Persistence of the extended psychosis phenotype in young people:

Link between vulnerability and clinical need

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Persistence of the extended psychosis phenotype in young people: Link between vulnerability and clinical need

Persistentie van het verlengde psychose fenotype in jongeren:
Link tussen kwetsbaarheid en klinische behoefte
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 16 september 2011 des middags te 12.45 uur

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Johanna Theodora Wilhelmina Wigman
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Nevertheless, if we look on man's whole mental life as it exists, on the life of men that lies in them apart from their learning and science, and that they inwardly and privately follow, we have to confess that the part of it of which rationalism can give an account is relatively superficial.

- William James

Voor mijn ouders

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1. Introduction

Psychosis and its classification

Psychosis is one of the most severe psychiatric conditions, in terms of both individual and societal burden (van Os & Kapur, 2009). Distortion of reality forms its central theme and symptoms may include feelings of paranoia, thought insertion or deletion and hearing voices. The most well-known psychotic disorder is schizophrenia, with a lifetime prevalence of 0.5-1.0% in the general population. When looking at the broader psychosis spectrum including all psychotic disorders, such as schizoaffective or schizophreniform disorder, lifetime prevalence is around 2-3% (van Os, Kenis & Rutten, 2010). Apart from impacting strongly on one's mental health, patients with schizophrenia are also more likely to be without home or work and have a life expectancy about 12-15 years less than the general population, due to suicide, violent death, decreased access to medical care and increased frequency of general risk factors, such as smoking or obesity (van Os & Kapur, 2009; Evers & Ament, 1995).

Psychotic disorders are usually classified using the Diagnostic and Statistical Manual of Mental Disorders, currently in its fourth edition (DSM-IV). The DSM forms the primary reference for clinical decision-making and is necessary for both communication between clinicians and the decision whether or not to offer treatment. However, the prominence of a categorical classification system does not imply that the underlying theoretical construct is also necessarily categorical in nature (Allardyce, Suppes, & van Os, 2007). The categorical view on psychosis has been subject to much critique over the last decades. One issue, for example, is the very high level of comorbidity between the distinct disorders, with over 50% of patients with psychiatric disorders meeting criteria for multiple disorders (Kessler et al., 2011; Buckly, Miller, Lehrer & Castle, 2009). Furthermore, the boundaries between categories are arbitrary and there is much heterogeneity in symptomatology between individuals with the same diagnosis (Lawrie, Hall, McIntosh, Owens & Johnstone, 2010; van Os & Kapur, 2009).

As an alternative to this categorical approach, dimensional views on psychopathology in general and psychosis in specific have gained influence over the years (Kruger & Markon, 2011). This dimensional approach assumes that psychotic phenomena exist as continuous constructs, extending from the general population into the clinical

population (van Os, Hanssen, Bijl & Ravelli, 2000), thus forming an "extended psychosis phenotype" (Howes & Kapur, 2009). Using dimensional diagnoses instead of categorical (van Os et al., 1999; Peralta & Cuesta, 2008; Rosenman, Korten, Medway, & Evans, 2003) or combining both approaches (Allardyce et al., 2007) is likely to be a better approach to conceptualize psychosis. One reason for this is that symptom dimensions are not diagnosis specific (Allardyce et al., 2007) and may be more specific than clinical diagnoses in describing the problems an individual encounters. With a next version of the DSM on the agenda, discussion on a categorical or continuous approach to psychopathology is still a hot topic of scientific debate (Brown & Barlow, 2005).

In this thesis, the term "subclinical" refers to symptoms below clinical level, i.e. without severe associated distress or experienced need for help. The distinction between "symptoms" and "experiences" follows the same logic: psychotic symptoms are associated with distress and help-seeking behavior (i.e. clinically relevant, but not necessarily leading to clinical disorder), whereas psychotic experiences may be also of a (albeit less) distressing nature, but do not prompt the individual to seek help (i.e. are thus always subclinical in nature) (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009).

The extended psychosis phenotype

The hypothesized extended psychosis phenotype captures not only clinical psychotic symptoms, but also psychotic experiences endorsed by non-clinical individuals (individuals without a psychiatric diagnosis, distress secondary to their experiences or need for clinical care (van Os et al., 2009)). The existence of such an extended continuum of psychosis has gained support over the last decades. Research suggests that psychotic symptoms and experiences, as well as the mechanisms underlying psychosis, are part of a continuous, albeit very skewed, distribution of which clinical psychotic disorder forms only a small part (Krabbendam, Myin-Germeys, & van Os, 2004).

Evidence for an extended psychosis continuum can be grouped into several themes. First, research supports the notion of a phenomenological continuum between clinical and subclinical psychosis. The prevalence of subclinical psychotic symptoms and experiences in the general population is much higher than that of psychotic disorder, indicating that

endorsing such experiences does not necessarily lead to need for care. Recent meta-analyses have shown that subclinical psychotic experiences, such as hallucinatory experiences or delusional thinking, are reported by as many as 10-30% of the general population (Nuevo, Chatterji, Verdes, Naidoo, Arango & Ayuso-Mateos, 2010; van Os et al., 2009; Stip & Letourneau, 2009). The dimensions underlying these symptoms have shown to be similar in both clinical and non-clinical psychosis (the latter referring to schizotypy, the non-clinical manifestation of psychosis at the level of personality structure) (Johns & van Os, 2001; Rossi & Daneluzzo, 2002; Vollema & Hoijtink, 2000). Second, there is evidence for longitudinal continuity of subclinical psychotic experiences developing into full florid psychosis (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Dominguez, Wichers, Lieb, Wittchen & van Os, 2011; Hanssen, Bak, Bijl, Vollebergh, & Os, 2005; Poulton et al., 2000; Rössler et al., 2007). Third, similar risk factors are thought to be of importance regarding aetiology along the full spectrum of the extended psychosis continuum. Both clinical and non-clinical psychosis are associated with (i) demographical risk factors such as younger age (a peak of symptoms in adolescence and a decrease after young adulthood) (Verdoux et al., 1998), being single or unemployed (Krabbendam, Myin-Germeys, Graaf et al., 2004) and gender, with women reporting more positive symptoms and men more negative symptoms (Verdoux & van Os, 2002); and (ii) (environmental) risk factors such as urbanicity, trauma, cannabis, neuroticism (Myin-Germeys, Krabbendam, & Os, 2003; van Os, Krabbendam, Myin-Germeys, & Delespaul, 2005). Finally, familial clustering is evident in regard to both symptomatology (Fanous, Gardner, Walsh & Kendler, 2001) and underlying cognitive (Barkus, Stirling, Hopkins, & Lewis, 2006; van Dael et al., 2005; Jabben, van Os, Janssen, Versmissen, & Krabbendam, 2007; Vollema & Postma, 2002) and psychophysiological (Myin-Germeys et al., 2003) mechanisms. For example, relatives of patients with schizophrenia show elevated levels of psychosis proneness, or the liability for experiencing psychotic symptoms, and similar but milder cognitive deviations as their affected family member (van Dael et al. 2005).

There is much evidence in favor of an extended psychosis continuum, but critical assessment of its validity and usefulness of the concept is necessary (David, 2010; Widiger, 2005). More solid research is needed, because the notion of an extended psychosis phenotype is relatively new. The translation of the use of psychopathological dimensions to

clinical practice has furthermore been described as unpractical and limited in its utility (Lawrie et al., 2010). Another issue is that although there is evidence of a psychometric continuum (or the blending of an extended psychosis continuum at the level of the general population into clinical psychotic disorders), there is also evidence that in spite of this continuum, the population may still be divided into two or more latent categories of liability to psychosis (Linscott & van Os, 2010; Kaymaz & van Os, 2010). It is also possible that these symptoms reported in both clinical and non-clinical populations differ qualitatively (Sommer, 2010). Such differences, such as the nature of voices heard, may be one of the particular factors that distinguish between non-clinical and (potentially) clinical symptoms. In sum, the paradigm of an extended psychosis phenotype seems a promising one, but needs more research.

Psychotic symptoms

Psychotic symptoms have been grouped into several interrelated dimensions. Classically, they are grouped according to positive, negative and disorganized symptom dimensions (Allardyce et al., 2007). More recent work, however, has suggested that psychosis can be best described by four dimensions, namely dimensions of positive psychotic symptoms (e.g. delusions and hallucinations), negative symptoms (e.g. decrease in speech, motivation or social contacts), cognitive symptoms (neurocognitive deficits) and affective symptoms, encompassing both depressive and manic symptoms (van Os & Kapur, 2009; van Os et al., 2010), although models with up to eight (Peralta & Cuesta, 2001) or nine (McGrath et al., 2009) dimensions have also been proposed. The dimensional structure of clinical psychotic disorder and non-clinical psychotic phenotypes such as schizotypy (Vollema & van den Bosch, 1995; Vollema & Hoijtink, 2000) or psychotic experiences at the level of the general population (Johns & van Os, 2001; Krabbendam, Myin-Germeys, de Graaf et al., 2004; Stefanis et al., 2002) is similar, suggesting continuity between clinical and subclinical phenotypes.

Factor analytical results indicate that these dimensions are interrelated but distinguishable psychopathological entities. This is further supported by the observation that these factors have been shown to be differentially associated with with external factors (Bentall & Fernyhough, 2008) and/or each other, as, for example, the negative symptom

dimension is associated with neurocognitive deficits, whereas positive and affective symptom dimensions are less related to cognition (Myin-Germeys & van Os, 2007). In line with this, the negative symptom dimension is associated with a neurodevelopmental pathway to psychosis (Murray & Lewis, 1987; Weinberger, 1987), whereas the positive symptom dimension is thought to be associated with environmental risk factors for psychosis, possibly representing an affective pathway to psychosis (Dominguez, Saka, Lieb, Wittchen & van Os, 2010; Myin-Germeys & van Os, 2007). In longitudinal research, negative symptoms have been shown to precede positive symptoms over time, but not the other way around (Dominguez et al., 2010). It may be useful to distinguish between these dimensions to better understand the psychosis phenotype; however, it should be kept in mind that these dimensions are strongly interrelated and all contribute to the full spectrum of the extended psychosis phenotype.

Positive symptoms

Epidemiological studies suggest that specifically the positive symptom dimension is predictive of transition to clinical disorder (Chapman et al., 1994; Scott, Martin, Welham et al., 2009; Welham et al., 2009). Within this positive symptom dimension, several subdimensions can be distinguished. For example, Stefanis and colleagues (2004b) reported the finding of four factors, representing four subdimensions, namely Paranoia, First rank symptoms, Hallucinations and Grandiosity. Verdoux and colleagues (1998) suggested seven dimensions, distinguishing Persecution, Thought disturbances, Grandiosity, Paranormal beliefs, Reference-Guilt, Religiosity and Apocalyptic ideas, as the best representation of psychotic experiences in non-ill individuals; both of these studies were done in adult populations. Furthermore, Yung and colleagues proposed models with three subdimensions in a clinical adolescent population (Bizarre experiences, Persecutory ideas and Magical thinking) (Yung et al., 2006) and four subdimensions in a non-clinical adolescent population (Bizarre experiences, Perceptual abnormalities, Persecutory ideas and Magical thinking) (Yung et al., 2009). A modified version of this latter four-factor model was later replicated in a population of both adolescents and young adults; here, the Magical thinking factor was replaced by Grandiosity (Armando et al., 2010).

These subdimensions are also thought to represent distinguishable but interrelated psychopathological entities. For example, subdimensions of positive symptoms have been found to be differentially related to other measures of psychopathology, such as depression (Yung et al., 2006, 2009). Thus, although interrelated, it is possible that only some (sub)dimensions of the extended psychosis continuum lie on a continuum with later psychopathology and are predictive of later psychiatric disorder. The study of the dimensional structure underlying subclinical positive psychotic experiences is the first topic of this thesis.

A longitudinal perspective

Only a minority of individuals endorsing these experiences will progress to clinical psychotic disorder, even though the prevalence of subclinical psychotic experiences, or psychosis proneness, is relatively high in the general population. There is evidence from birth cohorts (Poulton et al., 2000; Welham et al., 2009), general population cohorts (Dominguez et al., 2011; Hanssen, Bak, Bijl, Vollebergh & van Os, 2005; Werbeloff et al., 2009) and other longitudinal studies (Chapman et al., 1994) that subclinical psychotic experiences may precede the diagnosis of psychotic disorder and hospital admission by many years.

Much uncertainty remains, however, about how psychosis proneness actually develops over time in the general population. There are multiple developmental paths that may eventually end in psychosis; likewise, subclinical psychotic experiences may lead to very heterogeneous outcomes (Keshavan, DeLisi, & Seidman, 2011). Earlier studies have suggested that cross-sectional measurements of subclinical psychotic experiences may not be particularly useful as a specific risk factor for later clinical psychotic outcomes (Correll et al., 2005), in part because such experiences are so common (Yung et al., 2009) and dynamic (Nelson & Yung, 2009). Furthermore, results are inconsistent in regard to whether subclinical psychotic experiences have a specific (Cannon et al., 2001; van Meurs et al., 2009; Poulton et al., 2000) or a more general (Dhosssche, Ferdinand, van der Ende, Hofstra & Verhulst, 2002) predictive value for later psychopathology. However, even for those who do not develop clinical psychosis, subclinical psychotic experiences are associated with later psychopathological problems, such as depression (Dhossche et al., 2002). Additionally, many

risk factors associated with development of psychosis are not specific for psychosis, but are predictive of more general later psychopathology (Breetvelt et al., 2010; Laurens et al., 2007). More fine-tuning is therefore necessary regarding subclinical phenotypes and other factors that influence the development of psychosis to understand the different developmental pathways that individuals can follow. The development of the extended psychosis phenotype is the second topic of the current thesis.

Development of the extended psychosis phenotype

Modeling the development of psychotic experiences over time, in relation to functioning and the development of health care use, may offer more insight in the course of the extended psychosis phenotype over time. Such an approach may be fruitful since it takes into account the longitudinal stability of the psychotic experiences and excludes more incidental phenomena (Nelson & Yung, 2009). Previous longitudinal work (Dominguez et al., 2011; Mackie, Castellanos-Ryan, & Conrod, 2010; Rössler et al., 2007; Scott et al, 2009a,b; Welham et al., 2009, 2010) has shown that increasing or persistent levels of subclinical psychotic experiences over time are associated with risk factors for psychosis, higher levels of other psychopathology, such as depression, poorer functioning and higher need for care. Such a longitudinal approach may inspire theory on latent subgroups underlying the extended psychosis phenotype (Linscott & van Os, 2010), as well as on approaches to target these possibly high-risk groups (Rössler et al., 2007). Prospective research is important in this area, since it has been shown to have a much higher predictive value for later psychopathology than retrospective research, which usually underreports earlier levels of psychopathology (Moffitt et al., 2010).

Adolescence

A developmental perspective may be of particular importance during adolescence. Psychosis proneness is assumed to be at its peak during adolescence (Verdoux et al., 1998; Verdoux & Os, 2002) and psychotic symptoms may manifest themselves for the first time during this dynamic phase of life, characterized by rapid and substantial brain development (Lewis & Levitt, 2002; Verdoux et al., 1998; Verdoux & van Os, 2002).

Subclinical psychotic experiences are frequently reported in both clinical (Altman, Collins, & Mundy, 1997; Yung et al., 2006) and non-clinical (Fonseca-Pedrero, Lemos-Giraldez, Muniz, Garcia-Cueto, & Campillo-Alvarez, 2008; McGorry et al., 1995; Meng & Schimmelmann, 2009; Spauwen, Krabbendam, Lieb, Wittchen, & Os, 2003; Yung et al., 2009) adolescent populations. In fact, endorsing subclinical psychotic experiences during adolescence may even be considered developmentally quite normal (McGorry et al., 1995). The transitory developmental expression of psychosis during adolescence and early adulthood, however, may become abnormally persistent and lead to subsequent development of need for care depending on the exposure to environmental risk factors that interact with genetic liability for psychosis (Cougnard et al., 2007).

Shifts along the extended psychosis continuum

Psychosis is thought to develop as a product of both genetic liability and environmental influences (van Os et al., 2010). Even in individuals with 100% identical genes (in the case of monozygotic twins), the risk of a twin for developing schizophrenia is only 50% if the co-twin has schizophrenia. Additionally, not all individuals who are exposed to risk factors for psychosis actually become psychotic (van Os, Rutten & Poulton, 2008). Since both genetic and environmental risk factors are often present long before the first expression of psychotic problems, a developmental perspective may be the best approach to study the extended psychosis phenotype (Lewis & Levitt, 2002; Tsuang, Stone & Faraone, 2001).

Shifts along the extended psychosis continuum are thought to be an interactive process, with contextual factors leading to (i) persistence of more incidental, transitory symptoms and (ii) the development of need for care in individuals who are liable to psychosis (Cougnard et al., 2007). Deterioration and subsequent development of need for care is thought to be related to processes of psychological and biological sensitization, i.e. the phenomenon that responses to a certain stimulus become increasingly stronger when exposed repeatedly to similar stimuli of equal intensity, (Collip, Myin-Germeys, & van Os, 2008; van Os et al., 2010; van Winkel, Stefanis & Myin-Germeys, 2008) and many factors play a role in this process.

Characteristics of symptoms

Several studies have shown that the intensity/severity of the subclinical psychotic experiences and/or psychotic symptoms is predictive of later outcome in both clinical (Ultra High Risk [UHR]) (Cannon et al., 2008; Nelson & Yung, 2009) and subclinical populations (Hanssen et al., 2005). Distress caused by these symptoms also plays an important role (Hanssen et al., 2005; Jacobs, Myin-germeys, Derom, Vlietinck & van Os, 2005; Loewy, Johnson & Cannon, 2007). The level of preoccupation (Peters, Day, McKenna & Orbach, 1999), impact of symptoms on behavior (Johns & van Os, 2001) and cognitive interpretation of the symptoms (O'Connor, 2009; Garety, Bebbington, Fowler, Freeman & Kuipers, 2007; Morrison, 2001) have also all been shown to be important in determining outcome. The persistence of symptoms over time has been shown to be particularly predictive of later development of impairment or clinical psychotic disorder (Dominguez et al., 2011; Rössler et al., 2007; Schimmelmann, Michel, Schaffner, & Schultze-Lutter, 2011). The finding that psychotic symptoms may differ qualitatively in clinical and non-clinical individuals may also suggest that the nature of the symptoms may change (or influence changes) along the psychosis continuum. For example, voices heard by patients are often negative and hostile, whereas voices in non-clinical individuals are mostly benign and friendly (Sommer, 2010; Escher, Romme, Buiks, Delespaul & van Os, 2002; Daalman et al., in press).

Environmental factors

Some environmental risk factors have been consistently reported to increase the risk of both higher levels of psychotic symptoms and of higher prevalence of clinical psychosis, i.e. these factors may predict shifts upwards the psychosis continuum along the full spectrum. Many studies have shown the role of (psychological, physical and sexual) trauma during childhood and adolescence in the development of psychosis and psychotic symptoms/experiences (Arseneault et al., 2011; Cutajar et al., 2010; Fisher et al., 2010; Freeman & Fowler, 2009; Lardinois, Lataster, Mengelers, van Os & Myin-Germeys, 2011; Lataster et al., 2006; de Loore et al., 2007; Read, van Os, Morrison & Ross, 2005; Spauwen, Krabbendam, Lieb, Wittchen & van Os, 2006b). Other reported risk factors include developmental problems (Cannon et al., 2002), cannabis use (Henquet et al., 2005; McLaren, Silins, Hutchinson, Mattick, & Hall, 2009; Stefanis, Delespaul, Henquet et al.,

2004b; Verdoux, Sorbara et al., 2002), urbanicity (Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2004; Spauwen et al., 2006a; Stefanis, Delespaul, Smyrnis et al., 2004) and ethnic minority status (Cantor-Graae & Selten, 2005). Recently, the concept of 'social defeat' has been introduced. This captures ethnic minority status, low IQ and drug use in one dimension (Selten & Cantor-Graae, 2005). An interesting notion is that some of these environmental risk factors are suggested to only impact on an individual in a context in which the pertinent factor is rare (Zammit et al., 2010). For example, being single was shown to be a stronger risk factor for later psychosis in an area with fewer single-person households (van Os, Driessen, Gunther, & Delespaul, 2000). Some of these environmental risk factors may thus be in fact more psychological factors, since they depend strongly on perception and interpretation.

Psychological factors

Individual, psychological factors may also influence the transition to higher levels on the extended psychosis continuum (Krabbendam, Myin-Germeys, Bak & van Os, 2005). The personality trait of neuroticism, for example, has been shown to be associated with (subclinical) psychosis (van Os & Jones, 2001; Goodwin, Fergusson, & Horwoord, 2003; Krabbendam et al., 2002). In line with this is the finding that sensitivity to stress also predicts psychosis, since this concept shows a large overlap with neuroticism (Myin-Germeys & van Os, 2007). Depression is also a factor that is associated with psychosis along the full spectrum of the extended psychosis phenotype (van Rossum, Dominguez, Lieb, Wittchen & van Os, 2011; Yung, 2007). At the clinical end of the continuum, this is reflected by diagnoses such as schizoaffective or bipolar disorder, with co-occurring depressive and psychotic symptoms. Up to 50% of patients with schizophrenia experience co-morbid depression (Buckley et al., 2009). Depression has also been shown to predict transition from UHR status to clinical psychosis (Yung et al., 1998, 2003, 2004). Further down the continuum, subclinical psychosis and depression are associated in adolescent or young adult (Armando et al., 2010; Varghese et al., 2011; Yung et al., 2006; van Rossum et al., 2011; Fonseca-Pedrero et al., 2010) and adult (Krabbendam & van Os., 2005) general population samples. Using both self-report (Stefanis et al., 2002) and clinical interview data (Krabbendam et al., 2004), subclinical psychosis and depression have been shown to exist as

separate but correlated dimensions at the level of the general population. It has even been suggested that depression may exist, not only phenotypically, but also aetiologically, intermediate between normality and psychosis (van Os et al., 1999).

Coping also may moderate outcome. Like neuroticism and depression, coping is also related to psychosis at all levels of the extended psychosis continuum, with non-adaptive coping associated with poor outcome in chronic schizophrenia populations (Ritsner et al., 2003), following a first episode of psychosis (Boschi et al., 2000; Thompson, McGorry & Harrigan, 2003), in groups at UHR for psychotic disorder (Ruhrmann et al., 2008) and within the general population (Bak et al., 2003; Dangelmaier, Docherty & Akamatsu, 2006; Krabbendam et al., 2005; Schuldberg Karwacki & Burns, 1996).

Genetics

Not all individuals who are exposed to (external or internal) risk factors eventually develop psychosis; genetic liability to psychosis may moderate these effects (van Os et al., 2008). Genetic factors are assumed to play a role in schizophrenia (van Os & Kapur, 2009; van Os et al., 2010) and other psychotic disorders (Owen, Craddock, & Jablensky, 2007). Psychosis is thought to be a product of multiple genes (Harrison & Weinberger, 2005) and is assumed to arise through a complex interaction between genes and environmental factors (van Os et al., 2008). Heritability of schizophrenia is estimated at around 60% (Lichtenstein et al., 2009). In line with this are observations that the risk of a non-affected monozygotic co-twin of a person with schizophrenia is 50% (Harrison & Weinberger, 2005; Mittal, Ellman, & Cannon, 2008) and that up to 85% of patients with schizophrenia do not have a first- or second-generation relative with psychotic disorder (Mason & Beavan-Pearson, 2005). Genes and environment are unlikely to act in isolation (van Os et al., 2010). Instead, the focus is on "the synergistic co-participation where the effect of one is conditional on the other" (van Os et al., 2008; van Winkel et al., 2008, 2010).

The phenotype of schizophrenia has been criticised as being too broad to investigate the effects of genetics, environmental influences or their interaction (Angst, 2007; O'Donnovan, Craddock & Owen, 2008). Instead of comparing individuals with psychotic disorders with the rest of the population, a more fruitful paradigm may be to compare individuals with psychotic symptoms or experiences (including the clinical phenotype) with

individuals who do not endorse such experiences, since this may capture the hypothesized genetic variation that is shared between the clinical (disorder) and the non-clinical (symptoms or experiences) phenotypes (Kelleher et al., 2010; Lataster, Myin-Germeys, Derom, Thiery & van Os, 2009).

In sum, many factors play a role in the extended psychosis phenotype. However, most research discussed above is cross-sectional in design and investigated psychiatric diagnosis or subclinical psychotic experiences at a single time point. More longitudinal research is needed to study the role of such risk factors in the longitudinal course and in particular the persistence of subclinical psychotic experiences. This paradigm may be particularly suitable for studying adolescence, during which many physical, mental, social and spiritual changes are taking place (Steinberg, 1999) and psychosis proneness is highest (Verdoux et al., 1998). The study of psychological, biological and environmental risk factors in the development of the extended psychosis phenotype is the third and last topic of the current thesis.

The paradox of subclinical psychotic experiences

Subclinical psychotic experiences seem to form a paradox (Yung et al., 2006). The endorsement of subtle psychotic experiences in young people seems developmentally quite normal. For some individuals these experiences represent an indicator of liability to psychosis, but for most individuals, these experiences are transient in nature. Even within individuals at UHR for psychosis, most people do not transition to clinical psychosis (Cannon et al., 2008; Ruhrman et al., 2010; Yung, 2008). The difficulty, of course, is to distinguish between individuals who will experience differential outcomes. It is important to improve our understanding of the early, subclinical phases of psychosis and their development, because this will facilitate early recognition and possible intervention and will help to identify those individuals in whom early, subtle psychotic experiences may represent the prodromal period of a psychotic disorder.

Intervention

Intervention in psychosis has been shown to be both most effective and benign when delivered early (McGorry et al., 1995, 2006; Mrazek & Haggarty, 1994). The ultimate goal of such intervention is to delay, attenuate or even prevent transition to psychosis (Keshavan et al., 2011; McGorry et al., 1995). A better understanding of the developmental patterns of subclinical psychotic experiences and the role of risk- and protective factors may help to prevent more transient psychotic experiences from becoming persistent. Intervention may focus primarily on environmental factors, since these can be more easily manipulated than genetic factors (Cannon & Murray, 1998). This, in addition to the fact that adolescence is of such importance in the first onset and development of psychosis, offers a rationale for more investigation of developmental patterns of subclinical psychotic experiences in adolescence and factors that possibly influence for the development of clinical disorder.

This thesis

The literature discussed above demonstrates that the extended psychosis phenotype is a promising new approach for the study of psychosis, but that more research is warranted, particularly in regard to its underlying structure and development. Adolescence is an important period of life in which to apply this approach, since the extended psychosis phenotype may be particularly dynamic in this developmental time frame. The goal of the current thesis was to offer a better understanding of the extended psychosis phenotype, its underlying dimensions and its development in young people by addressing three central research questions:

1. What is the underlying structure of the extended psychosis phenotype?
2. How does the extended psychosis phenotype develop over time?
3. What factors play a role in this development?

These questions were all addressed by investigating young individuals, who are developmentally at increased risk for psychosis. Most studies in this thesis investigated adolescents from the general population; one study addressed help-seeking adolescents at increased risk for (psychotic) psychopathology and two studies concerned young adults from the general population.

In Chapter 2, the dimensional structure of subclinical positive psychotic experiences is addressed, using exploratory and confirmatory statistical techniques to identify the underlying dimensional structure of self-reported subclinical positive psychotic experiences in two large Dutch adolescent samples from the general population. Chapter 3 reports on the replication of this five-dimensional structure in a sample of young adult female twins from the general population. Chapter 4 describes the longitudinal study of developmental patterns of subclinical positive psychotic experiences in Dutch adolescents from the general population, followed from age 10 to 16, and the association of these distinct developmental courses with other measures of psychopathology, parental report and use of health care. Chapter 5 reports on the replication of this finding of distinct developmental patterns of subclinical psychotic experiences in an Australian adolescent population sample and relates these patterns to the use of different coping styles. Chapter 6 addresses the development of subclinical psychotic experiences in young adult female twins from the general population and the finding of a genetic component to these developmental patterns. Chapter 7 also addresses a genetic component to the developmental patterns reported in Chapter 4. Here, both indirect (parental psychopathology) and direct (molecular-genetic data) genetic measures are studied. In Chapter 8, the longitudinal association between subclinical psychotic experiences and depression is addressed in help-seeking adolescents. In Chapter 9, the findings of the previous chapters are integrated and discussed.

Part I | Dimensions of the extended psychosis phenotype

2. The structure of the extended psychosis phenotype in early adolescence: A cross-sample replication

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Schizophrenia Bulletin

The extended psychosis phenotype, or the expression of non-clinical positive psychotic experiences, is already prevalent in adolescence, and has a dose-response risk relationship with later psychotic disorder. In two large adolescent general population samples (n=5422 and n=2230), prevalence and structure of the extended psychosis phenotype was investigated. Positive psychotic experiences, broadly defined, were reported by the majority of adolescents. Exploratory analysis with Structural Equation Modelling (Exploratory Factor analysis followed by Confirmatory Factor Analysis) in Sample 1 suggested that psychotic experiences were best represented by five underlying dimensions; Confirmatory Factor Analysis in Sample 2 provided a replication of this model. Dimensions were labeled Hallucinations, Delusions, Paranoia, Grandiosity and Paranormal Beliefs. Prevalences differed strongly, Hallucinations having the lowest and Paranoia having the highest rates. Girls reported more experiences on all dimensions, except Grandiosity, and from age 12 to 16 years rates increased. Hallucinations, Delusions and Paranoia, but not Grandiosity and Paranormal beliefs, were associated with distress and general measures of psychopathology. Thus, only some of the dimensions of the extended psychosis phenotype in young people may represent a continuum with more severe psychopathology and predict later psychiatric disorder.

Introduction

The prevailing viewpoint is that the fundamental processes underpinning psychotic disorders such as schizophrenia are such that there is continuity and population distribution of experience (van Os et al., 2009). Subclinical phenotypes of psychosis can be readily identified, are more prevalent than the clinical phenotypes, and are associated with many of the same environmental and non-genetic risk factors as the clinical phenotypes, implying continuity of experience, even though taxometric evidence suggests that although there is continuity of experience, the population structure of psychosis—defined broadly to include liability states—may not be continuous with normality (Linscott & van Os, 2010).

Systematic review of general population studies suggests that, from an epidemiological perspective, psychotic experiences in non-ill people may represent the behavioral expression of increased liability for psychotic disorder (van Os et al., 2009). Although the great majority will never make the transition to clinical psychosis, even after extended periods of follow-up (Poulton et al., 2000), a continuous dose-response risk function exists between psychotic experiences and later disorder (van Os et al., 2009). Most of the studies on the psychosis continuum focused on adults rather than on young people, even though the expression of (clinical and subclinical) psychosis typically emerges in adolescence and steeply declines with age (Verdoux & van Os, 2002; Verdoux et al., 1998).

Adolescence is a period in which psychotic experiences are relatively frequently reported in unselected general population samples (Fonseca-Pedrero et al., 2008; Scott et al., 2009). The great majority of these experiences are transient (Cougnard et al., 2007), i.e. never progress to clinical psychotic disorder (Dominguez et al., 2011). Accordingly, only a small part of the total expression of risk in general population adolescent samples can be considered as true positive if used as a test for later psychopathology (McGorry et al., 1995). Even though psychotic experiences in unselected general population samples do predict transition to psychotic disorder (Linscott & van Os, 2010; Chapman et al., 1994; Hanssen et al., 2005; Welham et al., 2009; Werbeloff et al., 2009), some experiences, such as ideas of reference and suspicion arising in challenging social contexts may form part of the normal process of growing up. The non-perfect prediction of psychotic experiences may suggest underlying heterogeneity, for example related to different types of psychotic experience (Yung et al., 2009).

Although psychotic as well as schizotypal experiences can be grouped into several dimensions (Vollema & van den Bosch, 1995), including dimensions resembling negative symptoms, it is the dimension of positive experiences, i.e. hallucinations and delusions, that has been shown to strongly predict later clinical psychotic outcome in epidemiological studies (Chapman et al., 1994; Welham et al., 2009; Werbeloff et al., 2009), providing a rationale for an initial focus on positive psychotic experiences. Recent work suggests that the positive domain of psychotic experiences in fact represents several subdimensions. For example, Stefanis and colleagues (2004) distinguished four subdimensions (Paranoia, First rank symptoms, Hallucinations and Grandiosity), whereas Verdoux and colleagues (1998) proposed seven dimensions of delusional ideation (Persecution, Thought Disturbances, Grandiosity, Paranormal beliefs, Reference-Guilt, Religiosity and Apocalyptic ideas). Both these studies were conducted in adult non-clinical populations. In addition, Yung and colleagues (2006) reported three dimensions in a clinical adolescent population (Bizarre experiences, Persecutory ideas and Magical thinking) and four dimensions in general population adolescents (Bizarre experiences, Perceptual abnormalities, Persecutory ideas and Magical thinking) (2009). If different subdimensions exist within the positive psychotic dimension, the question rises whether the association with a psychopathological continuum resulting in elevated predictive values for transition to later psychotic disorder may differ between the different subdimensions in adolescents.

Given the fact that several studies show that not just the frequency of psychotic experiences *per se*, but rather the amount of associated distress predicts transition to need for care and onset of psychotic disorder (Hanssen et al., 2005; Bak et al., 2005; Garety et al., 2007; Jacobs et al., 2005; Krabbendam & van Os, 2005), the degree to which the association between psychotic experiences and distress may differ between the different subdimensions becomes an important first target for analysis. In addition, given the hypothesis of a continuum of psychopathology, analysis of differential associations between subdimensions of the extended psychosis phenotype on the one hand and general measures of psychopathology on the other may be productive.

The prevalence of psychotic experiences during adolescence is associated with both age and sex. Girls aged 12-18 years report more positive experiences than boys (Fonseca-Pedrero et al., 2008), in accordance with the finding that adult women report more positive experiences than men (Maric et al., 2003). In addition, although men have an earlier onset

of schizophrenia (i.e. have poorer prognosis of subclinical psychotic experiences) than women, girls may report psychotic experiences at an earlier age than boys, possibly because girls reach puberty at an earlier age than boys (Fosatti et al., 2003; Galdos, van Os & Murray, 1993).

The present study had four aims. First, the prevalence of the extended psychosis phenotype expressed as positive psychotic experiences was investigated in two large adolescent community samples (n=5422 and n=2230). Second, exploratory factor analysis followed by confirmatory factor analyses were conducted in order to investigate the structure in terms of underlying subdimensions of the extended psychosis phenotype. Third, prevalence of psychotic experiences was analyzed in relation to age and sex. Fourth, it was hypothesized that not all dimensions may be equally predictive of later psychopathology and that this would show as differential associations with distress and general psychopathology.

Study 1: Health Behavior in School aged Children study (HBSC).

Methods

Participants The sampling frame was the HBSC, a general population study investigating health, health behaviors and its social context in youth in Europe and North America (Currie et al., 2004). Participants were selected by a two-stage random sampling procedure, first at school level (proportionate to number in corresponding urbanization level) and second at class level (random selection). Response rate at school level was 47% and at class level 93%. Schools that did not participate did not differ from schools that did participate, resulting in a representative sample of Dutch adolescents. Detailed information on the selection procedure and non-response can be found in a report by Currie and colleagues (2002). The sample consisted of 5.422 adolescents aged 12-16 years (mean age 14.0; SD 1.3; 50% girls). Data were collected in October-November 2005.

Instruments The Community Assessment of Psychic Experiences (CAPE) positive experiences scale (20 self-reported items) was used to assess psychotic experiences (Stefanis et al., 2002; Konings et al., 2006). Each item assesses a) frequency and b) distress associated with the experience, both on a four-point scale (0=never/not distressed to 3=nearly always/very

distressed). The 20-item scale with both frequency and distress items included showed excellent internal consistency (Cronbach alpha = 0.94).

For model estimation, raw CAPE items were used. In order to investigate effects of sex and age, all 20 frequency items were dichotomized into 0=never and 1=sometimes, often or nearly always. This approach was used in order to be consistent with Yung and colleagues (2006, 2009), who previously developed this analytical framework. The sum of these 20 dichotomized item scores was used as continuous outcome score, indicating the total number of CAPE-item endorsements and hereafter referred to as "CAPE item score". Similar "CAPE subdimension item scores", using dichotomous items, were constructed for the five CAPE subdimensions. Internal consistency of the dichotomized items was good (Cronbach alpha = 0.83), and internal consistencies of the subdimensions Hallucinations, Delusions, Paranoia, Grandiosity and Paranormal beliefs was acceptable-good (Cronbach alpha of resp. 0.76, 0.78, 0.67, 0.69 and 0.66). In addition to the prevalence of the broadly defined contrast of "ever" versus "never", a narrow prevalence of psychotic experiences, for descriptive purposes, was also calculated, with items dichotomized as 0=never/sometimes and 1=often/nearly always.

In order to investigate associations between psychotic experiences and distress, a "frequency score" (sum of all original frequency items, not dichotomized) and a "distress score" (sum of all original distress items, not dichotomized) were calculated for every subdimension.

Given the fact that the CAPE may not be valid in a young age group, a pilot study at a Dutch high school was conducted in a sample of 120 adolescents aged 12-16 years (data not shown). Based on comments received during the debriefing procedure, several minor adaptations were deemed necessary. Thus, minor changes in the wording of some items were introduced. For example, the item about hearing voices when alone was extended with "not on tv or radio". In the introduction, it was explicitly stated that not everyone may experience these symptoms, but that it is important that everyone fills it in seriously. The pilot suggested both feasibility and validity of the CAPE.

The Strengths and Difficulties Questionnaire (SDQ) (Goodman, Meltzer & Bailey, 1998), a screening instrument for youth general psychopathology, was used to assess convergent validity of a psychopathological continuum of the subdimensions.

Statistical Analyses

Model development Analyses were done in Prelis 2.80 (Jöreskog & Sörbom, 1996a) and Lisrel 8.80 (Jöreskog & Sörbom, 1996b). Structural Equation Modelling (Exploratory Factor Analysis (EFA) followed by Confirmatory Factor Analysis (CFA)) was used in an exploratory framework to find a best fitting model. Subsequent models with number of factors ranging from one to six were investigated. Several fit indices were used. For acceptable model fit, χ^2 (Chi-square) should be low, Root Mean Square Error of Approximation (RMSEA) should be lower than 0.05 and the Comparative Fit Index (CFI) should be higher than 0.90. Data were defined as ordinal and estimation was done with weighted least squares (WLS) (Brown, 2006). Convergent validity of a psychopathological continuum of the subdimensions was assessed by correlating the dimensions with subscales of the SDQ. Correlation coefficients were compared statistically as described by Meng and colleagues (1992).

Age and sex In order to assess differences in CAPE item score between the sexes and different age groups, six ANOVA's were conducted with CAPE item score and the five CAPE subdimensions item scores as dependent variables and sex and age as fixed factors.

Distress The association between frequency score and distress score was investigated by predicting distress score with frequency score using linear regression, controlling for age and sex. Regression coefficients were compared statistically by Wald test. In this analysis, for each given item, only adolescents who reported an endorsement of at least "sometimes" on that item were included in analyses.

Results

Descriptives 95% of the participants endorsed at least one psychotic experience on the CAPE at least "sometimes". 43% endorsed at least one experience "often" or "almost always". The median CAPE item score was 6 experiences (inter-quartile range 3-9); the 90th percentile was 9 experiences.

Model development Building on results from initial EFA, CFA revealed that model improvements occurred from 1 to 5-factor solutions, estimated with Promax rotation, which allows factors to be correlated (data avaiable on request). The 6-factor solution showed no

improvement compared to the 5-factor solution, both in content and in model fit. The 5-factor model was the best model as it had the lowest χ^2 and RMSEA and the highest CFI (Table 1). In Figure 1, the structure of the model, standardized coefficients from latent variables to indicator variables and correlations between factors are depicted. All coefficients were at least 0.56 (mean factor loading 0.79). Furthermore, the latent variables were found to explain 60.3% percent of variance in the indicator variables. The five factors were labeled 'Paranoia', 'Grandiosity', 'Paranormal beliefs', 'Delusions' and 'Hallucinations'. Correlations among the five factors were high: the highest coefficients were found between Paranoia, Delusions, and Hallucinations (r>0.80). These results indicate that the level of discrimination between the dimensions varies, depending on the specific content. Prevalences of the factors are shown in Table 2 at broad (ever vs never) and narrow (never/sometimes vs often/nearly always) level.

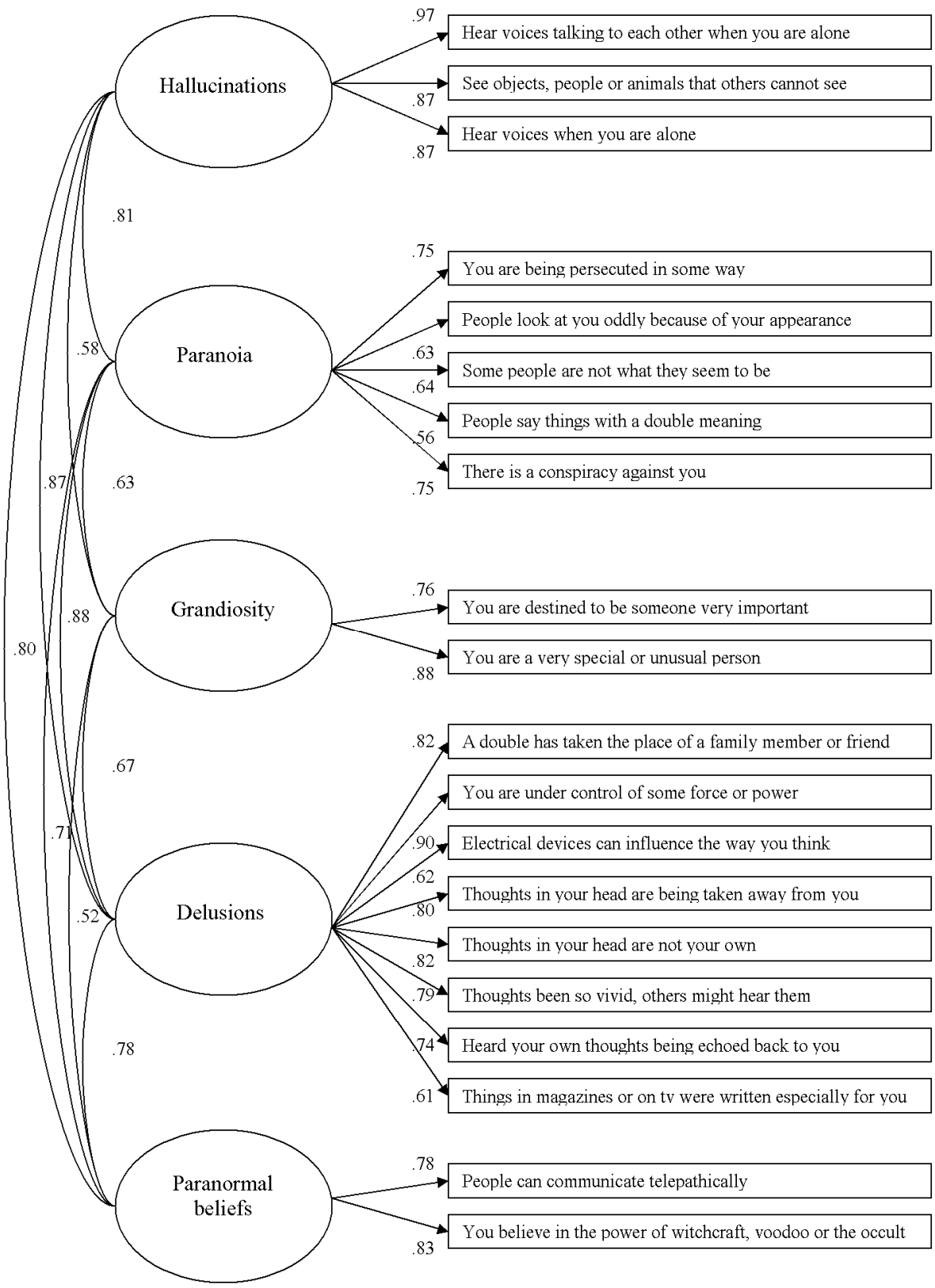
Table 1. Fit indices of the six factor models in HBSC (n=5422).

Models with number of factors	Fit index χ2	df	CFI	RMSEA
1 factor	1627.60	170	0.86	0.043
2 factors	1217.94	169	0.90	0.036
3 factors	1164.25	167	0.91	0.036
4 factors	951.37	164	0.93	0.032
5 factors	739.18	160	0.95	0.028
6 factors	814.18	156	0.94	0.030

Table 2. Broad and narrow prevalence rates of subdimensions in HBSC (n=5422).

Dimension	Prevalence rate "ever"	Prevalence rate "often"/"almost always"
Hallucinations	30.1	6.4
Delusions	66.5	11.2
Paranoia	89.7	26.4
Grandiosity	45.8	12.0
Paranormal beliefs	48.6	16.2
Any CAPE experience	94.8	43.3

Figure 1. Model with five dimensions, their standardized factor loadings and factor correlations in HBSC.



Convergent Validity with General Psychopathology In order to investigate associations between the five CAPE positive experience subdimensions on the one hand and general measures of psychopathology on the other, correlations were computed between the five CAPE subdimension item scores and the four subscales of the SDQ (Hyperactivity, Emotional problems, Conduct problems and Peer problems) (Table 3). Overall, Hallucinations, Delusions and Paranoia showed statistically significantly higher correlations with all SDQ scales (r=0.44-0.78) than Grandiosity and Paranormal beliefs, which had structurally lower correlations with all SDQ scales (r=0.18-0.55).

A similar pattern was apparent within each SDQ subscale. Thus, Hyperactivity was significantly more strongly associated with Hallucinations, Delusions and Paranoia than with Grandiosity (resp. Z=20.80, p<.001; Z=22.77, p<.001 and Z=21.77, p<.001) and Paranormal beliefs (resp. Z=16.67, p<.001; Z=16.17, p<.001 and Z=15.90, p<.001). A similar pattern was apparent for Emotional problems, statistically stronger associations being found with Hallucinations, Delusions and Paranoia compared to associations with Grandiosity (resp. Z=23.87, p<.001; Z=33.47, p<.001 and Z=45.04, p<.001) and Paranormal beliefs (resp. Z=8.02, p<.001; Z=16.02, p<.001 and Z=21.49, p<.001). Conduct problems were also associated statistically more strongly with Hallucinations, Delusions and Paranoia than with Grandiosity (resp. Z=17.6, p<.011; Z=18.18, p<.001 and Z=17.12, p<.001) and Paranormal beliefs (resp. Z=22.40, p<.001; Z=29.80, p<.001 and Z=17.12, p<.001). Finally, Peer problems were also associated statistically more strongly with Paranoia, Delusions and Hallucinations than with Grandiosity (resp. Z=22.69, p<.001; Z=11.36, p<.001 and Z=17,80, p<.001) and Paranormal beliefs (resp. Z=25,78, p<.001; Z=13.72, p<.001 and Z=11.98, p<.001).

Table 3. Correlations between the five CAPE subdimension item scores and the four subscales of the SDQ in HBSC (n=5422).

CAPE SDQ	Hallucinations	Delusions	Paranoia	Grandiosity	Paranormal Beliefs	CAPE item score
Hyperactivity	0.44* [de]	0.44* [de]	0.45* [de]	0.18* [abce]	0.29* [abcd]	0.43*
Emotional problems	0.64* [bcde]	0.68* [acde]	0.78* [abde]	0.34* [abce]	0.55* [abcd]	0.69*
Conduct problems	0.64* [de]	0.64* [de]	0.63* [de]	0.45* [abc]	0.46* [abc]	0.68*
Peer problems	0.55* [bcde]	0.58* [acde]	0.68* [abde]	0.45* [abc]	0.45* [abc]	0.64*

**p<.01*

[a] Differs from the correlation of this SDQ subscale with Hallucinations (p<.001)

[b] Differs from the correlation of this SDQ subscale with Delusions (p<.001)

[c] Differs from the correlation of this SDQ subscale with Paranoia (p<.001)

[d] Differs from the correlation of this SDQ subscale with Grandiosity (p<.001)

[e] Differs from the correlation of this SDQ subscale with Paranormal beliefs (p<.001)

Age and Sex The mean CAPE item score and CAPE subdimension item scores are shown for several age groups and for each sex in Table 4.

For both total CAPE and its subdimensions, girls had higher item scores than boys, with the exception of Grandiosity (Table 3). In addition, the item scores increased between the age of 12 and 16 years for total CAPE and particularly for the subdimensions Paranoia, Grandiosity and Paranormal beliefs.

Distress Associations between frequency score and distress score were different for the five dimensions, controlling for age and sex (Table 5). Associations between frequency score of Hallucinations, Delusions and Paranoia on the one hand with distress score on the other did not differ from each other (data not shown), but were all higher than the associations between distress score and Grandiosity frequency score (resp. $F(1,874)=216.81$; p<.001; $F(1,874)=164.24$, p<.001 and $F(1,874)=155.95$, p<.001) and the associations between distress score and Paranormal frequency score (resp. $F(1,874)=205.00$; p<.001; $F(1,874)=164.45$, p<.001 and $F(1,874)=157.23$, p<.001). Regression coefficients for Grandiosity and Paranormal beliefs were not significantly different from each other ($F(1,394)=0.16$, p<.69).

Table 4. Mean CAPE item score and CAPE subdimension item scores by age and sex and statistics for differences in item scores by sex and age in HBSC (n=5422).

	Boys					Girls					Age			Sex		
Dimension	12	13	14	15	16	12	13	14	15	16	F	df	p	F	df	p
Hallucinations	0.66 (1.0)	0.43 (0.8)	0.40 (0.4)	0.38 (0.8)	0.35 (0.7)	0.60 (0.9)	0.56 (0.9)	0.53 (0.9)	0.52 (0.9)	0.53 (0.8)	6.10	4	.001	15.62	1	.001
Delusions	1.62 (1.8)	1.54 (1.8)	1.58 (1.9)	1.52 (1.8)	1.52 (1.7)	1.80 (1.9)	1.78 (1.9)	1.74 (1.9)	1.90 (1.9)	2.17 (2.2)	0.99	4	.414	30.68	1	.001
Paranoia	2.44 (1.6)	2.43 (1.5)	2.47 (1.6)	2.71 (1.5)	2.75 (1.5)	2.87 (1.6)	3.07 (1.5)	3.17 (1.4)	3.23 (1.4)	3.46 (1.2)	10.16	4	.001	170.00	1	.001
Grandiosity	0.70 (0.8)	0.63 (0.8)	0.79 (0.8)	0.75 (0.8)	0.78 (0.8)	0.50 (0.7)	0.53 (0.7)	0.54 (0.7)	0.61 (0.8)	0.77 (0.8)	6.45	4	.001	33.34	1	.001
Paranormal	0.50 (0.7)	0.51 (0.7)	0.58 (0.8)	0.57 (0.8)	0.59 (0.8)	0.67 (0.8)	0.71 (0.8)	0.89 (0.8)	0.92 (0.8)	1.01 (0.8)	10.98	4	.001	142.42	1	.001
Any CAPE experience	5.93 (4.3)	5.54 (4.0)	5.83 (4.3)	5.93 (4.1)	5.99 (3.8)	6.44 (4.2)	6.65 (4.1)	6.88 (3.9)	7.18 (4.0)	7.94 (4.1)	4.71	4	.001	84.91	1	.001

Please note that not every subdimension has an equal number of items therefore maximum item scores differ per subdimension.

Table 5. Regression coefficients of association between frequency and distress within dimensions in HBSC (n=5422).

Dimension	β
Hallucinations	0.759*
Delusions	0.643*
Paranoia	0.682*
Grandiosity	0.199*
Paranormal beliefs	0.212*

**p<.001*

Study 2: TRacking Adolescents' Individual Lives Survey (TRAILS).

Methods

Participants TRAILS is a prospective cohort study among adolescents in the general Dutch population, investigating the development of mental and physical health from pre-adolescence into adulthood (de Winter et al., 2005). Three data collection waves have been completed: T1 (2001-2002), T2 (2003-2004) and T3 (2005-2007).

Of all individuals asked to participate in TRAILS (N=2935), 76% agreed to participate at T1 (N=2230; mean age 11.1 years; SD 0.6; 51% girls). Non-responders did not differ from responders in terms of psychopathology or in associations between individual characteristics and psychopathology. More detailed information on the selection procedures and non-response can be found elsewhere (de Winter et al., 2005). T3 was completed with 81% of the original number of participants (N=1816), at a mean age of 16.3 years (SD 0.7), of whom 52% were girls.

Instruments The 20 items of the CAPE positive dimension were used to assess psychotic experiences. Validity of subdimensions representing a continuum of psychopathology was assessed by correlating the dimensions with the subscales Internalizing problems, Externalizing problems and Thought problems of the Youth Self Report (YSR), a screening instrument for youth general psychopathology (Achenbach, 1991). The Thought problems subscale includes items like seeing or hearing things that other people do not see or hear, having thoughts that other people would find strange and being unable to get thoughts out of one's head. Data on both CAPE and YSR were collected at T3.

Statistical Analyses

Model replication and convergent validity An attempt was made to replicate the model observed in Study 1 with CFA and to compare it to four other models reported in the literature. Thus, five competing models were tested: a general 1-factor model, a 3-factor model reported by Yung and colleagues (2006), a 4-factor model described by Stefanis and colleagues (2002), another 4-factor model described by Yung and colleagues (2009) and the 5-factor model that was developed in Study 1. Again, data were ordinal and WLS was used for model estimation (Brown, 2005). Validity of the subdimensions in terms of a continuum of psychopathology was assessed by correlating the dimensions of the extended psychosis phenotype with subscales of the YSR. Correlation coefficients were compared statistically as described by Meng and colleagues (1992).

An age effect was not investigated, because the age range at T3 (15-17 years) was too narrow. Associations between frequency of experiences and distress were assessed similarly as in Study 1.

Results

Descriptives 94% of the participants endorsed at least one CAPE experience at least "sometimes". 39% endorsed at least one experience "often" or "nearly always". The median CAPE item score was 4 experiences (ICR 2-6) and the 90th percentile was 9 experiences. Internal consistency of the positive items was excellent (Cronbach alpha = 0.93).

Model replication Analyses were conducted in Mplus (Muthén & Muthén, 1998-2007). CFA was used to test the five competing models. Several fit indices were compared to see which model fitted best. With the highest CFI and the lowest χ^2 and RMSEA (Table 6), the 5-factor model was superior to the other models. Correlations between factors were comparable with those of Study 1. In Table 7, prevalences of the factors are shown at broad (ever vs never) and narrow (never/sometimes vs often/nearly always) level.

Table 6. Fit indices of the five competing models in TRAILS (n=2230).

	Fit index			
Models with number of factors	χ2	df	CFI	RMSEA
1 factor	829.28	107	0.78	0.064
3 factors	578.63	89	0.85	0.058
4 factors (Stefanis et al., 2004)	632.44	106	0.84	0.055
4 factors (Yung et al., 2009)	590.88	106	0.85	0.053
5 factors	352.28	105	0.92	0.038

Please not that Yung and colleagues (2006) used 18 out of 20 positive CAPE items for the 3 factor model; therefore the df is lower in this model.

Table 7. Broad and narrow prevalence rates of subdimensions in TRAILS (n=2230).

Dimension	Prevalence rate "ever"	Prevalence rate "often"/"almost always"
Hallucinations	13.7	1.8
Delusions	51.3	9.3
Paranoia	89.8	25.5
Grandiosity	40.8	7.7
Paranormal beliefs	46.6	13.3
Any CAPE experience	93.7	38.5

Convergent Validity with General Psychopathology In order to investigate the association between CAPE subdimension item scores and general measures of psychopathology, correlation coefficients were computed with three of the subscales of the YSR (Thought problems, Internalizing problems and Externalizing problems) (Table 8). Substantial correlations were found for Hallucinations, Delusions and Paranoia with Internalizing problems (r=0.49-0.70) and Externalizing problems (r=0.51-0.75) and particularly Thought problems (r=0.80-0.92). Grandiosity and Paranormal beliefs had consistently lower correlation coefficients with Internalizing (r=0.29 and 0.30), Externalizing (r=0.26 and 0.30) and Thought problems (r=0.60 and 0.66).

Within the YSR subscales, a similar pattern was seen. Thought problems was associated more strongly with Paranoia, Delusions and Hallucinations than with Grandiosity (resp. Z=16.02, p<.001; Z=23.63, p<.001 and Z=37.09, p<.001) or Paranormal beliefs (resp. Z=11.85, p<.001; Z=18.52, p<.001 and Z=32.88, p<.001). Similarly, Internalizing problems were associated more strongly with Paranoia, Hallucinations and Delusions than with

Grandiosity (resp. *Z*=23.32, *p*<.001; *Z*=20.32, *p*<.001 and *Z*=12.02, *p*<.001) and Paranormal beliefs (resp. *Z*=23.21, *p*<.001; *Z*=21.34, *p*<.001 and *Z*=10.65, *p*<001). Externalizing problems were also associated more strongly with Paranoia, Hallucinations and Delusions than with Grandiosity (resp. *Z*=28.45, *p*<.001; *Z*=19.93, *p*<001 and *Z*=15.03, *p*<.001) and Paranormal beliefs (resp. *Z*=26.75, *p*<.001; *Z*=17.64, *p*<001 and *Z*=11.51, *p*<.001).

Table 8. Correlations between the five CAPE subdimension item scores and three subscales of the YSR in TRAILS (n=2230).

YSR / CAPE	Hallucinations	Delusions	Paranoia	Grandiosity	Paranormal Beliefs	CAPE item score
Thought problems	0.92* [bcde]	0.85* [acde]	0.80* [abde]	0.60* [abce]	0.66* [abcd]	0.89*
Internalizing problems	0.62* [bcde]	0.49* [acde]	0.70* [abde]	0.29* [abc]	0.30* [abc]	0.59*
Externalizing problems	0.59* [bcde]	0.51* [acde]	0.75* [abde]	0.26* [abc]	0.30* [abc]	0.60*

** p<.01*
[a] Differs from the correlation of this YSR subscale with Hallucinations (*p*<.001)
[b] Differs from the correlation of this YSR subscale with Delusions (*p*<.001)
[c] Differs from the correlation of this YSR subscale with Paranoia (*p*<.001)
[d] Differs from the correlation of this YSR subscale with Grandiosity (*p*<.001)
[e] Differs from the correlation of this YSR subscale with Paranormal beliefs (*p*<.001)

Sex Girls had higher CAPE item scores than boys and similarly displayed higher CAPE subdimensions item scores on all subdimensions, except for Grandiosity, on which boys scored higher (Table 9). The mean CAPE item score and CAPE subdimension item scores are also shown in Table 9.

Table 9. Mean CAPE item score and CAPE subdimension item score by sex and statistics on sex differences in item scores in TRAILS (n=2230).

Dimension	Boys	Girls	Sex		
			F	df	p
Hallucinations	0.15 (0.5)	0.23 (0.6)	8.74	1	.003
Delusions	0.91 (0.5)	1.12 (1.4)	9.40	1	.002
Paranoia	1.91 (1.3)	2.48 (1.3)	80.42	1	.001
Grandiosity	0.62 (0.8)	0.51 (0.7)	10.91	1	.001
Paranormal	0.51 (0.7)	0.82 (0.8)	56.69	1	.001
Any CAPE experience	4.12 (3.1)	5.15 (3.2)	42.65	1	.001

Please note that not every subdimension has an equal number of items therefore maximum item scores differ per subdimension.

Distress Associations between frequency score and distress score were different for the five dimensions, controlling for age and sex (Table 10). Again, associations between frequency score of Hallucinations, Delusions and Paranoia on the one hand with distress score on the other did not differ from each other (data not shown), but were all higher than the associations between distress score and Grandiosity frequency score (resp. F(1,394)=55.99; *p*<.001; F(1,394)=33.40, *p*<.001 and F(1,394)=55.77, *p*<.001) and the association between distress score and Paranormal beliefs frequency score (resp. F(1,394)=93.81, *p*<.001; F(1,394)=46.62, *p*<.001 and F(1,394)=73.87, *p*>.001). Regression coefficients for Grandiosity and Paranormal beliefs were not significantly different from each other (F(1,394)=0.89, *p*<.30).

Table 10. Regression coefficients of association between frequency and distress within dimensions in TRAILS (n=2230).

Dimension	β
Hallucinations	0.625**
Delusions	0.642**
Paranoia	0.689**
Grandiosity	0.143**
Paranormal beliefs	0.094*

***p<.001*
** p<.005*

Discussion

The extended psychosis phenotype can be readily assessed in early adolescence, as the majority of adolescents in two large, independent general population samples (respectively 95% and 94%) endorsed at least one positive psychotic experience at least "sometimes" with medians of respectively 4 and 6 endorsements. In addition, respectively 43% and 39% endorsed at least one experience at the level of "often" or "nearly always". An underlying structure of five different subdimensions was found, labelled Hallucinations, Delusions, Paranoia, Grandiosity and Paranormal Beliefs. Girls reported more experiences than boys, with the exception of Grandiosity; an increase of experiences between the ages of 12 and 16 years was apparent. Of the five subdimensions, Hallucinations, Delusions and Paranoia showed the strongest associations with distress and general measures of youth psychopathology.

Whereas the prevalence of psychotic experiences in the general adult population is quite high (Eaton, Romanosky, Anthony & Nestadt, 1991; Hanssen et al., 2005; Rössler et al., 2007; Stefanis et al., 2002; Tien, 1991), prevalence is even higher during adolescence. Prevalences in the present study are higher than prevalences reported by Yung and colleagues (2009) when examined at the broad level contrasting occurrence of "ever" vs "never". In fact, prevalences at the narrow level of "often"/"nearly always" in the current samples are comparable to the prevalence at the broad level reported by Yung and colleagues (2009). However, the broadly defined prevalence in the current studies match the similarly broadly defined prevalence reported by Yung and colleagues (2006) in a non-psychotic clinical sample of adolescents aged 15 years (N=140), nearly 100% of which reported at least one positive psychotic experience. The broadly defined prevalence in the current studies also matches the prevalence of hallucinatory experiences in an adolescent general population reported by Scott and colleagues (2009). Converging results therefore indicate that positive psychotic experiences are quite common during adolescence, not only in clinical, but also in general population samples.

Several explanations for the finding of high rates can be brought to bear. Adolescents may in general be more self-conscious than adults; this could make them more susceptible to certain (paranoid) thoughts and perceptions (Steinberg, 1999). Furthermore, it is more difficult for adolescents to distinguish between relevant and irrelevant stimuli than it is for adults (Adleman et al., 2002); this could result in extra-sensory perceptions, such as hallucinations.

Given that non-clinical psychotic experiences are so highly prevalent among adolescents, a necessarily weak relationship can be inferred with later psychotic disorder (McGorry et al., 1995). Therefore, the underlying structure of positive experiences was further investigated. A model with five dimensions was found to describe the data best. These dimensions are comparable with those reported by Verdoux and colleagues (1998), who found seven delusional dimensions in a sample aged 19-95 years. Although items on religiosity and apocalyptic ideas were not included in the CAPE and items on hallucinations were not included in the study by Verdoux and colleagues, their remaining dimensions (Persecution, Thought Disturbances, Grandiosity, Paranormal beliefs and feelings of Reference-Guilt) are quite similar to the dimensions analyzed in the current report. Furthermore, the dimensions reported by Stefanis and colleagues (2004) (Paranoia, First

rank symptoms, Hallucinations and Grandiosity), Yung and colleagues (2006) (Bizarre experiences, Persecutory ideas and Magical thinking) and Yung and colleagues (2009) (Bizarre experiences, Perceptual abnormalities, Persecutory ideas and Magical thinking) are also conceptually comparable, the difference being that Paranormal beliefs was not reported by Stefanis and colleagues (2004), whereas Hallucinations and Delusions were grouped into a single dimension and Grandiosity and Paranormal beliefs into another in the study by Yung and colleagues (2006, 2009). These studies together suggest (i) a similar underlying structure of mild positive psychotic experiences across different age groups and (ii) a possible life-long stability of this structure.

Despite the fact that the five dimensions were correlated, the data suggest that it is useful to make a distinction between them. First, correlations between dimensions were substantial, but not perfect (i.e. not all above .80), suggesting partly different underlying mechanisms. Second, prevalences of the dimensions differed strongly, also as a function of gender and age. Third, the association between frequency and distress differed over the dimensions. Fourth, the dimensions correlated differently with screening instruments for general youth psychopathology. Fifth, literature suggests that different dimensions may be related to different risk factors; for example, trauma may be associated with hallucinations (Hammersly et al., 2003) and social stressors with paranoia (Simons et al., 2009). This all suggests that the dimensions truly represent partly different constructs.

Prevalence patterns in the dimensions were similar over the two samples, supporting the robustness of our findings. Experiences of Paranoia were reported the most and Hallucinations the least frequently. Prevalences of Delusions, Grandiosity and Paranormal beliefs were in between, in relatively comparable numbers. These patterns are comparable with those reported by Yung and colleagues (2006) and replicate their findings in a general population sample. The finding that girls reported somewhat more positive experiences than boys (96% versus 93% and 96% versus 91%) and in particular Paranormal beliefs, is in agreement with the literature (Maric et al., 2003; Rössler et al., 2007; Raine, 1992). Boys reported higher levels of Grandiosity, replicating the finding reported by Verdoux and colleagues (1998) in adult men. In line with Fonseca-Pedrero and colleagues (2008), our findings indicate that these sex-specific patterns are already present in an adolescent sample aged 12-16 years. This phenomenon matches the finding that the overall mental health (especially internalising problems) of girls seems to deteriorate over the course of

adolescence: with age, girls report increasing levels of psychological and psychosomatic problems (Vollebergh et al., 2006) and increased sensitivity to stressors (Bouma, Ormel, Verhulst & Oldehinkel., 2008). Thus, the findings agree with the large body of literature suggesting that adolescence may be a more stressful time for girls than for boys. Another explanation, however, may be that the higher level of positive experiences in girls may represent affect-driven changes in salience, secondary to higher rates of mood symptoms in girls (van Rossum et al., 2011). However, since girls do not score higher on every single sub-dimension, affective dysregulation may not account for the entire effect of female sex.

CAPE questions were phrased as "Have you ever…" and thus refer to lifetime cumulative incidence. Therefore, the observed age effects may difficult to interpret, as it is not known at what age the reported experiences occurred. However, it can be inferred that the data indicate that increasing age is associated with increasing level of psychotic experiences: if this were not the case, then 16-year olds would have to have the same level of experiences as 12-year olds, unless highly unlikely scenarios are assumed. The effect of age was observed over a relatively narrow age span of five years, suggesting that cohort effects cannot explain this finding, since five years is too narrow a span to encompass two cohorts. Therefore, the conclusion that levels of mild psychotic experiences indeed increase with age in early adolescence appears to be valid.

It was hypothesized that not all dimensions may be equally predictive of later psychopathology and that this would show as differential associations with distress and general psychopathology (Bak et al., 2005). The present results show that the relation between frequency of experiences and distress associated with the experiences is the strongest for Hallucinations, Delusions and Paranoia. Although Yung and colleagues (2006) found higher correlation coefficients between frequency and distress (likely because they studied a clinical sample), the patterns are again comparable: strong associations with distress were found for Bizarre experiences and Persecutory ideas and a weaker association with Magical thinking. In addition, the five subdimensions correlated differently with several subscales of two general measures of youth psychopathology. Hallucinations, Delusions and Paranoia were associated more strongly with all subscales of both measures than Grandiosity and Paranormal beliefs.

Based on these findings, the five subdimensions may be subdivided into two groups. One group represents the 'core' dimensions of the extended psychosis phenotype, i.e.

Hallucinations, Delusions and Paranoia, tapping into a continuum with more severe psychopathology, given the fact that they are associated more strongly with distress and general psychopathology. Another group represents cognitive experiences of Grandiosity and Paranormal beliefs, which may not form part of the extended psychosis phenotype in its continuity with severe mental illness.

The results should be interpreted in the context of the strengths and limitations of this study. One of the strengths is that the model was developed and replicated in two independent samples with a large number of representative school children. Recruitment and assessment of participants in schools may have had some disadvantages, such as the presence of peers and interviewers. However, this method also has some strong advantages: it is more anonymous, leads to lower non-response and high-risk groups are better represented than in household surveys (Vollebergh et al., 2006). A weakness is that our study did not use clinical interviews for assessment. However, previous studies have shown that mild positive psychotic experiences can be reliably investigated by both self-report and interviews by clinicians, although self-report inevitably will generate more random error (Allardyce et al., 2007). Another problem with self-report is the possibility that adolescents misinterpreted CAPE questions; however, a pilot study suggested that the CAPE is valid to use in an adolescent population and further, research assistants were present at the moment of administration to offer clarification if desired. Finally, the Grandiosity and Paranormal dimension were indexed by only two items each, which may limit their use as distinct psychometric assessment scales and may result in less stable estimates compared to the other factors. Ideally, latent factors should be defined by at least three indicators, to avoid, for example, model underidentification (Brown, 2006). However, the fact that these two dimensions were identified across two different samples, showed good model fit, as well as high factor loadings, supports their validity. Further studies should focus on optimizing assessment of these two dimensions.

3. Replication of the five-dimensional structure of positive psychotic experiences in early adulthood

Wigman, Vollebergh, Jacobs, Wichers, Thiery, Derom & van Os.

Re-submitted for publication (brief report)

Previous work has examined the structure of subclinical positive psychotic experiences. The current study, using Confirmatory Factor Analysis in a general population sample of young adult females, replicated a five-dimensional model, which showed excellent model fit. The results suggest stability of the five-dimensional model across adolescent and young adult life.

Introduction

Systematic review of general population studies suggests that there is continuity and population distribution of positive psychotic experiences that may be conceived as the non-silent behavioral expression of increased liability for psychotic disorder (van Os et al., 2009; Linscott & van Os, 2010). Studies have attempted to examine the underlying structure of positive psychotic experiences, given that different subdimensions may differ in their association with clinical syndromes, and thus in risk of transition to later psychotic disorder (Wigman et al., 2009). Therefore, further elucidation of the underlying structure of the extended psychosis phenotype is clinically relevant.

Several studies indicate that a multidimensional model may best describe the phenotype of positive psychotic experiences. Stefanis and colleagues (2004) reported four subdimensions (Paranoia, First rank symptoms, Hallucinations and Grandiosity and Verdoux and colleagues (1998) suggested seven dimensions of delusional ideation (Persecution, Thought Disturbances, Grandiosity, Paranormal beliefs, Reference-Guilt, Religiosity and Apocalyptic ideas as best representing these experiences in non-ill, adult populations. Furthermore, Yung and colleagues proposed models with three (Bizarre experiences, Persecutory ideas and Magical thinking) (Yung et al., 2006) and four (Bizarre experiences, Perceptual abnormalities, Persecutory ideas and Magical thinking) (Yung et al., 2009) subdimensions in respectively clinical and non-clinical adolescent populations; a modified version of this four-factor model was replicated in both adolescent and young adult populations by Armando and colleagues (2010), in which the Magical thinking factor was replaced by Grandiosity.

Recently, a five-dimensional model describing positive psychotic experiences as measured by the Community Assessment of Psychic Experiences (CAPE) in two general population samples of 12-16 year old adolescents (N=2230, age 15-16 years and N=5422, age 12-16 years) was presented (Wigman et al., 2009). This model distinguished Hallucinations, Delusions, Paranoia, Grandiosity and Paranormal beliefs as distinct dimensions of these experiences. The model was statistically superior to other models reported in the literature (as described above) and differentiated the subdimensions by their distinctive associations with secondary distress and other measures of psychopathology. However, the model needs replication in older populations to investigate its stability across different life phases. Furthermore, previous studies investigated mixed

samples, consisting of both males and females; addressing the dimensional structure of psychotic experiences in males and females separately may also increase our understanding of the subclinical psychosis phenotype. Therefore, the present study attempted to replicate the five-dimensional model in a young adult, female population. Since the five-factor model has already been shown to be the best repersentation of psychotic experiences in adolescents (Wigman et al., 2009), it was tested only, in the current investigation, against the four-factor model of Stefanis and colleagues (2004), which also applied to young adults. Since the model suggested by Armando and colleagues (2010) did not include all items of the CAPE, this model was not included.

Methods

Participants The present female-only sample was recruited for the study of gene-environment interactions in vulnerability for mental disorders as described previously (Derom et al., 2006; Jacobs et al., 2006; Wichers et al., 2007). Being a sub-study of this original study, the present sample consisted only of women. Originally, the sample included 621 subjects (575 twins and 46 of their non-twin sisters). Non-twin sisters, subjects with missing zygosity and subjects who participated without their twin were excluded. The final sample thus consisted of 566 subjects (283 twin pairs, 172 monozygotic and 111 dizygotic), with mean age 27.3 years (SD 7.5; range 18-46), all white and of Belgian origin.

Instrument The Community Assessment of Psychic Experiences (CAPE) positive experiences subscale (20 self-reported items) was used to assess psychotic experiences (Stefanis et al., 2004; Konings et al., 2006; Peters et al., 1999) at three measurements at approximately six monthly intervals. Each item in the CAPE rates two aspects of psychotic experiences: (i) frequency and (ii) associated distress, both rated on a four-point scale of never/not distressed (1); sometimes/a bit distressed (2); often/quite distressed (3); nearly always/very distressed (4). The frequency items showed excellent internal consistency (Cronbach's alpha >0.96 at all three measurement points).

Analyses Analyses were performed with Mplus 5.1 (Muthen & Muthen, 1998-2007). Three Confirmatory Factor Analyses (CFA's) were carried out (separately for T1, T2 and T3) with the 20 positive CAPE frequency items indicating the five factors Hallucinations, Delusions,

Paranoia, Grandiosity and Paranormal beliefs. CAPE items were defined as ordinal and estimation was done with weighted least squares (WLSMV). Analyses were controlled for hierarchical clustering of individuals within twins. Due to the relatively small sample size, categories with less than 10 subjects were merged with the category above (e.g. with only five subjects reporting an experience 'often', these were merged with the subjects that reported this 'sometimes'). This resulted in the deletion of items 9, 18 and 19 at T1 and T3 and of items 18 and 19 at T2. For consistency, item 9 was also deleted at T2.

Several fit indices were used to evaluate model fit. For good model fit, chi-square (χ^2) should be low; Root Mean Square Error of Approximation (*RMSEA*) should be lower than 0.08 or 0.05 and the Comparative Fit Index (*CFI*) higher than 0.90 or 0.95 for acceptable respectively good model fit (Brown, 2006). For comparing the five-factor model to competing models, *ΔCFI* (delta) and *ΔRMSEA* were used. If *ΔCFI*<0.010 and *ΔRMSEA*<0.015, the models do not differ (Chen, 2007).

Results

The five-factor model showed excellent fit at all three measurements (Table 1). Compared to a general one-factor model and the four-factor model by Stefanis and colleagues (2004), the five-factor model was superior to the other models at T2 and T3; at T1, it fitted equally well as the four-factor model. Factor loadings for the five-factor model were good (mean factor loading per factor between 0.616 and 0.892 for all factors at all time points) and comparable over time points. Thus, the five-factor model was the only model that was (one of) the best fitting models at all three time points.

Table 1. Fit indices of the three models (1, 4 and 5 factor models) at T1, T2 and T3.

	T1			T2			T3		
	1 factor	4 factors	**5 factors**	1 factor	4 factors	**5 factors**	1 factor	4 factors	**5 factors**
χ^2	251.70	159.93	**162.83**	240.88	176.36	**124.38**	171.64	146.05	**120.88**
df	119	113	**109**	119	113	**109**	119	113	**109**
p	<.0001	0.0024	**0.0006**	<.0001	0.0001	**0.1489**	0.0011	0.0198	**0.2056**
CFI	0.898	0.946	**0.959**	0.898	0.947	**0.987**	0.958	0.973	**0.990**
RMSEA	0.045	0.033	**0.030**	0.051	0.038	**0.019**	0.032	0.026	**0.016**

Table 2. Prevalences of experiences of the five subdimensions in HBSC (N=5422, age 12-16), TRAILS (N=2230; age 15-16, as reported in Wigman et al., 2009) and the present sample (N=566; age 18-46) at T0.

	Adolescents				*Young adults*	
	HBSC study		*TRAILS study*		*Twin study*	
	"Ever"	"Often/ Almost always	"Ever"	"Often/ Almost always"	"Ever"	"Often/ almost always"
Hallucinations	30.1	6.4	13.7	1.8	4.5	0
Delusions	66.5	11.2	51.3	9.3	28.4	0
Paranoia	89.7	26.4	89.8	25.5	87.4	4.3
Grandiosity	45.8	12.0	40.8	7.7	24.9	0
Paranormal beliefs	48.6	16.2	46.6	13.3	45.9	2.8
Any CAPE experience	94.8	43.3	93.7	38.5	90.0	1.8

Discussion

The five-dimensional model distinguishing Hallucinations, Delusion, Paranoia, Grandiosity and Paranormal beliefs showed excellent model fit in a general population sample of young adult females. This model was the only one model that fitted the data consistently as (one of) the best model(s) at all time points.

The present results not only support the notion that subclinical positive psychotic experiences are best represented by an underlying structure consisting of five subdimensions as found by Wigman and colleagues (2009), but it also suggests that this structure applies to the different life stages of adolescence and (young) adulthood. This is also underlined by the fact that the five-factor model described these experiences well at three consecutive time points. Furthermore, the findings suggest that this model applies to females separately as well as to men and women together.

Although the five-domain factorial structure was sustained at all three time points, some items had to be removed, given that too few respondents reported the endorsement of some experiences at least sometimes. This phenomenon can be understood in terms of data distributional skewness, which in this sample was even more accentuated than in adolescent populations in previous publications (Table 2). The level of skewness most likely can be explained by the fact that (i) the present population is older than the adolescent population in our previous study and (ii) psychotic experiences are strongly age-dependent (Verdoux et al., 1998; Peters et al., 1999; van Os et al., 2009).

A disadvantage of the present study is that analyses were carried out in a twin sample, in which scores of co-twins may be interdependent. However, interdependency of scores was controlled for in analyses. The present study relied on self-reported psychotic experiences. Although self-report inevitable leads to less accurate information, previous research has shown that both self-report and clinical interviews can be considered reliable for the assessment of these types of experiences (Allardyce et al., 2007; Kelleher et al., 2011; Konings et al., 2006).

Confirmation of the fact that positive symptoms of psychosis are clustered along distinct dimensions of experience may feed subsequent research on distinct cognitive and biological underpinnings. Furthermore, future work should address the five-dimensional model in male-only and mixed young adult populations to expand our understanding of the psychosis phenotype.

Part II | Development of the extended psychosis phenotype

4. Evidence for a persistent, environment-dependent and deteriorating subtype of subclinical psychotic experiences: a 6-year longitudinal general population study

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Psychological Medicine

Research suggests that subclinical psychotic experiences during adolescence represent the behavioral expression of liability for psychosis. Little is known, however, about the longitudinal trajectory of liability in general population samples.

Growth mixture modeling was used to examine longitudinal trajectories of self-reported positive psychotic experiences in the Youth Self Report, completed three times over a period of six years by a general population cohort of adolescents aged 10-11 years at baseline (N=2230).

Four groups with distinct developmental trajectories of Low, Decreasing, Increasing and Persistent levels of mild positive psychotic experiences were apparent. The Persistent trajectory was associated strongly with cannabis use, childhood trauma, developmental problems and ethnic minority status, consistently displayed strong associations with factors known to predict transition from subclinical psychotic experience to clinical psychotic disorder (severity of and secondary distress due to psychotic experiences, social and attentional problems and affective dysregulation) as well as with high levels of parental-reported psychotic experiences and use of mental health care at the end of the follow-up period. Progressively weaker associations were apparent for, respectively, the Increasing, Decreasing and Low trajectories.

The results suggest that the outcome of early developmental deviation associated with later expression of psychotic experiences is contingent on the degree of later interaction with environmental risks inducing, first, persistence of psychotic experiences and, second, progression to onset of need for care and service use. Insight into the longitudinal dynamics of risk states in representative samples may contribute to the development of targeted early intervention in psychosis.

Introduction

Meta-analyses of studies reporting rates of psychotic symptoms and experiences in the general population suggest the existence of an extended psychosis phenotype (Linscott & van Os, 2010), representing the behavioural expression of distributed genetic and non-genetic risk for psychotic disorder (van Os et al., 2009). Although the data on the one hand suggest a psychometric 'continuum', there is also evidence for an underlying latent categorical, non-continuous structure of the population (i.e. regardless of the presence of this continuum, the population may still be composed of several subgroups) (Kaymaz & van Os, 2010; Linscott & van Os, 2010).

Psychosis proneness appears to be age-related, peaking in adolescence and decreasing after that period (Verdoux et al., 1998; Peters et al., 1999). High rates of subclinical psychotic experiences have been reported in both clinical (Yung et al., 2006; Altman et al., 1997) and general population samples of adolescents (Wigman et al., 2009; Yung et al., 2009; McGorry et al., 1995). Longitudinal studies in general population samples, using follow-up intervals from six months to eight years, have shown that in most adolescents, psychotic experiences disappear over time and do not persist into adulthood (Wiles et al., 2006; Dominguez et al., 2011; Dhossche et al., 2002; Hanssen et al., 2005).

However, in a minority of adolescents, subclinical psychotic experiences progress to clinical psychotic illness. There is evidence from 2 birth cohorts (Poulton et al., 2000; Welham et al., 2008), 3 general population cohorts (Dominguez et al., 2011; Hanssen et al., 2005; Werbeloff et al., 2009) and other longitudinal work (Chapman et al., 1994) that subclinical psychotic experiences may precede the diagnosis of psychotic disorder and hospital admission for schizophrenia by many years. Suggested moderators in representative population samples of risk for clinical outcome are the severity of psychotic experiences (Hanssen et al., 2005; Poulton et al., 2000; Welham et al., 2008), early social functioning (Werbeloff et al., 2009), the type of coping the person develops (Bak et al., 2003), the degree of persistence of psychotic experiences over time (Dominguez et al., 2011), alterations in development and cognitive ability (Dominguez et al., 2010), the degree of admixture with affective dysregulation (van Rossum et al., 2011), and distress associated with experiences (Bak et al., 2005; Jacobs et al., 2005; Garety et al., 2007). In other words, not just the presence of psychotic experiences per se, but rather the psychopathological,

developmental and psychological context may moderate the likelihood of a clinical outcome (Kaymaz & van Os, 2010).

Much uncertainty remains, however, about how psychosis proneness develops over time in representative general population samples. A longitudinal developmental approach, modeling the trajectories of experiences over time, in relation to the development of health care use, may offer more insight in the time course of psychosis phenotypes, and feed theory on latent subgroups underlying the extended psychosis phenotype (Linscott & van Os, 2010) as well as on possible high-risk approaches targeting these groups (Rössler et al., 2007). For example, Mackie and colleagues (2010) followed 409 adolescents, aged 14 years, with elevated scores on one of four personality risk factors (hopelessness, anxiety-sensitivity, impulsivity and sensation-seeking), for two years and distinguished three distinct trajectories of subclinical psychosis: a Persistent, an Increasing and a Low subgroup. Research is needed to examine whether this approach can be extended to a more representative general adolescent population sample and a longer time span.

The present study addressed two issues. First, the development of subclinical positive psychotic experiences over time in early adolescents from the general population (10-16 years) was investigated by studying growth curves of subclinical psychotic experiences over time. Second, resulting trajectories were examined for differences in (i) relation to need for care and (ii) factors that the previous literature suggests predict transition to clinical psychotic disorder (including affective dysregulation, social functioning, attention, early development, distress, severity and persistence of experiences), (iii) environmental risks associated with clinical psychotic disorder such as urbanicity (March et al., 2008), ethnic minority status (Cantor-Graae & Selten, 2005), early trauma (Read et al., 2005), adolescent cannabis use (Henquet et al., 2005) and (iv) parental report on psychotic experiences over time.

Methods

Sample Adolescents were participants of the TRacking Adolescents' Individual Lives Survey **(**TRAILS), a prospective cohort study among adolescents in the general Dutch population. TRAILS investigates the development of mental and somatic health from pre-adolescence into adulthood. Three data collection waves were completed: T1 (2001-2002), T2 (2003-2004) and T3 (2005-2007). Detailed information on sample and selection procedures can be

found elsewhere (de Winter et al., 2005; Huisman et al., 2008). At T1, 2230 children participated (mean age 11.1 years, SD=0.6; 51% girls). At T2, 96% of these participants (N=2149; mean age 13.6 years, SD=0.5; 51% girls) and at T3, 81% of the original number of participants (N=1816; mean age 16.3 years, SD=0.7; 52% girls) were re-assessed. Mean number of months was 29.5 between T1 and T2 (SD=5.4; range 16.7-48.1) and 32.6 (SD=7.1; range 11.0-53.0) between T2 and T3.

Measures The subscale *Thought Problems* of the Youth Self Report (Achenbach, 1991a) (YSR) and the Child Behaviour Check List (Achenbach, 1991b) (parental report; CBCL) was used at all time points to assess early psychotic experiences. These validated (Verhulst et al., 1997; Verhulst et al., 1997) questionnaires have been developed to assess multiple informant child psychopathology and questions are the same in both variants. Items can be rated as not present (0), sometimes present (1) or very often present (2) in the past six months. Although this subscale is assumed to be tapping into subclinical psychotic experiences (Dhossche et al., 2002; Welham et al., 2008), not all individual items may reflect psychosis. Therefore, this self-report subscale was optimized in a pre-study in an independent sample (N=5422) of 12-16 year old adolescents (ter Bogt et al., 2003). Three items on skin picking, storing up things and sleeping less than other children were excluded based on their low Spearman inter-item correlations with the other items (all <.140 in the total sample and <.100 in the subsample with minimally 1 *Thought Problems* endorsement) (Streiner, 2003), leaving the following nine items: taking one's mind off things (9), thinking about self-harm (18), hearing things that others do not (40), twitching/nervous behaviour (46), repeating certain behaviours (66), seeing things that others do not (70), displaying behaviour that others find strange (84), having ideas that others find strange (85) and sleeping problems (100). Mean inter-item Spearman correlation was now 0.16-0.20 at all time points and thus acceptable. Furthermore, three (one for each measurement point) one-factor Confirmatory Factor Analyses were done to investigate if these nine items together would represent a single dimension. A one-factor model fitted the data well at T1 ($\chi^2(22)=102.08$, $p<.001$; *CFI*=0.966; *RMSEA*=0.040) T2 ($\chi^2(22)=159.82$, $p<.001$; *CFI*=0.926; *RMSEA*=0.056) and T3 ($\chi^2(22)=111.58$, $p<.001$; *CFI*=0.925; *RMSEA*=0.050). Therefore, these nine items were used for both self-report and parental report of *Thought Problems* of respectively the YSR and CBCL.

Further, the sum of all items of three other subscales *Anxiety/Depression* (13 items), *Social problems* (11 items) and *Attention problems* (9 items) of the YSR were also used (as proxies reflecting, respectively, affective dysregulation, social functioning and cognitive functioning); these subscales showed acceptable internal consistency (Cronbach's alpha for all scales on all waves ranged from 0.68-0.83, with the exception of *Social problems* at T3 (alpha 0.64)).

The Community Assessment of Psychic Experiences (CAPE) positive experiences subscale (20 self-reported items) was used to assess psychotic experiences at T3 (Stefanis et al., 2002; Konings et al., 2006). The CAPE is based on the Peters et al Delusions Inventory (Peters et al., 1999) (PDI), modified to also include hallucinatory experiences. Each item in the CAPE rates two aspects of psychotic experiences: (i) frequency and (ii) associated distress, both rated on a four-point scale of never/not distressed (1) to nearly always/very distressed (4). The frequency and distress items together showed good internal consistency (Cronbach's alpha=0.93). The five subdimensions of this positive scale (i.e. Hallucinations (Cronbach's alpha=0.82), Delusions (alpha=0.86), Paranoia (alpha=0.79), Grandiosity (alpha=0.65) and Paranormal beliefs (alpha=0.61)), identified in earlier research and computed as the sum of all frequency items of that specific sub-dimension (Wigman et al., 2009), were used as five continuous outcome measures.

Youth health care use was assessed by parental report. At T1, questions were phrased as (i) "Have you ever consulted (…) relating to the emotional or behavioural problems of your child?", (ii) "What was the age of your child at first contact with this health care professional?". At T2 and T3, health care questions reflected the interval since the last interview. Total health care use was defined as the sum of all health care consultations. Additionally, Total health care use was subsequently split into four categories (as recognised by the Dutch Care Authority): General care, Specialized mental health care, Youth/social care and Informal care (such as self-help group; religious counsellor). The proportion of adolescents that consulted any of these institutions was used in the analyses.

Occurrence of life-events before the age of 11 years was calculated as the sum of moving, hospitalization, sickness or death (of self, family or friends), parental divorce or being at least three months from home by parent report (all yes/no), plus a rating of the number of negative events experienced between (i) 0-5 and (ii) 6-11 years by self-report (scale 0-10). Trauma between 11 and 16 years was based on T2 and T3 assessments and

calculated as the sum-score of the following experiences: victim of violence, gossip, bullying or sexual harassment during the last two years by self-report (all yes/no) at T2 plus two ratings at T3: a rating of the number of negative events children experienced in the last two years by self-report (scale 0-10) and a rating of the stressfulness of the child's life by parent report (scale 0-10). Early development was indexed as the sum of parental report to questions of "Did your child have problems with…." eating, sleeping or concentration during the toddler period and of their child talking/walking late compared to other children and experiencing (all yes/no).

Analysis Analyses were conducted with Mplus 5.1 (Muthen & Muthen, 1998-2007). First, the development of self-reported *Thought Problems* over time (T1, T2 and T3) was analysed with a latent growth model (LGM). LGM is a variant of Structural Equation Modelling, in which two latent growth factors are identified, representing intercept (i.e. initial score) and slope (i.e. change in score over time) (Duncan et al., 1999). Indicators were set to load 1 on the intercept and to load 0 on slope at T1, 1 on slope at T2 and factor loading was freely estimated at T3. Means and variances of intercept and slope were estimated.

In order to evaluate the model, several fit indices were used (Brown, 2006). For good model fit, the χ^2 should be low; the Comparative Fix Index (*CFI*) should be above 0.90 or 0.95 and the Root Mean Square Error of Approximation (*RMSEA*) should be lower than 0.08 or 0.05 for respectively acceptable and good model fit. Full Information Maximum likelihood (FIML) estimation was used for model estimation and, given that data were non-normally distributed, a mean-adjusted χ^2 that is robust to non-normality was calculated (MLR) (Brown, 2006). Subsequently, different growth trajectories were assessed within this general growth model by conducting a Latent Class Analysis (LCA)., which identifies a set of mutually exclusive latent classes that account for the distribution of cases occurring within a cross-tabulation of observed variables (McCutcheon, 1987). Thus, LCA was used here to find the smallest number of classes of individuals with similar developmental trajectories of *Thought Problems*. The number of classes is decided based on several indices. A model with *N* number of classes is chosen if the Akaike Information Criterion (*AIC*) and the Bayesian Information Criterion (*BIC*) are low(est), the entropy (H) is acceptable (>0.80) to good (>0.90) and a model with one extra class is no longer significant according to the LMR-LRT

statistic. Factor loadings and (residual) variances of intercept and slope and their covariance were constrained to be equal for all classes.

Construct validity of the trajectories representing psychosis was assessed by testing for association with the five subdimensions of the CAPE positive symptom frequency dimension, using MANOVA with Trajectory membership as fixed factor and the CAPE subdimension frequency scores as dependent variables. Partial eta squared (η_p^2) was reported as an estimate of effect size (with $0.01<\eta_p^2<0.06$=small, $0.06<\eta_p^2<0.14$= medium and $\eta_p^2>.14$=large effect size).

Second, *Thought Problems* developmental trajectories were examined with respect to health care use, known predictors of clinical transition to psychotic disorder, and known risk factors for clinical psychotic disorder. Six MANOVAs were performed with Trajectory membership as fixed factor and mean levels of (i) anxiety/depression, (ii) social problems, (iii) attentional problems, (iv) parental report of *Thought Problems,* (v) distress scores of the five CAPE subdimensions and (vi) proportion of adolescents that had consulted health care institutions as dependent variables. Using multinomial logistic regression, the following known environmental risk factors for psychotic disorder were examined in relation to the different developmental trajectories: ethnic minority status (Dutch–non-Dutch, self reported), urbanicity (three levels of increasing urbanicity, defined by number of inhabitants), life-events before 11 years and trauma between 11-16 years (both in quintiles), cannabis use before 16 years ever and the amount of cannabis ever used (number of times cannabis was used: never, sometimes and often).

Results

Model development An unspecified growth model was found to describe the data well (i.e. a model in which growth between two adjacent time points is linear, but the overall growth across time points cannot be described by one simple straight line). In this model, the overall shape of growth from T1 over T2 to T3 is allowed to be nonlinear by freely estimating the slope growth parameter of T2 instead of fixing its value in a linear way (i.e., with the value 2). This model, depicted in Figure 1, showed good model fit, with $\chi^2(1)=1.238$; p=.26), a *CFI* of 0.999 and *RMSEA* of 0.010.

General development of Thought Problems *over time* The unstandardized mean intercept was 2.17 (95% CI 2.07, 2.27). The maximum score of the 12-item *Thought Problems* scale is 24, with a clinical cut-off score positioned at a value of 5 (Achenbach, 1991a) (calculated for 9 items, this would be 9/12*5=3.75). The intercept, therefore, was in the lower range of the scale and well below cut-off. The mean slope was significant (p<.001) and negative (unstandardized mean slope of -0.41; 95% CI -0.51, -0.31), indicating that the reported number of *Thought Problems* decreased significantly, but moderately, over time.

Different developmental trajectories Several subsequent LCA's were executed with increasing numbers of classes (Table 1) in order to distinguish distinct developmental trajectories. A model with four classes described the data well, since this model was significant and showed a good entropy value. Furthermore, *AIC* and *BIC* decreased when increasing the number of classes from three to four. Although these values were even lower for a model with five classes, this model was not significantly better than a model with four classes. Average class probabilities were high (0.84-0.94), indicating that participants were correctly assigned to their respective latent classes.

Table 1. Criteria for deciding the number of classes within the repeated measures of *Thought Problems.*

No of classes	H	AIC	BIC	LMR-LRT statistic	LMR-LRT *p*-value
2	0.902	23760	23822	494.245	0.0220
3	0.862	23406	23486	344.399	0.0371
4	0.859	23279	23370	140.363	0.0201
5	0.820	23217	23325	90.391	0.4202

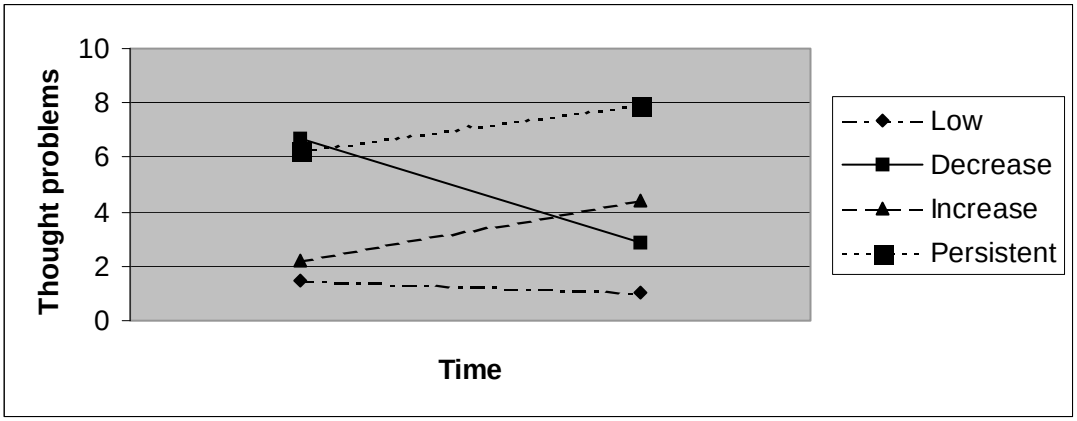
Note: AIC-Akaike Information Criterion; BIC=Bayesian Information Criterion; H= Entropy measure, which can vary between 0 and 1 with higher values indicating clearer discrimination of classes; LMR-LRT= Lo Mendell Rubin Likelihood- Ratio-Test.

The four classes represented different developmental trajectories (Figure 1). The first class with the largest number of participants (N=1804; 82% of the sample) was characterised by a low mean intercept (unstandardized mean intercept=1.44, 95% CI 1.31, 1.57) and a shallow negative slope (unstandardized mean slope -0.28, 95% CI -0.42, -0.15), and labelled the "Low" group. The second class (N=204; 9%) was characterised by a high intercept (unstandardized mean intercept=6.69, 95% CI 6.07, 7.30) and a steep negative slope (unstandardized mean slope=-3.81, 95% CI -4.48, -3.13), i.e. a decrease in *Thought*

Problems over time, described as the "Decreasing" group. The third class (N=163; 7%) was characterized by an average intercept (unstandardized mean intercept=2.20, 95% CI 1.81, 2.62) and a steep positive slope (unstandardized mean slope=2.24, 95% CI 1.66, 2.83), i.e. an increase in *Thought Problems* over time, and was labelled the "Increasing" group. The fourth class (N=41, 2%) was a characterized by a high intercept (unstandardized mean intercept=6.28, 95% CI 4.94, 7.82) and a significant positive slope (unstandardized mean slope= 1.64, 95% CI 0.10, 3.18). This group was called the "Persistent group".

Males and females were not equally distributed over the four classes ($\chi^2(3)=0.004$, $p<.001$). In the Low and Decreasing group, respectively 49 and 51% were girls. In the Increasing group and the Persistent group, respectively 66% and 68% were girls.

Figure 1. Visual representation of mean intercept and mean slope of the four trajectories: Low, Decreasing, Increasing and Persistent levels of *Thought Problems* over time.



Associations with the CAPE frequency and distress scores Class membership was strongly associated with T3 frequency scores of Hallucinations ($F(3,1633)=79.34$, $p<.001$, $\eta_p^2=0.13$), Delusions ($F(3,1633)=49.59$, $p<.001$, $\eta_p^2=0.08$), Paranoia ($F(3,1633)=74.95$, $p<.001$, $\eta_p^2=0.12$), Grandiosity ($F(3,1633)=19.37$, $p<.001$, $\eta_p^2=0.03$), and Paranormal beliefs ($F(3,1633)=31.36$, $p<.001$, $\eta_p^2=0.05$). A dose-response pattern was found: the Persistent group scored highest, followed respectively by the Increasing group, the Decreasing group and the Low group on all sub-dimensions.

CAPE distress associated with psychotic experiences was only assessed in participants who reported any psychotic experiences. Of those participants, 15% of the Low group had experienced any level of associated distress. In the Decreasing group this was 23%, whereas in the Increasing and in the Persistent group the proportions were 45% and

51% respectively. Class membership was significantly associated with the distress scores of Hallucinations ($F(3,416)=22.27$, $p<.001$, $\eta_p^2=0.14$), Delusions ($F(3,416)=23.06$, $p<.001$, $\eta_p^2=0.14$), Paranoia ($F(3,416)=35.13$, $p<.001$, $\eta_p^2=0.20$), Grandiosity ($F(3,416)=15.75$, $p<.001$, $\eta_p^2=0.10$), and Paranormal beliefs ($F(3,416)=6.35$, $p=.001$, $\eta_p^2=0.04$). Again, a dose-response pattern was found (Table 2).

Table 2. Associations between membership of the four groups (i.e. Low, Decreasing, Increasing and Persistent *Thought Problems* group) and CAPE mean (SD) frequency and mean (SD) distress scores, per subdimension and per group.

	Mean freq. score	SD	Mean distress score	SD
Hallucinations				
Low group	3.13[a]	0.48	3.58[a]	1.03
Decreasing group	3.25[a]	0.64	3.68[a]	1.09
Increasing group	3.71[b]	1.17	4.41[b]	1.43
Persistent group	4.52[c]	1.53	5.33[c]	1.77
Delusions				
Low group	8.96[a]	1.42	10.39[a]	3.17
Decreasing group	9.48[b]	1.80	11.34[a]	3.21
Increasing group	10.35[c]	2.67	12.96[b]	3.60
Persistent group	11.28[d]	2.52	15.14[c]	3.41
Paranoia				
Low group	7.34[a]	1.56	8.15[a]	2.37
Decreasing group	7.99[b]	1.71	8.60[a]	2.38
Increasing group	9.04[c]	1.84	10.48[b]	2.15
Persistent group	10.17[d]	2.04	12.24[c]	2.36
Grandiosity				
Low group	2.60[a]	0.92	2.58[a]	0.94
Decreasing group	2.94[b]	1.25	2.68[a,b]	1.02
Increasing group	3.05[b]	1.34	3.10[b]	1.12
Persistent group	3.55[b]	1.74	2.95[c]	1.60
Paranormal beliefs				
Low group	2.80[a]	1.16	2.53[a]	0.91
Decreasing group	3.10[b]	1.41	2.70[a,b]	1.04
Increasing group	2.52[c]	1.59	2.97[b]	1.08
Persistent group	4.52[d]	2.11	3.19[b]	1.21

Note: Different superscript letters refer to significant differences (p<.05) of mean scores between groups within subdimensions: if two subdimension scores are labelled with the same letter (e.g. 'a'), the scores of this subdimension do not differ between these two groups. If two scores are labelled with different letters, these scores differ.

Associations with use of health care The four trajectories did not differ in mean age of first contact with Total health care (F(3,887)=1.12, p=.34), use of Total mental health care or any of the four subcategories of care, except for mental health care at T3 (F(3,187)=2.80, p=.041): here the Persistent group reported significantly more use of mental health care than the other groups. Furthermore, non-significant consistent trends were seen: the Persistent group consistently reported the highest level of use of care, followed by the Increasing, the Decreasing and the Low group.

Associations with factors associated with transition to clinical psychotic disorder The four trajectory groups differed in mean level of Anxiety/depression at T1 (F(3,1617)=101.63, p<.001), T2 (F(3,1617)=82.02, p<.001), and T3 (F(3,1617)=122.49, p<.001). Similarly, they differed in mean level of Social problems at T1 (F(3,1617)=84.83, p<.001), T2 (F(3,1617)=75.35, p<.001), and T3 (F(3,1617)=92.47, p<.001) as well as in mean level of Attentional problems at T1 (F(3,1617)=71.41, p<.001), T2 (F(3,1617)=67.94, p<.001), and T3 (F(3,1617)=73.63, p<.001) (Table 3). The comparison of post-hoc contrasts showed that trajectory groups differed from each other at all time points, with the Persistent group consistently showing the highest scores on all dimensions by T3.

Parental report The four trajectories differed in mean level of *Thought problems* reported by parents at T1 (F(3,1113)=6.19, p<.001), T2 (F(3,1113)=11.86, p<.001) and T3 F(3,1113)=24.66, p<.001). Parents of the Persistent group reported the highest levels of Thought Problems in their offspring at all measurements, followed by the Increasing group, the Decreasing group and the Low group (Table 3).

Known risk factors for psychotic disorder Persistent group membership was associated significantly with ethnic minority group status (Table 4). Urbanicity was not consistently associated with belonging to the four groups, although a non-significant trend was seen. Cannabis use before age 16 significantly predicted Decreasing or Increasing group membership, but not Persistent group membership. The amount of cannabis ever used predicted, in a dose-response fashion, increasing or persistent levels of *Thought Problems* over time. Developmental problems, life-events before age 16 years and exposure to

trauma between ages 11-16 years all significantly predicted Decreasing, Increasing or Persistent group membership in a dose-response fashion.

Table 3. Mean (SD) Youth Self Report subscale scale scores of Anxiety/depression, Social problems, Attentional problems and parental report of Child Behavior Check List *Thought Problems* of the four groups (i.e. Low, Decreasing, Increasing and Persistent *Thought Problems* group) at T1, T2 and T3.

	T1	T2	T3
Anxiety/depression			
Low group	0.28 (0.24)[a]	0.28 (0.30)[a]	0.24 (0.25)[a]
Decreasing	0.62 (0.33)[b]	0.46 (0.32)[b]	0.35 (0.25)[b]
Increasing	0.38 (0.26)[c]	0.49 (0.31)[b]	0.56 (0.35)[c]
Persistent	0.65 (0.25)[b]	0.89 (0.45)[c]	0.95 (0.42)[d]
Total	*0.33 (0.27)*	*0.32 (0.30)*	*0.29 (0.29)*
Social problems			
Low group	0.33 (0.27)[a]	0.27 (0.22)[a]	0.23 (0.19)[a]
Decreasing	0.63 (0.29)[b]	0.44 (0.26)[b]	0.33 (0.21)[b]
Increasing	0.45 (0.30)[c]	0.45 (0.27)[b]	0.44 (0.24)[c]
Persistent	0.63 (0.23)[b]	0.72 (0.36)[c]	0.68 (0.35)[d]
Total	*0.37 (0.27)*	*0.31 (0.25)*	*0.27 (0.22)*
Attentional problems			
Low group	0.44 (0.28)[a]	0.51 (0.31)[a]	0.54 (0.32)[a]
Decreasing	0.76 (0.29)[b]	0.71 (0.31)[b]	0.72 (0.33)[b]
Increasing	0.54 (0.28)[c]	0.77 (0.31)[b]	0.85 (0.32)[c]
Persistent	0.79 (0.29)[b]	1.08 (0.35)[c]	1.09 (0.37)[d]
Total	*0.49 (0.30)*	*0.56 (0.33)*	*0.59 (0.33)*
Parental report of Thought problems			
Low group	0.86 (1.43)[a]	0.52 (1.05)[a]	0.41 (0.90)[a]
Decreasing	1.23 (1.99)[a,b]	0.90 (1.58)[b]	0.68 (1.30)[a]
Increasing	1.19 (1.67)[a,b]	1.21 (1.73)[b]	1.36 (2.28)[b]
Persistent	2.07 (2.12)[b]	1.20 (1.21)[b]	1.80 (2.21)[b]
Total	*0.93 (1.43)*	*0.62 (1.19)*	*0.52 (1.14)*

Note: Different superscript letters refer to significant differences (p<.05) of mean scores between groups within subdimensions: if two subdimension scores are labelled with the same letter (e.g. 'a'), the scores of this subdimension do not differ between these two groups. If two scores are labelled with different letters, these scores differ.

Next pages:

Table 4. OR's for Decreasing, Increasing and Persistent group with increasing load of risk factors with Low group as reference group.

Notes [1] Reference category; OR = Odds Ratio; CI = Confidence Interval; Risk factor levels are constructed as described in text; OR linear trend is the summary increase in risk with one unit change in risk factor. **p*<.05; ***p*<.01; ****p*<.001.

Risk factor	N total (%)	N (%) in Low group	N (%) in Decreasing group	N (%) in Increasing group	N (%) in Persistent group	Decreasing versus Low TP Group OR (95% CI)	Increasing versus Low TP Group OR (95% CI)	Persistent versus Low TP Group OR (95% CI)
Ethnicity								
Dutch	1928 (86%)	1581 (88%)	170 (83%)	135 (83%)	28 (68%)	1	1	1
Non-Dutch	302 (14%)	223 (12%)	34 (17%)	28 (17%)	13 (32%)	1.41 (0.96-2.10)	1.47 (0.96-2.26)	3.29 (1.68-6.45)***
Urbanicity								
Level 1 (lowest)	220 (10%)	186 (10%)	12 (6%)	14 (8%)	4 (10%)	1	1	1
Level 2	619 (28%)	491 (27%)	71 (34%)	44 (27%)	11 (27%)	3.65 (1.54-8.66)**	0.91 (0.44-1.89)	1.80 (0.21-15.52)
Level 3 (highest)	1391 (62%)	1127 (63%)	121 (60%)	105 (65%)	26 (63%)	2.24 (0.96-5.26)	1.07 (0.55-2.08)	3.37 (0.45-25.31)
OR Linear trend						*0.99 (0.77-1.28)*	*1.08 (0.80-1.46)*	*1.88 (0.89-3.99)*
Cannabis use before age of 16								
Never	1160 (70%)	957 (72%)	99 (63%)	75 (56%)	18 (62%)	1	1	1
Ever	490 (30%)	373 (28%)	59 (37%)	58 (44%)	11 (38%)	1.53 (1.09-2.16)*	1.98 (1.38-2.85)***	1.57 (0.73-3.35)
Frequency of use cannabis ever								
Never	1160 (70%)	962 (76%)	104 (69%)	78 (63%)	16 (57%)	1	1	1
Sometimes	321 (20%)	239 (19%)	35 (23%)	38 (30%)	9 (32%)	1.35(0.90-2.04)	1.96 (1.30-2.96)***	2.26 (0.99-5.19)
Often	93 (6%)	69 (5%)	12 (8%)	9 (7%)	3 (11%)	1.61 (0.84-3.07)	1.61 (0.77-3.34)	2.61 (0.74-9.19)
OR Linear trend						*1.30 (0.99-1.71)*	*1.49(1.13-1.98)**	*1.80 (1.06-3.05)**

Risk factor	N total (%)	N (%) in Low group	N (%) in Decreasing group	N (%) in Increasing group	N (%) in Persistent group	Decreasing versus Low TP Group OR (95% CI)	Increasing versus Low TP Group OR (95% CI)	Persistent versus Low TP Group OR (95% CI)
Developmental problems								
Level 1 (lowest)	812 (37%)	694 (39%)	61 (30%)	45 (29%)	7 (18%)	[1]	[1]	[1]
Level 2 and 3	543 (25%)	444 (25%)	41 (20%)	44 (28%)	10 (25%)	1.05 (0.69-1.59)	1.53 (0.99-2.35)	2.23 (0.84-5.91)
Level 4	588 (27%)	458 (26%)	70 (34%)	39 (25%)	16 (40%)	1.74 (1.21-2.50)**	1.31 (0.84-2.05)	3.46 (1.41-8.48)**
Level 5 (highest)	244 (11%)	173 (10%)	32 (16%)	29 (18%)	7 (17%)	2.10 (1.33-3.33)***	2.59 (1.58-4.24)***	4.01 (1.39-11.59)**
OR Linear trend						*1.22 (1.10-1.34)****	*1.17 (1.05-1.30)***	*1.38 (1.12-1.70)****
Life-events before age 11								
Level 1 (lowest)	620 (28%)	545 (30%)	26 (13%)	35 (22%)	6 (15%)	[1]	[1]	[1]
Level 2	420 (19%)	357 (20%)	35 (17%)	22 (14%)	2 (5%)	2.06 (1.22-3.47)**	0.96 (0.55-1.66)	0.51 (0.10-2.53)
Level 3	339 (15%)	278 (16%)	35 (17%)	22 (14%)	4 (7%)	2.64 (1.56-4.47)***	1.23 (0.71-2.14)	0.98 (0.24-3.94)
Level 4	413 (19%)	319 (18%)	46 (23%)	38 (24%)	9 (22%)	3.02 (1.83-4.99)***	1.86 (1.14-3.00)*	2.56 (0.90-7.27)
Level 5 (highest)	426 (19%)	297 (16%)	62 (30%)	44 (26%)	21 (51%)	4.38 (2.71-7.07)***	2.31 (1.45-3.68)***	6.42 (2.56-16.09)***
OR Linear trend						*1.37 (1.25-1.53)****	*1.26(1.13-1.40)****	*1.80 (1.41-2.29)****
Trauma between 11-16								
Level 1 (lowest)	492 (23%)	445 (26%)	26 (13%)	18 (11%)	3 (7%)	[1]	[1]	[1]
Level 2	580 (27%)	506 (30%)	36 (19%)	31 (19%)	6 (15%)	1.22 (0.72-2.05)	1.51 (0.84-2.74)	1.76 (0.44-7.07)
Level 3	565 (27%)	445 (26%)	62 (32%)	47 (29%)	8 (20%)	2.38 (1.48-3.84)***	2.61 (1.49-4.57)***	2.67 (0.70-10.11)
Level 4	327 (15%)	228 (13%)	50 (25%)	36 (22%)	13 (32%)	3.75 (2.28-6.19)***	3.90 (2.17-7.03)***	8.46 (2.39-29.98)***
Level 5 (highest)	157 (8%)	94 (5%)	21(11%)	31 (19%)	11 (27%)	3.82 (2.06-7.08)***	8.15 (4.38-15.19)***	17.36 (4.75-63.43)***
OR Linear trend						*1.50 (1/33-1.70)****	*1.68 (1.47-1.92)****	*2.18 (1.66-2.85)****

Discussion

The present study was, to our knowledge, the first that investigated developmental trajectories of mild positive psychotic experiences in a large, representative general population sample of adolescents, followed from age 10 to age 16 years. Four distinct developmental trajectories of *Thought Problems* over time were distinguished, labeled Low, Decreasing, Increasing and Persistent groups. The results suggest that both the Increasing and particularly the Persistent group represent the most important developmental patterns from a clinical and high-risk perspective, as these trajectories display persistent expression of subclinical psychosis, have the strongest associations with factors known to predict transition to clinical psychotic disorder, including the highest levels of severity of and secondary distress associated with psychotic experiences, the highest level of social problems, increasing levels of attentional problems and affective dysregulation, and a pattern of association with environmental risks that predict onset of clinical psychotic disorder. Furthermore, parental report of *Thought Problems* in the adolescents was consistently highest for these two groups, indicating higher levels of observable psychotic experiences and supporting the validity of the self-report measure of psychotic experiences. Of these two groups, the Persistent group seems the most relevant from a high-risk perspective. Although little significant differences were found for use of health care, the Persistent group displayed a clear trend of using more health care and in fact used more mental health care at the end of the follow-up period. A trend towards dose-response was found for almost all measurements of psychopathology, the Persistent group scoring highest, followed by, in order of decreasing strength of association, the Increasing, the Decreasing and the Low groups.

Expression of psychotic experiences over time is dynamic

Earlier studies have suggested that cross-sectional measurements of subclinical psychotic experiences may not be useful as a specific risk factor for later clinical psychotic outcomes (Correll et al., 2005), in part because they are so common (Yung et al., 2009). Furthermore, results are inconsistent regarding the question whether psychotic experiences have a specific (Poulton et al., 2000) or a more general (Dhosssche et al., 2002) predictive value for later psychopathology. The current results, in agreement with the findings of Mackie and colleagues (2010), suggest that for the purpose of creating subgroups enriched

in risk, a focus on dynamic trajectories of psychotic experiences over time may be more useful than creating categories based on cross-sectional information. Both genetic and environmental effects on psychiatric phenotypes are developmentally dynamic during the adolescent phase, with evidence for both innovation (new effects "coming on line") and attenuation (reduction in the influence of effects over time) (Kendler et al., 2008). Indeed, evidence suggests that the expression of subclinical psychotic experiences peaks during adolescence/young adulthood and then declines over the life course (Verdoux et al., 1998). The current study confirmed this pattern for the adolescent life phase by demonstrating that for the majority of the adolescent population the rate of psychotic experiences decreased over time. A small group of adolescents, however, showed a contrasting pattern of an increase or persistence in their level of psychotic experiences over time. The Persistent group may represent individuals on a neurodevelopmental pathway to psychosis (Murray & Lewis, 1987; Weinberger, 1987), since these participants consistently reported high levels of *Thought problems* and other pathology post-baseline, whereas the Increasing group may represent an affective pathway to psychosis, thought to be more reactive to environmental risk factors (Myin-Germeys & van Os, 2007). The existence of both an Increasing and a Decreasing group further illustrates the dynamics of subclinical psychosis in adolescence and suggests that protective factors may operate in addition to those that increase risk.

Persistence of psychotic experiences

Recent studies indicate that environmental risk factors may cause persistence of subclinical psychotic experiences in some individuals (Cougnard et al., 2007), and that greater levels of persistence in turn predict greater risk of transition to clinical psychotic disorder (Dominguez, 2011). Persistence of psychotic experiences may be related to an underlying process of dopamine sensitization, associated with repeated exposure to environmental risk factors acting on a final common pathway (Boileau et al., 2006; Collip et al., 2008; van Winkel et al., 2008). Only the Persistent developmental trajectory was consistently associated with many factors that predict or are associated with transition to clinical psychosis. Given the fact that the Decreasing and the Increasing trajectories were similarly but less strongly associated with developmental problems and stressful/traumatic events, the results suggest that early developmental vulnerability associated with later psychotic disorder may only become expressed in combination with additional exposure to

multiple environmental risks giving rise, first, to persistence of psychotic experiences, followed by onset of need for care and health care use, in agreement with evidence from other longitudinal work in representative population samples (Dominguez et al., 2010, 2011; Cougnard et al., 2007).

The finding that parental report of *Thought Problems* in adolescents was lower than adolescent self-report is in line with earlier work (Laurens et al., 2007). In addition, earlier studies have found that particularly parental reports of persisting symptoms are predictive of later psychotic pathology (Welham et al., 2008; Scott et al., 2009), in line with the current finding that the groups most at risk more often were described by their parents as having persistent psychotic experiences.

Environmental risk factors and their interactions with early developmental vulnerability may thus represent a useful focus for early intervention and prevention, since these determine the probability of a persisting and even deteriorating trajectory over time. Definition of risk based on cross-sectional information may be less suitable, given the risk of stigma and labeling (van Zelst, 2009) on the basis of a state that most likely represents a transitory experience over time and shows dynamic patterns. While acknowledging the risk of stigma and labeling, the data nevertheless support the idea of following children with (psychotic) problems for a longer period of time, assessing a broader range of psychopathology, as well as the possibility to target interventions based on certain environmental exposures (Bak et al., 2003). The Persistent group, considered at highest risk for clinical outcome, may represent the target group for early intervention; the Increasing group, considered at high risk for psychosis, may represent the target group for prevention.

Methodological issues

The results should be interpreted in the context of the strengths and limitations of this study. The major strength is that, to our knowledge, this is the first study that assesses the longitudinal development of individual experiences over time with growth modeling in a large, representative adolescent general population sample, addressing multiple domains of psychopathology as well as clinically relevant measures. Given that the more pathological groups were small, they would have been overlooked when analyzed at the level of the group as a whole.

The most important limitation is that the study only covered the age range of 10-16 years and did not cover the full critical age for psychosis and transition to psychotic disorder, nor did it use clinical interview to assess transition to formally defined psychotic disorder. Another important issue is the fact that the *Thought problems* subscale measures a broader range of psychopathology and does not *specifically* target psychotic symptoms. However, the trajectories can be assumed to represent subclinical psychotic experiences, as suggested by associations with the CAPE frequency scores, a validated instrument for the assessment of psychotic experiences (Konings et al., 2006). The largest differences in CAPE scores between the trajectories can be found in the dimensions of Hallucinations, Delusions and Paranoia, which previous work suggests are the dimensions with the greatest potential clinical impact (Wigman et al., 2009). Furthermore, η_p^2 was high particularly for these subdimensions, suggesting that the variance in these (psychotic) dimensions can be explained for a large part by development of *Thought Problems*. Further validation comes from the fact that membership of the Decreasing, the Increasing and particularly the Persistent group was associated with several known risk factors for psychotic disorder and symptoms. Another limitation is that only anxious/depressed, and not manic or negative symptoms were assessed. Social problems and attentional problems were chosen as representing respectively developmental social and neurocognitive measures; however, these measures are imprecise and an approximation at best. The choice for the *Attentional problems* scale of the YSR as representing attentional dysfunction follows earlier research (Welham et al., 2010); we extended this approach by selecting the *Social problems* scale as representing developmental social functioning. Although measures of health care use were available as an indicator of clinical outcome, the exact reason for consulting health care institutions was not known. Distinguishing several subgroups in a sample with LCA should not directly be seen as an indicator that the population consists of several subgroups (Bauer & Curan, 2003). More research is needed, to investigate if these subgroups truly represent the class-like heterogeneity in the population they suggest. The finding that the present four trajectories are differentially related to several known risk factors for psychosis and other measures of psychopathology may be considered a valid starting point; more research is needed, however, to expand these findings to other risk factors, both environmentally and genetically. Finally, measures of psychopathology in the present study were based entirely on self-report questionnaires. Self-report inevitably will lead to less accurate information;

however, previous studies have shown that both self-report and clinical interviews represent a reliable method to assess mild psychotic experiences (Allardyce et al., 2007; Kelleher et al., 2011). Further research may extend the present study by investigating dynamic patterns of expression of psychotic experiences in a psychometrically more rigorous manner and by investigating which risk and protective factors play a role in the longitudinal development of psychotic experiences.

5. The relationship between coping and subclinical psychotic experiences in adolescents from the general population – a longitudinal study

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Subclinical psychotic experiences during adolescence may represent liability for developing psychotic disorder. Both coping style and the degree of persistence of psychotic experiences may play a role in progression to clinical psychotic disorder, but little is known about the causal relationship between the two.

Path modeling was used to examine longitudinal relationships between subclinical positive psychotic experiences, and three styles of coping (Task-, Emotion- and Avoidance-oriented) in an adolescent general population sample (*N*=875) assessed three times in three years. Distinct developmental trajectories of psychotic experiences, identified with growth mixture modeling, were compared on use of these coping styles.

Over time, Emotion-oriented coping in general was bi-directionally related to psychotic experiences. No meaningful results were found for Task- or Avoidance-oriented coping. Females reported using a wider range of coping styles than males, but the paths between coping and psychotic experiences did not differ by gender. Persistence of psychotic experiences was associated with greater use of Emotion-oriented coping, whereas a decrease in experiences over time was associated with increased use of Task-orientated coping.

Emotion-oriented coping is the most important coping style in relation to psychotic experiences, as it may contribute to a “vicious cycle” and is associated with persistence of experiences. In addition, more Task-oriented coping may result in a decrease in psychotic experiences. Results suggest that opportunities for intervention may already be present at the level of subclinical psychosis.

Introduction

Subclinical psychotic experiences are common in the general population, implying a continuum of the psychosis phenotype (Johns & van Os, 2001; Scott et al., 2006; van Os et al., 2009, Yung et al., 2009; Nuevo et al., 2010). While most experiences are transient and resolve spontaneously (Dhossche et al., 2002; Hanssen et al., 2005; Wiles et al., 2006; Dominguez et al., 2011), a small proportion of individuals with mild psychotic experiences will progress to psychotic disorder (Poulton et al., 2000). Low-level delusional thinking and mild hallucinations often precede clinical disorder (e.g. Yung & McGorry, 1996; Poulton et al., 2000; Welham et al., 2008), particularly when persistent (Dominguez et al., 2011). During adolescence, when psychosis proneness is at its peak (Verdoux et al., 1998), subtle psychotic experiences are frequently reported (Yung et al., 2009; Wigman et al., 2009).

A suggested paradigm for understanding the development of psychosis is the *proneness – persistence – impairment model*. This model proposes that transition from subclinical psychosis to clinical disorder is preceded by the persistence of these subtle psychotic experiences and accompanied by progressive impairment, depending on additional psychopathological, developmental and psychological factors which lead to (i) persistence of these experiences and (ii) need for care (Cougnard et al., 2007; van Os et al., 2009). Focus on the development of subclinical psychotic symptoms over time, rather than on cross-sectional and possibly transient psychotic experiences, may be useful in distinguishing true underlying vulnerability to schizophrenia from incidental, benign experiences or clinical "noise" around a non-psychotic disorder (Nelson & Yung, 2009; Yung et al., 2009). Previous studies have found that persistence of subclinical psychotic experiences in general population samples is associated with poor outcome, such as diagnosis of psychotic disorder (Dominguez et al., 2011), poor social functioning (Rössler et al., 2007), high levels of depression (Mackie et al., 2010; Wigman et al., 2011d) or negative symptoms (Dominguez et al., 2010) and greater use of health care (Wigman et al., 2011d).

Coping style may play a role in shifts along the extended psychosis continuum, i.e. in persistence and possible development of clinical psychotic disorder (Krabbendam et al., 2005; Philips et al., 2009). Coping has been defined in a number of ways, one distinction being between Task-oriented coping (e.g. talking to someone, actively looking for a solution), Emotion-oriented coping (e.g. worry, self blame) and Avoidance-oriented coping

(e.g. distraction, social diversion) styles (Endler & Parker, 1990). In general, task-focussed coping is more adaptive in dealing with psychotic symptoms and daily stressors than emotionally-driven coping (Phillips et al., 2009). Such adaptive coping is related to feelings of control and higher levels of functioning (Bak et al., 2003; Krabbendam et al., 2005). Coping is related to psychotic symptoms at all levels of the extended psychosis continuum: non-adaptive coping is associated with poor outcome in chronic schizophrenia populations (Ritsner et al., 2003), first episode (Boschi et al., 2000; Thompson et al., 2003) and ultra-high risk for psychosis (Ruhrmann et al., 2008) samples, and within the general population (Schuldberg et al., 1996; Bak et al., 2003; Krabbendam et al., 2005; Dangelmaier et al., 2006).

Gender differences in coping with psychotic symptoms have been identified, but findings are inconsistent. Some studies show no differences between genders (Boschi et al., 2000; Dangelmaier et al., 2006; Modestin et al., 2009), whereas others report that females use more adaptive coping strategies than their male counterparts (Thompson et al., 2003).

To date, most research on coping and psychosis has been cross-sectional. This is a limitation, as it does not allow causal inferences to be drawn on the relationship between the two. To better identify individuals at highest risk of developing a psychotic disorder, longitudinal data is necessary to clarify the mechanisms that might be associated with the persistence of subclinical psychotic experiences and possible transition to psychotic disorder.

Investigating different coping styles in relation to developmental trajectories of subclinical psychotic experiences may inform possible preventive interventions, since coping with psychotic symptoms has been shown to be modifiable through psychotherapy (Farhall et al., 2007). Given that intervention may be most beneficial when applied before the onset of psychotic disorder (Mrazek & Haggerty, 1994; McGorry et al., 2006), the rationale for understanding the relationships between subclinical psychotic experiences and coping is evident.

The present study investigated the relationship between subclinical positive psychotic experiences and coping styles (Emotion-, Task- and Avoidance-oriented) over three years in a large adolescent general population cohort. First, the associations between subclinical positive psychotic experiences and different coping styles over time were

assessed bi-directionally. Second, distinct developmental trajectories of subclinical psychotic experiences were identified and compared on measures of general psychopathology. Third, the mean use of different coping styles was compared across each trajectory. Since higher levels of psychopathological problems are associated with the use of more coping styles in general (Escher et al., 2003), the proportional use of each coping style was also investigated.

It was hypothesized: (i) that the increased use of Emotion- and Avoidance-oriented coping would be longitudinally associated with higher levels of subclinical positive psychotic experiences, (ii) increasing or persistent trajectories of psychotic experiences would be associated with higher levels of psychopathology and lower functioning, and with (iii) more use of Emotion- and Avoidance-oriented, and less Task-oriented coping.

Methods

Participants Participants were recruited through secondary schools in Western Metropolitan Melbourne, Australia. Sixty secondary schools were approached and 34 consented (20 government, five Catholic and nine independent schools). Three data collection waves were completed: T1 (baseline), N=881; T2 (12 months after baseline assessment), N=652 (74% of original cohort); and T3 (three years after baseline assessment), N=512 (58% of original cohort). At baseline, 51% of the sample was female. Mean age was 15.6 (SD 2.6) years.

Procedure At T1, students were assessed via questionnaire during one study period. Trained research assistants were present to answer queries. All participants provided written informed consent and assent from their parent/guardian. The second wave of data collection (T2) was conducted 12 months later. This assessment comprised semi-structured interview and questionnaires. Written consent was again obtained from participants and from their parent/guardian if they were still under age 18. This process was repeated three years after baseline (T3). The study was approved by Research and Ethics Committees at the University of Melbourne, Victorian Department of Education and Catholic Education Office.

Instruments The Community Assessment of Psychic Experiences (CAPE) positive experiences subscale (20 self-reported items) was used to assess psychotic experiences in all study phases (Stefanis et al., 2002; Konings et al., 2006). Each item rates two aspects of psychotic

experiences (frequency and associated distress), on a four-point scale of never/not distressed (1) to nearly always/very distressed (4). The 20 frequency items showed good internal consistency at all time points (Cronbach's alpha=0.82 to 0.85). Sum score was used as continuous indicators of subclinical positive psychotic experiences. The number of participants with CAPE data at any assessment was N=875.

Coping styles were assessed using the adolescent version of the Coping Inventory for Stressful Situations (CISS) (Endler & Parker, 1990). Three different coping styles were assessed on a five-point scale of not at all (1) to very much (5). Task-oriented coping refers to purposeful efforts aimed at solving the problem, cognitively or physically. Emotion-oriented coping describes self-oriented emotional reactions, self-preoccupation and fantasizing. Avoidance-oriented coping refers to activities and cognitive changes intended to avoid the situation (Endler & Parker, 1990). Scores for each coping style were calculated as the sum of item scores per style at each time point. Proportional use of each coping style was calculated from the total amount of all coping styles used by the individual at each time point. Internal consistency of the CISS was good at all assessments (Cronbach's alpha=0.88 to 0.91).

The Centre for Epidemiologic Studies Depression Scale (CES-D) assessed self-reported depressive symptomatology over the past week (Radloff, 1977). The CES-D consists of 20 self-report items rating frequency of depressive symptoms. General mental health was measured using the General Health Questionnaire-12 (GHQ-12), a 12-item self-report screen for psychological strain in the general population (Goldberg & Williams, 1988). The Revised Multidimensional Assessment of Functioning Scale (RMAFS) is a 23-item self-report questionnaire, designed at Orygen Youth Health, to assess functioning in the domains of family, peer and general daily life. Items are rated from not at all/rarely applicable (0) to (almost) always applicable (5). Higher scores indicate better functioning.

Analyses Analyses were conducted with Mplus 5.1 (Muthen & Muthen, 1998-2007) and PASW Statistics 18. Full Information Maximum Likelihood (FIML) was used for estimation of missing values and, given data was non-normally distributed, robust ML (MLR) was used for model estimation. This method estimates a mean-adjusted χ^2 robust to non-normality (Brown, 2006). Differences between participants who completed all assessments and those

who dropped out at T2 or T3 were analysed using ANOVA for continuous variables and odds ratios (OR) for binary variables.

Step 1: Path analysis

Path analysis was used to investigate the relationships between subclinical positive psychotic experiences and the different coping styles (Task-, Emotion- and Avoidance-oriented) over time, using only observed variables. Paths were drawn to allow psychotic experiences to predict the three different coping styles over time and vice versa. The CAPE score and the three scores on the different coping styles were allowed to correlate at all time points, but the three coping styles were not allowed to predict other coping styles over time because this was not of primary interest.

Several fit indices were used for model evaluation (Brown, 2006). For good model fit, the chi-square (χ^2) should be low; the Comparative Fix Index (*CFI*) should be above 0.90 or 0.95 and the Root Mean Square Error of Approximation (*RMSEA*) should be lower than 0.08 or 0.05 for acceptable and good model fit respectively. Multi-group analysis on gender was conducted to investigate whether regression coefficients differed for gender. To do this, two models were compared: (i) a model with the different paths constrained to be equal for both genders and (ii) a model with the paths freely estimated. If the model with the freely estimated paths does not differ significantly from the constrained model, paths can be considered to be equal for females and males. Models do not significantly differ if $\Delta CFI<0.010$ and $\Delta RMSEA<0.015$ (Chen, 2007). Differences in mean coping scores between genders were assessed with MANCOVA, with the coping scores as dependent and gender as independent variables, controlled for age at T1. As secondary analyses, it was investigated whether the possible gender difference was due to rating bias or the number of coping styles effectively used. Coping style items were recoded to 0=never used this style or 1=ever used this style. MANOVA was used to assess the difference in the number of coping styles used by each gender.

Step 2: Latent growth modelling

First, the development of subclinical positive psychotic experiences over time was analysed using a latent growth model (LGM). LGM is a variant of Structural Equation

Modelling, in which two latent growth factors are identified, indicated by repeated observed variables and representing intercept (initial score) and slope (change in score over time) (Duncan et al., 1999).

Subsequently, different growth trajectories were assessed within this growth model by conducting Latent Class Analyses (LCA). In LCA, a set of mutually exclusive latent classes can be identified that account for the distribution of cases occurring within a cross-tabulation of observed variables (McCutcheon, 1987). Thus, LCA was used here to find the smallest number of classes of individuals with similar developmental trajectories of subclinical psychotic experiences. MANOVA was used to compare the different classes on CAPE frequency and distress, CISS coping style (mean and proportion), CES-D, GHQ-12 and RMAFS scores.

Results

Drop-out analyses There were no significant differences in age, socioeconomic status, CES-D or CAPE scores between participants who completed all study phases and those who dropped out at T2 or T3. Significantly more females participated in all phases compared to those who completed only T1 and T2 (OR=1.50, 95% CI=1.03, 2.17, p=.03). There were no other significant group differences in gender proportion. Participants who completed all study phases showed higher Task-oriented coping [F(3,829)=4.81, p=.003] and higher Emotion-oriented coping [F(3,819)=5.72, p=.001] at baseline than participants who only completed T1. There were no baseline group differences on Avoidance-oriented coping.

Step 1 - Path model The model with all paths included showed acceptable model fit [χ^2(28)=165.85; *CFI*=0.911 and *RMSEA*=0.075]. In Figure 1, all significant paths (p<.05) are shown (beta coefficients indicating path strength). As expected, coping styles were inter-correlated on the different time points, although Task-oriented and Emotion-oriented were not related at T1 and T3. All correlations between coping styles were positive. Subclinical psychotic experiences were (positively) correlated with Emotion-oriented coping at all three time points and (positively and negatively) with Task-oriented coping at T1 and T2, but never with Avoidance-oriented coping. Over time, Task-oriented coping at T1 predicted psychotic experiences at T2 (and vice versa). Emotional-oriented coping at T1 predicted

psychotic experiences at T2. Emotional-oriented coping at T2 predicted psychotic experiences at T3 (and vice versa).

The model with the paths freely estimated for females and males was not significantly better than the model with paths constrained to be equal for both genders (*ΔCFI*<0.004, *ΔRMSEA*<0.008), indicating that the regression coefficients were equal for females and males. Mean scores for each coping style at each time point are presented in Table 1. Females reported higher levels of all coping styles on all time points [F(9,945)=9.87, *p*<.001]. When scores were recoded to "never" versus "ever", the differences between genders remained significant, except in Task-oriented and Avoidance-oriented coping at T2. This suggests that the gender differences cannot be ascribed to females rating their use of coping styles as more often, but rather that females use a broader range of coping styles.

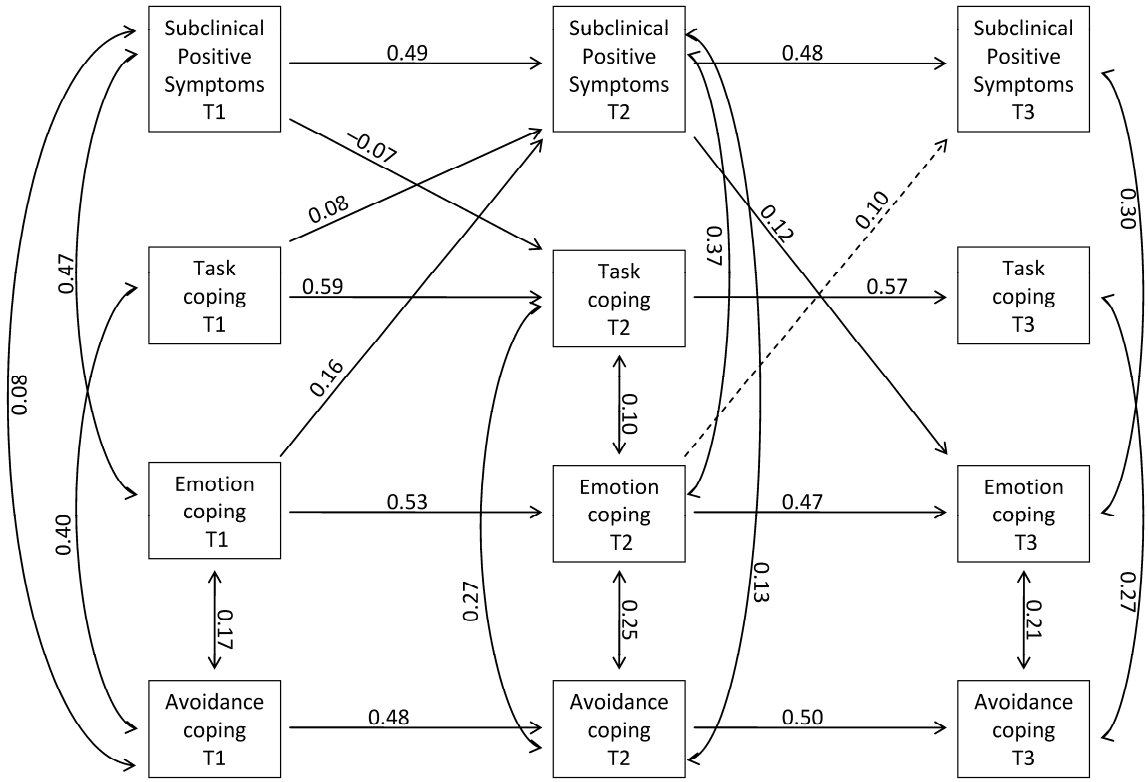

Figure 1. Path model of positive subclinical psychotic experiences and different coping styles (Task-, Emotion- and Avoidance-oriented).
Note: Only significant paths are depicted. The values represent beta coefficients. Minor differences in the model when controlled for depression are outlined in the Results section.

Effects of depression

Since (i) later analyses (see Step 2) showed that individuals with different trajectories of subclinical psychotic experiences demonstrated different levels of depressive symptomatology, and (ii) coping may be affected by depression, the cross-lagged path model was re-run controlling for depressive symptoms at all time points. This did not substantially change results: model fit was still good, and only one pathway, from Emotion-oriented coping at T2 to CAPE at T3, was no longer significant at conventional alpha (p<.08). Most regression coefficients did not decrease substantially (maximum decrease $\Delta\beta$=0.08), with the exception of two important pathways: the regression coefficient of Emotion-oriented coping at T1 predicting CAPE at T2 decreased from 0.16 to 0.08 and the regression coefficient of CAPE at T2 predicting Emotion-oriented coping at T3 increased from 0.12 to 0.24. Therefore, although different in strength, there was still a longitudinal association between CAPE score and Emotion-oriented coping from T1 to T3 when controlling for depression. Depression appears to play a (small) role in the association between coping and subclinical psychotic experiences, but cannot explain all of this relationship.

Table 1. Mean (SD) coping scores on the three different coping styles for males, females and total sample.

	T1	T2	T3
Task-oriented coping			
Male	34.3 (24.5)	28.4 (31.4)	19.4 (31.1)
Female	42.9 (20.7)	32.8 (31.0)	25.6 (31.7)
Total	*38.7(23.0)*	30.7 (31.3)	22.6 (31.6)
Emotion-oriented coping			
Male	24.6 (20.0)	19.2 (24.9)	12.1 (23.6)
Female	35.9 (20.0)	25.7 (26.9)	18.8 (26.5)
Total	30.4 (20.8)	22.5 (26.2)	15.6 (25.4)
Avoidance-oriented coping			
Male	35.0 (22.9)	24.5 (28.7)	15.4 (26.7)
Female	42.3 (21.9)	29.2 (28.7)	22.1 (28.7)
Total	38.8 (22.7)	26.9 (28.8)	18.9 (28.0)

Step 2- Linear growth model development A linear growth model was found to describe the data well (χ^2(1)= 2.04; p<.012; *RMSEA*=0.040 and *CFI*=0.993). In this case, the slope between T1 and T2 was fixed at 1, and the slope between T2 and T3 was fixed at 2, even though the difference between T1 and T2 was smaller than between T2 and T3. This

model had an unstandardized intercept of 31.33 (95% CI=30.87, 31.79) and unstandardized slope of -2.12 (95% CI=-2.34, -1.86) (p=0.001), indicating a significant decrease in level of subclinical psychotic experiences over time.

Different developmental trajectories of subclinical psychotic experiences Several subsequent LCA's were conducted with an increasing number of classes to distinguish trajectories of subclinical psychotic experiences (Table 2). A model with four classes best described the data. This model was significantly better than a model with three classes (p<.001) and showed a good entropy value (H=0.824). A model with five classes was not significantly better than a model with four classes. Average class probabilities were high (0.84-0.93), indicating that participants were correctly assigned to their respective latent classes.

The four classes represent different trajectories (Figure 2). The first class had the largest number of individuals (N=624; 71% of sample) and was characterized by a low intercept (unstandardized intercept 27.81) and small but significant decrease of subclinical psychotic experiences over time (unstandardized slope -0.72; p<.0001), hereafter labelled the "Low (subclinical psychosis) group". The second class consisted of 209 individuals (24%) and was characterized by a higher intercept (unstandardized intercept 37.43) and significant decrease in subclinical psychotic experiences over time (unstandardized slope -4.83; p<.0001), labelled the "Moderate-Decreasing group". The third group (N=35; 4%) was characterized by a very high intercept (unstandardized intercept 50.07) and very steep decrease over time (unstandardized slope -10.42; p<.0001), labelled the "Strong-Decreasing group". The last group was very small with only seven individuals (1%). It was characterized by high intercept (unstandardized intercept 44.94) and no significant change in subclinical psychotic experiences over time (unstandardized slope 1.04, p<.554), labelled the "Persisting group".

Table 2. Criteria for deciding the number of classes within the longitudinal trajectory of CAPE positive experiences.

No of classes	H	AIC	BIC	LMR-LRT statistic	LMR-LRT *p*-value
2	0.81	11447.238	11499.755	103.388	0.0342
3	0.85	11394.165	11456.230	54.595	0.2131
4	0.82	11354.798	11431.185	43.239	0.0011
5	0.82	11351.999	11442.709	8.386	0.2609
6	0.76	11345.575	11450.608	11.407	0.6701

Note. AIC-Akaike Information Criterion; BIC=Bayesian Information Criterion; H= Entropy measure, which can vary between 0 and 1 with higher values indicating clearer discrimination of classes; LMR-LRT= Lo Mendell Rubin Likelihood- Ratio-Test. Model is chosen if AIC and BIC are low(est), entropy is acceptable (>0.80) to good (>0.90) and succeeding models with one extra class at a time are no longer significant.

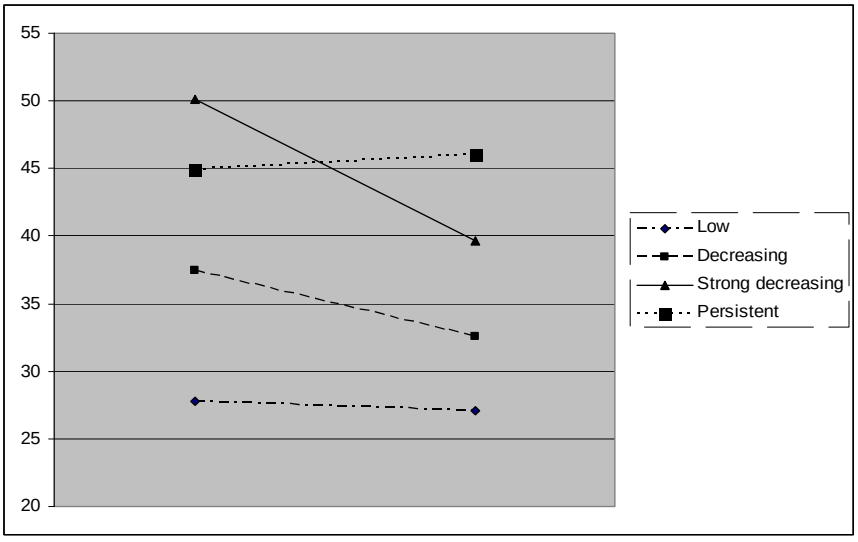

Figure 2. Visual representation of the four courses of subclinical psychotic experiences over time on total CAPE score at each time point.
Note. There is no significant change over time for the Persistent subgroup.

Subgroup characteristics The four subgroups, representing four different trajectories of subclinical psychotic experiences over time, did not differ in mean age [F(3, 855)=1.694; *p*<.167]. Males and females were not equally present in all groups [χ2(3)=9.912; *p*<.019]: in the Low group; 50% were female; in the Moderate-Decreasing group 54%, in the Strong-Decreasing group 62% and in the Persistent group 57%. Gender proportion was significantly different between the Low and Strong-Decreasing groups (OR=0.60, 95% CI=0.44, 0.83, *p*=.002).

The four subgroups differed significantly on CAPE distress scores [F(9,710)=60.0, *p*<.001], CES-D depression scores [F(9,1175)=19.0, *p*<.001], severity of general mental problems rated on the GHQ-12 [F(9,1102)=12.4, *p*<.001] and the RMAFS index of daily functioning [F(9,1029)=9.1, *p*<.001] at all time points (see Table 3). The level of distress mirrored the frequency of subclinical psychotic experiences. The Persistent group reported significantly higher levels of depression at all three time points. Functioning of the Moderate-Decreasing and Strong-Decreasing groups normalised over time. At T1, the Low group was significantly better functioning than all other groups, whereas at T3, the Persisting group showed significantly poorer functioning than all other groups.

Coping The four subgroups differed in overall use of coping styles [F(24, 1065)=4.641, *p*<.001] and in proportional use of coping styles [F(18, 1001)=3.645*, p*<.001] (Table 4). The highest mean scores for Emotion-oriented coping were consistently reported by the Persistent group. No significant group differences were found in the mean scores for Task-oriented coping, and only small, inconsistent differences for Avoidance-oriented coping.

In terms of the proportional use of each coping style (Table 4), no significant differences were found in Avoidance-oriented coping. All groups showed a trend for using a greater proportion of Task-oriented coping and lesser proportion of Emotion-oriented coping over time and these trends seem to be strongest in the Strong-decreasing group. The Persistent group consistently reported the lowest proportional use of Task-oriented coping and highest proportional use of Emotion-oriented coping.

Table 3. Mean (SD) scores of CAPE frequency and distress, CES-D, GHQ-12 and RMAFS per subgroup and in total.

	T1	T2	T3
CAPE *(Frequency score)*			
Low	28.2 (3.6)[a]	27.4 (4.1)[a]	26.6 (5.4)[a]
Moderate-Decreasing	38.1 (3.2)[b]	32.7 (5.7)[a]	28.2 (5.9)[b]
Strong-Decreasing	52.1 (4.0)[c]	38.0 (10.7)[b]	30.1 (4.5)[b]
Persistent	45.0 (5.6)[d]	44.7 (12.8)[b]	48.3 (4.1)[c]
Total	*32.0 (7.1)*	*29.5 (6.2)*	*27.5 (5.2)*
CAPE *(Distress score)*			
Low	10.8 (5.6)[a]	10.0 (6.5)[a]	8.1 (5.8)[a]
Moderate-Decreasing	25.3 (7.1)[b]	16.6 (8.1)[a]	10.2 (5.9)[b]
Strong-Decreasing	41.9 (11.7)[b]	24.3 (10.6)[b]	15.2 (7.4)[a,c]
Persistent	30.0 (8.9)[c]	30.4 (18.0)[c]	40.2 (8.5)[c]
Total	*15.9 (10.3)*	*12.5 (8.5)*	*9.4 (7.3)*
CES-D *(Depression score)*			
Low	11.30 (0.5)[a]	9.96 (0.5)[a]	11.33 (0.5)[a]
Moderate-Decreasing	20.16 (0.8)[a]	15.51 (0.8)[b]	14.41 (0.8)[b]
Strong-Decreasing	29.01 (2.3)[b]	19.80 (2.3)[b,c]	20.00 (2.4)[b]
Persistent	32.83 (3.7)[b]	30.67 (3.6)[c]	36.33 (3.8)[c]
Total	*13.99 (10.2)*	*11.96 (9.3)*	*12.81 (10.0)*
GHQ *(General Health)*			
Low	10.1 (5.1)[a]	9.2 (4.4)[a]	10.5 (4.8)[a]
Moderate-Decreasing	13.9 (6.6)[b]	11.0 (5.9)[b]	11.8 (6.3)[a]
Strong-Decreasing	19.1 (8.3)[c]	13.4 (8.7)[b]	13.8 (5.8)[a]
Persistent	24.0 (8.2)[c]	21.6 (10.6)[c]	23.0 (5.8)[b]
Total	*11.4 (6.2)*	*9.9 (5.3)*	*11.1 (5.4)*
RMAFS *(Functioning)*			
Low	74.9 (9.4)[a]	78.8 (8.4)[a]	78.3 (8.8)[a]
Moderate-Decreasing	69.3 (9.3)[b]	74.6 (8.9)[b]	75.5 (9.6)[b]
Strong-Decreasing	60.9 (12.0)[c]	72.2 (8.2)[b,c]	71.0 (9.5)[b]
Persistent	60.0 (14.01)[b,c]	61.8 (11.6)[c]	58.0 (11.2)[c]
Total	*72.9 (10.2)*	*77.4 (8.9)*	*77.1 (9.4)*

Note: Higher scores on frequency, distress and depression indicate greater pathology. Higher scores on GHQ and lower scores on RMAFS indicate poorer general mental health and functioning. Different superscript letters refer to significant differences (p<.05) of mean scores between groups: if two scores are labelled with the same letter (e.g. 'a'), the scores do not differ between these two groups. If two scores are labelled with different letters, these scores differ significantly.

Table 4. Mean score and proportional use of different coping styles per subgroup.

	Mean score for coping style - M (SD)			Proportional use of coping style - M(SD)		
	T1	T2	T3	T1	T2	T3
Task-oriented coping						
Low	43.9 (18.4)[a]	34.4 (30.6)[a]	25.6 (31.8)[a]	36.9 (7.1)[a]	38.5 (6.4)[a]	39.2 (7.5)[a]
Moderate-Decreasing	43.8 (17.6)[a]	37.3 (27.5)[a]	27.1 (30.5)[a]	33.3 (6.4)[b]	36.4 (6.1)[b]	36.9 (6.2)[b]
Strong-Decreasing	41.0 (17.4)[a]	24.4 (32.0)[a]	15.9 (31.4)[a]	31.1 (8.3)[b]	36.7 (6.7)[a,b]	38.2 (7.2)[a,b]
Persistent	39.7 (13.6)[a]	40.1 (23.8)[a]	37.9 (23.4)[a]	26.3 (6.1)[b]	28.7 (4.8)[c]	30.2 (6.3)[b]
Total	*43.7 (18.1)*	*34.7 (30.0)*	*25.7 (31.4)*			
Emotion-oriented coping						
Low	31.2 (16.0)[a]	24.2 (24.6)[a]	17.1 (24.5)[a]	26.9 (7.1)[a]	28.1 (6.1)[a]	27.8 (6.9)[a]
Moderate-Decreasing	41.5 (16.8)[b]	30.1 (25.5)[b]	20.3 (26.5)[a]	31.8 (8.0)[b]	30.6 (6.6)[b]	29.8 (7.3)[b]
Strong-Decreasing	48.5 (16.3)[b,c]	23.5 (30.2)[a,b]	13.9 (28.2)[a]	36.1 (7.7)[c]	32.9 (7.8)[b]	30.8 (7.6)[a,b]
Persistent	57.9 (13.0)[c]	51.3 (28.7)[b,c]	56.7 (10.4)[b]	39.9 (8.3)[b,c]	36.7 (6.2)[b]	37.0 (6.2)[b]
Total	*34.6 (17.1)*	*25.8 (25.3)*	*18.0 (25.3)*			
Avoidance oriented						
Low	42.6 (17.8)[a]	30.0 (28.1)[a]	21.1 (27.7)[a]	36.2 (6.5)[a]	33.5 (6.0)[a]	33.0 (6.3)[a]
Moderate-Decreasing	47.3 (15.4)[b]	33.6 (26.4)[a]	23.6 (28.3)[a,b]	34.9 (6.1)[a,b]	33.0 (4.6)[a]	33.2 (5.7)[a]
Strong-Decreasing	44.5 (16.3)[a,b]	21.3 (27.9)[a]	13.7 (27.6)[a]	32.8 (6.4)[b]	30.4 (6.4)[a]	31.0 (6.4)[a]
Persistent	40.3 (24.6)[a,b]	48.3 (25.8)[a]	50.0 (8.0)[b]	33.9 (3.1)[a,b]	34.6 (2.8)[a]	32.8 (2.0)[a]
Total	*43.7 (17.4)*	*30.7 (27.7)*	*21.6 (27.8)*			

Note: Higher scores indicate greater mean or proportional use of the coping style. Different superscript letters refer to significant differences (p<.05) between groups: when labelled with the same letter (e.g. 'a'), scores do not differ significantly. When labelled with different letters, scores do significantly differ.

Discussion

Subclinical psychotic experiences were related to coping style in the present adolescent general population sample. When examining the whole sample, Emotion-oriented coping and subclinical psychotic experiences enhanced each other over time, whereas associations with Task- and Avoidance-oriented coping were inconsistent or negligible. When different developmental trajectories of subclinical psychotic experiences were examined, the association with Emotion-oriented coping remained most prominent; persistence of subclinical psychotic experiences was associated with higher mean levels and higher proportional use of Emotion-oriented coping. In this analysis, Avoidance-oriented coping continued to show no significant relationship to subclinical psychotic experiences. However, the importance of Task-oriented coping was highlighted; an increase in proportional use of Task-oriented coping was associated with a decrease in subclinical psychotic experiences over time.

Emotion-oriented coping predicted subclinical psychotic experiences over time and vice versa, forming a vicious cycle. This finding, at a subclinical level, is consistent with previous research in adults with schizophrenia (Ritsner et al., 2003; Philips et al., 2009). Furthermore, a marked dose-response relationship was seen between developmental levels of subclinical psychotic experiences and Emotion-oriented coping - the more experiences endorsed, the more Emotion-oriented coping was used, particularly in the Persistent group. This group consistently reported the highest mean and proportional use of Emotion-oriented coping, even though at T1 the frequency of subclinical psychotic symptoms was higher in the Strong-Decreasing group. This suggests that Emotion-oriented coping is associated specifically with *persistence* of subclinical psychotic experiences, rather than the level of experiences at a single time point. Taken together, our findings suggest a casual relationship between persistence of subclinical psychosis and Emotion-oriented coping.

While no specific coping style is thought to be effective across all situations, Emotion-oriented coping is generally considered least adaptive (Phillips et al., 2009). In patients with schizophrenia, Emotion-oriented coping is associated with lower quality of life (Ritser et al., 2003) and hospital admission (Strous et al., 2005). There are several possible explanations for this relationship. Task-oriented coping, while considered most effective, may only be so in controllable situations. When a situation is uncontrollable, as subclinical

psychotic experiences may be, Emotion-oriented coping may be a better coping strategy (Parker & Endler, 1992). Secondly, psychotic symptoms may be associated with feelings of powerlessness and loss of control (Birchwood & Chadwick, 1997; Garety & Freeman, 1999; Krabbendam & van Os, 2005). This, coupled with confusion around the experiences, may elicit emotional, rather than active-cognitive coping. In line with the former explanation, the path from coping to psychotic experiences may be partly mediated by depression (Escher et al., 2003), which is strongly associated with subclinical psychotic experiences (Yung et al., 2006; van Rossum et al., 2011). Emotion-oriented coping may be particularly related to depression because it captures affective responses to stressors. When the relationship between coping and subclinical psychotic experiences was controlled for depression, there was evidence that depression accounted for some, but not all, of the variance.

Consistent with existing literature, we found that Task-oriented coping was associated with better functioning over time. This type of coping is generally considered most adaptive (Endler & Parker, 1990) and is associated with better outcome (Bak et al., 2003). Although the relationship was not detected when the sample was studied as a whole, the importance of Task-oriented coping was highlighted when the different trajectories were examined. Specifically, an increase in the proportional use of Task-oriented coping was associated with a decrease in subclinical psychotic experiences and better functioning over time.

The finding that Avoidance-oriented coping was not significantly related to subclinical psychotic experiences was somewhat surprising given that patients with schizophrenia often employ avoidance strategies (Philips et al., 2009). It could be hypothesized that Avoidance-oriented coping only begins to play a role when psychotic experiences become more pathological, i.e. in the clinical range of the extended psychosis continuum.

In this study, females reported using more coping styles at all time points (except Task- and Avoidance-oriented at T2) and using these different coping styles more often than males at almost all time points. The use of more coping styles by females is well documented in general (Hobfoll et al., 1994), but less consistently in relation to psychosis (Boschi et al., 2000; Thompson et al., 2003; Dangelmaier et al., 2006; Modestin et al., 2009). In this study, the paths between coping styles and subclinical psychotic experiences did not

differ be gender, suggesting that although the number and frequency of styles employed by each gender may differ, the pathways between coping and subclinical psychotic experiences are the same.

The finding of distinct trajectories of subclinical psychosis over time is similar to previous studies (Mackie et al., 2010; Wigman et al., 2011d). The overall patterns of subclinical psychotic experiences are conceptually comparable and confirm the dynamic nature of psychosis proneness in adolescence. In all of these studies, the largest proportion of adolescents had the lowest levels of subclinical psychotic experiences and other psychopathology. Other patterns (i.e. decreasing, increasing or persistent, all characterized by higher levels of subclinical psychotic experiences) were associated with greater psychopathology. The current findings are similar: reduction in subclinical psychotic experiences was associated with decreases in distress and depression, and improved general mental health and functioning. This study, however, is the first to relate these distinct trajectories to the use of different coping styles over time.

Results can be interpreted within the framework of the *proneness – persistence – impairment* model (Cougnard et al., 2007). Persistence of subclinical psychotic experiences is associated, at every time point, with (i) higher levels of Emotion-oriented (non-adaptive) coping, (ii) poorer functioning and mental health and (iii) higher levels of depression. Furthermore, an increase in proportional use of more adaptive coping (Task-oriented coping) is associated with decreased psychotic experiences and improved functioning. We speculate that Emotion-oriented coping may play a causal role in persistence of subclinical psychotic experiences, deterioration of functioning and development of impairment and need for care. Task-oriented coping may be important for breaking the cycle and decreasing the level of subclinical psychotic experiences.

In this context, the present findings have clinical implications. Improved understanding of the relationship between coping styles and subclinical psychotic experiences provide the possibility of preventative intervention. Interventions aimed at modifying coping styles may aid in decreasing subclinical psychotic experiences (French & Morrison, 2004; Farhall et al., 2007). The target of intervention would be to prevent or delay progression towards a clinical psychotic disorder (Yung & McGorry, 1996; Bak et al., 2003).

These results should be interpreted in the light of the study's strengths and

limitations. To our knowledge, this is the first study to assess interrelationships between coping styles and psychotic experiences over time in a general population sample. An important addition to existing literature lies in taking two perspectives; by first looking at broader associations between subclinical psychotic experiences and coping over time, and then linking the different trajectories with coping style. These associations were studied before the onset of clinical disorder, targeting the phase in which early intervention may be most effective.

A major limitation is that the most problematic subgroup, the Persistent group, consisted of only seven individuals, increasing risk of Type II error, skewed scores and a large deviation around the mean. Significant differences were evident even in this small sample, suggesting the relationships detected are a true effect; however replication is needed. The drop-out rate in this study was significant, although the method used for model estimation (FIML) incorporates all available data, without list-wise deletion and partially overcomes this issue. A further limitation is that self-report measures may lead to loss of information; however, several studies have shown self-report a reliable method to assess psychotic experiences (Allardyce et al., 2007; Kelleher et al., 2011). Future research should investigate the predictive value of the distinct trajectories of subclinical psychotic experiences for clinical disorder and the role of coping in this process. It is important to note that coping is only one of many factors that determine the persistence of subclinical psychotic experiences and outcome. Finally, coping is associated with many other factors, as underlined by the low coefficients found in the models. These factors, such as personality (Wong et al., 2009) and childhood abuse (Shapiro & Levendosky, 1999), should be incorporated in future studies.

6. A twin study of genetic and environmental determinants of abnormal persistence of psychotic experiences in young adulthood

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Evidence suggests subclinical psychotic experiences are more likely to cause transition to psychotic disorder if their expression becomes persistent. The study of longitudinal patterns of subclinical psychotic experiences may help to distinguish subgroups with transient and persistent psychotic symptoms, which may differ in risk of later psychosis.

The current study investigated patterns of developmental course of subclinical psychotic experiences in a general population sample of 566 female twins, aged 18-45 years. The positive symptoms subscale of the Community Assessment of Psychic Experiences (CAPE), completed three times in two years, was analyzed with growth modeling. Using Latent Class Analysis, two developmental courses were distinguished: a Persistent and a Low (expression of subclinical psychotic experiences) group.

The Persistent group reported significantly higher levels of depressive and negative symptoms and worse functioning in daily life. Childhood trauma (OR 3.26, $p<.0001$) and stressful life events over the study period (OR 3.15, $p=.031$) predicted membership of the Persistent group. Of the monozygotic (MZ) twins with their co-twin in the Persistent group, 49% also were in the Persistent group themselves (OR 9.32, $p<.0001$), compared to only 14% in the dizygotic (DZ) co-twins (OR 1.56, $p=0.42$) ($\chi 2(2)=22.97$; $p<.001$).

The findings suggest that persistence of subclinical psychosis is influenced by both genetic and environmental factors, providing the possibility to study the (possibly modifiable) aetiology underlying the longitudinal process of persistence of the early expression of psychosis liability.

Introduction

Subtle psychotic experiences are common in the general population (van Os et al., 2009), though mostly transient in nature (Dhossche et al., 2002; Dominguez et al., 2011; Hanssen et al., 2005; Wiles et al., 2006). However, for a minority of individuals, subtle psychotic experiences may be predictive of later psychotic disorder. Several recent studies suggest that delusional thinking and mild hallucinatory experiences may precede clinical psychotic disorder and hospitalization by many years (e.g. Hanssen et al., 2005; Poulton et al., 2000; Welham et al., 2008; Werbeloff et al., 2009), particularly if they are persistent over time (Dominguez et al., 2011).

Therefore, shifts along the extended psychosis phenotype over time from subclinical to clinical states of psychosis require further exploration. Recent research suggests that such transitions may be interactive (Cougnard et al., 2007) in that the progress and persistence of subclinical psychotic experiences may be moderated by several environmental factors, such as childhood trauma (Read et al., 2005), cannabis use (Henquet et al., 2005) and urban environment (Spauwen et al., 2006a). Other suggested moderators of outcome are individual factors such as coping style (Bak et al., 2003), distress associated with the experiences (Bak et al., 2005; Jacobs et al., 2005), the severity of experiences (Hanssen et al., 2005; Poulton et al., 2000; Welham et al., 2008) and level of admixture with affective symptoms (van Rossum et al., 2011). Thus, the likelihood of a clinical outcome depends on the psychopathological, developmental and psychological context of subclinical psychotic experiences, in addition to the presence of these experiences *per se* (Kaymaz & van Os, 2010).

Recent developmental models of psychosis propose a psychosis proneness – persistence – impairment model of disorder, suggesting that the transition from subtle subclinical psychosis to clinical disorder is preceded by persistence of psychotic experiences and accompanied by progressive impairment, depending on additional psychopathological, developmental and environmental factors (Cougnard et al., 2007; van Os et al., 2009). Studying dynamic courses over time may thus represent a useful paradigm in order to identify subgroups enriched in risk, since this perspective takes into account the longitudinal stability of the psychotic experiences, excluding the more transient phenomena.

Two recent studies using growth modeling to examine the longitudinal trajectory of self-reported subclinical positive psychotic experiences in adolescents identified different

trajectories of subclinical psychosis over time (Mackie et al., 2010; Wigman et al., 2011d). Mackie and colleagues (2010) conducted a two-year follow-up of 409 adolescents, aged 14 years at baseline, who scored high on one of four personality risk factors (hopelessness, anxiety-sensitivity, impulsivity and sensation-seeking) and distinguished three developmental subgroups of Persistent, Increasing and Low levels of psychotic experiences. In another six-year study in a general population sample of 2230 adolescents, aged 11 years at baseline (Wigman et al., 2011d), four subgroups were identified that were denominated Low, Decreasing, Increasing and Persistent levels of psychotic experiences. In both studies, subgroups with increasing or persistent psychotic experiences over time had higher comorbid anxiety and depression scores, higher levels of exposure to known risk factors for psychosis and greater use of health care (Mackie et al., 2010; Wigman et al., 2011d).

Given evidence that genetic factors associated with psychotic disorder may impact on early expression of psychotic experiences (Lataster et al., 2009), it is attractive to hypothesize that early persistence of psychotic experiences is also subject to genetic influences.

The present study aimed to validate and extend the work on distinct developmental courses of subclinical psychotic experiences over time, analyzing data pertaining to an independent cohort of young adult female twins, recruited from the general population. Associations were examined with known environmental risk factors, comorbid symptomatology and level of functioning; in addition, the hypothesis of genetic contribution to these different trajectories was examined.

Methods

Sample This study forms part of a general population twin study investigating gene-environment interactions in vulnerability for mental disorders, as described previously (Derom et al., 2006; Jacobs et al., 2006). Because genetic effects on psychopathology are likely sex-specific to a degree (Jacobs et al., 2006), only women were included in the original study, so that the current analyses also pertain to women only. Participants (twins) were recruited from the East-Flanders Prospective Twin Survey, a population-based survey that has prospectively recorded all multiple births in the province of East Flanders since 1964 (Derom et al., 2006). Originally, the sample included 621 subjects (575 twins and 46 of their non-twin sisters). The 46 non-twin sisters were excluded, as well as three subjects with

missing zygosity and six subjects who participated without their twin. The final sample thus consisted of 566 subjects (283 pairs of twins, 172 monozygotic and 111 dizygotic), with mean age 27.3 years (SD 7.5; range 18-46). Participants were interviewed five times (T0-T4) at approximately 3- to 4-monthly intervals. Participants were white and of Belgian origin. Sixty-one percent had a higher education, 37% had followed higher secondary school and 2% had finished primary school only. The majority was employed (61%) and in a relationship (75%).

Instruments The Community Assessment of Psychic Experiences (CAPE) (42 self-reported items) was used to assess subclinical psychotic experiences (Konings et al., 2006; Stefanis et al., 2004). The CAPE is based on the Peters et al. Delusions Inventory (PDI) (Peters et al., 1999), modified to also include hallucinatory experiences. Each item in the CAPE rates two aspects of subclinical psychotic experiences: (i) frequency and (ii) associated distress, both rated on a four-point scale of never/not distressed (1); sometimes/a bit distressed (2); often/quite distressed (3); nearly always/very distressed (4). The CAPE was assessed at T0, T2 and T4. The frequency items showed good internal consistency (Cronbach's alpha >0.96 at all three measurements). Standardized sum scores of the positive items sub-scale (20 items) were used as indicators for the growth model; standardized sum scores of the negative (14 items) and depressive (8 items) subscales were used to compare the different developmental groups.

An inventory of recent life events was made, based on the Interview of Recent Life Events (IRLE) (Paykel, 1997). Subjects reported whether or not they experienced 61 particular events in the past six months (at T0) or since the previous assessment (T1 – T4) and rated their impact on a five-point scale (from 1= very pleasant to 5= very unpleasant ; n T0=374 ; n T1=332, n T2=304, n T3=271, n T4=241). These recent life events were in the domain of ten categories : work, education, finance, health, bereavement, migration, courtship, marriage and cohabitation, legal and family/social relationships, all representing dateable occurrences involving changes in the external social environment. Internal occurrences such as changes in perceptions or satisfactions were excluded, with one exception: onset of physical illness, since the implications of this event are much the same as those of an event that is purely external in origin. Events rated as unpleasant (i.e. score of 4, « unpleasant » or score of 5 « very unpleasant) were included in the analysis and a

variable was constructed representing the number of such unpleasant events in the last six months confirm previous research (Jacobs et al., 2006). In the analyses, a Stressful Life Events (SLE) score was used, coded as: 0 SLE=0, 1 SLE=1, 2 SLE=2, 3 SLE=3, 4 SLE=4, 5 or more SLE=5.

Childhood adversity was assessed using a self-report questionnaire based on the Dutch translation of the original 70-item CTQ questionnaire (Arntz & Wessel, 1996; Bernstein et al., 1994) to score the amount of early adversity. However, only the items of a more recent and shorter CTQ version (Bernstein et al., 2003) were used and at the request of EFPTS, the most explicit items concerning sexual and physical abuse were omitted. The questionnaire thus consisted of 21 items reflecting positive events such as a happy childhood/youth, interparental/marital harmony/love, feeling safe and respect of privacy as well as negative events such as physical abuse, emotional neglect, material problems in parental household and stressful life events. Participants rated the frequency of the (positive or negative) experience during childhood and /or adolescence on a scale from 1 ('never') to 5 ('always'). Positive events were recoded so that higher scores reflected more adverse experiences. A continuous variable 'childhood adversity' was created as a weighted sum of all the 21 items of the questionnaire. Cronbach's alpha for this 21 item questionnaire was 0.93.

A Global Assessment of Functioning (GAF) score was rated for each participant by an interviewer with a mental health-related profession. The GAF scale has a 100-point range indexing overall psychological, social and occupational functioning of individuals over 18 years old, excluding physical and environmental impairment. The version with two separate scores was used: a symptom score and a handicap score (World Health Organisation, 1992).

The Hallucinations and Delusions sections of the Structured Clinical Interview for DSM-IV Axis-I Disoders (SCID-I), a structured interview for, among others, psychotic and affective disorders that produces standardized DSM-IV diagnoses (First et al., 2002), were also administered.

Analyses Analyses were conducted using Mplus 5.1 (Muthen & Muthen, 1998-2007) and STATA 11.0 (Statacorp, 2009). All analyses were controlled for hierarchical clustering of individuals within twins. First, the course of the total CAPE positive scale score over time (T0, T2 and T4) was analysed with a latent growth model (LGM). LGM is a variant of

Structural Equation Modelling (SEM), in which two latent growth factors are identified, indicated by repeated observed variables. These two factors represent intercept (i.e. initial score) and slope (i.e. change in score over time) (Duncan et al., 1999).

In order to evaluate the model, several fit indices were used (Brown, 2006). For good model fit, the χ^2 (chi-square) should be low; the Comparative Fix Index (*CFI*) should be above 0.90 or 0.95 for respectively acceptable and good fit and the Root Mean Square Error of Approximation (*RMSEA*) should be lower than 0.08 or 0.05 for respectively acceptable and good model fit. Full Information Maximum Likelihood (FIML) estimation was used for model estimation and, given that data were non-normally distributed, robust ML (MLR) was used, as this estimates a mean-adjusted χ^2 that is robust to non-normality (Brown, 2006). Subsequently, different growth courses were assessed within this general growth trajectory by conducting a Latent Class Analysis (LCA). In LCA, a set of mutually exclusive latent classes can be identified that account for the distribution of cases occurring within a cross-tabulation of observed variables (McCutcheon, 1987). Thus, in the present study, LCA was used to find the smallest number of classes of individuals with similar courses of CAPE positive scale score. The resulting course classes (a 'Persistent' class and a 'Low expression' class, see below) were then compared, using MANOVA, on (i) frequency and distress scores of the three CAPE dimensions obtained at the three measurements; ii) GAF scores.

Second, multilevel logistic regression using the XTLOGIT procedure in STATA was used to examine variables associated with class membership. Multilevel analysis was used since this method allows for the analysis of hierarchically clustered data, in this case taking into account clustering at the level of the twin pair. The independent variables included (i) the environmental risk factors childhood trauma before age 16 years, (ii) stressful life events during the time of the study, both defined as continuous variables, and (iii) genetic liability for psychosis. In order to model genetic risk (Kendler et al., 1995; Wichers et al., 2007), each subject was assigned an indicator of genetic liability for psychosis with value 0 indicating that their (monozygotic or dizygotic) co-twin did not belong to the Persistent class; value 1 indicating that the dizygotic co-twin belonged to the Persistent class and value 2 indicating that the monozygotic co-twin belonged to the Persistent class. Interactions between genetic liability and environmental risk factors were not investigated given low power.

Results

Model development A linear growth model was found to describe the data well ($\chi^2(1)$= 0.048; *p*<.827; *RMSEA*=0.000 and *CFI*=1.000). This model had an unstandardized intercept of -0.012 (95% CI –0.096 – 0.073) and an unstandardized slope of 0.008 (95% CI -0.032 – 0.049) (*p*=0.678), indicating an absence of significant overall change over time.

Different developmental courses Several subsequent LCA's were conducted with an increasing number of classes (Table 1) in order to distinguish distinct developmental courses. A model with two classes appeared to describe the data well, since this model was significant. Furthermore, although *AIC* and *BIC* decreased when increasing the number of classes from two to three, the model with three classes was not significantly better than a model with two classes (Table 1). Average class probabilities were high (0.91 and 0.99), indicating that participants were correctly assigned to their respective latent classes and entropy was also high (0.92).

Table 1. Criteria for deciding the number of classes within the repeated measures of the CAPE positive scale.

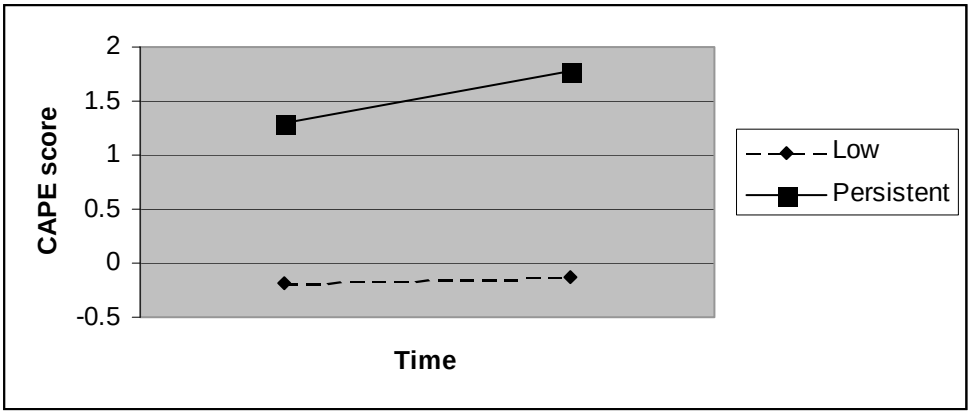
No of classes	H	AIC	BIC	LMR-LRT statistic	LMR-LRT *p*-value
2	0.916	3128	3176	198.273	0.0001
3	0.925	3043	3104	86.219	0.058
4	0.912	3006	3080	41.152	0.163

Note: AIC-Akaike Information Criterion; BIC=Bayesian Information Criterion; H= Entropy measure, which can vary between 0 and 1 with higher values indicating clearer discrimination of classes; LMR-LRT= Lo Mendell Rubin Likelihood- Ratio-Test. Model is chosen if AIC and BIC are low(est), entropy is acceptable (>0.80) to good (>0.90) and the model with one extra class is no longer significant.

As depicted in Figure 1, the two classes represent different developmental courses. The first class with the largest number of individuals (N=496; 88% of the sample) was characterized by a low intercept (unstandardized intercept -0.l9) and a small but significant decrease of experiences over time (unstandardized slope -0.06; *p*<.0001). This class was labelled the "Low (expression of subclinical psychosis) group". The second class consisted of 70 individuals (12% of the sample) and was characterized by a much higher intercept (unstandardized intercept 1.29) and a significant increase of experiences over time

(unstandardized slope 0.48; *p*<.0001). This group was labelled the "Persistent (subclinical psychosis) group".

Figure 1. Visual representation of the developmental courses of the Low Expression and the Persistent group.



Psychopathology, environmental risk factors, functioning and class membership The Persistent group scored higher than the Low Expression group on both Depressive and Negative CAPE frequency scores. The Persistent group also scored higher than the Low Expression group on the distress scores of both the Depressive and Negative dimensions, but not the Positive symptom dimension. The Persistent group scored higher than the Low Expression group on both Hallucination and Delusion SCID scores (Table 2). Furthermore, the Persistent group scored significantly lower on both the GAF-symptom and the GAF-handicap scales (Table 2).

Membership of the Persistent group was also associated with childhood trauma (OR 3.26; 95% CI 1.77-6.00; *p*<.0001) and stressful life events (OR 3.15; 95% CI 1.11-8.98; *p*<0.031).

Genetic liability and class membership Having a dizygotic co-twin in the Persistent group did not predict class membership (OR 1.56; 95% CI 0.52-4.69; *p*=0.424). In contrast, having a monozygotic co-twin in the Persistent group was strongly associated with class membership of the Persistent group, with large effect size (OR 9.32; 95% CI 4.73-18.45; *p*<.000). Forty-nine percent of the monozygotic twins in the Persistent group had their twin in the Persistent group; for the dizygotic twins this was 14% ($\chi^2(2)=22.97$; *p*<.001). In the Low

Expression group, 7% of the monozygotic and 13% of the dizygotic twins had their twin in the Persistent group ($\chi^2(2)=53.09$; $p<.001$).

Table 2. Standardized scores of the positive, depressive and negative subscales of the CAPE and GAF scores of the Persistent and the Low Expression group.

	T0	T2	T4
Positive symptoms			
Frequency			
Low Expression group	-0.19 (0.05)	-0.26 (0.04)	-0.31 (0.09)
Persistence group	1.21 (0.13)**	1.76 (0.12)**	2.25 (0.03)**
Distress			
Low Expression group	0.14 (0.07)	0.07 (0.08)	0.08 (0.08)
Persistence group	-0.16 (0.17)	0.36 (0.17)	-0.09 (0.17)
Depressive symptoms			
Frequency			
Low Expression group	-0.11 (0.06)	-0.17 (0.05)	-0.17 (0.06)
Persistence group	0.89 (0.16)**	0.22 (0.14)**	1.28 (0.15)**
Distress			
Low Expression group	0.02 (0.06)	-0.07 (0.06)	-0.10 (0.06)
Persistence group	0.48 (0.16)*	0.88 (0.15)**	0.76 (0.16)**
Negative symptoms			
Frequency			
Low Expression group	-0.12 (0.06)	-0.14 (0.05)	-0.14 (0.05)
Persistence group	0.69 (0.15)**	0.92 (0.15)**	1.13 (0.15)**
Distress			
Low Expression group	0.09 (0.06)	0.00 (0.06)	-0.06 (0.07)
Persistence group	0.36 (0.16)	0.61 (0.16)**	0.58 (0.17)**
GAF symptom score			
Low Expression group			89.39 (0.38)
Persistent group			84.23 (1.02)**
GAF handicap score			
Low Expression group			90.27 (0.91)
Persistent group			85.16 (0.34)**
SCID Hallucinations			
Low Expression group	0.03 (0.22)		0.02 (0.19)
Persistent group	0.14 (0.39)**		0.12 (0.38)*
SCID Delusions			
Low Expression group	0.12 (0.40)		0.08 (0.36)
Persistent group	0.31 (0.71)**		0.45 (0.80)**

* Significant difference from the Low Expression group, $p<.01$

** Significant difference from the Low Expression group, $p<.001$

NB The frequency scores of the Positive symptoms was used to identify the two courses. These scores are thus given only for a complete view but are not informative by themselves.

Discussion

This study investigated the existence of distinct courses of subclinical psychotic experiences in a group of young female adults, assessing the relationship of these distinct courses with both environmental and genetic risks and extending earlier findings that distinct courses of subclinical psychosis can be identified in the general population (Mackie et al., 2010; Wigman et al., 2011d). Two developmental courses were distinguished, labelled a Low Expression and a Persistent subclinical psychosis group. The Low Expression group was characterized by low levels of subclinical psychotic experiences and a small reduction in experiences over time. The Persistent group, in contrast, reported a high initial level of psychotic experiences and a further increase of experiences over time. The Persistent group reported higher levels of other psychopathology and showed relatively higher levels of impairment in daily life. Belonging to the Persistent group was associated with childhood trauma and recent stressful life events over the study period. In addition, evidence for genetic contribution was apparent for membership of the Persistent group, given the significant contrast in monozygotic and dizygotic concordance (49% vs 14%).

The finding of separate groups of individuals, differing in level and course of subclinical psychosis, fits earlier work (Mackie et al., 2010; Wigman et al., 2011d). In the present study only two subgroups were distinguished, whereas earlier work reported the existence of three and four subgroups (Mackie et al., 2010; Wigman et al., 2011d), suggesting a more dynamic nature of experiences in these samples. This may be attributed to the fact that both other studies were conducted in adolescent populations. Dynamic changes in experiences over time may be less pronounced in the present young adult sample, given the fact that the greatest developmental expression of psychosis proneness is in adolescence and declines dramatically after that age (Verdoux et al., 1998), just like more general dynamics and developmental changes associated with adolescence. The fact that the two developmental courses differed on measures of other psychopathology, clinical levels of psychotic symptoms, and functioning in daily life underlines the interpretation of these two groups as truly distinct types of individuals.

The role of childhood trauma in predicting Persistent group membership is in line with earlier studies (Spauwen et al., 2006b), as is the association with stressful life events (Myin-Germeys & van Os, 2007) and genetic risk (Lataster et al., 2009; Polanczyk et al.,

2010). Interestingly, the concordance rates for Persistent group membership for monozygotic (49%) and dizygotic (14%) twins strongly resemble the concordance rates of schizophrenia (Cardno & Gottesman, 2000), suggesting a highly heritable phenotype. Furthermore, the non-significant increase in odds to develop persistent sub-clinical psychosis in dizygotic twins at 'genetic risk' (OR 1.56, p=.424) and the large difference in effect size compared to monozygotic twins at 'genetic risk' (OR 9.32, p<.0001) not only indicates a substantial genetic component to the phenotype of persistent subclinical psychosis but also suggests gene-gene interactions (Sham, 1998).

The results of the present study should be interpreted in the context of its strengths and limitations. Fist, it is important to realize that the current paradigm is not suggesting a new method of categorizing individuals, but aims to understand the process of moving along the extended psychosis continuum better. An advantage was the recruitment of the young adult sample from the general population. However, the sample is relatively well educated and functioning well, so generalization of the findings should be carefully considered. The sample consisted of twins, allowing for inclusion of proxy measures of genetic risk. The advantage of twin proxy measures of genetic risk is that, while non-specific, this approach is (i) well validated and (ii) represents the net genetic load including all gene-gene interactions (van Os et al., 2008). Furthermore, the study builds on a recently suggested approach examining longitudinal course of psychotic experiences rather than using observations at a single point in time, and extends this approach into the young adult life phase. A limitation of the study is that it only consisted of women. This may be important in light of the high prevalence of affective symptoms in young adult females. Verdoux and colleagues (Verdoux et al., 1999) showed, consistently replicated by others (Hanssen et al., 2003, Varghese et al., 2011) that psychotic experiences tend to arise in a context of affective dysregulation. In a later extended analysis of this issue (van Rossum et al., 2011), it was shown that the issue of co-occurrence of affective dysregulation and psychotic experiences may be best considered not so much in a context of separate classes of "psychotic" and "affective non-psychotic" individuals, but rather as a phenomenon of overlapping dimensions occasioned both by shared liability and mutual causal influence. Thus, psychotic experiences indeed commonly exist in the context of affective dysregulation, but likely represent the same dimension of psychotic experiences and do not become a separate "class" because of the co-presence of affective dysregulation. Further studies should include male participants as well. Second, the

present study relied on self-report of subclinical psychotic experiences. Although self-report inevitable leads to less accurate information, previous research has shown that both self-report and clinical interviews can be considered as reliable methods for assessment of subclinical psychosis (Allardyce et al., 2007; Kelleher et al., 2011; Konings et al., 2006). Third, only two environmental stress-related risk factors were included in the study. Finally, no longitudinal information was available on the possible development of clinical psychotic disorder after the end of the study in individuals belonging to the Persistent group, which limits the conclusions of the present study, especially with regard to the clinical implications. Further research should focus on extending the study of developmental courses of subclinical psychosis in broader samples, e.g. including both sexes, different age spans and both clinical and non-clinical participants, over longer periods of time, including possible transition to psychotic disorder, and investigate the interaction between genes and environment (van Winkel et al., 2008, 2010) in relation to developmental trajectories of subclinical psychotic experiences more in depth.

7. Genes, childhood trauma and their interaction in the development of the extended psychosis phenotype in adolescence

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Both genetic and environmental factors are thought to play a role in the development of psychotic outcomes; however their respective contributions over time, including possible developmental interactions, remain largely unknown.

The contribution of genes and gene-childhood trauma interactions to the development of a subthreshold psychosis phenotype were studied in a general population sample of 2230 adolescents, followed from age 10 to age 16 years, using indirect (parental psychopathology) and direct (candidate genes) indicators of genetic liability. Outcome measures were (i) level of psychotic experiences at age 16 (assessed with the Community Assessment of Psychic Experiences – CAPE) and (ii) persistence of such experiences over the follow-up period (identified using growth mixture modelling on the Thought Problems subscale of the Youth Self Report).

Parental level of general psychopathology was associated with CAPE score (OR=1.08; $p<.043$ for highest quintile) but not with psychosis persistence. Parental psychotic psychopathology was associated with psychosis persistence (OR 3.72, 95% CI 1.07-12.98), but not with CAPE score. Associations with CAPE score were found for polymorphisms in CNR1, PLXNA2 and SCL6A3. Polymorphisms in COMT and TPH2 were associated with membership of the Persistent group. However, none of these molecular genetic associations survived correction for multiple testing. Childhood trauma was associated with CAPE score and subclinical psychosis persistence. No evidence was found for (direct or indirect) gene-by-trauma interaction.

The development and persistence of subthreshold psychotic symptoms is subject to both genetic and environmental influences. Childhood trauma and genetic effects may operate in parallel rather than synergistically.

Introduction

Environmental factors may play a role in the development of psychosis outcomes (van Os, Kenis, & Rutten, 2010). One of the most extensively studied environmental factors in this context is developmental trauma (Read et al., 2005). Early trauma has been associated with a later diagnosis of schizophrenia (or other psychotic disorder) (Cutajar et al., 2010; Lardinois et al., 2011; Fisher et al., 2006) as well as with subthreshold psychotic experiences (Arseneault et al., 2011; Lataster et al., 2006; de Loore et al., 2007; Schreier et al., 2009). Early trauma has also been associated with developmental dynamic patterns, particularly in terms of abnormal persistence, of psychotic experiences over time (Spauwen et al., 2006; Cougnard et al., 2007; Wigman et al., 2011c and 2011d).

Associations between traumatic experiences and psychosis have been found for emotional, physical and sexual abuse as well as for bullying, with more severe (e.g. sexual) trauma displaying the strongest associations (Cutajar et al., 2010; Read et al., 2005). Furthermore, associations were usually stronger with increasing frequency and severity of the trauma experienced (Arseneault et al., 2011; de Loore et al., 2007; Lataster et al., 2006; Read et al., 2005) and when there was an intention to harm (Arseneault et al., 2011). Analyses attempting to identify the most vulnerable developmental period for the risk-increasing effects of interpersonal traumatic experience remain inconclusive. For example, one study reported the strongest associations for exposure before the age of 12 years (Fisher et al., 2010), others for exposure after age 12 years (Cutajar et al., 2010) and yet others did not find evidence for effect modification by age (Arseneault et al., 2011; Spauwen et al., 2006).

The heritability of schizophrenia is currently estimated at around 60% (Lichtenstein et al., 2009). In line with this estimate are observations that the risk of developing psychosis for a non-affected monozygotic co-twin of a person with schizophrenia is 50% (Harrison & Weinberger, 2005; Mittal, Ellman, & Cannon, 2008) and that up to 85% patients with schizophrenia do not have a first- or second-generation relative with psychotic disorder (Mason & Beavan-Pearson, 2005). Genes and environment are unlikely to act in isolation (van Os et al, 2010). Instead, the focus is on “the synergistic co-participation where the effect of one is conditional on the other” (van Os, Rutten, & Poulton, 2008; van Winkel et al., 2008, 2010). Given that not all individuals who experience trauma develop psychosis, genetic liability may play a moderating role (van Os et al., 2008; Tsuang et al., 2001). One

study reported likely interaction between trauma and genetic liability (Pfeifer et al., 2010), and early adversity was shown to moderate genetic risk for psychosis outcomes in two adoption studies (Wahlberg et al., 1997; Wicks et al., 2010). Another recent study (Arseneault et al., 2010), however, found no evidence for interaction between genetic liability and specific measures of childhood trauma.

In order to capture gene-environment interactions, a fruitful paradigm may be to also study psychotic experiences below the threshold of clinical disorder, since subthreshold phenomena may better capture the genetic vulnerability that is shared between the clinical and the non-clinical phenotypes (Kelleher et al., 2010; Lataster et al., 2009) and may be less biased by secondary factors related to the disorder or its treatment (van Os et al., 2009; van Winkel et al., 2010).

Within the extended phenotype of subthreshold psychotic experiences, persistence of psychotic experiences over time may be of particular relevance, since this excludes more transient phenomena (Nelson & Yung, 2009) and has been shown to be most predictive of later (psychotic) psychopathology (Dominguez et al., 2011; Wigman et al., 2011a, 2011d). A recent study (Wigman et al., 2011c) reported that in female young adult twins from the general population, persistence of psychotic experiences was associated with childhood trauma. Additionally, persistence was subject to substantial genetic influence. Replication of these findings is needed in adolescence, a period of substantial brain plasticity in which interactions between genetic and environmental factors may directly impact on brain development (Verdoux & Os, 2002; Weinberger, 1987) and psychosis proneness has been shown to be particularly dynamic (Mackie et al., 2010; Wigman et al., 2011d).

The present study aims to investigate the contribution of genetic and gene-trauma interactive effects on developmental patterns of subthreshold psychotic experiences using both indirect (parental psychopathology) as well as direct molecular-genetic (candidate genes) measures in a large sample of adolescents from the general population, prospectively followed from age 10 to age 16 years.

Methods

Sample Participants were enrolled in the TRacking Adolescents' Individual Lives Survey **(**TRAILS), a prospective cohort study among adolescents in the Dutch general population. TRAILS investigates the development of mental and somatic health from pre-adolescence

into adulthood (de Winter et al., 2005; Huisman et al., 2008). Data of the first three data collection waves were used: T1 (2001-2002), T2 (2003-2004) and T3 (2005-2007). Detailed information on sample and selection procedures can be found elsewhere (de Winter et al., 2005; Huisman et al., 2008). At T1, 2230 children participated (mean age 11.1 years, SD=0.6; 51% girls). At T2, 96% of these participants (N=2149) were re-assessed (mean age 13.6 years, SD=0.5; 51% girls). T3 was completed with 81% of the original number of participants (N=1816; mean age 16.3 years, SD=0.7; 52% girls). Mean number of months was 29.5 between T1 and T2 (SD=5.4; range 16.7-48.1) and 32.6 (SD=7.1; range 11.0-53.0) between T2 and T3.

Measurements

Developmental courses of subthreshold psychotic experiences Developmental courses in the present sample were identified in an earlier analysis using growth mixture modelling (Wigman et al, 2011d), revealing four distinct developmental trajectories of Thought problems, representing different expression of subthreshold psychotic experiences over time, namely a Low (N=1804), Decreasing (N=204), Increasing (N=163) and Persistent (N=41) pattern. These trajectories were based on items of the optimized Thought Problem subscale of the Youth Self Report (Achenbach, 1991; Verhulst,, van der Ende & Koot, 1997), assessed three times between age 12 and age 16 years and represent distinct psycho(patho)logical courses in adolescence. Three items (on skin picking, storing up many things and sleeping less than other children) were excluded based on their low inter-item correlations with the other items (Wigman et al., 2011d), leaving nine items in the optimized scale. The four distinct developmental patterns differed in a dose-response manner in levels of associated psychopathology (anxiety/depression, social and attentional problems, distress secondary to psychotic experiences) and level of parental report of *Thought problems,* and were differentially associated with several risk factors associated with clinical psychotic disorder (ethnic minority status, cannabis use, developmental problems, stressful life events before age 11 years and trauma between ages 12 and 16 years) (Wigman et al., 2011d).

CAPE The Community Assessment of Psychic Experiences (CAPE) positive experiences subscale (20 self-reported items) was used to assess psychotic experiences at T3 (Stefanis et al, 2002; Konings et al, 2006). The CAPE is based on the Peters et al Delusions Inventory

(Peters et al, 1999) (PDI), modified to also include hallucinatory experiences. Each item in the CAPE rates two aspects of psychotic experiences: (i) frequency and (ii) associated distress, both rated on a four-point scale of never/not distressed (1); sometimes/a bit distressed (2); often/quite distressed (3); nearly always/very distressed (4). The frequency and distress items together showed good internal consistency (Cronbach's alpha=0.93). Since the CAPE scores were not normally distributed, the scores were divided into quintiles and treated as a categorical outcome variable.

Trauma Consistent with a previous report (Wigman et al., 2011d), occurrence of life-events before the age of 11 years was calculated as the sum of the following experiences: moving, hospitalization (of self or family), sickness or death (of self, family or friends), parental divorce or being at least three months from home by parent report (all yes/no), plus a rating of the number of negative events children experienced between (i) 0-5 and (ii) 6-11 years by self-report (scale 0-10). Consistent with a previous report (Wigman et al., 2011d), trauma between 11 and 16 years was based on T2 and T3 assessments and calculated as the sum-score of the following experiences: victim of violence, gossip, bullying or sexual harassment during the last two years by self-report (all yes/no) at T2 plus two ratings at T3: a rating of the number of negative events children experienced in the last two years by self-report (scale 0-10) and a rating of the stressfulness of the child's life by parent report (scale 0-10). A single trauma measure was constructed from these measures of trauma and life events, by dividing both scores by their quintiles (1-5) and calculating the sum of the two resulting 5-point scores, resulting in a ten-point trauma scale.

Parental psychopathology Parental psychopathology was measured at T1 with the Brief TRAILS Family History Interview (Ormel et al., 2005). Several syndromes (depression, anxiety, substance use, antisocial behaviour and psychosis) were introduced by a vignette describing the main symptoms and followed by a series of questions to assess lifetime occurrence, professional treatment, and medication use. Parental psychopathology was coded as (0)=(probably) not present; (1)=(probably) present, (2)=present with additional treatment/medication (substance use, depression, anxiety and psychosis) or having experienced police arrest (antisocial behaviour). These measures were recoded into (1) (probably) present and (0) not present. Two sum scores were calculated of (i) general parental psychopathology, by adding the number of all disorders present for both father

and mother and (ii) psychotic pathology by adding the scores of psychotic pathology of both father and mother.

Genotyping At T3, DNA was collected in 1465 adolescents (65.7% of total sample); of these, 99.6% were successfully genotyped. DNA was extracted from blood samples (N=1190) or with buccal swabs (Cytobrush®) (N=275) using a manual salting out procedure as described in Miller and colleagues (1988). Genotyping was performed on the Golden Gate Illumina BeadStation 500 platform (Illumina Inc., San Diego, CA, USA), according to manufacturer protocol by laboratory personnel blinded to the true identity of the individual samples. Genotyping was done at the Genetics Department, University Medical Center Groningen, The Netherlands. Genotyping data and clustering was performed in BeadStudio 3.0 (Illumina Inc., San Diego, CA, USA). 742 of the 768 SNPs (94.3%) could be successfully genotyped with call rates varying between 95% and 100%. All DNA samples could be amplified and concordance between DNA replicates (n=53) showed 100% genotyping accuracy. Data cleaning was in line with procedures recommended by Nolte et al., (2010). Calculations of linkage disequilibrium between SNPs were performed in Excel using an Expectation-Maximization algorithm. All individuals had good call rate: the highest proportion of missing data was 5.5%. After excluding one of each monozygotic sibling pair (N=2), one of each pair with genetic correlation (N=25) and subjects who were not from Dutch ancestry (N=312), genetic data for 1138 participants (51.0% of original sample) were included in the statistical analyses (12 of the excluded individuals with genetic correlation were of non-Dutch ancestry).

TRAILS was not specifically designed to study developmental patterns of subthreshold psychosis; it focused on normal and abnormal development in adolescence, including a range of psychiatric problems such as ADHD, autism, stress-sensitivity, depression and somatic problems, such as obesity or dysregulation of the HPA axis. An assay, designed within the framework of the various research questions of the TRAILS study, was used (available upon request). TRAILS has adopted a selective, hypothesis-based approach at the level of the individual studies. Thus, for the present study, SNPs were selected from the original list in two steps. First, genes were selected that (i) have a role in neurotransmitter systems that may play a role in schizophrenia or psychosis, i.e. serotonin (SLC6A4, TPH2), dopamine (COMT, DRD2, SLC6A3), and GABA/glutamate (CNR1, GABRA6, GRIK2) or (ii) are important in regulation of differential sensitivity to environmental

influences, in particular environmental stress (BDNF, IL1B, IL2, PLXNA2). Subsequently, the available SNPs within these genes were checked against a large, online database of genetic association studies of schizophrenia (www.szgene.org; Allen et al., 2008). All SNPs mentioned in the SzGene database were selected, irrespective of the meta-analytic result (positive, negative or insufficient data) as these are regularly updated and may change over time. Twenty-eight SNPs were thus selected; three of these were unsuccessfully typed and could not be used for analyses, namely rs1801028 (DRD2), rs1327175 (PLXNA2), and rs16944 (IL1B), leaving 25 for current analyses (see Appendix). All SNPs were in Hardy-Weinberg equilibrium (p>.05) and had good call rate (>90%).

Analyses First, main effects of trauma, parental psychopathology and individual SNPs predicting (i) CAPE score (in quintiles) and (ii) developmental course (class membership) were assessed. Molecular-genetic analyses on the 25 SNPs were pursued only in case the analysis of indirect genetic effects (using parental psychopathology) suggested evidence for a genetic component. Multinominal logistic regression was used to predict (i) CAPE score in quintiles, with the lowest quintile as reference group and (ii) developmental course class membership, with the Low group as reference group.

Second, interaction effects between parental psychopathology and trauma predicting (i) CAPE score and (ii) class membership were calculated. Interaction effects were tested additively, using binary regression, since biological synergism (i.e. the degree of co-participation of causes in producing some outcome) can be better estimated from additive statistical interaction than from the often-used multiplicative statistical interaction (Darroch, 1997; van Os et al., 2008). All analyses were controlled for gender. Again, molecular-genetic analyses were conducted only in case the analysis of indirect genetic effects (using parental psychopathology) suggested evidence for a genetic contribution.

For the purpose of the genetic analyses, genotypes were coded 0, 1 or 2 and modelled as a linear effect (Kendler et al., 1995; Wichers et al., 2007). P-values were corrected for multiple testing using Bonferroni correction. Bonferroni controls for all independent statistical tests (the number of SNPs and the number of phenotypes under study) and is considered conservative.

Results

Sample Data on both developmental trajectory of psychotic experiences and genetic information was available for 1104 individuals (49.5% of the original sample). Of individuals with genetic data, 891 were in the Low group, 109 in the Decreasing group, 88 in the Increasing group and 16 in the Persistent group. Participants with genetic data were slightly younger (16.4 versus 16.2 year, $p<.036$) and more often male (46.8% versus 47.3%, $p<.001$) than participants without genetic data; they did not differ in CAPE score. Psychopathology of parents was available for 2165 individuals (97.1% of the total sample).

Associations with trauma Trauma significantly predicted CAPE score in the third (OR 1.21, 95% CI 1.12, 1.31), fourth (OR 1.26, 95% CI 1.14, 1.8) and fifth (OR 1.40, 95% CI 1.29, 1.52) quintiles at T3 (second quintile: OR 1.07, 95% CI 0.99, 1.16). Trauma also significantly predicted class membership: it predicted belonging to the Decreasing (OR 1.32, 95% CI 1.21, 1.45), Increasing (OR 1.48, 95% CI 1.32, 1.65) and Persistent class (OR 2.24, 95% CI 1.65, 3.04).

Associations with parental psychopathology General parental psychopathology significantly predicted the highest quintile of CAPE score at T3 (OR 1.08, 95% CI 1.00, 1.17) but not the second (OR 0.96, 95% CI 0.88, 1.04), the third (OR 1.03, 95% CI 0.95, 1.11) or the fourth quintile (OR 1.07, 95% CI 0.98, 1.17). General parental psychopathology did not predict class membership (OR 1.05, 95% CI 0.97-1.14 for the Increasing group; OR 1.05, 95% CI 0.96-1.16 for the Decreasing group and OR 1.16, 95 % CI 0.99-1.35 for the Persistent group).

Psychotic psychopathology in the parents showed suggestive association with the highest quintile of CAPE score (OR 2.25, 95% CI 0.96, 5.27, $p<.063$) and significantly predicted membership of the Persistent class (OR 3.72, 95% CI 1.07-12.98) but not membership of the Increasing (OR 2.04, 95% CI 0.99-4.17) or Decreasing class (OR 0.53, 95% CI 0.13-2.23).

Associations with SNPs Since parental psychopathology predicted both CAPE score in quintiles at T3 and membership of the Persistent class, molecular genetic associations were assessed for these outcome measures. Main effects on CAPE score were found for SNPs in CNR1, PLXNA2 and SCL6A3 at a significance level of $p<.05$ (Table 1). Main effects predicting

membership of the Persistent group were found for SNPs in COMT and TPH2 (Table 2). However, none of these associations remained significant after Bonferroni correction.

Table 1. Main effects of SNPs on CAPE quintile score *before Bonferroni correction*

Gene / SNP	Risk allele	2nd quintile OR	2nd quintile p	3rd quintile OR	3rd quintile p	4th quintile OR	4th quintile p	5th quintile OR	5th quintile p
CNR1									
rs12720071	G							0.55	0.020
rs806368	G	0.71	0.028						
PLXNA2									
rs2478813	A			1.60	0.024			1.75	0.007
rs752016	G			1.63	0.003	1.45	0.052	1.54	0.011
SCL6A3									
Rs140700	A	0.56	0.013					0.62	0.050

Table 2. Main effects of SNPs on persistence of Thought Problems *before Bonferroni correction*

Gene / SNP	Risk allele	OR	p-value
COMT			
rs6269	G	0.51	0.049
rs4680	G	0.52	0.036
rs4818	C	0.45	0.025
rs4633	G	0.52	0.038
TPH2			
rs1843809	C	2.5	0.005

Interaction of parental psychopathology and trauma There were no interactions between general parental psychopathology and trauma in their effect on CAPE score at T3 in the first (*p*=.306), second (*p*=.342), third (*p*=.893), fourth (*p*=.703) or fifth (*p*=.697) quintile, nor were there any interaction effects in predicting belonging to the Low (*p*=.864), Decreasing (*p*=.560), Increasing (*p*=.988) or Persistent group (*p*=.586).

In addition, no interaction effects were found for psychotic parental psychopathology on the one hand and trauma on the other, in their effect on CAPE score at T3 in the first (*p*=.822), second (*p*=.476), third (*p*=.491), fourth (*p*=.191) or fifth (*p*=.164) quintile, nor were there any interaction effects in predicting belonging to the Low (*p*=.322),

Decreasing (p=.227), Increasing (p=.439) or Persistent group (p=.937). Therefore, additional molecular-genetic interactions were not analysed.

Discussion

The present study investigated the genetic component, as well as gene-trauma interactions, to the developmental patterns of subthreshold psychosis using both indirect (parental psychopathology) and direct (candidate genes) measures in a large sample of adolescents from the general population, prospectively followed-up from age 10 to age 16. Trauma significantly predicted both level of subthreshold psychotic experiences (CAPE score at T3) as well as different developmental courses of these experiences over time. General parental psychopathology predicted the (highest) level of subthreshold psychotic experiences at age 15-16 years, whereas psychotic parental pathology predicted the persistence of such experiences from age 10-16 years and showed a trend to predicting the cross-sectional level of subthreshold psychotic experiences at age 15-16. Associations with CAPE score were found for polymorphisms in CNR1, PLXNA2 and SCL6A3. Polymorphisms in COMT and TPH2 were associated with membership of the Persistent group. However, none of these molecular-genetic associations survived correction for multiple testing. Additionally, no evidence for an interaction between childhood trauma and genetic liability was found.

The finding that trauma is associated with both cross-sectional (Read et al., 2005) and longitudinal (Wigman et al., 2011d) levels of subthreshold psychotic experiences is in line with a large body of existing literature. The toxic effect of experience of early trauma may operate via both cognitive and biological sensitization (Collip et al., 2008; van Winkel et al., 2008). Cognitively, the experience of trauma may lead to negative appraisals and beliefs about the self, leading to an increased vulnerability for negative experiences. Biologically, trauma may lead to changes in the HPA axis and subsequently in the release of dopamine, thereby leading to long-lasting neurodevelopmental abnormalities (van Os et al., 2010). These processes of sensitization may both result in increased levels of psychotic experiences over time.

The associations between general parental psychopathology and levels of subthreshold psychotic experiences at age 15-16 years and between psychotic parental pathology and persistence of such experiences are of interest. Inconsistent results have

been reported regarding the question whether the predictive value of parental psychopathology for psychopathology in the offspring is disorder-specific (Goldstein, Buka, Seidman, & Tsuang, 2010; van Meurs et al., 2009), (internalising/externalising) spectrum-specific (Kessler, Davis, & Kendler, 1997) or more diffuse (Bijl, Cuijpers, & Smit, 2002; Keshavan et al., 2008). The present results suggest that general parental psychopathology is associated with a broader spectrum of mild psychotic symptomatology, as represented by the measurement of (cross-sectional) experiences at age 15-16 years, capturing both potentially transitory and persistent phenomena. These results are in line with recent findings that a substantial proportion of schizophrenia incidence, at the population level, is associated with non-psychotic disorders in first-degree relatives (Mortensen et al., 2010). In addition, psychotic parental psychopathology was associated with persistence of subthreshold psychotic experiences, which is thought to be of more predictive value for the development of clinical psychosis (Dominguez et al., 2011). The finding of a heritability component to subthreshold psychosis is in line with earlier work that found a genetic component to the endorsement of subthreshold psychotic experiences in twins from the general population (Lataster et al., 2009) and the persistence of such experiences in these twin participants (Wigman et al., 2011c).

However, no direct molecular-genetic effects were found. Effects were expected especially in predicting the developmental courses of experiences, since this has been suggested to capture the liability to psychosis better than cross-sectional assessments of psychotic experiences. However, these developmental courses and especially the ones indexing more liability to clinical disorder, consisted of small numbers of individuals and thus, statistical power was limited.

Low statistical power may also be an explanation for the fact that no interactions were found between childhood trauma and genetic liability. This finding is in contrast with the notion that genetic and environmental factors operate in synergism (van Os et al., 2008; van Winkel et al., 2008, 2010). It is, however, in line with earlier work by Arseneault and colleagues (2011) who found that the effect of trauma on later experience of psychotic symptoms was independent of genetic liability to psychosis. It is therefore possible that potentially causal effects of childhood trauma act independently of pre-existing genetic liability to increase risk of psychosis and that type, frequency and severity of the trauma are the crucial factors determining risk. Alternatively, methodological complications may hinder

the detection of interactions between childhood trauma and genetic liability for psychosis; for example, trauma is usually assessed retrospectively. Although some authors have suggested that individuals can recall early trauma reliably (Read et al., 2005), others have questioned this (Hardt & Rutter, 2004; Morgan & Fischer, 2007). Experimental designs using social stress as a proxy measure of sensitisation to 'intention-to-harm' experiences may be instrumental to study interactions between traumatic experiences and pre-existing genetic liability, as are prospective studies, although the latter are difficult to conduct (Cutajar et al., 2010).

The results of this study should be interpreted in light of its strengths and limitations. A major strength is that it addressed a large adolescent sample from the general population and that it followed the suggestion by Kelleher and colleagues (2010) to include subthreshold psychotic experiences in the study of genetic components to psychosis. Furthermore, the study used both cross-sectional and longitudinal measures of subthreshold psychotic experiences. However, some of the developmental trajectories of psychotic experiences represented only small numbers of individuals, thereby limiting statistical power. Although often used, Bonferroni correction may be considered too conservative (too strict), leading to over-correction of analyses. Additionally, the *Thought problems* subscale on which the trajectories are based covers a broader range of psychopathology and does not specifically target psychotic symptoms. However, as earlier work showed (Wigman et al, 2011d), the trajectories can be assumed to represent subthreshold psychotic experiences, as suggested by associations with the CAPE frequency scores, a validated instrument for the assessment of psychotic experiences (Konings et al. 2006), and their associations with several risk factors that are associated with psychosis such as secondary distress, cannabis use and trauma. Another limitation is that candidate genes and SNPs were selected from a pre-selected pool not specifically designed to study subthreshold psychosis. Nevertheless, the selected SNPs covered an acceptable range of genetic variation in the most important neurotransmitter systems implicated in psychotic disorders.

Appendix

The 25 SNPs that were selected for this study from all available SNPs at TRAILS (available upon request)

Gene	SNP
BDNF	rs6265
CNR1	rs806368
COMT	rs6269 rs4680 rs737865 rs4818 rs4633 rs165599
DRD2	rs1800497
PLXNA2	rs2478813 rs752016
IL1B	rs1143634
IL2	rs2069772
TPH2	rs11178997
GRIK2	rs2227281 rs2227283 rs2235076
SCL6A3	rs40184 rs11564758 rs2652511 rs2078247
SCL6A4	rs140700 rs2066713 rs2020942 rs25531

8. Subclinical psychosis and depression: Co-occurring phenomena that do not predict each other over time

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Schizophrenia Research

The path from subclinical psychotic experiences to clinical disorder is thought to be mediated by the persistence of subclinical psychotic experiences. One of the factors that is likely associated with this persistence is depression. Although commonly viewed as interrelated concepts, the exact relationship between subclinical psychosis and depression is not clear.

Cross-lagged path modeling was used to explore the relationship between subclinical psychosis and depression across and over time in an adolescent population seeking assistance for non-psychotic disorders (N=138), measured at four occasions over a two-year period.

Subclinical psychosis and depression were related to each other at every cross-sectional measurement, but did not predict each other over time. Subclinical psychotic experiences and depressive symptom levels were highest at baseline, when participants presented to the clinical service for help. In addition, the relationship between them was also strongest at baseline and decreased significantly over time.

The results suggest that psychosis and depression are interrelated phenomena that strongly co-occur in time, but longitudinally, one does not predict change in the other. Both psychopathological dimensions should be addressed when treatment is provided to adolescent help-seekers.

Introduction

The extended psychosis phenotype is assumed to exist on a continuum, with many individuals endorsing psychotic experiences below clinical significance (van Os et al., 2009; Yung et al., 2009; Nuevo et al., 2010). This view posits that psychotic experiences do not inevitably result in psychotic disorder. However, for some individuals with subclinical psychotic phenomena, disorder may develop depending on additional factors, such as secondary distress or intrusiveness, psychopathological co-morbidities or environmental influences. These may cause subclinical psychotic experiences to become persistent with subsequent impairment and need for care, consistent with the proneness – persistence – impairment model of psychosis (Cougnard et al., 2007).

One of the factors that may play a role in the process of shifting along the psychosis continuum may be depression (Yung, 2007; van Rossum et al., 2011). Depression and positive psychosis are considered separate but interrelated dimensions of psychotic disorder (van Os & Kapur, 2009) and are closely related on all levels of the continuum. Clinically, this is reflected by diagnoses such as schizoaffective or mood disorders with psychotic features, in which depressive and psychotic symptoms co-occur. Furthermore, comorbidity between schizophrenia and depression is very high; up to 50% of schizophrenia patients experience co-morbid depression (Buckley et al., 2009). In the earlier phases of psychotic illness, depression is a commonly reported symptom in the prodrome (Häfner et al., 2005; Iyer et al., 2008) and has been shown to predict transition from ultra-high risk status to frank psychosis (Yung et al., 1998, 2003, 2004). Further down the psychosis continuum, subclinical psychotic symptoms and depression are associated in adolescent (Armando et al., 2010; Mackie et al., 2010; Yung et al., 2006; Wigman et al., 2011d) and adult (Krabbendam et al., 2005a) general population samples. From a longitudinal perspective, data from general population samples show that the developmental patterns of subclinical experiences mirror depressive symptoms in a dose-response fashion over time (Yung, 2007; Wigman et al., 2011d). Additionally, the presence of depressive symptoms in combination with hallucinatory experiences increases the risk for a later diagnosis of clinical psychosis (Krabbendam et al., 2005b).

Although psychosis and depression often co-occur at clinical and subclinical levels, the exact nature of their relationship is unclear. Depression could directly impact psychotic symptoms (van Rossum et al., 2011) by inducing negative appraisal of external stimuli,

subsequently increasing psychotic symptoms (Freeman et al., 2001) and risk for clinical disorder (Yung et al., 2004). Conversely, experiencing psychotic symptoms may induce feelings of fear, hopelessness and depression (Krabbendam et al., 2005a). Other theories suggest that psychosis and depression exist on the same continuum, in that both may result from shared liability (Verdoux et al., 1999). More research is needed to elucidate this complex relationship further.

The current study aimed to investigate the co-occurrence of, and directional relationship between, subclinical psychosis and depression, across and over time. We investigated this association in an adolescent sample seeking help for general, non-psychotic psychopathology. The dynamic adolescent life phase is an interesting period for studying this association, since proneness for both psychosis (Verdoux et al., 1998) and depression (Costello et al., 2003) are at their peak. Subclinical psychotic experiences were assessed with the Community Assessment of Psychic Experiences (CAPE) and depressive symptoms with the Centre for Epidemiologic Studies Depression Scale (CES-D) questionnaires. Cross-lagged path modelling, a statistical method that enables the investigation of the longitudinal and directional nature of associations, was applied in the present study. Based on evidence for a causal relationship in both directions, it was hypothesised that subclinical psychotic experiences and depressive symptoms would predict each other in and across time.

Method

The setting Orygen Youth Health (OYH) is a public mental health program for young people between 15 and 24 years old. The catchment area of north and west metropolitan Melbourne, Australia, covers approximately 900,000 people, about 200,000 of whom are aged between 15 and 24. The service provided at OYH has three components: EPPIC (Early Psychosis Prevention and Intervention Centre), which is a service for people with first-episode psychotic disorder, the PACE (Personal Assessment and Crisis Evaluation) clinic, which targets individuals at ultra-high risk of psychosis, and Youthscope, a service for non-psychotic individuals.

Referrals to OYH are taken from a range of sources, including general practitioners (GPs) and other primary care services, school and university counselling services, drug and alcohol services, the justice system, and youth accommodation centres, as well as from

families and young people themselves. The procedure for entry into OYH is as follows: first, a brief telephone ‘‘triage’’ interview is undertaken with the referrer and the young person. Once basic criteria are met (i.e. age and location), the young person is referred to one of the three clinical teams (EPPIC, PACE, or Youthscope) for a face-to-face interview to determine eligibility and symptom profile. All young people who are recognized as meeting the criteria for EPPIC and PACE at this interview are accepted. However, because of the high prevalence of nonpsychotic disorders such as depression, there are many more young people referred to Youthscope than can be accepted. Thus, criteria have been established for acceptance into Youthscope. These are based largely on presence of a diagnosis of a nonpsychotic mental disorder, such as depression, anxiety, and/or severe personality disorder. Degree of risk of suicide or self-harm, disability or functional impairment, and previous history of unsuccessful treatment within primary care services are also taken into account by the Youthscope clinician. Many young people not accepted into Youthscope also have high rates of depressive symptoms and poor functioning. Those not accepted also include young people with a primary diagnosis of an uncomplicated substance use disorder or a primary diagnosis of oppositional defiant disorder. The study group for this project was taken from those who were referred to, but not necessarily accepted into, Youthscope.

Participants Two hundred and four young people (aged 15-24 years) referred to Youthscope between April and October 2003 were invited to participate. Exclusion criteria were: known organic cause for presentation, known intellectual disability (IQ<70), and inability to speak English. The overall participation rate was 72.5% (56 refusals). At baseline, 138 participants completed both the CAPE and CES-D. This is the sample included in the current analysis. The mean age was 17.7 (SD 2.6); 58% of the sample was female.

A full description of the psychiatric diagnoses of this cohort, assessed with the Structured Clinical Interview for DSM-IV (SCID; First et al., 1997), is described by Godfrey et al. (2005). Briefly, 46% had current major depressive disorder, 63% had an anxiety disorder and 27% had a substance use disorder. The most common comorbidity was mood and anxiety disorders, followed by substance use disorders in combination with other mental disorders, particularly mood and anxiety disorders (Godfrey et al., 2005).

Procedure Data were collected at four assessments: at T1 (baseline; N=138); at T2, (three months after baseline; N=116, 84.1% of original cohort); at T3 (six months after baseline; N=113, 81.9% of original sample); and at T4 (two years after baseline; N=99, 71.7% of original sample). The study was approved by the local Research and Ethics Committee.

Instruments The Community Assessment of Psychic Experiences (CAPE) positive experiences subscale (20 self-report items) was used to assess psychotic experiences (Stefanis et al., 2002; Konings et al., 2006). The CAPE is based on the Peters et al. Delusions Inventory (Peters et al., 1999) (PDI), modified to also include hallucinatory experiences. Each item in the CAPE rates (i) frequency and (ii) associated distress on a four-point scale. The frequency items showed good internal consistency at all time points (Cronbach's alpha: 0.86-0.91). The Centre for Epidemiologic Studies Depression Scale (CES-D) (20 self-report items) was used to assess depressive symptomatology in the past week (Radloff, 1977). This measure rates frequency of symptoms on a four-point scale. The CES-D has been validated in an Australian adolescent sample (Rey et al., 2001).The measure showed good internal consistency at all time points (Cronbach's alpha: 0.78-0.98). Sum scores of both questionnaires were used as continuous indicators with, higher scores indicate greater psychopathology.

Analysis Analyses were conducted with Mplus 5.1 (Muthen & Muthen, 1998-2007) and PASW Statistics 18 (SPSS Inc, Chicago, Illinois, 2010). Drop-out analyses were conducted using ANOVA and odd ratios (OR). Time effects of CAPE and CES-D scores were tested with Repeated Measures ANOVA.

Path modelling was used to investigate the relationships between CAPE and CES-D scores over time, using only observed variables. Full Information Maximum Likelihood estimation was used for missing data; furthermore, robust ML (MLR) was used for model estimation because data was not normally distributed. This method estimates mean-adjusted χ^2, robust to non-normality (Brown, 2006). Over time, CAPE scores were regressed on (i) earlier CAPE scores and (ii) earlier CES-D scores and vice versa. CAPE and CES-D scores were allowed to correlate at all time points; correlations were compared with Wald tests. Thus, a cross-lagged path model was established. CAPE and CES-D scores at T1 were controlled for age and gender.

Several fit indices were used for model evaluation (Brown, 2006). For acceptable model fit, chi-square (χ^2) should be low, Comparative Fix Index (*CFI*) should be above 0.90 and Root Mean Square Error of Approximation (*RMSEA*) should be lower than 0.08.

Results

Descriptives There were no significant differences between participants who completed all study phases and those who dropped out after T1 on age, gender, socio-economic status, or CES-D and CAPE scores at baseline. Table 1 shows mean scores (SD) of the CAPE and CES-D at the four time points. Both CAPE [F(3,171)=14,75; *p*<.001] and CES-D [F(3,216)=166,66; *p*<.001) scores decreased significantly over time. Between T1 and T4, CES-D scores decreased by 37.5%, while CAPE scores decreased by 14.5%. The proportion decrease in CES-D scores was significantly greater than that of CAPE scores (OR=0.29, 95% CI=0.081-0.995, *p*=0.049).

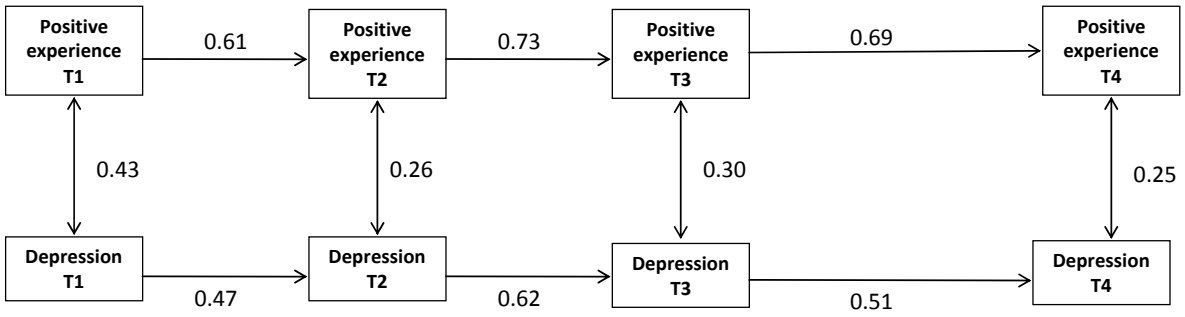
Table 1. Means (SD) of the CAPE and CES-D at all four time points.

	T1 Baseline	T2 3 months	T3 6 months	T4 24 months
CAPE – positive experiences	31.0 (9.0)	27.1 (7.4)	25.6 (7.5)	26.5 (8.2)
CES-D – depressive symptoms	28.9 (13.7)	23.0 (14.4)	20.2 (13.5)	18.1 (13.1)

Model development The model is depicted in Figure 1. A model with all paths fit the data reasonably: $\chi^2(24)=51.58$; *p*<.0001; *CFI*=0.903 and *RMSEA*=0.089. When non-significant paths were removed, model fit improved and both *CFI* and *RMSEA* were acceptable ($\chi^2(30)=55.487$; *p*<.003; *CFI*=0.910; *RMSEA*=0.075).

CES-D and CAPE scores were significantly and substantially correlated at all assessments (*p*<.001). The correlation decreased significantly between T1 and T2 (F(1)=6.06; *p*<.01), but not between other assessments. CAPE scores were significantly predicted by earlier CAPE scores (β 0.61-0.73). CES-D scores were significantly predicted by earlier CES-D scores (β 0.47-0.62). CAPE scores were never predicted by earlier CES-D scores, nor predicted CES-D scores over time. Effect sizes are reported in beta's, with a beta <0.10 representing a small effect, a beta of 0.10-0.30 a moderate effect and a beta >0.50 a large effect.

Figure 1. Path model of subclinical positive psychotic experiences and depressive symptoms. *Note:* only significant paths are depicted. Model was controlled for age and gender. Effect sizes are given in beta's.



Discussion

The present study investigated the direction and nature of the relationship between subclinical psychotic experiences and depressive symptoms across and over time in an adolescent population, which were help-seeking for general, non-psychotic psychopathology. Subclinical psychosis and depression were closely related at every assessment, but did not predict each other over time. The relationship was strongest at baseline, when participants presented to the service, and decreased significantly over time.

These results do not support the hypothesized longitudinal bidirectional relationship between subclinical psychosis and depression (van Rossum et al., 2011; Krabbendam et al., 2005a). Rather, results suggest that subclinical psychotic experiences and depression are interwoven phenomena that co-occur, but do not predict one another over time. However, this does not rule out the possibility of concurrent causation; that is, the notion that subclinical psychotic experiences and depression may exist as expressions of interrelated, yet distinguishable aspects of the same underlying factor.

The finding is consistent with suggestions that levels of depression mirror, almost exactly, levels of subclinical psychotic experiences in the general population (Yung et al., 2007; Wigman et al., 2011d). Van Os and Kapur (2009) suggest that psychosis consists of multiple domains (positive, negative, cognitive and affective symptoms). The present findings support this by demonstrating that depression and psychosis exist as parallel and comorbid phenomena, but change relatively distinguishably of one another. Other researchers have posited that psychosis and depression share a common liability (Verdoux et al., 1999) or common risk factors (Stefanis et al., 2002). These hypotheses are supported by previous findings in the general population. Using both self-report (Stefanis et al., 2002)

and clinical interview data (Krabbendam et al., 2004), subclinical psychosis and depression have been shown to exist as separate but correlated dimensions.

In the current study, depressive symptoms decreased more strongly over time than subclinical positive psychotic experiences. This may be explained by the fact that participants were referred to Youthscope for non-psychotic disorders (e.g., depression and anxiety). Treatment is likely to have been focused on reducing mood-related symptoms rather than subclinical psychotic experiences, leading depressive symptoms to improve more. The highest correlation between subclinical psychosis and depression was at presentation to the service. Over time, the relationship decreased, although the two are always significantly correlated. This decrease cannot be ascribed as inherent to the path model (i.e. that correlations at later time points are lower because these associations are more strongly controlled for), since the individual correlations also decreased over time (data not shown). This is a classic example of Berkson's bias; the phenomenon that two psychopathological dimensions are more highly correlated in clinical samples than at the general population level (Boccia et al., 2007).

The present findings should be interpreted in light of the strengths and weaknesses of the study. These results are important because they suggest that, over time, changes in one of these dimensions do not appear to lead to changes in the other, at least at this subclinical stage of the psychosis continuum. Self-report questionnaires were used for collecting data. This method may lead to data loss compared to clinical interviews, but several studies have shown that it is a reliable method to assess subclinical psychotic experiences (Allardyce et al., 2007; Kelleher et al., 2011). The fact that the sample is help-seeking can be either an advantage or a disadvantage. The interesting finding that the relationship between subclinical psychosis and depression was strongest at moment of presentation and decreased over time would have been impossible to find in a general population sample. However, because of the nature of this sample, the results may not be generalizable to psychotic, UHR or general population samples. Future research should aim at replicating the findings in different samples to fully understand the complex relations between these two concepts, since the dynamics between psychosis and depression may differ along the psychosis phenotype. It is also necessary to better understand other factors that may mediate the relationship.

9. Discussion

Goals

An increasingly influential paradigm for the study of psychosis is a dimensional one, in which psychosis is no longer seen as an all-or-nothing phenomenon, but rather as a continuum of severity, ranging from normal functioning on the one end through eccentricity and subclinical psychotic symptoms to clinical prodromes and florid psychosis on the other extreme end (van Dael et al., 2005). This shift from studying broad, heterogeneous and categorical concepts such as schizophrenia towards studying an extended psychosis phenotype that encompasses all cross-diagnostic psychotic phenomena, clinical and subclinical, seems a promising approach. However, more research is needed to fine-tune the exact phenotype to study and the mechanisms underlying the development of the psychosis phenotype. Since the pathway from the earliest and mildest expressions of psychosis to clinical disorder is highly variable and heterogeneous, a better understanding of the psychosis phenotype and its development into clinical states is important, especially from a clinical perspective, and may offer opportunities for early intervention or primary prevention of psychotic disorders.

The current thesis aimed to explore this extended psychosis phenotype by looking more in-depth at its underlying dimensions and its development over time. This was done in adolescence, a life phase during which psychosis proneness is at its peak, and in young adulthood, when psychosis proneness has decreased and is more stabilized (Verdoux et al., 1998). Hereby, an attempt was made to shed more light on the paradox (Yung et al., 2006) of former findings showing that subclinical psychotic experiences are quite common in young people (and therefore a seemingly normal developmental phenomenon) on the one hand, but are indicative for later psychotic problems for a minority of youngsters on the other hand. The thesis reports on in-depth study of the dimensions underlying the extended psychosis phenotype, a longitudinal perspective on its development and on factors impacting on this development, that have offered interesting insights in the nature of the extended psychosis phenotype and mechanisms at work along its continuum.

Furthermore, the studies described in the current thesis have suggested a new phenotype to study, namely developmental trajectories and in particular persistence of

psychotic experiences over time. This phenotype may form the connection between findings in the general population and findings in the help-seeking, pre-clinical population (i.e. individuals who are at (ultra high) risk for developing psychosis) since it is intermediate between these two populations in its psychotic expression. In this way, the "gap" that exists on the hypothesized psychosis continuum between general and clinical populations may be bridged by this phenotype of persisting subclinical psychotic experiences.

Prevalence and dimensions of the extended psychosis phenotype

The first part of this thesis studied the prevalence and dimensional structure underlying subclinical positive psychotic experiences using a cross-sectional research design in both adolescence and young adulthood. Psychotic symptoms may manifest themselves for the first time during adolescence, when psychosis proneness is assumed to be at its peak (Verdoux et al., 1998). The studies described in Chapter 2 are in line with these findings: the majority of adolescents of two large, independent general population samples (respectively 95% and 94%) endorsed at least one psychotic experience at least sometimes and respectively 43 % and 39% endorsed at least one experience often. These numbers are much higher than the 10-30% of adult individuals who report the endorsement of such experiences (Nuevo et al., 2010; van Os et al., 2009), in line with the age-dependent character of psychosis proneness. This developmental, age-dependent character of psychosis proneness is also confirmed by the finding that the prevalence of subclinical psychotic experiences in young adult females is much lower than in adolescents. The prevalences of subclinical psychotic experiences in the adolescent samples are comparable to earlier work on help-seeking, non-psychotic adolescents (Yung et al., 2006); furthermore, the prevalence of the subdimension Hallucinations matches the prevalence of hallucinatory experiences in an adolescent general population sample reported by Scott and colleagues (2009).

The fact that the prevalences reported in these two adolescent population samples are so high might be partly explained by the fact that items on paranoid ideation were included in the questionnaire that was used. This dimension is not always included in work on subclinical psychotic experiences, which focuses often only on hallucinations and/or delusions (e.g. Scott et al., 2009; Dhossche et al., 2002). The inclusion of Paranoia, the most

commonly reported psychotic experience while quite strongly correlated to the other dimensions, may have contributed to these very high reported prevalences.

In sum, this thesis joins the large existing body of literature that reports on the prevalence of subclinical psychotic experiences in the general population in both adolescence and young adulthood, supporting the idea of an extended psychosis phenotype. Furthermore, it supports the notion that psychosis proneness is maximal during adolescence and decreases with progressing age.

To investigate the dimensional structure underlying subclinical positive psychotic experiences, exploratory analyses were used in a Dutch adolescent population sample (HBSC), which suggested an underlying structure of five subdimensions as the best representation of such experiences at this age. These subdimensions were labeled Hallucinations, Delusions, Paranoia, Grandiosity and Paranormal beliefs. This five-dimensional structure was replicated in another large, adolescent general population sample (TRAILS) and also in a young adult population sample of female twins. In the adolescent as well as in the young adult samples, the model was furthermore tested against several other (one, three or four dimensional) models suggested in the literature; the five-dimensional model proved superior in both adolescent and young adult samples. Taken together, these findings may suggest life-long stability of this underlying structure.

Patterns of prevalence of the subdimensions in the two adolescent samples were similar: in both samples, Paranoia was the most reported subdimension and Hallucinations the least. In both samples, girls scored higher on all subdimensions except Grandiosity, on which boys scored higher; this latter finding is in line with earlier work showing similar differences between adult males and females (Rössler et al., 2007; Maric et al., 2003; Verdoux et al., 1998; Raine, 1992). These converging patterns support the robustness of the findings. Since the young adult sample consisted only of females, no comparisons on gender can be made. Interestingly, however, also in young females, the most reported subdimension was Paranoia and the least reported subdimension Hallucinations. Prevalences of Paranoia and Paranormal beliefs, on which women are known to score higher than men (Raine, 1992), were almost as high in young adult females as in adolescents. Prevalences of the other subdimensions, however, were much lower in young adulthood.

Although correlated, the five dimensions are suggested to represent distinguishable dimensions of psychopathology. Several arguments can be given for the usefulness of distinguishing between these five subdimensions. First, the dimensions are differentially related to other measures of psychopathology. The findings in Chapter 2 showed that Hallucinations, Delusions and Paranoia were more distressing and more strongly related to both internalizing and externalizing psychopathology than Grandiosity and Paranormal beliefs. Given that not the experiences *per se*, but rather contextual factors such as associated distress (e.g. Bak et al., 2005) and the degree of co-occurrence of affective dysregulation (van Rossum et al., 2011) may determine the outcome (Kaymaz & van Os, 2010), these differential associations may be important for course and eventual outcome. Second, prevalences of the subdimensions differed strongly, also as function of gender and age (as said, most subdimensions are reported more frequently by girls, except Grandiosity). Third, the literature and findings from the current thesis suggests that different subdimensions may be differentially related to environmental risk factors for psychosis: trauma has, for example, been associated with hallucinations (Hammersly et al., 2003) and social stressors with paranoia (Simons et al., 2009). Thus, only some of these subdimensions, namely Hallucination, Delusions and Paranoia, may tap into the extended psychosis phenotype in their continuity with mental illness.

Development of the extended psychosis phenotype

The second part of this thesis investigated the development of subclinical positive psychotic experiences over time in several general population samples, by assessing distinct developmental trajectories of such experiences in longitudinal studies in both adolescents and young adults. First, in a large general population sample of Dutch adolescents (TRAILS), four groups were found with respectively low, increasing, decreasing and persistent levels of subclinical psychotic experiences over a six-year period. The validity of these distinguishable trajectories was underlined by showing that these four groups also differed on other measures of psychopathology, such as anxiety/depression, in a dose-response way, with the persistent group reporting the highest levels of psychopathology, followed respectively by the increasing, the decreasing and the low groups. Furthermore, belonging to respectively the Persistent, Increasing and Decreasing group was associated with several risk factors known to predict psychosis, such as trauma and developmental problems, also in a dose-

response fashion. The Persistent group also used more mental health care at the end of the follow-up period.

These results were replicated in an Australian sample of adolescents from the general population, in which these developmental trajectories were also related to the use of different coping styles. Here, four groups with respectively low, moderate-decreasing, strong-decreasing and persistent levels of subclinical positive psychotic experiences were found. These four groups were compared on three styles of coping: Task-, Emotion and Avoidance-oriented coping. In general, Task-oriented coping is usually considered as the most adaptive form of coping, whereas Emotion- and Avoidance-oriented coping are seen as less adaptive. When investigating the whole sample, subclinical positive psychotic experiences were associated over time with Emotion-oriented coping in particular. When comparing the four developmental trajectories of experiences, persistence of experiences was shown to be associated with more use of Emotion-oriented coping – the least adaptive coping style. A decrease in experiences over time was furthermore associated with an increased use of Task-oriented coping. Thus, non-adaptive (Emotion-oriented) coping seems to form a vicious cycle with persistence of psychotic experience, whereas adaptive (Task-oriented) coping seems to be associated with increasing levels of adaptive functioning in general, including decreasing levels of psychotic experiences.

Taken together, the development of mild psychotic experiences has been shown to be quite dynamic in adolescence. Both adolescent samples revealed a large majority reporting low levels of subclinical psychotic experiences and a very small group of individuals with persistently high levels of such experiences over time. The groups with the low levels of psychotic experiences represent the adolescents who may experience transitory, developmentally normal levels of psychosis proneness. The small groups of individuals with high and persistent levels of psychotic experiences over time, found in both the Dutch and the Australian samples, are interesting from a clinical perspective: the persistent group for prevention and the increasing group for early intervention. In both samples, these individuals also reported the highest levels of other psychopathology, such as anxiety and depression, functioned at the lowest levels in daily life and used the most health care services. Clearly, these individuals encounter many problems in their young lives and seem to be caught in a spiral of deteriorating functioning over time.

Apart from converging findings of groups with respectively low and persistent levels of subclinical positive psychotic experiences in these two samples, more contrasting findings were found with respect to the other dynamic developmental patterns. Whereas an increasing and a decreasing course were found in the Dutch study, two decreasing patterns, differing in frequency of the experiences, were found in the Australian sample. These differences may be due to the instruments used (Youth Self Report vs CAPE), the age of the participants (10-16 vs 15-18 years) and the time of follow-up (six years vs three years). Regarding the age difference, for example, it may be the case that in the slightly older Australian sample a possibly earlier increasing group has already "split up": some individuals may decrease again in their relatively high level of experiences (represented by the strong-decreasing group) and other may have become persistent in their experiences (the persistent group).

The development of subclinical positive psychotic experiences was furthermore addressed in a general population sample of young adult (twin) females. Two developmental trajectories were found here, characterized by respectively low and persistently high levels of experiences over time. The dynamics of the development of the extended psychosis phenotype are thus less pronounced and more stabilized in young adults, in line with the literature (Verdoux et al., 1998). In sum, both the prevalence of subclinical positive psychotic experiences and their dynamics decrease dramatically after adolescence.

This peak of psychosis proneness during adolescence, reflected by high rates of endorsement of subclinical positive psychotic experiences, may be due to the developmental nature of adolescence, which is characterized by many biological, psychological and sociological changes (Steinberg, 1999). Biologically, adolescence is a period of great brain plasticity and many hormonal changes. Psychologically, questions of identity and individuality become increasingly important (Meeus, Iedema, Maassen & Engels, 2005). Sociologically, relationships with parents and peers are re-defined and shifts in separation and bonding are seen, as well as the more general striving for an independent position in society.

All these changes may lead to temporary feelings of insecurity, heightened sensitivity to the changing social context and thus a developmental increase in subtle psychotic experiences in several, interacting ways. Psychological changes may lead to an increased

self-consciousness in young people, which in turn may make them more liable to certain paranoid thought and perceptions (Steinberg, 1999). Additionally, changes in relations with parents and peers, in combination with different opinions on (borders of) the self and others may lead to a tendency to interpret behaviour of others as threatening.

The adolescent brain is still developing and has not reached maturity, with different functions developing at different stages (Crone, 2008). For example, the frontal part of the brain matures as one of the latest parts and therefore, executive functioning develops as one of the latest cognitive functions (Gazzaniga, Ivry & Mangun, 2002). One of these still developing executive functions is inhibition. The fact that inhibition is not fully developed yet in adolescents may offer one possible explanation for the higher prevalence of, for example, hallucinations, as it may be more difficult for the adolescent brain than for the adult brain to distinguish between relevant and irrelevant stimuli (Adleman et al., 2002). Another factor that may play a role in the endorsement of psychotic experiences is dopamine. Higher levels of dopamine have been suggested to lead to an increased sensitivity for the endorsement of psychotic experiences (Howes & Kapur, 2009; van Os et al., 2009). The level of dopamine is changing dramatically during adolescence and thus, adolescents may be extra prone to such experiences.

When considering all changes that are taking place during adolescence, it can even be suggested that endorsing some subclinical psychotic experiences during adolescence should be considered developmentally normal (McGorry et al., 1995). When taking a longitudinal, developmental perspective, this would entail that only a minority of these adolescents experiencing subclinical psychotic experiences will deteriorate, psychologically and functionally, and eventually develop clinical psychosis accompanied by need for care. These individuals will first become at Ultra High Risk (UHR) for psychosis and subsequently may or may not transition to clinical psychotic disorder. There is, however, a gap in the conceptualization of the psychosis continuum between phenotypes of subclinical psychosis and phenotypes of UHR status for psychosis, i.e. a gap between the general population and a help-seeking population. A focus on the persistence of subclinical psychotic experiences over time may form the bridge between general population samples and UHR samples in studying (the development of) psychosis, since this may form an intermediate phenotype. Thus, this paradigm offers the possibility to study the extended psychosis phenotype at the

level of the general population while focusing on a more specific phenotype that may be indicative for later psychotic development.

The existence of multiple distinct developmental trajectories of subclinical psychotic experiences as revealed in this thesis may be interpreted in the context of two possible pathways to psychosis, namely a neurodevelopmental pathway and an affective pathway (Myin-Germeys & van Os, 2007). The notion of a neurodevelopmental pathway already has a long history (Murray & Lewis, 1987; Weinberger, 1987). In youngsters on this pathway, early deviations in biology, social development and personality, cognition and motor activity (Cannon et al., 2002; Lewis & Levitt, 2002; Mason & Beavan-Pearson, 2005; Welham et al., 2009) are present long before onset of the distinct features of clinical psychosis. Individuals who in the current thesis are identified as having persistently high levels of psychotic experiences may be on such a neurodevelopmental pathway to psychosis. This suggestion is supported by the fact that particularly persistence of experiences seems to have a genetic component to it. This early onset, neurodevelopmental pathway is characterized by early, subtle negative symptoms, followed by the onset of positive symptoms (Dominguez et al., 2010). The experience of positive psychotic experiences, as addressed in the studies in the current thesis, may thus be considered a secondary expression of a liability to psychosis in these individuals.

The other pathway to psychosis is thought to be a more affective one and is characterized in particular by the endorsement of positive psychotic experiences. This pathway is thought to be more reactive to environmental factors and to come on line later in life (Myin-Germeys & van Os, 2007). In the current thesis, individuals who report initially normal but increasing levels of psychotic experiences over time may be on this more affective pathway to psychosis. Furthermore, several known risk factors for psychosis were associated with these increasing levels of psychotic experiences. The fact that many of these risk factors were also associated with *persistence* of experiences can be understood in light of the concept of sensitization, both on a biological and behavioral level (Collip et al., 2008; van Winkel et al., 2008). Sensitization refers to the phenomenon of responses to a certain stimulus, for example trauma, becoming increasingly stronger when exposed repeatedly to similar stimuli of equal intensity. Biologically, this may refer to increased release of dopamine on repeated exposure; behaviorally, this may refer to increased stress responses to similar stimuli on repeated exposure. The group with decreasing levels of psychotic

experiences may be less sensitive to environmental risk factors and may therefore not follow an affective pathway towards psychosis.

Taken together, the studies described in this thesis suggest that early developmental vulnerability, which is associated with later psychotic disorder and to which there is a genetic component, only becomes expressed in combination with additional exposure to multiple environmental risks, giving rise to, first, persistence of experiences and, second, the onset of need for care and use of services, in line with the psychosis proneness – persistence – impairment model (Cougnard et al., 2007).

Development and its context

Several factors have been shown in this thesis to be predictive of developmental patterns, and in particular persistent or increasing levels of subclinical psychotic experiences. The experience of trauma, one of the most extensively studied risk factors in relation to psychosis (Read et al., 2005), has been associated with later diagnosis of schizophrenia (or other psychotic disorder) (Cutajar et al., 2010; Fisher et al., 2006; Lardinois, et al., 2010) as well as with subclinical psychotic experiences (Arseneault et al., 2011; Lataster et al., 2006; de Loore et al., 2007). The current thesis showed that trauma also is associated with *persistence* of subclinical psychotic experiences in both adolescents and young adults. The use of cannabis was also shown to be associated with developmental trajectories of psychotic experiences with use of cannabis in the Dutch adolescent sample, in line with a large body of evidence supporting such an (possible causal) association (McLaren et al., 2010; van Winkel et al., 2010). Furthermore, ethnic minority status and developmental problems were also associated with persistence of psychotic experiences in Dutch adolescents. The first is in line with earlier findings of an increased risk for psychosis in ethnic minorities (Cantor-Raae & Selten, 2005). The second fits with many studies reporting on early developmental deviances in individuals who later are either at increased risk for psychosis or have indeed developed psychosis (Cannon et al., 2002).

Of the many psychological factors that play a role in shifts along the psychosis continuum, two were addressed in the current thesis in relation to subclinical positive psychotic experiences, namely coping and depression. Both these psychological concepts have shown to be associated with psychosis along its full spectrum. Since depression and coping are also closely related to each other (Endler & Parker, 1990), their role in relation to

psychosis may be even better understood when combining them. Addressing these concepts by looking at the interrelationships of respectively depression and coping with subclinical psychotic experiences over time was also an attempt to explain the mechanisms underlying shifts along the psychosis continuum.

The importance of Emotion-oriented coping styles, with coping strategies such as worrying and being angry or sad, in the development of psychosis seems intuitively understandable, especially when also taking into account the role of depression. Since Emotion-oriented coping includes many aspects that could also be considered as symptoms of depression (e.g. worrying, being sad), it is not surprising that both are similarly associated with subclinical psychotic experiences. However, this association is not completely mediated by depression (Chapter 8) and thus, coping and depression seem to play partly independent roles, at least in the high risk for psychosis phase on the psychosis continuum. Whereas depression may exist more as a parallel phenomenon with psychosis (which does not exclude mutual influence in time), coping may actually impact on the changing level of psychotic experiences over time.

The role of depression is further highlighted by the studies of developmental trajectories of subclinical psychotic experiences over time. In all three longitudinal studies addressing this development, the levels of depression or anxiety/depression mirror the level of psychotic experiences, suggesting that subclinical psychosis and depression form somewhat overlapping phenomena and may even share an underlying vulnerability (Verdoux et al., 1999). This is in line with the findings from Chapter 8, which have shown that positive psychotic experiences and depressive symptoms are always closely related in time, but that change in one does not predict change in the other.

Since not all individuals who are exposed to environmental risk factors develop psychosis, it is assumed that genetic liability to psychosis plays a moderating role (van Os et al., 2008; Tsuang et al., 2001). Genetic components have been found for clinical (van Os et al., 2009, 2010; Owen et al., 2007) and subclinical (Lataster et al., 2009) psychosis. The current thesis adds to the existing literature the finding, reported in two independent studies, that there is evidence for a genetic component to the *persistence* of subclinical psychotic experiences in individuals from the general population; one by studying twins and one by studying adolescents and their parents. The study in young adult female twins showed that having a monozygotic twin with persistent levels of psychotic experiences

increased an individual's chance of also endorsing persistence of such experiences by nine times. The study in Dutch adolescents showed that the risk of persistence of subclinical psychotic experiences in adolescence is almost four times higher for children whose parents have experienced psychotic problems.

An interaction of genetic liability for psychosis and trauma was also investigated on the persistence of psychotic experiences in adolescents. However, no interactions were found for (either direct or indirect) genetic components with trauma. This is in contrast with the notion that the impact of both genetic and environmental factors is thought to operate in synergism (van Os et al., 2008; van Winkel et al., 2008, 2010). Although in line with earlier work by Arseneault and colleagues (2011) who found that the effect of trauma on later experience of psychotic symptoms was independent of genetic liability to psychosis, power problems may also explain why no interactions were found.

All findings are thus in line with earlier suggestions of these factors as risk factors for (clinical and subclinical) psychosis. However, the studies presented in this thesis are the first to report their associations with the longitudinal course of subclinical psychotic experiences. This, and especially the finding of a dose-response predictive value of most factors in predicting the more pathological developmental trajectories, underlines the validity of the courses as representing different levels of liability to psychosis.

Implications

One of the most important theoretical implications refers to the question whether subclinical psychotic experiences should *really* be called psychotic. The current thesis supports the notion of an extended psychosis phenotype. However, the term "extended" refers not simply to "broadening" the concept of psychosis, but rather to "lengthening" it, i.e. to extend is along its developmental pathway. From this perspective, subclinical psychotic experiences may be indeed referred to as such, since they are thought to represent the very early phases of a developmental pathway that may end in clinical psychosis. Studying the extended psychosis phenotype thus aims to identify individuals who may eventually develop clinical psychosis as early as possible. Early detection and intervention are very important because this reduces the chances of (severe) disruption of functioning in daily life, development of secondary (psycho)pathology and stigmatization (van Zelst, 2009).

Besides supporting the theoretical notion of an extended psychosis phenotype, the current thesis furthermore offers a connecting, intermediate phenotype for two different stages along the extended psychosis continuum, namely the experience of subclinical psychosis at the level of the general population and being at the Ultra High Risk (UHR) for psychosis in a help-seeking population. It furthermore supports a more dimensional approach towards the development of psychopathology in general, since overlap between other dimensions of psychopathology, such as depression, is seen over time. Some steps have already been made recently towards a more dimensional, broader view on psychopathology, covering all DSM disorders. For example, a distinction between externalizing and internalizing spectrum disorders has been suggested, incorporating almost all DSM diagnoses (Vollebergh et al., 2001; Krueger, Caspi, Moffit & Silva, 1998; Krueger, 1999; Kessler et al., 2011; Kendler et al., 2003, 2011). However, psychosis has often been excluded from these studies and only recently have attempts been made to include psychosis spectrum disorders in this framework. Results suggest that psychosis or thought problems should be considered as a separate dimension, although it is correlated with other psychopathological dimensions (Kotov et al., 2010; Markon et al., 2010).

From a more clinical perspective, a focus on this phenotype of *persisting* subclinical psychotic experiences is suggested to be a fruitful paradigm for identifying individuals at increased risk for the development of psychosis. As stated earlier, incidental psychotic experiences may be transient and not very specific or valid in predicting later psychotic pathology. A focus on persistence of such experiences, however, filters out more transient phenomena (Nelson & Yung, 2009), while still addressing the general population, i.e. early on the developmental pathway towards psychosis. This offers opportunities for early detection, intervention and perhaps even prevention: if the vicious cycle of psychotic experiences, deteriorating functioning and increasing levels of other psychopathology can be broken, shifts upwards the psychosis continuum, i.e. towards clinical levels of psychosis, may be prevented.

Better understanding of mechanisms that may drive shifts over the psychosis continuum, such as the impact of depression or coping, may offer valuable opportunities for intervening at every moment in this development, thus preventing persistence or increasing symptom levels. Since both coping (Farhall et al., 2007) and depression (Reinecke, Ryan &

Dubois, 1998) can be improved with cognitive therapy, for example cognitive behavioral therapy, avenues for intervention can readily be found.

Parents of individuals with persisting levels of psychotic experiences reported consistently high levels of thought problems in their offspring. These parental-reported levels of experiences were lower than the self-reported levels by their children, in line with earlier work (Laurens et al., 2007). Since parental levels of, particularly persistent experiences, have been shown to be predictive of later psychotic psychopathology (Scott et al., 2009; Welham et al., 2009), these findings suggest that parents should always be involved when assessing young individuals who are suspected of endorsing psychotic experiences.

Methodological issues

The findings reported in this thesis should be interpreted in the light of its strengths and limitations. The main strength of the thesis is that the questions addressed have been studied in multiple samples and using multiple instruments. Both the dimensional structure and the development of subclinical psychotic experiences have been replicated in two or three samples using several instruments; this contributes to the robustness of the findings and strengthens the interpretation of the results as meaningful. An important consideration to keep in mind is that the studies in Part I argue for the notion of subclinical psychotic experiences as a multidimensional construct. However, in Part II, when studying the longitudinal development of these experiences, a unidimensional approach of these experiences is used. This can be understood in several ways. First, although preferred, longitudinal data may not always be present. When only cross-sectional data is available, in-depth assessment of the current experiences in form of a "symptom profile" of the youngster may be informative, enlarging the specificity of the symptoms and subsequently also indication for treatment. Second, all these subdimensions still are part of the extended psychosis phenotype, although not all subdimensions may be on a continuum with psychopathology in equal ways (i.e. some subdimensions may be more pathological in nature than others). The study of the development of the extended psychosis phenotype over time is a relatively new field of research. Therefore, all these subdimensions are taken into account when taking the first steps into a more longitudinal perspective.

Although it is known that persistence of subclinical psychotic experiences is associated with later (psychotic) psychopathology (Dominguez et al., 2011; Rössler et al., 2007), the studies discussed in this thesis do not have an eventual clinical outcome measure and thus cover only part of the extended psychosis continuum. However, studies in ultra high risk adolescents have shown that eventual transition to clinical psychosis is not the sole criterion for good or bad outcome (Yung et al., 2010): even in individuals who do not transition, quality of life and level of functioning may be low (Lin et al., in press). In line with this latter limitation is the fact that the critical period for the development of psychosis is not fully covered by the adolescent samples. However, the thesis also included two studies in young adults and one study in help-seeking adolescents; therefore, the scope of the thesis is still quite broad. Another limitation is that most information, including reports on the psychotic experiences, was collected via self-report, which inevitably leads to loss of information. However, earlier work has shown that self-reported subclinical psychotic experiences are valid (Allardyce et al., 2007), also in young people (Kelleher et al., 2011). One study reports on the association between subclinical psychotic experiences and depression in help-seeking adolescents; these findings may not be generalizable to individuals from the general population and should be interpreted carefully.

Directions for future research

Future research may address, first of all, the limitations as discussed above. Thus, the study of developmental trajectories may be extended by addressing the development of the separate subdimensions over time, investigating the development of the extended psychosis phenotype for longer periods of time, well into (young) adulthood and assessed with clinical interviews in addition to self-reported data, and take psychiatric diagnoses as outcome of the developmental trajectories to assess their actual predictive value. Furthermore, the development of the extended psychosis phenotype may be studied at different levels of this psychosis continuum, for example in individuals at high-risk for psychosis or after a first episode, since even within this group outcome is very heterogeneous (Yung et al., 2010). In general, the dynamics of the extended psychosis phenotype need more investigation, in both adolescence and young adulthood, to understand more of the natural course and factors that play a risk-increasing or protective role. Psychosis does not occur spontaneously; more knowledge on the pathway towards

decompensation into clinical psychosis offers, first, a better understanding of a phenotype that may form an integral part of human experience (Stip & Letourneault, 2009) but is still poorly understood, and, second, good opportunities for early intervention and perhaps even prevention of shifts upwards the psychosis continuum.

Conclusion

The present thesis has investigated the extended psychosis phenotype from a cross-sectional and a longitudinal perspective, in both adolescents and young adults from the general population by looking in-depth at its symptomatology and development over time. It argues that the extended psychosis phenotype can be addressed at the level of the general population in meaningful ways, by investigating both its dimensions and its development. The results presented have shown that psychosis proneness is a multidimensional construct that is very dynamic, particularly during adolescence. Many (biological, psychological and sociological) factors play a role in its development, such as trauma, cannabis use, depression, coping and genetic liability for psychosis; thus, it demonstrates that the development of psychosis over time takes place in a broader context.

The thesis has contributed to a better understanding of the dimensions and the development of the extended psychosis phenotype and its context and has suggested a new phenotype to study, namely developmental trajectories of psychotic experiences over time. This phenotype, being intermediate between subclinical psychotic experiences in healthy individuals and high-risk status for psychosis in its psychotic expression, may form the bridge that covers the gap on the hypothesized psychosis continuum between general and clinical populations. This thesis will hopefully form the starting point of a promising approach of research in this field.

10. Summary

Psychosis is one of the most severe psychiatric conditions, in terms of both individual and societal burden. A distortion of reality forms it central theme and symptoms may include hearing voices, paranoid feelings, apathy, thought disturbances and depression. The pathway from the earliest and mildest expressions of psychosis to clinical disorder is highly variable and heterogeneous. A better understanding of the psychosis phenotype and its development into clinical states is important, since this offers opportunities for early intervention or primary prevention of psychotic disorders.

Psychosis is currently conceptualized as an extended, or continuous, phenotype, ranging from normal functioning at one end, through eccentricity and subclinical psychotic experiences, to clinical prodromes and florid psychotic disorder at the other end. The manifestation of this (liability to) psychotic psychopathology is represented by a continuous distribution of psychotic symptom severity/intensity in the general population.

Recent research has shown that mild psychotic experiences have a lifetime prevalence of 10-30% in non-ill adults, in stark contrast with the much lower prevalence of clinical psychotic disorder at 2-3%. In other words, psychotic experiences do not necessarily persist or induce need for care. During adolescence, a dynamic developmental phase of life with many changes, mild psychotic experiences may be often endorsed. For most individuals, the early expression of subclinical psychotic experiences, or psychosis proneness, is transitory. In a minority, however, such experiences may persist, lead to distress, impaired functioning and eventually clinical psychosis. The course and outcome of subclinical psychosis is thought to depend not on the experiences per se, but more on their psychopathological, developmental and psychological context.

The current thesis aimed to increase our understanding of the extended psychosis phenotype in young people, its underlying structure and development, and factors that impact on this development. This, in turn, will provide avenues for early intervention, with the ultimate goal to delay, attenuate or even prevent transition to clinical disorder. The focus on the dimensional structure and the developmental course of subclinical psychosis, rather than on clinical psychotic illness or cross-sectionally defined subclinical psychosis

experiences, is a relatively new and promising approach to the construct of subclinical psychosis, especially in adolescence.

The current thesis reports on data from several samples of young individuals, including four general population samples: two large Dutch adolescent samples, an Australian adolescent sample and a Belgian sample of young adult female twins. One study reports on data from a sample of Australian help-seeking adolescents.

The studies in this thesis showed that many adolescents reported incidental mild psychotic experiences, underlining the high level of psychosis proneness in this developmental life phase. This psychosis proneness decreased with age, demonstrated by the lower levels of psychotic experiences reported by the young adult female sample compared to the adolescent samples.

The dimensional structure underlying subclinical psychosis was also addressed in the current thesis. A model with five subdimensions was shown to describe these experiences well in two large adolescent samples from the general population. These five dimensions were labeled Hallucinations, Delusions, Paranoia, Grandiosity and Paranormal beliefs. This five-dimensional structure was found to be superior to other models that have previously been reported in the literature. Furthermore, this model was replicated in young adulthood, suggesting life-long stability of this underlying structure. These five subdimensions, although substantially correlated, may represent (partly) distinguishable concepts, since they were differentially related to other measures of psychopathology, such as depression and distress caused by the experiences. Prevalences of the subdimensions differed strongly, as a function of gender and age; for example, girls reported higher scores than boys on all subdimensions except Grandiosity. Paranoia was the most reported subdimension and Hallucinations the least in both adolescent samples and also in the young adult females. In general, the subdimensions of Hallucinations, Delusions and Paranoia were hypothesized to be the more pathological subdimensions, whereas Grandiosity and Paranormal beliefs could be viewed as more “normal” dimensions of human experience. Therefore, it appears that only some of the subdimensions (i.e. Hallucinations, Delusions and Paranoia) may tap into the extended psychosis phenotype in their continuity with mental illness.

The development of the extended psychosis phenotype over time in several general population samples was the next topic of this thesis. First, four groups were found with respectively low, increasing, decreasing and persistent levels of subclinical psychotic

experiences over a six-year period in the Dutch adolescent sample. These four groups also differed in other measures of psychopathology, such as anxiety/depression. The level of these other measures of psychopathology mirrored the level of psychotic experiences over time. Belonging to respectively the Persistent, Increasing and Decreasing group was associated with several risk factors known to predict psychosis, such as trauma and developmental problems, with the strongest prediction for the persistent group, followed by the increasing and the decreasing group. The Persistent group also used more mental health care by the end of the follow-up period and parents of this group consistently reported the highest level of thought problems in their offspring.

Second, the finding of distinct developmental trajectories was replicated in the Australian general population sample of adolescents. These trajectories were found to be associated with the use of different coping styles. Here also four groups with respectively low, decreasing, strong-decreasing and persistent levels of subclinical positive psychotic experiences were found. Again, the group with the persistently high levels of psychotic experiences reported the highest levels of associated psychopathology and lowest levels of functioning in daily life and a dose-response relationship with these variables was found for the other three groups. These four groups were compared on three types of coping style (Task-, Emotion and Avoidance-oriented coping). When studying the whole sample, subclinical positive psychotic experiences were associated most strongly over time with Emotion-oriented coping, which is considered a non-adaptive coping style. When comparing the four developmental trajectories, it was shown that persistence of experiences was associated with more use of Emotion-oriented coping. A decrease in experiences over time was associated with increased use of the more adaptive Task-oriented coping style.

Third, two developmental trajectories were found in a general population sample of young adult females, characterized by respectively low and persistently high levels of experiences over time. Again, the young females in the Persistent group reported highest levels of depression and lowest levels of functioning in daily life.

In all samples, the group with low levels of expression of psychosis represented the best functioning individuals. These groups were also the largest subgroups of all samples. All three samples revealed the existence of a very small group of individuals with persistently high levels of subclinical psychotic experiences. These groups consistently reported high levels of co-morbid psychopathology, worst functioning in daily life and greatest use of

health care. Other dynamic developmental patterns (of increasing and decreasing levels of experiences) were only seen in the adolescent samples; these dynamics were less pronounced in the young adult sample, when psychosis proneness is assumed to be over its maximum peak and to be more stabilized and less dynamic.

Belonging to these developmental trajectories, in particular the persistent trajectory, was predicted by several factors. In both adolescence and young adulthood, trauma and stressful life events predicted increasing and persistent levels of psychotic experiences over time. Furthermore, it was shown in the Dutch adolescent sample that ethnic minority status, cannabis use and developmental problems predicted decreasing, increasing and persistent levels of psychotic experiences in a dose-response fashion.

A genetic component was found to the persistence of subclinical psychotic experiences. The study of young adult female twins showed that having a monozygotic twin with persistent levels of psychotic experiences increased an individual's chances of also endorsing persistence of such experiences by nine times. The study of Dutch adolescents showed that the risk of persistence of subclinical psychotic experiences in adolescence was almost four times higher for children whose parents have suffered from psychotic problems. However, no direct genetic effects at molecular-genetic level were found in this latter study. Furthermore, no interactions were found for either direct or indirect genetic components with trauma.

Subclinical psychotic experiences are thought to be predictive for later clinical psychosis, as is, more strongly, Ultra High Risk (UHR) status. In other words, it is assumed that there is a dose-response function of risk between psychotic experiences/symptoms and later psychotic disorder. There is, however, a gap in the conceptualization of the psychosis continuum between subclinical psychosis at the level of the general population and UHR status for psychosis: there is no clear phenotype on the hypothesized psychosis continuum connecting individuals from the general population and individuals who are seeking help for their psychotic experiences. Investigating the *persistence* of subclinical psychotic experiences over time may form the bridge between general population samples and UHR samples in the study of (the development of) psychosis, because this paradigm offers the possibility to study the extended psychosis phenotype at the level of the general population while focusing on a more specific phenotype that may be indicative for later psychotic development. Studying this phenotype of persisting subclinical psychotic experiences that

can be seen as intermediate between general population and clinical population may thus be a fruitful paradigm for identifying individuals at increased risk for the development of psychosis.

In sum, this thesis has shown that psychosis proneness is a multidimensional construct that is very dynamic, particularly during adolescence. Many (biological, psychological and sociological) factors play a role in its development, such as trauma, cannabis use, depression, coping and genetic liability for psychosis; thus, it demonstrates that the development of psychosis over time takes place in a developmental and psychopathological context. The thesis has contributed to a better understanding of the dimensions and the development of the extended psychosis phenotype and its context. The work described in this thesis has also suggested a new phenotype to study, namely the developmental trajectories of psychotic experiences over time and in particular its persistence. This phenotype may form the bridge covering the gap on the psychosis continuum between general and clinical populations. This thesis will hopefully form the starting point of a promising approach of research in this field.

11. Samenvatting

Een psychose is één van de zwaarste psychiatrische aandoeningen, zowel in termen van individuele als maatschappelijke last. Een verstoring van de werkelijkheid vormt het centrale thema van een psychose. Voorbeelden van symptomen zijn onder andere het horen van stemmen, gevoelens van paranoia (achterdocht) of apathie, het ervaren van een verstoorde gedachtegang en depressie. De bekendste psychotische stoornis is schizofrenie, een aandoening die ongeveer 1% van de bevolking treft en die gekenmerkt wordt door meerdere psychotische episodes. De ontwikkeling van de vroegste en mildste expressie van psychose tot een klinische stoornis is zeer variabel en divers. Beter begrip van het concept psychose en de ontwikkeling ervan tot klinische stoornissen is belangrijk, omdat dit mogelijkheden biedt voor vroege interventie bij of zelfs preventie van psychotische stoornissen.

De huidige wetenschappelijke visie op psychose is een continue visie, waarin psychose gezien wordt als een continu fenotype. Dit continue psychose fenotype loopt van normaal functioneren aan het ene eind van het zogenoemde “psychose continuüm”, via excentriciteit en milde (subklinische) psychotische ervaringen, naar klinische psychose aan het andere eind van het continuüm. Er is dus niet alleen sprake van ofwel gezonde ofwel psychotische mensen, maar psychotische ervaringen kunnen in meer of mindere mate voorkomen bij verschillende mensen.

Subklinische psychotische ervaringen komen voor bij 10-30% van gezonde volwassenen. Dit is een groot verschil met psychotische *stoornissen*, die maar bij 2-3% van de mensen voorkomen. Met andere woorden, psychotische ervaringen zijn niet per definitie van blijvende aard en leiden niet onvermijdelijk tot het ontwikkelen van een stoornis of behoefte aan hulp. Vooral tijdens de adolescentie, een dynamische ontwikkelingsfase vol veranderingen, kunnen subklinische psychotische ervaringen veel voorkomen. Voor de meeste jonge mensen zijn dit soort ervaringen van voorbijgaande aard. Voor een klein deel van deze mensen kunnen zulke ervaringen echter van meer blijvende, persisterende aard zijn en kunnen ze leiden tot stress, slechter functioneren en uiteindelijk tot een klinische psychose. Het beloop en de uitkomst van milde psychotische ervaringen hangt niet zozeer

van de ervaringen *op zich* af, maar meer van de context waarin ze zich voordoen. Zo kunnen dit soort ervaringen bijvoorbeeld vooral van blijvende aard zijn als ze gepaard gaan met veel stress of depressie.

Dit proefschrift heeft ten doel het begrip van het psychose continuüm in jonge mensen te vergroten, door de onderliggende structuur en de ontwikkeling van subklinische psychotische ervaringen te bestuderen, evenals factoren die daar een rol in spelen. Meer inzicht hierin biedt mogelijkheden voor vroege interventie, met als uiteindelijke doel het uitstellen, verzachten of zelfs voorkomen van een psychose. De focus op de dimensionele structuur en de ontwikkeling van subklinische psychotische ervaringen in plaats van op klinische stoornissen of op meer incidentele psychotische ervaringen is een nieuwe en veelbelovende benadering van het continue psychose fenotype, en in het bijzonder in de adolescentie.

In dit proefschrift zijn drie grote onderzoeksgroepen van adolescenten onderzocht, twee Nederlandse en een Australische. Verder is een grote groep Belgische vrouwelijke jong-volwassen tweelingen onderzocht. Elk van deze groepen vormt een representatieve steekproef van de algemene bevolking. In deze groepen is de onderliggende structuur van milde psychotische ervaringen onderzocht, de ontwikkeling van dit soort ervaringen en factoren die daar een rol in spelen. Ten slotte is ook een groep hulp-zoekende Australische adolescenten onderzocht; in deze groep is de associatie tussen subklinische psychotische ervaringen en depressie onderzocht.

De studies in dit proefschrift hebben aangetoond dat subklinische psychotische ervaringen voorkomen bij de grote meerderheid van de adolescenten en bevestigen daarmee dat de gevoeligheid voor dit soort ervaringen hoog is tijdens deze levensfase. Deze gevoeligheid neemt af met de leeftijd, aangezien de jong volwassen vrouwen veel minder van dit soort ervaringen rapporteerden.

De onderliggende structuur van subklinische psychotische ervaringen is ook onderzocht in dit proefschrift. Een model met vijf sub-dimensies bleek een goede beschrijving te zijn voor dit soort ervaringen in de twee Nederlandse adolescente groepen uit de algemene populatie. Deze vijf dimensies waren Hallucinaties, Wanen, Paranoia, Grootheidswaan en Paranormale overtuigingen. Deze structuur bleek ook een goede beschrijving van dit soort ervaringen in de jong volwassen vrouwen en was ook een betere beschrijving van subklinische psychotische ervaringen dan andere modellen die eerder

gerapporteerd zijn in de literatuur. Samen suggereren deze studies levenslange stabiliteit van deze onderliggende structuur. Deze vijf dimensies waren gecorreleerd (oftewel: hingen samen), maar vertegenwoordigen ook deels verschillende concepten, die op bepaalde vlakken goed te onderscheiden zijn. Zo hingen de dimensies bijvoorbeeld verschillend samen met andere maten van psychopathologie, zoals depressie. Verder verschilden de prevalenties erg per dimensie, ook per geslacht en leeftijd. Zo rapporteerden meisjes hogere scores dan jongens op vier van deze dimensies, met uitzondering van Grootheidswaan, waar jongens hoger op scoorden. Verder kwamen gevoelens van Paranoia het meest voor en Hallucinaties het minst, bij zowel de adolescenten als de jong volwassenen. In het algemeen kan gesteld worden dat Hallucinaties, Wanen en Paranoia de meest pathologische (ziekelijke) dimensies zijn en dat Grootheidswaan en Paranormale overtuigingen meer gezien kunnen worden als normale dimensies van menselijke ervaring. Dit, omdat deze twee dimensies minder leidden tot stress en minder sterk samenhingen met andere psychopathologie, zoals depressie. Slechts sommige dimensies van subklinische psychotische ervaringen lijken dus op een continuüm met psychopathologie te liggen.

De ontwikkeling van het continue psychose fenotype over tijd in verschillende groepen uit de algemene populatie vormde het volgende onderwerp van dit proefschrift. Drie studies toonden aan dat deze ontwikkeling dynamisch van aard is in de adolescentie en meer gestabiliseerd in de jong volwassenheid. In de Nederlandse groep adolescenten werden er vier groepen gevonden, met respectievelijk lage, afnemende, toenemende en persistent hoge niveaus van psychotische ervaringen over de tijd. Dit werd gemeten over een periode van zes jaar. Deze vier groepen verschilden in mate waarin zij andere psychopathologische symptomen ervoeren, zoals angst/depressie, waarbij de groep met persistent hoge niveaus van ervaringen de meeste andere problemen rapporteerden, gevolgd door de toenemende groep, de afnemende groep en de lage groep. De persistente groep maakte verder het meest gebruik van (geestelijke) gezondheidszorg en de ouders van de jongeren in deze groep rapporteerden ook de hoogste niveaus van denkproblemen bij hun kinderen. In het algemeen kan dus gesteld worden dat de adolescenten in de persistente groep, en in mindere mate de jongeren in de toenemende groep, een verhoogd risico lopen op het ontwikkelen van een psychose. Verder blijkt dat deze ontwikkeling niet in isolatie plaatsvindt, maar dat er sprake is van multipele psychosociale problematiek, meer zorggebruik en meer signalering hiervan door de ouders.

Dynamische ontwikkelingstrajecten van subklinische psychotische ervaringen over tijd werden ook gevonden in de groep Australische adolescenten. Hier werd de ontwikkeling van subklinische psychotische ervaringen ook gerelateerd aan verschillende coping stijlen (oftewel: manieren waarop mensen met problemen omgaan). In deze groep werden ook vier groepen gevonden, met respectievelijk lage, afnemende, sterk-afnemende en persistent hoge niveaus van subklinische psychotische ervaringen. Ook hier functioneerden de jongeren in de persistente groep het slechtst en rapporteerden zij de hoogste mate van depressie, gevolgd door de afnemende groep, de sterk-afnemende groep en de lage groep. Deze groepen werden ook vergeleken op hun manieren om waarop zij omgaan met problemen (hun "coping stijlen"). Wanneer de hele groep bestudeerd werd, bleken subklinische psychotische ervaringen over de tijd in het bijzonder geassocieerd te zijn met Emotie-gerichte coping. Dit soort coping refereert naar manieren als piekeren, verdrietig zijn en angstig of boos worden om om te gaan met problemen en wordt meestal gezien als niet-adaptief. Wanneer de vier groepen met verschillende ontwikkelingen van subklinische psychotische ervaringen over de tijd vergeleken werden, bleek dat met name de persistente groep gebruik maakte van deze coping stijl. Een afname van psychotische ervaringen over de tijd (zoals ervaren door de afnemende en sterk-afnemende groep) hing samen met toenemend gebruik van Taak-gerichte coping. Dit type coping beschrijft meer adaptieve stijlen zoals actief zoeken naar een oplossing van het probleem, praten met iemand, etc.

De ontwikkeling van psychotische ervaringen over de tijd werd ook onderzocht in de groep jong volwassen vrouwen. In deze groep werden twee ontwikkelingspatronen gevonden, namelijk een groep met lage en een groep met persistent hoge niveaus van subklinische psychotische ervaringen. Wederom rapporteerden de individuen in de persistente groep de hoogste niveaus van depressie en de laatste niveaus van functioneren in het dagelijks leven.

In alle drie deze studies waren de jonge mensen in de groepen met lage niveaus van psychotische ervaringen diegenen die het beste functioneerden. Deze groepen waren ook steeds de grootste groepen binnen iedere studie. Verder werd ook in alle drie de studies steeds een kleine groep mensen gevonden die persistent hoge niveaus van ervaringen rapporteerden. Deze groepen functioneerden in elke studie het slechtst, rapporteerden veel andere psychopathologie en maakten het meest gebruik van zorg. Andere dynamische ontwikkelingspatronen (toenemende of afnemende patronen) werden alleen bij de

adolescenten gezien. In de jong volwassenen waren deze dynamische patronen niet aanwezig. Dit is in overeenstemming met de aanname dat de gevoeligheid voor psychotische ervaringen het hoogst (en het meest dynamisch) is tijdens de adolescentie en afneemt met de leeftijd.

Het behoren tot deze groepen en vooral tot de persistente groep werd voorspeld door verschillende factoren die geassocieerd zijn met het ontwikkelen van een klinische psychose. Dit onderstreept de interpretatie dat deze groepen een weerspiegeling zijn van (verschillende gradaties van) kwetsbaarheid voor psychose. In zowel de adolescentie als de jong volwassenheid voorspelden het ervaren van trauma en stressvolle gebeurtenissen hogere niveaus van psychotische ervaringen over de tijd. In de adolescente groep bleek verder dat het behoren tot een etnische minderheid, het gebruik van cannabis en het hebben van problemen in de ontwikkeling (bijvoorbeeld later leren lopen of praten dan leeftijdsgenootjes) voorspellend zijn voor het hebben van subklinische psychotische ervaringen. De voorspellende waarde van deze factoren was het hoogst voor de persistente groep, lager voor de toenemende groep en het laagst voor de afnemende groep, ten opzichte van de lage groep.

Verder werd er ook een erfelijke component gevonden in persistentie van subklinische psychotische ervaringen over de tijd. De studie bij jong volwassen vrouwen toonde aan dat wanneer iemands eeneiige tweeling persistente psychotische ervaringen heeft, de kans dat diegene zelf ook persistente ervaringen heeft, negen keer groter is dan voor iemand wiens eeneiige tweeling dit niet heeft. Verder toonde de studie in de Nederlandse adolescenten aan dat het risico op persistente subklinische psychotische ervaringen bijna vier keer hoger is als de ouders ook te maken hebben gehad met psychotische problematiek. Echter, op moleculair-genetisch niveau werden geen effecten gevonden. Verder werden er ook geen interacties gevonden tussen genetische kwetsbaarheid en het ervaren van trauma.

Subklinische psychotische ervaringen zijn voorspellend voor latere klinische psychose. Het hebben van een Ultra Hoog Risico (UHR) status voor psychose, gekenmerkt door bijvoorbeeld een familiegeschiedenis van psychose of incidentele psychotische symptomen, heeft een nog hogere voorspellende waarde. Er wordt dus aangenomen dat er een dosis-respons relatie is, waarbij het risico op een toekomstige psychotische stoornis toeneemt met het aantal (en intensiteit van) psychotische ervaringen/symptomen. Er is

echter een hiaat op het veronderstelde psychose continuüm tussen de subklinische psychose en de UHR-status voor psychose, oftewel tussen de algemene populatie en de hulp-zoekende populatie. Persistentie van subklinische psychotische ervaringen kan de brug vormen om dit gat in de studie van (de ontwikkeling van) psychose te overbruggen, omdat het een tussenliggend fenotype vormt qua psychotische expressie. Dit paradigma biedt de mogelijkheid om het continue psychose fenotype te onderzoeken op het niveau van de algemene populatie met een focus op een specifiek fenotype dat indicatief kan zijn voor latere psychotische ontwikkeling. Daarom kan dit een zinvolle benadering zijn om mensen met een verhoogd risico op psychose tijdig te identificeren.

Samenvattend heeft dit proefschrift aangetoond, dat de gevoeligheid voor psychose een multidimensioneel construct is, met vooral in de adolescentie een dynamische aard. Verder toont het proefschrift aan dat de ontwikkeling van psychose over tijd plaatsvindt in een context van (biologische, psychologische en sociologische) ontwikkeling en psychopathologie, waarbij vele factoren een rol spelen, zoals trauma, cannabis gebruik, depressie, coping en erfelijke kwetsbaarheid. Het proefschrift heeft bijgedragen aan een beter begrip van de dimensies en de ontwikkeling van het continue psychose fenotype en zijn context. Het heeft verder een nieuw fenotype voorgesteld om te onderzoeken, namelijk de ontwikkelingstrajecten van subklinische psychotische ervaringen over tijd, en in het bijzonder persistentie van deze ervaringen. Dit fenotype vormt mogelijk de overbrugging van het gat op het psychose continuüm tussen de algemene populatie en de klinische populatie. Dit proefschrift vormt hopelijk het startpunt van veel onderzoek in deze veelbelovende benadering op het gebied van psychose.

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Curriculum Vitae

Hanneke Wigman (1983) begon in 2001 met de studie psychologie aan de Radboud Universiteit Nijmegen. Tijdens deze studie heeft zij ook het Honoursprogramma van de universiteit gevolgd. Eind 2005 studeerde zij cum laude af in de richting Neuro- en revalidatie psychologie. In haar laaste studiejaar heeft zij praktijkstage gelopen bij GGZ Meerkanten te Ermelo en hier haar aantekening psychodiagnostiek behaald. Voor haar scriptie heeft zij zes maanden gewerkt op het Clinical Neuroscience Laboratory aan de University of California, Los Angeles. In 2006 begon ze aan haar promotie traject op het project “Subklinische psychotische ervaringen bij vroeg adolescenten”, een samenwerking tussen de Universiteit Utrecht en Universiteit Maastricht. De eerste twee jaar van dit traject werkte zij in Groningen, waar ze meewerkte aan de dataverzameling voor de TRAILS studie waaraan het promotie project verbonden is. In 2010 bracht zij twee maanden door aan de University of Melbourne, Australië, waar zij een werkbezoek bracht aan ORYGEN Youth Health. In 2011 rondde zij haar proefschrift af en ontving zij een Kootstra Talent Fellowship. Momenteel is zij als post-doc verbonden aan de Universiteit Maastricht en Universiteit Utrecht.

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