Dissecting the psychosis continuum

DISSECTING THE PSYCHOSIS CONTINUUM
RISK FACTORS ALONG THE PATHWAY FROM EXPERIENCES TO DISORDER

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Voor Mark en Iris

Paranimfen

Sanne Peeters

Tirza Wagenvoort

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Chapter 1

General introduction

Eric (21): *"Since a couple of weeks, whenever I go outside of my house, I get the feeling that I am being watched by someone through cameras. I do not know who is watching me or why I am being watched, but it makes me very uncomfortable. Although I am not a 100% sure about it and when I am at home again I think I am being silly for thinking this, it prevents me from going outside of my house unless I really need to."*

Eric also reported he was feeling more down and less energetic over the last couple of months. He was spending less time on his studies because he found it more difficult to focus. He also spent less time with his friends, because he felt uncomfortable when leaving his house, although when he was with his friends he could enjoy spending time with them.

Lisa (16): *"When I am alone a male voice starts talking and sometimes even shouting at me… The voice is telling me I am dumb and ugly and that I have to hurt myself. The voice never stops when I am alone, the volume goes down a bit when I put music on very loud but it never goes away completely. It makes me very anxious and depressed, I can hardly sleep because of it and I cannot focus on anything else."*

Lisa had been treated for over a year for depressive symptoms, she was failing in school, having dropped out in the last 4 weeks before the summer holiday and now sat alone in her room for most of the time. She had contact with one friend, although only via text messages. She had shared with her parents and her therapist that she had as a young girl been a victim of sexual abuse. However, she was very afraid to tell her parents and therapist about these frightening experiences that had slowly developed after her depressive symptoms had started.

These are just two examples of the many different (subclinical) psychotic symptoms reported by young people who shared their personal stories with me during the clinical diagnostic interviews I conducted in search for individuals at 'clinical high risk' for psychosis (CHR-P) and individuals who (had) experienced a first episode of psychosis (FEP). In addition to their psychotic experiences, both are reporting reduced social and role functioning. Lisa was experiencing an almost continuous auditory hallucination (statement 2) and was suffering from a psychotic episode. In contrast, Eric's suspicious beliefs (statement 1) were not fully crystallised and had not crossed the psychosis threshold. His symptoms were still at a 'subclinical' or 'attenuated' level that met criteria for being 'at clinical high risk' for the development of a psychotic episode. These statements illus-

trate that both full-blown and subclinical psychotic symptoms are often associated with distress and a drop in social and role functioning.

From psychotic-like experiences and subclinical symptoms to psychotic disorder

Psychotic disorders are associated with a high burden for patients themselves as well as for their family members and friends. This is directly due to significant impairments in academic performance and occupational functioning, difficulties with interpersonal relationships and substantially compromised subjective quality of life, as well as a high financial burden due to costs for providing care and indirectly by loss of productivity[1]. It is therefore important to gain more insight in the developmental mechanisms of psychotic disorders, which will help to optimize early interventions targeting both symptom reduction and improvement of functioning and quality of life. The goal of early intervention is to prevent transition to full blown psychotic symptoms in CHR-P individuals as well as preventing the development of recurrent symptoms in those who have experienced a first psychotic episode.

In order to elucidate the complex and multi-factorial aetiology of psychotic disorder, in which genetic and environmental factors including obstetric complications, urbanization, migration, cannabis use, and childhood trauma as well as their interactions are implicated[2, 3], focus has shifted from the population of psychotic disorder patients, especially schizophrenic patients, to individuals with subclinical expressions of positive psychotic symptoms at the lower end of the psychosis continuum. These include psychotic-like experiences (PLEs, based on self-report measures) or true subclinical psychotic symptoms reported by individuals from the general population, CHR-P patients and unaffected first-degree relatives of psychotic patients. Investigation of subclinical symptoms allows examination of factors that precede transition to psychosis and more importantly impact on functioning, irrespective of an eventual specific psychotic disorder diagnosis.

From a research perspective using general population samples has the important advantage that subclinical psychotic symptoms are much more prevalent than psychotic disorders and inclusion does not dependent on help-seeking. This allows for true population-based epidemiological research into the pathophysiology, course and treatment of subclinical symptoms in representative population-based contexts. The advantage of studying CHR-P patients and unaffected first-degree relatives is that average transition rates of 22-36%[4] and 10%[6] respectively, are much higher than the transition rate of 0.6% in the general population[4, 5]. This allows for investigation of factors related to transition

as well as protective factors in non-converters. First-degree relatives of psychotic disorder patients also show an increased risk of developing psychotic disorder compared to individuals from the general population (respectively 10% compared to 0.6%)[5, 6]. Additionally, these first-degree relatives also report more subclinical psychotic symptoms than healthy controls[7-9] and they share both a genetic vulnerability and environmental risk factors with their affected relative. Investigation of PLEs and subclinical psychotic symptoms will help to determine the pathway from early expression on towards clinical needs, especially in longitudinal studies in which these samples are repeatedly assessed over time. This allows prospective investigation of psychosocial risk factors for psychotic illness development and the role of comorbid psychopathology in the progression toward psychosis. Another important benefit of studying individuals with PLEs and subclinical psychotic symptoms is that there is no confounding due to antipsychotic treatments or chronicity effects.

The first part of this thesis therefore focusses on the lowest end of the psychosis continuum: PLEs and subclinical psychotic symptoms reported by individuals of the general population and unaffected first-degree relatives of psychosis spectrum patients. As these can be assessed through measures of ('subjective') self-report and ('objective') clinical interviews, the studies in this first part focus on the distinction between self-reported psychotic experiences versus 'clinically validated' psychotic symptoms.

The second part of this thesis focusses on the group of help-seeking individuals with subclinical psychotic symptoms meeting the criteria for being 'at clinical high risk' for the development of psychosis (hereinafter: CHR-P). Studies using the Experience Sampling Method (ESM) in psychotic disorder patients have provided important information on the prevalence and phenomenology of psychotic symptoms in daily life and have shown that psychotic patients are characterised by increased emotional and symptomatic stress reactivity in response to small daily life hassles. Studies in CHR-P patients and patients with a first episode of psychosis will reveal whether these specific processes precede the onset of psychosis or if they are the result of illness progression. Specifically, studies in this part of the thesis investigate differences in emotional and symptomatic stress reactivity, phenomenology and temporal dynamics of emotional and psychotic symptoms between CHR-P and (first episode) psychotic patients in the context of daily life.

Phenomenology of psychosis

Psychotic disorders constitute a multidimensional syndrome that is expressed in a spec-

trum of related *diagnostic* categories including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, depression/bipolar disorder with psychotic features, substance-induced psychotic disorder, psychotic disorder not otherwise classified, which affect around 3.5% of the population[10]. Psychosis rarely occurs before the age of 14 years, but there is a sharp increase in its prevalence between the ages of 15-17 year[11]. Overall, about 50% of people who develop a psychotic disorder will do so by the time they are in their early 20s. The mean age of onset tends to be a little younger in males (18-25 years) than females (25-35 years)[11, 12].

Psychotic disorders are characterised by problems recognizing and understanding reality. The positive psychotic symptoms can be distinguished into (1) delusions, bizarre or non-bizarre in nature; (2) hallucinations, visual, auditory, tactile, gustatory and/or olfactory in nature; and (3) disorganised behaviour. While these positive symptoms are thought of as specific characteristics or 'phenotypes', individuals with psychotic disorders often also experience other general symptoms in varying degrees across the diagnostic categories (i.e. transdiagnostic) forming the clinical psychosis spectrum. These are negative symptoms (i.e. restricted affect, anhedonia and motivational problems), affective dysregulation (depressive and/or (hypo) manic affect) and cognitive problems with regard to memory, attention, executive functioning and social cognition. Psychotic disorders are therefore characterised by high clinical heterogeneity and presence of psychotic symptoms typically waxes and wanes, with variety in severity of symptoms and symptom-free periods even in chronic patients[13-15].

This high clinical heterogeneity is also found at the level of subclinical or attenuated psychotic symptoms. The "transdiagnostic and extended psychosis phenotype"[16, 17] has been proposed to account for the finding that (subclinical) psychotic symptoms are commonly reported by non-help seeking individuals from the general population, predominantly during adolescence and early adulthood[18-20], with a prevalence of ~7%[17, 21]. In ~80% these are transient in nature, persistence occurs in the remaining ~20% and ~7% of individuals develop a psychotic disorder, with an annual transition rate below 1%[16, 22, 23]. In this model, at any phenomenological or temporal stage along the psychosis continuum may individuals become help seeking and meet CHR-P criteria, of which some will develop psychotic disorder. The model can account for the high comorbidity of symptoms[24], especially anxiety and affective disturbances at clinical and subclinical level[25-27]. Importantly, this model is proposed to underlie the diagnostic categories of schizophrenia spectrum and bipolar disorders[17], thereby overcoming the limitations of the current

psychiatric classification systems which consider psychiatric disorders as separate entities that do not overlap.

Although population studies have consistently reported that subclinical psychotic symptoms are relatively common, prevalence rates seem to be dependent upon the assessment strategy used. Prevalence rates in studies that rely on self-report measures are more than three times higher than those of studies using interview-based assessments[16]. Furthermore, studies in which self-reported psychotic experiences (SRPE) were reassessed by clinical interview, only about 40% of those were then confirmed as truly psychotic in nature[11, 12]. SRPE not confirmed by clinical interview are referred to as 'false positive' (FP) SRPE. These findings highlight an important discrepancy between 'subjective' self-report of psychotic experiences and the 'objective' evaluations of clinicians. Van Nierop and colleagues used data from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2)[28] and found that, compared to individuals from the general population who had never had a psychotic experience, individuals with FP SRPE were characterised by higher levels of non-psychotic psychopathology and neuroticism, had experienced more childhood adversity and were functioning less well physically, socially and mentally. However, associations with psychopathology, social functioning, psychosocial factors as well as help seeking in general and specifically for SRPE were generally less strong than for those with confirmed psychotic symptoms. FP SRPE were therefore suggested to represent the mildest form of risk along the extended psychosis continuum[28]. However, very little is known about the course and development of FP SRPE over time and which psychopathological and psychosocial factors are predictive for possible differential outcomes.

Genetics of psychosis

The high clinical heterogeneity of psychotic disorders is mirrored by high genetic heterogeneity[29]. Although the high heritability estimates of 70-85% for schizophrenia and 60-85% for bipolar disorder[30] indicate that about 60-85% of the observed individual differences in these patients are attributable to genetic individual differences while the remaining part is related to the environment, genetic studies have been unable to find 'the' psychosis gene. Genome-wide association studies (GWAS) in schizophrenia patients have led to the discovery of large numbers (100 thousand–1 million) of genetic variants called 'single nucleotide polymorphisms' (SNPs), each associated with very small effect sizes that even cumulatively explain only a modest proportion of the genetic predisposition for psychotic disorder[31]. However, the combined effect of these individual SNPs is

captured in a Polygenic Risk Score (PRS) calculated for each individual, which can be used as an index for genetic risk in studies examining the complex interactions between genetic and environmental (GxE) factors underlying psychosis development. Furthermore, a genetic overlap between schizophrenia and affective disorders has been suggested by recent results of molecular genetic studies[32, 33].

The clinical high risk for psychosis state

As the statement of Eric at the start of this chapter in which he describes his feelings of being watched and the distress and disruption in normal function he is experiencing illustrates, some individuals with subclinical psychotic symptoms are help-seeking and meet criteria for being at clinical high risk for psychosis (CHR-P), also known as the "at-risk mental state" (ARMS), "prodromal" and ultra-high-risk (UHR) state. This construct of a clinical high-risk state for psychosis has been proposed in order to capture the pre-psychotic phase, describing people presenting with potentially prodromal symptoms, as retrospective studies showed that in around three-quarter of first admitted psychotic disorder patients the disorder began with a prodromal phase, which lasted, on average, 5 years[34, 35].

The CHR-P state can be diagnosed using CHR-P and/or basic symptoms (BS) criteria[36] and requires the presence of 1 or more of the following: (i) subclinical or "attenuated" psychotic symptoms (unusual thought content, non-bizarre ideas, perceptual abnormalities and/or disorganised speech); (ii) brief limited intermittent psychotic episode (BLIP); (iii) trait vulnerability plus a marked decline in psychosocial functioning (i.e. genetic risk and deterioration syndrome [GRD]). The Comprehensive Assessment of At-Risk Mental State (CAARMS)[37] and the Structured Interview for Prodromal Symptoms (SIPS) (including the companion Scale of Prodromal Symptoms [SOPS])[38] are the most often used semi-structured interviews to determine CHR-P status. Basic symptoms are subjectively experienced disturbances of different domains, including perception, thought processing, language, and attention, that are distinct from classic psychotic symptoms in that they are independent of abnormal thought content and reality testing and insight into the symptoms psychopathologic nature is intact[39]. BS are assessed with the Schizophrenia Proneness Instrument, adult version (SPI-A)[40].

Many individuals with psychotic experiences meeting CHR-P criteria have clinically debilitating symptoms of comorbid diagnoses. Most often reported are anxiety, depression and substance use disorders. Similar to psychotic disorder patients, CHR-P patients are

often characterised by high neuroticism and high levels of negative symptoms. Significant impairments in academic performance and occupational functioning, difficulties with interpersonal relationships and a substantially compromised subjective quality of life are often observed[41-46]. A large meta-analysis has shown that transition risk from CHR-P to clinical psychosis is ~22% after 1 year, which increases to 36% after 3 years[4]. Meta-analytic results also show that CHR-P state is heterogeneous in terms of longitudinal diagnoses, with 73% of transitions resulting in 'schizophrenic' psychoses and 11% in 'affective' psychosis, so current CHR-P diagnostic criteria appear to be strongly biased toward an identification of early phases of schizophrenic rather than affective psychoses[47].

Overall, the majority of CHR-P studies have focussed on transition risk, although recent studies of outcome in non-converters show that while the majority of individuals do not convert to psychosis, full remission of CHR-P status occurs in less than half of non-converters, with the others still reporting subclinical psychotic symptoms[48-52]. Furthermore, nonpsychotic disorders have been found to co-occur with diagnosis of CHR-P status in most cases, and remain highly prevalent, in terms of incidence of new non-psychotic disorder and recurrence of previous disorder[48, 49]. The CHR-P state is therefore predictive of broad psychopathology in addition to transition to psychotic disorder and fits well within the broad model of clinical staging in psychiatry[53-57]. This model uses the high risk paradigm in a broad context in which relatively non-specific sub diagnostic mental distress predicts not only psychotic but also non-psychotic outcome. Focus lies on early mental distress and non-specific interventions which can help prevent development of more severe, specific and relatively treatment-resistant psychiatric syndromes. This allows for stage-specific treatment, varying from non-specific non-pharmacological self-management approaches in the early stages to more active treatments in the advanced stages.

The affective pathway to psychosis: evidence from experiences sampling method studies

It has long been suggested that stress plays an important role in the emergence and course of psychotic disorder[58-62]. The vulnerability-stress model states that whenever a stressor exceeds the individuals' vulnerability level psychotic symptoms will emerge. The individual's vulnerability level is assumed to be a stable within-person characteristic based on genetic predisposition. There is overwhelming epidemiological evidence that stressful life events[63], childhood adversity[64] and small everyday hassles[65, 66] are associated with the formation and progression of psychotic symptoms. These findings highlight the role that environmental stress-exposure plays in both the development of PE in the general population[21] and the trajectory towards psychotic disorders[61].

Furthermore, poor self-esteem and neuroticism, a personality trait characterized by increased affective reactivity and sensitivity to stress[67], often characterise psychotic patients and CHR-P individuals[46, 68] and have been found to predict onset of psychotic symptoms[69].

A promising approach to help elucidate the role of stress as a potential causal factor for psychosis development is to zoom into the microenvironment of everyday life. The Experience Sampling Method (ESM) is an excellent tool to capture subtle, moment-to-moment emotions and symptomatology and their dynamics and associations with contextual factors in the flow of daily life[70-73]. It is a structured within-day momentary self-assessment technique that provides frequent assessment of current mood, thoughts, symptoms imbedded in their context (e.g. location, company, activity), and these repetitive momentary assessments are ecologically valid and free of cognitive biases that hamper retrospective questionnaires[71, 74]. Most of the ESM research in the last three decades has been performed by providing subjects with a digital wristwatch and a set of ESM self-assessment forms collected in a booklet for each day. Advancements in technology now allow electronic or digital ESM assessments by means of a PDA or mobile phone app. The ESM device (wristwatch, PDA or mobile phone) emits a signal (beep) at ten unpredictable moments in a semi-random schedule of 90-minute time blocks between 07:30 and 22:30[71].

ESM has several advantages in comparison to conventional research methods in the field of psychopathology[75]. First, ESM studies are ecologically valid as they allow studying individuals within their own real-life environment. Second, in contrast to traditional retrospective assessment approaches, ESM assesses momentary experiences elicited by simple and straightforward questions that are less prone to biases and forgetting. Third, questionnaires and most interviews do not focus how contextual factors impact on the variation in symptoms, mood or other constructs in daily life. ESM on the other hand is situated in the complex context of daily life and is able to measure the variation in symptoms and mood in response to environmental factors present in daily life. Fourth, questionnaires and interviews require patients to be aware of the dynamics of symptoms and their interactions with other factors. However, as different constructs like symptoms, mood, stress and social company are measured separately from each other and only associated to each other in the analyses conducted by the researcher, ESM provides information of which the participant is not aware and therefore not influenced by an individual's own expectations. Fifth, ESM allows for cross-sectional (chapter 4) as well as

longitudinal study (chapter 5) of variation and dynamic relationships as data collection results in multiple assessments over time.

Previous ESM studies have shown that when confronted with everyday small stressors psychotic disorder patients display increased emotional and symptomatic responses[76, 77]. Increased reactivity to stress in daily life is especially found in patients with high levels of positive psychotic symptoms and low levels of negative symptoms[78]. Unaffected first-degree relatives of psychotic patients also display elevated emotional and behavioural responses in the face of everyday life stress[76]. Subsequent studies have shown that increased stress-reactivity clusters within families and a genetic correlation between increased stress reactivity and the positive psychotic dimension have been shown for clinical[79] and subclinical symptoms[80]. Furthermore, there is a role for environmental factors as environmental exposures to stress in the form of life events[81] and childhood trauma[82] have been found to explain the elevations in stress reactivity in part. Taken together, these results suggest that increased emotional and symptomatic reactivity to stress, also referred to as 'behavioural sensitization'[83], reflects an affective pathway to psychosis that is suggested to underlie a more reactive, episodic type of psychosis that characterises a subgroup of patients with predominantly positive psychotic symptoms[59].

Examination of emotional and symptomatic stress reactivity in those at CHR-P will help determine if behavioural sensitization occurs before the onset of psychotic disorder and an elevated level of stress reactivity is a mechanism underlying psychosis development. Palmier-Claus and colleagues[84] have examined stress-reactivity in a sample of CHR-P patients, psychotic disorder patients and healthy controls. Interestingly, it was the CHR-P group that showed significantly elevated emotional stress reactivity for stressful activities and social situations compared to healthy controls and psychotic patients. Intensity of symptomatic stress reactivity was comparable to psychotic patients. These results suggest that stress sensitization occurs before onset of psychotic disorder. Very recently, the study of Reininghaus and colleagues[85] examined emotional and symptomatic stress-reactivity in CHR-P and FEP patients. Results echoed and expanded those of Palmier-Claus and colleagues[84].

Phenomenology and temporal dynamics of psychotic experiences in daily life

The prospective, longitudinal character of ESM assessments allows for examination of the phenomenology and temporal dynamics of psychotic experiences in daily life[71, 74]. Prevalence rates of hallucinations in daily life in psychotic disorder patients were be-

tween 40-73%[86-88]. Visual and auditory hallucinations were found to often co-occur. Oorschot and colleagues[87] investigated the temporal dynamics of hallucinations and the relationships with emotions and delusions. Their results suggested that delusional ideation might precede hallucinatory episodes in daily life, rather than result from a hallucination. Additionally, affective dysregulation might not play a primary role in hallucination onset.

Prevalence rates of paranoia or persecutory delusions in daily life are between 49-67% in psychosis spectrum patients[88, 89]. Results of studies across the psychosis continuum have indicated an important role for emotions, especially anxiety and low levels of self-esteem in triggering or contributing to the maintenance of paranoid symptoms[90-94]. Self-esteem is not constantly low but fluctuates in paranoid patients[95]. Furthermore, self-esteem instability was found to be specifically related to paranoid symptoms and not positive psychotic symptoms in general[96]. One ESM study of psychotic disorder patients demonstrated that an increase in the level of anxiety and a decrease in the level of self-esteem were predictive of the onset of a paranoid episode. Furthermore, negative emotions and a low level of self-esteem were associated with paranoid episodes[97].

Outline and aims and of the thesis

The overall aim of this thesis is to identify risk factors for the development of psychotic disorder by examining the phenomenology of psychotic symptoms at a macro-level and at micro-level of daily life in those at the lower end of the psychosis continuum. The studies in this thesis examine (subclinical) psychotic symptoms and associated factors in individuals from the general population, unaffected first-degree relatives of psychotic disorder patients, CHR-P patients, FEP patients and long-term psychotic disorder patients, allowing for comparisons across different stages of the continuum. The first part of this thesis focusses on subclinical psychotic symptoms reported in the general population and unaffected first-degree relatives of psychotic disorder patients.

This thesis starts with an investigation of FP SRPE by individuals of the general population, using uses baseline and 3-year follow-up data from the second Netherlands Mental Health and Incidence Study (NEMESIS-2, n=4683), a longitudinal study of mental disorders in a representative cohort of Dutch adults. FP SRPE are proposed to represent the lowest risk for transition to psychosis along the extended psychosis continuum, as they are not confirmed as true psychotic symptoms through objective clinical evaluation. The study in **chapter 2** is a prospective follow-up study of the previously investigated sample

of individuals with FP SRPE at baseline[28]. We examine if baseline FP SRPE predict reduced psychosocial functioning and the occurrence of psychopathology at 3-year follow-up. Furthermore, we investigate which psychopathological and psychosocial factors predict the differential outcomes of persistence of FP SPRE and transition to validated psychotic symptoms.

The high expression of subclinical psychotic symptomatology in unaffected first-degree relatives of psychotic patients[7, 8] is likely attributable to both shared genes and environment with the patient relative. In contrast, the expression of subclinical psychotic symptomatology in general population samples is more likely to be associated with environmental effects[16, 98, 99]. As PRS reflects the influence of the genetic component on the clinical expression of the diverse psychotic symptoms, positive associations are assumed to exist between PRS as an index of genetic risk and self-report and clinical interview measures of subclinical psychotic symptoms. However, early reports on these associations were inconclusive[100-102]. Therefore, in **chapter 3** the associations between PRS and subclinical psychotic symptoms assessed with a (subjective) self-report measure and an (objective) interview measure are examined in unaffected first-degree relatives of patients with psychotic disorders and healthy comparison subjects from the general population. Given that siblings of psychotic disorder patients have more genetic overlap with these patients than individuals from the general population, it is hypothesized that the association between PRS and measures of psychosis proneness will be stronger in relatives of patients than in individuals from the general population. Associations with affective episodes are also investigated as psychotic patients often show affective dysregulation and GWAS studies showing considerable overlap between schizophrenia and other psychiatric disorders including affective psychoses.

The second part of this thesis focusses on examination of psychotic symptoms in daily life in CHR-P patients, patients with a first episode of psychosis and long-term psychotic disorder patients. The study in **chapter 4** investigates emotional and symptomatic stress reactivity in daily life in individuals at CHR-P, chronic psychotic disorder patients and healthy controls to further examine the role of elevated emotional and symptomatic stress-reactivity in the onset of psychotic disorder. Previous ESM studies with psychotic patients reported that elevation of the level of negative affect was associated with the occurrence of momentary psychotic symptoms[88, 103, 104]. We therefore examine the association between momentary psychotic symptoms and negative affect as a measure of distress in CHR-P individuals and long-term psychotic patients.

To date no study has investigated prevalence of perceptual abnormalities or hallucinations and suspiciousness in daily life specifically in CHR-P or first episode psychosis patients, whereas this has been done previously in psychotic disorder patients. Similarly, the temporal dynamics of hallucinations and suspiciousness in daily life and the relationships with emotional processes, anxiety and self-esteem are unknown. The study in **Chapter 5** is the first to examine the phenomenology of hallucinations and delusions in the realm of daily life and their temporal relationship to emotion, anxiety and self-esteem in CHR-P and FEP patients. Results of this study will help to further elucidate factors involved in the onset and maintenance of suspicious and hallucinatory symptoms. We compare current findings with previous findings in psychotic disorder patients.

Lastly, in **chapter 6**, the main results of the work presented in this thesis are integrated and discussed. In addition, clinical implications and future perspectives are addressed.

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Chapter 2

'False positive' self-reported psychotic experiences in the general population: an investigation of outcome, predictive factors and clinical relevance

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ABSTRACT

Aims. Self-reported psychotic experiences (SRPE) by individuals from the general population are often unconfirmed by clinical interview and referred to as 'false positive' (FP) SRPE. FP SRPE have been suggested to represent the mildest form of risk along the extended psychosis continuum. However, little is known about their (clinical) outcome and evolution over time. Aims of this study were to prospectively examine, in individuals with FP SRPE, (1) the prevalence of remission, persistence and transition to validated PE at 3-year follow-up; (2) potential baseline psychopathological and psychosocial predictors of persistence of FP SRPE and transition to validated PE, and (3) whether those with persistent FP SRPE and validated PE already differed on psychopathology and psychosocial factors at baseline. We tested the hypotheses that (i) individuals with FP SRPE would be more likely to have SRPE and validated PE at follow-up, and (ii) that FP SRPE would be predictive of lower functioning and more psychopathology and help-seeking behaviour at follow-up.

Methods. Baseline (*n*=6646) and 3-year follow-up (*n*=5303) data of the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2), a general population research project on prevalence, incidence, course, and consequences of psychiatric disorders was used. Self-report of PE was followed by clinical interview to determine clinical validity. Presence of mood, anxiety and substance use disorders, childhood adversity, help-seeking and functioning as well as PE characteristics (number, frequency, distress and impact) were used in the analyses which included only individuals with complete data for both assessments waves (*n*=4683).

Results. At baseline, 454 participants had any FP SRPE; of these 372 participants had complete follow-up data available. Those with baseline FP SRPE were significantly more likely to report SRPE (OR=3.58; 95% CI 2.38-5.40, $p<0.001$) and validated PE (OR=6.26; 95% CI 3.91-10.02, $p<0.001$) at follow-up. Baseline FP SRPE also predicted presence of mood and anxiety disorders, reduced functioning and help-seeking at follow-up. Several baseline psychopathological, psychosocial and PE characteristics were predictive for the persistence of SRPE. These factors also differentiated groups with FP SRPE or validated PE from those with remitted FP SRPE at follow-up.

Conclusions. 'False positive SRPE', are not truly 'false' as they index risk for development of clinically relevant psychotic symptoms, development of mood and anxiety disorders and reduced functioning. Self-reported PE, even unconfirmed, warrant 'watchful waiting' and follow-up over time especially when they are reported by individuals with reduced psychosocial functioning and general psychiatric problems.

INTRODUCTION

There is evidence that the psychosis phenotype is expressed along a continuum, ranging from mild, subclinical psychotic experiences (PE) to full-blown psychotic disorder, also referred to as the "extended psychosis phenotype"[1-3]. The prevalence of PE of 5.8-7.2% in the general population[4, 5] is much higher than the lifetime prevalence of 0.4%-0.7% for psychotic disorder in the schizophrenia spectrum[6, 7]. Even though a large percentage of PE are not associated with distress and most are transitory in nature[4, 8], PE do predict transition to clinical psychotic disorder and hospital admission for psychosis, especially when PE are more severe in terms of frequency, number and persistence over time[2, 3, 9]. Furthermore, PE have been found to be associated with (childhood) traumatic experiences, neuroticism, substance use and/or dependence, as well as global, cognitive, social, and role impairment and are often reported by individuals with non-psychotic illness[10-16]. Furthermore, the associations between PE and other mental disorders have been found to be bidirectional in nature[17].

Although general population studies consistently report that PE are relatively common, there are substantial differences in reported prevalence rates. In their systematic reviews of prevalence and incidence of PE, Linscott and Van Os[4, 18] reported that PE were most prevalent in studies using self-reports of participants, with rates were more than three times larger than in studies using interview-based assessments. Two studies in which self-reports were followed by clinical reassessment reported that ~40% of self-reported psychotic experiences (SRPE) were confirmed by clinical interview[19, 20].

Little is known about the progression of PE over time and the characteristics of individuals who report SRPE that cannot be confirmed by clinical interview, also referred to as 'false positive' (FP) SRPE. Only one prospective population-based study examined risk for future psychotic disorder in those with FP SRPE and validated PE[21]. Both types of PE were associated with risk for psychotic disorder at 3-year follow-up, with greater risk for those with confirmed PE than those with FP SRPE. More recently, van Nierop *et al.*[20] specifically compared cross-sectional psychopathological and psychosocial characteristics of groups with FP SRPE, clinically validated PE and controls without SRPE. Their results showed that, compared to individuals reporting no PE, those with at least one FP SRPE were more likely to have a lifetime mood, anxiety or substance use disorder, reported higher levels of neuroticism, were more likely to be characterized by psychosocial risk indicators including childhood adversity, bullying, recent negative life events as well as cannabis use. This group

was also characterized by worse social, physical and mental functioning, assessed over the last month. However, when those with FP SRPE were compared to those with validated SRPE, associations with psychopathology, social functioning, psychosocial factors as well as help seeking in general and specifically for SRPE were generally less strong.

This evidence may suggest that FP SRPE are not 'truly' false-positive but represent the mildest expression of psychosis proneness along the extended psychosis continuum[20]. However, further investigation of the characteristics, course and outcomes of FP SRPE as well as examination of the impact of psychopathological and psychosocial factors on the outcomes of persistence and progression to validated PE is needed before such conclusion can be substantiated. Additionally, further examination of the impact of FP SRPE on later psychological and psychosocial functioning is necessary to determine the clinical relevance of FP SRPE in terms of the development of functional impairment and need for care.

In the present study, we therefore aimed to prospectively examine the development and clinical significance of FP SRPE at baseline over a 3-year follow-up period. We examined (1) rates of remission, persistence of FP SRPE and transition to validated PE; (2) if individuals with baseline FP SRPE were more likely to report new PE, both self-reported as well as clinically validated PE, than individuals without FP SRPE; and (3) the predictive value of FP SRPE on current mental, social, general functioning, the occurrence of recent mood, anxiety and/or substance disorders as well as need for care. Furthermore, we aimed to examine (4) which psychopathological and psychosocial characteristics measured at baseline were predictive of persistence of FP SRPE and transition to validated PE; and (5) if those with persistent FP SRPE and those who made the transition to validated PE at follow-up differed regarding the expression of psychopathological and psychosocial factors present at baseline compared to those with remitted FP SPRE at follow-up.

In line with the psychosis continuum model in which FP SRPE are suggested to be the mildest expression of risk for psychotic disorder[20], we hypothesized that (1) individuals with baseline FP SRPE would be significantly more likely to report PE at follow-up, both FP SRPE and validated PE, than individuals without SRPE at baseline; (2) the presence of FP SRPE at baseline would be predictive of reduced functioning and presence of mood- anxiety and substance use disorders at follow-up; and (3) psychopathological and psychosocial factors, previously found to distinguish those with FP SRPE from those without SRPE and known to be associated with (transition to) psychotic disorder, would predict both the persistence of FP SRPE as well as the progression towards validated PE over the follow-up period.

METHODS

Study cohort

This study used data from the first wave (baseline), performed from November 2007 to July 2009 and second wave collected three years later from November 2010 to June 2012, of the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2), version 2.0. This is a longitudinal study of prevalence, incidence, course, and consequences of psychiatric disorders in the Dutch general population aged 18 to 64 years. The study was approved by a Medical Ethics committee. After having been informed about the study aims, respondents provided written informed consent. For a more detailed description of the NEMESIS-2 methods see de Graaf *et al.*[22, 23]. At baseline 6646 persons were interviewed (response rate: 65.1%). All baseline respondents were approached for follow-up and 5303 persons could be interviewed again (response rate 80.4%, with those deceased excluded). Attrition was not related to any 12-month mental disorder at baseline, after controlling for sociodemographic characteristics [24]. For the current analyses, only participants with complete data for both baseline and follow-up measurements were selected, which had to include clinical re-interview when PE were reported.

Instruments

Assessment of PE

Studies on earlier Composite International Diagnostic Interview (CIDI) versions concluded that the CIDI assesses common mental disorders with generally acceptable reliability and validity, with the exception of psychosis[25, 26]. Therefore, a psychosis add-on instrument was constructed, based on the section of psychotic symptoms in CIDI versions 1 and 2. It consisted of 20 PE, each rated 'yes', 'no', 'don't know' or 'refuse to answer', each assessed by a lay interviewer. As clinical relevance of PE may be difficult to diagnose by lay interviewers [27] and interviewers made no clinical judgment about participants' answers, reported experiences may be considered an extension of 'self-report'. At baseline, the assessment period spanned the entire lifetime of a participant, at follow-up the assessment period spanned the time between baseline and follow-up. Whenever a PE was endorsed, the subject was asked to state, on a 1 (rarely) to 4 (almost always) scale, how often this experience occurred (Frequency), how much it bothered them (Distress), to what extent the experience had an influence on their daily professional and social activities (Impact) and at which age it first occurred. The age of first onset, number of SRPE, the averages of Frequency, Distress and Impact at baseline were used as predictors in the analyses.

Individuals who endorsed at least one SRPE at baseline and/or one SRPE at follow-up at the respective initial interview were contacted within eight weeks for clinical re-interview over the telephone by an experienced clinician at the level of psychologist or psychiatrist. Re-interviews were conducted using questions from the Structured Clinical Interview for DSM-IV SCID-I, [28] and all findings were discussed with a second clinician. At baseline, 1081 participants (16.3%) endorsed at least one PE. Of these, 794 participated in clinical re-interview (73.5%). For 454 (58.2%) SRPE were determined as FP. At follow-up, 440 out of the total 5303 (8.3%) participants reported that at least one SRPE had occurred since baseline. Of these, 367 (83.4%) participants were available for re-interview.

For the analyses six relevant groups were selected (Figure 1). The 372 (of 454) participants with FP SRPE at baseline and all data available at follow-up were divided over three subgroups based on PE status at follow-up: (1) at least one SRPE confirmed by clinical re-interview: the 'Transition to validated PE' group; (2) one or more SRPE, all determined FP by clinical re-interview: the 'Persistent FP SRPE' group; (3) no SRPE: the 'Remitted FP SRPE' group. Given the small number of participants who made the transition to validated PE in the current study (n=28) we chose not to examine transition to psychotic disorder as an outcome, as was done previously by Bak *et al.*[21].

Participants without SRPE at baseline were similarly divided over subgroups based on PE status at follow-up: (4) one or more SRPE, with at least one confirmed PE by clinical re-interview: the 'Validated incident PE' group; (5) one or more SRPE, all non-confirmed by clinical re-interview: the 'FP incident SRPE' group; (6) absence of SRPE: the 'control' group.

Demographics, risk factors and psychopathology at baseline

Participants were interviewed at home by trained interviewers who were not clinicians with the CIDI version 3.0[29]. Neuroticism was assessed using the Eysenck Personality Questionnaire (EPQ-revised short scale)[30, 31]. Four types of childhood adversity (physical, emotional, sexual and psychological) and peer victimization were assessed using a questionnaire based on NEMESIS-1, and dichotomized (yes or no). Sexual abuse was assessed as 'yes' when it had happened at least once, physical, emotional and psychological abuse when it had happened sometimes or more often, and bullying when it had happened regularly before the age of 16. Presence of ten possible negative life events in the previous twelve months was measured, based on the Brugha Life events section and

dichotomized (yes or no)[32]. Cannabis use was assessed in the section Illegal Substance Use of the CIDI 3.0 and analysed as a dichotomous variable indicating regular use (≥ 1 time per week during the last year. Continuous ratings of general, mental and physical health and social functioning over the past month were assessed by the Medical Outcomes Study Short-form Health Survey (SF-36)[33, 34]. Help seeking in the past 12 months from psychiatrists or psychologists for any psychiatric problem including drug or alcohol problems was also assessed.

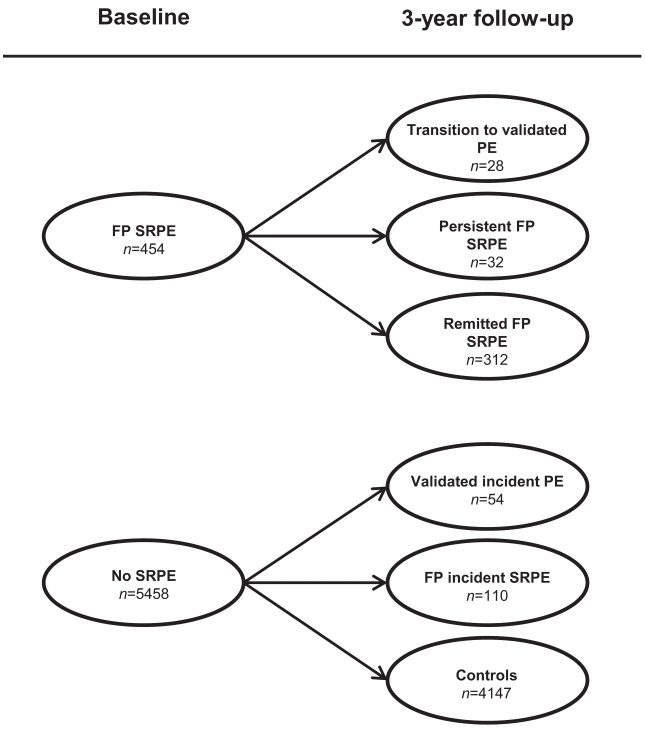

Fig. 1. Sample distribution at baseline and 3-year follow-up.

Analyses

All analyses were performed in STATA, version 13[35]. Logistic regression was used to test the hypothesis that individuals with baseline FP SRPE are significantly more likely to report PE at follow-up than individuals without baseline SRPE (hypothesis 1). The association between presence of baseline FP SRPE as the independent variable and presence

of SRPE at follow-up as dependent variable was examined, *a priori* controlling for age and sex. As SRPE were either confirmed or rejected by clinical re-interview at follow-up we ran two models reflecting both outcomes as the dependent variables: (1) any SRPE (FP and validated PE combined); and (2) clinically validated PE only. Logistic regression was also used to test if baseline FP SRPE predicted presence of any mood, anxiety or substance use disorder in the last year before follow-up assessment and help-seeking in general and specifically for PE. Linear regression was used to test if baseline FP SRPE predicted reduced mental, social, physical and general health functioning in the last month at follow-up (hypothesis 2).

In order to test the hypothesis that risk indicators known to be associated with (transition to) psychotic disorder would predict continued self-report of PE (i.e. persistence of SRPE) over the follow-up period within the group with baseline FP SRPE (hypothesis 3), logistic regression was applied, a priori controlling for age and sex. Presence of SRPE (regardless if these were validated at clinical re-interview) as compared to absence of SRPE at follow-up, served as the dependent variable. Psychopathological and psychosocial risk indicators as well as PE characteristics served as independent variables. Furthermore, multinomial logistic regression, *a priori* controlling for age and sex, was applied to examine if associations with risk indicators would be more pronounced in individuals who persist in reporting FP SRPE and those who display progression towards validated PE, compared to individuals with remitted FP SRPE. In all regression models predictors were entered in separate analyses.

RESULTS

Sample

The mean age of the total sample (n=4683) with complete data available at baseline and follow-up was 44.8 (SD=12.3, range 18-68), with comparable mean ages in the subgroups (table 1). The groups differed significantly on gender distributions (χ^2=17.0, p=0.004), education level (χ^2=38.2, p<0.001) and job status (χ^2=20.6, p=0.001). At baseline, participants available for clinical re-interview did not differ from non-responders with regard to age, lifetime psychiatric disorders, sex, or employment status, while educational attainment was significantly lower (χ^2=8.1, p=0.045). Non-responders were characterized by more SRPE than participants (t(1079)=5.14, p<0.001). At follow-up participants available for clinical re-interview did not differ from non-responders with regard to age, lifetime anxiety and substance use disorder, sex, educational level or employment status as measured at baseline. However, non-responders had more SRPE (t(438)=3.49, p<0.001) and lifetime mood disorders (χ^2=5.7, p=0.02) at baseline.

Psychotic experiences

FP SRPE at baseline and PE at follow-up

Sixty of the 372 participants with baseline FP SRPE (16.1%) had at least one SRPE at follow-up. These were clinically validated at re-interview for 28 participants (46.7%). Participants with baseline FP SRPE were significantly more likely to have any SRPE as well as clinically validated PE at follow-up than participants without baseline SRPE (Table 2).

FP SRPE at baseline and psychopathology and functioning at follow-up

The presence of baseline FP SRPE was significantly associated with the presence of any mood or anxiety disorder in the previous year, reduced current general mental, social, physical and overall health functioning, as well as general help-seeking at follow-up (Table 2).

Table 1. NEMESIS-2 Baseline Sample and Prevalence Characteristics

	Total sample	**Controls**	**Remitted FP SRPE**
	N (%)	*N (%)*	*N (%)*
Total group	4683 (100)	4147 (88.6)	312 (6.7)
	Mean age 44.8	Mean age 44.9	Mean age 44.7
	(SD 12.3)	(SD 12.3)	(SD 12.2)
Men	2141 (45,7)	1931 (46.6)	119 (38.1)
	Mean age 45.1	Mean age 45.2	Mean age 44.2
	(SD 12.3)	(SD 12.2)	(SD 12.7)
Women	2542 (54.9)	2216 (53.4)	193 (61.9)
	Mean age 44.7	Mean age 44.6	Mean age 45.0
	(SD 12.3)	(SD 12.4)	(SD 11.9)
Paid job	3588 (76.6)	3205 (77.3)	233 (74.7)
No Job	1095 (23.4)	942 (22.7)	79 (25.3)
Education			
Primary education	191 (4.1)	162 (3.9)	14 (4.5)
Lower sec. education	1200 (25.6)	1028 (24.8)	97 (31.1)
Higher sec. education	1511 (32.3)	1330 (32.1)	105 (33.6)
Higher professional/ university education	1781 (38.0)	1627 (39.2)	96 (30.8)

FP, false positive; SRPE, self-reported psychotic experiences; PE, psychotic experiences

Table 2. Results of logistic and linear regression analyses: associations between presence of baseline FP SRPE and presence of SRPE and validated PE, current functioning, presence of psychopathology and help-seeking at follow-up, as compared to no baseline SRPE, adjusted for sex and age

Dichotomous variable	***OR***	***95% int.***	***P***
SRPE at follow-up	3.58	2.38 - 4.40	<0.001
Validated PE at follow-up	6.26	3.91 - 10.02	<0.001
Any mood disorder[a]	2.62	1.77 - 3.86	<0.001
Any anxiety disorder[a]	2.56	1.81 - 3.64	<0.001
Any substance disorder[a]	1.60	.90 - 2.85	ns
Help seeking, general[a,b]	2.05	1.56 -2.69	<0.001
Help seeking, specific[a,c]	1.44	.54 - 3.82	ns

ns, not significant; OR, odds ratio; *B,* beta coefficient. [a] Presence in the last year before follow-up assessment; [b] General: psychiatric problems, including drug- or alcohol-related help seeking; [c] Specific: psychotic experiences

Persistent FP SRPE	Transition to validated PE	Incident FP SRPE	Incident validated PE
N (%)	*N (%)*	*N (%)*	*N (%)*
32 (0.7)	28 (0.6)	110 (2.3)	54 (1.1)
Mean age 45.8	Mean age 45.9)	Mean age 44.7	Mean age 43.0
(SD 12.5)	(SD 10.3	(SD 12.4)	(SD 12.9)
17 (53.1)	6 (21.4)	45 (40.9)	23 (42.6)
Mean age 43.5	Mean age 49.5	Mean age 44.2	Mean age 42.2
(SD 13.9)	(SD 11.6)	(SD 12.0)	(SD 11.6)
15 (46.9)	22 (78.6)	65 (59.1)	31 (57.4)
Mean age 48.4	Mean age 44.9	Mean age 45.1	Mean age 43.6
(SD 10.4)	(SD 10.0)	(SD 12.7)	(SD 11.9)
26 (81.2)	16 (57.1)	76 (69.1)	32 (59.3)
6 (18.8)	12 (42.9)	34 (30.9)	22 (40.7)
2 (6.2)	4 (14.3)	5 (4.5)	4 (7.4)
10 (31.3)	7 (25)	38 (34.6)	20 (37.0)
14 (43.8)	10 (35.7)	34 (30.9)	18 (33.3)
6 (18.7)	7 (25)	33 (30.0)	12 (22.2)

Continuous variable	*B*	*95% int.*	*P*
General mental functioning	-2.37	-3.68 - -1.06	<0.001
General social functioning	-3.74	-5.67 - -1.82	<0.001
General physical functioning	-2.55	-4.37 - -.74	<0.01
General health functioning	-4.37	-6.21 - -2.52	<0.001

Table 3. Results of logistic regression analyses: associations between baseline psychopathological, psychosocial and PE factors and persistence of SRPE at follow-up as compared to remission, adjusted for sex and age

Dichotomous variable	*OR*	*95% int.*	*P*
Lifetime mood disorder	1.91	1.08 - 3.39	0.03
Lifetime anxiety disorder	2.08	1.16 - 3.70	0.01
Lifetime substance disorder	1.56	0.82 - 2.97	ns
Neuroticism	3.02	1.65 - 5.52	<0.001
Sexual abuse < 16	1.40	0.65 - 3.04	ns
Physical abuse < 16	1.58	0.73 - 3.42	ns
Emotional abuse <16	1.75	0.96 - 3.20	ns
Psychological abuse <16	1.93	1.08 - 3.44	0.03
Regular bullying <16	1.23	0.60 - 2.52	ns
Negative life events past year	1.45	0.79 - 2.68	ns
Regular cannabis use (≥1/wk, last year)	1.55	0.39 - 6.11	ns
Help seeking, general[a]	1.97	1.06 - 3.66	0.03
Help seeking, specific[b]	1.08	0.35 - 3.30	ns

ns, not significant; OR, odds ratio. [a] General: psychiatric problems, including drug- or alcohol-related help seeking; [b] Specific: psychotic experiences

Table 4. Results of multinomial logistic regression showing the effect of baseline psychopathological and psychosocial characteristics on PE status at follow-up, adjusted for sex and age

	Persistent FP SRPE vs. Remitted FP SRPE (ref)		
Dichotomous variable	*RRR*	*95% int.*	*P*
Lifetime mood disorder	1.59	0.74 - 3.44	ns
Lifetime anxiety disorder	1.68	0.77 - 3.67	ns
Lifetime substance disorder	1.35	0.59 - 3.12	ns
Neuroticism (high/low)	2.97	1.34 - 6.58	0.007
Sexual abuse < 16	1.62	0.57 - 4.62	ns
Physical abuse < 16	0.74	0.21 - 2.61	ns
Emotional abuse <16	1.22	0.51 - 2.88	ns
Psychological abuse <16	2.02	0.94 - 4.33	0.07
Regular bullying <16	1.26	0.48 - 3.30	ns
Negative life events past year	1.78	0.77 - 4.14	ns
Regular cannabis use (≥1/wk, last year)	0.83	0.10 -7.07	ns
Help seeking, general[a]	1.81	0.78 - 4.19	ns
Help seeking, specific[b]	na		

na, not available; ns, not significant; RRR, relative risk ratio. [a] General: psychiatric problems, including drug- or alcohol-related help seeking; [b] Specific: psychotic experiences

Continuous variable	*OR*	*95% int.*	*P*
General mental functioning	0.98	0.965 - 0.996	0.02
General social functioning	0.98	0.97 - 0.995	0.007
General physical functioning	0.99	0.99 - 1.01	ns
General health functioning	0.98	0.97 - 0.996	0.01
Onset of SRPE (age in years)	1.00	0.98 - 1.03	ns
Number of SRPE	1.43	1.09 - 1.87	0.01
Frequency of SRPE	1.48	1.05 - 2.09	0.03
Distress of SRPE	1.15	0.87 - 1.52	ns
Impact of SRPE	1.25	0.87 - 1.77	ns

Transition to validated PE vs. Remitted FP SRPE (ref)			**Transition to validated PE vs. Persistent FP SRPE (ref)**		
RRR	***95% int.***	***P***	***RRR***	***95% int.***	***P***
2.32	1.05 - 5.10	0.04	1.45	0.51 - 4.15	ns
2.60	1.18 - 5.73	0.02	1.54	0.54 - 4.42	ns
1.88	0.76 - 4.66	ns	1.39	0.43 - 4.49	ns
3.08	1.31 - 7.28	0.01	1.04	0.34 - 3.22	ns
1.24	0.44 - 3.49	ns	0.76	0.19 - 3.11	ns
2.94	1.14 - 7.54	0.03	3.96	0.88 - 17.72	0.07
2.45	1.10 - 5.44	0.03	2.01	0.66 - 6.15	ns
1.83	0.82 - 4.08	ns	0.90	0.31 - 2.59	ns
1.20	0.45 - 3.19	ns	0.96	0.26 - 3.55	ns
1.17	0.51 - 2.69	ns	0.66	0.21 - 2.06	ns
2.70	0.51 - 14.24	ns	3.27	0.25 - 42.47	ns
2.15	0.94 - 4.93	0.07	1.19	0.39 - 3.64	ns
2.45	0.77 - 7.85	ns	na		

Risk factors for persistence of any SRPE at follow-up

Results of logistic regression analyses showed several risk indicators measured at baseline to be predictive for the continued presence or 'persistence' of SRPE at follow-up (Table 3). These included the occurrence of a lifetime mood disorder, a lifetime anxiety disorder, lower general health, social and mental functioning assessed over the last month, high level of neuroticism, the occurrence of psychological abuse before the age of 16 years and help seeking for general psychological problems. Moreover, persistence of SRPE was predicted by the number and frequency of baseline SRPE. More information about prevalence rates and other characteristics of the examined psychopathological and psychosocial variables can be found in supplementary tables S1 and S2.

Persistence of FP SRPE and transition to validated PE

Results of multinomial logistic regression analyses showed that persistence of FP SRPE, as compared to remission of FP SRPE at follow-up, was significantly predicted by presence of high neuroticism and lower general mental functioning. The occurrence of psychological abuse before the age of 16 years just failed to reach statistical significance (Tables 4 and 5).

Table 5. Results of multinomial logistic regression showing the effect of baseline psychopathological and SRPE characteristics on PE status at follow-up, adjusted for sex and age

	Persistent FP SRPE vs. Remitted FP SRPE (ref)		
Continuous variable	***B***	***95% int.***	***P***
General mental functioning	-0.02	-0.04 - 0.0001	0.05
General social functioning	-0.01	-0.03 - 0.003	ns
General physical functioning	-0.003	-0.02 - 0.02	ns
General health	-0.01	-0.03 - 0.01	ns
Onset of SRPE (age in years)	0.01	-0.03 - 0.05	ns
Number of SRPE	0.12	-0.30 - 0.54	ns
Frequency of SRPE	0.35	-0.11 - 0.80	ns
Distress of SRPE	0.06	-0.33 - 0.44	ns
Impact of SRPE	0.29	-0.15 - 0.74	ns

b, beta coefficient

Transition to validated PE at follow-up was significantly predicted by presence of a lifetime anxiety disorder, a lifetime mood disorder, high neuroticism, the occurrence of physical and/or emotional abuse before age 16 and lower health in general. A greater number of baseline SRPE was also associated with transition to validated symptoms, while an increased frequency of these experiences just failed to reach significance. Furthermore, in general, effect sizes were larger than those of the group with persistent FP SRPE, although none reached statistical significance when directly compared (Tables 4 and 5).

Transition to validated PE vs. Remitted FP SRPE (ref)			**Transition to validated PE vs. Persistent FP SRPE (ref)**		
B	***95% int.***	***P***	***B***	***95% int.***	***P***
-0.02	-0.04 - 0.003	ns	0.003	-0.03 - 0.03	ns
-0.02	-0.03 - -0.004	0.01	-0.006	-0.03 - 0.01	ns
-0.007	-0.03 - 0.01	ns	-0.004	-0.03 - 0.02	ns
-0.03	-0.04 - -0.01	0.004	-0.02	-0.04 - 0.006	ns
-0.005	-0.04 - 0.03	ns	-0.02	-0.07 - 0.03	ns
0.54	0.21 - 0.86	0.001	0.41	-0.08 - 0.90	ns
0.44	-0.03 - 0.91	0.07	0.09	-0.53 - 0.71	ns
0.22	-0.15 - 0.58	ns	0.16	-0.35 - 0.66	ns
0.15	-0.34 - 0.64	ns	-0.14	-0.76 - 0.48	ns

DISCUSSION

3-year outcomes of baseline FP SRPE: remission, persistence and transition

Our study setup allowed us to collect information about PE in an adult general population sample through self-report and interview-based clinical assessment at baseline and 3-year follow-up. The distinction between 'false positive' and validated PE could therefore be made at both baseline and follow-up. This allowed for an investigation of the prognostic value of baseline FP SRPE on the continued report of PE, psychopathology and functioning at follow-up as well as examination of the association between possible risk indicators assessed at baseline and the differential outcomes of baseline FP SRPE at follow-up.

Discontinuity or remission of PE (83.9%) was the most prevalent outcome, as previously reported[4]. However, results also confirmed the hypothesis that individuals with baseline FP SRPE were more likely to again report SPRE at follow-up. They were ~3.5 times more likely to report any SRPE at follow-up and more importantly, ~6 times more likely to report clinically validated PE than participants without baseline SRPE.

Clinical implications of FP SRPE: current functioning, psychopathology and help-seeking

Presence of baseline FP SRPE predicted lower current mental and social functioning as well as physical and general health functioning at follow-up. Additionally, presence of any current (in the previous year) mood or anxiety disorder and help-seeking behaviour were predicted by FP SRPE. Combined with a previous finding that FP SRPE were predictive of transition to psychotic disorder[21], our results confirm the suggestion by van Nierop and colleagues[20] that individuals reporting FP PE represent a subgroup with the mildest subthreshold expression of psychosis along the psychosis continuum, in which PE are more likely to remain subclinical although need for care may eventually develop. Therefore, SRPE not confirmed by clinical interview, also referred to as 'false positive SRPE', are not truly 'false' as they still index risk for validated psychosis as well as future presence of mood- and/or anxiety disorder and reduced functioning. In clinical practice, even false positive SRPE thus warrant a 'watchful waiting' approach, especially when they co-occur with additional psycho(social) problems, in order to intervene promptly when PE do become more crystallized and distressing and therefore clinically relevant.

Predictors of persistence of SRPE

Our study extends the findings of previous general population studies that did not make a distinction between validated and FP SRPE and reported an effect of persistence of SPRE on help-seeking and impairment at follow-up[8, 36]. It also extends the findings of Bak *et al*[21], who found baseline FP SRPE to be associated with transition to psychotic disorder while not examining possible associated psychopathological and psychosocial factors. More and more frequent baseline SRPE, a diagnosis of mood disorder, anxiety disorder, high neuroticism, lower social and mental functioning and general health in the previous month, childhood adversity (psychological abuse) and help seeking for psychological problems were identified as significant predictors for persistence of SRPE.

Not unexpected, more and more frequent baseline FP SRPE were found to predict persistence of SRPE, as both have been previously associated with risk of transition to psychotic disorder[9]. Previous studies have found an increase in help-seeking and need for subsequent mental health service use in individuals with SRPE[37, 38], especially when reporting multiple PE. In contrast, distress and impact did not predict persistence of SRPE. One explanation might be that at baseline any lifetime PE were assessed. Some of those might have existed for a long time and some might no longer have been present at baseline assessment, possibly lowering ratings of distress and impact. Less distress and impact was also reflected by the fact that only four participants (all with validated PE at follow-up) were seeking help specifically for PE. Furthermore, our results are in line with other general population studies of individuals with PE[13, 17, 39, 40], as well as in individuals meeting criteria for the Ultra High Risk state for psychosis[41], showing high comorbidity with mood and anxiety symptoms and disorders.

Characteristics of persistence of FP SRPE and transition to validated PE

This study is unique in the fact that it could directly investigate possible differences in psychopathological and psychosocial characteristics related to persistence of FP SRPE, as well as transition to validated PE. While the group with persistent FP SRPE was distinguishable from those with remitted FP SRPE by lower general mental functioning in the last month and high neuroticism, the transition group was, in addition to these factors, also characterized by the presence of a lifetime mood and/or anxiety disorder, instances of childhood adversities and lower health in general as well as more SRPE at baseline. Findings extend those of Van Nierop *et al.*[20] who reported that individuals with validated baseline PE were more often characterised by mood and anxiety disorder and four times more likely to seek help for their PE. In conclusion, the present study was able to show,

in a longitudinal design, that those who will later develop validated PE were already characterized by high levels of lifetime psychopathology and exposure to psychosocial risk indicators at baseline.

Theoretical implications

Van Os and Linscott[2] proposed an "extended psychosis phenotype" reflecting a behavioural expression of vulnerability for psychotic disorder in the general population. It implies that PE are not exclusive to, and can occur independently of, psychotic disorder. At any point in time, most likely when PE persist over time, individuals may become help-seeking, with transition to psychotic disorder eventually occurring in some. This model has recently been reformulated into an "extended and transdiagnostic psychosis phenotype" to account for anxiety and affective symptoms often coexisting alongside PE[42] and suggests that it is the co-expression of comorbid symptoms that may result in greater severity, socio-environmental risk and poorer functioning. Importantly, a recent study on PE in the general population showed that the relationship between PE and mental disorders is bi-directional in nature[17]. The probability of transition to a clinical psychotic disorder increases as the load of socio-environmental adverse factors such as instances of childhood trauma increases[16]. Our findings provide further evidence for the validity of this model.

Strengths and limitations

Results of this study should be interpreted in the context of its strengths and limitations. A strength is the size of the baseline sample. Furthermore, as the study set-up allowed us to distinguish between FP SRPE and clinically validated PE at baseline and follow-up, this is the first longitudinal study able to examine differential outcomes and characteristics of FP SRPE in the general population.

There are some methodological limitations. First, outcomes of persistence of FP SRPE and transition to validated PE were rare (0.7% and 0.6% of the total baseline sample and 8.6% and 7.5% of those with SRPE at follow-up and available for re-interview, respectively), which may have impacted on the statistical power in analyses examining associations with psychopathological and psychosocial characteristics, especially when groups were compared. Second, we relied on retrospective reports of lifetime PE at baseline assessment and as a result could have occurred many years before which may have impacted on the recall of these experiences. Third, as self-report of PE was gathered during an interview with a lay interviewer this may have led to less acknowledgment of PE than on

a traditional pen-and-paper self-report assessment. Fourth, as we could only select data of those participants with complete data at baseline and follow-up, not all tested individuals could be included in some of the analyses. At baseline, non-participants of clinical re-interview were characterized by higher number of SRPE. At follow-up, non-participants reported higher numbers of SRPE and had more often a lifetime mood disorder. It is therefore possible that the effect sizes would have been different if all data had been available. Finally, it has been shown that PE are more common in children compared to adolescents and adults[43, 44].The current sample comprises an adult sample with a wide age range and although the sample was nationally representative for The Netherlands, younger subjects were somewhat underrepresented[23]. This might have led to an underestimation of the prevalence of both the persistence of SRPE and transition to validate PE over time. Similarly, the impact of risk factors might be different in younger age groups and studies including child and adolescent samples are therefore needed.

In conclusion, this study showed SRPE not confirmed by clinical interview are often accompanied by symptoms of general psychiatric problems, reports of childhood adversity and lower psychosocial functioning, especially in those for whom FP SRPE persist or progress into clinically relevant psychotic symptoms. FP SRPE furthermore increase the likelihood of future general psychopathology and lower functioning and therefore warrant follow-up over time.

SUPPLEMENTARY MATERIALS

Table S1. Baseline assessment - prevalence rates for dichotomous variables; psychopathological and psychosocial characteristics

	Total sample	Controls	Remitted FP SRPE
Dichotomous variables	*N (%)*	*N (%)*	*N (%)*
Lifetime mood disorder	905/4683 (19.3)	743/4147 (17.9)	89/312 (28.5)
Lifetime anxiety disorder	854/4683 (18.2)	706/4147 (17.0)	76/312 (24.7)
Lifetime substance disorder	729/4683 (15.6)	607/4147 (14.6)	70/312 (22.4)
Neuroticism (high/low)	1548/4607 (33.6)	1285/4077 (31.5)	136/310 (43.9)
Sexual abuse <16	357/4607 (7.8)	295/4077 (7.2)	40/310 (12.9)
Physical abuse <16	348/4607 (7.6)	284/4077 (7.0)	35/310 (11.3)
Emotional abuse <16	652/4607 (14.2)	527/4077 (12.9)	75/310 (24.2)
Psychological abuse <16	728/4607 (14.6)	595/4077 (14.6)	81/310 (26.1)
Regular bullying <16	615/4603 (13.4)	515/4073 (12.6)	56/310 (18.1)
Negative life events past year	2248/4607 (48.8)	1913/4077 (46.9)	196/310 (63.2)
Regular cannabis use (≥1/wk, past year)	69/3780 (1.8)	52/3419 (1.5)	10/241 (4.2)
Help seeking, general[a]	506/4607 (11.0)	398/4077 (9.8)	62/310 (20.0)
Help seeking, specific[b]	na	na	19/292 (6.1)

FP, false positive; SRPE, self-reported psychotic experiences; PE, psychotic experiences; na: not available;
[a] General: psychiatric problems, including drug- or alcohol-related help seeking; [b] Specific: psychotic experiences

Table S2. Baseline assessment - means, minimum, maximum and SDs for continuous variables; psychopathology, general health, social functioning, and severity of SRPE

	Total sample	Controls	Remitted FP SRPE
Continuous variables	*Mean (min – max) (SD)*	*Mean (min – max) (SD)*	*Mean (min – max) (SD)*
General mental functioning	84.5 (8-100) (12.4)	85.1 (8-100) (11.9)	81.6 (20-100) (14.6)
General social functioning	91.5 (0-100) (17.0)	92.1 (0-100) (16.4)	87.9 (0-100) (20.5)
General physical functioning	92.6 (0-100) (16.2)	93.0 (0-100) (15.8)	90.1 (10-100) (18.1)
General health functioning	73.3 (0-100) (17.5)	73.9 (0-100) (17.0)	69.3 (10-100) (19.5)
Onset of SRPE (age in years)	-	-	27.9 (3-62) (12.9)
Number of SRPE	-	-	1.4 (1-6) (0.8)
Frequency of SRPE	-	-	1.7 (1-4) (0.8)
Distress of SRPE	-	-	1.8 (0-4) (1.0)
Impact of SRPE	-	-	1.4 (0.5-4) (0.7)

FP, false positive; SRPE, self-reported psychotic experiences; PE, psychotic experiences; SD, standard deviation

Persistent FP SRPE	Transition to validated PE	Incident FP SRPE	Incident validated PE
N (%)	*N (%)*	*N (%)*	*N (%)*
12/32 (37.5)	14/28 (50.0)	28/110 (25.4)	19/54 (35.2)
11/32 (34.4)	13/28 (46.4)	33/110 (30.0)	15/54 (27.8)
10/32 (31.3)	8/28 (28.6)	21/110 (19.1)	13/54 (24.1)
21/31 (67.7)	20/28 (71.4)	61/109 (56.0)	25/52 (48.1)
5/31 (16.1)	5/28 (17.9)	9/109 (8.3)	3/52 (5.8)
3/31 (9.7)	7/28 (25.0)	10/109 (9.2)	9/52 (17.3)
8/31 (25.8)	13/28 (46.4)	14/109 (12.8)	15/52 (28.9)
13/31 (41.9)	11/28 (39.3)	18/109 (16.5)	10/52 (19.2)
6/31 (19.4)	6/28 (21.4)	20/109 (18.3)	12/52 (23.1)
23/31 (74.2)	19/28 (67.9)	62/109 (56.9)	35/52 (67.3)
1/26 (3.9)	2/23 (8.7)	3/90 (3.2)	1/47 (2.1)
9/31 (29.0)	10/28 (35.7)	18/109 (16.5)	9/52 (17.3)
0/32 (0)	4/28 (14.3)	na	na

Persistent FP SRPE	Transition to validated PE	Incident FP SRPE	Incident validated PE
Mean (min – max) (SD)	*Mean (min – max) (SD)*	*Mean (min – max) (SD)*	*Mean (min – max) (SD)*
76.5 (16-100) (18.9)	76.1 (24-100) (19.9)	79.5 (16-100) (14.3)	79.5 (28-100) (16.6)
82.0 (0-100) (24.0)	75.9 (0-100) (28.9)	89.5 (37.5-100) (16.5)	85.4 (25-100) (20.3)
89.1 (40-100) (16.5)	86.8 (10-100) (20.8)	90.0 (25-100) (17.4)	82.3 (10-100) (25.3)
65.9 (30-100) (17.9)	57.1 (0-100) (26.8)	69.2 (25-100) (17.5)	65.6 (15-100) (21.0)
29.8 (5-52) (13.2)	27.0 (2-59) (15.5)		
1.4 (1-4) (0.8)	2.0 (1-7) (1.5)	-	-
1.9 (1-4) (0.9)	2.0 (1-3) (0.7)	-	-
1.8 (1-4) (1.0)	2.0 (1-4) (1.1)	-	-
1.5 (1-4) (0.8)	1.5 (1-3) (0.6)	-	-

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3

Chapter 3

Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopment, emotion regulation and attribution of salience

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ABSTRACT

Background: The liability-threshold model of psychosis risk predicts stronger phenotypic manifestation of the polygenic risk score (PRS) in the healthy relatives of patients, as compared with healthy comparison subjects.

Methods: First-degree relatives of patients with psychotic disorder (871 siblings and 812 parents) and healthy comparison subjects (*n*=523) were interviewed three times in 6 years. Repeated measures of two psychosis phenotypes, the Community Assessment of Psychic Experiences (CAPE; self-report – subscales of positive, negative and depressive symptoms) and the Structured Interview for Schizotypy – Revised (SIS-R; clinical interview – subscales of positive and negative schizotypy), were examined for association with PRS. Interview-based lifetime rate of depressive and manic episodes were also examined, as was association with repeated measures of intelligence quotient (IQ).

Results: In the relatives, PRS was associated with CAPE/SIS-R total score (respectively, *B*=0.12, 95% CI 0.02-0.22 and *B*=0.11, 95% CI 0.02-0.20), the SIS-R positive subscale (*B*=0.16, 95% CI 0.04–0.28), the CAPE depression subscale (B = 0.21, 95% CI 0.07–0.34), any lifetime affective episode (OR 3.1, 95% CI 1.04-9.3), but not with IQ (*B*=−1.8, 95% CI −8.0 to 4.4). In the controls, similar associations were apparent between PRS on the one hand and SIS-R total score, SIS-R positive, SIS-R negative, any lifetime affective episode and, in contrast, lower IQ (*B*=−8.5, 95% CI −15.5 to 1.6).

Conclusion: In non-ill people, polygenic risk for psychotic disorder is expressed pleiotropically in the domain of neurodevelopment, emotion regulation and attribution of salience. In subjects at elevated genetic risk, emerging expression of neurodevelopmental alterations may create floor effects, obscuring genetic associations.

INTRODUCTION

There is strong evidence that measures of psychosis proneness in non-clinical populations are associated with a family history of psychotic disorder[1, 2]. However, early reports on associations between measures of psychosis proneness in the general population and genome-wide association study (GWAS)-based polygenic risk scores (PRS) for schizophrenia[3, 4] are inconclusive[5-8]. Any association between psychosis proneness and PRS may be stronger in relatives of patients, compared with the general population, given that expression of psychosis-related phenotypes likely is attributable to genes shared with the patient relative[9, 10], whereas expression of psychosis-related phenotypes in general population samples may be associated more with environmental effects[2, 11, 12]. We therefore hypothesized that the link between PRS and expression of psychosis phenotypes would be stronger in relatives of patients, who share liability genes with their ill relative, as compared with the general population, whose level of genetic liability is much lower.

Data pertained to patients with psychotic disorder (*n*=1119), their parents (*n*=920) and siblings (*n*=1059) and healthy comparison subjects (*n*=586) participating in the baseline, 3-year and 6-year follow-up assessments of the Genetic Risk and Outcome of Psychosis (GROUP) study. Repeated measures of two psychosis phenotypes, indexed with the Community Assessment of Psychic Experiences (CAPE; self-report) and the Structured Interview for Schizotypy – Revised (SIS-R; clinical interview), were examined for association with PRS. Given strong associations between psychosis phenotypes and measures of affective dysregulation[13-18], affective outcomes were also included in the analyses. Given the commonly hypothesized notion that genetic effects in schizophrenia are mediated through altered neurodevelopment[19], neurocognition was also examined in relation to PRS.

METHODS

GROUP study

Full details of the GROUP study have been presented elsewhere[20, 21]. In representative geographical areas in the Netherlands and Belgium, patients were identified through clinicians working in regional psychotic disorder services, whose caseload was screened for inclusion criteria. Subsequently, a group of patients presenting at these services either as out-patients or in-patients were recruited for the study. Healthy comparison subjects were selected through random mailings to addresses in the catchment areas of the cases. The GROUP study was not conducted in a geographically well-defined small area, as it in fact included the majority of mental health services in the Netherlands, and a substantial part of mental health services in Dutch-speaking Belgium. Healthy comparison subjects could not be representative in all aspects, as an exclusion criterion was absence of a family history of psychotic disorder. The goal was to collect a group of healthy comparison subjects that (i) was collected from the same geographical area as the case in the relevant mental health service, (ii) was sufficiently large to allow for chance variation and (iii) was frequency-matched in age- and sex distribution to the siblings and (iv) had absence of family history of psychotic disorder. Table 1 shows that healthy comparison subjects, siblings and parents had similar sex distributions whilst healthy comparison subjects and siblings did not have large differences in age.

Table 1. Baseline demographics of GROUP participants in current analysis

	Age			Education[a]		IQ		Urbanicity at birth[b]		
	Mean	S.D.	% Female	Mean	S.D.	Mean	S.D.	Mean	S.D.	*n*
Healthy comparison subjects	31.10	10.70	0.55	2.95	1.27	110.16	14.79	2.57	1.68	523
Siblingss	27.85	8.32	0.53	2.63	1.48	104.00	15.21	2.52	1.63	871
Parents	54.83	6.83	0.57	2.53	1.57	103.54	16.68	2.26	1.58	812
Total	38.55	15.08	0.55	2.69	1.46	105.31	15.90	2.51	1.64	2206

[a] Education (Verhage): range 0 (no education), 3–5 (school diploma) to 8 (university degree).
[b] Urbanicity: 1=<500/km2; 2 500–1000/km^2; 3=1000–1500/km^2; 4=1500–2500/km^2; 5=2500+/km^2.

Sample

The full GROUP sample at baseline consisted of 1119 patients with non-affective psychotic disorder, 1059 siblings of these patients, 920 parents of the patients and 586 unrelated healthy comparison subjects.

Inclusion criteria were: (i) age range 16–50 years and (ii) good command of Dutch language. For patients, an additional inclusion criterion was the presence of a clinical diagnosis of non-affective psychotic disorder. Healthy comparison subject status was confirmed by using the Family Interview for Genetic studies[22] with the healthy comparison subject as informant, to establish absence of first degree relatives with a psychotic disorder. Diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria[23], assessed with the Comprehensive Assessment of Symptoms and History (CASH) interview[24] or Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1)[25]. The majority of patients had a DSM-IV diagnosis of schizophrenia (DSM-IV 295.x; *n*=940, 84%). In the sibling and healthy comparison subject groups, there were respectively, 154 (14%) and 59 participants (10%) with a history of a common mental disorder at baseline, the majority of whom had a mood disorder (DSM-IV 296.x). The study was approved by the standing ethics committee, and all the subjects gave written informed consent in accordance with the committee's guidelines.

Sample for analysis

For the purpose of the current analyses, siblings, parents and healthy comparison subjects groups were included. Analyses were restricted to the European white ethnic group (*n*=2218, or 87% out of a total of

2565 siblings, parents and healthy comparison subjects groups at baseline) given the fact that prevalence of risk alleles varies widely across ethnic groups, as may the risk associated with individual alleles, and evidence exists of differential effects of PRS across ethnic groups[26]. Observations of siblings and healthy comparison subjects who made a possible (*n*=2, of whom 1 of European white ethnic group) or definite (*n*=16, of whom 11 of European white ethnic group) transition to a psychotic disorder over the follow-up period, and thus were re-classified as patients, were excluded from analysis. Applying ethnicity and transition criteria thus resulted in a baseline sample of 523 healthy comparison subjects, 871 siblings and 812 parents of siblings (total sample: *n*=2206). Of the 2206, the number of individuals with data permitting calculation of the PRS was 1578 (72%) with approximately equal proportions across healthy comparison subjects (73%), siblings (67%) and parents (75%).

SIS-R

The SIS-R was administered to healthy comparison subjects, parents and siblings. The SIS-R is a semi-structured interview containing 20 schizotypal symptoms and 11 schizo-

typal signs rated on a 4-point scale[27, 28]. Symptoms are defined as verbal responses to standardized questions concerning, for example, magical ideation, illusions and referential thinking. Signs refer to behaviours that are rated by the interviewer such as goal directedness of thinking and flatness of affect. Questions and rating procedures are standardized. Guided by previous research, 33 item scores were reduced a priori to two-dimensional scores, representing the means of seven positive schizotypy items (covering the areas of referential thinking, psychotic phenomena, derealisation, magical ideation, illusions and suspiciousness) and eight negative-disorganized schizotypy items (covering the areas of social isolation, sensitivity, introversion, restricted affect, disturbances in associative and goal-directed thinking, poverty of speech and eccentric behaviour).

CAPE

The CAPE (www.cape42.homestead.com) was developed in order to rate self-reports of lifetime psychotic experiences[29]. Items are modelled on patient experiences as contained in the Present State Examination, 9th version[30], schedules assessing negative symptoms such as the Scale for the Assessment of Negative Symptoms (SANS)[31] and the Subjective Experience of Negative Symptoms (SENS)[32] and scales assessing depressive symptoms such as the Calgary Depression Scale[33]. Items are scored on a 4-point scale. In the current analyses, CAPE dimensions of frequency of positive experiences (20 items), negative experiences (14 items) and depressive experiences (eight items) were included (measured at baseline and 3- and 6-year follow-up), representing the person's perceived psychosis load over the lifetime (at baseline) or in the past 3 years (follow-up). A total score representing the mean of all items was calculated for each dimension.

Manic and depressive episodes

Lifetime rate of depressive and manic episodes were derived from the CASH interview (data available for 3 of the 4 centres).

Intelligence quotient (IQ)

At baseline and 3-year follow-up, IQ was estimated based on the four-subtest version (Information, Block Design, Digit Symbol Coding and Arithmetic)[34] of the Wechsler Adult Intelligence Scale (WAIS-III)[35]. At 6-year follow-up, IQ was estimated based on a short version of the WAIS-III short form: the Digit Symbol Coding subtest, uneven items of the Arithmetic subtest, uneven items of the Block Design subtest, every third item of the Information subtest[36].

Follow-up

Healthy comparison subjects and siblings were eligible for follow-up; parents were only assessed at baseline. Of the 523 healthy comparison subjects and 871 siblings at baseline, 80% (*n*=1115) were assessed at 3-year follow-up (healthy comparison subjects: 79%, *n*= 415; siblings: 80%, *n*=700) and 69% (*n*=973) at 6-year follow-up (healthy comparison subjects: 68%, *n*=357; siblings: 71%, *n*=616). Ratings of CASH, SCAN, SIS-R and CAPE at follow-up reflected the period between baseline and first follow-up, and between first and second follow-up, respectively. Mean time to first follow-up was 3.3 years (S.D.=0.5) and mean between first and second follow-up was 3.1 years (S.D.=0.4).

Genotyping, imputation and PRS

Genotyping was performed using two platforms. A total of 1434 participants (758 patients, 676 healthy comparison subjects) were genotyped on the Illumina platform for 547 383 SNPs on the Illumina HumanHap 550k v3.0 beadchip. A second group of 1968 participants (393 patients, 154 controls and 1421 healthy relatives) were genotyped for 929 556 SNPs using the Affymetrix genome-wide Human SNP Array version 6.0.

A binary data set of the Illumina platform was generated including 547 383 genotyped variants in 1434 subjects. We excluded 36 samples showing a sex mismatch between recorded and the genetically determined gender type, leaving 1,398 people for further analysis. We excluded SNPs that were haploid or had missing rates per SNP of >0.10, or a MAF of <0.01 or a HWE p value<0. 00001 (in healthy comparison subjects) and excluded individuals, with a missing rate >10%, altogether yielding 515 286 variants and 1393 individuals (737 patients and 656 healthy comparison subjects) for further analysis. Next, a binary data set of Affymetrix platform was generated including 929 556 SNPs genotyped in 1968 subjects (393 patients and 1575 relatives), of which 729 597 SNPs and 1968 individuals passed the standard quality processing checks. We successfully converted genetic coordination of all variants (except for 57 from Illumina and 86 from Affymetrix) from Human NCBI36/hg18 to GRCh37/hg19 using Liftover (online tools) for all samples. Next, we imputed both platform samples on the backbone of 1000 G Phase-3 reference haploblocks, as implemented in the Haplotype Reference Consortium (HRC)[37], using the Michigan Imputation Server and the SHAPEIT option for phasing. This yielded 46 178 415 imputed variants, which was reduced to 16 353 433 SNPs after selecting SNPs with a quality score (info score) threshold of >0.30, of which 9 067 392 variants and 1393 subjects passed the post-imputation QC. As for Affymetrix genotypes, 1kG-based impu-

tation yielded 46 178 419 imputed SNPs, which were reduced to 9 122 501 SNPs after implementing post-imputation quality controls in 1968 subjects. These were included in the next step.

In order to calculate PRS, we obtained summary statistics of the genome-wide association study from the Psychiatric Genomic Consortium-2 (PGC2)[38], which included the GROUP subjects. We performed meta-analysis again while excluding GROUP samples as well as other Dutch samples, including a total of 17 104 566 SNPs, of which 8 242 976 SNPs were common with imputed GROUP genotypes from Illumina-based variants and 8 290 712 variant from Affymetrix-based variants. Following the approach taken by the international psychiatric GWAS consortium, we calculated a PRS at the metagwas p-threshold of <0.1 for association with Schizophrenia by PGC2. This included 2 302 038 SNPs of which 1 481 064 SNPs were common with the Illumina genotype dataset, and 1 483 770 SNPs were common with the Affymetrix genotype data set (1 455 047 SNPs are common across both platforms). Furthermore, we repeated our association analysis at p-threshold of <0.01, which constituted 449 794 SNPs (364 121 common with the Illumina platform, 363305common with the Affymetrix platform and 360 150 SNPs common across both platforms). We used PRSice[39] software to calculate PRS; by LD clumping of r2 value < 0.2, at distance threshold of 250 kb, while adjusting for 10 eigenvectors calculated by Eigenstrat[40]. This led to inclusion of 119 653 SNPs from the Illumina platform and 119 271 SNPs from Affymetrix for estimating PRS at p-metagwas<0.1; and 25 250 SNPs from the Illumina and 25 152 SNPs from the Affymetrix platform to estimate PRS at p-metagwas<0.01. We calculated different PRS using different p value thresholds, from 0 to 0.50, and checked the explained variances at the different threshold of PRS on schizophrenia using Nagelkerke's R-square. The analyses are based on the p-threshold of 0.01 with sensitivity analyses for the p-threshold of 0.1. For ease of interpretation, a constant was added to the two PRS scores, so that the minimum value was 0.

Analyses

GROUP database version 5.0 was used for all analyses. Random intercept multilevel regression models (given clustering of individuals within families as well as clustering of repeated measures within subjects) with SIS-R and CAPE measures as dependent variables were fitted using the MIXED routine in the Stata program, version 14[41]. Independent variables were PRS, a priori corrected for age and sex. In addition, binary outcomes of CASH lifetime depressive and manic episode were modelled using the Stata MEQRLOGIT multilevel random intercept logistic regression routine, similarly adjusted for age and sex.

In order to examine robustness of findings with regard to assumptions of normality, log-transformed outcomes were additionally examined, using the Stata LNSKEW0 routine. LNSKEW0 creates newvar=ln(+/−exp− k), choosing k and the sign of exp so that the skewness of newvar is zero. In order to assess to what degree associations between PRS and measures of psychosis proneness were independent, regression analyses were conducted for one measure of psychosis proneness, corrected for all the others. In order to examine to what degree any association between PRS and measures of psychosis proneness were mediated by IQ, IQ was added to the analyses as a covariate.

RESULTS

Descriptive results and interaction by group

Sample characteristics are displayed in Table 1. Values of the CAPE and SIS-R total score, lifetime depressive and manic episodes and PRS are shown in Table 2, by group and sex. CAPE and SIS-R subscale scores, by group and sex, are shown in Table 3.

Table 2. Depression and mania outcomes, and polygenic risk scores by group and by sex

	% Depressive episode[a]		% Manic episode[a]		PRS		
	Rate	*n*	Rate	*n*	Mean	S.D.	*n*
Group							
Healthy comparison subjects	0.27	445	0.02	445	0.60	0.21	382
Siblings	0.33	656	0.04	656	0.83	0.15	586
Parents	0.30	583	0.02	583	0.83	0.15	610
Sex							
Men	0.22	739	0.03	739	0.77	0.20	720
Women	0.37	945	0.03	945	0.77	0.19	858
Total	0.30	1684	0.03	1684	0.77	0.19	1578

PRS, polygenic risk score.
[a]Lifetime rate, calculated with baseline sample as denominator and including episodes occurring over the 6-year post-baseline follow-up period in the numerator.

The PRS of the healthy comparison subjects (0.60, S.D.=0.21) was significantly lower than the PRS in the combined group of parents and siblings (0.83, S.D.=0.15; p<0.001). The PRS in the group of parents and siblings was significantly correlated with the PRS in the patient group (r=0.30, p<0.0001).

Graphical examination of the scatterplots of PRS on the one hand and CAPE/SIS-R total scores (Fig. 1a–d), CAPE subscale scores (Fig. 2a–f), SIS-R subscales scores (Fig. 3a–d) and IQ (Fig. 4a, b) on the other suggests association between PRS and various aspects of psychopathology and cognition in both groups.

Associations in relatives and healthy comparison subjects

Given the graphical suggestion of differences in the pattern of associations, analyses were conducted separately for relatives and the healthy comparison group. The pattern of correlation between the CAPE and SIS-R total and subscale scores were similar for relative and healthy comparison subjects, in that within-instrument scale correlations were high, whereas between-scale correlations were only moderate (Table 4).

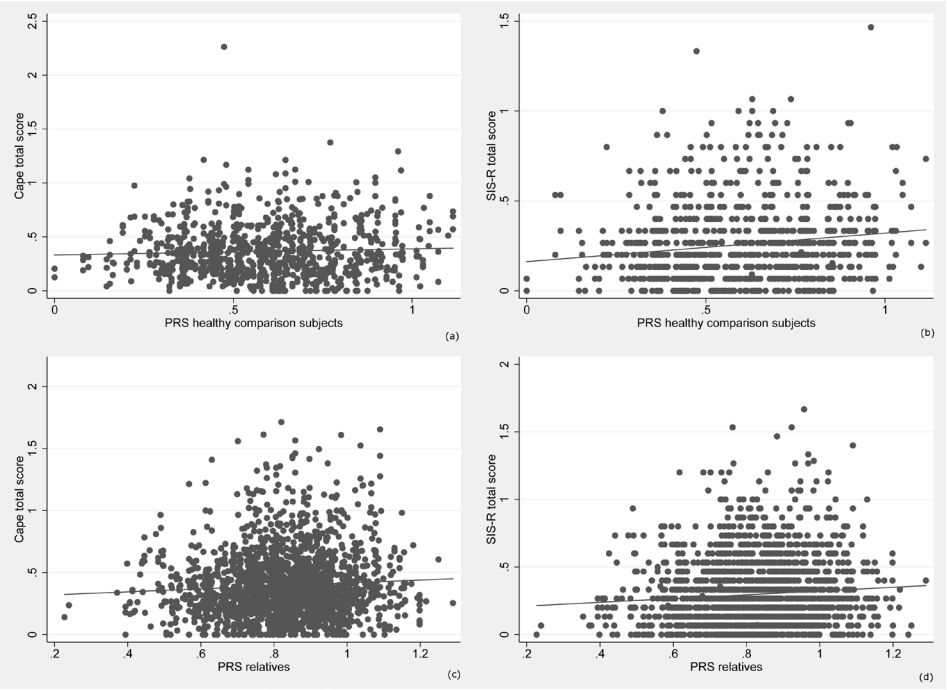

Fig. 1. (a–d) Scatterplots with linear regression line of polygenic risk score (PRS) on the one hand, and, on the other, Community Assessment of Psychic Experiences (CAPE) total score in healthy comparison subjects (Fig. 1a); Structured Interview for Schizotypy – Revised (SIS-R) total score in healthy comparison subjects (Fig. 1b); CAPE total score in relatives (Fig. 1c); and SIS-R total score in relatives (Fig. 1d).

Results of the multilevel random regression analyses are shown in Tables 5–7. In the relatives (Table 6), PRS was associated with CAPE total score (*B*=0.12, 95% CI 0.02–0.22, *p*=0.015), SIS-R total score (*B*= 0.11, 95% CI 0.02–0.20, *p*=0.013) as well as with CAPE depression (*B*=0.21, 95% CI 0.07–0.34, *p*=0.004) and the SIS-R positive subscale (*B*=0.16, 95% CI 0.04–0.28, *p*=0.008). Analyses with log-transformed scales showed similar results (Table 5). Analyses of the CAPE the SIS-R subscales, in which subscales were controlled for each other, showed that associations were reducible to the association with CAPE depression, which continued to be associated with PRS (*B*=0.10, 95% CI 0.02–0.19, *p*=0.021) whereas the association with the SIS-R positive subscale was rendered non-significant (Table 5).

The association between CAPE depression and PRS was not affected by IQ, as the association with CAPE depression remained similar when IQ was added in addition to age and sex (*B*=0.20, 95% CI 0.06–0.34, *p*=0.005).

Table 3. Cape and SIS-R subscale scores by group and by sex

		CAPE total			CAPE POS			CAPE-NEG		
Time		Mean	S.D.	*n*	Mean	S.D.	*n*	Mean	S.D.	*n*
	Group									
1	HCS	0.42	0.23	502	0.19	0.17	500	0.48	0.32	500
	Siblings	0.45	0.27	767	0.19	0.18	765	0.54	0.38	765
	Parents[a]	0.41	0.23	692	0.13	0.13	692	0.50	0.33	692
2	HCS	0.30	0.23	401	0.08	0.12	401	0.39	0.31	400
	Siblings	0.35	0.28	675	0.10	0.14	673	0.46	0.40	674
	Parents[a]	-	-	-	-	-	-	-	-	-
3	HCS	0.32	0.26	343	0.08	0.15	343	0.41	0.34	343
	Siblings	0.35	0.28	594	0.08	0.12	593	0.47	0.40	593
	Parents[a]	-	-	-	-	-	-	-	-	-
	Sex									
1	Men	0.40	0.23	890	0.17	0.16	889	0.50	0.33	889
	Women	0.45	0.26	1071	0.17	0.17	1068	0.52	0.35	1068
2	Men	0.30	0.24	478	0.10	0.13	478	0.42	0.35	478
	Women	0.36	0.28	598	0.09	0.13	596	0.45	0.39	596
3	Men	0.31	0.25	419	0.09	0.13	418	0.43	0.36	418
	Women	0.36	0.29	518	0.08	0.13	518	0.46	0.39	518

CAPE, Community Assessment of Psychic Experiences (subscales of positive, negative and depressive symptoms); SIS-R, Structured Interview for Schizotypy – Revised (subscales of positive and negative schizotypy).
[a] Parents baseline measures only.

In the healthy comparison subjects (Table 6), PRS was associated with the SIS-R total score (*B*=0.16, 95% CI 0.07–0.25, *p*=0.000) and both the SIS-R positive subscale (*B*=0.22, 95% CI 0.10–0.35, *p*=0.000) and the SIS-R negative subscale (*B*=0.11, 95% CI 0.03–0.19, *p*=0.10) (Table 6). Analyses with log-transformed scales were similar (Table 6). In the analysis in which all subscales were controlled for each other, only the association with the SIS-R positive subscale remained significant (*B*=0.14, 95% CI 0.05–0.24, *p*=0.004; Table 6).

Analyses of association between PRS and CASH based lifetime depressive and manic episodes revealed evidence for association in both the relatives (OR any affective episode=3.1, 95% CI 1.04–9.3, *p*=0.043) and the healthy comparison subjects (OR any affective episode=3.4, 95% CI 0.9–12.7, *p*=0.075) (Table 7).

In the relatives, no large or significant association was apparent between PRS and IQ in a separate model of IQ, corrected for age and sex (*B*=−1.8, 95% CI −8.0 to 4.4; *p*=0.566). In the healthy comparison subjects, there was evidence for an association between IQ

CAPE-DEP			SIS-R total			SIS-R positive			SIS-R negative		
Mean	S.D.	*n*	Mean	S.D.	*n*	Mean	S.D.	*n*	Mean	S.D.	*n*
0.59	0.34	502	0.27	0.25	515	0.30	0.35	515	0.24	0.23	514
0.61	0.38	767	0.31	0.28	858	0.36	0.41	858	0.26	0.24	858
0.60	0.35	692	0.29	0.24	806	0.25	0.30	806	0.32	0.28	806
0.43	0.35	401	0.26	0.20	402	0.27	0.29	402	0.24	0.21	400
0.49	0.40	675	0.29	0.25	683	0.31	0.34	683	0.28	0.25	683
-	-	-	-	-	-	-	-	-	-	-	-
0.48	0.41	343	0.27	0.21	336	0.28	0.29	336	0.25	0.22	336
0.50	0.41	594	0.30	0.24	598	0.31	0.31	598	0.29	0.25	598
-	-	-	-	-	-	-	-	-	-	-	-
0.52	0.32	890	0.28	0.25	984	0.28	0.33	984	0.29	0.27	983
0.67	0.38	1071	0.30	0.27	1195	0.33	0.38	1195	0.27	0.25	1195
0.40	0.34	478	0.27	0.23	486	0.26	0.30	486	0.27	0.25	485
0.53	0.40	598	0.29	0.24	599	0.32	0.34	599	0.26	0.23	598
0.42	0.36	419	0.29	0.24	420	0.28	0.30	420	0.29	0.27	420
0.55	0.44	518	0.29	0.22	514	0.31	0.31	514	0.27	0.22	514

and PRS, adjusted for age and sex (*B*=−8.5, 95% CI −15.5 to −1.6; *p*=0.017). The association between PRS and IQ in the healthy comparison subjects remained after controlling for SIS-R total score (*B*=−7.5, 95% CI −14.5 to −0.4; *p*=0.038). Similarly, the association between PRS and SIS-R total score in the healthy comparison subjects remained after controlling for IQ (*B*=0.16, 95% CI 0.07–0.25; *p*=0.001).

Sensitivity analyses at PRS p-threshold of 0.1

Results for the sensitivity analyses were at the PRS p-threshold of 0.1 were very similar to the analyses at the P-threshold of 0.01. The association between PRS and IQ was slightly weaker in the healthy comparison group (*B*=−7.1, 95% CI −15.1 to 0.9, *p*=0.081). In the relatives group, associations between PRS and the CAPE positive and negative subscale were also significant and associations were not reducible to CAPE depression but to the SIS-R positive subscale.

Table 4. Pattern of Pearson's correlation coefficients between psychopathology measures in relatives (top) and controls (bottom)

	SIS-R total	CAPE total	SIS-R negative	CAPE negative	SIS-R positive	CAPE positive	CAPE depressive
Relatives							
SIS-R total	1						
CAPE total	0.50	1					
SIS-R negative	0.82	0.42	1				
CAPE negative	0.45	0.92	0.43	1			
SIS-R positive	0.88	0.42	0.44	0.35	1		
CAPE positive	0.38	0.65	0.19	0.48	0.42	1	
CAPE depressive	0.45	0.93	0.39	0.75	0.38	0.49	1
HCS							
SIS-R total	1						
CAPE total	0.46	1					
SIS-R negative	0.82	0.36	1				
CAPE negative	0.40	0.90	0.36	1			
SIS-R positive	0.89	0.42	0.46	0.33	1		
CAPE positive	0.33	0.68	0.16	0.49	0.39	1	
CAPE depressive	0.43	0.92	0.35	0.72	0.38	0.50	1

CAPE, Community Assessment of Psychic Experiences (subscales of positive, negative and depressive symptoms); SIS-R, Structured Interview for Schizotypy – Revised (subscales of positive and negative schizotypy); HSC, healthy control subjects.

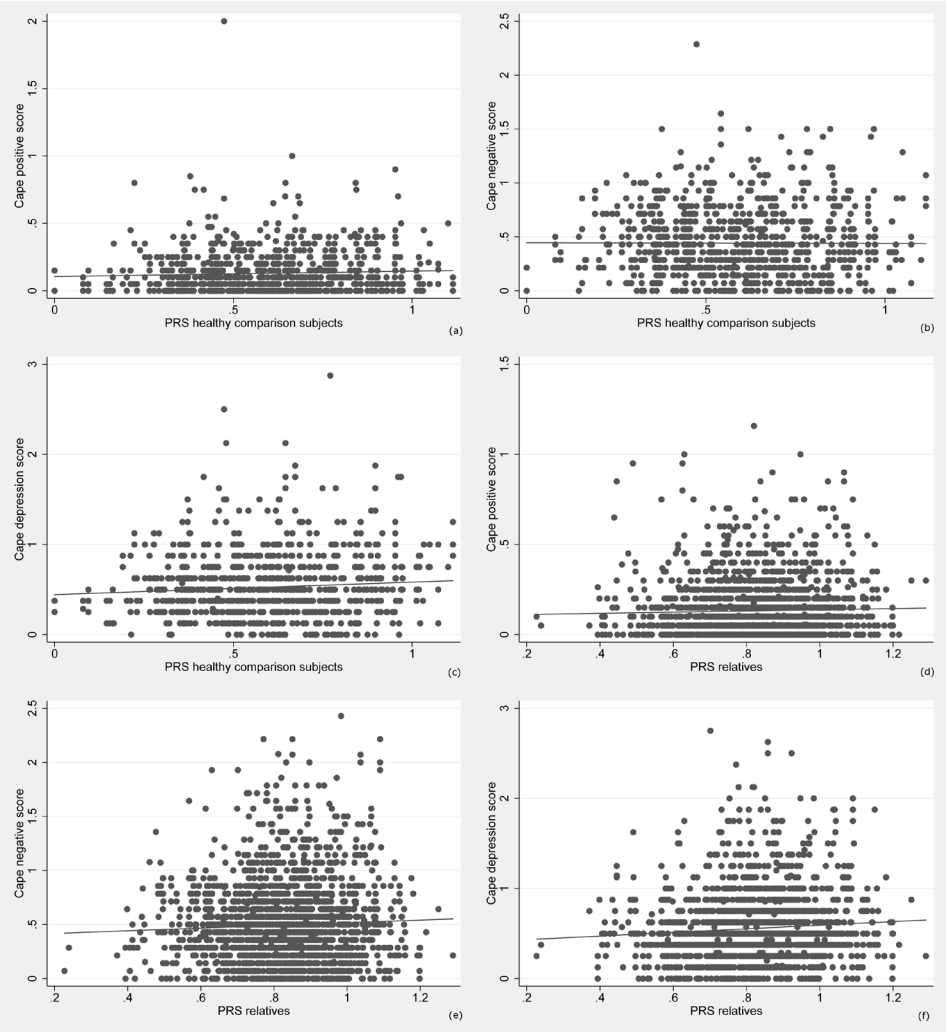

Fig. 2. (a–f) Scatterplots with linear regression line of polygenic risk score (PRS) on the one hand, and, on the other, Community Assessment of Psychic Experiences (CAPE) positive score in healthy comparison subjects (Fig. 2a), CAPE negative score in healthy comparison subjects (Fig. 2b), CAPE depression score in healthy comparison subjects (Fig. 2c), CAPE positive score in relatives (Fig. 2d), CAPE negative score in relatives (Fig. 2e), CAPE depression score in relatives (Fig. 2f).

Table 5. Results of regression analyses in relatives of patients

	Association of psychopathology measure with PRS		
	B (0.95% CI)	*p*	*n*
Measure			
CAPE total	0.12 (0.02-0.22)	0.015	1916
CAPE positive	0.04 (-0.02 to 0.10)	0.150	1913
CAPE negative	0.13 (-0.01 to 0.27)	0.075	1914
CAPE depressive	0.21 (0.07-0.34)	0.004	1916
SIS-R total	0.11 (0.02-0.20)	0.013	2071
SIS-R positive	0.16 (0.04-0.28)	0.008	2071
SIS-R negative	0.08 (-0.02 to 0.17)	0.103	2071

[a] NA: analyses were conducted with the five subscales: CAPE positive, CAPE negative, CAPE depressive, SIS-R positive, SIS-R negative.
B, regression coefficient; 95% CI, 95% confidence interval; *p, p*-value; *n*, number of observations, PRS, polygenic risk score; CAPE, Community Assessment of Psychic Experiences (subscales of positive, negative and depressive symptoms); SIS-R, Structured Interview for Schizotypy – Revised (subscales of positive and negative schizotypy).

Table 6. Results of regression analyses in healthy control subjects

	Association of psychopathology measure with PRS		
	B (0.95% CI)	*p*	*n*
Measure			
CAPE total	0.04 (-0.07 to 0.14)	0.465	911
CAPE positive	0.03 (-0.04 to 0.10)	0.451	910
CAPE negative	-0.13 (-0.15 to 0.12)	0.848	909
CAPE depressive	0.11 (-0.04 to 0.26)	0.147	911
SIS-R total	0.16 (0.07-0.25)	0.000	921
SIS-R positive	0.22 (0.10-0.35)	0.000	921
SIS-R negative	0118 (0.03 to 0.19)	0.000	919

[a] NA: analyses were conducted with the five subscales: CAPE positive, CAPE negative, CAPE depressive, SIS-R positive, SIS-R negative.
B, regression coefficient, 95% CI, 95% confidence interval; *p, p*-value; *n*, number of observations, PRS, polygenic risk score; CAPE, Community Assessment of Psychic Experiences (subscales of positive, negative and depressive symptoms); SIS-R, Structured Interview for Schizotypy – Revised (subscales of positive and negative schizotypy).

Association of log-transformed psychopathology measure with PRS			Association of psychopathology subscales with PRS, corrected for the other subscales		
B (0.95% CI)	*p*	*N*	*B* (0.95% CI)	*p*	*N*
0.16 (0.01-0.31)	0.032	1916	NA[a]		
0.32 (-0.01 to 0.65)	0.059	1913	-0.01 (-0.05 to 0.04)	0.083	1884
0.12 (-0.05 to 0.28)	0.170	1914	-0.04 (-0.13 to 0.05)	0.385	1884
0.21 (0.07-0.36)	0.005	1916	0.10 (0.02-0.19)	0.021	1884
0.24 (0.04-0.43)	0.016	2071	NA[a]		
0.51 (0.19-0.83)	0.002	2071	0.08 (-0.02 to 0.18)	0.136	1884
0.14 (-0.06 to 0.33)	0.166	2071	0.02 (-0.06 to 0.10)	0.616	1884

Association of log-transformed psychopathology measure with PRS			Association of psychopathology subscales with PRS, corrected for the other subscales		
B (0.95% CI)	*p*	*N*	*B* (0.95% CI)	*p*	*N*
0.01 (-0.17 to 0.19)	0.917	911	NA[a]		
0.20 (-0.27 to 0.66)	0.400	910	-0.00 (-0.06 to 0.05)	0.872	889
-0.07 (-0.24 to 0.10)	0.431	909	-0.10 (-0.19 to 0.01)	0.030	889
0.07 (-0.11 to 0.24)	0.441	911	0.08 (-0.02 to 0.18)	0.093	889
0.40 (0.18-0.63)	0.000	921	NA[a]		
0.60 (0.28-0.93)	0.000	921	0.14 (0.05- 0.24)	0.004	889
0.31 (0.09-0.33)	0.005	919	0.04 (-0.03 to 0.11)	0.244	889

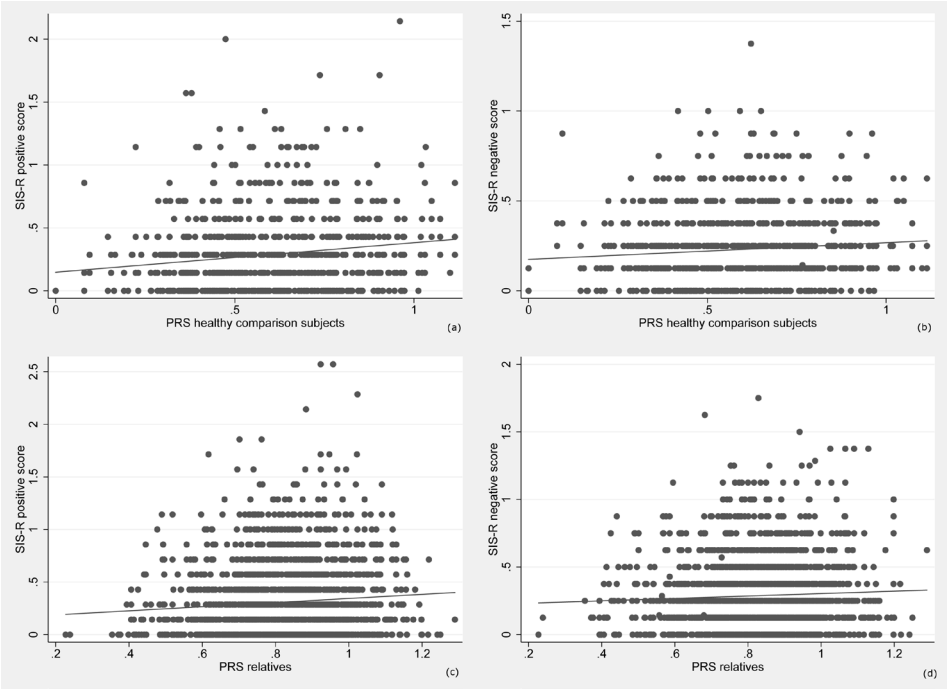

Fig. 3. (a–d) Scatterplots with linear regression line of polygenic risk score (PRS) on the one hand, and, on the other, Structured Interview for Schizotypy – Revised (SIS-R) positive score in healthy comparison subjects (Fig. 3a), SIS-R negative score in healthy comparison subjects (Fig. 3b), SIS-R positive score in relatives (Fig. 3c), SIS-R negative score in relatives (Fig. 3d).

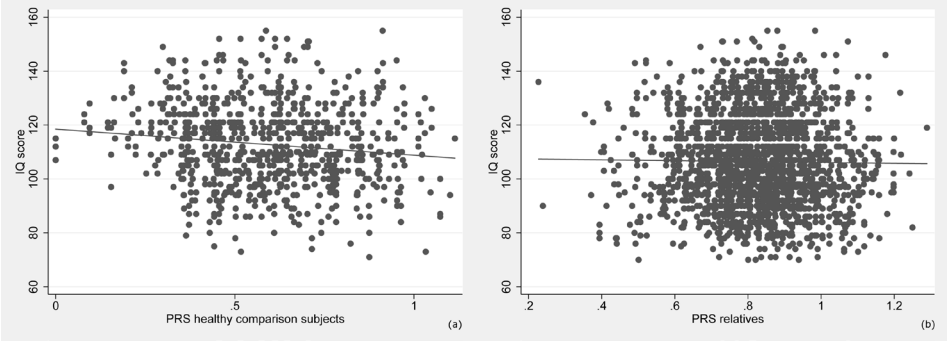

Fig. 4. (a, b) Scatterplots with linear regression line of polygenic risk score (PRS) on the one hand and, on the other, intelligence quotient (IQ) score in the healthy comparison subjects (Fig. 4a) and IQ score in the relatives (Fig. 4b).

Table 7. Results of regression analyses in baseline sample for lifetime manic and depressive episodes (including episodes over 6-year follow-up) in relatives and healthy comparison subjects. Odds ratio reflects association between polygenic risk score on the one hand, and depressive/manic episode on the other

	Relatives			Healthy control subjects		
	OR (0.95% CI)	*p*	*n*	OR (0.95% CI)	*p*	*N*
Measure						
Depressive episode	2.6 (0.9-7.9)	0.089	911	3.4 (0.9-13.0)	0.069	323
Manic episode	6.4 (0.3-132.6)	0.228	910	0.7 (0.01-38.2)	0.867	323
Affective episode[a]	3.1 (1.04-9.3)	0.043	909	3.4 (0.0-12.7)	0.075	323

[a] Any depressive or manic episode.

OR, odds ratio; 95% CI, 95% confidence interval; *p, p*-value*; n*, number of observations

DISCUSSION

The main findings were that (i) PRS was pleiotropically associated with measures of affective dysregulation, aberrant salience and neurocognition; (ii) The association between neurocognition and PRS was present in the healthy comparison subjects but not in the relatives, and was independent of CAPE/SIS-R measures; (iii) Interview-based SIS-R measures appeared to be more sensitive than CAPE-based self-reports in detecting genetic association in the healthy comparison group.

According to the liability-threshold model, a person with a number of risk variants lower than or equal to the critical threshold would not develop schizophrenia, whereas a person with more risk variants would[42]. As individuals at higher than average genetic risk, such as the first-degree relatives of patients, have higher levels of psychometric and neurocognitive endophenotypes associated with psychotic disorder[10, 43], associations between PRS and such endophenotypes may be more apparent in this group. However, in the current analysis, there was no evidence that associations between PRS and measures of psychopathology and cognition were stronger in the relatives of patients as compared with a group of healthy comparison subjects. Indeed, given stronger evidence for association between PRS and cognition in the healthy control group, the results suggest it may be more, not less difficult to demonstrate associations in the relatives.

A previous investigation in this sample, focussing on the association between childhood trauma and IQ, reported a similar finding in that the association between IQ and childhood trauma was large in the healthy comparison group, intermediate in the relatives and not apparent in the patient group[44]. Thus, in subjects at higher than average (environmental or genetic) risk, emerging expression of phenotypic alterations may create floor effects, obscuring associations. The results of this study again suggest that particularly measures in the neurodevelopmental domain may be sensitive to such a floor effect, as associations between PRS and subthreshold measures of psychopathology were apparent in both the relative and the healthy comparison groups.

Affective dysregulation, aberrant salience and genetic liability to psychosis

There is a well-established link between affective dysregulation and psychosis, both at the level of clinical illness[45, 46], subthreshold psychotic experiences[13-18], so-called clinical high-risk states[47] and in the early prodromal stages[48]. In addition, many studies have suggested an important role of affective dysregulation in the formation of psychotic symp-

toms[49-53], and molecular genetic studies suggest an overlap between schizophrenia and affective illness[54, 55].

There is evidence that psychosis represents a severity dimension of an initial state of affective dysregulation[17, 56] and that clinical high risk samples with high risk of conversion to psychotic disorder mainly consist of individuals with affective dysregulation[57]. Therefore, early states of affective dysregulation may give rise to more severe states in which psychotic symptoms arise[58]. Additional exposure may be required for psychotic symptom formation, research showing higher risks of psychotic symptom formation with progressively greater level of exposure to environmental risk factors[59-61].

The findings agree with the literature, suggesting that the association between genetic risk and psychosis proneness is not only mediated by psychoticism and neurodevelopmental alterations, but also by measures of affective dysregulation. The effects of polygenic risk thus may be examined further in network models, focussing particularly on the strength of the connection between affective dysregulation, cognition and psychotic symptoms. Similarly, gene–environment interactions may converge at the level of the connection between affective dysregulation, cognition and psychotic symptoms.

Cognitive alterations and neurodevelopmental hypothesis

The premorbid cognitive alterations in schizophrenia are one of the core findings supporting the neurodevelopmental hypothesis[62]. There was evidence for an association between IQ and PRS, however it may be hypothesized that environmental exposures such as childhood trauma, that have been shown to also impact cognitive development[63-66] may also play a causal role in the development of cognitive alterations in psychosis[44, 67-69]. In addition, genetic variation and epistasis not included in the PRS may contribute to cognitive alterations as well. It has been reported that less than a fifth of the effect of family history on the occurrence of psychotic disorder is mediated by PRS[70], leaving room for the impact of other genetic factors, assuming not all of the remainder of the effect of family history is 'environmental'.

Given evidence that most of the overall effect of a schizophrenia diagnosis on cognitive performance is mediated through a single common factor, indicating that a generalized cognitive deficit is a core underlying feature[71], a general measure like IQ arguably is the most useful to examine in the context of associations with PRS. There have been conflicting reports on associations between measures of cognition and schizophrenia polygenic

scores in patient and control samples using a variety of different cognitive measures[19, 72, 73], however no previous report has examined the association in a large sample of non-ill individuals at higher than average genetic risk with repeated measures of IQ over time. Given evidence for an association between PRS and IQ in healthy control group, it may be hypothesized that PRS for schizophrenia is expressed, at least in part, as a cognitive measure that correlates with IQ.

Methodological issues

The results should be interpreted in the light of several methodological considerations. First, although the sample size was substantial, it was still relatively small for a molecular genetic study. Nevertheless, effect sizes were detectable. A previous general population study with a larger sample suggested a weak association with CAPE negative scores however in that study[5], CAPE positive and CAPE depression scores were not included. Given that CAPE negative scores are strongly associated with CAPE depression scores (0.7 in the current study), the reported association with CAPE negative scores may be considered compatible with the current findings[7], given that CAPE depression in the healthy comparison group directionally showed the same type of association as in the relatives, albeit weaker. In any case, the results of this study show that self-reports of psychosis-proneness in the general population may not be sensitive in detecting genetic associations. Second, it could be argued that lack of association between IQ and PRS in the relatives cannot be interpreted fully without examination of the association between IQ and PRS in their patient relatives; if the association is present in the patient group but not in their relatives, this may indicate that PRS can contribute to IQ in interaction with other genetic or non-genetic factors that patients may have been differentially exposed to. However, analysis of the association between repeated measure of IQ and PRS in the patient group (1304 observations in 596 patients) similarly yielded no evidence of association (B=1.7, 95% CI -4.5 to 7.9; p=0.597). Third, it could be argued that the association between PRS and measures of affective dysregulation in the relatives is confounded by PRS-associated poor illness outcome in the patients, negatively impacting mental health of the relatives. However, the absence of an association between PRS and cognitive alterations, which are associated with poor outcome, makes it unlikely that PRS is associated with poor outcome. Although PRS was associated with positive symptoms of psychosis, positive symptoms are not associated with poor outcome. In order to verify this issue analytically, we re-examined the association between PRS and CAPE depression, additionally adjusting the analysis for the following outcome measures in the patient relative: number of unmet needs, measures with the Camberwell Assessment of Needs[74], GAF-symptoms

and GAF-disability[75]. This adjustment did not reduce the association (*B*=0.22, 95% CI 0.08–0.36, *p*=0.003). Finally, although two different genotyping platforms were used, one for controls and another for relatives, the use of imputation across platforms can be considered an effective way to control for this. In addition, analyses in the relatives were entirely within-platform, and analyses in the healthy comparison subjects was also largely within platform.

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4

Chapter 4

Clinical High Risk for psychosis: the association between momentary stress, affective and psychotic symptoms.

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ABSTRACT

Objective: The aim of this study was to assess associations between momentary stress and both affective and psychotic symptoms in everyday life of individuals at clinical high risk (CHR), compared to chronic psychotic patients and healthy controls, in search for evidence of early stress sensitization. It also assessed whether psychotic experiences were experienced as stressful.

Method: The experience sampling method was used to measure affective and psychotic reactivity to everyday stressful activities, events and social situations in 22 CHR patients, 24 patients with a psychotic disorder and 26 healthy controls.

Results: Multilevel models showed significantly larger associations between negative affect (NA) and activity-related stress for CHR patients than for psychotic patients (p=0.008) and for CHR compared to controls (p<0.001). Similarly, the association between activity-related stress and psychotic symptoms was larger in CHR than in patients (p=0.02). Finally, the association between NA and symptoms (p<0.001) was larger in CHR than in patients.

Conclusion: Stress sensitization seems to play a role particularly in the early phase of psychosis development as results suggest that CHR patients are more sensitive to daily life stressors than psychotic patients. In this early phase, psychotic experiences also contributed to the experience of stress.

INTRODUCTION

It has long been suggested that stress plays an important role in the emergence and course of psychotic disorder[1-5]. Stressful life events[6], childhood adversity[7], as well as small everyday hassles[8, 9] have been associated with the development and course of psychotic disorder. In order to further elucidate the role of stress in the aetiology of psychotic disorder, attention has shifted to studies of the putative prodromal phase of a psychotic disorder. Participants in such studies are those who experience subclinical psychotic symptoms and meet well established prodromal criteria that describe them to be at ultra-high risk (UHR)[10] or clinical high risk (CHR)[11] for a transition to disorder. In the present study, the term clinical high risk is utilized.

CHR patients may be more exposed to stressful experiences. Findings regarding the number of life events in CHR patients compared to controls are mixed, with some studies reporting an association between the occurrence of traumatic experiences as well as other negative life events and the expression of subclinical psychotic symptomatology[12-19], while other studies reported no difference in the number of major life events[20, 21] or even significantly fewer life events[22]. Alternatively, CHR patients may specifically differ in their tolerance of stress. Indeed, life events[19, 22], as well as daily life hassles[19] were appraised as significantly more upsetting by CHR patients than controls. Additionally, CHR patients reported impaired tolerance and increased functional impairment in response to normal stress compared to healthy controls[20] and higher self-reported psychosocial stress levels compared to first-episode psychosis patients[23].

Previous studies with the Experience Sampling Method (ESM, a structured diary technique in which subjects are asked in normal daily life to report their thoughts, feelings and symptoms, and also the context (e.g. location, company, activity) and the appraisal of the context, several times per day) have shown a higher emotional and psychotic reactivity to small daily life stressors, in psychotic patients, their unaffected relatives, and in those at psychometric risk for psychotic disorder when compared to healthy controls[2, 24-27]. It has been suggested that the (repeated) exposure to early severe stressors increases sensitivity to small stresses in daily life[2, 4, 28], and that this process of 'behavioural sensitization' is a vulnerability marker for psychosis.

However, until now, only one ESM study[29] has investigated both emotional and symptomatic reactivity to daily life stress in a sample of CHR participants. Compared to psychot-

ic patients and controls, the CHR group experienced greater negative affect (NA) when confronted with stressful activities and social situations, but not after unpleasant events (i.e., emotional stress reactivity). Both the CHR and psychotic patient group showed an increase in psychotic symptoms in response to daily life stressors (i.e., psychotic stress reactivity), in comparison to controls. However, psychotic stress reactivity was comparable across patient groups. The results suggest that stress reactivity for small daily life stressors and therefore early stress sensitization occurs before the onset of psychotic disorders and is not just the consequence of a chronic illness.

What is often neglected in stress research is that psychotic experiences in themselves may be an important source of distress. A recent study[30] has shown that intensity of distress related to subclinical symptoms was related to transition risk. Furthermore, ESM studies with psychotic patients have reported that psychotic symptoms are associated with distress and an increase of NA[31-33]. This may be particularly true for CHR patients, for whom these experiences are new.

Aims of the study

Our aim was to examine 1) whether emotional reactivity to stress differs in Clinical High Risk patients, chronic psychotic patients and healthy controls, 2) whether psychotic reactivity to stress differs in CHR patients versus chronic psychotic patients, and 3) whether psychotic symptoms in itself are increasing negative affect in both patient groups.

METHODS

Sample

The sample consisted of 27 patients who were diagnosed with a non-affective psychotic disorder, 27 participants at CHR for psychosis, and 27 healthy controls. Participants in the CHR group were between 18 and 45 years of age, and had at least one of the following: (i) attenuated positive symptoms; (ii) brief limited intermittent psychotic symptoms (BLIPS), both assessed with the Structured Interview for Prodromal Symptoms (SIPS) [34]; (iii) presence of at least 2 basic symptoms (e.g., subtle thought and speech disturbances) assessed with the Schizophrenia Prediction Instrument, Adult version (SPI-A)[35]; (iv) a significant drop in functioning (30% or more on the Global Assessment of Functioning (GAF) Scale for at least 1 month within the last year) in combination with genetic risk; or (v) a significant drop in functioning plus a diagnosis of schizotypal personality disorder. Momentary assessment data for the CHR group were collected in an add-on study of the 'PREVENT' project (for more details see[36]), a large German multisite early recognition and intervention in psychosis project. CHR participants who took part in PREVENT were randomly assigned to cognitive behavioural therapy, treatment with Aripiprazole (Abilify©) and medical management or placebo plus medical management. As the study is not finished yet, disclosure of the assignments of our participants is not yet possible. ESM data collection was started directly after inclusion in the PREVENT.

Controls between the ages of 18 and 45 years were recruited by advertisements at the University of Bonn and other public buildings in Bonn. The Structured Clinical Interview for DSM-IV axis I disorders (SCID-I)[37] was used to assess axis I disorders in the CHR group and to exclude any participants with a psychiatric disorder from the control group. Control participants were also excluded in case of a family history of psychotic disorder.

The ESM data of the psychotic patients were gathered as part of an add-on study to the Genetic Risk and Outcome of Psychosis (GROUP) study[38], which investigated risk and protective factors for psychosis. Patients were recruited through in-and out-patient mental health facilities in the Southern part of the Netherlands and (the Dutch speaking part of) Belgium. Inclusion criteria for the patient group were age 16-60 years and a diagnosis of schizophrenia or schizoaffective disorder as assessed with the Comprehensive Assessment of Symptoms and History (CASH)[39]. Patients with substance-related psychosis and psychosis with a known organic cause were excluded. For the current analyses, only those patients with minimum illness duration of 5 years since their first psychotic epi-

sode were selected. Exclusion criteria for all three groups were a history of brain disease or head injury with loss of consciousness. All participants gave written informed consent, conforming to local ethics committee guidelines.

The Experience Sampling Method

The Experience Sampling Method (ESM) is a within-day, momentary self-assessment technique[40, 41]. Participants received a digital wristwatch and self-assessment forms collected in a booklet for each day. Ten times a day on six consecutive days, the watch emitted a signal (beep) at unpredictable moments between 7:30 a.m. and 10:30 p.m. After each beep, participants were asked to immediately report their thoughts, mood, symptoms, current context (e.g., their location, social company, activities), and subjective appraisals of the current situation. All self-assessments were rated on 7-point Likert scales. To ensure reliability of the completed reports, participants also recorded the time of completion of the report, which was compared with the time at which the watch had emitted a signal. All reports completed more than 15 minutes after the signal were excluded from the analyses, since previous work[42] has shown that reports completed after this interval are less reliable and consequently less valid. Participants with less than 20 valid reports (out of 60) were excluded from the analysis.

Assessment of mood

Negative affect was assessed at each beep with six mood related adjectives (down, guilty, insecure, lonely, anxious, irritated) rated on seven-point Likert scales (1=not at all, 7=very). However, detailed factor analyses based on the ESM data collected in several studies conducted in our department, have shown that the 'down' and 'irritated' variables have high negative cross-loadings on the positive affect measure (personal communication[43]). Therefore, mean scores on the items 'guilty', 'insecure', 'lonely' and 'anxious' were used as a measure of NA in the analyses.

Assessment of momentary psychotic symptoms

Psychotic symptomatology was assessed at each beep with seven symptom related items. Hallucinations were asked directly ('I hear voices' and 'I see things that are not really there'), while the presence of delusions was assessed indirectly by items that include aspects of mental states that are directly associated with delusions in schizophrenia[44, 45]. These were: 'I cannot get these thoughts out of my head'; 'I feel suspicious'; 'I feel unreal' and 'My thoughts are influenced by others'. The item 'I am afraid I will lose control' is related to psychosis in general.

Assessment of momentary stress

Stress was conceptualized as the subjectively appraised stressfulness of distinctive (social) events and minor disturbances that continually happen in the natural flow of daily life. Three different stress measures were computed. For *Activity-related stress,* the question 'What are you doing?' served as a starting point. Subsequently, three questions (i.e., 'I would rather do something else'; 'This is difficult for me' and 'I can do this well', reverse coded) were scored on a 7-point Likert scale (1 to 7), and were combined into a mean activity-related stress variable. *Event-related stress* was based on the question 'What was the most important event since the last beep?' Participants subsequently scored how pleasant/unpleasant the event was on a bipolar scale (-3 very unpleasant, 0 neutral, +3 very pleasant). Positive events (scores 1, 2 and 3) were recoded to zero, and negative scores multiplied by -1 (i.e., higher scores now reflect higher stress/unpleasantness levels) for the event-related stress variable. For *Social stress* participants were asked to indicate whether they were in the company of others or alone. If they were in company of one or more persons, they were asked to rate the item 'I would prefer to be alone' (1 to 7). This score was used as the social stress variable.

Analyses

Groups were compared with respect to continuously measured baseline characteristics by means of ANOVAs. Chi-square tests were used to compare groups with respect to categorical variables. Group comparisons (ANOVAs) were also performed to test whether the average levels of NA, momentary psychotic symptoms as well as stress related to unpleasant activities, events and social situations differed between the psychotic patients, CHR patients and controls.

For the further analyses, we used multivariate multilevel models[46, 47], an extension of standard hierarchical linear models when analysing multiple (correlated) outcomes. In particular, a certain pair of variables (e.g., activity stress and NA) was repeatedly measured within participants using ESM, as described earlier. For each participant, we therefore had up to 60 (measurement occasions) × 2 (outcomes) = 120 observations available. The data therefore conformed to a three-level structure, with the two outcomes nested within measurement occasions ("beeps"), which in turn were nested within participants. To model the association between the two outcomes at the participant and at the beep level, we used a linear mixed-effects model with two correlated random effects at the participant level (corresponding to two dummy variables indicating whether a particular row of data corresponded to outcome 1 or outcome 2) and with correlated residuals at

the beep level. The variance-covariance matrices of the random effects at the participant level and the residuals at the beep level were allowed to be fully unstructured. Age and gender and their interactions with the dummy variables were included as covariates in the model, since previous ESM research has shown a heightened affective stress response in female compared to male psychotic patients[48] and participants in the psychotic patient group were older than those in the CHR and control groups. As it can be hypothesized that the association between stress and psychotic symptoms is influenced by low mood (i.e., high NA), we ran the models testing the association between stressors and momentary psychotic symptoms both with and without NA and it's interactions with the dummy variables as covariates.

Models were fitted separately in each of the three groups. To test whether the degree of association (i.e., correlation) between two outcomes differed between the groups at the beep level, we extracted the estimated correlations with their corresponding standard errors and then conducted Wald-type tests (i.e., $z = (\hat{\rho}_1 - \hat{\rho}_2)/\sqrt{SE[\hat{\rho}_1]^2 + SE[\hat{\rho}_2]^2}$, where $\hat{\rho}_1$ and $\hat{\rho}_2$ are the beep-level correlations for the first and second group, respectively, and $SE[\hat{\rho}_1]$ and $SE[\hat{\rho}_2]$ denote the corresponding standard errors). The models were fitted with restricted maximum likelihood (REML) estimation using the mixed routine in Stata 13.1[49].

We used this method to investigate whether: (i) the association strength between stress (activity-related, event-related and social) and NA differed between the CHR and psychotic patient groups as well as the CHR and healthy control groups; (ii) the association strength between stress and momentary psychotic symptoms differed between the CHR and psychotic patients groups, once in the standard model and once in the model with NA added as a covariate; and (iii) the association strength between momentary psychotic symptoms and negative emotions (symptoms as stressor) differed between CHR and psychotic patients.

RESULTS

Participants and descriptive statistics

The total sample consisted of 27 healthy controls, 27 CHR patients, and 27 psychotic patients. Inclusion criteria were incomplete for three CHR participants and were therefore excluded. After dropping the invalid beeps (i.e., filled out more than 15 minutes after the actual beep) and selecting those participants who had filled out a minimum of 20 valid beeps, 26 healthy controls, 22 CHR, and 24 patients remained, with a total number of 2950 observations and a mean number of 41.0 (S.D=9.8) beeps.

Demographic and clinical characteristics are shown in Table 1. The patients were significantly older than both the CHR patients and controls ($F(2,69)=17.01$, p <0.001, Tukey-Kramer: patients>CHR, controls, $p<0.001$). Gender ($\chi^2=1.61$, $p=0.45$) and education level ($\chi^2=6.13$, $p=0.41$) were similarly distributed over the three groups.

Table 1. Sociodemographic and clinical characteristics of the research sample.

	Psychotic patients (*n*=24)	Clinical High Risk patients (*n*=22)	Control subjects (*n*=26)
Demographic variables			
Age[a, b], mean (SD), range	33.9 (8.8), 20-50	25.2 (5.0), 19-38	24.5 (3.6), 19-33
Gender (m/f)	15/9	17/5	16/10
Civil status, *n* (%)			
Not married	15 (63)	19 (86)	21 (81)
Married/living together	6 (25)	1 (5)	4 (15)
Divorced	3 (12)		
Widowhood			1 (4)
Missing		2 (9)	
Work situation, *n* (%)			
Household	1 (4)		
School/Education	1 (4)	14 (64)	17 (65)
Regular work	12 (50)	3 (14)	8 (31)
Structured work	3 (13)		
Non-structured activities	5 (21)	4 (18)	
Other			1 (4)
Missing	2 (8)	1 (4)	

Table 1. Continued.

	Psychotic patients (*n*=24)	Clinical High Risk patients (*n*=22)	Control subjects (*n*=26)
Education level, *n* (%)			
No education		1 (5)	
Secondary school	17(71)	15 (68)	22 (85)
Higher education	7(29)	5 (23)	4 (15)
Missing		1 (5)	
Clinical variables			
DSM IV axis I diagnosis (*n)*			
Schizophrenia	15		
Schizoaffective Disorder	7		
Brief Psychotic Disorder	1		
Delusional Disorder	1		
Major Depression		7	
Dysthymia		1	
Social Phobia		2	
OCD		2	
PTSD		1	
Panic Disorder		1	
Alcohol misuse		1	
No diagnosis		10	26
Psychotic episodes (PE) , mean (SD), range	2.7 (1.7), 1 - 8		
Illness duration, mean (SD), range	9.6 (5.2), 5.0 - 21.5		
Age of first PE, mean (SD), range	24.3 (6.7), 12 - 41		
Anti-psychotic medication use y/n/?	18/4/2		
PANSS Positive symptoms	1.83 (0.77)		

[a] Patients are significantly older than controls (p<0.001).
[b] Patients are significantly older than Clinical High Risk patients (p<0.001).

The groups did not differ on the mean number of valid beeps (see Table 2). The CHR and psychotic patient groups reported significantly more NA and momentary psychotic symptoms when compared with the controls (see Table 2 for all results). The CHR group, but not the patient group reported significantly more activity-related and social stress in comparison to controls. Furthermore, social stress was significantly higher in CHR patients compared to psychotic patients, while the psychotic patients did not differ from controls. No other significant differences were observed.

Table 2. Means (standard deviations) and F test statistics of the number of valid beeps and ESM variables for psychotic patients, CHR patients and controls.

	Mean (SD) [a]					
	Psychotic patients (*n*=24)	Clinical high risk patients (*n*=22)	Control subjects (*n*=26)	*F* (*df*=2, 69)	*p*	Tukey-Kramer[b]
Valid beeps	41.5 (10.5), range 20 - 60	38.5 (9.7), range 21 - 58	42.7 (9.3), range 23 - 56	1.14	0.33	
Activity-related stress	2.53 (0.87)	2.80 (0.69)	2.28 (0.53)	3.22	0.046	3 < 2*
Event-related stress	0.21 (0.43)	0.27 (0.25)	0.15 (0.11)	1.00	0.37	
Social stress	1.66 (0.75)	2.59 (1.27)	1.54 (0.60)	9.42	0.0002	1 < 2** & 3 < 2***
NA	1.95 (0.98)	2.02 (0.84)	1.17 (0.21)	10.11	0.0001	3 < 1**, 2**
MPS	1.67 (0.71)	1.68 (0.61)	1.07 (0.17)	10.38	0.0001	3 < 1**, 2**

NA, negative affect; MPS, momentary psychotic symptoms.
[a] For each subject, a mean was calculated over all reports, and the mean per subject was additionally aggregated over the group to obtain the group mean (SD).
[b] 1. Psychotic patients; 2. CHR; 3. Controls.
*$p \leq 0.05$, ** $p \leq 0.01$, ***$p \leq 0.001$.

(i) Is the association between stress and negative affect different in the three groups?

The results of the multivariate multilevel models showed the correlation coefficients between NA and activity-related, event-related and social stress all to be positive, for the psychotic patient group, CHR group and control group (range 0.11 - 0.28, see Table 3). For NA and activity-related stress the association was significantly stronger in the CHR group compared to both the psychotic patient group (Z=-2.67, p=0.008) as well as the healthy controls (Z=3.68, p=0.0002), as displayed in Figure 1. The associations between NA and event-related stress and NA and social stress were not significantly different in the three groups.

Table 3. Multivariate multilevel model correlations at beep level between the stress variables, Negative Affect and Momentary Psychotic Experiences, controlled for age and gender.

	Psychotic patients			Clinical High Risk patients		
Association	CC	SE	95% CI	CC	SE	95% CI
AS & NA	0.16	0.03	0.09 - 0.22	0.28	0.03	0.21 - 0.34
ES & NA	0.15	0.03	0.09 - 0.21	0.16	0.03	0.09 - 0.23
SS & NA	0.20	0.04	0.13 - 0.27	0.16	0.05	0.07 - 0.25
AS & MPS	0.14	0.03	0.07 - 0.20	0.24	0.03	0.17 - 0.30
AS & MPS[a]	0.09	0.03	0.03 - 0.15	0.11	0.03	0.05 - 0.18
ES & MPS	0.08	0.03	0.01 - 0.14	0.16	0.04	0.09 - 0.23
ES & MPS[a]	0.03	0.03	-0.03 - 0.10	0.08	0.04	0.01 - 0.15
SS & MPS	0.15	0.04	0.07 - 0.23	0.19	0.04	0.10 - 0.27
SS & MPS[a]	0.09	0.04	0.01 - 0.17	0.12	0.05	0.03 - 0.21
NA & MPS	0.33	0.03	0.27 - 0.38	0.53	0.03	0.48 - 0.58

CC, correlation coefficient; SE, standard error; 95% CI, 95% confidence interval; NA, negative affect; MPS, momentary psychotic symptoms; AS, activity-related stress; ES, event-related stress; SS, social stress.

(ii) Is the association between stress and momentary symptoms different for Clinical High Risk vs. psychotic patients?

The correlation coefficients between momentary psychotic symptoms and activity-related, event-related and social stress were positive for both the CHR patients and psychotic patients (range 0.08 - 0.24, see Table 3). For momentary psychotic symptoms and activity-related stress the association was significantly stronger in the CHR group compared to the psychotic patient group (Z=-2.29, p=0.02). While the association between symptoms and event-related stress was stronger in the CHR group as compared to psychotic patients, it did not reach statistical significance (Z=-1.66, p=0.10). No group differences were detected for symptoms and social stress. In the additional analyses where NA was added as a covariate in the models, the association between activity-related stress and symptoms was no longer significantly different between groups (Z=-0.53, p=0.60), as were none of the other comparisons.

(iii) Are momentary psychotic symptoms more emotionally distressing for Clinical High Risk vs. psychotic patients?

Positive associations between momentary psychotic experiences and NA were found for the CHR and psychotic patient groups (see Table 3). Group comparison showed the association to be significantly larger in the CHR group than in the psychotic patients group (Z=-5.42, p<0.001), as displayed in Figure 1.

Control subjects			Group comparisons Wald test[b]			
			1 vs. 2 (ref)		2 vs.3 (ref)	
CC	SE	95% CI	*Z*	*P*	*Z*	*P*
0.11	0.03	0.05 - 0.17	-2,67	0.008	3.68	<0.001
0.12	0.03	0.06 - 0.18	-0.25	0.80	1.00	0.32
0.15	0.04	0.08 - 0.23	0.74	0.46	0.08	0.93
			-2.29	0.02		
			-0.53	0.60		
			-1.66	0.10		
			-1.04	0.30		
			-0.60	0.55		
			-0.47	0.64		
			-5.42	<0.001		

[a.] Results of models with NA included as a covariate.
[b.] 1. Psychotic patients; 2. CHR; 3. Controls.

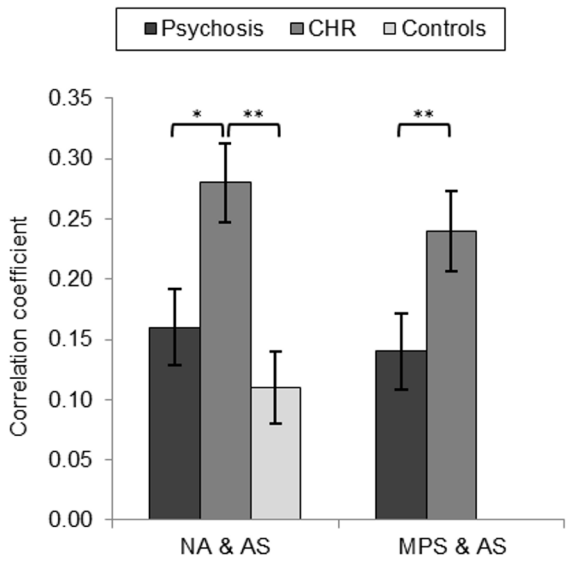

Fig. 1. Left: Correlation coefficients between negative affect (NA) and activity-related stress (AS) per group. Right: Correlation coefficients between momentary psychotic symptoms (MPS) and activity-related stress per group.
*$p \leq 0.01$, ** $p \leq 0.001$.

DISCUSSION

This study investigated emotional and psychotic reactivity to daily life stress in those at risk for a psychotic disorder compared to chronic psychotic patients and healthy controls. As hypothesized, our results showed increased emotional stress reactivity, particularly related to activities, to be associated with psychosis, mainly at the early stages of illness. Contrary to our hypothesis, psychotic-reactivity in response to unpleasant activities was increased in CHR compared to chronic psychotic patients. This suggests that emotional and psychotic stress sensitization occurs prior to the development of a full-blown psychotic state. Furthermore, as hypothesized, CHR patients experienced the psychotic symptoms as more distressing compared to chronic patients.

Emotional and psychotic stress reactivity

Our results of increased emotional stress reactivity in CHR compared to chronic patients are replicating the findings of Palmier-Claus and colleagues[29]. Furthermore, results are in line with studies in CHR samples using questionnaires showing higher psychosocial stress sensitivity in CHR participants compared to controls[23], reduced tolerance to normal stress[20], higher self-reported distress in response to life events[19, 22] as well as to daily life stressors[15, 50], especially for those reporting life events to be more distressing, suggestive of stress sensitization[19]. Psychotic stress reactivity, however, was stronger in the CHR patients compared to psychotic patients, contrary to our hypothesis based on the findings of Palmier-Claus and colleagues[29]. One possible explanation for this difference may be related to selection of the psychotic patients. We specifically selected psychotic patients with an illness duration of at least 5 years, to compare our CHR group with chronic patients. The patient sample of Palmier-Claus and colleagues[29] is likely more mixed with both recent onset and more chronic patients, as they did not provide specific inclusion criteria in that regard. This is reflected in the difference in mean illness duration, with our sample having a mean illness duration of 9.6 (SD=5.2) years compared to 6.5 (SD=8.2) years reported in their paper. Psychotic stress reactivity may thus be more characteristic of the early psychotic phase and becoming less prominent when illness duration progresses.

There are several other possible explanations for our findings of heightened emotional and psychotic stress reactivity in CHR patients compared to the chronic psychotic patients. First, the CHR may experience more severe stressors or these may occur more often than those experienced by the patient group, as was indeed confirmed by our

findings of increased activity and social stress in this group. As high levels of social anxiety have been reported to characterize help-seeking CHR patients[51, 52], more exposure to social activities in our CHR group helps to explain the difference with the psychotic patients, who have possibly adjusted their lives in order to avoid stressful (social) situations. Alternatively, less exposure to activities, events and social situations might be a consequence of more negative symptoms[53], which has been related to lower social functioning, work performance, and social skills. In accordance with this, a recent study comparing negative symptoms in psychotic and CHR patients[54] reported that psychotic patients differed from CHR patients by reporting less motivation for engagement with family and recreational activities. However, as negative symptoms are profound not only in psychotic patients but also in help-seeking CHR patients[55] and the recent study of Cressman and colleagues[51] showed the level of anhedonia to be comparable to that of psychotic patients, the influence on the reported group difference in exposure to (social) activities is probably limited.

Second, a recent study has reported that CHR patients do not seem to possess the skills to effectively cope with stress in general. Compared to healthy controls, CHR patients used more maladaptive coping strategies (e.g., blaming one's self for the occurrence of the event) and fewer adaptive (e.g., choosing to reinterpret the event in a positive fashion) coping strategies, and the use of these strategies might limit their functioning even further or exacerbate symptoms[56]. Furthermore, use of adequate coping strategies like stress reduction has been found to predict an improvement with regard to psychotic symptoms over time[57].

Third, most of our psychotic patients used anti-psychotic medication. It could therefore be that anti-psychotic medication partly dampens emotional and psychotic stress reactivity, resulting in the difference observed between our patient groups. Some evidence comes from a recent study[58] in which psychotic patients who use antipsychotic medication subjectively reported dampened emotional experience. However, as not all our psychotic patients were using antipsychotic medication and some of the CHR patients have been using medication, use of antipsychotics is unlikely to fully explain the difference in stress reactivity between the groups.

Finally, the results of our sensitivity analyses investigating the influence of low mood on psychotic reactivity underscore the close relationship between stress, symptoms and low mood. When NA was added to the psychotic stress reactivity models, it was no

longer significantly higher in the CHR group compared to more chronic patients, suggesting that psychotic stress reactivity is mediated by low mood at the early phases of illness.

Psychotic symptoms and distress

The current study provided evidence that psychotic symptoms in themselves may be a source of distress, particularly in CHR patients. These symptoms are relatively new for CHR patients and belief conviction may not have been fully developed. The unknown nature of these symptoms may intensify the levels of distress. Results of a recent study on stigma related to labels and symptoms of CHR also identified subclinical psychotic symptoms in themselves to be a source of distress[59]. CHR patients experienced more stigma from symptoms than from the psychosis risk-label, and specifically the "shame" related to symptoms was associated with depression.

Another possible explanation might be that CHR patients may have received no or limited treatment, either psycho-education or psychological treatment, for these symptoms as ESM assessment started just after identification of CHR status, which may result in less effective coping strategies. A previous ESM study of psychotic patients[33] indeed showed that a greater endorsement of a psychological explanation of delusions and hallucinations was related to less disruption of functioning, less distress and less NA. On the other hand, chronic patients may differ from CHR patients in coping strategies they use to deal with the symptoms. Lardinois and colleagues[31] showed that psychotic patients who used more non-psychotic coping strategies (i.e., active problem-solving or avoiding, passive illness behaviour and problem-avoiding) had more conscious appraisal of distress associated with symptoms than those who adopted a more symptomatic coping strategy, for example following or obeying orders induced by the symptoms or locking oneself in.

Theoretical and clinical implications

Overall, our findings further support the hypothesis that increased stress reactivity can be viewed as an affective pathway to psychosis[2]. They also highlight the important role of distress, represented in this study as an increase in NA, with the emergence of psychotic symptoms. The results suggest that CHR patients may get caught in a downward spiral of feeling distressed by their psychotic symptoms, which may in turn increase the intensity of psychotic symptoms.

Our findings underscore the need for early intervention in CHR patients in order to interrupt this vicious cycle. Decreasing stress reactivity as well as decreasing the distress

associated with the psychotic symptoms is relevant in this respect. The newest generation of Cognitive Behavioural Therapies (CBTs) puts high emphasis on the context (hence the name "contextual CBT"). Stress reduction techniques, which incorporate elements of Mindfulness or Acceptance and Commitment Therapy may be an effective treatment strategy (for a review see[60]). Given the observation that CHR patients coping strategies are often ineffective and can enhance symptoms[56] and use of adequate strategies have been found to be predictive of improvement in psychotic symptoms[57], interventions that help CHR patients to develop and apply adequate coping strategies are also likely to be effective.

Limitations

The results should be viewed in the light of several methodological issues. First, as with all ESM studies, measurements are based on subjective reports. Therefore, it can be argued that the results are not psychometrically precise. However, although subjective reports are considered less reliable (e.g., do all participants interpret or answer the questions identically?), previous research indicates that subjective reports can be valid and are important in order to understand the changes in symptoms[61].

Second, the items used to assess momentary psychosis are relatively broad, as items were used that participants could self-report about. However, one could question whether they truly reflect a psychotic state. For example, 'I cannot get these thoughts out of my head' may equally reflect anxiety or depression. A principal component analysis on the psychosis items resulted in two factors, one factor representing hallucinations (the two hallucination items) and all the other items loading equally on a second factor, which would then reflect delusions. However, does this second factor truly reflect delusions? All items scored equally strong on the factor delusions including 'I feel suspicious', or 'My thoughts are influenced by others', suggesting that the composite score most likely represents delusions. Furthermore, previous studies from our group showed that the psychosis score as used in the current paper had concurrent validity (as the ESM psychosis scores were significantly correlated with the score on the positive items but not the negative items of the PANSS) and convergent validity using the known-groups technique)as it distinguished patients from relatives and controls[26]). This supports that the composite score of all items does reflect psychosis. However, the psychosis items could be strengthened in future research for example by using focus groups with people who have experienced psychosis.

Third, the study was cross-sectional and therefore no direct causality can be inferred from these results. Furthermore, the possibility of reverse causality cannot be excluded. There is a possibility that increased NA or increased levels of psychotic symptoms influence the subjective appraisal of the environment or that increased NA causes psychotic symptoms to be experienced as more intense. However, as was suggested previously, the overall effect would still be for the individual to experience psychosis associated with an environmental event[26].

Fourth, the possible influence of medication use to the examined associations could not be tested in the current study, since CHR medication use was not yet available. While at present disclosure of treatment is not yet available, CHR participants did receive either cognitive behavioural therapy, treatment with Aripiprazole (Abilify©) plus medical management or a placebo plus medical management. The majority of psychotic patients used anti-psychotic medication at the time of testing. Future studies are needed to examine the effect of medication use properly by comparing patients groups with and without anti-psychotic medication use.

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Chapter 5

Temporal dynamics of hallucinations and suspiciousness in clinical high risk and first episode psychosis

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ABSTRACT

Background: Hallucinations and persecutory delusions are core features of (subclinical) psychosis, often causing considerable distress. The phenomenology of hallucinations and persecutory delusions has previously been investigated in the realm of daily life in psychosis spectrum patients and we aimed to extend this investigation to patients with a first psychotic episode (FEPs) and individuals at clinical high risk for psychosis (CHR-Ps). The prevalence, course and the co-occurrence of hallucinations and feelings of suspiciousness in daily life, as well as their temporal relation to emotions, anxiety and self-esteem were investigated over a 6-day period.

Methods: The Experience Sampling Method, a structured diary technique, was used to investigate hallucinatory experiences and suspiciousness in daily life in a pooled data-set of 33 CHR-Ps and 34 FEPs. Hallucinations were defined using participants' scores on the items "I see things that are not really there" and "I hear voices", and suspiciousness with the item "I feel suspicious".

Results: Overall, 24% of CHR-Ps and 39% FEPs reported hallucinations and 91% and 58% reported suspiciousness, respectively. Hallucinations and suspiciousness co-occurred regularly within the same person in both CHR-Ps and FEPs. Anxiety, negative emotions, decreased self-esteem and delusional ideation accompanied hallucinatory and paranoid episodes. Decreased self-esteem preceded suspiciousness in FEPs and CHR-Ps, as did increased delusional intensity and visual hallucination intensity for CHR-Ps.

Discussion: Hallucinations and suspiciousness are common in CHR-P and FEP and regularly co-occur. Low self-esteem and delusional ideation may precede suspiciousness, while anxiety is elevated during hallucinatory and paranoid episodes.

INTRODUCTION

Hallucinations and delusions including feelings of suspiciousness and persecution are considered core positive symptoms of psychosis spectrum disorders. These symptoms are reported by chronic patients, by patients experiencing a first psychotic episode (FEPs) and at an attenuated level in those individuals meeting criteria for clinical high risk for psychosis (CHR-Ps). However, the actual phenomenology of these experiences, especially in these early phases of psychosis, has hardly been investigated. The few reporting prevalence rates found hallucinations in 73% and delusions in 74% of FEPs[1]. In contrast, 34-60% of CHR-Ps reported hallucinations while 82% had delusions[2, 3]. Furthermore, co-occurrence of hallucinations and delusions was found to be relatively high (~40%) in the CHR-P state[2], and with 80% even higher in FEPs, while 18% reported only delusions and 2% had only hallucinations[4].

Results of studies examining the content of these (attenuated) psychotic symptoms in more detail have shown that persecutory ideation including being 'monitored' was reported by 54% of FEPs[1] and 54% of CHR-Ps[5]. Auditory hallucinations have been reported by 70% of FEPs and 29-57% had visual hallucinations with the majority of those being relatively mild in nature and often described as 'vague shadows'[1, 6]. Furthermore, visual and auditory hallucinations seem to co-occur in 84-88% of individuals[6, 7].

Previous studies have used the Experience Sampling Method to investigate persecutory delusions and auditory and visual hallucinations in daily life of psychosis spectrum patients. ESM is a structured self-assessment technique in which participants are prompted at random intervals throughout the day to report their current experiences[8]. With this method, it is possible to investigate subjective experiences that are related to delusions such as feeling suspicious, unreal, experiencing loss of control, having intruding thoughts or the idea that your thoughts are influenced by others as well as hallucinations. Prevalence rates in daily life were between 49-67% for persecutory delusions and 40-73% for hallucinations[9-13]. Furthermore, it was also clear that delusions and hallucinations are often reported together in daily life.

Two studies have used ESM to explore the temporal dynamics of delusions and hallucinations. For example, when the intensity of suspiciousness is increasing, how long does that last over time? And what is predictive of such an increase? For episodes of persecutory delusions, it was found that anxiety and low self-esteem preceded onset of these

episodes whereas all negative emotions (feeling down, irritated, lonely, anxious) and reductions in self-esteem where present during an episode[14]. With regard to hallucinations, it was found that auditory and visual hallucinations are discrete phenomena with distinct points of onset and termination, which were associated with higher negative affect and may be preceded by delusional ideation[10]. Combined these findings indicate that the intensity of these experiences fluctuates over periods of hours and days[10, 13, 15] and suggest that despite psychotic experiences in daily life being a persistent problem, patients are not constantly engulfed by their symptoms.

However, the phenomenology and temporal dynamics of delusions and hallucinations have not been examined in patients with a first psychotic episode or those at clinical high risk for the development of psychosis. Therefore, using ESM in a sample of CHR-P and FEP we examined (i) the prevalence and course of hallucinations and delusions with a specific focus on suspiciousness, over a 6-day period, (ii) the difference in prevalence and course of these experiences between the two patient groups, and (iii) the temporal association between the onset of a hallucinatory/suspicious episode and the intensity of emotional experiences and self-esteem.

METHODS

Sample

The current sample comprised of 33 CHR-P individuals and 34 FEP patients. Momentary assessment data were pooled from two ESM studies investigating early psychosis. Data of 23 CHR-Ps were collected in an add-on study[16] of the 'PREVENT' project, a large German multisite early recognition and intervention in psychosis project (for more details see [17]). The data of 10 CHR-Ps and 34 FEPs were collected the IThink study, as part of a study of early psychosis and participants were recruited in the south of the Netherlands and Belgium.

All participants were between 15 and 45 years of age. Participants in the CHR-P group had at least one of the following: (i) attenuated positive symptoms; (ii) brief limited intermittent psychotic symptoms (BLIPS), both assessed with the Structured Interview for Prodromal Symptoms (SIPS, for PREVENT)[18] or the Comprehensive Assessment of At Risk Mental State (CAARMS)[19]; (iii) presence of at least 2 basic symptoms (e.g., subtle thought and speech disturbances) assessed with the Schizophrenia Prediction Instrument, Adult version (SPIA, for PREVENT[20]; (iv) genetic risk (i.e. a first degree relative with psychotic disorder) or a diagnosis of schizotypal personality disorder; all in combination with a significant drop in functioning of 30% or more on the Global Assessment of Functioning (GAF) Scale for at least 1 month within the last year. For the FEP group, participants were included if onset of their first and only psychotic episode had occurred within two years prior to participation and were assessed with the Comprehensive Assessment of Symptoms and History (CASH) [21]. Participants with psychosis due to a known organic cause were excluded. All participants gave written informed consent, conforming to local ethics committee guidelines.

The Experience Sampling Method

The Experience Sampling Method (ESM) is a within-day, momentary self-assessment technique[8, 22]. Participants received either a digital wristwatch and self-assessment forms collected in a booklet for each day (PREVENT) or a PDA, the 'PsyMate'. Ten times a day on six consecutive days, the watch or PDA emitted a signal (beep) at unpredictable moments between 7:30 a.m. and 10:30 p.m. After each beep, participants were asked to immediately report their thoughts, mood, symptoms, current context (e.g., their location, social company, activities), and subjective appraisals of the current situation. All self-assessments were rated on 7-point Likert scales. To ensure reliability of the com-

pleted reports, participants using the watch and booklets participants recorded the time of completion of the report which was compared with the time at which the watch had emitted a signal. All reports completed more than 15 minutes after the signal were excluded from the analyses, since previous work[23] has shown that reports completed after this interval are less reliable and consequently less valid. Participants with less than 20 valid reports (out of 60) were excluded from the analysis.

ESM measures

Suspiciousness and delusional intensity

Intensity of suspicious feelings was measured using the item "I feel suspicious". Delusional intensity was measured using five items ("I feel suspicious", "I cannot get these thoughts out of my head", "I'm afraid I will lose control", "I feel unreal" and "My thoughts are influenced by others") rated on 7-point Likert scales.

Hallucinatory intensity

Auditory hallucinatory (AH) intensity was assessed with the item "I hear voices" and visual hallucinatory (VH) intensity was assessed with the item "I see things that are not really there" (rated on 7-point Likert scales, ranging from 1 not at all to 7 very).

Suspicious and hallucinatory episodes

A suspicious episode was defined as one or more consecutive moments with a score of ≥3 on the item "I feel suspicious". A hallucinatory episode was defined as one or more consecutive moments with a score of ≥3 on either or both of the items "I hear voices" and "I see things that are not really there". As was done previously[10, 14], we took a liberal approach to missing data allowing a maximum of one missing data point per episode since this was a naturalistic study (although nights were considered as interruptions). In order to analyse temporal dynamics and relation to emotions, anxiety, self-esteem and delusions and if applicable suspiciousness and AH and VH hallucinations, moments were categorized as either the last moment before an suspicious or hallucinatory episode, the first moment in an episode, a moment during an episode (not first or last moment), the last moment during an episode, the first moment after an episode and unrelated to an episode (i.e., all the other moments; see Figures 1 and 2). Length of episodes was calculated by adding the number of beeps inside an episode.

Emotional experience, anxiety and self-esteem

Participants' momentary mood states were assessed with 7 mood adjectives rated on 7-point Likert scales (1 not at all to 7 very). The mean score on items "I feel cheerful/ relaxed/ satisfied" represented positive affect (PA). The items "I feel insecure/lonely/ anxious/guilty" constituted negative affect (NA). All analyses were conducted with both this general measure of NA and with the single item "I feel anxious". The mean score on the items "I like myself", "I am ashamed of myself" and "I doubt myself" (both reverse coded) represented self-esteem.

Statistical analyses

The CHR-P and FEP groups were compared on sociodemographic and ESM characteristics by means of t-tests and chi-square tests for continuous and dichotomous variables, respectively. Two-sided independent samples T-test were used to examine group differences in momentary NA, PA, anxiety, self-esteem, suspiciousness, delusional as well as auditory and visual hallucinatory intensity between individuals reporting hallucinations and/or delusions during the ESM assessment period and those who did not in the CHR-P and FEP groups separately. T-tests were also used to directly compare the CHR-P and FEP groups on these variables. For the further analyses, multilevel linear modelling techniques were used to study the dynamics of suspiciousness and hallucinations. Models were fitted with maximum likelihood estimation (MLE) using the XTREG module in Stata 13.1[24]. Age and sex were a priori added to the models as covariates. Effect sizes from predictors in the multilevel model were expressed as *B*, representing the fixed regression coefficient. Analyses on episodes were carried out on participants reporting at least one suspicious or AH/VH episode, and separately per experience and per group. In the analyses on the dynamics of suspiciousness and hallucinations, moments within an episode were compared with observations unrelated to these experiences. In these models, current suspicious and delusional intensity, AH and VH intensity, affect and self-esteem were dependent variables and phase of the suspicious or hallucinatory episode (unrelated to episode, last moment before episode, first moment in episode, moment during episode, last moment during episode and first moment after episode, see Figures 1 and 3) the independent variable. The estimated *B*'s with their corresponding standard errors were extracted from the models and entered in Wald-type tests in order to examine differences in effect sizes between the CHR-P and FEP groups for each of the phases of suspicious and hallucinatory episodes.

RESULTS

Sample and descriptive statistics

Sixteen (2 CHR-P and 14 FEP) of 83 recruited participants were excluded from the analyses because of an insufficient number of valid ESM observations (<20). The final sample therefore comprised 67 participants, divided in 33 CHR-Ps and 34 FEPs. The groups did not differ on the number of valid reported moments. FEPs reported significantly higher levels of PA (M=3.55 (.80) vs. M=4.27 (1.00), t=3.23, p<0.01) compared to CHR-Ps. CHR-Ps reported significantly higher delusional intensity (M=2.31 (1.13) vs. M=1.69 (.87), t=-2.52, p<0.05) and suspiciousness (M=2.15 (1.04) vs. M=1.61 (.83), t=-2.37, p<0.05) than FEPs. In contrast, FEPs reported higher AH intensity than CHR-Ps, although this failed to reach statistical significance (M=1.62 (1.46) vs. M=1.16 (.49), t=1.73, p=0.09), and groups did not differ on VH intensity. Additional information regarding sociodemographic characteristics and ESM reports is summarized in Table 1.

Prevalence and course of suspiciousness and hallucinations

Thirty of 33 CHR-Ps (91%) reported ESM increased suspiciousness, at 400 out of 1140 moments (35%), comprising a total of 173 suspicious episodes (mean 5.8, range 1-12). Mean episode duration was 2.3 moments and in 53% of these episodes the length was restricted to 1 moment. Twenty of 34 FEPs (59%) reported ESM increased suspiciousness, at 160 out of 672 moments (24%), resulting in 92 suspicious episodes (mean 4.6, range 1-16). Mean episode duration was 1.7 moments and in 68% of episodes the duration of the episode was 1 moment. Of all individuals reporting suspicious episodes, 22 CHR-Ps (73%) and 9 FEPs (45%) did not report additional hallucinations. In contrast, all eight CHR-Ps and 11 of 13 FEPs (85%) with hallucinations reported also suspiciousness and both experiences occurred within the same moment for 6 of these CHR-Ps (75%) and 7 (64%) of these FEPs, respectively, representing ~20% of all recorded moments. One CHR-P participant reported paranoia during all assessed moments.

Eight of 33 CHR-Ps (24%) reported ESM-hallucinations. Of these, 1 reported only AHs, 3 reported only VHs, 1 reported both AHs and VHs although in separate moments and 3 reported AHs and VHs to co-occur in the same moment. Among those CHR-Ps reporting hallucinations (either AHs, VHs or both) hallucinations were present at 68 out of 298 moment (23%), composing a total of 34 hallucinatory episodes (mean 4.3, range 1-9). Mean episode duration was 2.0 moments and the length was restricted to one moment in 68% of the hallucinatory episodes.

Table 1. Demographic, clinical and ESM characteristics

	Clinical High Risk (*n*=33)	FEP (*n*=34)	FEP vs. CHR
Demographic variables			
Age, mean (SD), range	23.3 (5.3), 15-38	22.8 (5.1), 16-31	*t*= -.41, ns
Gender (m/f)	23/10	19/15	ns*
Civil status, *n* (%)			ns*
Not married	29 (88)	31 (91)	
Married/living together	2 (6)	3 (8)	
Unknown	2 (6)	-	
Work situation, *n* (%)[a]			ns*
School/Education	23 (70)	18 (53)	
Regular work	4 (12)	6 (18)	
Structured work	-	2 (6)	
Non-structured activities	4 (12)	5 (15)	
Other/unknown	2 (6)	3 (9)	
Education level, *n* (%)			*p*<0.01
No education	1 (3)	-	
Primary school	-	2 (6)	
Secondary school	21 (64)	11 (33)	
Higher education	10 (30)	20 (61)	
Unknown	1 (3)	-	
ESM episode data			
Number of valid reports, mean (SD), range	38.2 (8.8), 20-58	35.8 (9.4), 21-58	*t*= -1.07, ns
Number of hallucinatory episodes, mean (SD), range	34, 4.3 (3.5), 1-9	60, 4.6 (3.3), 1-9	*t*=.24, ns
Length of hallucinatory episodes (moments), mean (SD), range	2.0 (1.8), 1-7	3.7 (3.1), 1-10	*t*=2.92, *p*<0.01
Number of paranoid episodes, mean (SD), range	174, 5.6 (3.3), 1-12	91, 4.8 (4.4), 1-16	*t*= -.76, ns
Length of paranoid episodes (moments), mean (SD), range	2.3 (2.0), 1-10	1.7 (1.5), 1-8	*t*=-2.45, *p*<0.05

NOS, not otherwise specified; ESM, Experience Sampling Method; SD, standard deviation; ns, not significant.*Fisher's Exact test [a] due to rounding, percentages may not add exactly to 100%.

Thirteen of 34 FEPs (39%) reported ESM-hallucinations. Of these, 6 reported only AHs, 1 reported VHs and AHs on separate moments and 6 reported AHs and VHs to co-occur within the same moment. Together FEPs reported hallucinations (either AHs, VHs or both) at 221 out of 477 moments (46%), comprising 60 hallucinatory episodes (mean 4.6, range 1-9). Mean episode duration was 3.7 moments and in 37% of the episodes

the length was 1 moment. One CHR-P participant and 4 FEPs reported hallucinations during at least 90% of all moments, with 1 FEP reporting hallucinations present during all assessed moments (56 out of 60).

Difference in prevalence and course of suspiciousness and hallucinations in CHR-P versus FEP

More CHR-Ps than FEPs reported paranoia (X^2=9.10, p=0.003). In contrast, the groups did not differ on the number of participants reporting hallucinations or the number of suspicious and hallucinatory episodes. However, the duration of suspicious episodes was significantly shorter in FEPs than in CHR-Ps, while the duration of hallucinatory episodes was significantly longer in FEPs than in CHR-Ps (see Table 1).

Emotional state, anxiety, self-esteem and delusional and hallucinatory intensity

Suspicious episode

CHR-Ps with suspicious episodes reported higher intensity of momentary psychotic experiences, anxiety and NA and lower PA and self-esteem than those without suspicious episodes, although none reached statistical significance (Table 2). In contrast, suspicious FEPs reported significantly lower levels of PA and self-esteem, higher levels of NA and anxiety as well as higher overall delusional intensity than non-suspicious FEPs. Direct comparison of FEPs and CHR-Ps with increased suspiciousness showed that FEPs reported significantly higher AH intensity, while the reverse effect was observed for PA.

Focussing on those participants who experienced episodes of suspiciousness, Figure 1a and 1b illustrate that both CHR-Ps and FEPs reported the presence of some delusional ideation even in moments unrelated to suspicious episodes. Both CHR-Ps and FEPs reported significantly lower levels of self-esteem and PA as well as higher levels of NA, anxiety, AH intensity and delusional intensity during an episode compared to moments unrelated with the episodes (Table 3, Figure 1a & 1b). In the CHR-P group there were small but significant increases in delusional and AH intensity even before episode onset and a small but significant peak in AH intensity occurred the first moment after the end of the suspicious episode (Table 3 & figure 1a). Furthermore, small but significant levels of suspiciousness lingered even after the end of an episode, as did the decrease in self-esteem. In addition, FEPs showed a significant decrease in self-esteem and PA before the onset of an episode (Table 3 & figure 1b). Finally, direct comparison of FEPs and CHR-Ps showed that the decrease in PA before onset of the episode in FEPs was also significant compared to CHR-Ps, for whom PA levels were comparable to moments

unrelated to an episode. During an episode FEPs reported significantly higher AH and VH intensity, paranoia, delusional intensity, more NA and anxiety and lower self-esteem compared to CHR-Ps (Table 3).

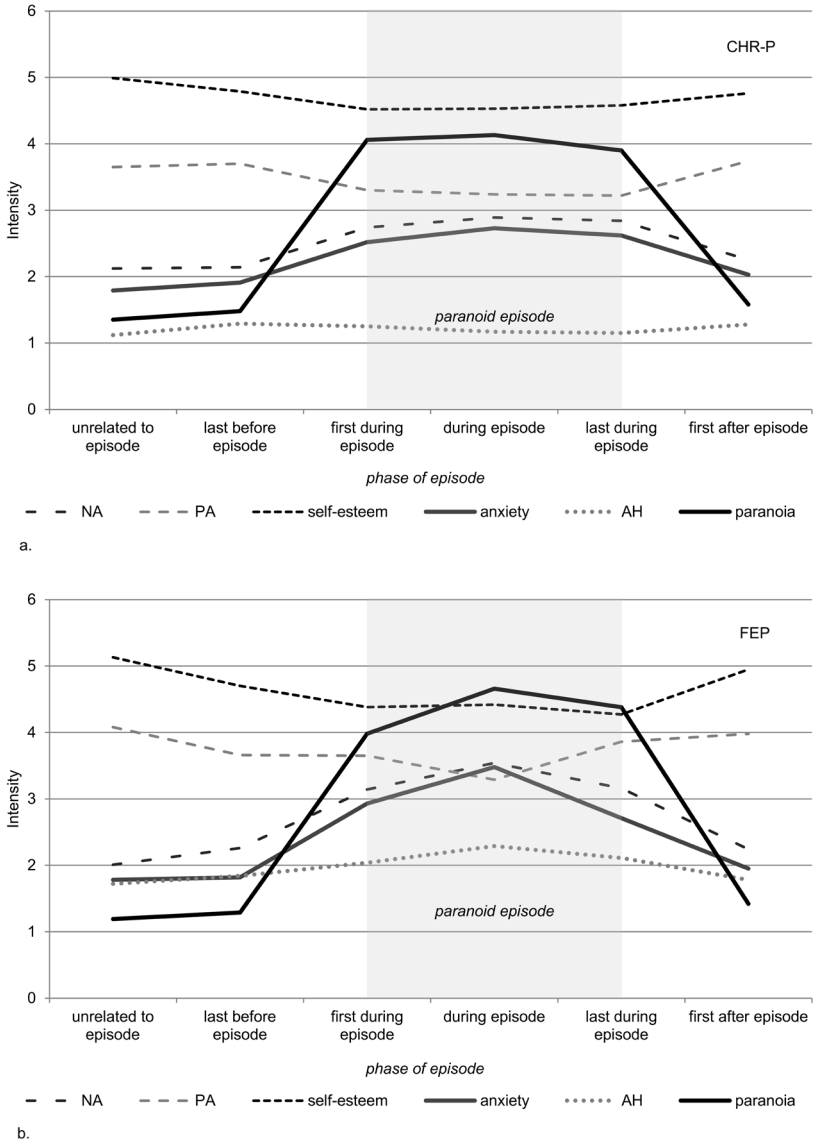


Fig. 1. Dynamics of suspicious episodes in CHR-P (1a) & FEP (1b)

Table 2. Comparison on group level

		Mean (SD)		
		Hal (1)	**No Hal (2)**	***t-test* 1 vs. 2**
Negative affect	CHR-P	2.95 (1.33)	2.09 (.86)	*t*=2.14, *p*=0.04
	FEP	2.34 (1.41)	1.61 (.57)	*t*=2.14, *p*=0.04
Positive affect	CHR-P	3.40 (.75)	3.60 (.82)	*t*= -.64, ns
	FEP	4.05 (1.14)	4.40 (.91)	*t*= -.99, ns
Self-esteem	CHR-P	4.14 (1.50)	5.10 (1.23)	*t*= -1.82, *p*=0.08
	FEP	4.82 (.1.57)	5.72 (.81)	*t*= -2.22, *p*=0.03
Anxiety	CHR-P	2.48 (1.46)	1.88 (.97)	*t*=1.33, ns
	FEP	2.19 (1.47)	1.42 (.47)	*t*=2.25, *p*=0.03
Delusional intensity	CHR-P	2.89 (1.36)	1.91 (.81)	*t*=2.51, *p*=0.02
	FEP	2.14 (1.12)	1.28 (.29)	*t*=3.37, *p*<0.01
Suspiciousness	CHR-P	2.63 (.98)	2.17 (1.19)	*t*=.99, ns
	FEP	1.86 (1.10)	1.29 (.43)	*t*=2.16, *p*=0.04
AH intensity	CHR-P	1.65 (.86)	1.00 (.01)	*t*=3.90, *p*<0.001
	FEP	2.61 (2.04)	1.01 (.02)	*t*=3.63, *p*=0.001
VH intensity	CHR-P	1.70 (1.25)	1.00 (.005)	*t*=2.89, *p*=0.01
	FEP	1.93 (1.67)	1.00 (.01)	*t*=2.58, *p*=0.01

Hal: Hallucination(s) reported; Suspic: suspiciousness reported. *p<0.05, ** p<0.01, *** p<0.001.

Mean (SD)			FEP vs. CHR-P	
Suspic (3)	**No Suspic (4)**	***t-test* 3 vs. 4**	***t-test 1***	***t-test* 3**
2.40 (1.04)	1.25 (.10)	*t*=1.89, *p*=0.07	*t*=.98, ns	*t*= -.35, ns
2.29 (1.16)	1.31 (.32)	*t*=3.09 *p*<0.01		
3.51 (.82)	3.95 (.34)	*t*= -.89, ns	*t*=1.44, ns	*t*=1.53, ns
3.92 (1.07)	4.76 (.65)	*t*= -2.59, *p*=0.01		
4.77 (1.36)	5.88 (.40)	*t*= -1.39, ns	*t*=.98, ns	*t*=.50, ns
4.96 (1.36)	5.97 (.65)	*t*= -2.55, *p*=0.02		
2.12 (1.13)	1.15 (.10)	*t*=1.46, ns	*t*= -.43, ns	*t*= -.17, ns
2.06 (1.21)	1.22 (.33)	*t*=2.51, *p*=0.02		
2.24 (1.04)	1.26 (.42)	*t*=1.59, ns	*t*= -1.38, ns	*t*= -1.20, ns
1.89 (.97)	1.21 (.27)	*t*=2.55, *p*=0.02		
2.40 (1.13)	1.06 (.06)	*t*=2.02, *p*=0.05	*t*= -1.61, *ns*	*t*= -1.82, *p*=0.07
1.85 (.90)	1.01 (.03)	*t*=3.50, *p*=0.001		
1.17 (.51)	1.00 (.00)	*t*=.58, ns	*t*=1.26, ns	*t*=2.00, *p*=0.05
1.80 (1.54)	1.40 (1.36)	*t*=.75, ns		
1.19 (.69)	1.00 (.00)	*t*=.46, ns	*t*=.34, ns	*t*=1.40, ns
1.61 (1.40)	1.01 (.01)	*t*=1.59, ns		

Table 3. Dynamics of suspiciousness

		Phase 1 (*B*)	**Phase 2** (*B*)
Negative affect[a]	CHR-P	.01 (.10)	.61 (.08)***
	FEP	.26 (.15)	1.15 (.11)***
	FEP vs. CHR-P	Z=1.31, ns	Z=3.96, *p*<0.001
Positive affect[a]	CHR-P	.05 (.14)	-.35 (.10)**
	FEP	-.43 (.17)*	-.44 (.12)***
	FEP vs. CHR-P	Z= -2.19, *p*<0.05	Z= -.59, ns
Self-esteem[a]	CHR-P	-.20 (.10)*	-.47 (.07)***
	FEP	-.43 (.14)**	-.75 (.11)***
	FEP vs. CHR-P	Z= -1.29, ns	Z= -2.15, *p p*<0.05
Anxiety[a]	CHR-P	.12 (.14)	.71 (.11)***
	FEP	.05 (.20)	1.18 (.15)***
	FEP vs. CHR-P	Z= -.29, ns	Z=2.55, *p*<0.05
Delusional intensity[a]	CHR-P	.28 (.07)***	1.07 (.06)***
	FEP	.11 (.10)	.910 (.07)***
	FEP vs. CHR-P	Z= -1.35, ns	Z= -1.80, ns
Suspiciousness [a]	CHR-P	.14 (.09)	2.72 (.07)***
	FEP	.10 (.12)	2.78 (.09)***
	FEP vs. CHR-P	Z= -.25, ns	Z=.53, ns
AH intensity[a]	CHR-P	.17 (.06)**	.14 (.05)**
	FEP	.12 (.15)	.31 (.11)**
	FEP vs. CHR-P	Z= -.30, ns	Z=1.50, ns
VH intensity[a]	CHR-P	.02 (.06)	.04 (.04)
	FEP	.05 (.13)	.07 (.10)
	FEP vs. CHR-P	Z=.22, ns	Z=.29, ns

*p<0.05, **p<0.01, ***p<0.001. Phase 1: last moment before onset of episode; Phase 2: first moment of episode; Phase 3: during episode; Phase 4: last moment of episode; Phase 5: first moment after end of episode. AH=auditory hallucinations, VH=visual hallucinations [a] Regression coefficient indicates the difference in intensity of the variables as compared to moments unrelated to a paranoid episode

Phase 3 (*B*)	**Phase** 4 (*B*)	**Phase 5** (*B*)
.76 (.09)***	.72 (.10)***	.13 (.10)
1.53 (.19)***	1.16 (.19)***	.21 (.17)
Z=3.70, *p*<0.001	Z=2.04, *p*<0.05	Z=.43, ns
-.41 (.12)**	-.43 (.14)**	.09 (.14)
-.79 (.21)***	-.22 (.21)	-.08 (.18)
Z= -1.59, ns	Z=.86, ns	Z= -.73, ns
-.46 (.09)***	-.41 (.10)***	-.23 (.10)*
-.71 (.18)***	-.86 (.18)***	-.17 (.16)
Z= -1.24, ns	Z= -2.21, *p*<0.05	Z= .36, ns
.93 (.13)***	.82 (.14)***	.24 (.14)
1.71 (.24)***	.94 (.24)***	.17 (.22)
Z=2.87, *p*<0.01	Z=.42, ns	Z= -.27, ns
1.04 (.07)***	1.08 (.08)***	.19 (.08)
1.31 (.12)***	1.36 (.12)***	.17 (.11)
Z=2.00, *p*<0.05	Z=1.94, *p*=0.05	Z= -.16, ns
2.78 (.08)***	2.56 (.09)***	.24 (.09)*
3.46 (.14)***	3.18 (.14)***	.21 (.13)
Z=4.16, *p*<0.001	Z=3.67, *p*<0.001	Z= -.16, ns
.05 (.06)	.03 (.06)	.17 (.07)*
.58 (.18)**	.39 (.18)*	.06 (.16)
Z=2.80, *p*<0.01	Z=1.87, ns	Z= -.61, ns
.02 (.05)	-.04 (.06)	.02 (.06)
.31 (.16)	.69 (.16)***	.05 (.14)
Z=1.77, ns	Z=4.35, *p*<0.001	Z=.19, ns

Table 4. Dynamics of hallucinations

		Phase 1 (*B*)	**Phase 2** (*B*)
Negative affect[a]	CHR-P	.10(.28)	.43 (.21)*
	FEP	.54 (.27)*	.91 (.18)***
	FEP vs. CHR-P	Z=1.14, ns	Z=1.76, ns
Positive affect[a]	CHR-P	.51 (.36)	-.60 (.26)*
	FEP	.17 (.30)	-.38 (.20)
	FEP vs. CHR-P	Z= -.73, ns	Z=.66, ns
Self-esteem[a]	CHR-P	.29 (.26)	.09 (.19)
	FEP	-.36 (.24)	-.65 (.16)***
	FEP vs. CHR-P	Z= -1.83, ns	Z= -2.96, *p*<.01
Anxiety[a]	CHR-P	.60 (.40)	.85 (.29)**
	FEP	.63 (.35)	1.06 (.23)***
	FEP vs. CHR-P	Z=.06, ns	Z=.56, ns
Delusional intensity[a]	CHR-P	-.03 (.23)	.53 (.17)*
	FEP	.29 (.19)	.91 (.13)***
	FEP vs. CHR-P	Z=1.04, ns	Z=1.81, ns
Suspiciousness[a]	CHR-P	-.27 (.43)	.17 (.32)
	FEP	.55 (.34)	.58 (.22)**
	FEP vs. CHR-P	Z=1.50, ns	Z=1.07, ns
AH intensity[a]	CHR-P	.02 (.20)	1.81 (.14)***
	FEP	-.08 (.19)	3.32 (.13)***
	FEP vs. CHR-P	Z= -.33, ns	Z=7.93, *p*<.001
VH intensity[a]	CHR-P	-.21 (.20)	1.30 (.15)***
	FEP	.02 (.25)	.81 (.17)***
	FEP vs. CHR-P	Z=.71, ns	Z= -2.16, *p*<0.05

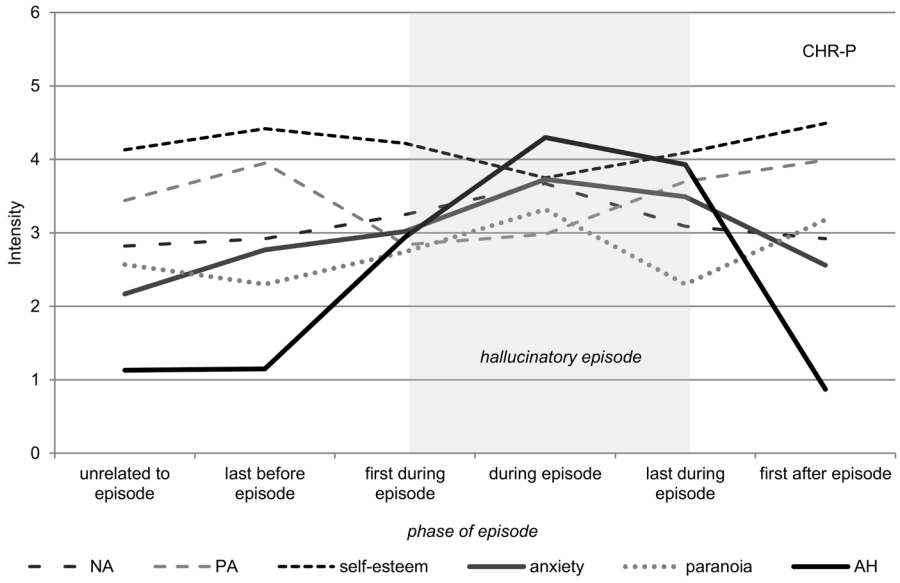
*p<0.05, **p<0.01, ***p<0.001. Phase 1: last moment before onset of episode; Phase 2: first moment of episode; Phase 3: during episode; Phase 4: last moment of episode; Phase 5: first moment after end of episode. AH=auditory hallucinations, VH=visual hallucinations [a] Regression coefficient indicates the difference in intensity of the variables as compared to moments unrelated to a paranoid episode

Phase 3 (*B*)	**Phase 4** (*B*)	**Phase 5** (*B*)
.85 (.34)*	.27 (.36)	.10 (.26)
1.02 (.20)***	.83 (.22)***	.81 (.44)
Z=.44, ns	Z=1.33, ns	Z=1.39, ns
-.46 (.41)	.26 (.45)	.55 (.33)
-.53 (.22)*	-.12 (.25)	-.39 (.48)
Z= -.15, ns	Z= -.75, ns	Z= -1.62, ns
-.38 (.31)	-.04 (.33)	.36 (.24)
-.78 (.18)***	-.64 (.20)**	-.51 (.39)
Z= -1.11, ns	Z= -1.53, ns	Z= -1.89, ns
1.56 (.48)**	1.32 (.40)*	.39 (.38)
1.30 (.26)***	1.14 (.29)***	1.19 (.57)*
Z= -.47, ns	Z= -.31, ns	Z=1.19, ns
.72 (.33)*	.34 (.35)	.26 (.26)
1.02 (.14)***	1.06 (.16)***	.21 (.30)
Z=.90, ns	Z=1.69, ns	Z= -.09, ns
.52 (.51)	-.27 (.55)	.61 (.40)
.81 (.25)**	.75 (.28)**	.68 (.55)
Z=.52, ns	Z=1.64, ns	Z=.10, ns
3.17 (.22)***	2.80 (.25)***	-.26 (.18)
3.65 (.14)***	3.36 (.16)***	-.26 (.35)
Z=1.79, ns	Z=1.93, ns	Z= -.05, ns
1.95 (.25)***	2.12 (.26)***	-.23 (.19)
1.02 (.17)***	1.10 (.21)***	.28 (.40)
Z= -2.97, p<0.01	Z= -3.05, p<0.01	Z=1.13, ns

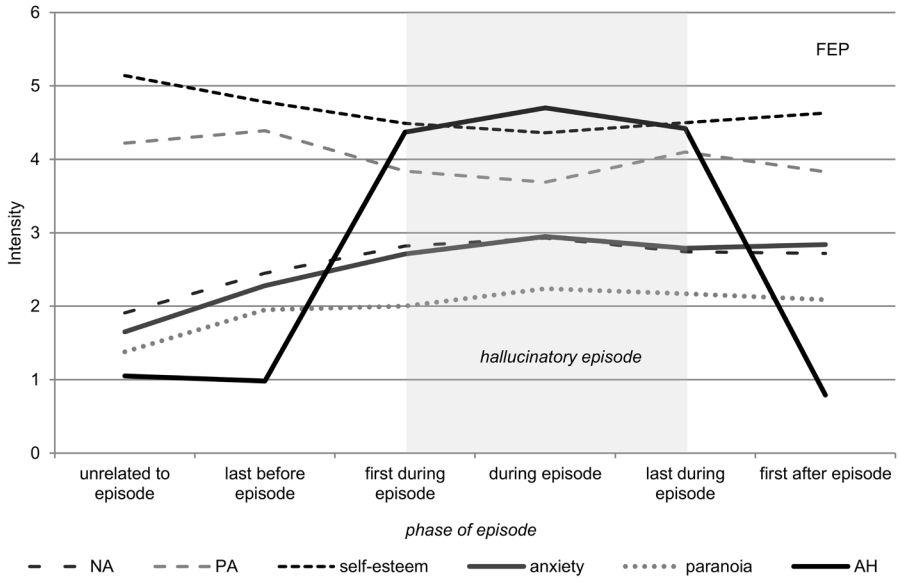
Hallucinatory episode

CHR-Ps with hallucinations reported significantly higher levels of NA, delusional intensity as well as AH and VH intensity compared to CHR-Ps without hallucinations, while self-esteem was lower at trend level (Table 2). FEPs reporting hallucinations had significantly higher levels of NA, anxiety, suspiciousness, delusional, AH and VH intensity as well as lower self-esteem compared to FEPs without hallucinations.

When we focus on those participants who did report hallucinations, Figures 2a and 2b illustrate that suspiciousness and delusional ideation are elevated in moments unrelated and just before onset of hallucinatory episodes, although especially in the CHR-P group. CHR-Ps reported a significantly lower level of PA and higher levels of NA, anxiety and delusional intensity during an episode compared to moments unrelated to an episode (Table 4 & Figure 2a). FEPs reported significantly lower levels of self-esteem and PA as well as higher levels of NA, anxiety, delusional intensity and suspiciousness during a hallucinatory episode. For the CHR-Ps, no significant differences were found on moments prior or following an episode as compared to moments unrelated to an episode, whereas for FEPs a significant increase in NA occurred prior to the onset of a hallucinatory episode (Figure 2b). Furthermore, anxiety, NA and suspiciousness levels remained elevated after the episode ended, although the latter two this increase did not reach statistical significance. Direct comparison of CHR-P and FEP groups showed that FEPs were characterised by a significantly lower level of self-esteem and a higher level of AH intensity than CHR-Ps at the onset of an episode, while differences did not remain significant during an episode. In contrast, VH intensity was significantly increased in CHR-Ps compared to FEPs during all phases of a hallucinatory episode (Table 4).



a.



b.

Fig. 2. Dynamics of hallucinations in CHR-P (2a) & FEP (2b)

DISCUSSION

Main findings

This is the first study to examine hallucinations and suspiciousness in the context of daily life over a six-day period in participants in the early stages of psychosis. More CHR-Ps than FEPs reported suspiciousness (91% vs. 58%, respectively), the duration of suspicious episodes was longer and comprised more than a third of all recorded moments in CHR-Ps. FEPs reporting suspiciousness in daily life had more distress as reflected by more NA, anxiety and delusional intensity and lower self-esteem than those FEPs not reporting suspiciousness. In the CHR-P group these differences were less distinct. In contrast, hallucinations (AH, VH or both) were more often reported by FEPs than CHR-Ps (39% vs. 24%, respectively) and hallucinatory episodes lasted longer in FEPs. Whereas in the CHR-P group suspiciousness was reported as an isolated experience, report of hallucinations was accompanied by suspiciousness in almost all individuals regardless of clinical status. In both groups, individuals with hallucinations also reported significant higher NA, anxiety and delusional intensity and lower self-esteem than those without and intensity of AH was higher in FEPs than in CHR-Ps, suggesting that presence of hallucinations reflects a more severe illness state. This study furthermore showed that hallucinatory and suspicious episodes are discrete phenomena with distinct points of initiation and termination and are accompanied by increases in NA, anxiety and delusional ideation. Decreases in self-esteem were apparent in FEPs during both types of episodes, while it was only characteristic for suspicious episodes in CHR-Ps. Our findings showed that both groups, but especially CHR-Ps, showed elevated levels of suspiciousness and delusional ideation that increased further during episodes. Finally, only FEPs showed changes in affect prior to onset of both types of episodes.

Phenomenology and temporal dynamics of suspicious and hallucinatory episodes

Current results are in line with previous studies using ESM showing that despite psychotic experiences in daily life being a persistent problem, individuals are not constantly engulfed by their symptoms in their daily lives[10-12, 14], as symptoms were present in 23-46% of moments in those reporting symptoms. Fifty-nine percent of individuals suffering from a first psychotic episode reported suspicious feelings to occur in daily life, which is comparable to the 54% of FEPs who reported specific persecutory ideas including the feeling of being 'monitored' in a cross-sectional study[1] and the 49-67% of psychotic disorder patients in previous studies using ESM[11, 12]. In contrast, 91% of individuals at clinical high risk for psychosis reported suspiciousness in daily life, even more than in a previ-

ous study which found subclinical delusions in 82% of their sample[2] and 54% reporting paranoid feelings[5]. Less than half of FEPs with daily life suspiciousness reported this as their only symptom compared to almost three-quarter of CHR-Ps. Currently suspicious FEPs were clearly distressed by these symptoms as they reported more NA, anxiety, delusional intensity and lower self-esteem than current symptom-free FEPs. In contrast, these effects were less apparent for currently suspicious CHR-Ps. Interestingly, episode duration was longer in CHR-P compared to FEPs and CHR-Ps reported significantly more suspiciousness and more general delusional ideation (i.e. feeling unreal, fear of losing control, getting stuck in ones thinking and the idea that other might influence ones thoughts) than FEPs. Therefore, the CHR-P state can be argued to reflect a primarily 'suspicious-delusional state'.

Hallucinations were reported by 39% of FEPs in daily life, a rate very similar to the 40% reported by Oorschot and colleagues[10] in their study of psychosis spectrum patients, although lower than in other studies using ESM[11, 13]. However, those studies used a more liberal approach in defining hallucinations (minimal score of 2 rather than 3) possibly explaining the difference with this study. Our reported rate is lower than that of ~70% for auditory hallucinations[1, 6], although more similar to 29-57% for visual hallucinations in FEPs in cross-sectional studies[1, 6]. A possible explanation is that FEPs were allowed to be in remission if their psychotic episode had occurred within the previous 2 years. Furthermore, 31 of the 34 FEPs used or had previously used anti-psychotic medication likely resulting in less prevalent current symptoms in daily life.

Furthermore, reflecting results of previous cross-sectional studies and studies using ESM[4, 11, 13], hallucinations and suspiciousness almost always clustered within the same individuals with a first psychotic episode. Similarly, even though only about a quarter of CHR-Ps reported hallucinations in daily life, which were less prevalent than in cross-sectional studies[2, 3], all these individuals also experienced feelings of suspiciousness. Both CHR-Ps and FEPs were thus characterised by a 'hallucinatory-delusional state', which was associated with more as reflected by higher NA, anxiety, delusional intensity and lower self-esteem compared to individuals without current hallucinations. Combined these results suggest that presence of hallucinations is related to a more severe stage of psychotic illness. However, FEPs spend more time in this mixed state as duration of hallucinatory episodes was significantly longer than in CHR-Ps.

Our results confirm previous results showing that hallucinations have a fairly sudden onset and termination[10, 13] and show that this also applies to suspiciousness, overall suggesting that both are on/off phenomena as illustrated by Figures 1 and 2. However, these figures also show that both FEPs and CHR-Ps are reporting low intensity delusional ideation even in moments not related to suspicious and hallucinatory episodes and this is especially apparent for CHR-Ps with hallucinations. This might explain why we did not find a significant increase in delusional ideation before onset of a hallucinatory episode as reported by Oorschot and colleagues[10] in psychosis spectrum patients. However, whereas suspiciousness and delusional ideation accompanied hallucinations at the onset and over the course of episodes in FEPs, delusional ideation increased only during longer episodes in CHR-Ps (i.e. episodes lasting ≥2 moments). In contrast, a small increase in delusional intensity was apparent in CHR-Ps in the last moment before onset of suspicious episodes, as were small increases in AH which intensified over the course of the episodes in both groups. Similarly, Ben-Zeev and colleagues[12] found that increased perceptual abnormalities in psychosis spectrum patients preceded persecutory ideation. Current results show that the interplay between hallucinations and delusions varies slightly over the different phases of illness.

Psychotic patients are characterised by highly variable levels of self-esteem and this instability was especially related to paranoid feelings[15]. In our study, reduced self-esteem was more apparent for suspicious episodes than for hallucinatory episodes, for which it was present in FEPs. In contrast, even before onset of suspicious episodes self-esteem was decreased and decreased further over the duration of episodes, as was reported for a sample of participants with experiences ranging across the paranoia continuum[14]. This reduction remained even after the end of an episode in CHR-Ps. Our findings further emphasise the important role of negative self-evaluation in the development of suspiciousness and consistent with the suggestion suspicious individuals assume others to share their own negative evaluations of themselves, which in elicits the perceived malevolence of others[14].

As reported by previous ESM studies with participants across the psychosis continuum and psychotic patients with acute paranoia and hallucinations[10, 11, 14], we found both experiences to be accompanied be a decrease in positive emotions and increases in negative emotions and anxiety in FEPs, although individual differences in these relationships have been reported[25]. Current results are furthermore in line with cross-sectional studies showing increased anxiety levels in patients with (auditory) hallucinations and per-

secutory delusions[26-29]. Importantly, our results expand these findings by showing that these effects also apply in the clinical high risk for psychosis state.

Anxiety has been found to be a strong predictor of onset and intensity of paranoid and hallucinatory episodes in daily life[13, 14], although current results are less conclusive. Anxiousness was somewhat although not significantly elevated prior to onset of hallucinations or paranoia in both CHR-P and FEP patients. A previous study of Oorschot and colleagues[25] found that an anxious state was only apparent in the moment before a paranoid episode in a small number of their psychotic patients. This might also be the case for current participants. In contrast, hallucinations and suspiciousness were accompanied by increases in anxiety. Worrying and rumination have been found to predict delusional and hallucinatory experiences and distress[9]. Feeling worried and having ruminating thoughts, accompanied by a drop in self-esteem are likely triggers of psychotic experiences, which in turn elicit anxiety. This suggestion is supported by our finding that anxiety remained increased after the end of a hallucinatory episode for FEP patients, for whom the content of hallucination might be more disturbing and a source for ruminating thoughts, whereas anxiety dropped after the end of a hallucination in CHR-Ps.

Theoretical implications

Both cognitive and biological theories of psychosis argue that transition to psychosis is the results of the co-occurrence of hallucinations and delusions[30-32]. Subtle perceptual alterations or anomalous experiences occurring in an early phase can be very disturbing and warrant an explanation resulting in the gradual formation of delusional ideas under the influence of emotional processes. In line with these theories, epidemiological studies have shown that these perceptual alterations or hallucinations along with the distress they cause and accompanied by depressive symptoms have been associated with development of more severe types or secondary delusions. These secondary delusions concern loss of control (e.g. thought withdrawal and insertion, thought broadcasting) and belief that emotions, impulses and/or actions are controlled by an outside force, which in turn are associated with poorer outcome in psychotic patients[33-37].

Taken together current findings on prevalence and phenomenology of psychotic experiences in daily life in the early phase of psychosis are in line with epidemiological studies showing that clustering of hallucinations and delusions as compared to either symptoms in isolation, results in a deepened psychotic state[34, 35]. In this 'hallucinatory-delusional state' experiences become more persistent, associated with negative symptoms and an

increased risk of clinical outcome[38, 39] and this state occurs more often in individuals with higher levels of exposure to genetic and environmental risk factors[34, 35], suggesting it forms a crucial stage in the development of psychotic disorder. It is therefore attractive to hypothesize that the relatively small current subsample of CHR-Ps (24%) reporting both types of experiences in daily life are more likely to make the transition to psychotic disorder than those reporting suspiciousness only, although follow-up studies are needed to confirm this hypothesis.

Clinical implications

The current findings have implications for clinical practice. Thorough investigation of the exact nature of (attenuated) psychotic symptoms is needed as severity and risk for transition is likely to be higher for individuals reporting both suspiciousness and hallucinations. Clinicians need to be aware of the central role of emotion-related processes, anxiety and self-esteem for the occurrence of hallucinations and suspiciousness in daily life not only in patients with a first episode of psychosis for whom these processes are relevant with respect to prevention of illness progression, but also for those at high clinical risk for transition to psychosis. Use of momentary assessment can help to unravel symptom patterns as they supply both the individual patient and clinician with large amount of detailed information about symptoms and their relationships with mood, anxiety, self-esteem all in the social context of daily life.

In psychotic spectrum patients investigation of different 'types' of paranoia (i.e. "poor me" and "bad me") has shown that a complicated relationship exists with self-esteem, experiential avoidance and social stress in which paranoia sometimes has a beneficial effect on self-esteem and possibly serve a protective mechanism[40-42]. Future studies in CHR-P and FEP groups are needed to determine the exact role of all these processes in these populations. Taken together, these findings warrant for a systematic evaluation of the type of paranoia and self-esteem (variability) to determine the best treatment strategy which can help improve self-esteem regulation and in turn symptomatology and anxiety.

Limitations

The results of this study should be interpreted in the context of several methodological limitations. First, as with all ESM studies, measurements are based on subjective reports. Therefore, it can be argued that the results are not psychometrically precise. However, although subjective reports are considered less reliable (e.g., do all participants in-

terpret or answer the questions identically?), previous research indicates that subjective reports can be valid and are important especially in order to understand the changes in symptoms[43]. In addition, as we combined two samples, data was gathered with help of an electronic device and by the use of a paper-and-pencil diary method. The paper-and pencil method has been questioned as it may lead to poor participant compliance. However, previous studies have demonstrated that the traditional paper-and-pencil diary methods are not inferior to electronic diary methods with regard to compliance rates[44, 45].

Second, our measure of paranoia 'I feel suspicious' was defined more narrowly than in previous ESM studies of paranoid or persecutory ideation[9, 14]. However, prevalence rates were similar to earlier studies. Further investigation of the content of paranoid beliefs and their relationship to emotional processes may help therapies to focus on the mechanism of change in suspicious thinking instead of focussing solely on symptom reduction. Third, given the small number of CHR-P and FEP participants who only reported either visual or auditory hallucinations, we were not able to investigate the temporal dynamics of auditory and visual hallucinations separately as was done by Oorschot and colleagues[10] in a large sample of psychotic spectrum patients. Furthermore, as we were unable to assess the precise nature of content of auditory and visual hallucinations, we could not discern whether these were more crystallized in FEPs compared to CHR-Ps. However, results of this study showed that regardless of participant status, psychotic experiences in daily life were related with low mood and anxiety. Future studies with larger samples should examine these factors in more detail.

Fourth, as with all ESM studies of symptomatology, the random-sampling design might have caused an underestimation of hallucination and paranoia frequency, since we cannot rule out the possibility that patients are less prone to respond to a beep when hallucinating or feeling suspicious. Alternatively, we might have missed hallucinations or paranoia occurring between beeps. Furthermore, episode duration may have been overestimated as it is possible that we may have missed symptom-free periods in between consecutive beeps. In contrast, an episode duration may have been underestimated in participants who reported hallucinations or paranoia (almost) continuously as per definition we defined the end of an episode as the last moment of the day. However, our results also indicated that the majority of episodes were present only during one moment, suggesting that the on and offset of hallucinatory and paranoid episodes is highly variable.

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6

Chapter 6

General discussion

Psychotic disorders are associated with a high burden for patients themselves as well as for their family members and friends. Early identification and intervention for subclinical psychotic symptoms may influence illness trajectory, possibly averting the transition to fully-fledged psychotic disorder and improving functioning and quality of life. To accomplish this goal psychosis research and clinical care have started to focus on investigation of subclinical psychotic symptoms in help-seeking individuals meeting criteria for clinical high risk for psychosis (CHR-P) as well as in non-help seeking individuals from the general population and unaffected first-degree relatives of psychotic disorder patients.

The current thesis aimed to gain more insight in mechanisms and risk factors involved in the development from subclinical psychotic symptoms to clinically relevant psychotic symptoms and psychotic disorder. The occurrence of (subclinical) psychotic symptoms was studied across the psychosis continuum in individuals from the general population, unaffected first-degree relatives of psychotic disorder patients, patients at clinical high risk for psychosis (CHR-P), patients with a first psychotic episode (FEP) and long-term psychotic disorder patients.

The first part of this thesis focussed on the epidemiology of development of subclinical psychotic symptoms in individuals from the general population and unaffected relatives of psychotic disorder patients as assessed through both self-report and clinical interview measures. Using a longitudinal design, in **chapter 2** we examined the progression and outcome of baseline 'false-positive' self-reported psychotic experiences (FP SRPE) over a 3-year follow-up period in individuals from the general population, which have been suggested to represent the lowest expression of psychosis risk along the continuum. We showed that 'False positive SRPE', are not truly 'false' as they index risk for development of clinically relevant psychotic symptoms, presence of mood and anxiety disorders and reduced functioning. Self-reported PE, even unconfirmed, therefore warrant 'watchful waiting' and follow-up over time especially when they are reported by individuals with reduced psychosocial functioning and general psychiatric problems. In **chapter 3** we examined in a sample of unaffected first-degree relatives of psychotic disorder patients and healthy controls if genetic risk, as reflected by the Polygenic Risk Score for schizophrenia (PRS), was associated with the expression of psychosis conceptualized as subclinical psychotic symptoms assessed through both self-report and clinical interview. We found that while PRS was not associated with subclinical psychotic symptoms obtained through self-report, it was associated with subclinical symptoms obtained in a clinical

interview in both unaffected first-degree relatives and healthy controls. PRS was furthermore positively associated with the lifetime number of affective episodes.

The second part of this thesis aimed at exploring the phenomenology of psychotic experiences in daily life in CHR-P patients, patients with a first episode of psychosis (FEP) and long-term psychotic disorder patients, to examine differences and similarities between the at-risk for psychosis stage, an 'intermediate' stage and an 'endpoint' stage along the extended psychosis continuum. The Experience Sampling method (ESM) was applied to zoom in into the microenvironment to study the dynamics of momentary psychotic experiences over time in the context of daily living. In **chapter 4** we examined emotional and symptomatic stress-reactivity to daily life stressors as potential risk factors for psychosis development. We found that stress sensitization seems to play a role particularly in the early phase of psychosis development as results suggest that CHR-P patients are more sensitive to daily life stressors than long-term psychotic disorder patients, as they showed higher levels of emotional and symptomatic stress reactivity. In this early phase, momentary psychotic symptoms also contributed to the experience of stress as they were associated with an increase in negative affect.

Finally, in **chapter 5** we specifically investigated the phenomenology of hallucinations and suspiciousness and their relationship with mood, anxiety and self-esteem in CHR-P and FEP patients. Episodes of suspiciousness were more prevalent than hallucinatory episodes and this was especially prominent for the CHR-P patients for whom episodes of suspiciousness lasted longer than for FEP patients, while only a minority reported hallucinations. Although hallucinations were more prevalent in FEP patients, episode duration was longer in CHR-P patients. Both symptoms were often reported by the same individual and co-occurred regularly at the same moment. Suspiciousness and hallucinations had a fairly sudden onset and ending, implying they are discrete on/off phenomena. Intensity of delusional ideation, negative affect and anxiety increased whereas self-esteem decreased during suspicious and hallucinatory episodes, indicating that these (subclinical) symptoms were distressing.

The benefit of combining subjective self-report and objective interview measures in psychosis research

Psychopathology relates per definition to the expression of subjectively distressing 'abnormal' experiences. In psychosis research and clinical practice, both self-report and interview measures are used to assess presence of anomalous experiences and the degree

in which they are distressing and pathological. Self-report measures have the advantage of being less time consuming than interviews, however, these are subjective in nature making it uncertain whether all individuals interpret and answer questions identically. Especially when (subclinical) psychotic symptoms are retrospectively assessed through self-report, is it possible that interpretation and answer style are under the influence of factors such as personal relevance, recency effects, novelty, significance or mood. Furthermore, self-report measures are unable to filter contextual information needed to determine the clinical validity and relevance of reported 'psychotic symptoms'[1]. In contrast, contextual information can be elicited through semi-structured clinical interviews by trained and experienced clinicians. This distinction in results based on assessment method[2, 3] is illustrated by findings that in general population studies prevalence rates of subclinical psychotic symptoms obtained by self-report measures are several times higher than those obtained through clinical interview[4-8]. Some of these self-reported psychotic symptoms are true (subclinical) psychotic symptoms, although around 40% are not truly psychotic in nature and are referred to as 'false-positive' self-reported psychotic experiences (FP SRPE).

Examples of FP SRPE are hearing or seeing a departed loved one during a bereavement period, or solely having hallucinations after use of a specific hallucinogenic drug[9]. Furthermore, factor analyses of self-reported PLEs assessed with the CAPE[10], the self-report instrument which was used in **chapter 3**, in help-seeking non-psychotic individuals and in individuals from the general population have identified several subtypes being persecution/paranoia, bizarre experiences, hallucinations, and paranormal beliefs/magical thinking[11, 12]. Whereas persecution, bizarre experiences and hallucinations were more likely to be associated with distress and poor functioning and may represent expressions of underlying vulnerability for psychotic disorder, this was not found for paranormal beliefs and magical thinking, suggesting these may be a normal personality variant. Furthermore, in the general population sample very few endorsed experiencing bizarre experiences, perceptual abnormalities or persecutory ideas subtypes for a large proportion of time, and magical thinking was the most common subtype of self-reported psychotic symptoms that was endorsed as 'always or almost always' present[12]. We can therefore argue that the majority of self-reported psychotic symptoms in both healthy controls and unaffected relatives were those of the paranormal beliefs and magical thinking subtype, which are unlikely to present true risk for psychotic disorder.

Some researchers have therefore argued that subclinical psychotic symptoms detected through self-report measures only have minimal direct clinical significance for the prediction of psychosis onset[1, 8, 9]. However, an earlier study with a different general population sample found FP SPRE to predict transition to psychotic disorder, although the effect size was smaller than in individuals with validated psychotic symptoms[13]. In **chapter 2** we confirmed that even FP SRPE are clinically relevant for psychosis development as well as for the development of general psychopathology. Individuals reporting these were 6 times more likely to develop clinically significant (subclinical) psychotic symptoms and had a higher likelihood of reduced functioning and more general psychopathology than healthy controls. Interestingly, individuals who developed valid psychotic symptoms after first reporting FP SRPE were already different at baseline from individuals for whom FP SRPE were transitory in nature. This supports the suggestion that (subclinical) psychotic symptoms are the outcome of more severe baseline severity of multidimensional psychopathology[14-16]. The group of individuals that transitioned to valid psychotic symptoms showed more mood and anxiety problems, high neuroticism, reported more childhood adversities and were more often help-seeking and reported more and more frequent FP SRPE.

Use of self-report measures of psychotic experiences in both the general and clinical population will result in an overestimation of their prevalence. In turn, this might delude the effects of true subclinical symptoms on transition risk and functioning. However, when combined, self-report and clinical interview measures can provide valuable information about psychosis development and directions for future research into risk factors and targets for treatment, especially when used in longitudinal studies.

In clinical care, self-report measures of psychotic experiences should always be followed by a clinical interview. Importantly, chapter 2 illustrated that even non-confirmed or FP SRPE should not be dismissed as irrelevant, as they predicted higher levels of general psychopathology and help-seeking. Regular reassessment of even FP SRPE for individuals remaining in care for other psychological problems is therefore recommended.

Overall, the scientific and clinical significance of subclinical psychotic symptoms will thus depend strongly on the manner and context in which these are assessed. The findings of **chapter 3** illustrate this point. We found that Polygenic Risk Score (PRS) for schizophrenia was positively and significantly associated with subclinical psychotic symptoms assessed with an objective interview measure in both unaffected first-degree relatives of psychotic patients and healthy controls. In contrast, PRS was not associated with PLEs

assessed with a self-report measure. These results thus suggest that studies of gene-environment relationships in psychosis are more likely to be informative when objective interview measures of subclinical psychotic symptoms are used. As suggested previously[9], it can be recommended that future studies of subclinical psychotic symptoms should only use self-report measures as a screening tool. PLEs should then be examined in detail by clinical interview. The use of a semi-structured psychosis risk assessment interview like the CAARMS or the SIPS is advised as it allows validation of an experience as a true subclinical symptom while also obtaining detailed information about the frequency of a symptoms and determination of CHR-P or psychosis status.

Even though retrospective self-report has important issues that have to be considered, self-report measures can be very informative when experiences are not assessed retrospectively but in real time by use of simple and straightforward questions as is done with the Experiences Sampling Method (ESM)[17, 18]. When assessment of experiences is 'in the moment', answers are less prone to the occurrence of biases and forgetting that hamper traditional retrospective assessment approaches[19]. The ESM method has several other advantages. It allows the assessment of various constructs including quality of life and psychopathology as well as psychological mechanisms like stress-sensitivity and coping that are difficult to assess using cross-sectional questionnaires. ESM studies are ecologically valid as they allow studying individuals within their own real-life environment. ESM is situated in the complex context of daily life and therefore able to measure the variation in symptoms and mood in response to environmental factors present in daily life, whereas questionnaires and most interviews do not focus on how contextual factors impact these outcome variables. In addition, questionnaires and interviews require patients to be aware of the dynamics of symptoms and their interactions with other factors. However, as different constructs like symptoms, mood, stress and social company are measured separately from each other and only associated to each other in the analyses conducted by the researcher, ESM provides information that the participant is not aware of and therefore not influenced by an individual's own expectations. Finally, ESM allows for the cross-sectional as well as longitudinal study of variation and dynamic relationships given that data collection encompasses multiple assessments over time which creates a detailed picture of the occurrence and the dynamics of symptoms, mood and other constructs in daily life.

Studies using ESM in psychotic disorder patients have provided valuable information on the phenomenology of positive symptoms[20-26], negative symptoms[27-29] and their relationship to emotions and contextual factors, but also social functioning[29, 30] in daily life.

Importantly, ESM has significantly improved our understanding of the association between a number of putative psychological mechanisms and psychotic symptoms[31]. It has shown that psychotic patients are characterised by increased emotional and symptomatic reactivity when confronted with everyday small stressors[32, 33]. Other ESM studies have investigated putative psychological mechanisms and their relationship with (subclinical) psychotic symptoms including cognitive self-consciousness[34], meta-cognitive beliefs[34, 35], self-esteem[26, 35, 36], coping[37], cognitive appraisal[25], affective disturbance[20, 38], enhanced threat anticipation and experiences of aberrant novelty and salience[39].

The studies in **chapter 4** and **chapter 5** have further extended ESM research to the early phase of psychosis in FEP patients and before onset of psychosis in CHR-P patients. Providing evidence for the hypothesis that enhanced stress sensitivity is an underlying mechanism for psychosis development, we found in **chapter 4** that CHR-P patients show increased emotional stress reactivity for small daily life hassles not only compared to healthy controls, but to long-term psychotic disorder patients as well. Our results are very similar to findings of two other recent ESM studies in CHR-P and (first episode) psychotic disorder patients[39, 40], suggesting that stress sensitization seems to play a role particularly in the early phase of psychosis development. Furthermore, psychotic disorder patients show symptomatic reactivity to small daily life stressors. This process of 'behavioural sensitization' has been argued to reflect an affective pathway to psychosis that underlies a more reactive, episodic type of psychosis that characterizes a subgroup of patients with predominantly positive psychotic symptoms[41]. Results in **chapter 4** showed that symptomatic stress reactivity for stressful activities was stronger in CHR patients than in long-term psychotic disorder patients, although the other two recent studies did not find differences between CHR-Ps and (first episode) psychotic patients[39, 40]. Behavioural sensitization thus occurs before onset of psychotic disorder and is not just the result of chronic psychotic illness.

The ESM study in **chapter 5** is the first to examine the phenomenology of positive (subclinical) psychotic symptoms in daily life, thereby expanding our knowledge about the characteristics of these symptoms. Our results highlight the existence of similarities and differences between CHR-P and FEP patients regarding the prevalence and dynamics of suspiciousness and hallucinations in daily life and their dynamic relationships with mood, anxiety and self-esteem as such providing targets for early interventions.

Expanding the experience sampling method to clinical practice

In scientific studies, important information regarding inter-individual and intra-individual differences is lost due to averaging data over groups. This is illustrated by a previous study where rather than performing group comparisons, particular symptoms patterns and internal and contextual triggers for paranoia were examined per individual[24]. Whereas previous studies[22, 25] and our study in **chapter 5** showed that paranoia is related to increased anxiety levels at group level, the study of Oorschot and colleagues[24] focussed on emotions preceding and following paranoia in each individual and found that both the emotional state preceding paranoid thoughts and the emotional impact of these thoughts showed large and meaningful variation between individuals with psychotic disorder patients. In some, emotional changes preceded paranoia whereas anxiety resulted from having paranoid thoughts in others. For others, paranoia was followed by a state of relaxation. In addition, results of this particular study also pointed out the importance of intra-individual differences in symptoms in the flow of daily life. It was shown that whereas one patient had a clear 'peak' in paranoia-level and low paranoia intensity during the rest of the day, another reported a steady medium paranoia-level throughout the day. However, by averaging these scores as is done in group comparisons this resulted in an overall medium daily paranoia level for both patients, obscuring clinically relevant information.

These results clearly highlight the value of ESM as an additional diagnostic tool in regular clinical practice. It allows tailoring of diagnosis and treatment planning to the needs of a specific patient and treatment monitoring. Rapid feedback is now available due to data collection via smart phone applications, which have also simplified the user experience and reduced the logistic burden of data collection and analysis. This allows ESM to be applied as an ecological momentary intervention (EMI)[42, 43]. In a review of the EMIs in psychiatry it was found that few studies have investigated the possibilities and the efficacy. However, these studies underscored feasibility and acceptability of mobile health (mHealth) approaches in patients with severe mental illness. Importantly, EMIs provide the opportunity for intervening in dynamics of daily life between the individual and his/her environment that may be at the core of psychiatric symptom. Furthermore, an integration of EMI and real-life assessment using ESM seems to promote greater efficacy, especially when the intervention can be provided in moments when intervention is needed [44]. Finally, it has been argued that costs may be reduced and outcomes may be improved by implication of blended care in which face-to-face treatment is combined with ESM-based intervention in daily life to enhance application of psychological inter-

ventions under real-world conditions[42]. ESM offers the opportunity to enhance self-monitoring, self-insight and personalized health care, and the results of studies in this thesis suggest that EMIs should aim application of at stress reduction techniques in daily life in CHR-P and FEP patients. If stress reactivity is subsequently reduced this might reduce the occurrence of suspicious feelings and hallucinations, which in turn will have a positive effect on mood and prevent strong decreases of self-esteem which often occurs during these symptoms and reduce anxiety.

Beyond the high-risk for psychosis state: importance of a broad clinical staging approach of mental disorders

In order to promote early detection of individuals at high risk for the development and active intervention with the goals to delay or even prevent onset of first episode psychotic disorder the Clinical High-Risk state for psychosis (CHR-P) paradigm was introduced about 2 decades ago. It has accumulated a lot of knowledge on subclinical psychotic symptoms and risk factors for psychosis development. The transition rate of up to 29% of CHR-P patients at 2-year follow-up and of 36% after 3 years [45, 46] and the finding that ~70% of CHR-P patients develop schizophrenic psychoses[47], makes this CHR-P state a specific marker for research on predictors and mechanisms of developing psychosis[48]. This average transition rate of 36% after three years suggest that current CHR-P criteria, emphasizing onset or worsening of subclinical psychotic symptoms, are still insufficient in predicting imminent onset of psychosis and thus in need of refinement[49]. Recently, the CHR-P paradigm has also been critiqued on other points[14], among them that the focus lies solely on 'risk' and 'transition' and that by doing so any subclinical positive symptoms are implicitly treated as a pathway to schizophrenia and imminent bad outcome. It has also been argued that determining psychosis risk solely on the presence of subclinical psychotic symptoms is too restrictive, transition rates are only high because of sample enrichment strategies rather than the criteria themselves, and differential outcomes other than transition (i.e. remission and persistence of subclinical symptoms) as well as the presence of other psychopathological symptoms as markers of relative poor outcome of multidimensional psychopathology in terms of functioning have been largely ignored. Furthermore, the fact that CHR-P patients are help-seeking limits their epidemiologically representativeness for the broad range of psychotic experiences and subclinical symptoms in the general population of which not all are associated with distress or other forms of psychopathology. Finally, referring to CHR-P patients as if they are a class is not warranted as samples differ widely due to different sampling strategies and exclusion criteria across studies regarding previous use of anti-psychotic medication, mood

stabilizers, presence of manic symptoms and previous drug-induced psychotic states, which strongly limits generalisability of findings.

However, while these methodological concerns certainly demand attention and improvement, the other concerns raised have certainly been noted before[50] and CHR-P researchers have acknowledged that the specific focus on psychosis is too narrow and epidemiologically incomplete. The need to refine criteria has prompted investigation of other factors than subclinical positive psychotic symptoms that might be predictive for transition including social and role functioning and negative symptoms, both found to predict transition and low functioning over time[51-54]. In addition, recent studies[55-57] have shown that the 3 subgroups making up the CHR-P state differ in their risk for transition, with the BLIPS group having the highest risk followed by the subclinical symptoms group while the genetic vulnerability group was not associated with an increased transition rate compared to the group not meeting CHR-P criteria. However, by focussing on outcomes broader than transition, a very recent study showed that all 3 subgroups did not differ on severity of baseline negative symptoms or long-term non-transition outcomes including positive and negative symptom severity, psychosocial functioning and prevalence of non-psychotic disorders at follow-up[58]. This led the authors to suggest that when the CHR-P construct is viewed not simply as a marker of psychosis, but rather as a transdiagnostic risk state signifying need for clinical care, their findings do not support segregation of CHR-P groups into separate clinical entities as proposed based on the findings of differential transition risk[55, 59]. Finally, the combined results of a number of studies indicate that the positive symptom category of thought disorder/conceptual disorganization may constitute a robust clinical predictor of transition in CHR-P sample[60-66]. In line with these findings a recent study found that prediction of onset of psychosis was improved by using a state-dependent prognostic model which included the negative psychotic symptoms of observed flattened affect and subjective impaired motor functioning, impaired social functioning and distress associated with suspiciousness[49].

In recent years an increasing number of studies have investigated outcomes other than transition and focus has shifted to factors associated with low functioning. It has become apparent over the last decade that clinical implications of CHR-P status extend beyond risk of transition to psychosis. Most individuals who meet CHR-P criteria will not develop a psychotic disorder[46, 57, 67] but will experience persistent subclinical psychotic symptoms[67, 68], large impairments in psychosocial functioning and quality of life, similar to those in other psychiatric disorders[69, 70] and high rates of non-psychotic, especially

mood and anxiety symptoms and disorders [68, 70, 71] which all warrant treatment in their own right, while only in 35% of individuals subclinical symptoms will fully remit[72]. Such findings have already driven a reframing of CHR-P as a clinical state signifying pluripotent, transdiagnostic risk and the need for clinical care, rather than simply a marker of psychosis risk and are in line with the clinical staging model of psychiatry[50, 73-79].

This model positions an individual along a continuum of illness which is defined according to stages: Stage 0: no current symptoms, Stage 1a: help-seeking with distress, Stage 1b: subclinical syndrome and Stages 2 to 4: full threshold disorder with varying degrees of recurrence and severity[76, 77]. In this broad model of staging in psychiatry the focus is shifted from the narrow focus in the CHR-P paradigm to a general syndrome of early mental distress requiring non-specific psychological self-management interventions to prevent more severe stages of psychopathology which includes the CHR-P state (stage 1b), which may develop in more specific, and relatively treatment-resistant, syndromes later on. This allows for the introduction of stage-specific treatments, varying from non-specific non-pharmacological self-management approaches in the early stages to more active treatments in the advanced stages[50, 75]. It offers a conceptual framework than can guide the search for risk and protective factors for disease progression from incidental non-distressing PLEs in the general population to psychotic symptoms in long-term psychotic disorder patients.

Importantly, the general staging model allows for overlap in symptoms of different diagnostic outcomes in a particular individual, which is common especially in the earlier phases of disease progression but is not recognized by the current diagnostic criteria. This is also apparent for psychosis as studies have shown the existence of an important link between mood and anxiety symptoms and psychosis, which is found at the level of clinical illness[80-82], subclinical psychotic symptoms[83-85] and PLEs[16, 86-91], and many studies have suggested an important role for affective dysregulation in the formation of psychotic symptoms[41, 92-94]. The results of **chapter 3** add evidence to the transdiagnostic nature of psychosis as we found that genetic risk for psychosis reflected by PRS is not only expressed as subclinical psychotic symptoms, but also as affective dysregulation in the form of positive associations between PRS and the lifetime number of affective episodes in both unaffected first-degree relatives and healthy controls. This finding is in line with molecular genetic studies that suggest overlap between schizophrenia and affective disorders[95, 96].

Early identification of subclinical psychotic symptoms: when and where?

Psychotic disorder has an enormous impact on the lives of patients and their loved ones, and even subclinical psychotic symptoms are often distressing. In addition, many individuals meeting CHR-P criteria have clinically debilitating symptoms of comorbid diagnoses, including anxiety, depression and substance abuse. Similar to psychotic disorder patients, CHR-P individuals are often characterised by high neuroticism and high levels of negative symptoms and significant impairments in academic performance and occupational functioning, difficulties with interpersonal relationships and a substantially compromised subjective quality of life[97-102]. Therefore, identification and intervention should happen as early as possible. Importantly, whereas extension of screening with self-report measures to help-seeking individuals in primary mental health care will help to detect individuals for whom subclinical psychotic symptoms are distressing and are at increased risk for psychotic disorder, extending early detection to non-help seeking populations by for example screening adolescents in schools or via the internet will not be efficient[103]. Given that psychotic experiences are reasonably common and mostly non-distressing in the general population[104, 105] and adolescents in particular[12, 15], and the study of van Nierop and colleagues[7] has shown that psychotic experiences not validated by clinical interview (FP SPRE) were about 2 times more prevalent than confirmed psychotic symptoms, it can be argued that the detection of some people who are genuinely at risk will be at the cost of valuable resources invested in a high amount of clinical interviews of individuals whom are not distressed by or seeking help for these experiences in which it might trigger the development of self-perceived stigma. Taken together, early identification and intervention of subclinical psychotic symptoms is important and screening with short screening instrument like the Prodromal Questionnaire[106] or CAPE-15[107] should be widely implemented in mental health care practice. In the Netherlands, the EDIE-NL project[108] has resulted in implementation of the screening approach in all help-seeking patients in some of the large mental health services throughout the country. A positive score on the screening is followed by clinical interview to determine presence of CHR-P state or psychosis.

Clinical implications and directions for future research

Early intervention can be enhanced by gaining more insight in mechanisms and factors that determine increasing levels of subclinical psychotic symptoms and the eventual development of psychosis. Several studies of CHR-P patients have found low social functioning to be predictive for the development of psychosis. The study presented in **chapter 2** further highlights the importance of targeting low social functioning in early

interventions as it showed that individuals who developed future psychotic symptoms were already characterised by deterioration in social functioning. Social skills training and family involvement to create a supportive environment can help to improve social functioning[109] which in turn might prevent further development of psychotic symptoms. **Chapter 2** furthermore showed that individuals with baseline FP SRPE who subsequently developed psychotic symptoms were characterised by the personality trait of high neuroticism, which is a tendency to show emotional instability, and react with increased anxiety, fear, and sadness[110]. In addition, high neuroticism was the strongest predictor for the continued self-report of psychotic experiences. Given that psychotic patients with high neuroticism tend to have more severe and distressing positive symptoms[111] and both psychotic and CHR-P patients often use ineffective coping styles under stress[110, 111] that can even enhance symptoms[112], and use of adequate strategies has been found to improve psychotic symptoms[113], interventions that help CHR patients to develop and apply adequate coping strategies are likely to be effective.

Increased emotional stress reactivity in daily life can be regarded as an expression of the high neuroticism trait and **chapter 4** provided evidence that increased emotional stress reactivity in daily life not only characterizes psychotic disorder patients but is present in CHR-P patients. This effect was even stronger than in long-term psychotic disorder patients. In line with psychological models on psychosis development[92, 94] and based on all findings we can conclude that increased emotional stress reactivity plays an important role in the development and maintenance of psychotic symptoms, particularly in the at-risk phase. Whether increased emotional stress reactivity is truly a causal mechanism underlying the affective pathway to psychosis remains to be examined. Future studies are needed to investigate whether CHR-P patients that convert are characterised by higher emotional stress reactivity than those who do not.

Finally, the ESM studies in **chapter 4** and **chapter 5** both provided evidence that (subclinical) psychotic symptoms are distressing. Detailed analysis of the temporal dynamics of suspiciousness and hallucinations showed that both are associated with increases in anxiety, negative affect and a decrease in positive affect and self-esteem. In the Dutch EDIE-NL early intervention protocol, CHR-P patients receive Cognitive Behavioural Therapy (CBT) that focusses on broad psychoeducation on dopamine sensitization and the effects on perception and reasoning, exercises to become aware of cognitive biases and to correct these, behavioural experiments and homework task in addition to care as usual for other mental health problems. CBT targets appraisal processes that accompany

perceptual aberrations and suspiciousness to normalize these extraordinary experiences in order to prevent delusion formation and avoidance behaviours that consolidate symptoms.

In contrast to this traditional CBT protocol in which treatment focusses directly on the presence and content of (subclinical) psychotic symptoms, the newest generation of contextual CBTs puts high emphasis on the context and includes Acceptance and Commitment Therapy (ACT). ACT may be an effective treatment strategy as it encourages detached acceptance of unpleasant thoughts and experiences. Although more research is needed, results of pilot studies of ACT in psychotic disorder patients showed positive effects[114-116]. Furthermore, a recent feasibility study in a sample of general outpatient population showed that ACT in daily life was an acceptable and feasible mHealth intervention, suitable for a broad range of mental health problems[117]. Currently, the effectiveness of a newly developed ecological momentary intervention that targets elevated stress sensitivity, altered reward-experience, and psychological flexibility based on principles of ACT in CHR-P patients is being evaluated. This ongoing ACT in daily life study extends standard ACT therapy with real life training and exercises through a dedicated device, thereby enhancing participants' ACT-based skills and techniques. If found to be effective, ACT can serve as a valuable alternative for patients who benefit less from CBT.

Finally, as discussed previously, ESM can now be used as a diagnostic tool to examine the dynamics of psychotic symptoms, mood, self-esteem and social factors for each individual patient. ESM can also be applied to monitor treatment progress, by investigating the effect on symptoms as well as mood, social functioning and quality of life. However, the studies in **chapter 4** and **chapter 5** used items to examine psychotic symptoms that were previously developed for psychotic disorder patients. Especially the item investigating auditory hallucinations needs refinement for the CHR-P population, as these are mostly characterised by subtle auditory alterations. The current item 'I hear voices' might have resulted in CHR-P patient not reporting other, more subtle forms of auditory disturbances, which implies that current results might reflect a underestimation of the prevalence of these experiences in individuals with subclinical symptoms. Refined items need to be developed and validated in both individuals with subclinical symptoms and psychotic disorder patients in order to improve not only ESM in psychosis research and clinical practice.

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Epilogue

SUMMARY

Better knowledge of the risk factors for and mechanisms and processes underlying the developmental pathway(s) from psychotic experiences to psychotic disorders is crucial for the development of more effective early treatment options. The current thesis titled '*Dissecting the psychosis continuum risk factors along the pathway from experiences to disorder'* examines potential mechanisms and risk factors for psychosis in the lower end of the psychosis continuum. The first part of this thesis focussed on psychotic experiences (self)reported by in individuals from the general population, and by family members of psychotic patients who represent a group of individuals at elevated genetic high risk for psychosis (chapter 2 and 3). The second part of this thesis focussed on the examination of affective and psychotic symptomatology in the daily lives of individuals at clinical high risk for psychosis and first episode psychotic patients (chapters 4 and 5).

Chapter 1 provides an overview on the epidemiology, aetiology and genetics of psychotic disorders and the clinical high risk state. The proposed 'affective pathway to psychosis' and findings of previous research with the Experience Sampling Method (ESM) are introduced.

In c**hapter 2,** two different, often used measures of psychotic experiences were administered in a large longitudinal general population study (NEMESIS-II): a self-report measure and a more extensive clinical interview. For those individuals who had self-reported psychotic experiences that were subsequently assessed as "false-positive" after clinical interview (FP SRPE) at baseline the course and outcome 3-year follow-up was examined. We prospectively examined (1) the prevalence of remission and persistence of FP SRPE and transition to validated PE; (2) potential baseline psychopathological and psychosocial predictors of persistence of FP SRPE and transition to validated PE, and (3) whether those individuals with persistent FP SRPE and validated PE at follow-up were already differed on psychopathology and psychosocial factors at baseline compared to individuals who did not report new SRPE during the follow-up period. Results indicated that those individuals with baseline FP SRPE were significantly more likely to report SRPE and validated PE at follow-up. Baseline FP SRPE also predicted presence of mood and anxiety disorders, reduced functioning and help-seeking at follow-up. Several baseline psychopathological, psychosocial and PE characteristics were predictive for the persistence of SRPE. These baseline factors also differentiated groups with FP SRPE or validated PE from those with remitted FP SRPE at follow-up.

In **chapter 3**, the association between self-report and interview based assessments of psychotic symptoms and the Polygenic Risk Score (PRS) as an index for genetic risk for psychosis was examined in non-psychotic sibling and parent of patients with a psychotic disorder, a group with elevated genetic risk for psychosis and (non-psychotic) controls who are at an average genetic risk for psychosis. This study uncovered that PRS as an index for genetic risk for psychosis was associated with positive psychotic symptoms obtained via clinical interview but not with the self-report measure. These results thus suggest that studies of gene-environment relationships in psychosis are more likely to be informative when objective interview measures of subclinical psychotic symptoms are used. PRS was also associated with presence of affective episodes (depression and/or mania), suggesting that the association between genetic risk and psychosis proneness is not only mediated by positive symptomatology, but also by measures of affective dysregulation.

In the study presented in **Chapter 4** affective and psychotic stress reactivity for small daily life stressors were examined in individuals at clinical high risk (CHR-P), chronic psychotic patients and healthy controls. Previous research has shown that psychotic disorder patients and their first-degree relatives are characterised by increased affective and psychotic stress reactivity. Early stress sensitisation might be an underlying mechanism in CHR-P patients for the transition from subclinical psychotic symptoms to full-blown psychosis. In chapter 4, the association between small daily life stressors and negative affect (NA) and psychotic experiences measured with the Experience Sampling Method (ESM) was studied. Additionally, we assessed if psychotic experiences were experienced as stressful by examining the association between psychotic experiences and NA. We found that stress sensitization seems to play a role particularly in the early phase of psychosis development as results showed that CHR-P patients were more sensitive to daily life stressors than chronic psychotic patients. In this early phase, psychotic experiences also contributed to the experience of stress.

In **Chapter 5,** a study of the phenomenology of hallucinations and persecutory delusions in the realm of daily life is presented. Hallucinations and persecutory delusions are core features of (subclinical) psychosis, often causing considerable distress. The phenomenology of auditory and visual hallucinations and suspiciousness has previously been investigated in the realm of daily life in psychosis spectrum patients and we aimed to extend this investigation to patients with a first psychotic episode (FEP) and individuals at clinical high risk for psychosis (CHR-P), using ESM over a 6-day period. The prevalence,

course and the co-occurrence of hallucinations and feelings of suspiciousness in daily life as well as the temporal relationship of these experiences with emotions, anxiety and self-esteem were examined. We found that hallucinations and suspiciousness are common in CHR-P and FEP and regularly occur together, although group differences were apparent. Furthermore, individuals with hallucinations reported more NA, anxiety and delusional intensity and lower self-esteem than those without, suggesting that presence of hallucinations reflects a more severe illness state. Finally, the results have clinical value as they provide information about changes in mood, and self-esteem preceding and during suspicious and hallucinatory episodes which can serve as targets for (personalised) treatment.

Finally, **chapter 6** summarizes the results of the research presented in this thesis. Mechanisms and risk factors for the developmental pathway from psychotic experiences to psychotic disorder are discussed and integrated. Additionally, methodological considerations, implications for clinical practice and recommendations for future research are also provided.

SAMENVATTING

Het vergroten van de kennis over de risicofactoren en de onderliggende mechanismen betrokken bij de ontwikkeling van psychotische ervaringen tot psychotische stoornissen is belangrijk. Deze kennis kan gebruikt worden om interventies die gericht zijn op preventie van psychose te verbeteren. Dit proefschrift getiteld '*Dissecting the psychosis continuum risk factors along the pathway from experiences to disorder'* onderzoekt potentiële onderliggende mechanismen en risicofactoren voor de ontwikkeling van psychotische stoornissen aan de onderkant van het psychose continuüm. In het eerste deel van dit proefschrift worden psychotische ervaringen onderzocht die (zelf)gerapporteerd worden door individuen uit de algemene bevolking. Ook worden psychotische ervaringen van familieleden van patiënten met een psychotische stoornis onderzocht, een groep mensen met een verhoogd genetische risico op het ontwikkelen van een psychotische stoornis (hoofdstuk 2 en hoofdstuk 3). Het tweede deel van dit proefschrift omvat onderzoeken naar veranderingen in stemming en psychotische ervaringen in het dagelijks leven van individuen met verhoogd risico op psychose (clinical high risk, CHR) en patiënten die hun eerste psychotische episode doormaken (hoofdstuk 4 en hoofdstuk 5).

Hoofdstuk 1 geeft een overzicht van de epidemiologische kenmerken, etiologie en genetica van psychotische stoornissen en de CHR groep. De zogenaamde 'affectieve weg naar psychose' en eerdere resultaten van onderzoeken met de Experience Sampling Methode (ESM) worden geïntroduceerd.

In **hoofdstuk 2**, werden twee vaak toegepaste meetinstrumenten voor psychotische ervaringen gebruikt in een groot longitudinaal onderzoek bij individuen van de algemene bevolking: een zelf-rapportage vragenlijst en een klinisch interview. De ontwikkeling en beloop van de psychotische ervaringen na drie jaar werd onderzocht bij de groep van individuen waarvan de zelf-gerapporteerde psychotische ervaringen op baseline met het klinisch interview als 'vals-positief' (FP SRPE) werden beoordeeld. We onderzochten (1) de prevalentie van a) remissie en b) persistentie van FP SPRE en c) transitie naar gevalideerde psychotische symptomen; (2) de voorspellende waarde van psychopathologische en psychosociale kenmerken gemeten op baseline voor de persistentie van FP SRPE en transitie naar gevalideerde psychotische symptomen; en (3) of de groepen (a, b en c) op baseline al verschilden van elkaar op gebied van psychopathologische en psychosociale factoren. Er werd gevonden dat individuen met FP SRPE bij baseline een hogere kans hadden op het rapporteren van psychotische ervaringen bij follow-up

dan degenen die niet eerder psychotische ervaringen rapporteerden. De aanwezigheid van baseline FP SRPE was voorspellend voor de aanwezigheid van een stemming en/of angststoornis, verminderd functioneren en het zoeken van hulp voor klachten bij follow-up. Het aanhouden van (zelf-gerapporteerde) psychotische ervaringen werd voorspeld door de aanwezigheid van ander psychische problemen en het aantal en de frequentie van zelf-gerapporteerde psychotische ervaringen bij baseline. De individuen met persistente vals-positieve psychotische ervaringen alsook individuen gevalideerde psychotische symptomen verschilden op deze baseline factoren van de individuen die geen psychotische ervaringen meer hadden gedurende de follow-up periode (remissiegroep).

In **hoofdstuk 3** werd de associatie tussen psychotische ervaringen en de 'Polygenic Risk Score' (PRS), een index voor genetisch risico voor psychose, onderzocht. Psychotische ervaringen werden gemeten met een zelf-rapportage lijst en een interview. Dit werd gedaan in een groep van niet-psychotische eerstegraads familieleden (broers/zussen en ouders) van psychotische patiënten die een verhoogd genetisch risico hebben voor het ontwikkelen van een psychose en (niet-psychotische) controles, die een gemiddeld risico lopen. Deze studie toonde aan dat de PRS geassocieerd was met subklinische positieve psychotische symptomen die naar voren kwamen tijdens het interview. Deze relatie werd niet gevonden met zelf-gerapporteerde symptomen. De resultaten suggereren dat onderzoek naar gen-omgevingsrelaties bij psychose informatiever zal zijn wanneer een objectief interview wordt gebruikt om aanwezigheid van subklinische psychotische symptomen te bepalen. De PRS was ook geassocieerd met de aanwezigheid van affectieve episodes (depressie en/of manie). Dit resultaat suggereert dat de associatie tussen genetisch risico en psychosegevoeligheid niet alleen beïnvloed wordt door positieve symptomen, maar ook door de aanwezigheid van affectieve disregulatie.

In de studie gepresenteerd in **hoofdstuk 4** werd affectieve en psychotische stress reactiviteit voor kleine stressoren in het dagelijks leven onderzocht in individuen met verhoogd psychoserisico (CHR-P), chronische psychotische patiënten en gezonde controles. Eerder onderzoek toonde aan dat patiënten met een psychotische stoornis en hun eerstegraads familieleden gekenmerkt worden door hogere affectieve en psychotische stress reactiviteit ten opzichte van controles. Vroege stress sensitisatie is mogelijk een mechanisme betrokken bij de transitie van subklinische psychotische symptomen naar psychose. In hoofdstuk 4 werd de associatie tussen dagelijkse stressoren en negatief affect (NA) en psychotische ervaringen onderzocht, gemeten met de Experience Sampling Methode (ESM). Daarnaast werd onderzocht of psychotische ervaringen als stressvol

ervaren werden door de associatie tussen psychotische ervaringen en NA te onderzoeken. Uit deze studie blijkt dat stress sensitisatie een belangrijke rol in de vroege fase van het psychose ontwikkelingsproces speelt. CHR-P patiënten waren gevoeliger voor dagelijkse stressoren dan chronisch psychotische patiënten. In deze vroege fase blijken psychotische ervaringen zelf ook een bron van stress te zijn.

In **hoofdstuk 5** werd een studie van de fenomenologie van hallucinaties en achterdochtwanen in het dagelijks leven gepresenteerd. Deze kernsymptomen van (subklinische) psychose veroorzaken vaak veel leed. De fenomenologie van auditieve en visuele hallucinaties en achterdocht is eerder onderzocht in het dagelijks leven in psychose spectrum patiënten. De huidige studie had als doel dit in kaart te brengen voor eerste psychose patiënten (FEP) en individuen met verhoogd risico op psychose (CHR-P) met behulp van ESM gedurende een zesdaagse periode. De prevalentie, het verloop en het tegelijk optreden van hallucinaties en gevoelens van achterdocht, maar ook de temporele relaties van deze ervaringen met emoties, angst en zelfvertrouwen werden onderzocht. Er werd gevonden dat hallucinaties en achterdocht vaak en geregeld samen voorkomen bij CHR-P en FEP patiënten, hoewel er ook groepsverschillen gevonden werden. Daarnaast rapporteerden individuen met hallucinaties meer NA, angst en hogere intensiteit van waanideeën en minder zelfvertrouwen dan individuen die geen hallucinaties ervaarden. Dit suggereert dat de aanwezigheid van hallucinaties een ernstiger ziekteproces reflecteert. De resultaten brengen veranderingen in stemming en zelfvertrouwen voorafgaand en tijdens episodes met achterdocht en hallucinaties in beeld. Deze informatie kan gebruikt worden om (gepersonaliseerde) zorg te optimaliseren.

Tot slot wordt in **hoofdstuk 6** een samenvatting gegeven van de resultaten van het onderzoek gepresenteerd in dit proefschrift. Mechanismen en risico factoren onderliggend aan de ontwikkeling van psychotische ervaringen tot psychotische stoornis worden besproken. Daarnaast worden methodologische aandachtspunten, implicaties voor de klinische praktijk en aanbevelingen voor toekomstig onderzoek beschreven.

VALORISATION

Societal relevance

Psychotic disorders are associated with high burden for patients themselves as well as for their family members and friends, although prevalence is relatively low (0.5-1% for schizophrenia, 2.5-3.5% for psychotic disorders[1]). This is directly due to significant impairments in academic performance and occupational functioning, difficulties with interpersonal relationships and experiences of stigmatisation and discrimination, all resulting in substantially reduction in quality of life. Additionally, expenses for mental disorders and psychotic disorders in particular are among the highest of all healthcare expenses in the Netherlands[2]. The total costs for mental disorders including psychotic disorders are the combination of direct healthcare costs, non-medical costs including extra resources for social service and education, and indirect costs due to work absence or early retirement. These indirect costs may emerge from impairments, disability, premature death, and legal problems due to loss of productivity[3], and form the largest proportion of all costs for psychotic patients[4]. Overall, it can be concluded that psychotic disorders are a substantial burden for the affected individual, his/her social circle, those involved in the life and treatment of these patients and for society as a whole. Therefore, early diagnosis, intervention and preferably prevention are needed. A better understanding of the phenomenology, underlying mechanisms and psychological processes involved in the transition of subclinical symptoms towards disorder will help to reach that goal.

In order to elucidate the complex and multi-factorial aetiology of psychotic disorders and to improve prevention and intervention strategies focus of research has shifted from the population of psychotic disorder patients, especially schizophrenic patients, to first episode psychosis patients and at the lower end of the psychosis continuum to individuals with subclinical psychotic symptoms at clinical high risk for psychosis (CHR-P) as well as (non-help seeking) individuals in the general population with psychotic-like experiences. The current thesis investigated potential mechanisms and risk factors involved in the development from incidental psychotic-like experiences and subclinical psychotic symptoms to a first psychotic episode. The epidemiology and phenomenology of these experiences and associated factors was examined in both in longitudinal studies and Experiences Sampling Method (ESM) studies in daily life.

Target audience

The findings of this thesis are relevant for individuals with subclinical psychotic symptoms, psychotic patients, health care professionals and policy makers.

The results of **chapter 2** and **chapter 3** provide important information for both health care professionals as well as policy makers. Self-report measures for psychotic experiences are effective as screening instruments for the presence of potential (subclinical) psychotic symptoms, which should then be examined in detail by clinical interview. The use of a semi-structured psychosis risk assessment interview like the CAARMS or the SIPS is advised as it allows validation of an experience as a true subclinical symptom while also obtaining detailed information about the frequency of a symptoms and determination of CHR-P or psychosis status. Importantly, it has been suggested that clinical early detection teams may need to further extend their services into the community so that these individuals have better access to specialized mental health care[5]. However, in **chapter 2** it was found that (false-positive) self-reported psychotic experiences by individuals from the general population were mostly transitory in nature and only a small subsample of individuals developed true psychotic symptoms. This finding supports the recommendation that screening with self-report measures and subsequent assessment of CHR-P state should be primarily offered to selected samples of subjects who are already distressed by mental problems and seeking help for them[6]. Use for prevention in non-help-seeking subjects in the general population should be discouraged[7], as this strategy is not cost-effective due to false-positive rates.

The results of **chapter 2** highlight the importance of targeting low social functioning in early interventions as individuals who developed future psychotic symptoms were already characterised by deterioration in social functioning. Social skills training and family involvement to create a supportive environment can help to improve social functioning[8] which in turn might prevent further development of psychotic symptoms.

Chapter 2 furthermore showed high neuroticism (i.e. a tendency to show emotional instability, and react with increased anxiety, fear, and sadness[9]) is an important predictor of persistence and further development of psychotic symptoms. The results of **chapter 4** further highlight the close relationship between stress, symptoms and low mood. Increased emotional reactivity for small daily life stressors in individuals at clinical high risk for psychosis may be an important underlying mechanism in the process towards transition to psychotic disorder. Furthermore, (subclinical) psychotic symptoms can be

regarded as an additional source of distress. So both CHR-P and first episode psychosis patients are thus likely to benefit from psychoeducation and non-specific early interventions aimed at stress-reduction and enhancement of effective coping skills.

Results of **chapter 5** stress the need for thorough investigation of the exact nature of subclinical psychotic symptoms. Results tentatively suggest that severity of symptoms and risk for transition are likely to be higher for individuals reporting both feelings of suspiciousness as well as hallucinations, although this should be examined more carefully in a longitudinal study. Health care professionals need to be aware of the central role of emotion-related processes, anxiety and self-esteem for the occurrence of hallucinations and suspiciousness in daily life. Use of ESM can help bridge the gap between the professional's office and the patient's daily life. It can help to unravel symptomatic and behavioural patterns as it supplies both the individual patient and clinician with large amount of detailed, reliable and ecologically valid information about symptoms and their relationships with mood, anxiety, self-esteem all in the social context of daily life.

Innovation and implementation

Recently, studies have started to investigate the application of ESM interventions. Currently, the effectiveness of a newly developed ecological momentary intervention that targets elevated stress sensitivity, altered reward-experience, and psychological flexibility based on principles of Acceptance and Commitment Therapy (ACT) in CHR-P and first episode psychosis patients is being evaluated in the INTERACT study. The effectiveness of ACT is compared with a treatment as usual control group, of which some receive participants receive CBT specifically developed to treat (subclinical) psychotic symptoms. This ongoing ACT in daily life study extends standard ACT therapy with real life training and exercises through a dedicated device, thereby enhancing participants' ACT-based skills and techniques. Furthermore, a new study will use ESM as a monitoring and detection tool for changes in affective and psychotic symptomatology that could serve as warning signs for relapse in psychotic patients who are in symptomatic remission and want to gradually reduce and stop their anti-psychotic medication use.

The use of ESM in clinical practice and psychosis care specifically is still limited, but has great potential to improve personalized treatment as ESM is now available via mobile phone applications. Recent development and availability of web-based feedback systems offers patients and health care professionals access to real-life data on emotional en symptomatic dynamics. ESM can help to refine the diagnostic process and monitor af-

fective and psychotic symptomatology in daily life. As mood and symptoms are assessed 'in the moment' and in the context of daily life, they are not influenced by memory biases hampering traditional retrospective clinical interviews and questionnaires assessing longer time periods. ESM allows patients to accurately report changes in their emotions and behavioural pattern and reveals which emotional and/or behavioural patterns are in need of change. The implementation of ESM in clinical practice does require that professionals are trained in how gain access to, and then interpret and use ESM data in a therapeutic fashion.

As part of my activities as a psychologist at the mental healthcare institute GGzE Eindhoven, division Early Psychosis, I am involved in the implementation of ESM as a diagnostic and monitoring tool as part of regular care for first episode psychosis patients. In this fashion I can implement the knowledge of ESM that I gained during my PhD track in clinical practice. Furthermore, I am able to contribute to both of the above mentioned ESM studies as a research practitioner.

Knowledge dissemination

The present research was and will be published in peer-reviewed journals and presented at national and international research conferences. In this way, research results and methodological developments can be discussed with other scientists, what in turn stimulates development and refinement of knowledge and theories about the development of psychotic disorders. Furthermore, the results were and will be made public at more clinically oriented conferences to inform health care professionals and policy makers. By involving health care professionals in research projects, especially those focussed on the development and refinement of treatment options, valuable information can be gained on flaws of current options and feasibility of proposed solutions. By working together, scientists and health care professionals can greatly impact on the lives of patients and their families and society as a whole by developing and implementing more efficient treatment options. Finally, results were and will be made public conferences and symposia, magazines and websites managed by patient organisations that are easily accessible to the general population including patients and their families. It is the responsibility of the scientific community to actively involve patients and their families in scientific research. They can provide valuable insights on challenges they are facing, provide feedback on interventions and when relevant, on the usability of (proposed) technological tools. Adequate dissemination of knowledge will help to reduce stigmatisation in professionals, patients and the general population.

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CURRICULUM VITAE

Yori van der Steen werd geboren op 26 juli 1986 te Roermond. In 2004 behaalde zij haar VWO diploma aan het Bisschoppelijk College Schöndeln te Roermond. Hierna behaalde zij in 2008 haar Bachelor Cognitieve Psychologie aan de Universiteit Maastricht. In 2008 behaalde ze tevens haar Master Rechtspsychologie aan de Universiteit Maastricht. In 2010 vervolgde zij haar studies met de premaster en vervolgens Master Neuropsychologie aan de Universiteit Utrecht, waarvoor ze haar klinische en wetenschappelijke stage liep op de afdeling Psychiatrie van het Universitair Medisch Centrum Utrecht. Hier kwam ze voor het eerst in aanraking met patiëntenzorg en onderzoek binnen het spectrum van psychotisch stoornissen. In april 2012 behaalde zij hiervoor haar diploma. In juli 2013 startte zij haar promotietraject bij de afdeling Psychiatrie en Neuropsychologie van de Universiteit Utrecht in het team van Prof. Myin-Germeys. In 2015 startte ze ook met het doctoraat programma bij het Center for Contextual Psychiatry van de KU Leuven, België als onderdeel van het gezamenlijk promotietraject. Gedurende haar promotietraject werkte ze aan verschillende onderzoeksprojecten en werkzaam bij GGz Eindhoven binnen het vroegdetectie team voor psychose. Momenteel werkt Yori als psycholoog binnen het centrum voor vroege psychose van GGz Eindhoven, waarbij ze patiëntenzorg en onderzoek met de experience sampling methode combineert.

PUBLICATIONS

Scientific publications in international peer-reviewed journals

van der Steen Y, Myin-Germeys I, van Nierop M, Ten Have M, de Graaf R, van Dorsselaer S, van Os J, van Winkel R. (2018) *'False-positive' self-reported psychotic experiences in the general population: an investigation of outcome, predictive factors and clinical relevance.* Epidemiology and Psychiatric Sciences.

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In progress articles

van der Steen Y, van Winkel R, Lataster T, Wagner M, Myin-Germeys I. *Temporal dynamics of hallucinations and suspiciousness in clinical high risk and first episode psychosis.* In preparation.

Scientific communications related to this thesis

2017 Oral presentation at the Annual Conference of the Society for Ambulatory Assessment (Luxembourg, Luxumbourg)

2016 Poster presentation at the 5th Biennial Schizophrenia International Research Society Conference of the Schizophrenia International Research Society (Florence, Italy)

2015 Poster presentation at the Annual Meeting of the Society for Research in Psychopathology (New Orleans, USA)

2014 Oral presentation at the 42nd Voorjaarscongres van der Nederlandse Vereniging voor Psychiatrie (NVvP) (Maastricht, the Netherlands)

THESIS DEFENSES FROM MHENS - SCHOOL FOR MENTAL HEALTH AND NEUROSCIENCE

2013

Rob Havermans: **Bipolar disorder in daily life; Mood and cortisol responses to naturally occurring events.** Supervisor: Prof.dr. M. de Vries; Co-Supervisor: Dr. N. Nicolson.

Véronique Moers-Hornikx: **Deep brain stimulation and the cerebellum.** Supervisors: Prof.dr. J. Vles / Prof.dr. Y. Temel; Co-Supervisor: Dr. G. Hoogland.

Nicole Veldhorst-Janssen: **Intranasal delivery of rapid acting drugs.** Supervisors: Prof.dr. M. Marcus / Prof.dr. C. Neef; Co-Supervisor: Dr. P.H. van der Kuy.

Stéphanie Knippenberg: **Vitamin D and Multiple Sclerosis: immunological and clinical outcome.** Supervisor: Prof.dr. J. Cohen-Tervaert; Co-Supervisors: Dr. J. Damoiseaux / Dr. Y. Bols.

Erik D. Gommer: **Dynamic Cerebral Autoregulation: from methodology towards clinical application.** Supervisors: Prof.dr. W.H. Mess / Prof.dr. R.B. Panerai, UK; Co-Supervisor: Dr.ir. J.P.H. Reulen.

Olga A.H. Reneerkens: **Can PDE inhibition improve cognition ? Translational insights.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. J. Prickaerts.

Lyzel S. Elias-Sonnenschein: **Clinical and biomarker correlates of genetic risk factors for Alzheimer's disease.** Supervisor: Prof.dr. F.R.J. Verhey; Co-Supervisor: Dr. P.J. Visser.

Diego F. Mastroeni: **Epigenetic Dysregulation and the Pathophysiology of of Alzheimer's Disease.** Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. P.D. Coleman, Sun City, Arizona; Co-Supervisors: Dr. B.P.F. Rutten / Dr. D.L.A. van den Hove.

Leonidas Chouliaras: **Epigenetic Regulation in Aging and Alzheimer's disease: A translational perspective.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. B.P.F. Rutten / Dr. D.L.A. van den Hove.

Liesbeth Knaepen: **Perinatal events and altered pain sensitivity in later life.** Supervisors: Prof.dr. E.A.J. Joosten / Prof.dr. D. Tibboel, EUR; Co-Supervisor: Dr. J. Patijn.

Marisela Martinez-Claros: **Hippocampal plasticity and corticosterone: From dendrites to behaviour.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. J.L. Pawluski / Dr. J. Prickaerts.

Marcus D. Lancé: **A circle of improvement in bleeding management: from laboratory to clinic and back.** Supervisors: Prof.dr. M.A.E. Marcu / Prof.dr. J.W.M. Heemskerk; Co-Supervisor: Dr. Y.M.C. Henskens.

Hilde Braakman: **Imaging the brain; neuronal correlates of cognitive impairment in children with frontal lobe epilepsy**. Supervisors: Prof.dr. A.P. Aldenkamp / Prof.dr. J.S.H. Vles; Co-Supervisors: Dr.ir. W.H. Backes / Dr. P.A.M. Hofman.

Willem H. van Zwam: **Aneurysmal subarachnoid hemorrhage: imaging strategies and cost-effectiveness aspects in diagnostic work-up and post-therapeutic follow-up.** Supervisors: Prof.dr. J.T. Wilmink / Prof.dr. J.E. Wildberger; Co-Supervisor: Dr. P.A.M. Hofman.

Klara De Cort: **The Pathogenesis of Panic Disorder.** Supervisors: Prof.dr. I. Myin-Germeys / Prof.dr. E.J.L. Griez; Co-Supervisors: Dr. K.R.J. Schruers / Dr. I. Van Diest, Leuven.

Kim van Wijck: **Mind the Gap; experimental studies on splanchnic hyperfusion and gastrointestinal integrity loss in man**. Supervisors: Prof.dr. W.A. Buurman / Prof.dr. C.H.C. Dejong; Co-Supervisor: Dr. K. Lenaerts.

Yvette Roke: **Antipsychotic-induced hyperprolactinemia in children and adolescents with mainly autism spectrum disorders. Prevalence, symptoms, clinical consequences and genetic risk factors.** Supervisors: Prof.dr. P.N. van Harten / Prof.dr. J.K. Buitelaar (RUN); Co-Supervisor: Dr. A. Boot (UMCG).

Fleur Goezinne: **Retinal detachment surgery: pre and postoperative prognostic factors.** Supervisors: Prof.dr. F. Hendrikse / Prof.dr. C.A.B. Webers; Co-Supervisor: Dr. E.C. La Heij (Amsterdam).

Ralph L.J.G. Maassen: **The Merits of Videolaryngoscopy during Glottic Visualisation for Endotracheal Intubation.** Supervisors: Prof.dr. M. Marcus / Prof.dr. A. van Zundert (University of Queensland).

Maria J. de Sousa Guerreiro: **The role of sensory modality in age-related distraction.** Supervisor: Prof.dr. C.M. van Heugten; Co-Supervisor: Dr. P.W.M. van Gerven.

Ine Rayen: **Effects of developmental fluoxetine exposure on neurobehavioral outcomes.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. J.L. Pawluski / Dr. T.D. Charlier (Ohio University, USA).

Nynke M.G. Bodde: **Psychogenic non-epileptic seizures; a separate disorder or part of a continuum?** Supervisors: Prof.dr. R. van Oostenbrugge / Prof.dr. K. Vonck (UZ Gent); Co-Supervisors: Dr. R. Lazeron / Dr. A. de Louw (Epilepsiecentrum Kempenhaeghe, Heeze).

Alejandro M. Gomez: **Novel strategies for making myasthenia less gravis: targeting plasma cells and the neuromuscular junction.** Supervisor: Prof.dr. M.H. De Baets; Co-Supervisors: Dr. M. Losen / Dr. P. Martinez-Martinez.

Mohammad S. Rahnama'i: **Prostaglandins and Phosphodiesterases in the Urinary Bladder Wall.** Supervisors: Prof.dr. Ph. Van Kerrebroeck / Prof.dr. S. de Wachter (Universiteit Antwerpen); Co-Supervisor: Dr. G. van Koeveringe.

Mariken B. de Koning: **Studying biomarkers in populations at genetic and clinical high risk for psychosis.** Supervisors: Prof.dr. T. Amelsvoort / Prof.dr. J. Booij (AMC).

Fabien Boulle: **Epigenetic regulation of BDNF/TrkB signaling in the pathophysiology and treatment of mood disorders**. Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. L. Lanfumey (Universiteit Parijs); Co-Supervisors: Dr. D. van den Hove / Dr. G. Kenis.

2014

Iris Nowak-Maes: **Tinnitus; assessment of quality of life & cost-effectiveness.** Supervisors: Prof.dr. M. Peters / Prof.dr. B. Kremer; Co-Supervisors: Dr. M. Joore / Dr. L. Anteunis.

Marjolein Huijts: **Cognitive function in patients with cerebral small vessel disease.** Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-Supervisors: Dr. A.A. Duits / Dr. J. Staals.

Markus Gantert: **Fetal inflammatory injury as origin of long term disease: Lessons from animal models.** Supervisors: Prof.dr. B. Kramer / Prof.dr. L. Zimmermann; Co-Supervisor: Dr. A. Gavilanes.

Elke Kuypers: **Fetal development after antenatal exposures: Chorioamnionitis and maternal glucocorticoids.** Supervisors: Prof.dr. B.W. Kramer / Prof.dr. H.W. Steinbusch / Prof. dr. Suhas G. Kallapur (University of Cincinnati, Ohio, USA).

Pieter Kubben: **Ultra low-field strength intraoperative MRI for Glioblastoma Surgery.** Supervisor: Prof.dr. J.J. van Overbeeke; Co-Supervisor: Dr. H. van Santbrink.

Laura Baijens: **Surface electrical stimulation of the neck for oropharyngeal dysphagia in Parkinson's disease: therapeutic aspects and reliability of measurement.** Supervisor: Prof.dr. B. Kremer; Co-Supervisor: Dr. R. Speyer, Townsville.

Janneke Hoeijmakers: **Small fiber neuropathy and sodium channels; a paradigm shift.** Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-Supervisors: Dr. C.G. Faber / Dr. I.S.J. Merkies.

Stephanie Vos: **The Role of biomarkers in preclinical and prodromal Alzheimer's disease.** Supervisor: Prof.dr. F.R. Verhey; Co-Supervisor: Dr. P.J. Visser.

Muriël Doors: **The Value of Optical Coherence Tomography in Anterior Segment Surgery.** Supervisors: Prof.dr. R.M. Nuijts / Prof.dr. C.A. Webers; Co-Supervisor: Dr. T.T.J.M. Berendschot.

Anneke Maas: **Sleep problems in individuals with genetic disorders associated with intellectual disability.** Supervisors: Prof.dr. I. Curfs / Prof.dr. R. Didden.

Sebastiaan van Gorp: **Translational research on spinal cord injury and cell-based therapies; a focus on pain and sensorimotor disturbances.** Supervisors: Prof.dr. B. Joosten / Prof.dr. M. van Kleef; Co-Supervisors: Dr. J. Patijn / Dr. R. Deumens, KU Leuven.

Andrea Sannia: **High risk newborns and brain biochemical monitoring.** Supervisor: Prof. dr. J.S.H. Vles; Co-Supervisors: Dr. D. Gazzolo, Alessandria, Italy / Dr. A.W.D. Gavilanes.

Julie A.D.A. Dela Cruz: **Dopamine mechanisms in learning and memory: Evidence from rodent studies.** Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. R.J. Bodnar, New York; Co-Supervisor: Dr. B.P.F. Rutten.

René Besseling: **Brain wiring and neuronal dynamics; advances in MR imaging of focal epilepsy.** Supervisors: Prof.dr. A.P. Aldenkamp / Prof.dr.ir. W.H. Backes; Co-Supervisor: dr. J.F.A. Jansen.

Maria Quint-Fens: **Long-term care after stroke; development and evaluation of a long-term intervention in primary care**. Supervisors: Prof.dr. J.F.M. Metsemakers / Prof.dr. C.M. van Heugten / Prof.dr. M. Limburg, Almere; Co-Supervisor: dr. G.H.M.I. Beusmans.

Veronique Moulaert: **Life after survival of a cardiac arrest; the heart of the matter.** Supervisors: Prof.dr. J.A. Verbunt / Prof.dr. C.M. van Heugten / Prof.dr. D.T. Wade, Oxford, UK.

Feikje Smeets: **The hallucinatory-delusional state: a crucial connection in the psychosis symptom network.** Supervisor: Prof.dr. J. van Os; Co-Supervisor: Dr. T. Lataster.

Lies Clerx: **Alzheimer's disease through the MR-eye; novel diagnostic markers and the road to clinical implementation".** Supervisor: Prof.dr. F. Verhey; Co-Supervisors: Dr. P.J. Visser / P. Aalten.

Sonny Tan: **The subthalamic nucleus in Parkinson's disease.** Supervisors: Prof.dr. Y. Temel / Prof.dr. H.W.M. Steinbusch / Prof.dr. T. Sharp, Oxford, UK / Prof.dr. V. Visser-Vandewalle, Koln.

Koen van Boxem: **The use of pulsed radiofrequency in the management of chronic lumbosacral radicular pain.** Supervisors: Prof.dr. M. van Kleef / Prof.dr. E.A.J. Joosten; Co-Supervisor: Assoc. Prof.dr. J. van Zundert.

Jérôme Waterval: **Hyperostosis cranialis interna**. Supervisors: Prof.dr. J.J. Manni / Prof. dr. R.J. Stokroos.

Sylvie Kolfschoten-van der Kruijs: **Psychogenic non-epileptic seizures; the identification of neurophysiological correlates.** Supervisors: Prof.dr. A.P. Aldenkamp / Prof.dr. K.E.J. Vonck, Universiteit Gent; Co-Supervisors: Dr. J.F.A. Jansen / Dr. R.H.C. Lazeron, Kempenhaeghe.

Wouter Pluijms: **Spinal cord stimulation and pain relief in painful diabetic: polyneuropathy, a translational approach.** Supervisors: Prof.dr. M. van Kleef / Prof.dr. E.A. Joosten; Co-supervisor: Dr. C.G. Faber.

Ron Handels: **Health technology assessment of diagnostic strategies for Alzheimer's disease.** Supervisors: Prof.dr. F.R.J. Verhey / Prof.dr. J.L. Severens (EUR); Co-Supervisor: Dr. M.A. Joore / Dr. C.A.G. Wolfs.

Evelyn Peelen: **Regulatory T cells in the pathogenesis of Multiple Sclerosis: potential targets for vitamin D therapy.** Supervisors: Prof.dr. R.M.M. Hupperts / Prof.dr. J.W. Cohen Tervaert; Co-Supervisor: Dr. J.G.M.C. Damoiseaux / Dr. M.M.G.L.Thewissen, Diepenbeek.

Reint Jellema: **Cell-based therapy for hypoxic-ischemic injury in the preterm brain.** Supervisors: Prof.dr. B.W.W. Kramer / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. W.T.V. Germeraad / Dr. P. Andriessen, Veldhoven.

Maria Wertli: **Prognosis of Chronic Clinical Pain Conditions: The Example of Complex Regional Pain Syndrome 1 and Low Back Pain.** Supervisors: Prof.dr. M. van Kleef; Co-Supervisor: Dr. F. Brunner, Zürich / Dr. R. Perez, VUmc.

Dagmar Zeef: **An experimental model of Huntington's disease: Validation & Stimulation.** Supervisors: Prof.dr. Y. Temel / Prof.dr. H.W.M. Steinbusch; Co-supervisor: Dr. A. Jahanshahi.

Jeroen Decoster: **Breaking Down Schizophrenia into phenes, genes and environment.** Supervisors: Prof.dr. I. Myin-Germeys / Prof.dr. M. De Hert, KU Leuven; Co-Supervisor: Dr. R. van Winkel.

Eaja Anindya Sekhar Mukherjee: **Fetal Alcohol Spectrum Disorders: exploring prevention and management.** Supervisor: Prof.dr. L.M.G. Curfs; Co-Supervisor: Prof. S. Hollins, St. George's University of London, UK.

Catherine van Zelst: **Inside out; On stereotype awareness, childhood trauma and stigma in psychosis.** Supervisors: Prof.dr. Ph. Delespaul / Prof.dr. J. van Os.

Ibrahim Tolga Binbay: **Extended Psychosis Phenotype in the Wider Social Environment.** Supervisor: Prof.dr. J. van Os; Co-Supervisor: Dr. M. Drukker.

Frank Van Dael: **OCD matters in psychosis.** Supervisors: Prof.dr. J. van Os / Prof.dr. I. Myin-Germeys.

Pamela Kleikers: **NOXious oxidative stress: from head toe too and back.** Supervisors: Prof.dr. H.H.H.W. Schmidt / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. B. Janssen.

José Luis Gerardo Nava: **In vitro assay systems in the development of therapeutic interventions strategies for neuroprotection and repair.** Supervisors: Prof.dr.med. J. Weis / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. G.A. Brook, RWTH Aachen.

Eva Bollen: **Cyclic nucleotide signaling and plasticity.** Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. R. D'Hooge, KU Leuven; Co-Supervisor: Dr. J. Prickaerts.

2015

Jessica A. Hartmann: **A good laugh and a long sleep; Insights from prospective and ambulatory assessments about the importance of positive affect and sleep in mental health.** Supervisor: Prof.dr. J. van Os; Co-Supervisors: C.J.P. Simons / Dr. M. Wichers.

Bart Ament: **Frailty in old age; conceptualization and care innovations.** Supervisors: Prof.dr. G.I.J.M. Kempen / Prof.dr. F.R.J. Verhey; Co-Supervisor: Dr. M.E. de Vugt.

Mayke Janssens: **Exploring course and outcome across the psychosis-continuum.** Supervisor: Prof.dr. I. Myin-Germeys; Co-Supervisor: Dr. T. Lataster.

Dennis M.J. Hernaus: **Dopayours is not dopamine: genetic, environmental and pathological variations in dopaminergic stress processing.** Supervisor: Prof.dr. I. Myin-Germeys; Co-Supervisors: Prof.dr. F.M. Mottaghy / Dr. D. Collip.

Ingrid M.H. Brands: **The adaptation process after acquired brain injury Pieces of the puzzle**. Supervisors: Prof.dr. C.M. van Heugten / Prof.dr. D.T. Wade, Oxford UK; Co-Supervisors: Dr. S.Z. Stapert / Dr. S. Köhler.

Francesco Risso: **Urinary and salivary S100B monitoring in high risk infants.** Supervisor: Prof.dr. J.S.H. Vles; Co-Supervisors: Dr. D. Gazzolo, Genoa,Italy / Dr. A.W.D. Gavilanes.

Alessandro Borghesi: **Stem and Progenitor Cells in Preterm Infants: Role in the Pathogenesis and Potential for Therapy.** Supervisor: Prof.dr. L. Zimmermann; Prof.dr. B. Kramer; Co-Supervisors: Dr. D. Gazzolo, Genoa,Italy / Dr. A.W.D. Gavilanes.

Claudia Menne-Lothmann: **Affect dynamics; A focus on genes, stress, and an opportunity for change.** Supervisor: Prof.dr. J. van Os; Co-Supervisors: Dr. M. Wichers / Dr. N. Jacobs.

Martine van Nierop: **Surviving childhood new perspectives on the link between childhood trauma and psychosis.** Supervisors: Prof.dr. I. Myin-Germeys / Prof.dr. J. van Os; Co-Supervisor: Dr. R. van Winkel.

Sylvia Klinkenberg: **VNS in children; more than just seizure reduction.** Supervisors: Prof. dr. J. Vles / Prof.dr. A. Aldenkamp; Co-Supervisor: Dr. H. Majoie.

Anouk Linssen: **Considerations in designing an adult hearing screening programme.** Supervisor: Prof.dr. B. Kremer; Co-Supervisors: Dr. L. Anteunis / Dr. M. Joore.

Janny Hof: **Hearing loss in young children; challenges in assessment and intervention.** Supervisors: Prof.dr. B. Kremer / Prof.dr. R. Stokroos / Prof.dr. P. van Dijk, RUG; Co-Supervisor: Dr. L. Antheunis.

Kimberly Cox-Limpens: **Mechanisms of endogenous brain protection; Clues from the transcriptome. S**upervisors: Prof.dr. J. Vles / Prof.dr. L. Zimmermann; Co-Supervisor: Dr. A. Gavilanes.

Els Vanhoutte: **Peripheral Neuropathy outcome measures; Standardisation (PeriNomS) study part 2: Getting consensus.** Supervisors: Prof.dr. C. Faber / Prof.dr. P. van Doorn; Co-Supervisor: Dr. I. Merkies, Spaarne ziekenhuis Hoofddorp.

Mayienne Bakkers: **Small fibers, big troubles; diagnosis and implications of small fiber neuropathy.** Supervisors: Prof.dr. C. Faber / Prof.dr. M. de Baets; Co-Supervisor: Dr. I. Merkies, Spaarne ziekenhuis Hoofddorp.

Ingrid Kramer: **Zooming into the micro-level of experience: An approach for understanding and treating psychopathology.** Supervisor: Prof.dr. J. van Os; Co-Supervisors: Dr. M. Wichers, UMC Groningen / Dr. C. Simons.

Esther Bouman: **Risks and Benefits of Regional Anesthesia in the Perioperative Setting.** Supervisors: Prof.dr. M. van Kleef / Prof.dr. M. Marcus, HMC, Qatar / Prof.dr. E. Joosten; Co-Supervisor: Dr. H. Gramke.

Mark Janssen: **Selective stimulation of the subthalamic nucleus in Parkinson's disease; dream or near future.** Supervisors: Prof.dr. Y. Temel / Prof.dr. V. Visser-Vandewalle, Keulen / Prof.dr. A. Benazzouz, Bordeax, France.

Reina de Kinderen: **Health Technology Assessment in Epilepsy; economic evaluations and preference studies.** Supervisors: Prof.dr. S. Evers / Prof.dr. A. Aldenkamp; Co-Supervisor: Dr. H. Majoie / Dr. D. Postulart, GGZ O-Brabant.

Saskia Ebus: **Interictal epileptiform activity as a marker for clinical outcome.** Supervisors: Prof.dr. A. Aldenkamp / Prof.dr. J. Arends, TUE / Prof.dr. P. Boon, Universiteit Gent, België.

Inge Knuts: **Experimental and clinical studies into determinants of panic severity.** Supervisor: Prof.dr. I. Myin-Germeys; Co-Supervisor: Dr. K. Schruers; Influencing panic.

Nienke Tielemans: **Proactive coping post stroke: The Restored4Stroke Self-Management study.** Supervisors: Prof.dr. C. van Heugten / Prof.dr. J. Visser-Meily, UMC Utrecht; Co-Supervisor: Dr. V. Schepers, UMC Utrecht.

Tom van Zundert: **Improvements Towards Safer Extraglottic Airway Devices.** Supervisors: Prof.dr. A.E.M. Marcus / Prof.dr. W. Buhre / Prof.dr. J.R. Brimacombe, Queensland, Australia / Prof.dr. C.A. Hagberg.

Tijmen van Assen: **Anterior Cutaneous Nerve Entrapment Syndrome Epidemiology and surgical management.** Supervisors: Prof.dr. G.L. Beets / Prof.dr. M. van Kleef / Dr. R.M.H. Roumen / Dr. M.R.M. Scheltinga, MMC Veldhoven.

Rohit Shetty: **Understanding the Clinical, Immunological and Genetic Molecular Mechanisms of Keratoconus.** Supervisors: Prof.dr. R.M.M.A. Nuijts / Prof.dr. C.A.B. Webers.

Christine van der Leeuw: **Blood, bones and brains; peripheral biological endophenotypes and their structural cerebral correlates in psychotic disorder.** Supervisor: Prof.dr. J. van Os; Co-supervisor: Dr. M. Marcelis.

Sanne Peeters: **The Idle Mind Never Rests; functional brain connectivity across the psychosis continuum.** Supervisor: Prof.dr. J. van Os; Co-supervisor: dr. M. Marcelis.

Nick van Goethem: α7 nicotinic acetylcholine receptors and memory processes: mechanistic and behavioral studies. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisor: Dr. J. Prickaerts.

Nicole Leibold: **A Breath of fear; a translational approach into the mechanisms of panic.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. K.R.J. Schruers / Dr. D.L.A. van den Hove.

Renske Hamel: **The course of mild cognitive impairment and the role of comorbidity.** Supervisor: Prof.dr. F.R.J. Verhey; Co-supervisors: Dr. I.H.G.B. Ramakers / Dr. P.J. Visser.

Lucia Speth: **Effects of botulinum toxin A injections and bimanual task-oriented therapy on hand functions and bimanual activities in unilateral Cerebral Palsy.** Supervisors: Prof.dr. J. Vles; Prof.dr. R. Smeets; Co-supervisor: Dr. Y. Janssen-Potten, Adelante Hoensbroek.

Yuan Tian: **The effects of Lutein on the inflammatory pathways in age-related macular degeneration (AMD).** Supervisors: Prof.dr. C. Webers; Prof.dr. A. Kijlstra, WUR; Co-supervisor: Dr. M. Spreeuwenberg; Dr. H. Tange.

Peggy Spauwen: **Cognition and Type 2 diabetes; the interplay of risk factors.** Supervisors: Prof.dr. F. Verhey; Prof.dr. C. Stehouwer; Co-supervisor: Dr. M. van Boxtel

Marc Hilhorst: **Crescentic glomerulonephritis in ANCA associated vasculitis.** Supervisors: Prof.dr. J. Cohen-Tervaert; Co-supervisor: Dr. P. van Paassen

Martin Gevonden: **The odd one out: exploring the nature of the association between minority status and psychosis.** Supervisors: Prof.dr. J-P. Selten; Prof.dr. J. Booij, Uva; Prof. dr. I. Myin-Germeys

Bart Biallosterski: **Structural and functional aspects of sensory-motor Interaction in the urinary bladder.** Supervisors: Prof.dr. Ph. Van Kerrebroeck; Prof.dr. S. De Wachter, UvAntwerpen; Co-supervisors: Dr. G. van Koeveringe; Dr. M. Rahnama'i.

Alexandra König: **The use of information and communication technologies (ICT) for the assessment of patients with Alzheimer's Disease and related disorders.** Supervisors: prof.dr. F. Verhey; prof.dr. Ph. Robert, Nice, Fr; Co-supervisors: dr. P. Aalten; dr. R. David, Nice. Fr.

Michelene Chenault: **Assessing Readiness for Hearing Rehabilitation.** Supervisors: prof. dr. M.P.F. Berger; prof.dr. B. Kremer; Co-supervisor: dr. L.J.C. Anteunis.

Anand Vinekar: **Retinopathy of Prematurity. Recent advances in tele-medicine screening, risk factors and spectral domain optical coherence tomography imaging.** Supervisor: prof.dr. C.A.B. Webers; Co-supervisor: dr. N.J. Bauer

Fleur van Dooren: **Diabetes and Depression: exploring the Interface between Pathophysiological and Psychological factors.** Supervisors: prof.dr. F.R.J. Verhey; prof.dr. J.K.L. Denollet, UvT; prof.dr. F. Pouwer, UvT; Co-supervisor: dr. M.T. Schram.

Gabriëlla Pons van Dijk: **Taekwondo and physical fitness components in middle-aged healthy volunteers; the Sekwondo study.** Supervisors: prof.dr. J. Lodder; prof.dr. H. Kingma; Co-supervisor: dr. A.F. Lenssen.

Yara Pujol López: **Development and psychoneuroimmunological mechanisms in depression.** Supervisor: prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. G. Kenis; Dr. D. van den Hove; Dr. Aye Mu Myint, München.

Romina Gentier: **UBB^{+1}; an important switch in the onset of Alzheimer's disease.** Supervisors: Prof. H. Steinbusch; Prof. D. Hopkins; Co-supervisor: Dr. F. van Leeuwen.

Sanne Smeets: **Insights into insight: studies on awareness of deficits after acquired brain injury.** Supervisor: Prof. C. van Heugten; Prof. R. Ponds; Co-supervisor: Dr. I. Winkens

Kim Beerhorst: **Bone disease in chronic epilepsy: fit for a fracture.** Supervisor: Prof. A. Aldenkamp; Prof. R. van Oostenbrugge; Co-supervisor: Dr. P. Verschuure.

Alex Zwanenburg: **Cerebral and cardiac signal monitoring in fetal sheep with hypoxic-ischemic encephalopathy.** Supervisor: Prof. T. Delhaas; Prof. B. Kramer; Co-supervisors: Dr. T. Wolfs; Dr. P. Andriessen, MMC.

Ismail Sinan Guloksuz: **Biological mechanisms of environmental stressors in psychiatry.** Supervisor: Prof. J. van Os; Co-supervisors: Dr. B. Rutten; Dr. M. Drukker.

Seyed Ehsan Pishva MD: **Environmental Epigenetics in mental health and illness.** Supervisor: Prof.dr. J. van Os; Co-supervisors: Dr. B.P.F. Rutten; Dr. G. Kenis.

Ankie Hamaekers: **Rescue ventilation using expiratory ventilation assistance; innovating while clutching at straws.** Supervisors: Prof.dr. W.F. Buhre; Prof.dr. M. van Kleef.

Rens Evers. **22q11.2 deletion syndrome: intelligence, psychopathology and neurochemistry at adult age.** Supervisors: Prof.dr. L.M.G. Curfs; Prof.dr. T. v. Amelsvoort.

Sarah-Anna Hescham. **Novel insights towards memory restoration.** Supervisor: Prof.dr. Y. Temel; Co-supervisor: Dr. A. Blokland; Dr. A. Jahanshahi.

João P. da Costa Alvares Viegas Nunes. **Insulin receptor sensitization improves affective pathology in various mouse models.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. K-P. Lesch; Dr. T. Strekalova; Dr.B.H. Cline, Oxford.

Yanny Ying-Yee Cheng. **Clinical Outcomes After Innovative Lamellar Corneal Transplantation Surgery.** Supervisor: Prof.dr. R.M.M.A. Nuijts; Co-supervisor: Dr. J.S.A.G. Schouten.

2016

Oliver Gerlach. **Parkinson's disease, deterioration during hospitalization.** Supervisor: Prof.dr. R. van Oostenbrugge; Co-supervisor: Dr. W. Weber.

Remo Arts. **Intracochlear electrical stimulation to suppress tinnitus.** Supervisor: Prof.dr. R.J. Stokroos; Co-supervisor: Dr. E.L.J. Georg.

Mitchel van Eeden. **The €- Restore4stroke study: Economic evaluation of stroke care in the Netherlands.** Supervisors: Prof.dr.mr. S.M.A.A. Evers; Prof.dr. C.M. v. Heugten; Co-supervisor: dr. G.A.P. van Mastrigt.

Pim Klarenbeek. **Blood pressure and cerebral small vessel disease.** Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-supervisor: Dr. J. Staals.

Ramona Hohnen. **Peripheral pharmacological targets to modify bladder contractility.** Supervisor: Prof.dr. Ph.E.V. van Kerrebroeck; Co-supervisors: Dr. G.A. van Koeveringe; Dr. M.A. Sahnama'i; Dr. C. Meriaux.

Ersoy Kocabicak. **Deep brain stimulation of the subthalamic nucleus: Clinical and scientific aspects.** Supervisors: Prof.dr. Y. Temel; Prof.dr. K. van Overbeeke; Co-supervisor: Dr. A. Jahanshahi.

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Anna Schüth. **Three-dimensional bladder tissue morphology.** Supervisors: Prof.dr. G.A. van Koeveringe; Prof.dr. M. v. Zandvoort, Aachen; Prof.dr. Ph. V. Kerrebroeck.

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Nele Claes. **B cells as multifactorial players in multiple sclerosis pathogenesis: insights from therapeutics.** Supervisors: Prof.dr. V. Somers, Hasselt; Prof.dr. R. Hupperts Co-supervisors: Prof.dr. P. Stinissen, dr. J. Fraussen, Hasselt.

Olaf Schijns. **Epilepsy surgery and biomarkers from history to molecular imaging.** Supervisors: Prof.dr. J.J. van Overbeeke; Prof.dr. H. Clustermann, Aachen; Co-supervisors: dr. G. Hoogland; dr. M.J.P. v. Kroonenburgh.

Lizzy Boots. **Balanced and Prepared; development and evaluation of a supportive e-health intervention for caregivers of people with early-stage dementia.** Supervisors: Prof.dr. F.R.J. Verhey; Prof.dr. G.I.J.M. Kempen; Co-supervisor: dr. M.E. de Vugt.

Wouter Donders. **Towards patient-specific (cerebro-) vascular model applications.** Supervisors: Prof.dr. T. Delhaas; Prof.dr.ir. F.N. van de Vosse, TUE; Co-supervisor: dr.ir. W. Huberts.

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