (*β*=-0.21, t=-2.51, *p*=.013) and malevolence (*β*=-0.21, *t*=-2.44, *p*=.016). After adjusting for age, both resistance and malevolence were significantly predicted by neuroticism (*β*=0.27, *t*=3.47, *p*=.001 and *β*=0.16, *t*=2.04, *p*=.044, respectively) and group (*β*=0.27, *t*=3.51, p=.001 and *β*=0.27, *t*=3.47, *p*=.001, respectively; see Table 3). The neuroticism x group interaction effect was not significant for either resistance or malevolence (*ps*>.05), indicating that the associations between neuroticism and resistance against AVH and perceived malevolence of voices were not significantly different between clinical and non-clinical voice hearers.

Table 3. Hierarchical regression analyses for testing the association between neuroticism and cognitive-affective responses to AVH

	Distress	**Resistance**	**Malevolence**	**Power**
Coefficients				
1. *β* (Age)	**-0.20**	**-0.21**	**-0.21**	--
2. *β* (Neuroticism)	**0.18**	**0.27**	**0.16**	**0.19**
β (Group)	**0.32**	**0.27**	**0.27**	**0.22**
3. *β* (Neuroticism × Group)	-0.03	-0.02	-0.02	0.06
Equation *F*	**11.92**	**13.53**	**9.88**	**7.91**
df	3,142	3,143	3,143	2,144
R^2	0.20	0.22	0.17	0.10

Note. Significant findings are indicated in bold. In the regression model for each dependent variable, age was entered at the first level (except for in the model for power), neuroticism and group at the second level, and neuroticism × group at the third level of independent variables. As the neuroticism × group interaction was not significant, Equation *F*, *df*, and R^2 were based on the models with the interaction terms excluded.

Hierarchical linear regression models revealed no significant effect of age, gender or years of education on power. Neuroticism and group significantly predicted power (*β*=0.19, *t*=2.28, *p*=.024 and *β*=0.22, *t*=2.66, *p*=.009, respectively), whereas their interaction effect did not reach significance (*β*=0.06, *t*=0.58, *p*=.565; see Table 3).

As an exploratory investigation, mediation models were tested, with neuroticism as IV, perceived malevolence and power of voices as mediators, and hallucinatory distress and resistance as DVs. Malevolence and power significantly mediated the association between levels of neuroticism and distress (Sobel tests: for malevolence z=3.16, p=.002; for power z=2.76, p=.006), and the association between levels of neuroticism and resistance (Sobel test: for malevolence z=3.16, p=.002; for power z=2.74, p=.006).

Childhood trauma, neuroticism and cognitive-affective reactions to voices

One-way MANOVA showed a significant group difference on CTQ-SF scores (Wilks' Lambda F(10,562)=6.18, p<.001, η^2p=.10), after adjusting for demographic variables (see Table 4). Follow-up univariate ANOVAs revealed significant group differences on CTQ-SF total score and all subscales (ps≤.001). Patients had higher scores than non-clinical voice hearers on physical abuse and the total score (ps<.05), while both AVH groups had higher scores on all CTQ-SF dimensions than the healthy controls (ps<.01). Results of group differences remained the same before and after bootstrapping.

Table 4. Childhood traumatic experiences (M±SD) on CTQ-SF across groups

	Patients (N = 40)	Non-clinical voice hearers (N = 135)	Healthy controls (N = 126)	F-test (F, p)	
Emotional abuse	13.23 ± 6.73	10.67 ± 4.96	7.23 ± 2.86	**F = 27.85**	**p < .001**
Physical abuse	8.13 ±5 .05	6.55 ± 3.33	5.47 ± 1.25	**F = 10.31**	**p < .001**
Sexual abuse	8.73 ± 5.69	7.66 ± 4.48	5.73 ± 1.85	**F = 9.56**	**p < .001**
Emotional neglect	15.10 ± 5.55	12.81 ± 4.97	10.86 ± 4.18	**F = 9.81**	**p < .001**
Physical neglect	8.53 ± 3.86	7.50 ± 2.65	6.62 ± 2.07	**F = 7.18**	**p = .001**
Total score	53.70 ± 21.84	45.19 ± 15.61	35.87 ± 8.50	**F = 22.04**	**p < .001**

Note: Significant findings are indicated in bold.

Mediation models of neuroticism, childhood trauma, and cognitive-affective reactions to AVH by using data from both clinical and non-clinical voice hearers (n=175) are shown in Table 5. After adjusting for the effect of age, CTQ-SF total score significantly predicted distress, resistance, malevolence, and power (Step 1). However, for all models, when neuroticism was entered into the regression (i.e. Step 2), the predictive effect of CTQ-SF total score reduced to non-significance and that of neuroticism becomes significant. These results suggested that neuroticism fully mediated the relationship between childhood trauma and cognitive-affective reactions to AVH.

Table 5. Regression analyses for testing the mediation effects of neuroticism in the relationship between childhood trauma and cognitive-affective reactions to AVH

	Distress		Resistance		Malevolence		Power	
	Step 1	Step 2	Step 1	Step 2	Step 1	Step 2	Step 1	Step 2
Coefficients								
1. β (Age)	-0.23	-0.19	-0.25	-0.18	-0.25	-0.21	-0.15	-0.11
β (CTQ)	**0.18**	0.14	**0.19**	0.12	**0.17**	0.13	**0.18**	0.14
2. β (Neuroticism)		0.21		0.29		0.19		0.18
Equation *F*	6.41	6.57	7.16	9.61	6.69	6.26	3.87	4.19
df	2,143	3,142	2,144	3,143	2,144	3,143	2,144	3,143
R^2	0.07	0.10	0.08	0.15	0.08	0.10	0.04	0.06
ΔR^2	0.08	0.04	0.09	0.08	0.09	0.03	0.05	0.03
F_{change}	6.41	6.40	7.16	13.29	6.69	5.04	3.87	4.65

Note: Significant findings are indicated in bold. In Step 1, age and CTQ were entered as independent variables; and in Step 2, neuroticism was entered as a third independent variable.

To further explore the effects of neuroticism on mediating the links between specific types of childhood trauma and reactions to AVH, additional mediation analyses were conducted (test statistics available from the first author). Rather than testing the mediation effect of CTQ-SF total score as a whole, we tested the mediation effects of each of the CTQ-SF subscores respectively. At Step 1, we found that emotional abuse and physical abuse significantly predicted distress, resistance, malevolence, and power. Emotional neglect predicted distress and resistance, whereas physical neglect predicted resistance and power. Sexual abuse did not predict any of the cognitive-affective reactions to AVH. At Step 2, the effects of emotional abuse and physical abuse on all four aspects of cognitive-affective reactions to AVH were fully mediated by neuroticism. The effects of emotional neglect and physical neglect on resistance were fully mediated by neuroticism. The effect of emotional neglect on distress and the effect of physical neglect on power were partially mediated by neuroticism.

Discussion

This study examined the relationship between neuroticism, cognitive-affective reactions to auditory verbal hallucinations (AVHs) and childhood traum. In view of the evidence that AVHs are experienced by patients with varied psychiatric diagnoses, as well as individuals in the general population, the present study adopted a single-symptom approach and compared patients experiencing frequent AVHs, non-patients experiencing frequent AVHs, and non-voice-hearers in the general population. All our hypotheses were confirmed: (i) we found a positive association between neuroticism and level of hallucinatory distress; (ii) there was a positive association between neuroticism and a tendency to resist AVHs and to appraise them as malevolent and powerful; (iii) neuroticism mediated the relationship between childhood traumatic experiences and cognitive-affective reactions to AVHs.

We demonstrated the role of neuroticism in predicting cognitive-affective responses to AVHs. Whilst there was a graded difference in level of neuroticism across the three groups, it is most intriguing that, in both clinical and non-clinical voice-hearers alike, a higher level of neuroticism was associated with more emotional distress and behavioral resistance in response to AVHs, as well as a stronger tendency to perceive voices as malevolent and powerful. Therefore, even among voice hearers who did not have a diagnosis of any psychotic disorder, those who are higher on neuroticism are more likely to respond to voices in a way that is characteristic among patients with psychosis, albeit to an attenuated degree. Consistent with the stress research findings that neuroticism heightens an individual's affective reactivity to stressors and renders an individual to consider experiences as dangerous and threatening (Barlow et al., 2004, 2014), our results support that such links between neuroticism and cognitive-affective reactions to general stressors applies also to the psychopathology of AVH. More specifically, we found that the association between neuroticism and hallucinatory distress was fully mediated by perceived malevolence of voices. To put into the cognitive-behavioral framework of hallucinations (Birchwood & Chadwick, 1997; Van der Gaag et al., 2003; Trower et al., 2004), it is possible that voice-hearers who are more neurotic are more emotionally reactive to voices and appraise voices as more negative and powerful, hence adopting a resistant and avoidant coping strategy, which in turn maintains the severity and distress of the voices (Lysaker et al., 2003, 2007).

The present study added to the literature on the relationship between childhood trauma and hallucinations. We found that childhood trauma was related to how an individual responds to the voices cognitively and affectively. Such association was the most robust for emotional abuse and physical abuse, and was also

evident for emotional neglect and physical neglect. Notably, all effects of childhood trauma on psychological reactions to AVH were mediated by neuroticism. Therefore, even though it has been suggested that a history of trauma does not necessarily affect the negativity of voice content (Daalman et al., 2012), it contributes to overall occurrence of AVHs, and more specifically, maladaptive reactions to voices by increasing the individual's emotional reactivity and sense of threat. As this was the first time that childhood trauma was found to predict cognitive-affective reactions to AVHs via neuroticism, our mediation results warrant replication by future studies.

There are several limitations to this study. First of all, this study set out to recruit patients with experiences of AVHs, without limiting to psychotic disorders only. Therefore, whilst all patients had a psychotic disorder, some presented with comorbidities. There was also heterogeneity in terms of symptom profile, duration of illness, and response to treatment. It has been shown that the experience of and reactions to AVH may differ across stages of illness (Larkin 1979; Nayani & David, 1996) and diagnosis (Cutting, 1987; Kingdon et al., 2010; Mitchell et al., 1991). Although this sample was representative of the recruitment site, we cannot quantify how the link between neuroticism and the individual's reactions to voices compares between patients with or without comorbidities, or patients at different stages of illness. Therefore, one needs to be cautious when generalizing our findings to more specific diagnostic groups. Secondly, although we have excluded non-clinical participants with active emotional disorders, since neuroticism has been shown to be associated with levels of depression and anxiety, including a clinical measure of these emotions would have made our methodology more stringent. Thirdly, the reliability of retrospective self-report of childhood trauma may be questionable. Against these caveats, this study extended the current literature on auditory verbal hallucinations by examining the associations between individuals' personality, cognitive and affective reactions to voices, and history of trauma.

In conclusion, our results shed more light on how voice hearers interact with the symptom, and the role of neuroticism as a putative mechanism linking childhood trauma and psychological reactions to voices.

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Author contributions

SHS, MJHB and IES conceived of the idea of the project and determined the study design. SHS, XG and MJHB conducted the data analysis. All authors reviewed and approved of the final manuscript.

Completing financial interests

All authors have declared no conflicts of interest.

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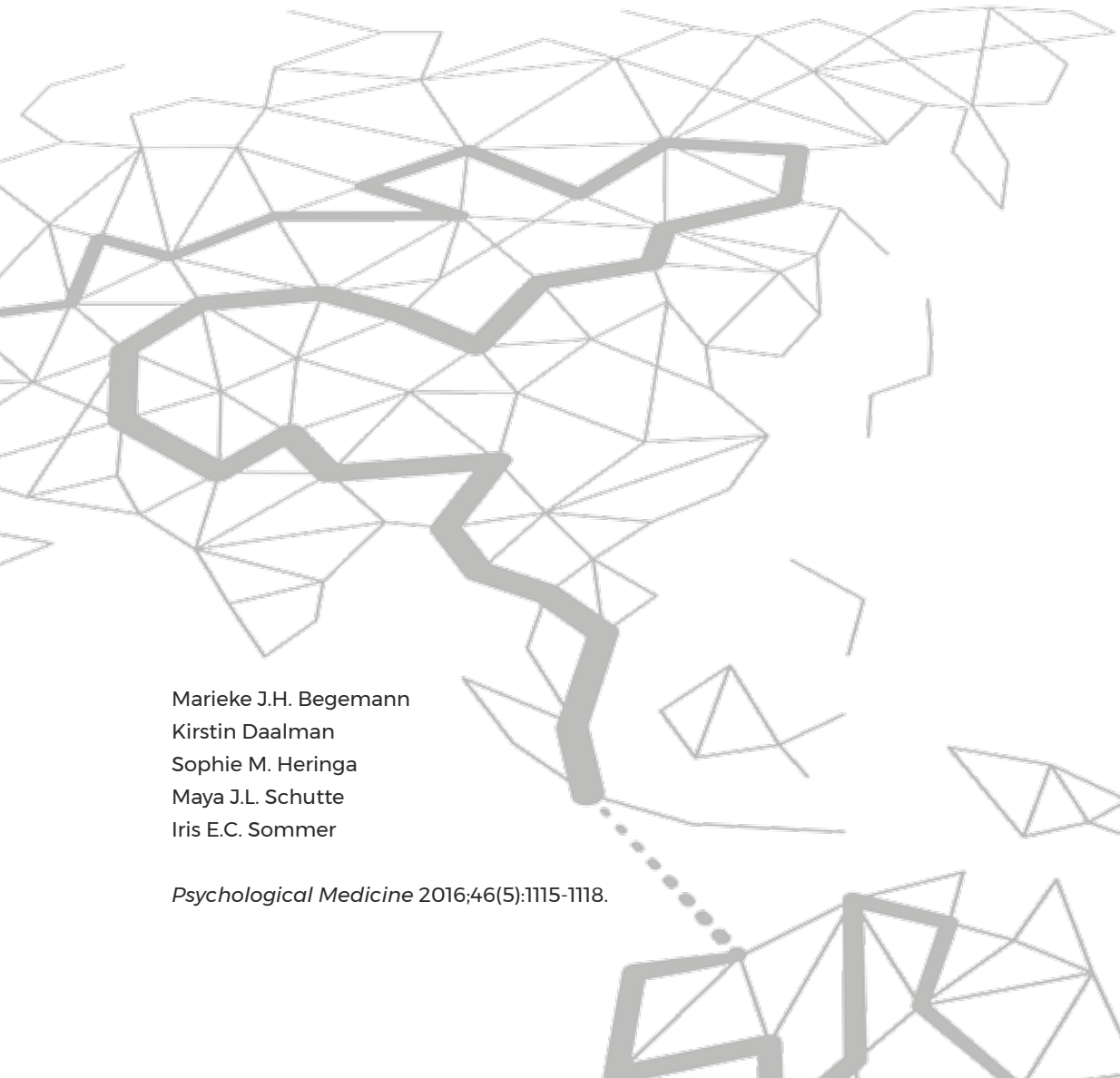
Africa

During my first years in research, I had the opportunity to live in and travel through different African countries. Because of my work at a children day-care, I realized the importance of being granted the possibility to fully develop your cognitive potentials.

CHAPTER 4-I

Cognitive impairment as a vulnerability marker for psychosis: the confounding role of childhood trauma



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Introduction

Van Dam et al. (2015) describe childhood trauma as a contributor to vulnerability for psychosis and depressive symptoms. In this context, the role of cognitive functioning deserves attention, as cognitive impairment precedes the onset of psychosis (Bora et al., 2014; Agnew-Blais et al., 2015) and is associated with childhood trauma (Aas et al., 2012). Reduced cognitive functioning and childhood trauma may be both part of the causal pathway to the development of psychosis later in life (Reichenberg, 2005). The neurodevelopmental view of psychosis states that negative environmental influences such as trauma in addition to early developmental (genetic) abnormalities give rise to psychotic symptoms (Reichenberg, 2005; Owen et al., 2011).

The underlying mechanisms of the association between childhood trauma and increased risk for psychosis are unknown. Early traumatic events are associated with reduced cognitive functioning in the domains of executive functioning, working memory and (verbal) intellectual abilities, which is largely similar to the cognitive profiles of patients with psychotic disorders and people at ultra-high risk (Reichenberg, 2005; Aas et al., 2012). It can therefore be hypothesized that childhood trauma exerts neurobiological consequences that contribute to psychosis-associated cognitive impairment.

Our group studied psychotic experiences such as auditory verbal hallucinations in non-clinical individuals (Daalman et al., 2011). These individuals do not have a history of hospitalisation or use of anti-psychotic medication and do not show marked negative symptomatology, which are important confounding factors. This population shows reduced cognitive performance in the domains executive functioning, working memory and language (Daalman et al., 2011) and, interestingly, reports high rates of childhood trauma, similar to patients with a psychotic disorder (Daalman et al., 2012). We investigated whether increased exposure to early traumas can explain the reduced cognitive performance associated with a vulnerability to experience psychotic symptoms, in non-clinical adults with and without psychotic experiences.

Methods

Participants and procedures

We included 101 non-clinical individuals with psychotic experiences (auditory verbal hallucinations) and 101 controls (selection procedures and inclusion criteria described previously; Daalman et al., 2011, 2012). Participants did not meet criteria

for DSM-IV diagnosis. Neuropsychological assessment included several cognitive domains (Daalman et al., 2011). Childhood trauma was rated using the Childhood Trauma Questionnaire Short Form (CTQ-SF; Bernstein et al., 2003). Both groups were similar with regard to gender, age, handedness and education (Daalman et al., 2011).

Statistics

Correlations between CTQ-SF score and cognitive test scores were calculated using non-parametric Spearman's rho. To address the effect of childhood trauma, we conducted step-wise regression analyses for those cognitive measures that were significantly lowered in individuals with psychotic experiences in our previous study (Daalman et al., 2011). Group was included as a predictor in the first step, CTQ-SF score was added in the second step for the following outcome measures: verbal inhibition (Stroop interference task), working memory (Digit-span backward [WAIS-III]), verbal abilities (Vocabulary test and Similarity test [WAIS-III]), and intelligence (National Adult Reading Task). If trauma severity is a significant factor in explaining the association between reduced cognitive performance and psychotic experiences, adding CTQ-SF score to the regression model will reduce the significance level of this association (partial explanatory variable) or render it non-significant (full explanatory variable).

Results

Individuals with non-clinical psychotic symptoms reported more childhood trauma as indicated by the CTQ-SF (M=45.1, SD=15.7), compared to controls (M=36.4, SD=8.6), t=23.7, p<.001. Associations between cognitive performance and CTQ-SF score were corrected for multiple analyses, using Bonferroni correction. Given the 14 cognitive tests, the significance level was set at p <.0036. Childhood trauma was related to reduced verbal inhibition (Stroop interference: ρ=.210, p=.003). Childhood trauma was unrelated to other cognitive measures (ρ=-.167 to .110, all p>.0036). Childhood trauma fully explained the previously found association between reduced verbal inhibition and non-clinical psychotic features (Daalman et al., 2011), as group was no longer a significant predictor for Stroop interference when adding CTQ-SF score (Table 1). Childhood trauma also accounted for the association between non-clinical psychotic symptoms and reduced working memory. Childhood trauma was of no explanatory value with regard to the association between psychotic features and reduced verbal abilities, nor intelligence (Table 1).

Table 1. Step-wise regression analyses evaluating the effect of childhood trauma in explaining the reduced cognitive functioning associated with non-clinical auditory verbal hallucinations

			B (SE)	*Beta*	*t*	*p*-value	R^2	*Adj* R^2	*p*-value	ΔR	*p*-value
Executive functioning and working memory											
Stroop interference	**Step 1**	Non-clinical psychotic experiences	6.44 (-2.34)	.19	2.75	.007	.036	.032	.007 [a]		
	Step 2	Non-clinical psychotic experiences	4.21 (2.44)	.13	1.73	.086	.073	.064	<.001 [a]	.073	.005 [a]
		Total CTQ-SF	0.26 (0.09)	.20	2.81	.005					
Digit-span backward	**Step 1**	Non-clinical psychotic experiences	-0.78 (0.29)	-.19	-2.73	.007	.036	.031	.007 [a]		
	Step 2	Non-clinical psychotic experiences	-0.67 (0.30)	-.16	-2.23	.027	.042	.032	.014	.006	.275
		Total CTQ-SF	-0.01 (0.01)	-.08	-1.09	.275					
Lexical access and abstract reasoning											
Vocabulary test (WAIS III)	**Step 1**	Non-clinical psychotic experiences	-6.33 (1.26)	-.34	-5.03	<.001	.112	.108	<.001 [a]		
	Step 2	Non-clinical psychotic experiences	-5.69 (1.33)	-.30	-4.29	<.001	.122	.113	<.001 [a]	.010	.140
		Total CTQ-SF	-0.07 (0.05)	-.10	-1.48	.140					
Similarities test (WAIS III)	**Step 1**	Non-clinical psychotic experiences	-1.73 (0.56)	-.21	-3.07	.002	.045	.040	.002 [a]		
	Step 2	Non-clinical psychotic experiences	-1.72 (0.60)	-.21	-2.87	.005	.045	.036	.010 [a]	.000	.927
		Total CTQ-SF	-0.002 (0.02)	-.01	-0.09	.927					
Intelligence											
National adult reading test	**Step 1**	Non-clinical psychotic experiences	-5.25 (1.24)	-.29	-4.23	<.001	.082	.077	<.001 [a]		
	Step 2	Non-clinical psychotic experiences	-4.45 (1.31)	-.24	-3.41	<.001	.098	.089	<.001 [a]	.016	.063
		Total CTQ-SF	-0.09 (0.05)	-.13	-1.87	.063					

Note. Abbreviations: SE: Standard error; CTQ-SF: Childhood Trauma Questionnaire Short Form; WAIS, Wechsler Adult Intelligence Scale.
[a] Given the five cognitive tests, we corrected for multiple analyses using Bonferroni correction by dividing the significance level of 0.05 by 5, therefore set at $p < 0.01$.

Discussion

In adults with and without non-clinical psychotic experiences, we observed a correlation between level of childhood trauma and reduced verbal inhibition in the domain of executive functioning. Childhood trauma fully explained the previously observed associations between psychotic experiences and reduced executive functioning, as well as lower working memory performance. Childhood trauma was not relevant for the relations between non-clinical psychotic experiences and reduced verbal abilities or intelligence.

Our results extend the finding of Van Dam et al. (2015) that childhood trauma increases the vulnerability for psychotic symptoms later in life, by showing its potential impact on executive functioning and working memory performance. These cognitive domains are largely supported by the prefrontal cortex, just like many cognitive and negative symptoms of primary psychotic disorder resemble symptoms associated with frontal abnormalities (Reichenberg, 2010). The prefrontal lobes play a central role in the neurodevelopmental hypothesis of psychosis, as they are especially vulnerable to stress and mature late, in the phase when early brain abnormalities following genetic and environmental influences are hypothesized to interfere with normal brain development (Reichenberg, 2014).

Interestingly, Van Dam et al. also show a vulnerability after trauma for depressive symptoms. Several psychiatric disorders are characterized by impairments in executive functioning and working memory as well as increased exposure to trauma, such as depression, post-traumatic stress disorder, and bipolar disorder. (Gould et al., 2012). In these conditions, the mechanisms may be similar, which implies that prevention of childhood trauma could be a mean to forestall severe dysfunction from cognitive impairments in psychiatric disorders.

Our results indicate that a history of childhood trauma is an underlying factor for the association between cognitive impairment and psychotic experiences, especially executive functioning and working memory. We emphasize the need for future studies to establish whether early cognitive dysfunction constitutes an independent general vulnerability marker for psychosis, or if it (partly) results from the neurobiological consequences of trauma early in life.

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Conflicts of interest
None.

Ethical standards
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Africa

During my first years in research, I had the opportunity to live in and travel through different African countries. Because of my work at a children day-care, I realized the importance of being granted the possibility to fully develop your cognitive potentials.

CHAPTER 4-II

Childhood trauma as a neglected factor in psychotic experiences and cognitive functioning

Marieke J.H. Begemann
Sophie M. Heringa
Iris E.C. Sommer

JAMA Psychiatry 2016;73(8):875-876.

Letter to the editor

Mollon and colleagues (2016) present data from a population-based study, evaluating neuropsychological functioning in adults with subclinical psychotic experiences. As rightly noted by the authors, previous studies have not adjusted for key sociodemographic confounders. Mollon et al. (2016) therefore evaluated ethnicity, occupation, cannabis use and common mental disorders - all were found to correlate significantly with both psychotic experiences and cognitive performance. Adjusting for these factors notably reduced differences in cognitive functioning between individuals with psychotic experiences and those without. Yet, we believe that one important confounder was not corrected for in the Mollon study (2016).

Here, we would like to highlight childhood trauma as another important factor in the association between neuropsychological functioning and the experience of psychotic symptoms, which is often neglected in the literature. Trauma exposure early in life increase the risk for psychosis and is also associated with cognitive dysfunction (Aas et al., 2012), especially of functions subserved by the frontal lobe as this brain region has a gradual natural maturation course. A recent study (Begemann et al., 2015) including a similar sample of non-clinical adults with and without psychotic features (*n*=202), indeed showed that childhood trauma fully explained the relation between psychotic experiences and reduced executive functioning as well as lower working memory performance.

The results by Mollon (2016) and similar studies clearly demonstrate the complexity of the association between neuropsychological functioning and psychotic experiences. The role of environmental risk factors in the development of cognitive dysfunction has not been adequately investigated. This can lead to confounding of results and could perhaps account for some of the inconsistent findings reported previous studies. Childhood trauma and sociodemographic factors may constitute a common underlying vulnerability for both psychotic experiences and cognitive deficits. Alternatively, cognitive dysfunction may be the means by which environmental influences such as childhood trauma and an unfavorable sociodemographic millieu increase the risk for developing psychotic experiences later in life.

Now that cognitive dysfunctioning is increasingly recognized as a core vulnerability factor for psychosis, we need to carefully examine the effects of relevant covariates, as also noted in the editorial by Gur (2016) that accompanied the Mollon et al. (2016) article. Future large longitudinal studies are needed to understand the temporal sequence and complex interplay between different genetic and environmental factors. In addition to sociodemographic factors, childhood trauma is a crucial factor that should not be omitted in studies investigating the association between cognitive dysfunction and psychotic experiences.

Conflict of Interest Disclosures

None of the authors have any conflict of interest or funding support relating to this manuscript.

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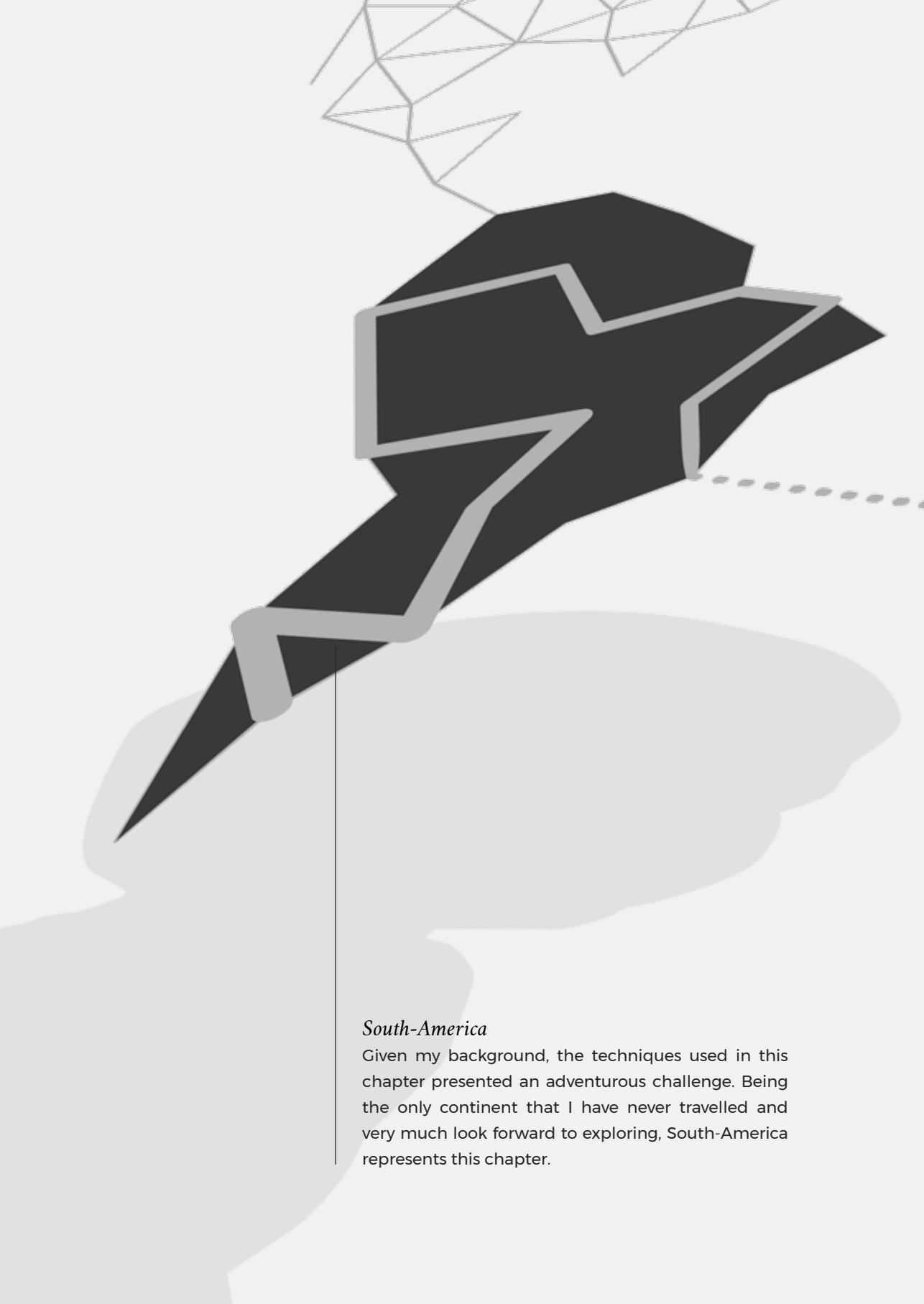

South-America

Given my background, the techniques used in this chapter presented an adventurous challenge. Being the only continent that I have never travelled and very much look forward to exploring, South-America represents this chapter.

CHAPTER 5-I

Childhood trauma-specific reductions in limbic gray matter volume: still in the dark

Marieke J.H. Begemann
Maya J.L. Schutte
Iris E.C. Sommer

JAMA Psychiatry 2015;72(4):398.

Letter to the editor

In their recent article, Van Dam and colleagues (2014) report an unique association between childhood trauma (CT) and decreased gray matter volumes (GMV) in the left limbic regions, both in individuals with substance use disorder (SUD) and in healthy controls. By disentangling the separate influences of CT and psychopathology on GMV, the authors make an important contribution as literature on the specific effects of CT in the absence of psychiatric symptomatology has been scarce and inconsistent. However, their conclusion that the found GMV reductions in left limbic regions are uniquely associated with CT may be a bit premature.

The majority of studies conducted on GMV alterations associated with childhood adversities investigated subjects with a concurrent diagnosis such as major depressive disorder or post-traumatic stress disorder (Dannlowski et al., 2012). As highlighted by Dannlowski et al. (2012), it is therefore difficult to infer whether limbic abnormalities related to CT are only evident in individuals who develop psychopathology later in life, or if these alterations are detectable consequences of CT in persons without any psychiatric history.

Limbic abnormalities have repeatedly been reported for various psychiatric conditions (Godsil et al., 2013), while the possibly mediating or moderating role of CT is rarely taken into consideration in these studies. Van Dam et al. (2014) investigate this association using an elegant design - their results indeed suggest that previous findings on GMV reductions in patients with SUD may actually relate to CT. When evaluating their results for CT, 24% of the controls with CT were also affected by a psychiatric disorder compared to only 5.5% of controls without CT, a significant difference. As such, we wonder if psychiatric history really was no confounding factor as the authors suggested. We would therefore like to know whether the association between CT and reduced GMV in the left limbic regions can be replicated in their group of HCs only, when subjects with concurrent psychiatric history are excluded from analysis.

The specific association between CT and limbic regional volumes is as yet still in the dark and in fact (sub)clinical psychiatric symptoms may have contributed to previous reports on structural abnormalities. It is important to study individuals without concurrent psychiatric disorders, as only a minority of children exposed to traumatic experiences will develop a psychiatric disorder later in life. To further understand the influence of traumatic experiences during childhood, future studies need to determine the specific effects of traumatic childhood experiences on brain abnormalities with as little bias as possible.

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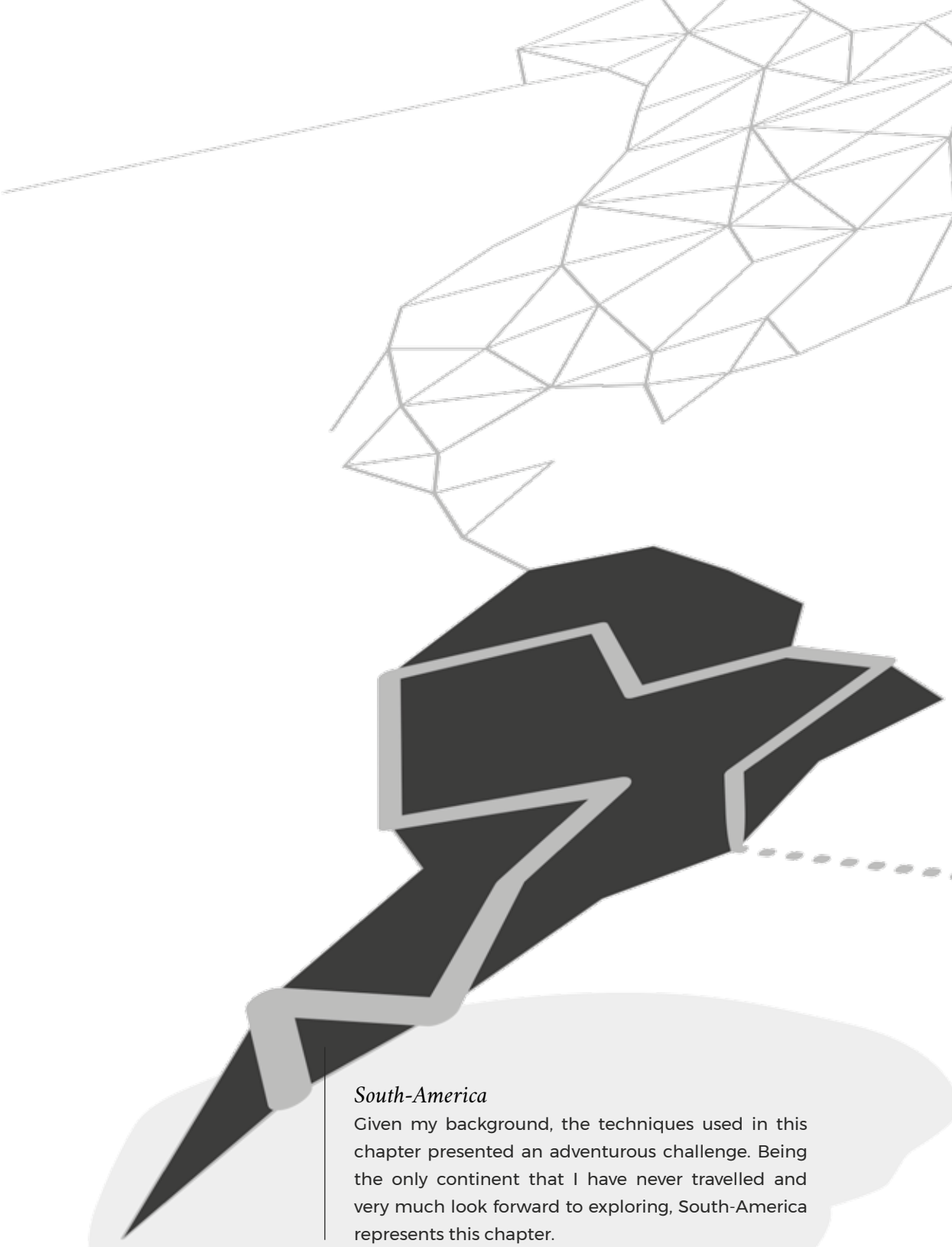

South-America

Given my background, the techniques used in this chapter presented an adventurous challenge. Being the only continent that I have never travelled and very much look forward to exploring, South-America represents this chapter.

CHAPTER 5-II

Examining the neurobiological impact of childhood trauma: an important role for frontal and insular regions

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In draft.

Abstract

Importance

Childhood trauma may increase the risk for psychiatric illness by its negative impact on brain development. Studies investigating the association between childhood trauma and deviations in gray matter volume have shown inconsistent findings, often restricted by a region-of-interest approach with a sole focus on the amygdala and hippocampus and without controlling for the presence of psychiatric illness.

Objective

First, using a whole-brain approach in a large cross-diagnostic sample (*n*=554) of healthy individuals and patients with a bipolar type-I or psychotic disorder, we investigated the neurobiological correlates of childhood trauma by evaluating gray matter volume. Follow-up analyses were conducted to evaluate the effect of psychiatric illness. Second, we investigated to what extent these trauma-related structural correlates could be observed in both groups separately (healthy individuals versus patients).

Design, setting and participants

Participants were recruited as part of three different studies, all conducted in the University Medical Center Utrecht (the Netherlands) between 2007 and 2016. We included 554 participants: 220 healthy individuals without a psychiatric history, 250 patients with a bipolar-I disorder and 84 patients with a psychotic disorder. Childhood trauma was evaluated with the Childhood Trauma Questionnaire (CTQ-SF). Anatomical T1 MRI scans were acquired at 3T. FreeSurfer was used to assess regional brain morphology.

Main outcomes

Associations between severity of childhood trauma and gray matter volume across the brain, in the presence *and* in the absence of psychopathology.

Results

In the total sample, childhood trauma severity was associated with bilateral reductions in frontal and insular gray matter volumes. In the right hemisphere, medial orbitofrontal and superior frontal volume reductions were ▶

related to childhood trauma. These associations remained when adjusting for psychiatric illness, with the exception of the right superior frontal subregion. However, when evaluating both groups separately, these structural correlates of childhood trauma were mainly observed in patients. Healthy controls did show trauma related reductions in right medial orbitofrontal region, while this association was not significant in the patient group.

Conclusion and relevance

Our results suggest that gray matter reductions in the frontal and insular regions are important neurobiological correlates of childhood trauma. For future research, a whole brain approach should be applied, as cortical rather than subcortical areas may be the main correlate of childhood trauma contributing to the development of psychopathology.

Keypoints

Question

What are the neurobiological correlates of childhood trauma across the brain, both in the presence and in the absence of psychiatric illness?

Findings

Using a whole-brain approach in a large cross-diagnostic sample (*n*=554) of healthy individuals and patients with a bipolar-I or psychotic disorder, childhood trauma was associated with reduced frontal and insular gray matter volume. These trauma-related volume reductions were mainly visible in patients.

Meaning

Gray matter reductions in the frontal and insular areas are important neurobiological correlates of childhood trauma. Future research should apply a whole brain approach, as cortical rather than subcortical areas may be the main correlate of childhood trauma, contributing to the development of psychopathology.

Introduction

Childhood trauma increases the risk for psychiatric illness later in life (Green et al., 2010). Early stress is often proposed as a key environmental factor underlying the abnormal brain development that leads to the emergence of psychiatric illnesses (Hart & Rubia, 2012), with gray matter being less heritable and more affected by early environment than white matter (Lim et al., 2014). Although childhood trauma has been linked to reduced gray matter volume in various brain structures, most studies are limited by their region-of-interest (ROI) approach (Hart & Rubia, 2012; Lim et al., 2014). Moreover, previous research has typically studied subjects with psychiatric conditions (McCrory et al., 2011; Carrion & Wong, 2012; Hart & Rubia, 2012; Lim et al., 2014), leaving it unclear to what extent such abnormalities can indeed be attributed to the impact of childhood trauma, or whether these alterations reflect the illness itself (Dannlowski et al., 2012; Begemann et al., 2015).

Most studies have applied an ROI-approach to focus on the impact of childhood trauma on the hippocampus and amygdala, yet results are inconsistent (Hart & Rubia, 2012; Lim et al., 2014; McRory et al., 2011). Albeit restricted by relatively small sample sizes, the majority of studies using an unbiased whole-brain approach have not found a relation between childhood trauma and gray matter reductions in the hippocampi or amygdalae (Lim et al., 2014). A recent meta-analysis on whole-brain studies however, did report a smaller right hippocampus in adults with a history of childhood trauma (Paquola et al., 2016). Whole-brain approaches have also implicated other brain areas not investigated by ROI studies, including gray matter reductions in the prefrontal, thalamic, insular, parietal and temporal regions (Lim et al., 2014; Paquola et al., 2016). Importantly, childhood trauma has been related to a range of neurocognitive consequences, such as reduced academic performance and lower IQ, deficits in emotion and reward processing, attention, memory, working memory and inhibitory control (Hart & Rubia, 2012; Lim et al., 2014). This raises the question whether the commonly proposed hippocampal and amygdala regions are indeed the brain structures that are most sensitive to childhood trauma.

Besides the analysis approach (ROI vs whole brain), the presence of psychiatric diagnosis is an important factor that further complicates the interpretation of previous studies (Dannlowski et al., 2012; Begemann et al., 2015). Gray matter alterations linked to childhood trauma clearly show overlap with brain regions affected in various psychiatric diagnoses, including the prefrontal and limbic regions (McRory et al., 2011; Hart & Rubia, 2012; Carrion & Wong, 2012). The presence of psychiatric illness seems partially inevitable, as high rates of childhood trauma are prevalent in patients with a psychiatric illness whereas the majority of

healthy individuals endorse low trauma scores. Notably, studies relating childhood trauma to gray matter volume in the context of psychopathology often focus on one diagnostic category, despite the fact that childhood trauma is a general risk factor for a broad range of psychiatric diagnoses (Green et al., 2010). With clinical, cognitive and genetic approaches emphasizing similarities across various psychiatric diagnoses (Caspi et al., 2013; Snyder et al., 2015; Robbins et al., 2012; Mansell et al., 2008; Cross-disorder Group of the Psychiatric Genomics Consortium, 2013), the common impact of trauma on brain structure across different psychiatric disorders deserves attention.

While there is a strong association between childhood trauma and psychopathology, only a minority of maltreated children will eventually develop a psychiatric illness. Studying healthy individuals will aid our understanding of the neurobiological impact of traumatic events early in life independent of psychiatric illness, which can provide more insight in neurobiological correlates that underpin psychiatric resilience following childhood trauma (Paquola et al., 2016). As of yet, the few recent studies specifically investigating trauma-related alterations in maltreated individuals without any psychiatric history are relatively small and mainly used an ROI approach (Cohen et al., 2006; Dannlowski et al., 2012; Korgaonkar et al., 2013; Riem et al., 2015; Souza-Queiroz et al., 2016). Their findings remain inconclusive, with some reporting volume reductions in the hippocampus (Dannlowski et al., 2012; Samplin et al., 2013; Riem et al., 2015) and amygdala (Korgaonkar et al., 2013 [only in adolescents, not in adults], Souza-Queiroz et al., 2016), while others do not detect hippocampal (Cohen et al., 2005; Korgaonkar et al., 2013, Souza-Queiroz et al., 2016) or amygdala abnormalities (Cohen et al., 2005; Dannlowski et al., 2012). Importantly, the few studies conducting a (supplementary) whole-brain analysis have shown volume reductions in the prefrontal regions, anterior cingulate, insula, and caudate nuclei (Cohen et al., 2005; Dannlowski et al., 2012; Korgaonkar et al., 2013).

When reviewing past findings, it becomes apparent that the neurobiological correlates of childhood trauma are still in the dark, as methodological and psychopathy-related factors may have contributed to previous reports. We need to broaden our view beyond the common proposition of the hippocampus and amygdala, and evaluate whether there are childhood trauma-related alterations that are shared across individuals, while accounting for the effects of psychiatric illness. This study implemented a whole-brain, cross-diagnostic approach, with the largest sample size yet applied in this field of research.

Our aim was twofold:

1. We examined whole-brain gray matter correlates of childhood trauma in 554 participants, including healthy individuals without a psychiatric history as well as in patients with bipolar type-I disorder and patients with schizophrenia spectrum disorder. We subsequently evaluated the effect of psychiatric illness in this association, by taking patient status into account.
2. We investigated to what extent these trauma-related structural correlates could be observed in both groups separately (220 healthy individuals and 334 patients) - in other words in the absence versus presence of psychiatric symptomatology.

Methods

Participants

Participants were recruited as part of three different studies conducted in the University Medical Center Utrecht (the Netherlands): Bipolar Genetics study (described by Vreeker et al., 2016), Spectrum study (Sommer et al., 2010) and Simvastatin for recent-onset psychosis (Begemann et al., 2015, baseline data). Participants were ≥18 years of age. This is the first study combining the structural Magnetic Resonance Imaging (sMRI) data of these studies to relate childhood trauma to volume reductions. A total of 554 participants were included, consisting of 220 healthy individuals without a current or past psychiatric diagnosis, and 334 patients. The patient group was comprised of 251 bipolar type-I patients and 83 patients with a schizophrenia spectrum disorder, as defined by the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR; American Psychiatric Association et al., 2000). Presence or absence of psychopathology was established using the Structured Clinical Interview for DSM-IV (SCID-I24), the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998), or the Comprehensive Assessment of Symptoms and History Interview (CASH; Andreasen et al., 1992). Studies were approved by the relevant medical ethical committee, and all participants gave written informed consent. More details on the in- and exclusion of the studies are described in the eAppendix in Supplement.

Childhood trauma

Childhood trauma was assessed with the Childhood Trauma Questionnaire–Short Form (CTQ-SF; Bernstein et al., 2013). This 25-item version evaluates five trauma subtypes: sexual abuse, physical abuse and emotional abuse, together with physical neglect and emotional neglect. Trauma severity was calculated by adding

these five subscales, resulting in a CTQ-SF total score. Good internal consistency reliability has been reported in both clinical and community samples (Bernstein et al., 2013; Scher et al., 2001).

Structural Magnetic Resonance Imaging

Structural MRI scans of the whole brain were acquired on the same 3T Philips Achieva medical scanner for all three studies, equipped with an 8-chanell SENSE headcoil (Philips, Best, The Netherlands). Three-dimensional high-resolution T1-weighted images (high-res T1) were obtained with the following parameters; 200 contiguous sagittal slices (TE=4.6 ms, TR=10 ms, flip angle=8˚, FOV=240 mm, 0.75×0.75×0.80 mm3 voxels). For some participants (see Table 1), T1-weighted images (T1) with a slightly lower resolution were available: 160 contiguous sagittal slices (TE=4.6 ms, TR=10 ms, flip angle=8˚, FOV=224 mm, 1×1×1 mm3 voxels).

All 554 scans were checked for radiological abnormalities by a radiologist, who was blind to subject status (healthy individual or patient). Structural images were processed using the automated segmentation pipeline of FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu) (Fischl et al., 2004). By automatic parcellation of the cortical and subcortical structures, gray matter was divided into 82 distinct anatomical volumes of the Desikan-Killiany atlas (Desikan et al., 2006). |Segmentations were manually checked for volumes deviating significantly from the population mean (i.e. more than 2 standard deviations [*SD*]) regarding total gray matter volume, thickness (left and right), surface area (left and right) and intracranial volume (ICV). When visual inspection of these images showed gross scan or segmentation faults, these segmentations were deemed unfit for further analysis. Images from two participants showed radiological abnormalities, two scans showed segmentation faults and seven scans were of insufficient quality, resulting in 543 scans suitable for analysis. The eleven excluded participants (four healthy controls, two bipolar-I patients and five schizophrenia patients) did not differ (>2*SD*) from the remaining sample on demographic variables or childhood trauma score.

We evaluated seven subcortical gray matter volumes, including the nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen and thalamus. In addition, 34 cortical gray matter volumes were combined to distinguish five cerebral lobar volumes (Fischl et al., 2004; Desikan et al., 2006): frontal (*n*=11), temporal (*n*=9), parietal (*n*=5), occipital (*n*=4), cingulate gyrus (*n*=4). The insula is part of several lobes and was therefore evaluated as a separate region. To calculate a general measure of total cerebral brain volume, total gray and white matter volumes were combined.

Statistical analysis

Statistical analyses were performed using SPSS software, version 22.0. Group-differences in demographic characteristics were evaluated using chi-squared tests for categorical variables and t-tests for continuous variables. The neurobiological correlates of childhood trauma were investigated in two steps:

1. We explored the neurobiological correlates of childhood trauma across the brain by performing multiple linear regressions in the whole sample, with CTQ-SF total score as predictor (age, gender and cerebral brain volume as covariates; type of scan was included as a dummy variable [high-res T1 vs T1]). Seven subcortical gray matter volumes and five cortical lobes plus the insula were evaluated (combining left and right hemisphere volumes). Analyses were Hochberg-adjusted, using a false discovery rate (FDR) of 5% (q<.05) (Benjami & Hochberg, 1995). Structure(s) associated with childhood trauma were further examined by separating left and right volumes, and subsequently cortical subregions (differentiating between cortical thickness and surface area), Hochberg-corrected.

   Subsequently, to evaluate the effect of psychiatric illness, we repeated significant regressions as hierarchical regression analyses: adding group membership (healthy controls vs patients) in the second step with medication status as additional covariate (binary variable representing whether or not the patient was currently on an antipsychotic, antidepressant or mood stabilizer).
2. To investigate the extent to which childhood trauma was associated with gray matter volume in the absence versus the presence of psychiatric symptomatology, significant regressions were repeated within the two groups separately: healthy controls and patients. Childhood trauma was entered as predictor (age, gender, and cerebral brain volume as covariates; medication status was included for the patient group).

Results

Demographic characteristics of the 554 participants are provided in Table 1. Patients did not differ from the healthy controls in terms of age, gender or years of education. Childhood trauma severity was higher in patients compared to healthy individuals (see Table 1); bipolar-I patients and patients with a psychotic disorder did not differ with regard to reported childhood trauma rates (t(516.44)=5.30, p=.055). Total cerebral brain volume was smaller and left and right lateral ventricles were larger in the patient group (see Table 1). Bipolar-I patients had

a smaller brain volume than patients with a psychotic disorder (t(121.19)=-2.62, p=.010) and larger ventricles (left: t(143.64)=2.87, p=.005; right: t(131.03)=2.31, p=.022).

Table 1. Demographics and clinical data of the total sample

	Healthy controls (n=220)		Patients (n=334)		Test statistic	p-value
Age in years, mean (*SD*)	34.80	(14.53)	44.41	(13.70)	t(552)=-0.99	p=.322
Gender (male/female)	98 /	122	175 /	159	χ^2=3.27	p=.071
Years of education	13.88	(2.57)	13.40	(3.14)	t(537)=1.95	p=.051
Psychiatric diagnosis						
Bipolar Disorder type I	0		250			
Schizophrenia spectrum disorder	0		84			
Medication						
Mood stabilizers (yes/no)	0		164	(49.1%)		
Antidepressive medication (yes/no)	0		78	(23.4%)		
Antipsychotic medication (yes/no)	0		181	(54.2%)		
	Healthy controls (n=216)		Patients (n=327)			
Childhood trauma						
CTQ-SF total score (*SD*)	34.72	(10.74)	40.17	(13.10)	**t(516.40)=5.30**	**p<.001**
MRI						
Type of MRI scan (high res T1 vs T1)	173 /	43	294 /	33	**χ^2=10.41**	**p=.001**
Total cerebral volume (*SD*)	1071083.93	(108882.09)	1047943.53	(105640.00)	**t(552)=-2.49**	**p=.013**
Left lateral ventricle (*SD*)	9205.29	(4915.17)	12004.08	(7161.63)	**t(552)=4.45**	**p<.001**
Right lateral ventricle (*SD*)	8726.41	(4760.03)	10900.58	(6166.56)	**t(552)=4.67**	**p<.001**

Note. *SD*: standard deviation; high res: high resolution; vs: versus.

Cross-diagnostic neurobiological correlates of childhood trauma

In the total sample (*n*=543), childhood trauma severity (CTQ total score) was significantly associated with gray matter reductions in the frontal lobe (ß=-.052, *p*=.005) and insula (ß=-.076, *p*=.007) (Hochberg-corrected for 13 comparisons, see Table 2). While childhood trauma was negatively related to most other gray matter volumes, these associations did not reach significance when corrected for multiple testing: amygdala (ß=-.052, *p*=.107), nucleus accumbens (ß=-.049, *p*=.119), caudate (ß=-.028, p=.399), hippocampus (ß=-.040, *p*=.238), pallidum (ß=.047, *p*=.128), putamen, (ß=-.004, *p*=.894), thalamus (ß=-.010, *p*=.722), temporal lobe (ß=-.038, *p*=.056), parietal lobe (ß=.003, p=.879), occipital lobe (ß=-.005, *p*=.869), nor the cingulate gyrus (ß=-.001, *p*=.981). Within the frontal lobe, trauma severity was associated with smaller volumes in both the left and the right hemisphere (ß=-.048, *p*=.012 and ß=-.055, *p*=.004, respectively). While statistical significance within subregions of the left frontal lobe did not survive FDR correction, childhood trauma was associated with smaller gray matter volumes in the right medial orbitofrontal (ß=-.095, *p*=.003) and the right superior frontal subregion (ß=-.065, *p*=.010). For the insula, trauma was associated with gray matter reductions in both hemispheres (left: ß=-.081, *p*=.009, right: ß=-.065, *p*=.029).

Subsequently, to evaluate the effect of psychiatric illness in these associations, patient status was entered in the model together with medication status as covariate. No significant increase in explained variance could be detected when presence of psychiatric diagnosis was included in the regression models (see Table 2). Moreover, after correcting for psychiatric illness, childhood trauma remained associated with gray matter reductions in all frontal (sub)regions - except for the trauma-related reductions in the right superior frontal region which did not survive FDR correction. For the insula region, childhood trauma remained a significant predictor for total gray matter volume, and for the left and right insula separately (see Table 2). For the separate analyses on thickness and surface area of the cortical (sub)regions, please refer to eTable 1 in Supplement.

Table 2. Neurobiological correlates of childhood trauma

			b	*(SE)*	*Beta*	*Sign.*	*Adj R^2/ΔR*
Total frontal volume							
	Step 1.	Childhood trauma[a]	**-67.99**	**(24.03)**	**-0.05**	***p*=.005**	**0.836*** **
	Step 2.	Childhood trauma [a]	**-63.20**	**(24.68)**	**-0.05**	***p*=.011**	**0.838*** **
		Group[b] (H vs. Pat)	1151.70	(957.96)	0.03	*p*=.230	*ΔR*=0.003
Left frontal volume							
	Step 1.	Childhood trauma[a]	**-31.03**	**(12.29)**	**-0.05**	***p*=.012**	**0.824*** **
	Step 2.	Childhood trauma[a]	**-29.28**	**(12.64)**	**-0.05**	***p*=.021**	**0.826*** **
		Group[b] (H vs. Pat)	632.71	(490.66)	0.04	*p*=.198	*ΔR*=0.003
Right frontal volume							
	Step 1.	Childhood trauma[a]	**-36.97**	**(12.81)**	**-0.05**	***p*=.004**	**0.824*** **
	Step 2.	Childhood trauma[a]	**-33.91**	**(13.15)**	**-0.05**	***p*=.010**	**0.826*** **
		Group[b] (H vs. Pat)	518.68	(510.35)	0.03	*p*=.310	*ΔR*=0.004
	Right medial orbitofrontal volume						
	Step 1.	Childhood trauma[a]	**-4.33**	**(1.47)**	**-0.10**	***p*=.003**	**0.492*** **
	Step 2.	Childhood trauma[a]	**-4.45**	**(1.52)**	**-0.10**	***p*=.004**	**0.490*** **
		Group[b] (H vs. Pat)	-18.22	(58.93)	-0.02	*p*=.757	*ΔR*=0.003
	Right superior frontal volume						
	Step 1.	Childhood trauma[a]	**-12.58**	**(4.86)**	**-0.07**	***p*=.010**	**0.688*** **
	Step 2.	Childhood trauma[a]	**-10.96**	**(5.01)**	**-0.06**	***p*=.029**	**0.690*** **
		Group[b] (H vs. Pat)	156.27	(194.55)	0.03	*p*=.422	*ΔR*=0.004
Total insular volume							
	Step 1.	Childhood trauma[a]	**-9.53**	**(3.54)**	**-0.08**	***p*=.007**	**0.608*** **
	Step 2.	Childhood trauma[a]	**-10.62**	**(3.66)**	**-0.09**	***p*=.004**	**0.607*** **
		Group[b] (H vs. Pat)	195.19	(142.04)	0.06	*p*=.170	*ΔR*=0.002
Left insular volume							
	Step 1.	Childhood trauma[a]	**-5.15**	**(1.97)**	**-0.08**	***p*=.009**	**0.534*** **
	Step 2.	Childhood trauma[a]	**-5.68**	**(2.04)**	**-0.09**	***p*=.005**	**0.532*** **
		Group[b] (H vs. Pat)	100.78	(79.00)	0.06	*p*=.203	*ΔR*=0.002
Right insular volume							
	Step 1.	Childhood trauma[a]	**-4.38**	**(2.00)**	**-0.06**	***p*=.029**	**0.571*** **
	Step 2.	Childhood trauma[a]	**-4.94**	**(2.07)**	**-0.07**	***p*=.018**	**0.570*** **
		Group[b] (H vs. Pat)	94.36	(80.49)	0.05	*p*=.242	*ΔR*=0.002

Note. H: healthy controls without a psychiatric history; Pat: patients with a Bipolar type-I or psychotic disorder; SE: standard error; Sign: significance level; Adj: adjusted.
[a] Childhood trauma as a predictor, with age, gender, cerebral brain volume and type of scan (high-resolution T1 vs T1) as covariates.
[b] Group (healthy individual vs patient) was included in the second step, with medication status as covariate

Healthy individuals versus patients

To investigate whether the neurobiological correlates of childhood trauma were distinctively specific for absence or presence of psychopathology, significant regressions were repeated for each of the two groups (healthy individuals and patients) separately (see Table 3). Healthy individuals only showed trauma-related gray matter reductions in the right medial orbitofrontal region, while the other associations did not reach significance. In the patient group, childhood trauma was associated with reductions in total frontal lobe volume, which was also found when evaluating both hemispheres separately and within the right medial orbitofrontal region. However, the relation between childhood trauma and reduced gray matter in the right medial orbitofrontal region did not remain significant after FDR correction. Moreover, trauma-related reductions were observed in total insular gray matter volume, as well as in the left and right insular regions (see Table 3). eTable 1 provides results for thickness and surface area (in Supplement). A separate evaluation of the bipolar-I patients and the psychotic disorder group indicated that results in the total patient sample were not driven by one of these diagnoses. While childhood trauma was associated with reduced frontal and insular volumes in both groups, these associations did not reach significance (Hochberg-corrected; eTable 2).

Table 3. Neurobiological correlates of childhood trauma, healthy individuals versus patients.

	Healthy individuals (*n*=216)				Patients (*n*=327)			
Childhood trauma as a predictor for:	*b*[a]	*(SE)*	*Beta*	*Sign.*	*b*[b]	*(SE)*	*Beta*	*Sign.*
Total frontal lobe volume	-42.74	(47.02)	-0.027	*p*= .364	**-69.22**	**(27,96)**	**-0.058**	*p*= **.014**
Left frontal lobe volume	-15.40	(24.33)	-0.019	*p*= .527	**-33.53**	**(14,16)**	**-0.057**	*p*= **.019**
Right frontal lobe volume	-27.34	(24.89)	-0.033	*p*= .273	**-37.81**	**(15,14)**	**-0.062**	*p*= **.013**
Right medial orbitofrontal volume	**-8.55**	**(2.76)**	**-0.158**	*p*= **.002**	-2.79	(1,82)	-0.066	*p*= .126
Right superior frontal volume	-4.05	(9.04)	-0.017	*p*= .655	**-13.53**	**(5,99)**	**-0.078**	*p*= **.025**
Total insular volume	-4.61	(6.27)	-0.031	*p*= .463	**-13.22**	**(4,56)**	**-0.114**	*p*= **.004**
Left insula	-5.20	(3.52)	-0.068	*p*= .141	**-5.92**	**(2,53)**	**-0.100**	*p*= **.020**
Right insula	0.59	(3.57)	0.007	*p*= .869	**-7.30**	**(2,58)**	**-0.115**	*p*= **.005**

Note. SE: standard error; Sign: significance level.
[a] Childhood trauma as a predictor, with age, gender, cerebral brain volume and type of scan (high- resolution T1 vs T1) as covariates.

Discussion

We present findings from the largest whole-brain, cross-diagnostic study yet applied in this field of research, based on pooled data from three different cohorts, all scanned on the same scanner with the same protocol. In the total sample of healthy individuals and patients with a bipolar-I or psychotic disorder, we found that childhood trauma severity was associated with bilateral reductions in frontal and insular gray matter volumes. In the right hemisphere, childhood trauma was associated with volume reduction in the medial orbitofrontal and superior frontal cortex. Importantly, these associations remained significant when adjusting for the presence of psychiatric illness, accept for the right superior frontal region. However, when evaluating the healthy individuals and the patient group separately, these structural correlates of childhood trauma were mainly observed in patients. Healthy controls did show trauma related reductions in right medial orbitofrontal region, while this association did not reach significance in the patient group.

The associations between childhood trauma and gray matter reductions in the frontal and insular regions are in line with previous studies in patient and healthy samples (whole-brain and ROI) (McCrory et al., 2011; Hart & Rubia, 2012; Lim et al., 2014; Gould et al., 2012). In fact, albeit restricted by relatively small sample sizes, the most robust finding from previous whole-brain studies was the relation between childhood trauma and reduced gray matter volume in the frontal cortices (Lim et al., 2014; Paquola et al., 2016). Functional MRI studies have also shown reduced activation in the frontal and insular regions in individuals with a history of childhood trauma (Lim et al., 2014). We did not observe trauma-related volume reductions in the hippocampus or amygdala and, importantly, the use of an ROI approach yielded a similar result as these associations did not reach significance without FDR correction. Our findings suggest that not the hippocampus and amygdala, but the frontal and insular cortices are the most sensitive brain regions when exposed to stressful experiences early in life.

In the total sample, these trauma-related frontal and insular volume reductions remained significant when accounting for the presence of psychiatric illness and medication use, which suggests a common impact of childhood trauma on these regions. However, when separately evaluating the healthy group and the patient sample, we found that these neurobiological correlates of trauma were mainly observed in patients but not in the group of healthy individuals. One possible explanation is that because healthy individuals score on the lower end of the trauma spectrum and display less variation, alterations of gray matter volume were too subtle to be of significance. We also know that trauma importantly interacts with other susceptibility factors in affecting brain development,

including genetic loading as suggested by twin and family studies (Goodkind et al., 2015; Picchioni et al., 2017). Within our group of healthy individuals, we did observe trauma related gray matter reductions in the right medial orbitofrontal subregion which is in line with previous research (Dannlowski et al., 2012). Although the insula, anterior cingulate gyrus, hippocampus, amygdala and caudate have also been implicated (Cohen et al., 2006; Dannlowski et al., 2012; Korgaonkar et al., 2013), we could not replicate these earlier findings. Interestingly, the involvement of the right orbitofrontal cortex in emotion, mood, and social regulation could underlie the subclinical-levels of anxiety, borderline, depression, mania and psychotic symptoms that have been observed in maltreated individuals without a psychiatric history (Damasio, 1994; Grover et al., 2007; Kaymaza et al., 2007; De Castro-Catala et al., 2016). Moreover, this region supports higher-order cognitive functions, and this may explain why reduced executive functioning has been linked to childhood trauma severity (Gould et al., 2012; Begemann et al., 2016). The orbitofrontal subregion matures relatively late and suboptimal functioning may not become apparent until adolescence or early adulthood (Bachevalier & Loveland 2006). Notably, the association between trauma and reduced right medial orbitofrontal volume did not reach significance in our patient group, which suggests that clinical factors such as illness duration and medication effects presumably impact gray matter volume in this subregion (Weinberger et al., 2002).

In our cross-sectional patient group, childhood trauma was associated with reductions in frontal and insular gray matter volumes, which did not appear to be driven by either BP-I disorder or psychosis. Our results shed new light on previous studies investigating neurobiological alterations in patient samples (Ellison-Wright & Bullmore, 2010; Haijma et al., 2013; Gupta et al., 2015; Morey et al., 2016; Sandoval et al., 2016; Shah et al., 2017), that have traditionally attributed their findings of frontal and insular abnormalities to disease specific factors while not accounting for childhood trauma. Moreover, these results add to the recent discovery of a transdiagnostic neurobiological substrate for psychiatric illness (Goodkind et al., 2015). After conducting an exceptionally large meta-analysis (193 studies, n=15 892), Goodkind and colleagues (2015) showed that volume reductions in the insula and dorsal anterior cingulate cortex were shared across six different diagnoses, including schizophrenia, bipolar disorder, depression, substance dependence, obsessive-compulsive disorder and anxiety. They also observed common prefrontal abnormalities, which appeared to be driven by psychotic disorders (Goodkind et al., 2015). We did not observe this to be the case in our patient group. Moreover, studies that have directly contrasted different diagnostic groups also report shared volume reductions in both the insular and frontal regions - not only when comparing bipolar disorder and schizophrenia (Ellison-Wright & Bullmore,

2010; Arnone et al., 2009), but also between bipolar disorder and unipolar depression (Wise et al., 2016), and depression and borderline personality disorder (Depping et al., 2016). Thus, the observed childhood trauma-related volume reductions may well extent beyond our diagnostic categories of bipolar-I and psychotic disorder.

When interpreting the neurobiological impact of childhood trauma, interpretation of current results is limited by the use of data that were collected within a single time-frame. Longitudinal studies are needed to evaluate when, how and to what extent brain development is affected by stressful experiences early in life. While our results suggest that the impact of childhood trauma does not differ between bipolar-I and psychotic disorder, this cannot be ruled our considering the difference in sample sizes. Replication across other diagnoses is needed before we can conclude that the neurobiological impact of childhood trauma is truly a cross-diagnostic risk factor.

In conclusion, we found that childhood trauma was associated with bilateral gray matter volume reductions in the frontal and insular cortices, but not with volume decreases in hippocampi and amygdala. Based on a heterogeneous sample of healthy individuals and patients with a bipolar-I or psychotic disorder, our results support the proposition that early trauma constitutes an environmental factor possibly underlying the diverging brain development involved in psychiatric illness.

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Supplement: eAppendix

Methods

A total of 554 subjects were recruited as part of three different studies, conducted in the University Medical Center Utrecht (the Netherlands): *Bipolar Genetics*, *Spectrum study* and *Simvastatin for recent-onset psychosis*. All participants were ≥18 years of age. Healthy control subjects did not have a current or past psychiatric diagnosis. Patients met Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (American Psychiatric Association, 2000) criteria for bipolar disorder type I (BD-I) or a schizophrenia spectrum disorder. Studies were approved by the relevant medical ethical committee, all participants gave written informed consent.

The *Bipolar Genetics* study investigated genetic and phenotypic information of patients with bipolar disorder type I (BD-I), first-degree relatives and controls (Vreeker et al., 2015). For the current study, we included 250 BD-I patients who were recruited via clinicians, the Dutch patients' association, pharmacies and advertisements. In addition, we included 133 controls who were enrolled via advertisements and by inviting individuals who previously participated in a study and had agreed to be contacted for new research. Presence or absence of psychopathology was established using the Structured Clinical Interview for DSM-IV (SCID-I, First et al., 1997).

The *Spectrum study* examined psychotic experiences across the continuum of patients with a psychotic disorder and the general population. We included data from 48 patients with a schizophrenia spectrum disorder who were enrolled via clinicians and the Dutch patients' association. Healthy controls were recruited by means of a website 'www.verkenuwgeest.nl' ('explore your mind', see Sommer et al., 2010). Visitors of this Website filled out a self-report questionnaire that is designed to quantify the tendency to hallucinate in healthy individuals (modified version of the Launay and Slade Hallucination Scale [LSHS]), they were subsequently invited to visit the UMCU. Psychiatric diagnosis (in patients) or the absence of psychopathology (in healthy individuals) was evaluated using the Comprehensive Assessment of Symptoms and History Interview (CASH, Andreasen 1992). A total of 87 healthy individuals were included in current study, who did have not a history of psychiatric illness. Of these individuals, 37 reported frequent auditory verbal hallucinations (at least once a month, for more than 1 year). These individuals are regarded as healthy controls since the presence of a psychotic disorder had been ruled out by a psychiatrist, as they did not show professional, psychological or social dysfunction. We know that these individuals report similar high rates of childhood trauma as found in patients (Sommer et al., 2010), thereby inclusion leads to a better distribution of childhood trauma rates in the healthy control group.

Simvastatin for recent-onset psychosis is an ongoing medication trial (Begemann et al., 2016), investigating the augmenting effects of simvastatin treatment (40 mg/daily) versus placebo. Participants will use study medication for one year and visit the UMCU approximately once every three months for study measurements. We included baseline data for 36 patients with a diagnosis of a schizophrenia spectrum disorder, who had been recruited via collaborating health institutions. Psychiatric diagnosis was confirmed using the Comprehensive Assessment of Symptoms and History Interview (CASH, Andreasen 1992).

Table e1. Childhood trauma and thickness and surface area, in the total sample and for the healthy and patient group separately

		Thickness				Surface area				
		b	(*SE*)	*Beta*	Sign.	Adj $R^2/\Delta R$	*b*	(*SE*)	*Beta*	Sign.	Adj $R^2/\Delta R$
Right medial orbitofrontal region											
Step 1.	Childhood trauma[a]	**-0.0013**	**(0.0005)**	**-0.092**	***p*=.014**	**0.316*** **	-0.84	(0.55)	-0.051	*p*=.121	**0.483*** **
Step 2.	Childhood trauma[a]	-0.0008	(0.0005)	-0.061	*p*=.112	**0.329*** **	-1.22	(0.55)	-0.074	*p*=.027	**0.496*** **
	Group (H vs. Pat)[b]	-0.0156	(0.0204)	-0.045	*p*=.446	**ΔR=0.018***	4.49	(21.37)	0.011	*p*=.834	**ΔR=0.016****
Right superior frontal region											
Step 1.	Childhood trauma[a]	0.0000	(0.0004)	0.002	*p*=.951	**0.320*** **	-4.67	(1.84)	-0.070	*p*=.011	**0.633*** **
Step 2.	Childhood trauma[a]	0.0005	(0.0005)	0.040	*p*=.285	**0.348*** **	-5.36	(1.90)	-0.080	*p*=.005	**0.633*** **
	Group (H vs. Pat)[b]	0.0008	(0.0176)	0.003	*p*=.964	**ΔR=0.033*** **	59.24	(73.75)	0.035	*p*=.422	ΔR =0.002
Left insula											
Step 1.	Childhood trauma[a]	-0.0014	(0.0005)	-0.117	*p*=.004	**0.182*** **	-0.70	(0.65)	-0.034	*p*=.286	**0,.505*** **
Step 2.	Childhood trauma[a]	-0.0011	(0.0005)	-0.088	*p*=.037	**0.190*** **	-1.14	(0.67)	-0.056	*p*=.091	**0.505*** **
	Group (H vs. Pat)[b]	-0.0114	(0.0197)	-0.037	*p*=.564	ΔR=0.015*	44.46	(26.00)	0.085	*p*=.088	ΔR =0.008
Right insula											
Step 1.	Childhood trauma[a]	-0.0014	(0.0005)	-0.107	*p*=.009	**0.183*** **	-0.51	(0.75)	-0.022	*p*=.499	**0.486*** **
Step 2.	Childhood trauma[a]	-0.0008	(0.0005)	-0.064	*p*=.124	**0.206*** **	-1.13	(0.77)	-0.049	*p*=.141	**0.494*** **
	Group (H vs. Pat)[b]	-0.0269	(0.0212)	-0.080	*p*=.206	**ΔR=0.029*** **	54.98	(29.69)	0.094	*p*=.065	**ΔR=0.012****
				Thickness					**Surface area**		
Childhood trauma as a predictor for:		*b*[c]	(*SE*)	*Beta*	Sign.		*b*[c]	(*SE*)	*Beta*	Sign.	
Right medial orbitofrontal region											
	Healthy individuals[a]	-0.0019	(0.0009)	-0.113	*p*=.049		-2.14	(0.97)	-0.111	*p*=.029	
	Patients[c]	-0.0004	(0.0006)	-0.032	*p*=.544		-0.88	(0.67)	-0.056	*p*=.194	
Right superior frontal region											
	Healthy individuals[a]	0.0005	(0.0008)	0.035	*p*=.530		-2.98	(3.25)	-0.037	*p*=.359	
	Patients[c]	0.0005	(0.0005)	0.044	*p*=.394		**-6.22**	**(2.35)**	**-0.100**	***p*=.008**	
Left insula											
	Healthy individuals[a]	-0.0010	(0.0009)	-0.070	*p*=.265		-1.04	(1.18)	-0.042	*p*=.376	
	Patients[c]	-0.0011	(0.0006)	-0.096	*p*=.083		-1.20	(0.82)	-0.063	*p*=.148	
Right insula											
	Healthy individuals[a]	0.0002	(0.0009)	0.012	*p*=.848		0.00	(.33)	0.000	*p*=.999	
	Patients[c]	-0.0013	(0.0007)	-0.100	*p*=.067		-1.60	(0.95)	-0.074	*p*=.092	

Abbreviations: H: healthy controls without a psychiatric history; Pat: patients with a Bipolar type-I or psychotic disorder; SE: standard error; Sign: significance (p-value); Adj: adjusted.

[a] Childhood trauma as a predictor, with age, gender, cerebral brain volume and type of scan (high-resolution T1 vs T1) as covariates.

[b] Group (healthy individual vs patient) was included in the second step, with medication status as covariate.

[c] Childhood trauma as a predictor, with age, gender, cerebral brain volume, type of scan (high-resolution T1 vs T1) and medication status as covariates.

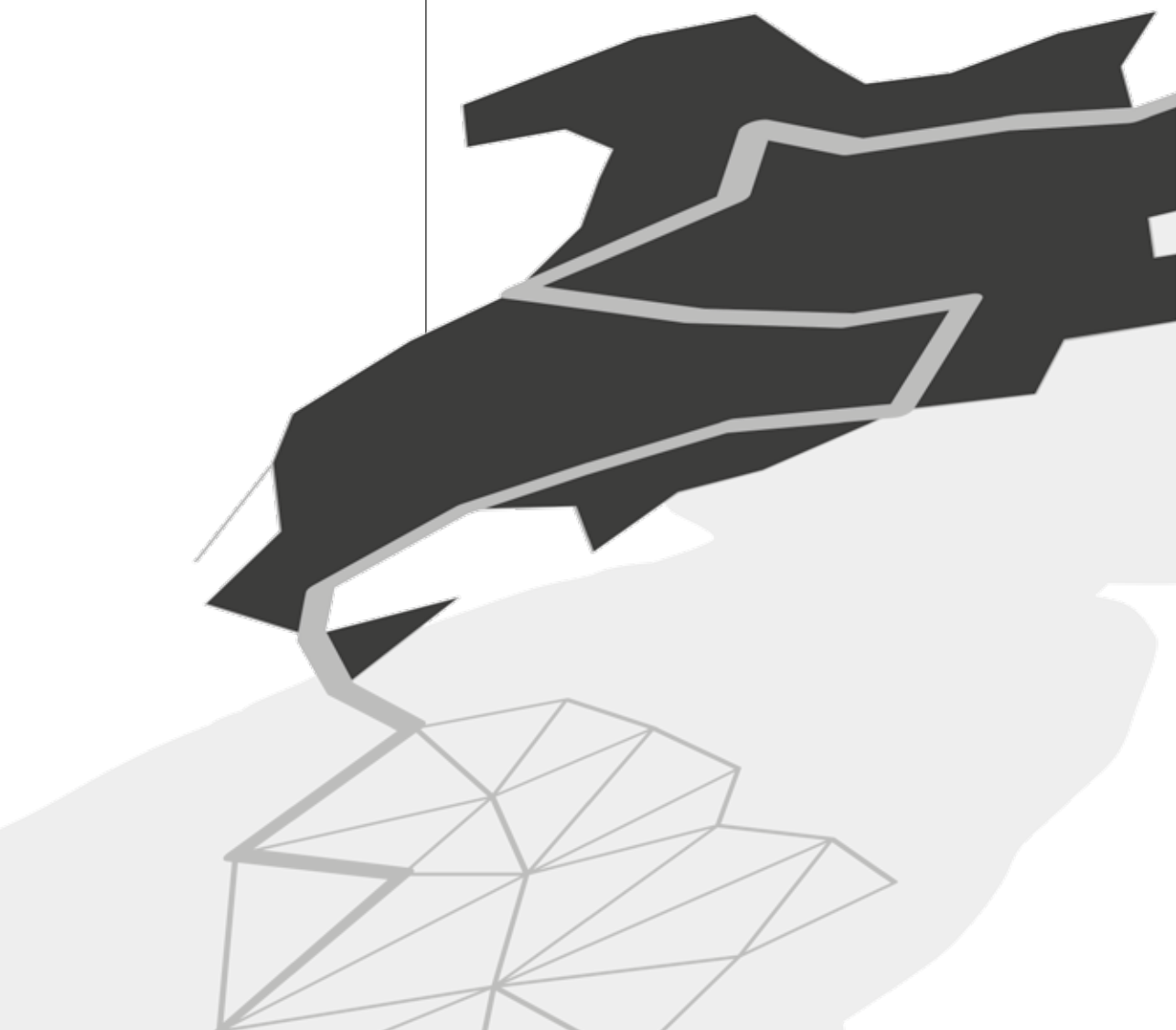
Table e2. Childhood trauma and gray matter volume, thickness and surface area, separately for bipolar-I disorder and patients with a psychotic disorder.

		Patients with a bipolar-I disorder (*n*=248)				Patients with a psychotic disorder (*n*=79)			
Childhood trauma as a predictora for:		*b*[a]	(*SE*)	*Beta*	Sign.	*b*[a]	(*SE*)	*Beta*	Sign.
Total frontal lobe region	volume	-88.10	(34.86)	-0.069	*p*= .012	-44.82	(48.78)	-0.044	*p*= .362
Left frontal lobe	volume	-44.66	(17.73)	-0.071	*p*= .012	-20.21	(25.21)	-0.041	*p*= .426
Right frontal lobe	volume	-43.43	(18.72)	-0.066	*p*= .021	-24.63	(26.15)	-0.047	*p*= .350
Right medial orbitofrontal	volume	-2.67	(2.20)	-0.059	*p*= .227	-1.64	(3.57)	-0.045	*p*= .649
	thickness	-0.001	(0.0008)	-0.063	*p*= .305	0.0005	(0.0013)	0.050	*p*= .695
	surface area	-0.56	(0.84)	-0.032	*p*= .511	-1.088	(1.18)	-0.080	*p*= .362
Right superior frontal	volume	-12.03	(7.32)	-0.064	*p*= .102	-18.96	(11.41)	-0.139	*p*= .102
	thickness	-0.0001	(0.0006)	-0.009	*p*= .887	0.0007	(0.0011)	0.076	*p*= .539
	surface area	-4.20	(2.85)	-0.061	*p*= .142	-8.96	(4.76)	-0.176	*p*= .065
Total insular region	volume	-11.69	(5.53)	-0.096	*p*= .036	-16.29	(8.80)	-0.152	*p*= .069
Left insula	volume	-6.02	(2.95)	-0.098	*p*= .042	-6.46	(5.48)	-0.116	*p*= .244
	thickness	-0.0009	(0.0007)	-0.078	*p*= .223	-0. 0014	(0.0014)	-0.126	*p*= .319
	surface area	-1.44	(1.00)	-0.072	*p*= .148	-1.11	(1.69)	-0.063	*p*= .516
Right insula	volume	-5.67	(3.23)	-0.084	*p*= .080	-9.84	(4.50)	-0.173	*p*= .033
	thickness	-0.0009	(0.0008)	-0.066	*p*= .272	-0.0020	(0.0016)	-0.165	*p*= .206
	surface area	-1.42	(1.18)	-0.061	*p*= .231	-1.88	(1.77)	-0.096	*p*= .294

[a] Childhood trauma as a predictor, with age, gender, cerebral brain volume, type of scan (high-resolution T1 vs T1) and medication status as covariates.

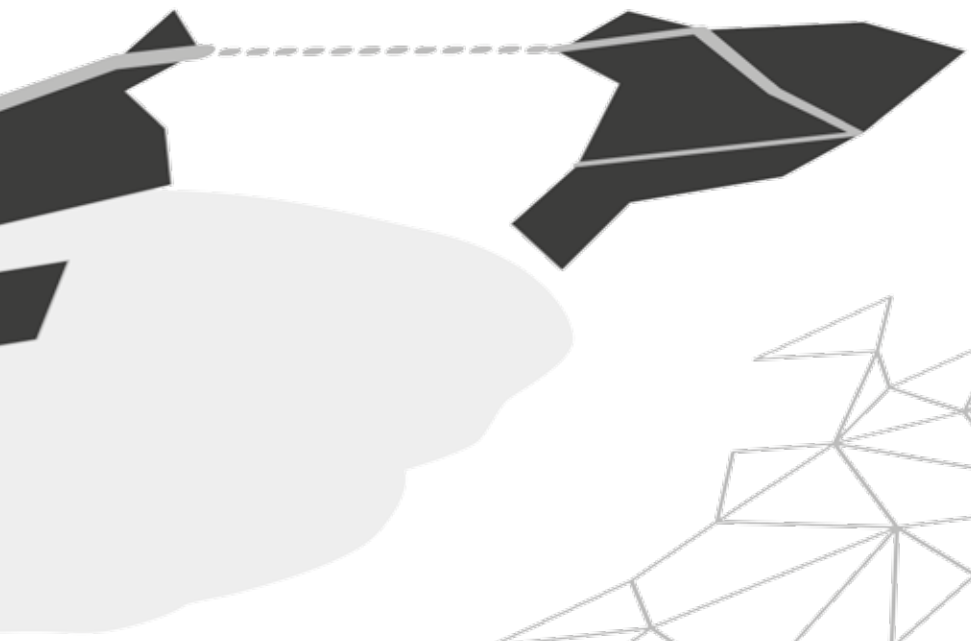
North-America

During my first oral presentation at the ICOSR conference in Orlando (Florida, USA), adult stress was an important topic of discussion (the talk itself was quite an adult stressor for me too, at that time). Represented by this continent, the recent findings presented in this chapter shed more light on this matter.



CHAPTER 6

Beyond childhood trauma: stressful events early and later in life in relation to psychotic experiences



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Introduction

Traumatic experiences during childhood increase the risk for psychopathology later in life (Danese & Baldwin, 2016), yet the underlying mechanisms remain elusive. In the context of psychotic disorders, Reininghaus and colleagues (2016) recently found support for the notion that enhanced sensitivity and increased threat anticipation to stress are important psychological mechanisms in the pathways from childhood trauma to psychosis (as put forward by Morgan and Hutchinson, 2010). The question is whether these mechanisms are relevant to the development of psychotic symptoms with a need for care, or merely contribute to a more general vulnerability for psychotic experiences, including *those without a need for care*. This can be studied by comparing patients with a psychotic disorder to individuals with frequent non-clinical psychotic experiences. We previously found that both groups reported equally high rates of childhood trauma (Daalman et al., 2012), suggesting that traumatic experiences early in life make a person vulnerable for psychotic experiences in general rather than forming a specific risk factor for a full-blown psychotic disorder. Notably, only a minority of maltreated children eventually develop psychotic experiences, whether or not part of a psychotic disorder, whereas others do not develop such experiences. To understand these differences, we need to gain more insight into the mechanisms involved in the pathways from childhood trauma to clinical and non-clinical psychotic experiences in adulthood.

During the past years, interest has increased regarding the role of stressful events after childhood in the development of psychotic experiences or a psychotic disorder. In individuals who have experienced maltreatment as a child, the risk for trauma exposure later in life is elevated (Acierno et al., 1999; Kim et al., 2014), which could be viewed as a second hit. According to meta-analytic data, exposure to adult stressful life events is associated with a higher risk of subsequent onset of a psychotic disorder or psychotic experiences, compared with controls (OR=3.19; 95%CI 2.15–4.75) (Beards et al., 2013). However, none of the included studies adjusted for childhood trauma (Beards et al., 2013), while the impact of stressful events on psychotic experiences later in life may be greater in individuals with a history of maltreatment. For instance, Read and colleagues (2003) found that a combination of both child and adult abuse, rather than either one alone, best predicted psychotic symptoms in psychiatric patients. In a population-based study by Morgan et al. (2014), early abuse and life events combined synergistically to increase the odds of subclinical psychotic experiences. In a population-based 10-year prospective study, only the highest levels of exposure to adversity (≥10 recent events) was related to psychotic symptoms, and this relation was stronger in individuals who were maltreated during childhood (Lataster et al., 2012).

Till recently, studies rarely considered the subjective interpretation of life events (Beards et al., 2013). However, as Reininghaus and colleagues (2016) demonstrated, psychological and cognitive mechanisms are important when evaluating the effects of childhood trauma and stressful events later in life. Indeed, when childhood trauma and adult trauma are related to both psychotic experiences as well as psychotic disorders, the question remains why some individuals pass the psychosis threshold while others do not.

By studying patients with a psychotic disorder, individuals with frequent non-clinical psychotic experiences and controls without psychotic experiences, we aimed to investigate:

1. The main effects of stressful life events after childhood and accompanying subjective ratings (impact, feelings of helplessness and perceived danger), on the odds of having a psychotic disorder versus having non-clinical psychotic experiences versus having no psychotic experiences;
2. The relative effects of childhood trauma and stressful events after childhood and their subjective ratings, by combining these factors in one model;
3. The synergistic effect by the combination of childhood trauma and stressful life events after childhood, following past work in this area (Lataster et al., 2012; Morgan et al., 2014).

Methods

Participants and procedures

We included 103 patients with a psychotic disorder, 134 individuals with non-clinical psychotic experiences (predominantly auditory verbal hallucinations) and 125 healthy controls (procedures described in Sommer et al., 2010; Daalman et al., 2012). The Life Stressor Checklist Revised (LSC-R; Wolfe et al., 1996) was used to evaluate stressful life events after childhood (yes/no, 26 items), endorsed items were summed. Follow-up questions addressed the age at which the event took place and to what extent the event still had impact on the participants' life during the past year (1-5 Likert scale; total impact scores divided by the number of endorsed events provided mean impact scores). For 15 possible traumatic items, two additional questions assessed whether participants believed they had been in danger and whether they had experienced feelings of helplessness (yes/no; total number of times divided by the number of experienced events provided percentages). All participants with ≤1 item missing were included. The Childhood Trauma

Questionnaire Short Form (CTQ-SF; Bernstein et al., 2003) was available for 99 patients, 127 individuals with non-clinical psychotic experiences and 124 controls, evaluating childhood trauma severity (25 items, 1-5 Likert scale) on five trauma subtypes: emotional, physical, and sexual abuse, and emotional and physical neglect. Cut-off scores for moderate to severe exposure were used to classify presence or absence of (one or more subtypes of) trauma (Daalman et al., 2012).

Ethical standards

All procedures were in accordance with the ethical standards of the Dutch institutional committees on human experimentation and with the declaration of Helsinki (1975, as revised in 2013).

Statistics

1. Multinomial logistic regression was used to quantify associations between stressful events after childhood (LSC-R total score and subjective ratings) and having clinical psychotic symptoms (patients) vs. having non-clinical psychotic experiences vs. having no psychotic experiences (controls), adjusting for age and gender. This was repeated for childhood trauma severity (CTQ-SF total score). Explorative correlations were calculated between childhood trauma and stressful events after childhood plus accompanying subjective ratings (mean impact, helplessness and danger; Spearman's ρ).
2. To examine their relative effects, predictors were combined in a multinomial logistic regression model (age and gender as covariates).
3. Synergistic effects of childhood trauma and stressful events after childhood were evaluated by comparing the interaction term in relation to their individual effects using a multinomial logistic regression model (Lataster et al., 2012; Morgan et al., 2014).

Results

Main effects

Gender was equally distributed, mean age differed between the three groups as patients were younger than healthy controls (Table 1). The number of stressful events after childhood (LSC-R total score) was associated with having a psychotic disorder (OR=1.28) and non-clinical psychotic experiences (OR=1.13) (Table 1). For each additional life event, the odds increased with 28% for having clinical psychotic symptoms (i.e. belonging to the patient group) and with 13% for having non-clinical psychotic experiences. The number of stressful events after childhood

was associated with similar odds for having a psychotic disorder or non-clinical psychotic experiences.

Higher impact of these events increased the odds for psychosis (OR=2.56) and non-clinical psychotic experiences (OR=1.65) (Table 1). Interestingly, each point increase in mean impact score was associated with 1.55-fold greater odds for psychosis over non-clinical psychotic experiences (OR=1.55). Each percentage-point increase in helplessness score increased the odds for psychosis with 3.1% (OR=1.03) and with 1.8% for non-clinical psychotic experiences (OR=1.02). Therefore, a 50% increase in mean helplessness rating would be associated with 4.71-fold greater odds for psychosis ($e^{50x0.031}$) and 2.46-fold greater odds for non-clinical psychotic experiences ($e^{50x0.018}$). Moreover, this 50% increase in helplessness score would nearly double the odds for psychosis versus non-clinical psychotic experiences (OR=1.01; 50% increase equals 1.92[$e^{50x0.013}$]). Perceived danger of stressful events was associated with psychosis (OR=1.01) but not with non-clinical psychotic experiences, the odds for having a psychotic disorder or non-clinical psychotic experiences were similar.

Every point increase in childhood trauma severity (CTQ-SF total score) was associated with higher odds for a psychotic disorder (OR=1.08) as well as non-clinical psychotic experiences (OR=1.07), odds for clinical versus non-clinical psychotic experiences were similar. Childhood trauma correlated significantly with the number of stressful events after childhood (ρ=0.403; within patients: ρ=0.377; individuals with non-clinical psychotic experiences: ρ=0.325; controls: ρ=0.348; all p-values <.001). Childhood trauma was related to higher impact scores (ρ=0.193) and helplessness ratings (ρ=0.195, p-values ≤.001), but not to experienced danger (ρ=−0.012, p=.843).

Relative effects

When all factors were combined in multinomial regression (age and gender as covariates), the model was significant ($\chi^2(14)=103.20$, $p<.001$) and showed a good fit to the data (Pearson $\chi^2(588)=601.21$, $p=.302$), with moderate predictive value of 32.8% (Nagelkerke pseudo $R^2=0.328$; no multicollinearity problems were found). While the associations with stressful events after childhood and perceived danger were weakened, perceived impact was associated with higher odds for having a psychotic disorder versus controls (OR=1.98), see Table 1. Helplessness remained associated with increased odds for having a psychotic disorder (OR=1.02) and for non-clinical psychotic experiences (OR=1.01) and, notably, with higher odds for clinical versus non-clinical psychotic experiences (OR=1.01). Childhood trauma remained associated with increased odds for clinical psychotic symptoms (OR=1.06) as well as non-clinical psychotic experiences (OR=1.05).

Table 1. Childhood trauma and stressful events after childhood in patients, individuals with non-clinical psychotic experiences and healthy controls.

Characteristics	**Patients**	**Individuals with non-clinical PE**	**Healthy controls**	Test statistic[a]	*p*-value	
n	103	134	125			
Male *n* (%)	40 (39%)	40 (30%)	39 (31%)	$\chi^2(2)=2.37$	*p*=.305	
Age in years, mean (*S.D.*)	38.14 (12.29)	42.01 (12.76)	42.89 (14.32)	$F(2)=4.052$	***p*=.018**	Post-hoc: **Pat<C (*p*=.021)** Non-clinical PE=C (*p*=1.00) Pat=non-clinical PE (*p*=.08)
Life events after childhood (LSC-R)						
Number of events, mean (*S.D.*)	5.05 (3.01)	5.65 (3.13)	3.74 (2.59)			
Impact[b], mean (*S.D.*)	2.62 (1.06)	2.15 (0.99)	1.74 (0.87)			
Helplessness[c], % of events (*S.D.*)	72.46% (34.15)	56.30% (39.07)	31.46% (36.35)			
Feeling in danger[c], % of events (*S.D.*)	51.77% (35.89)	43.96% (37.41)	34.18% (35.66)			
Childhood trauma (CTQ-SF), mean (*S.D.*)	46.67 (20.05)	45.20 (15.45)	35.43 (8.18)			

Main effects Multinomial logistic regression analysis[d]	**Patients vs. controls** OR (95%CI)	*p*-value	**Non-clinical PE vs. controls** OR (95%CI)	*p*-value	**Patients vs. non-clinical PE** OR (95%CI)	*p*-value
Life events after childhood (LSC-R)						
Number of events	**1.28 (1.15-1.43)**	***p*<.001**	**1.13 (1.19-1.45)**	***p* <.001**	0.97 (0.89-1.07)	*p*=.559
Impact[b]	**2.56 (1.85-3.53)**	***p*<.001**	**1.65 (1.22-2.22)**	***p*=.001**	**1.55 (1.19-2.03)**	***p*=.001**
Helplessness[c]	**1.03 (1.02-1.04)**	***p*<.001**	**1.02 (1.01-1.03)**	***p*<.001**	**1.01 (1.01-1.02)**	***p*=.001**
Feeling in danger[c]	**1.01 (1.01-1.02)**	***p*=.003**	1.01 (1.00-1.02)	*p*=.060	1.01 (1.00-1.01)	*p*=.180
Childhood trauma (CTQ-SF)	**1.08 (1.05-1.10)**	***p*<.001**	**1.07 (1.04-1.09)**	***p*<.001**	1.01 (0.99-1.03)	*p*=.219
Relative effects Multinomial logistic regression analysis[d]	**Patients vs. controls** OR (95%CI)	*p*-value	**Non-clinical PE vs. controls** OR (95%CI)	*p*-value	**Patients vs. non-clinical PE** OR (95%CI)	*p*-value
Gender (Ref: male)						
Female	**2.79 (1.29-6.01)**	***p*=.009**	1.91 (0.97-3.76)	*p*=.060	1.46 (0.76-2.79)	*p*=.256
Age	**0.96 (0.94-0.99)**	***p*=.010**	0.89 (0.96-1.01)	*p*=.109	0.98 (0.96-1.01)	*p*=.159
Life events after childhood (LSC-R)						
Number of events	1.04 (0.90-1.19)	*p*=.636	1.12 (0.98-1.27)	*p*=.090	0.93 (0.83-1.04)	*p*=.179
Impact[b]	**1.98 (1.31-3.01)**	***p*=.001**	1.44 (0.98-2.12)	*p*=.067	1.38 (0.99-1.90)	*p*=.051
Helplessness[c]	**1.02 (1.01-1.03)**	***p*<.001**	**1.01 (1.00-1.02)**	***p*=.005**	**1.01 (1.00-1.02)**	***p*=.025**
Feeling in danger[c]	1.01 (0.99-1.02)	*p*=.289	1.00 (0.98-2.12)	*p*=.490	1.00 (0.99-1.01)	*p*=.608
Childhood trauma (CTQ-SF)	**1.06 (1.03-1.09)**	***p*<.001**	**1.05 (1.02-1.08)**	***p*=.001**	1.01 (0.99-1.03)	*p*=.375

Significant findings are indicated in **bold**. Abbreviations: PE: Psychotic experiences; LSC-R: Life Stressor Checklist Revised; CTQ-SF, Childhood Trauma Questionnaire-Short Form; vs.: versus; Pat: Patients with a psychotic disorder; non-clinical PE: non-clinical psychotic experiences; C: healthy controls; OR: odd ratio; CI: Confidence Interval; [a]Group differences were explored using chi-square and ANOVA. [b]Impact scores were summed and divided by the LSC-R total score; [c]For potentially traumatic items, the number of times that people had felt helpless or had felt that they were in danger during the event were summed and divided by the number of experienced events (maximum of 15) to provide percentages (OR=regression coefficient per each percentage-point increase (e^{β}; 50% increase = $e50x^{\beta}$). [d]Adjusted for age and gender, OR=regression coefficient per each unit increase of the predictor variable (e^{β}).

Synergic effect

A history of childhood trauma was reported in 51.5% of the patients, compared to 53.5% of the individuals with non-clinical psychotic experiences and 28.2% of the controls. A history of childhood trauma increased the odds for psychosis (OR=2.06; 95%CI: 0.65 to 6.61, *p*=.001), as did stressful events after childhood (OR=1.20; 95%CI: 1.03 to 1.40, *p*=.021). However, the interaction effect of both factors was not significant (OR=1.05, 95%CI: 0.84 to 1.30; *p*=.667). The higher odds for non-clinical psychotic experiences after a history of childhood trauma bordered on significance (OR=3.05; 95%CI: 0.99 to 9.36, *p*=.051), while every additional life event after childhood increased the odds by 31% (OR=1.31; 95%CI: 1.14 to 1.51, *p*<.001). Again, the combined effect was not significant (OR=0.95; 95%CI: 0.78 to 1.17, *p*=.635). Childhood trauma and stressful events after childhood were both associated with similar odds for having a psychotic disorder versus non-clinical psychotic experiences (OR=0.67; 95%CI: 0.22 to 2.05, *p*=.490 and OR=0.92; 95%CI:0.79 to 1.06, *p*=.240, respectively), with no interaction effect (OR=1.10; 95%CI:0.91 to 1.33, *p*=.314).

Discussion

This study confirms and extends previous findings showing that childhood trauma and stressful life events after childhood are both related to psychosis as well as non-clinical psychotic experiences. Childhood trauma was also associated with increased exposure to stressful events after childhood. However, contrary to a population-based study (Morgan et al., 2014), these factors did not combine synergistically in relation to psychotic experiences. In another population-based study, a synergistic effect between childhood and recent adversity was observed only in case of ≥10 recent stressors (Lataster et al., 2012). Thus, the interaction between childhood and later adversity in relation to psychotic experiences remains unclear.

Furthermore, subjective ratings of stressors after childhood were related to psychosis (impact, helplessness and perceived danger) and non-clinical psychotic experiences (impact and helplessness). Previous work found that recent-onset schizophrenia patients appraise stressors as less controllable and their coping as less effective (Horan et al., 2005) and that individuals at ultra high-risk for psychosis are more distressed by events and feel that they cope more poorly (Phillips et al., 2012). Notably, our results show that impact and helplessness both increased the odds for psychosis over non-clinical psychotic experiences.

As suggested by Reininghaus et al. (2016), early trauma may impact these subjective reactions to later stressors. Indeed, we found that childhood trauma severity correlated with impact, helplessness and perceived danger of

later stressful events. After adjusting for childhood trauma, helplessness remained associated with psychosis and with non-clinical psychotic experiences. Feelings of helplessness remained associated with increased odds for psychosis over non-clinical psychotic experiences. This implies that individuals with frequent non-clinical psychotic experiences are able to cope more adaptively with childhood trauma and stressful events, which they experience at equally high rates as patients with a psychotic disorder.

In conclusion, our findings support the hypothesis that both childhood trauma and stressful events later in life contribute to a general vulnerability for psychotic experiences that may or may not be part of a psychotic disorder. Maladaptive reactions to stressors later in life may be implicated in the pathways from adverse experiences to psychosis. This is important, as youngsters with childhood trauma may benefit from training to improve coping skills to deal with later life events. Even though such skills may not prevent the development of psychotic signs, full-blown psychotic disorders may be prevented this way.

Conflicts of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013.

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The world map

Summarizing and discussing the findings from previous chapters, this chapter represents a worldly perspective on the results from the different continents.

CHAPTER 7

Summary and general discussion

The research described in this dissertation explored different pathways by which childhood trauma can be linked to the development of psychotic experiences later in life. This final chapter provides a summary and discussion of our main findings, together with methodological considerations and clinical implications.

Summary

General prevalence of auditory hallucinations

This dissertation started with an investigation on the prevalence of auditory hallucinations in the general population. In **chapter 2**, we combined estimates from 25 population-based studies in meta-analysis, including a total of 84 711 participants. We found that auditory hallucinations were reported by almost 10% of the general population during lifetime. Notably, prevalence rates were higher in children and adolescents compared to adults and elderly. These results highlight the relatively common character of auditory verbal hallucinations and underscore the importance of investigating potential mechanisms underlying these psychotic experiences in clinical as well as non-clinical individuals.

Neuroticism

Childhood trauma predicts the occurrence of auditory verbal hallucinations and, more specifically, how a person responds to these voices cognitively and affectively. Neuroticism could be a potential mediating factor in shaping these maladaptive reactions to voices. In **chapter 3**, we found a graded difference in levels of neuroticism across patients with a psychotic disorder, non-clinical individuals with frequent auditory verbal hallucinations and controls. In both clinical and non-clinical individuals alike, higher levels of neuroticism were associated with more resistance and more emotional distress in response to their voices, together with an increased tendency to perceive voices as malevolent and powerful. While childhood trauma severity predicted these maladaptive responses to voices, each of these associations were fully explained by levels' of neuroticism. This is the first study to demonstrate that childhood trauma is linked to maladaptive reactions to voices via higher levels of neuroticism. Our results indicate that a neurotic personality could be an important trauma-related vulnerability marker for the development of psychotic experiences with a need for care.

Cognitive functioning

Cognitive impairment is a vulnerability factor for the development of psychotic experiences, and childhood trauma may be an important factor underlying

this association. In **chapter 4**, we investigated cognitive performance in non-clinical adults with and without psychotic features, thus preventing disease-related bias. Increased exposure to childhood trauma was associated with reduced verbal inhibition in the domain of executive functioning. Moreover, trauma severity fully explained the reduced executive functioning and working memory performance that has been associated with the vulnerability to experience psychotic symptoms. Childhood trauma did not account for the relations between non-clinical psychotic experiences and reduced verbal abilities or intelligence. These findings indicate that reduced cognitive functioning, especially those supported by frontal brain regions, may constitute a general underlying mechanism by which childhood trauma increases the risk for the development of psychotic symptoms later in life.

Brain structure

Childhood trauma may increase the risk for psychiatric illness by its negative impact on brain development. In **chapter 5**, we investigated the neurobiological correlates of childhood trauma using a cross-diagnostic approach. In a large sample of healthy individuals and patients diagnosed with a bipolar-I or psychotic disorder, trauma severity was associated with bilateral volume reductions in the frontal and insular regions of the brain. Within the right frontal lobe, childhood trauma was related to reduced gray matter volume in the medial orbitofrontal and superior frontal regions. These associations remained when adjusting for psychiatric illness, with the exception of the right superior frontal subregion. When evaluating both groups separately however, these structural correlates of childhood trauma were mainly observed in patients. We did observe an association between trauma and gray matter reductions in the right medial orbitofrontal region, but not in patients. Our results implicate that gray matter reductions in the frontal and insular areas are important neurobiological correlates of childhood trauma. As these regions support higher-order cognitive functions, this may explain why reduced executive functioning has been linked to a history of childhood trauma. Future research should apply a whole brain approach, as cortical rather than subcortical areas may be the main correlate of childhood trauma, contributing to the development of psychopathology.

Stressful events after childhood

A history of childhood trauma increases the risk of being exposed to stressful events later in life. In **chapter 6**, we investigated the role of stressful events *after childhood*, in the development of psychotic experiences or a psychotic disorder. We found that a higher number of stressors experienced after childhood was

associated with psychosis as well as non-clinical psychotic experiences. Notably, a higher perceived impact and feelings of helplessness in response to these stressors differentiated between these two groups, with increased odds for psychosis over non-clinical psychotic experiences. Childhood trauma was related to an increased number of stressors encountered later in life, yet early and later trauma did not combine synergistically in our included groups. Importantly, childhood trauma severity was associated with maladaptive responses to later stressors (higher impact, helplessness and perceived danger). After adjusting for childhood trauma, feelings of helplessness during life stressors after childhood still increased the odds for psychosis over non-clinical psychotic experiences. Our results suggest that, while individuals with frequent non-clinical psychotic experiences experience equal high rates of stressful events after childhood as patients with a psychotic disorder, they are able to cope more adaptively.

Discussion

The road map: from childhood trauma to psychotic experiences

The studies described in this dissertation highlight two important aspects of psychotic experiences. First, we confirmed that auditory hallucinations are quite common in the general population, with one in every ten individuals reporting such an experience during their lifetime. Prevalence rates are even higher in children and adolescents compared to adults and elderly. Thereby, we disprove the popular notion that psychotic experiences are rare and invariably indicative of mental illness. A public understanding of the common nature of psychotic experiences can help in de-stigmatizing these phenomena in general, and psychotic illness in particular. Moreover, our findings highlight the need to investigate the mechanisms by which these psychotic experiences arise and, importantly, why some individuals pass the psychosis threshold while others do not. Second, we identified several important pathways that could be involved in the development of psychotic experiences and psychosis, by using childhood trauma as a starting point. Based on our findings, we argue that traumatic experiences during childhood may cause abnormal development of the frontal and insular cortices, resulting in reduced executive functioning and working memory, emotional instability and maladaptive coping later in life.

Although different theories on the aetiology of psychosis have been proposed, our findings can be best viewed in light of the neurodevelopmental hypothesis (Rapaport et al., 2005; Fatemi et al., 2009). This influential framework posits that schizophrenia is the end stage of pathologic processes that occur early in brain

development, resulting from a combination of genetic and environmental causes. The abnormal development of the brain starts as early as fetal development, long before the brain approaches its adult anatomical state (Rapaport et al., 2005; Fatemi et al., 2009). This aberrant neurodevelopment subsequently leads to the activation of pathologic neural circuits during adolescence or young adulthood, causing psychotic symptoms. Epidemiological, developmental and neuroimaging studies have provided much support for this theory (Rapaport et al., 2005).

Together with urbanicity and immigration status, childhood trauma is one of the environmental factors of which the potential contribution to this process has received strong replication (Rapaport et al., 2005). Neurodevelopmental research has established that the brain is extremely sensitive to stressors that are encountered early in life (Read et al., 2001). Notably, the effects of early stress on the developing brain have shown important overlap with the biological abnormalities found in schizophrenia patients. Similarities include overreactivity of the hypothalamic–pituitary–adrenal (HPA) axis, neurochemical imbalances within dopaminergic, serotoninergic and norepinephrinergic neurotransmission and structural changes of the brain, including cerebral atrophy and ventricular enlargement (Read et al., 2001). The traumagenic neurodevelopmental model as composed by Read et al. (2001) therefore attributes a central role to childhood trauma within the development of schizophrenia, by postulating that the neurological and biochemical abnormalities found in schizophrenia are at least partly caused by the exposure to adverse experiences during childhood. As a note of caution however, it must be noted that many patients with schizophrenia do not have a history of childhood trauma, while the majority of severely traumatized children will never develop psychosis. Yet, there certainly is an association between schizophrenia and trauma and its exact relation may help understand the genesis of this disorder.

While exposure to stressors causes as cascade of biological responses, the hypothalamic-pituitary-adrenal (HPA) axis will be shortly discussed as it is one of the primary neurobiological systems that becomes activated (Pruessner et al., 2017). The hypothalamus secretes corticotropin-releasing hormone and vasopressin, stimulating the release of adrenocortropic hormone from the pituitary. In turn, the adrenal cortex releases glucocorticoids, including cortisol. Prolonged activation of the HPA axis due to persistent stressors can result in chronic hypersecretion of these glucocorticoids. This may cause permanent dysregulation of the HPA axis when negative feedback mechanisms become impaired (Pruessner et al., 2017). Dysregulation of the HPA-axis is a well-replicated finding in psychosis (Read et al., 2001). The effects of HPA on brain structure and function can be explained by different biological mechanisms. For example, glucocorticoids augment

various neurotransmitter systems that have been implicated in schizophrenia, including alterations in the dopaminergic system (Read et al., 2009; Pruessner et al., 2017). Moreover, glucocorticoids modulate immunological and inflammatory reactions, by stimulating the release of cytokines and C-reactive protein (Baumeister et al., 2015). This influence on the immune system may also impact brain development. Increased inflammation has been linked to reductions in brain-derived neurotrophic factor (BDNF) levels, which is an important neurotrophic factor for neurogenesis in both developing and adult brains (Mondelli et al., 2011; Pruessner et al., 2017). Interestingly, a recent study has shown that a history of childhood trauma and high levels of recent stressors was associated with lower BDNF expression through an inflammation-mediated pathway (Mondelli et al., 2011).

When evaluating the effects of stress-induced HPA axis dysfunction on brain development, our finding of trauma-related frontal and insular gray matter loss (**chapter 5-II**) is consistent with this neurodevelopmental view of schizophrenia. The frontal lobes are importantly involved in HPA axis functioning through mediating fronto-cortical pathways and are thus especially vulnerable to the negative effects of stress (Read et al., 2009). The frontal regions mature relatively late, which coincides with the typical onset of schizophrenia spectrum disorders in late adolescence. This protracted development of the frontal lobes also provides context for our findings in **chapter 2**. The common character of psychotic experiences, specifically during childhood and adolescence, is thought to reflect typical development (van Os et al., 2009). A decrease in incidence can be expected with advancing age due to the development of more advanced cognitive functions that are supported by the frontal lobes (van Os et al., 2009). In **chapter 4**, we show that reduced verbal inhibition in the domain of executive functioning and lower working memory is indeed linked to the vulnerability for psychotic experiences in non-clinical individuals and that this association can be explained by exposure to childhood trauma. Structural and functional integrity of these frontal regions is also implicated when managing stress reactivity, by means of adaptive coping skills. In **chapter 3**, we found that neuroticism mediates the link between childhood trauma and maladaptive responses to voices. This line of thought also fits our results from **chapter 6**, in which childhood trauma was associated with increased exposure to stressful events after childhood and less adaptive reactions to these later stressors.

Importantly however, both patients with a psychotic disorder and non-psychotic individuals with frequent auditory verbal hallucinations report equal high rates of childhood trauma (Daalman et al., 2012). The question therefore remains why some individuals pass the psychosis threshold, while others do not. Our findings imply that patients are more vulnerable to the impact of childhood

trauma compared to the non-clinical individuals with frequent psychotic experiences. These non-clinical individuals do show increased levels of neuroticism, decreased cognitive functioning and subtle gray matter reductions, but to a much lesser degree than patients (So et al., 2016; Daalman et al., 2011; van Lutterveld et al., 2014). Increased stress-sensitivity is an important characteristic for psychosis, and individuals with frequent non-clinical psychotic experiences appear to cope more adaptively with childhood trauma and stressful events later in life - which they experience at equally high rates as patients with a psychotic disorder. As highlighted in the traumagenic neurodevelopmental model, the increased vulnerability for psychosis arises from a complex interplay between genetic and environmental factors. Future longitudinal studies are needed to understand the temporal sequence and complex interplay between these different factors.

Exploring the biological mechanisms by which childhood trauma is linked to the development of non-clinical and clinical psychotic experiences can also provide new leads for improving treatment methods. As described above, one potential pathway entails the involvement of the immune system. Several lines of evidence have implicated that childhood trauma may be an important environmental factor that increases the inflammatory status in the brains of patients with a psychotic disorder, which could lead to neurodevelopmental abnormalities (Fatemi et al., 2009; Aas et al., 2014). In addition to studies separately linking inflammation to childhood trauma as well as psychotic symptoms, a pro-inflammatory phenotype has been specifically demonstrated in schizophrenia patients with a positive history of childhood trauma (Aas et al., 2014; Dennison et al., 2012). We have previously demonstrated that anti-inflammatory agents show promising results in treating psychotic symptoms, by including 26 double-blind randomized controlled trials in meta-analysis (Sommer et al., 2014). We are currently undertaking a double-blind placebo-controlled trial to evaluate the effects of simvastatin in patients with recent-onset psychosis, combining anti-inflammatory with cardioprotective properties (methods are described in Begemann et al., 2015). Effects on symptomatology, cognitive functioning and brain volume are investigated. In addition, immunological and metabolic parameters are assessed in blood samples to possibly predict treatment response. By also evaluating childhood trauma severity, we can investigate whether a potential association between pro-inflammatory markers and treatment response is mediated by a history of childhood trauma.

Methodological considerations

The findings reported in this dissertation need to be interpreted in light of both the strengths and the weaknesses of the applied methods. With regard to

chapter 2, we must note that the quality of a meta-analysis stands with the quality of the included studies. By following systematic guidelines and well-defined criteria for studies to be included, this meta-analysis was conducted to the best of our abilities.

In addition, the assessment of childhood trauma in **chapters 3 through 6** was subjective and retrospective, which is the case in most studies into this topic. As a result, recall and reporting bias may have affected study results. Nonetheless, the retrospective and prospective reporting of childhood trauma has proven to be reliable in both clinical and non-clinical populations and to be stable across time (Bernstein et al., 1997; Bernstein et al., 2003; Scher et al., 2001). It is also important to note that previous research has typically assessed childhood trauma by dichotomizing individuals into those who report traumatic childhood events and those who have no such history. However, we have chosen to evaluate the severity of childhood trauma as a continuous measure. This approach is not only supported by the dose-response relationship that is usually found for the impact of childhood trauma of different outcome measures, we also take into consideration those individuals who score just below the cut-off values but have experienced a stressful childhood.

Furthermore, the cross-sectional nature of the studies in **chapters 2 through 6** does not allow conclusions about the directionality of the results. There is still much debate whether childhood trauma plays a causal role in the development of clinical and non-clinical psychotic experiences later in life. The causality of early traumatic experiences is difficult to prove. A genetic vulnerability may underlie both the development of psychotic experiences later in life as well as an increased risk for trauma exposure - a parent with a psychotic disorder may provide a negative childhood environment in addition to the genetic propensity for the disorder to their children (Fisher et al., 2014). There is also the case of reverse causality, meaning that individuals who will develop a psychotic disorder later in life may already display deviating behavior which makes them vulnerable to be exposed to harmful behavior by others around them (for example emotional neglect by their parents or bullying by their peers) (Sideli et al., 2012). Nonetheless, several lines of research implicate that childhood trauma importantly contributes to the development of psychotic experiences and full-blown psychotic disorder. There is the dose-response relationship documented by many studies, with more severely maltreated patients showing more severe psychotic symptoms (Larkin & Read 2008). In addition, longitudinal studies have shown that a history of childhood trauma predicts the development of psychotic symptoms later in life (Larkin & Read 2008; Janssen et al., 2004). Another study found that children reported more (mild) psychotic symptoms during at the time that they were

bullied, while these experiences decreased or ceased when the bullying stopped (Kelleher et al., 2013).

Finally, in **chapter 2 through 6**, the potential limitation of selection bias must be noted. The clinical and non-clinical individuals who participated in these studies may not be representative as the will to participate alone can create a bias – which is unfortunately inherent to research.

Relevance to clinical practice and future prospects

Childhood trauma is disproportionately experienced by individuals who have psychotic experiences, schizophrenia, and other psychiatric conditions. It is therefore imperative that clinicians in the field of mental health care enquire routinely about this subject. Notably, patients vary widely in their disease course and outcome, even within one diagnostic category. Clinicians should be aware that a history of childhood trauma is an important factor in this context, as maltreated individuals with different disorders have an earlier age at onset, greater symptom severity, more comorbidity and reduced social and occupational functioning (Cotter et al., 2015; Teicher & Samson, 2013). Moreover, childhood trauma can negatively affect therapeutic alliance and the adherence to treatment, and patients who have been exposed to childhood trauma show a poorer treatment response than those without this history (Teicher & Samson, 2013). In addition, the profiles of patients with non-adherence and low service engagement are strongly predicted by childhood trauma.

However, the subject of traumatic experiences during childhood is a very personal and delicate topic. When a possible diagnosis of (comorbid) PTSS is not considered and patients do not spontaneously mention the experience of traumatic events during their childhood, clinicians not always specifically address this issue. As a result, the subject of childhood trauma can be an important elephant in the room of clinicians. Patients often feel ashamed to talk about these distressing events, but disclosure rates do increase enormously when people are actively asked about these experiences (Read & Fraser, 1998). Guidelines about when and how to inquire about childhood trauma have been published to inform clinicians (Read, 2006; Read et al., 2007). Although clinicians must account for time demands when making assessment choices in present times, good screening can be done in a time-efficient manner. The questionnaire used in our studies only takes five minutes to fill out and can easily be adapted for clinical use. The five types of abuse and neglect as evaluated by the CTQ-SF appear to have a particularly large and long-lasting impact. When time permits however, it can be advised to also address other forms of childhood adversity, such as parental loss, separation and bullying.

More knowledge on the relation between negative events during childhood and the development of psychotic experiences can importantly aid in the development of prevention and treatment strategies. Preventing children from being exposed to maltreatment altogether would be the most obvious action that can be taken. The estimated population attributable risk is estimated to be 33% - which means that if childhood adversities would be entirely removed from the population, the number of individuals with a psychotic disorder would be reduced by one third (Varese et al., 2012). Preventing the abuse and neglect of children remains an important issue that requires a comprehensive and multi-dimensional public health approach by engaging patients, health care providers, policymakers and researchers. For children who have already been exposed to traumatic experiences early in life, a timely signaling of emotional, cognitive and social difficulties is crucial as the effects of early intervention strategies may be larger when applied at a younger age (Vita et al., 2013; Sommer et al., 2016). For example, cognitive remediation therapy could be promising for improving cognitive and social functioning. Beneficial effects of cognitive remediation have been shown in patients with a psychotic disorder and notably, improvements are larger when applied at a younger age (Vita et al., 2013). Moreover, cognitive normalization after remediation treatment is predicted by higher cognitive functioning (particularly executive functions and verbal memory) before start of therapy (Vita et al., 2013). It has therefore been argued that cognitive remediation should be implemented as soon as reduced cognitive deficits become apparent and treatment is most effective, which is during childhood (Sommer et al., 2016). In addition, anti-bullying programs for children and young adolescents can be implemented to improve social outcomes (Sommer et al., 2016). Notably, children who are delayed in their cognitive, social or behavioral development have an increased risk of being bullied by their peers, which in turn has been associated with the developing of psychotic symptoms later in life (Van Dam et al., 2012). With regard to neurotic personality traits and maladaptive coping skills, cognitive behavioral therapy may lead to more constructive and positive cognitions and behavior, reducing stress reactivity in response to encountered to life events (Tarrier, 2008).

Childhood trauma also plays a significant role when treating a patient that has already developed a psychotic disorder. As shown in this dissertation and by previous studies, a variety of trauma-related vulnerabilities can be evaluated in case a patient presents with a history of childhood trauma. This includes an extensive evaluation of personality characteristics, neuropsychological functioning and coping skills. Different treatment approaches are now emerging that specifically target these trauma-related vulnerabilities. Cognitive remediation therapy can be implemented to improve neurocognitive and social cognitive deficits (Wykes et al.,

2011; Statucka & Walder, 2013). In addition, cognitive behavioral therapy has shown beneficial effects in patients to reduce maladaptive reactions to symptoms (such as auditory verbal hallucinations) or other stressful events (Gaudian & Herbert, 2006). Furthermore, strategies have been developed that specifically target the interpersonal relationship impairments caused by early trauma (Bateman & Fonagy, 2009). Finally, established PTSD guidelines can be followed in case of co-occurring PTSD. Studies have shown that exposure-based therapy and eye movement desensitization and reprocessing (EMDR) therapy can also be used safely and effectively in patients with psychosis (Frueh et al., 2009; Van den Berg et al., 2015).

Conclusive remarks

The findings in this research emphasize that the significance of psychotic experiences goes beyond psychopathology, as psychotic experiences are common across the general population. We found that increased levels of neuroticism, reduced executive functioning, gray matter loss in the frontal and insular regions and maladaptive coping with stressful events encountered later in life, are important mechanisms by which childhood trauma may increase the risk for psychotic experiences and psychosis. Future exploration, ideally in longitudinal datasets, is necessary to identify the pathways that link a history of childhood trauma to the development of psychotic experiences and psychosis later in life.

Psychotic disorders have long been viewed as almost inevitably chronic, with little hope for sustained remission or recovery. During the past seven years, I had the privilege of meeting a lot of different people - they were all diagnosed with a psychotic disorder and each had their own moving story. Although it is a difficult path to follow, I learned that a psychotic disorder is not a life-long sentence. This is illustrated by the story of professor John Nash, who was awarded the Nobel Memorial Prize in Economic sciences in 1994, for his contributions to game theory.

> *I still see things that are not here.*
> *I just choose not to acknowledge them.*
> *Like a diet of the mind, I just choose not to indulge certain appetites;*
> *like my appetite for patterns; perhaps my appetite to imagine and to dream.*
>
> *- A Beautiful Mind -*

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CHAPTER 8

Nederlandse samenvatting

Routekaart naar psychose: trauma in de kindertijd als de onzichtbare rugzak

Schizofrenie en aanverwante psychotische stoornissen hebben een flinke impact op het leven van patiënten en hun naasten. Veel voorkomende symptomen zijn het verlies van realiteitsbesef, verminderde emotionele reacties en problemen met denken zoals concentratie- en geheugenproblemen. Kenmerkend zijn ook de hallucinaties, met name het horen van stemmen of geluiden die anderen op dat moment niet kunnen horen - ook wel auditief (verbale) hallucinaties genoemd.

Deze psychotische ervaringen kunnen tevens voorkomen bij andere aandoeningen zoals een bipolaire stoornis of een borderline persoonlijkheidsstoornis, maar ook bij de ziekte van Parkinson, Alzheimer of gehoorverlies. Het is zelfs zo dat mensen zonder psychiatrische of somatische aandoening regelmatig psychotische ervaringen kunnen hebben - zij het meestal in milde vorm. Daarom worden psychotische ervaringen ook wel beschreven in termen van een continuüm: met aan de ene kant milde en/of voorbijgaande ervaringen bij gezonde mensen zonder klinische aandoening, en aan de andere kant psychotische symptomen zoals gezien wordt bij patiënten.

Een belangrijke risicofactor voor het ontwikkelen van zowel klinische als niet-klinische psychotische ervaringen is het doormaken van traumatische ervaringen tijdens de kindertijd. Onderzoek heeft aangetoond dat patiënten met een psychotische stoornis bijna drie keer zo vaak een traumatische kindertijd hebben gehad in vergelijking met gezonde mensen. Opvallend is dat mensen zonder psychiatrische aandoening maar mét frequente psychotische ervaringen, ook vaker trauma hebben meegemaakt tijdens hun kinderjaren. Er is nog maar weinig bekend over de manieren waarop deze vroege traumatische ervaringen ertoe kunnen leiden dat dat mensen later in hun leven psychotische ervaringen ontwikkelen, of zelfs een psychose. Dit proefschrift onderzoekt op welke manieren trauma in de kindertijd gerelateerd is aan het ontwikkelen van psychotische ervaringen, met andere woorden: welke routes er lopen tussen trauma en psychose.

Prevalentie

In **hoofdstuk 2** hebben we onderzocht hoe vaak psychotische ervaringen nu eigenlijk voorkomen in de algemene bevolking. Hierbij hebben we specifiek gekeken naar auditieve hallucinaties, dus het horen van stemmen of geluiden die andere mensen op dat moment niet waarnemen. Voor deze studie hebben we de gegevens van 25 eerder uitgevoerde onderzoeken kunnen combineren, waardoor onze inschatting uiteindelijk gebaseerd is op 84 711 individuen uit de algehele populatie. We vonden dat bijna 1 op de 10 mensen

weleens een auditieve hallucinatie heeft gehad tijdens zijn of haar leven. Ook hebben we aangetoond dat deze ervaringen vaker voorkomen bij kinderen en adolescenten dan bij volwassenen en ouderen. De onderzoeksresultaten geven aan dat relatief veel mensen weleens een auditieve hallucinaties heeft en dat het belangrijk is om te onderzoeken welke mechanismen hieraan ten grondslag liggen, zowel bij gezonde mensen als bij patiënten.

Neuroticisme

Trauma in de kindertijd vergroot de kans op het ontwikkelen van auditief verbale hallucinaties, en voorspelt ook hoe iemand op deze stemmen zal reageren. In **hoofdstuk 3** onderzochten we in hoeverre de persoonlijkheidstrek neuroticisme een rol speelt bij het vormen van negatieve reacties jegens stemmen. We vonden dat patiënten met een psychotische stoornis het hoogst scoorden op neuroticisme, oftewel de tendens tot emotionele instabiliteit. Mensen zonder psychotische stoornis maar mét psychotische symptomen scoorden hier net onder, en mensen uit de controlegroep (zonder aandoening en zonder psychotische symptomen) hadden de laagste score. Een neurotische persoonlijkheid was gelinkt aan meer emotionele last en weerstand als reactie op de stemmen, dit gold zowel voor patiënten als voor mensen zonder psychotische stoornis. Neuroticisme ook gerelateerd aan de mate waarop de stemmen als kwaadwillend en machtig werden ervaren. Daarnaast vonden we dat trauma in de kindertijd gerelateerd was aan negatieve reacties jegens stemmen - dat wil zeggen, meer emotionele last en weerstand evenals kwaadwillendheid en macht van de stemmen. Opvallend genoeg konden deze verbanden geheel verklaard worden door de mate van neuroticisme. Daarmee is dit de eerste studie die aantoont dat trauma in de kindertijd gelinkt is aan negatieve reacties jegens stemmen via neurotische persoonlijkheidstrekken. Dit maakt dat een neurotische persoonlijkheid een belangrijke trauma-gerelateerde kwetsbaarheidsfactor zou kunnen zijn voor het ontwikkelen van psychotische ervaringen, waar klinische zorg voor nodig is.

Cognitief functioneren

Een andere belangrijke kwetsbaarheidsfactor voor het ontwikkelen van psychotische ervaringen is een verminderd cognitief functioneren. Hiermee worden problemen in het denkvermogen bedoeld. zoals moeilijkheden om op woorden te komen of problemen met aandacht en concentratie. Trauma in de kindertijd heeft een negatief effect op cognitie en zou daarom een belangrijke onderliggende factor kunnen zijn. In **hoofdstuk 4** hebben wij het denkvermogen van mensen zonder psychotische stoornis onderzocht, waarvan 101 deelnemers

regelmatig psychotische ervaringen had en de andere 101 (controle)deelnemers dergelijke ervaringen niet had. We vonden dat mensen die meer trauma hadden ervaren tijdens hun kindertijd, minder goed waren in zogenaamde verbale inhibitie – oftewel, zij konden verbale informatie minder goed onderdrukken. Eerder onderzoek vond dat mensen met frequente psychotische ervaringen gemiddeld minder goed scoren op verbale inhibitie en werkgeheugen, en deze studie toont aan dat dit (deels) verklaard kan worden doordat deze mensen vaker jeugdtrauma hebben meegemaakt. Met andere woorden, de negatieve invloed van trauma op het cognitief functioneren, specifiek de functies die ondersteund worden door de frontale gebieden van de hersenen, kan de kwetsbaarheid voor het ontwikkelen van psychotische symptomen later in het leven mede vergroten.

Hersenvolume

Stressvolle gebeurtenissen vroeg in het leven zouden de kans op het ontwikkelen van een psychose, en psychiatrische aandoeningen in het algemeen, mogelijk kunnen vergroten door hun negatieve impact op de hersenontwikkeling. In **hoofdstuk 5** hebben we onderzocht welke hersengebieden samenhangen met trauma in de kindertijd, oftewel de neurobiologische correlaten van trauma. Dit hebben we gedaan in een grote steekproef van gezonde mensen en patiënten met een bipolaire stoornis (type I) of een psychotische stoornis. In de gehele groep was trauma in de kindertijd gerelateerd aan verminderde grijze stof in de frontale gebieden en de insula, zowel in de linker als de rechter hersenhelft. Specifiek in het rechter frontaal gebied was trauma geassocieerd met minder grijze stof in de mediale orbitofrontale en de superieure frontale subgebieden. De gevonden associaties bleven bestaan wanneer er gecorrigeerd werd voor groep (gezond vs. patiënt), behalve in het rechter superieure frontale subgebied. Toen we de twee groepen (gezond vs. patiënt) apart bekeken, bleek echter dat deze trauma-gerelateerde verminderingen in grijze stof met name voorkomen in de patiënten. Opvallend genoeg was dit patroon omgekeerd voor het rechter mediale orbitofrontale subgebied – hier was trauma wel gerelateerd aan verlies van grijze stof in de gezonde groep, maar dit verband werd niet geobserveerd bij patiënten. De resultaten van deze studie wijzen er dus op dat juist de frontale gebieden en insula kwetsbaar zijn voor traumatische gebeurtenissen vroeg in het leven, in tegenstelling tot de hippocampus en amygdala die vaak in eerder onderzoek zijn gevonden. Trauma in de kinderijd is daarmee een belangrijke omgevingsfactor is die onderliggend zou kunnen zijn aan de abnormale hersenontwikkeling welke uiteindelijk kan leiden tot psychopathologie.

Stress na de kindertijd

Mensen die een traumatische kindertijd hebben gehad, maken later in hun leven ook vaker stressvolle gebeurtenissen mee. In **Hoofdstuk 6** vonden we dat wanneer iemand meer stressvolle levensgebeurtenissen meemaakt na zijn of haar kindertijd, de kans groter is op het hebben van psychotische ervaringen; zowel in het kader van een psychose als zonder psychotische aandoening. Opvallend was dat wanneer deze gebeurtenissen een grotere impact hadden op de persoon, of wanneer diegene zich vaker hulpeloos had gevoeld, dit vooral de kans verhoogde op het ontwikkelen van een psychotische stoornis en niet zozeer op het ontwikkelen van niet-klinische psychotische ervaringen. Daarnaast onderstrepen onze resultaten dat trauma in de kindertijd gerelateerd is aan een groter aantal stressvolle gebeurtenissen later in het leven. Daarbij was trauma gerelateerd aan subjectieve reacties op deze latere gebeurtenissen (grotere impact, gevoelens van hulpeloosheid en gevaar). Wanneer er gecorrigeerd werd voor dit effect van trauma in de kindertijd, bleek dat gevoelens van hulpeloosheid nog steeds een verhoogde kans gaven op het hebben van een psychotische stoornis ten opzichte van niet-klinische psychotische ervaringen. Onze resultaten impliceren dat mensen met psychotische ervaringen maar zonder psychotische stoornis, beter om kunnen gaan met stressvolle gebeurtenissen dan patiënten - ondanks dat zij deze net zo vaak meemaken. Mogelijk heeft deze stressbestendigheid hen behoedt voor het ontwikkelen van een psychotische stoornis.

Conclusie: routekaart van trauma in de kindertijd naar psychotische ervaringen

De studies in dit proefschrift belichten twee belangrijke aspecten van psychotische ervaringen. Ten eerste tonen we aan dat auditieve hallucinaties vrij vaak voorkomen in de algehele populatie: 1 op de 10 mensen rapporteren een dergelijke ervaring gedurende hun leven. Deze prevalentie ligt hoger bij kinderen en adolescenten. Dit betekent dat psychotische ervaringen helemaal niet zo ongewoon zijn als vaak wordt gedacht. Meer begrip van het relatief frequente voorkomen van dit soort ervaringen kan helpen om dit fenomeen in het algemeen, maar ook psychotische stoornissen in het bijzonder, te de-stigmatiseren.

Ten tweede hebben we verschillende routes geïdentificeerd die een link leggen tussen trauma in de kindertijd en psychotische ervaringen later in het leven. We vonden dat neurotische persoonlijkheidstrekken, een verminderd executief functioneren, verminderd grijze stof volume in de frontale en insula gebieden, en verminderde mogelijkheden om te kunnen omgaan met stressvolle gebeurtenissen later in het leven, stuk voor stuk belangrijke achterliggende mechanismen zijn waardoor trauma in de kindertijd het risico op psychotische ervaringen en psychose kan verhogen.

CHAPTER 9

Dankwoord

Dankwoord

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> *You are the only reason I am. You are all my reasons. Thank you.*
>
> *- A Beautiful Mind -*

CHAPTER 10

List of Publications

Publications

Articles marked with an asterics (*) relate to the work described in this dissertation.

*** Begemann MJH**, Maijer K, Palmen SJMC, Leucht S, Sommer IEC. Auditory hallucinations across the lifespan: a systematic review and meta-analysis. *Psychological Medicine,* accepted.

Postma TS, Nasib LG, Schutte MJL, Bohlken MM, Martens P, van 't Hag E, Veerman S, **Begemann MJH**, Sommer IEC. Statins as an adjuvant therapy for schizophrenia: Current evidence and a systematic overview of double-blind placebo-controlled trials. *The Scientific Pages of Brain Disorders* 2017;1(1):12-19.

*** Begemann MJH**, Heringa SM, Sommer IE. Childhood trauma as a neglected factor in psychotic experiences and cognitive functioning. *JAMA Psychiatry* 2016;73(8):875-876.

* **Begemann MJH**, Daalman K, Heringa SM, Schutte MJL, Sommer IEC. Childhood trauma as a risk factor for psychosis: The confounding role of cognitive functioning. *Psychological Medicine* 2016;46(5):1115-1118.

Dauwan M, **Begemann MJH**, Heringa SM, Sommer IEC. Exercise improves clinical symptoms, quality of life, global functioning, and depression in schizophrenia: A systematic review and meta-analysis. *Schizophrenia Bulletin* 2016;42(3):588-599.

* So SH, **Begemann MJH**, Gonga X, Sommer IE. Relationship between neuroticism, childhood trauma and cognitive-affective responses to auditory verbal hallucinations. *Scientific Reports* 2016;6:34401.

* **Begemann MJH**, Schutte JL, Sommer IE. Childhood trauma–specific reductions in limbic gray matter volume: Still in the dark. *JAMA Psychiatry* 2015;72(4):398

Begemann MJH, Schutte JL, Slot MIE, Doorduin J, Bakker PR, van Haren NEM, Sommer IE. Simvastatin augmentation for recent-onset psychotic disorder: a study protocol. *BBA Clinical* 2015;4:52–58.

Begemann MJH, Heringa SM, Goverde AJ, Sommer IEC. Sex hormones and oxytocin augmentation strategies in schizophrenia: A quantitative review. *Schizophrenia Research* 2015;168(3):603-613.

Sommer IE, Van Westrhenen R, **Begemann MJH**, De Witte LD, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia; an update. *Schizophrenia Bulletin* 2014;40(1):181–191.

Veerman SRT, Schulte PFJ, **Begemann MJH**, de Haan L. Non-glutamatergic augmentation strategies to clozapine: A review and meta-analysis. *Pharmacopsychiatry* 2014;47(07):231-238.

Van Lutterveld R, Van den Heuvel MP, Diederen KMJ, De Weijer AD, **Begemann MJH**, Brouwer RM, Daalman K, Blom JD, Kahn RS, Sommer IE. Cortical thickness in individuals with nonclinical and clinical psychotic symptoms. *Brain* 2014;137(10):2664-2669.

Veerman SRT, Schulte PFJ, **Begemann MJH**, Engelsbel F, de Haan L. Clozapine augmented with glutamate modulators in refractory schizophrenia: A review and meta-analysis. *Pharmacopsychiatry* 2014;47(06):185-194.

Van Lutterveld R, Diederen KMJ, Koops S, **Begemann MJH**, Sommer IEC. The influence of stimulus detection on activation patterns during auditory hallucinations. *Schizophrenia Research* 2013;145(1-3):27-32.

Sommer IE, Witte LD, **Begemann MJH**, Kahn RS. Non-steroidal anti-inflammatory drugs in schizophrenia: Ready for practice or a good start? A meta-analysis. *Journal of Clinical Psychiatry* 2012;73(4):414-419.

Begemann MJH, Dekker CF, van Lunenburg M, Sommer IE. Estrogen augmentation in schizophrenia: a quantitative review of current evidence. *Schizophrenia Research* 2012;141(2-3):179-184.

Sommer IE, **Begemann MJH**, Temmer A, Leucht S. Pharmacological augmentation strategies for schizophrenia patients with insufficient response to clozapine: A quantitative literature review. *Schizophrenia Bulletin* 2011;38(5):1003-1011.

Planned publications

* **Begemann MJH**, Schutte MJL, Abramovic L, Boks MP, van Haren NEM, Mandl RCW, Ophoff RA, Vinkers CH, Bohlken MM, Sommer IEC. Examining the neurobiological impact of childhood trauma: an important role for frontal and insular regions. *In preparation*.

Dauwan M, **Begemann MJH**, Slot ME, Lee EHM, Sommer IEC. Physical exercise improves quality of life, depressive symptoms, and cognition across chronic brain disorders: a transdiagnostic systematic review and meta-analysis. *Submitted*.

Ottens TH, Sommer IE, van Wijgerden A, **Begemann MJH**, Schutte MJL, Cramer MJ, Suijker WJ, van Dijk D, Slooter AJ. Hallucinations after cardiac surgery: a prospective observational study. *Submitted*.

Stevelink R, Abramovic L, Verkooijen S, Ophoff R, **Begemann MJH**, Cahn W, Kahn RS, Sommer IEC, Boks MP, Mandl R, van Haren NEM , Vinkers CH. The relation between childhood abuse and white matter integrity in bipolar disorder patients and healthy controls. *In preparation*.

Presentations

Begemann MJH, Daalman K, Heringa S, Sommer IEC. From childhood trauma to psychosis: The confounding role of cognitive functioning. *Poster presentation at the Schizophrenia International Research Society (SIRS)*, Florence, Italy, 2016.

Begemann MJH, Daalman K, Sommer IEC. Childhood trauma and auditory verbal hallucinations. *Oral presentation at the International Congress of Schizophrenia Research (ICOSR)*, Orlando, Florida, 2013.

Begemann MJH, Dekker CF, van Lunenburg M, Sommer IEC. Estrogen augmentation in schizophrenia: A quantitative review of current evidence. *Poster presentation at the Schizophrenia International Research Society (SIRS)*, Florence, Italy, 2012.

CHAPTER 11

Curriculum vitae

Marieke Begemann was born in Gorinchem, the Netherlands, on December 29th in 1987. She finished her secondary education at the Gymnasium Camphusianum in Gorinchem in 2006. She started a bachelor's degree in Psychology at Utrecht University and graduated cum laude in 2009. During her master's in Neuropsychology, she did her clinical internship at the Department of Psychiatry of the University Medical Center Utrecht supervised by Dr. Ron Hijman. She subsequently performed a scientific internship at the same department under supervision of Prof. Dr. Iris Sommer, focusing on the efficacy of clozapine augmentation strategies in the treatment of schizophrenia. She obtained her master's degree cum laude.

In 2010, Marieke started working as a research assistant at the University Medical Center Utrecht in the team of Iris Sommer. She was appointed study coordinator of a multicenter randomized double-blind placebo-controlled trial on the efficacy of simvastatin treatment in patients with a recent-onset psychotic disorder. During her first years of research, she developed an interest in childhood trauma as a risk factor for psychotic experiences and started a PhD track in 2013. She has combined her work in the field of research with a teaching position in Neuropsychology at Utrecht University.

Marieke will continue to work as a postdoc in the lab of Prof. Dr. Sommer as the coordinator of the HAMLETT study (Handling Antipsychotic Medication: Long-term Evaluation of Targeted Treatment), which is conducted in close collaboration with 22 health care centers throughout the Netherlands.

Marieke Begemann werd geboren op 29 december, te Gorinchem. Zij behaalde haar gymnasium diploma aan het Gymnasium Camphusianum te Gorinchem in 2006 en begon met haar studie Psychologie aan de Universiteit Utrecht. In 2009 behaalde zij haar bachelor diploma cum laude. Tijdens haar master Neuropsychologie heeft zij haar klinische stage uitgevoerd op de afdeling Psychiatrie van het Universitair Medisch Centrum Utrecht onder supervisie van dr. Ron Hijman, waarvoor zij haar Basis-aantekening Psychodiagnostiek heeft verkregen. Vervolgens heeft zij op deze afdeling tevens haar scriptie geschreven onder begeleiding van prof. dr. Iris Sommer. In 2010 behaalde zij haar masterdiploma cum laude.

Hierna was Marieke werkzaam als onderzoeksassistent in het team van Iris Sommer. In 2013 werd zij benoemd tot coördinator van een gerandomiseerde, dubbelblinde, placebo-gecontroleerde studie naar de effectiviteit van simvastatine in de behandeling van recent-ontstane psychose. Gedurende haar eerste jaren in het onderzoeksveld raakte zij geïnteresseerd in trauma in de kindertijd als risicofactor voor psychotische ervaringen en begon in 2013 met haar promotieonderzoek. Zij heeft haar werk bij het Universitair Medisch Centrum gecombineerd met een aanstelling als docent bij de afdeling Functieleer aan de Universiteit Utrecht.

Inmiddels vervult Marieke een post-doc positie in het team van prof. dr. Iris Sommer als coördinator van de HAMLETT studie naar de effecten van het vroegtijdig afbouwen van anti-psychotische medicatie, welke wordt uitgevoerd in samenwerking met 22 gezondheidszorginstellingen binnen heel Nederland.