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Developmental course of subclinical positive and negative psychotic symptoms and their associations with genetic risk status and impairment

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ABSTRACT

The proneness-persistence-impairment (PPI) model states that psychotic experiences are more likely to lead to impairment if their expression becomes persistent. Higher genetic risk for psychosis is known to affect proneness and persistence of subclinical positive symptoms. Less is known about potential effects of genetic risk on the course of subclinical negative symptoms, impairment, and their subsequent associations. The current study examined these issues in a large sample ($n = 1131$), consisting of individuals with higher genetic risk (siblings of patients with psychotic disorders, $n = 703$) and lower genetic risk (controls without a family member with lifetime psychosis, $n = 428$). Psychotic experiences were assessed with the CAPE questionnaire, at two time points three years apart. Participants were allocated to one of four groups representing developmental course: stable low, decreasing, increasing or persisting subclinical positive/negative symptoms. Lifetime clinical psychosis was an exclusion criterion at baseline. Higher genetic risk status was found to be associated with a persisting course of both subclinical positive and negative symptoms, symptom-related distress and functional impairment. There is no evidence for an effect of genetic risk status on the association between developmental course and impairment. The results of the current study underline the importance of assessing psychotic experiences in the context of genetic risk, multidimensional and over time. Additionally, the current findings both underscore and contribute to the PPI model: psychotic experiences are more likely to lead to impairment if their expression becomes persistent, both in individuals with higher and lower genetic risk for psychosis.

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1. Introduction

Subclinical manifestations of the psychosis phenotype, also referred to as psychotic experiences, are found to be present in the general population with prevalence rates ranging up to 17.5% (Van Os et al., 2009). Studies often use the term ‘psychotic experiences’ interchangeably with a multitude of other terms all developed to

reflect vulnerability for schizophrenia-spectrum pathology, such as ‘psychotic-like experiences’, ‘subclinical psychotic symptoms’, ‘schizotypy’, ‘schizotypal symptoms’, ‘psychosis-proneness’ and ‘attenuated psychotic symptoms’ (Kwapil and Barrantes-Vidal, 2015). In the current study we choose to use the term psychotic experiences, defined as multidimensional (including both subclinical positive and negative psychotic symptoms) psychometric risk for psychosis based on the Community Assessment of Psychic Experience (CAPE; www.cape42.homestead.com), a reliable and valid self-report questionnaire for dimensions of psychotic experiences in non-clinical samples (Konings et al., 2006).

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Findings of large general population studies show that for the vast majority of people, estimated between 75% and 90% (Van Os et al., 2009), psychotic experiences are transient and not indicative of need for care (Hanssen et al., 2005; Linscott and van Os, 2013). A minority of individuals, on the other hand, will make a transition to clinical psychosis, with an estimated prevalence rate around 4% (Van Os et al., 2009). The proneness–persistence–impairment model of psychotic disorders states that the transition from psychotic experiences to clinical psychosis is preceded by the persistence of psychotic experiences and is accompanied by increasing impairment, depending on additional risk factors (Cougnard et al., 2007; Van Os et al., 2009). Previous research has indeed demonstrated that persistence of psychotic experiences is associated with transition to clinical psychosis and/or need for care (Cougnard et al., 2007; Dominguez et al., 2011; Wigman et al., 2011a; Wigman et al., 2011b) as well as functional impairment (Dominguez et al., 2011; Kaymaz et al., 2012; De Loore et al., 2011; Rossler et al., 2007; Wigman et al., 2011b). Moreover, in a cohort of adolescents progressively stronger associations with severity of psychotic experiences, symptom-related distress and functional impairment have been reported for respectively a stable low, decreasing, increasing and persisting trajectory of psychotic experiences (Wigman et al., 2011b).

However, studies focusing on the temporal course of psychotic experiences in non-clinical samples have almost exclusively focused on the subclinical manifestation of the positive symptom dimension of psychotic disorders: delusional ideation and perceptual anomalies. There is indication that the negative symptom dimension of psychotic disorders, consisting of symptoms such as blunted affect and avolition, is also present in the general population in attenuated forms (Maric et al., 2004; Stefanis et al., 2002). Furthermore, there is evidence for familial liability between subclinical and clinical expressions of both the positive and the negative symptom dimension of psychosis (Fanous et al., 2001; Lataster et al., 2014).

Subclinical negative psychotic symptoms (from here-on referred to as ‘negative symptoms’) are clinically relevant, as they are predictive of onset of clinical psychosis (Demjaha et al., 2012; Valmaggia et al., 2013), mental health care use (Dominguez et al., 2011; Maric et al., 2004) and functional impairment (Cohen and Davis, 2009; Dominguez et al., 2011; Kwapil et al., 2013), independent of subclinical positive psychotic symptoms (from here-on referred to as ‘positive symptoms’). Additionally, there is indication of added value in assessing the course of negative symptoms over time, as the persistence of negative symptoms has been found to predict the onset and persistence of positive symptoms, and particularly their co-occurrence is found to predict help-seeking behaviour and dysfunction due to symptoms (Dominguez et al., 2010).

Previous research has shown that exposure to environmental risk factors such as childhood trauma (Read et al., 2005), cannabis use (Moore et al., 2007) and an urban environment (Krabbendam and van Os, 2005), increase the risk of persistence of positive symptoms in the general population (Cougnard et al., 2007). With regard to genetic risk, prior research in a general population female twin-sample has indicated genetic factors in the early prevalence of positive symptoms (Lataster et al., 2009a), and in particular a substantial genetic contribution to the persistence of positive symptoms is found (Wigman et al., 2011a). Dominguez et al. (2010) found indication for differences in risk factors between positive and negative symptoms in a non-clinical sample of adolescents and young adults: positive symptoms were found to be associated with environmental exposures, such as trauma and cannabis use, whereas negative symptoms were found to be associated with a pattern of socio-demographic associations possibly indicative of earlier developmental impairment, such as younger age and low education. These findings lead Dominguez et al. (2010) to hypothesize that genetic vulnerability and abnormal brain development may particularly drive the persistence of negative symptoms. In studies using variants of the schizotypy construct, the contribution of genetic

factors to both the positive and negative symptom dimension is a well-established fact (e.g. Kendler et al., 1995).

In summary, findings of previous studies in non-clinical samples provide evidence that genetic risk for psychosis affects the proneness to and persistence of positive symptoms. To a lesser degree, there is indication for a contribution of genetic risk to the developmental course of negative symptoms. In addition, proneness to and persistence of both positive and negative symptoms are suggested to independently predict clinical and functional impairment. No studies to date have focused on the contribution of genetic risk to the relation between course of psychotic experiences and clinical and functional impairment.

The current study aims to replicate findings of previous studies regarding proneness and persistence of psychotic experiences, and aims to expand on previous studies by investigating a plausible genetic contribution to the proneness–persistence–impairment model, separate for positive and negative symptoms. To fulfil these aims, we examined associations between genetic risk status, the (three year) course of positive and negative symptoms and clinical and functional impairment in a large non-clinical sample, consisting of siblings of patients diagnosed with a psychotic disorder (representing higher genetic risk status for psychosis) and healthy controls without a first degree family member with a psychotic disorder (representing lower genetic risk status for psychosis). Clinical impairment is defined as symptom-related distress and transition to clinical psychosis. Functional impairment is defined in terms of social functioning and subjective quality of life. It was expected that (1) individuals with a higher genetic risk for psychosis (siblings) are more likely to experience a persistent course of both positive and negative symptoms compared to individuals with lower genetic risk (controls), (2) higher genetic risk status for psychosis (sibling status) predicts higher levels of clinical and functional impairment, (3) persistent course of both positive and negative symptoms independently predict higher levels of clinical and functional impairment, (4) the association between persistent course and impairment is more pronounced in individuals with a higher genetic risk status (siblings) compared to individuals with a lower genetic risk (controls).

2. Methods

2.1. Participants and procedures

Data pertain to the baseline and follow-up measure of the GROUP (Genetic Risk and Outcome of Psychosis) study, an ongoing longitudinal multicenter cohort study (for details see Korver et al., 2012). For the current study, only sibling- and healthy control-data were used. Participants were recruited in selected geographical areas in the Netherlands and Belgium. Inclusion criteria were: (i) age between 16 and 50 years, (ii) good command of the Dutch language, (iii) being able and willing to give informed consent. Siblings had a brother or sister meeting the DSM-IV-TR (APA, 2000) criteria for a non-affective psychotic disorder. Siblings were not allowed to meet criteria for a lifetime diagnosis of any psychotic disorder at baseline. Healthy control participants had no lifetime diagnosis of a psychotic disorder at baseline and no first-degree relative with a lifetime psychotic disorder. The standing ethics committee approved the study, and all the subjects gave written informed consent in accordance with the committee's guidelines.

2.2. Measures

2.2.1. Developmental course of psychotic experiences

Psychotic experiences (from hereon: PE) were assessed with the self-report questionnaire Community Assessment of Psychic Experience (CAPE; www.cape42.homestead.com). Studies using the CAPE in general population samples have shown good psychometric properties in terms of reliability and validity (Konings et al., 2006). The CAPE positive and negative symptom frequency scales were used for analyses. The developmental course of PE was based on the presence or absence of high

PE at baseline (lifetime presence) and (3-year) follow-up (interval presence), reflected in a mean score in the fourth quartile on the CAPE frequency scales, assessed for positive and negative symptoms separately. Cut-offs for positive and negative symptoms were resp. 0.31 and 0.72 at baseline, and 0.15 and 0.65 at follow-up. Participants were allocated to one of four groups representing developmental course: (0) *stable low*: high PE absent at both time points, (1) *decreasing*: high PE present at baseline but absent at follow-up, (2) *increasing*: high PE absent at baseline but present at follow-up, and (3) *persistent*: high PE present at both time points.

2.2.2. Clinical outcome

Transition to clinical psychosis was defined as the onset of florid psychotic symptoms (hallucinations, delusions, formal thought disorder and/or inappropriate/bizarre behavior), between baseline and follow-up, fulfilling DSM-IV criteria (APA, 2000) for a psychotic disorder as assessed by the Comprehensive Assessment of Symptoms and History (CASH; (Andreasen et al., 1992) at follow-up. For more details on criteria for transition to clinical psychosis we refer to Van Nierop et al. (2013). Overall symptom-related distress was assessed with the CAPE, based on the sum of positive, negative and depressive symptom distress scales, with higher scores reflecting more distress (range per item: 0–3, 20 items for the positive subscale, 14 items for the negative subscale and 8 items for the depressive subscale).

2.2.3. Functional outcome

Social functioning was assessed using the Social Functioning Scale (SFS) (Birchwood et al., 1990), a widely used instrument to measure areas of functioning essential for successful community maintenance. The total score on the SFS was used as a measure of overall social functioning in the past three months. Higher scores on the SFS indicate higher levels of social functioning (range: 93.36–134.93). The World Health Organization Quality of Life (WHOQOL-BREF; (WHO, 1998) was used to rate subjective quality of life (QoL) over the past two weeks. The sum score of the four domains (physical, psychological, social and environmental) was used, with higher scores reflecting better QoL (range: 26–130).

2.3. Analyses

Analyses were run using Stata, version 12 (Statacorp, 2011). We first investigated the association between genetic risk status and the developmental course of positive/negative subclinical symptoms. Multinomial logistic regression analyses were run using the MLOGIT command. Genetic risk status (lower risk (healthy controls): 0 vs. higher risk (siblings): 1) was used as independent variable and the developmental course of positive/negative symptoms as dependent variable. In Model 1, age and gender were added as possible confounders. Also, the course of negative symptoms was added as covariate in the model of positive symptoms and vice versa (Model 2). As observations of individuals within the same family are more similar and residuals are not independent, cluster-robust standard errors were computed, using the CLUSTER option.

We then investigated the associations between genetic risk status and functional and clinical outcome. Linear regression analyses using the XTLMIXED command were run, using genetic risk status as independent variable and functional (QoL or social functioning) or clinical outcome (overall symptom-related distress) as dependent variables, adding age and gender as covariates. Standard errors were corrected for hierarchical clustering of the data at the family-level.

In order to study the association between the developmental course of subclinical positive/negative symptoms on the one hand and functional or clinical outcome on the other, linear regression analyses with developmental course as independent variable and functional (QoL or social functioning) or clinical outcome (overall symptom-related distress) as dependent variable were run for the entire sample using the

XTLMIXED command. Because there were relatively few individuals that transitioned to clinical psychosis, instead of allocating them to four groups, resulting in small or empty groups, we divided them into two groups (dichotomising the course-variable) resulting in a group *with* persisting symptoms and a group *without* persisting symptoms. For the analyses with transition as dependent variable, we performed logistic regression analyses with developmental course containing two levels (with/without persisting symptoms) as independent variable. Standard errors were corrected for hierarchical clustering of the data at the family-level. Results for the course of subclinical positive symptoms were corrected for the course of negative symptoms and vice versa. Also, age and gender were added as possible confounders. For the model of CAPE total distress (at follow-up), CAPE total distress at baseline was added as a covariate.

Finally, in order to assess the role of genetic risk status in the subsequent road to impairment, the group x developmental course interaction was tested in the different outcome models of positive symptoms and negative symptoms using linear regression analyses with the XTLMIXED command as described above.

3. Results

3.1. Sample

Of the 1646 siblings and controls in the GROUP sample at baseline, baseline and follow-up CAPE scores were available for 1131 subjects (703 relatives and 428 controls). Due to missing values in the dependent variables or covariates, sample sizes for the analyses ranged from $n = 1007$ to $n = 1131$. See Table 1 for detailed sample characteristics. Mean time to follow-up was 2.9 years ($SD = 0.2$). A contingency table of the individuals in the positive and negative symptom categories is presented in Table 2a (for controls) and Table 2b (siblings).

3.2. Effect of genetic risk on the course of psychotic experiences

Significant associations were found between genetic risk status and the developmental course of PE when correcting for age and gender, with siblings experiencing higher levels of persisting courses of both positive and negative symptoms compared to controls (Table 3, Model 1). When additionally correcting for the alternate symptom cluster, only the association between genetic risk status and course of negative symptoms remained significant (Table 3, Model 2).

3.3. The effect of genetic risk status on clinical and functional outcome

Correcting for age and gender, significant associations were present between genetic risk status and functional as well as clinical outcome at follow-up. Genetic risk status was found to be associated with lower levels of social functioning ($B = -1.78$, $P < 0.001$, 95% CI = -2.58 ; -0.98), lower quality of life ($B = -0.81$, $P = 0.04$, 95% CI = -1.61 ; -0.01) and higher overall symptom-related distress ($B = 0.08$, $P = 0.015$, 95% CI = 0.02 ; 0.15) at follow-up. Siblings also showed a trend

Table 1
Sample characteristics (at baseline).

	Controls ($n = 428$)	Siblings ($n = 703$)
Age (mean)(SD)	31.3 (10.7)	27.8 (8.0)
Gender (% male)	56	55
Education (%)		
No education	0	0
Primary school	2	5
Secondary school	13	19
High school	31	21
Vocational education	44	42
University	10	13

Table 2a
Number of individuals per developmental course for controls.

Positive symptoms	Negative symptoms				Total N (%)
	Stable low	Decreasing	Increasing	Persisting	
Stable low	350	22	22	2	385 (90.2)
Decreasing	15	1	1	2	19 (4.4)
Increasing	10	0	3	3	16 (3.7)
Persisting	4	1	1	1	7 (1.6)
Total N (%)	379 (88.8)	24 (5.6)	16 (3.7)	8 (1.9)	427 (100)

towards an elevated risk of developing a clinical psychosis, though this effect did not reach statistical significance in the current sample (OR = 2.2, 95% CI = 0.47; 10.58).

3.4. Developmental course of psychotic experiences and clinical outcome

When correcting for age, gender and the course of the alternate symptom cluster (negative symptoms), increasing subclinical positive symptoms were found to be associated with higher levels of overall symptom-related distress, and persisting subclinical positive symptoms were associated with transition to clinical psychosis (Table 4). For negative symptoms, increasing and persisting symptoms were associated with higher levels of overall symptom-related distress, independent of the course of positive symptoms. Persisting negative symptom course was not independently associated with transition to psychosis (Table 4).

3.5. Developmental course of psychotic experiences and functional outcome

Compared to the reference category (stable low) and corrected for age, gender and negative symptoms, we found increasing and persisting positive symptoms to be associated with both poorer social functioning and QoL at follow-up (Table 5). For negative symptoms, we found decreasing, increasing and persisting negative symptoms to be associated with poorer social functioning and QoL, independent of positive symptoms (Table 5).

3.6. The effect of genetic risk on the associations between course and outcome

When examining the interaction between genetic risk status and the developmental course of PE in the models of functional and clinical outcome, no significant interactions were found (results not shown). Controls and siblings did not differ significantly in the association between the course of positive or negative symptoms and any clinical or functional outcome measures. For the model of transition to clinical psychosis, the interaction could not be tested due to the small amount of individuals that transitioned (n = 10; 8 siblings, 2 controls).

Table 2b
Number of individuals per developmental course for siblings.

Positive symptoms	Negative symptoms				Total N (%)
	Stable low	Decreasing	Increasing	Persisting	
Stable low	529	25	30	16	600 (85.3)
Decreasing	24	11	5	6	46 (6.5)
Increasing	11	3	7	6	27 (3.8)
Persisting	9	5	3	13	30 (4.3)
Total N (%)	573 (81.5)	44 (6.3)	45 (6.4)	41 (5.8)	703 (100)

Table 3
Associations between genetic risk status and developmental course.

	Model 1 ^a		Model 2 ^a	
	RRR ^b	95% CI	RRR ^b	95% CI
Positive symptoms ^c				
Decreasing	1.46	0.85 ; 2.53	1.25	0.71 ; 2.17
Increasing	0.98	0.52 ; 1.85	0.70	0.36 ; 1.38
Persisting	2.68*	1.10 ; 6.55	1.79	0.68 ; 4.69
Negative symptoms ^c				
Decreasing	1.15	0.69 ; 1.93	1.12	0.66 ; 1.90
Increasing	1.77	0.96 ; 3.25	1.72	0.93 ; 3.17
Persisting	3.51**	1.62 ; 7.63	2.98**	1.33 ; 6.68

* P < 0.05, ** P < 0.01

^a Model 1: The association between genetic risk and course corrected for age, sex and for clustering at the family-level. Model 2: also corrected for the alternate symptom cluster.

^b Relative Risk Ratio, representing the relative risk of experiencing a specific symptom course for individuals with higher genetic risk (siblings) relative to individuals with lower genetic risk (controls).

^c Stable-low is used as the reference category

4. Discussion

The main aim of the present study was to investigate a plausible genetic contribution to the proneness-persistence-impairment model in a large non-clinical sample consisting of individuals with higher genetic risk (siblings) and lower genetic risk for psychosis (controls), separate for subclinical positive and negative symptoms. In line with our initial expectation, we found that siblings are more likely to experience a persistent course of both positive and negative symptoms compared to controls. Also, mostly in line with our initial expectations, we found that sibling status and persistent course of both positive symptoms and negative symptoms are associated with most types of clinical and functional impairment. However, the association between persistent course and impairment was not significantly different in siblings compared to controls.

4.1. Genetic risk status predicts course of psychotic experiences

In line with our first expectation, the findings of the current study show that both subclinical positive and negative symptoms are more likely to persist in siblings of patients with a psychotic disorder compared to controls. After correction for the alternate symptom cluster (in addition to age and gender), this association remained present for negative symptoms, but was no longer statistically significant for positive symptoms. This may suggest that genetic vulnerability particularly drives the course of negative symptoms, as has been proposed by Dominguez et al. (2010). A second explanation is that genetic risk may be (partly) associated with the co-occurrence of positive and negative symptoms, which is in line with a proposed multidimensional construct of subclinical expression of the psychosis phenotype (e.g. Kwapil

Table 4
Associations between developmental course and clinical outcome in the total sample

	Positive symptoms		Negative symptoms	
	B ^a	95% CI	B ^a	95% CI
Transition to psychosis				
Persisting vs non-persisting	3.32*	0.76 ; 5.89	1.80	-0.67 ; 4.27
Total distress ^b				
Decreasing	-0.10	-0.21 ; 0.00	0.03	-0.08 ; 0.14
Increasing	0.20**	0.07 ; 0.33	0.50***	0.39 ; 0.60
Persisting	-0.05	-0.20 ; 0.09	0.56***	0.42 ; 0.69

* P < 0.05, ** P < 0.01, *** P < 0.001

^a Corrected for age, sex, clustering at the family-level and the alternate symptom cluster

^b Stable-low is used as the reference category

Table 5

Associations between developmental course and functional outcome.

	Social functioning		Quality of life	
	B ^a	95% CI	B ^a	95% CI
Positive symptoms ^b				
Decreasing	-0.93	-2.42 ; 0.57	-0.46	-0.99 ; 0.07
Increasing	-4.32***	-6.16 ; -2.49	-1.38***	-2.04 ; -0.73
Persisting	-2.69**	-4.71 ; -0.67	-1.20**	-1.92 ; -0.47
Negative symptoms ^b				
Decreasing	-3.28***	-4.73 ; -1.83	-1.11***	-1.63 ; -0.59
Increasing	-5.43***	-6.73 ; -3.88	-2.05***	-2.60 ; -1.50
Persisting	-9.29***	-11.09 ; -7.49	-3.59***	-4.24 ; -2.95

** P < 0.01, *** P < 0.001

^a Corrected for age, sex, clustering at the family-level and the alternate symptom cluster^b Stable-low is used as the reference category.

and Barrantes-Vidal, 2015). A third, -not mutually exclusive- explanation may lie in the relatively high correlation between the positive and negative clusters ($r = 0.50$ at baseline and 0.54 at follow-up) combined with the relatively low number of individuals with persistent positive symptoms in the current sample (see Table 2a and 2b). When corrected for the course of negative symptoms, part of the variation in positive symptoms is also 'filtered out'. This may have influenced the results for positive symptoms more than for negative symptoms, as there were fewer individuals with persistent positive symptoms. Finally, it is possible that the course of negative symptoms may partly reflect depressive symptoms. Although adequate discriminative validity for (subclinical) depressive and negative symptoms has been demonstrated, they are also found to be highly correlated ($r = 0.72$) (Stefanis et al., 2002). Similarly, in the current study, we found high correlations between (subclinical) negative and depressive symptoms ($r = 0.71$ at baseline and 0.78 at follow-up).

4.2. Genetic risk status predicts impairment

Regarding the association between genetic risk status and impairment, we found sibling status to predict lower levels of social functioning and lower subjective quality of life at follow-up, corrected for age and gender. As far as we are aware, this is the first study that links genetic risk status for psychosis with both clinician-rated (social functioning) and subjective functional impairment (quality of life). Unfortunately, no data on functional outcome were available at baseline for siblings and controls in the GROUP study, so correcting for baseline social functioning and quality of life was not possible. A similar study in the patient sample of the GROUP study, however, showed that correcting for baseline functioning did not change the results (Janssens et al., 2016).

Additionally, we found that sibling status predicts higher overall symptom-related distress at follow-up, when correcting for baseline symptom-related distress, age and gender. This finding is in line with earlier studies associating genetic risk status for psychosis with higher stress-reactivity, e.g. a study by Myin-Germeys et al. (2001), who found intermediate levels of emotional reactivity to stress in first-degree relatives of patients with psychotic disorders compared to patients and controls, and Lataster et al. (2009b), who found associations between genetic risk status for psychosis, psychotic experiences and reactivity to stress.

In the current study, siblings also showed a trend towards an elevated risk of developing a clinical psychosis, but this effect did not reach statistical significance. This may be attributed to a power problem, due to the relatively low number of individuals who suffered first onset of clinical psychosis in the current sample ($n = 10$, 8 siblings and 2 controls). As the expression of psychotic symptoms is known to peak in adolescence and early adulthood and decreases over time (Verdoux et al., 1998), our relatively low rate of transition may have been affected by the rather high mean age of the participants in the current study (see Table 1).

4.3. Course of psychotic experiences predicts impairment

In line with our hypothesis, we found increasing and persistent course of both positive and negative symptoms to be associated with lower social functioning and quality of life, when correcting for age, gender and the alternate symptom cluster. This finding is in line with earlier studies regarding symptom course and functional impairment (Cohen and Davis, 2009; Dominguez et al., 2011; Kaymaz et al., 2012; Kwapiil et al., 2013; De Loore et al., 2011; Rossler et al., 2007; Wigman et al., 2011b). Additionally, we found that decreasing negative symptoms were associated with more functional impairment at follow-up, compared to individuals with stable low negative symptoms. This suggests that having experienced negative symptoms (in spite of potential 'recovery' from these negative symptoms) may still serve as a risk factor for functional impairment. This is in line with the hypothesis by Dominguez et al. (2010) that negative symptoms may be associated with earlier developmental impairment.

Increasing course of positive and negative symptoms and persisting course of negative symptoms, but not positive symptoms, were found to be associated with overall symptom-related distress. The latter finding may indicate habituation to psychotic experiences in terms of emotional response, but could also be explained by a power problem due to the relatively low number of individuals with persistent positive symptoms in the current sample, as has been mentioned before. Furthermore, we found that persisting positive, but not persisting negative symptoms, were independently associated with transition to clinical psychosis. This may be explained by construct overlap between subclinical and clinical psychosis, and the well documented fact that clinical psychosis is usually preceded by persistent subclinical positive symptoms (Cougnard et al., 2007; Dominguez et al., 2011; Wigman et al., 2011a; Wigman et al., 2011b).

4.4. No interaction between genetic risk status and course for levels of impairment

In contrast with our expectation, no significant interaction effect was found between genetic risk status and course in the prediction of impairment, indicating that once an individual experiences persistent symptoms, both siblings and controls are equally at risk of developing clinical (in terms of symptom-related distress) and functional impairment. This finding underscores the validity of the proneness-persistence-impairment model, in individuals with both higher and lower genetic risk for psychosis.

4.5. Methodological considerations

Several potential limitations of the current study have been touched on earlier in the Discussion section. For one, some of the findings of the current study may have been limited by statistical power problems, due to the relatively low number of individuals who experienced persistent positive symptoms and who transitioned to clinical psychosis in the current sample. Other aforementioned potential limitations are the lack of correction for (the course of) depressive symptoms mainly in regard to (the course of) negative symptoms, and the lack of feasibility to correct for baseline functional impairment.

Furthermore, phenomenology alone using a self-report measure may not fully capture the vulnerability for schizophrenia-spectrum pathology, as has been mentioned, for instance, by Thaker et al. (1996). Also, developmental course of psychotic experiences was currently assessed at two time-points. Variation in severity of psychotic experiences within-subjects in between time-points is possible. Still, when at two 'random' time-points the severity of psychotic experiences is high, it is likely that these experiences are more persistent over time (i.e. of high severity all the time or a large percentage of time). Finally, as has been mentioned in the Introduction section, so far many terms have been developed to reflect vulnerability for schizophrenia-spectrum

pathology, yet general consensus on the operationalization of terms is lacking. In response to the this issue, authors have recently called for the need of development of a multidimensional model unifying all symptoms constructs that represent vulnerability for schizophrenia-spectrum pathology (Kwapil and Barrantes-Vidal, 2015). The results of the current study underline the importance of assessing psychotic experiences in the context of genetic risk, multidimensional (including both subclinical positive and negative symptoms) and over time.

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Conflict of interest

None.

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