Statistical approaches to explore clinical heterogeneity in psychosis

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CHAPTER 5

The predictive value of neurocognition and social cognition for the development of psychotic experiences in siblings of people with psychotic disorders

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Abstract

Background: Neurocognitive and social cognitive impairments are associated with psychotic experiences in individuals with psychotic disorders. Diminished cognitive functioning has also been found in non-affected siblings at genetic high risk for psychosis. Our aim is to investigate the relationship of neurocognitive and social cognitive measures with course and impact of psychotic experiences in siblings of people with psychotic disorders.

Methods: Data were obtained from the Genetic Risk and Outcome of Psychosis (GROUP) project: a longitudinal multi-center cohort study in the Netherlands and Belgium. Neurocognitive and social cognitive functioning was assessed at baseline in 873 siblings (age of 35 years or less) of individuals with psychotic disorders. Frequency and distress of psychotic experiences were assessed at baseline and 3-year follow-up. A mixture of generalized linear mixed-effects model was used to test for associations.

Results: Poorer baseline verbal learning performance predicted the occurrence of psychotic experiences after three years and the distress associated with these psychotic experiences. Moreover, better baseline performance on a Theory of Mind (ToM) task was associated with a decrease of psychotic experiences over three years. Baseline distress was associated with poorer recognition of angry and neutral faces and strikingly, with better recognition of faces in general.

Conclusion: Verbal learning and ToM were found to be predictive of frequency, distress and course of psychotic experiences over three years respectively. Our findings suggest that even though cognitive functioning is poorer in people at GHR, this poorer functioning is not a robust predictor of the course of psychotic experiences.

Keywords: cognition; genetic high risk; ultra-high risk; neurocognition; social cognition; siblings; psychosis

1. Introduction

Neurocognitive and social cognitive deficits are core features of psychotic disorders and are associated with psychotic experiences (Heinrichs and Zakzanis, 1998; Doody et al., 1998; Elvevag and Goldberg, 2000), poor every day functioning and reduced quality of life (Pijnenborg et al., 2009; Green et al., 2000; Green et al., 2004; Alptekin et al., 2005; Irani et al., 2012). A milder degree of cognitive impairment may be already present in attenuated form in people at clinical high risk (CHR) for psychosis (Lencz et al., 2006; Addington et al., 2008; Becker et al., 2010; Kim et al., 2011) as well as in non-affected individuals at genetic high risk (GHR) for psychosis (Kremen et al., 1994; Appels et al., 2003; Snitz et al., 2006; Meijer et al., 2012; Quee et al., 2014). In line with this, several studies found brain abnormalities in cognitively impaired relatives at GHR (Bhojraj et al., 2011; Crossley et al., 2009), consistent with fronto-temporal dysfunctions seen in patients with schizophrenia (Crossley et al., 2009; Chua et al., 2007; Gur et al., 2000; Hirayasu et al., 2001). These findings suggest that neurocognitive and social cognitive deficits precede the onset of psychosis instead of being a consequence of psychosis (Bora et al., 2014).

The lifetime risk of developing schizophrenia in the general population is 1%, the risk of siblings at GHR thought to be approximately ten times higher (Gottesman and Wolfgram, 1991). However, certainly not all CHR or GHR individuals show an increase in psychotic experiences over time and/or make the transition to a psychotic disorder. It is suggested that cognitive functioning is associated with both the prevalence and course of psychotic experiences over time in these high risk groups.

There are several studies that examined cognitive functioning in high risk groups. Unfortunately, most studies on cognitive functioning in high risk groups are of cross-sectional design, comparing cognitive performance of CHR groups (Addington et al., 2008; Frommann et al., 2011; van Rijn et al., 2011; Myles-Worsley et al., 2007; Kim et al., 2010; Thompson et al., 2012; Chung et al., 2008) and GHR (Meijer et al., 2012; Myles-Worsley et al., 2007; Hughes et al., 2005; Klemm et al., 2006; de Achaval et al., 2010; Bertisch et al., 2008) with (first-episode) schizophrenia patients and/or healthy controls. These studies found cognitive alterations in CHR and GHR individuals, mostly at a level that is in-between healthy controls and individuals with psychotic disorders. Although these studies provide insight in the cognitive domains associated with psychosis, they do not give information on the direction of causality of the relation between cognitive functioning and increase in psychotic experiences. To this end, longitudinal studies would be needed.

However, the longitudinal studies that were done focused on the relationship between cognitive functioning and transition to psychosis as a discrete outcome and not on increased psychotic experiences as a continuous measure. By focusing exclusively on transition, information on cognitive variables that are continuously associated with an increase of psychotic symptoms is lost. Previous studies on transition showed that cognitive functioning is more impaired in those who transitioned compared with those who did not (Becker et al., 2010; Bora et al., 2014; Keefe et al., 2006; Pukrop et al., 2007; Riecher-Rossler et al., 2009; Kim et al., 2011; Agnew-Blais and Seidman, 2013), but did not consistently report specific cognitive factors to be predictive of transition to psychosis (Addington and Barbato, 2012) .

Regardless of cognitive functioning, distress caused by psychotic experiences is an important predictor of transition to psychosis and of a more severe course in general (Garety et al., 2007). However, little is known about the relationship between cognitive functioning and distress caused by psychotic experiences in at risk samples. One previous study showed hypothalamic-pituitary-adrenal (HPA) axis abnormalities, which are an indicator of distress, are associated with poorer cognitive functioning, in children with a heightened risk for psychotic disorders that, suggesting at least a cross-sectional association between distress and cognition in high risk groups (Cullen et al., 2014).

In sum, although it is assumed that certain cognitive variables may be related to vulnerability for psychosis, while others may be more related to the actual onset of the disorder (Bora et al., 2014), it is not exactly clear which cognitive variables are associated with the frequency and increase of psychotic experiences over time. In the current longitudinal cohort study these issues will be addressed in a large GHR sample.

The aim of this study is to investigate the relationship of neurocognitive and social cognitive measures with the frequency and course of psychotic experiences and distress caused by these experiences in a large GHR sample. Given that psychotic experiences are dimensional rather than dichotomous in at risk groups (van Os et al., 2009), the primary outcomes of the current study are the presence and course of psychotic experiences over time rather than transition to psychotic disorder. It is expected that poorer cognitive functioning at baseline is associated with both frequency and distress of psychotic experiences three years later and the change in psychotic experiences and associated distress over three years. Since there is hardly any literature on the association between distress caused by psychotic experiences and cognitive functioning, this association will be examined in an exploratory way.

2. Methods

2.1. Subjects

Data were collected as part of the longitudinal observational multicenter study Genetic Risk and Outcome of Psychosis (GROUP) in the Netherlands and Belgium on vulnerability and resilience in both patients with a non-affective psychotic disorder, their unaffected family members and non-related controls. The details of the GROUP study have been presented elsewhere (Korver et al., 2012). For the present study, data from baseline and 3-year follow-up were used. Siblings were asked to participate if they had at least one participating sibling with a DSM-IV (American Psychiatric Association, 2000) diagnosis of non-affective psychotic disorder. Siblings could be included if they (i) were between 16 and 50 years, (ii) had a good command of Dutch language and (iii) had no lifetime psychotic disorder at baseline, which was assessed with the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al., 1992) or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) (Wing et al., 1990). For this study, all siblings with age >35 were excluded, because this generally considered the upper boarder of the age-range in which psychotic disorders usually have their onset. Siblings diagnosed with a lifetime psychotic disorder were included in the patient group. Finally, the sample at baseline (data release version 3.02) consisted of 873 unaffected siblings of individuals with psychotic disorders. For 136 families, more than one sibling of the patient was included. To examine the specificity of the descriptive results, 386

healthy control subjects were included with age ≤35 years. Controls were excluded if they had a life-time psychotic disorder of a first-degree family member with a life-time psychotic disorder. Other inclusion and exclusion criteria for controls were same as for siblings.

The GROUP study was approved by the Medical Ethics Committee of the University Medical Center Utrecht. All The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from all participants.

2.2. Measures

Psychotic experiences and cognitive functioning were assessed using multiple instruments presented in a fixed order by trained research assistants (for details see (Korver et al., 2012)).

2.3. Psychotic experiences

The dependent variables were the frequency of psychotic experiences and the amount of distress of those experiences as measured by the Community Assessment of Psychic Experiences (CAPE) (Konings et al., 2006). The CAPE is a widely applied self-report questionnaire consisting of 42 items (www.cape42.homestead.com) on three dimensions: positive psychotic-like experiences (20 items), negative symptoms (14 items) and depressive symptoms (8 items) (Stefanis et al., 2002). For the present analyses, only the positive dimension was included. Subjects were asked to indicate the frequency of PE and the amount of distress resulting from these experiences on a 4-point Likert scale, ranging from 'sometimes' to 'nearly always'. Only if frequency was rated positively, the experienced distress thereof was measured on a 4-point Likert scale, ranging from 'a bit' to ‘very distressed'. A weighted mean score was calculated for psychotic experiences frequency and distress at baseline and follow-up measurement respectively. At baseline, lifetime prevalence of psychotic experiences was assessed, while at follow-up PE occurring during the last three years was assessed. Transition to psychosis between baseline and 3-year follow-up was based on a diagnosis of psychotic disorder, as assessed with the CASH or SCAN (Andreasen et al., 1992; Wing et al., 1990).

2.4. Measures of neurocognition and social cognition

The cognitive battery was based on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus (Nuechterlein et al., 2004) and included the domains of verbal learning and memory, sustained attention and vigilance, executive functions (set shifting and problem solving), visuospatial abilities, processing speed, verbal comprehension, working memory, global cognitive functioning and social cognition, including ToM and emotion perception. General face recognition was included to correct for non-emotional facial recognition (see Table 1). Baseline and 3-year follow-up measurement psychotic experiences were included, whereas for neurocognitive and social cognitive functioning only baseline measurement was analyzed.

2.5. Substance use

Baseline cannabis use was included as a confounding factor because of its association with both cognitive functioning (van der Meer et al., 2014) and PE (van Winkel and GROUP Investigators, 2015). Cannabis use (yes/no) was assessed with the Composite International Diagnostic Interview (CIDI) (WHO, 1990).

2.6. Statistical Analyses

2.6.1. Descriptive

Socio-demographic, neurocognition and social cognition characteristics of siblings at baseline were compared with healthy controls using the Mann-Whitney U test, T-test or Chi-square test depending on the type of variable.

2.6.2. Attrition and Missingness

Differences on baseline cognitive measures and PE between drop-outs and non-drop-outs for siblings and control subjects were analyzed. There were many differences between responders and non-responders on cognitive measurement. These differences are presumably all related to symptoms of psychotic disorders and therefore, we assumed that results based on complete cases would most likely be biased. The attrition rates for both outcomes were calculated as Attrition (%) = 100 − (siblings available at follow-up/siblings available at baseline based on outcomes) (Howie and Straker, 2016). To reduce attrition with this young group of siblings, we dealt with missing data in statistical way where attrition is difficult to avoid (Hansen et al., 1985; Davis et al., 2002; Horton and Kleinman, 2007; Howie and Straker, 2016). The missing values in the outcomes and independent variables arose from a combination of absenteeism, attrition, or a failure to complete the questionnaire on time. In this study, the missing data patterns showed approximately one-third of the individuals responded on all dependent and independent variables at baseline and three years. Ignoring missing data yielded biases as it does not differentiate missing at random mechanism (Little and Rubin, 2002). Therefore, multiple imputation was applied to address missing data in outcomes and independent variables. A fully conditional specification (FCS) predicted mean matching (PMM) method was used to impute missing values for both continuous and categorical variables (van Buuren, 2007), and 20 imputed datasets each with sample size of 873 siblings were generated. All variables, including socio-demographic (age, gender, ethnicity and education), cannabis use, neurocognitive and social cognitive measures as well as the dependent variables at both time points were included in the imputation model. Subsequently, each dataset was analyzed with the appropriate statistical model (e.g. mixed effects models). Parameter estimates and their associated variances were pooled with Rubin's rule (Rubin, 1987).

2.6.3. Mixture distribution model

Observations within siblings were not independent (repeated measures). Therefore, generalized linear mixed-effects model was used to estimate the unique association between measures of neurocognition and social cognition and the development of psychotic experiences. Since our two outcome variables included only zeros (many siblings did not report symptoms) or non-negative

values, these distribution of these variables are extremely skewed (Supplementary Figure S1-S2). Therefore, the outcome variables (continuous part) were modeled with a lognormal distribution allowing random effects. Subsequently, a logistic regression with random effect model was used for estimating Bernoulli probability of a true nonzero score on the frequency of psychotic experiences or the amount of distress of those psychotic experiences in siblings. More specifically, intensity part of the outcome modeled with generalized linear mixed effects model (i.e. random effects lognormal model) and binary parts were modeled with generalized linear mixed effects model. These two models were to be analyzed at the same time. Therefore, we combined these two forming it as mixture distribution model or mixture of generalized linear mixed effects model (Tooze et al., 2002), allowing random intercepts (e.g. siblings) in both binary and continuous parts. We considered both correlated and uncorrelated mixture of generalized linear mixed-effects model to analyze the data. The mathematical expression and the estimation process are summarized in the method section of the supplementary materials. Briefly, the correlated mixed-distribution model was maximized by using quasi-Newton optimization of a likelihood approximated by adaptive Gaussian quadrature (Molenberghs and Verbeke, 2006; Tooze et al., 2002; Zeger and Karim, 1991). Two parts of the uncorrelated mixed distribution models were maximized separately by adaptive Gaussian quadrature. A SAS macro MIXCORR (Tooze et al., 2002) was used to fit the correlated and uncorrelated model. Within the MIXCORR macro, we fitted the models using PROC GENMOD and PROC NLMIXED and the results were used as starting values for the final estimation of the model parameters for both correlated and uncorrelated mixed effects models using PROC NLMIXED (Tooze et al., 2002).

The selected independent variables (Table 1) in the statistical model including time (categorical) were all considered as fixed effects. Since we were interested in change in PE frequency and distress, the interaction of the cognitive variables with time was our main focus. Generalized linear mixed model and linear mixed model were used to select the candidate independent variables for binary and continuous parts respectively using pooled type-III analysis of fixed effects p-values.

Two sets of variables were identified in the candidate independent variables selection model. The first set contained the confounding factors (age, gender, education, and cannabis use), which were always included in every model selection step. The second set contained the neurocognitive and social cognitive measures, which were eliminated one by one. The process continued with a backward elimination procedure on the pooled type-III analysis of fixed effects p-values until all remaining independent variables were significant at α=0.05. The main effects cannot be excluded if they interact with time. Finally all the selected candidate independent variables were used in the proposed mixture of generalized linear mixed effects model (correlated and uncorrelated) to estimate the model parameters. All analyses were done using two-tailed tests at a 5% significance level. The statistical analyses were performed using Statistical Analysis System, version 9.4.

Table 1: Measures of neuro and social cognition

Cognitive domain	Test	Outcome measure	Reference
Neurocognition			
Verbal learning and memory	Word Learning Task (WLT)	Immediate recall (total score of three15-word learning trials) and retention rate (delayed recall /maximum score immediate recall)	(Brand and Jolles, 1985)
Sustained attention and vigilance	Continuous Performance Test (CPT-HQ)	Sensitivity Index (number of correct detections of targets minus the number of false alarms for non-target stimuli	(Nuechterlein and Dawson, 1984)
Set Shifting	Response Shifting Task (RST)	Accuracy Cost Score (proportion correct in the imitation condition minus proportion correct in the reversal condition)	(Bilder et al., 1992; Meiran et al., 2000)
Global cognitive functioning	Wechsler Adult Intelligence Scale (WAIS-III, short form)	IQ	(Wechsler, 1997)
Problem solving and visuospatial abilities	Block Design	Total raw score (0-68)	
Speed of processing	Digit Symbol Coding	Total raw score (0-133)	
Verbal comprehension	Information	Total raw score (0-28)	
Working memory	Arithmetic	Total raw score (0-22)	
General face recognition	Benton Facial Recognition Test (BFRT)	Total amount of correctly matched faces	(Benton et al., 1983)
Social cognition			
Theory of Mind	Hinting Task	Total score (0-20)	(Versmissen et al., 2008)
Emotion perception	Degraded Facial Affect Recognition Task (DFAR)	The proportion of correctly identified happy, fearful, angry and neutral faces and the proportion of total correctly identified faces	(van 't Wout et al., 2004)

3. Results

3.1. Sample

At baseline, the total sample consisted of 873 siblings and 386 controls. At baseline, 757 (86.7%) siblings and 364 (94.3%) controls completed the CAPE frequency scale and 651 (74.6%) siblings and 278 (72.02%) controls at 3-year follow-up. The attrition rates for siblings and controls on PE frequency were 14% and 23.6% respectively. For the CAPE distress scale, numbers were 748 (85.7%) siblings and 364 (94.3%) controls at baseline and 649 (74.3%) siblings and 276 (71.5%) controls at 3-year follow-up. Similarly, the attrition rates for siblings and controls on PE distress were 13.2% and 24.2% respectively. In total, seven siblings (0.8%) and two controls (0.5%) made the transition to psychosis between baseline and follow-up. It should be considered that about 11.6% at baseline and 1.1% at 3-year follow-up of the siblings of the present study had mood disorders. They were all included as siblings or controls in the analyses. At baseline, none of the siblings and controls were treated with antipsychotics or other psychotropic medication (e.g. antidepressants), while at 3-year follow-up six of the siblings who transitioned to psychosis used antipsychotics. None of the controls used anti-depressive or anti-psychotic medication. The mean duration between baseline cognitive testing and follow-up for siblings and controls were 39.4 months (SD=5.6) and 39.2 months (SD=5.5) respectively.

3.2. Descriptive analysis

Table 2a demonstrates the demographic characteristics and neurocognitive and social cognitive performance at baseline and their comparison between siblings and controls. Siblings' mean age was significantly higher, their mean scores on tests of verbal learning, IQ, problem solving and visuospatial abilities, speed of processing, verbal comprehension, working memory, ToM and emotion perception (DFAR Percent of angry face) were significantly lower than that of controls at baseline.

Sibling who dropped-out showed poorer cognitive performance at baseline on verbal learning and memory ($p<0.05$), problem solving and visuospatial skills ($p<0.001$), speed of processing ($p=0.001$), verbal comprehension ($p<0.001$), working memory ($p<0.001$) and had a lower IQ ($p<0.001$) (see Supplementary Table S1-S2 for details). Drop-outs reported less or equal psychotic experiences at baseline compared with non-drop-outs, but this effect was not significant (Supplementary Table S2). In controls, drop-outs reported more psychotic experiences at baseline than non-dropouts, and the effects on psychotic experiences frequency was significant ($p=0.011$) but not significant on psychotic experiences distress (Supplementary Table S1). The relationships (Spearman correlation coefficients) between all neuro- and social cognition measurements and their significance level for both controls and siblings were presented in the Supplementary Table S3-S4.

A large majority of both siblings (87.9%) and controls (85.4%) reported psychotic experiences at baseline (ranging from 'sometimes' to 'nearly always'), of whom more than half of both siblings (57.9%) and controls (58.2%) indicated that the psychotic experiences resulted in emotional distress (ranging from 'a bit' to 'very distressed') respectively (see Table 2b). The percentage of both siblings and controls with psychotic experiences was significantly lower at follow-up than at baseline, as was the percentages of people experiences distress from these symptoms (see Table 2b).

Table 2a: Demographic, neuro and social cognition characteristics at baseline[‡]

Variable/group	Controls (N=386)		Siblings (N=873)	
	Mean±SD or (%)	Missing N (%)	Mean±SD or (%)	Missing n (%)
Age in years, mean±SD	23.81±5.50	0	24.92±5.33***	0
Gender, Female %	52.33	0	54.30	0
Ethnicity, Caucasian %	89.81	13 (3.37)	82.53	3 (0.34)
Education[a] , mean±SD	5.16±1.78	1 (0.26)	4.95±2.09	16 (1.83)
Cannabis use past 12 months, Yes %	20.68	4 (1.04)	21.25	7 (0.80)
Neurocognition, mean±SD:				
Immediate Recall[b]	29.15±5.04	6 (1.55)	27.19±5.62***	25 (2.86)
Retention Rate[c]	0.83±0.15	12 (3.11)	0.84±0.17	36 (4.12)
Sensitivity Index[d]	97.80±6.85	35 (9.07)	96.72±10.39	85 (9.74)
Accuracy Cost Score[e]	0.12±0.19	37 (9.59)	0.14±0.22	86 (9.85)
IQ[f]	109.36±14.52	6 (1.55)	102.66±15.54***	33 (3.78)
Block Design[g]	48.66±13.52	5 (1.30)	45.50±14.89***	21 (2.41)
Digit Symbol Coding[h]	85.12±13.98	5 (1.30)	80.13±15.31***	18 (2.06)
Information[i]	18.55±4.77	5 (1.30)	16.73±5.23***	19 (2.18)
Arithmetic[j]	15.15±4.21	5 (1.30)	13.79±4.46***	19 (2.18)
Benton Facial[k]	23.24±2.01	8 (2.07)	23.21±2.16	26 (2.98)
Social Cognition, mean±SD:				
Hinting Task	19.10±1.21	10 (2.59)	18.80±1.70**	24 (2.75)
Degraded Facial Affect Recognition (DFAR):				
Percent happy faces	88.83±10.69	30 (7.77)	88.40±10.65	66 (7.56)
Percent fearful faces	56.02±17.50	30 (7.77)	54.52±19.19	66 (7.56)
Percent angry faces	71.52±18.81	30 (7.77)	69.42±18.98*	66 (7.56)
Percent neutral faces	81.69±14.87	30 (7.77)	80.23±15.15	66 (7.56)

[‡]Table presents mean±SD or number (%); [a]Education (Verhage, 1965): range 0 (no education), 3-5 (school diploma), 6-8 (professional education/university degree); [b]Immediate Recall: WLT Immediate Recall; [c]Retention rate: WLT Retention Rate; [d]Sensitivity Index: Continuous Performance Test Sensitivity Index; [e]Accuracy Cost Score: Response Shifting Task Accuracy Cost Score; [f]IQ: WAIS-III Intelligence Quotient; [g]Block Design: WAIS-III Block Design; [h]Digit Symbol Coding: WAIS-III Digit Symbol Coding; [i]Information: WAIS-III Information; [j]Arithmetic: WAIS-III Arithmetic; [k]Benton Facial: Benton Facial Recognition Test. Significance levels: ***p <0 .001, **p <0 .01 and *p < 0.05.

Table 2b: Descriptive statistics for the outcomes at baseline and three years follow-up[‡]

Outcomes	Controls (n=386)				Siblings (n=873)			
	Baseline		Follow-up		Baseline		Follow-up	
	Mean±SD	Missing %	Mean±SD	Missing %	Mean±SD	Missing %	Mean±SD	Missing %
PE frequency	0.21±0.19	5.7	0.10±0.13	27.98	0.22±0.21	13.29	0.12±0.19	25.43
PE distress	0.40±0.44	5.7	0.30±0.46	28.50	0.41±0.47	14.32	0.39±0.57	25.66
People with/without symptoms								
	With	Without	With	Without	With	Without	With	Without
	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD	%
PE frequency	0.24±0.18	14.56	0.15±0.14	36.69	0.25±0.20	12.15	0.18±0.20	32.72
PE distress	0.68±0.38	41.76	0.77±0.42	61.23	0.71±0.42	42.11	0.91±0.54	57.63

[‡]Outcome variables were measured by the Community Assessment of Psychic Experiences (CAPE); table presents mean±SD and percentage of missingness and without symptoms at each time point.

3.3. Neurocognitive and social cognitive predictors for symptom development

For both outcomes with and without correlated random effects models was fitted using MIXCORR macro. For the score of the frequency of psychotic experiences, only four datasets out of 20 passed the convergence, so we pooled the parameter estimates based on the existing imputed datasets (04) which were estimable with MIXCORR macro (Supplementary Table S5). Due to the problem of convergence and correlation coefficient between the random effects of occurrence and intensity of psychotic experiences frequency that was very high (ρ=0.941), a single random effect instead of two was the best way to analyze the data. So, we fitted the two-part model incorporating a single random intercept for the intensity part and a scale parameter. The random effect of binary part was then calculated using the random effect of intensity part and the scale parameters for binary part.

Table 3 shows the pooled parameter estimates derived from the mixture of generalized linear mixed effects model for the frequency of psychotic experiences. The psychotic experiences frequency scores indicated a significant interaction effect between the score of Immediate Recall and time at three years in the occurrence part (p=0.024) and the score of Hinting Task and time at three years in the intensity part (p=0.020) respectively. A higher score on Immediate Recall at baseline was associated with an average decrease (OR=*exp*(-0.068)=0.93) of having psychotic experiences in siblings three years later. A higher score for Hinting Task at baseline was associated with an average decrease (-0.053) in psychotic experiences frequency three years later. A significant main effect was found for the score on the Degraded Facial Affect Recognition Task (DFAR) percentage of neutral faces for the intensity of the frequency of psychotic experiences. A higher score for the DFAR recognition of neutral faces was associated with less psychotic experiences at baseline. DFAR recognition score did not have an effect on a change in psychotic experiences frequency over time (absence of interaction effect). A lower score on the sensitivity index of the Continuous Performance Test-HQ and a higher score for Benton Facial Recognition Test (were associated with more psychotic experiences frequency at trend level, not reaching significance). The variance of common random intercept was 0.325, which indicated siblings observed 32.5% of the variation on both the occurrence and the intensity of score of psychotic experiences frequency.

Table 4 shows the pooled parameter estimates derived from the mixture of generalized linear mixed effects model for the amount of distress of those with psychotic experiences. The model was fitted with and without correlated random effects and correlated random effect model was better than the uncorrelated random effect model based on pooled AIC (3127.97) and log likelihood ratio test (p=0.004). The interaction effect between the score on Immediate Recall and time at three years was significant for occurrence of PE (p=0.027). A higher score of Immediate Recall (indicating better verbal learning) at baseline was associated with a decrease (OR=*exp*(-0.056)=0.94) of experiencing distress by siblings with psychotic experiences three years later. DFAR percentages of angry faces, neutral faces and BFRT showed significant main effects for the occurrence of distress of psychotic experiences but these cognitive variables were consistent over time. Percentages of angry faces and neutral faces showed negative association, and BFRT showed positive association of having psychotic experiences distress. There were no significant additional main effects for the intensity of the experienced distress of psychotic experiences, although a trend (P=0.08) was seen of the interaction of neutral faces and time at three years for intensity of psychotic experiences distress. The random

effects in the correlated mixed-distribution model $\sigma_1^2$and σ_2^2 explained the unobserved heterogeneity among siblings (Tooze et al., 2002). The variance of the random effect $\sigma_1^2 = 2.57$ indicated the high variability of the probability of a nonzero psychotic experiences distress among siblings with similar covariate patterns, and $\sigma_2^2 = 0.08$ allowed to have consistently low mean of nonzero values of psychotic experiences distress. The correlation coefficient between the random effects of occurrence and intensity of the experienced distress of psychotic experiences was 43.8%, indicating consistently high occurrence probability to have consistently high mean of nonzero values of psychotic experiences (Table 4).

Table 3: Pooled parameter estimates and fit statistics for the frequency of positive psychotic experiences*

Parameter	Estimate	S.E.	95% C.I		P-value
			Lower	Lower	
Occurrence (Logistic)					
Intercept	1.849	1.314	-0.731	4.429	0.1598
Age	-0.009	0.023	-0.054	0.037	0.7027
Sex	0.083	0.213	-0.335	0.500	0.6982
Education	-0.078	0.058	-0.192	0.036	0.1818
Cannabis Use	-0.650	0.274	-1.188	-0.112	0.0179
Benton facial[a]	0.068	0.041	-0.013	0.148	0.0982
Immediate Recall[b]	0.041	0.026	-0.009	0.091	0.1076
Time (3 years)	0.061	0.841	-1.594	1.716	0.9423
Immediate Recall*Time (3 years)	-0.068	0.030	-0.127	-0.009	0.0240
Var(Random Effect): $\eta^2\sigma_1^2$	2.997	0.669	1.683	4.311	<.0001
Scale Parameter (η)	3.038	0.367	2.317	3.760	<.0001
Intensity (Lognormal)					
Intercept	-0.889	0.463	-1.801	0.022	0.0558
Age	-0.002	0.006	-0.015	0.010	0.7066
Sex	0.028	0.056	-0.082	0.139	0.6168
Education	-0.042	0.016	-0.073	-0.011	0.0084
Cannabis Use	-0.137	0.068	-0.270	-0.004	0.0440
Sensitivity Index[c]	-0.005	0.003	-0.011	0.000	0.0649
Percent neutral faces[d]	-0.004	0.002	-0.007	0.000	0.0307
Hinting Task	0.019	0.018	-0.016	0.054	0.2813
Time (3 years)	0.505	0.432	-0.347	1.358	0.2438
Hinting Task*Time (3 years)	-0.053	0.023	-0.099	-0.008	0.0204
Var(Random Effect): σ_1^2	0.325	0.036	0.254	0.396	<.0001
Var (Residual): σ_e^2	0.115	0.018	0.080	0.149	<.0001
Fit Statistics					
Criterion (Pooled)	Value				
AIC	-370.383				
-2LL	-414.383				

*The model adjusted for age, gender, education, and cannabis used in past 12 months; [a]Benton Facial: Benton Facial Recognition Test; [b]Immediate Recall: WLT Immediate Recall; [c]Sensitivity Index: Continuous Performance Test Sensitivity Index; [d]Percent neutral faces: Degraded Facial Affect Recognition Task percent neutral faces; AIC: Akaike Information Criterion; -2LL: -2Log Likelihood.

Table 4: Pooled parameter estimates and model comparison for the amount of experienced distress of positive psychotic experiences*

Parameter	Uncorrelated Model					Correlated Model				
	Estimate	S.E.	95% C.I		P-value	Estimate	S.E.	95% C.I		P-value
			Lower	Upper				Lower	Upper	
Occurrence (Logistic)										
Intercept	0.074	1.255	-2.391	2.538	0.9532	0.074	1.253	-2.386	2.535	0.9527
Age	-0.031	0.020	-0.071	0.009	0.1335	-0.031	0.020	-0.070	0.009	0.1336
Sex	0.792	0.197	0.404	1.181	<.0001	0.791	0.198	0.402	1.179	<.0001
Education	-0.115	0.053	-0.219	-0.010	0.0314	-0.117	0.053	-0.222	-0.013	0.0279
Cannabis Use	0.084	0.235	-0.377	0.545	0.7204	0.085	0.234	-0.375	0.546	0.7153
Percent angry faces[a]	-0.010	0.005	-0.019	0.000	0.047	-0.010	0.005	-0.020	-0.001	0.0377
Percent neutral faces[b]	-0.016	0.006	-0.027	-0.004	0.0064	-0.016	0.006	-0.027	-0.005	0.0055
Benton facial[c]	0.089	0.044	0.003	0.175	0.0414	0.088	0.044	0.001	0.174	0.0462
Time (3 years)	0.537	0.693	-0.829	1.902	0.4397	0.539	0.692	-0.824	1.903	0.4366
Immediate Recall[d]	0.008	0.020	-0.030	0.047	0.6776	0.012	0.020	-0.027	0.050	0.5531
Immediate Recall*Time (3 years)	-0.056	0.025	-0.105	-0.006	0.0268	-0.055	0.025	-0.105	-0.006	0.0271
Var(random intercept): σ_1^2	2.555	0.538	1.496	3.613	<.0001	2.566	0.555	1.474	3.658	<.0001
Intensity (Lognormal)										
Intercept	-0.722	0.220	-1.154	-0.290	0.0011	-0.726	0.222	-1.161	-0.291	0.0011
Age	-0.001	0.005	-0.011	0.010	0.9836	-0.001	0.005	-0.011	0.010	0.8705
Sex	0.118	0.050	0.020	0.216	0.0179	0.132	0.052	0.031	0.233	0.0109
Education	-0.015	0.014	-0.042	0.011	0.2572	-0.019	0.014	-0.046	0.009	0.178
Cannabis Use	0.006	0.062	-0.115	0.127	0.9243	0.003	0.062	-0.118	0.125	0.9551
Time (3 years)	0.653	0.248	0.163	1.143	0.0092	0.650	0.248	0.161	1.138	0.0095
Percent neutral faces	0.001	0.002	-0.003	0.005	0.6464	0.000	0.002	-0.003	0.004	0.8109
Percent neutral faces*Time (3 years)	-0.005	0.003	-0.011	0.001	0.0922	-0.005	0.003	-0.012	0.001	0.0808
Var(res): σ_e^2	0.311	0.034	0.244	0.379	<.0001	0.311	0.034	0.243	0.379	<.0001
Var(random intercept): σ_2^2	0.070	0.028	0.014	0.126	0.015	0.076	0.030	0.017	0.135	0.0123
Covariance	...	...	...	...	...	0.193	0.101	-0.006	0.392	0.0571
Correlation (ρ)	...	...	...	...	...	0.438				
Model comparison (Fit Statistics)										
Criterion (Pooled)	Value					Value		Difference in -2LL		P-value
AIC	3134.30					3127.97				
-2LL	3090.30					3081.97		8.33		0.004

*The model adjusted by age, gender, education, and cannabis used in past 12 months; [a]Percent angry faces: Degraded Facial Affect Recognition Task percent angry faces. [b]Percent neutral faces: Degraded Facial Affect Recognition Task percent neutral faces; [c]Benton Facial: Benton Facial Recognition Test; [d]Immediate Recall: WLT Immediate Recall; AIC: Akaike Information Criterion; -2LL: -2Log Likelihood.

4. Discussion

In the current study, we examined the predictive value of neurocognition and social cognition for the development of psychotic experiences over time in a large sample of siblings at genetic high risk (GHR) for psychotic disorder. At baseline 87.9% of the siblings reported psychotic experiences, of which 57.9% indicated that the psychotic experiences resulted in distress. At follow-up 67.3% of the siblings reported psychotic experiences in the past three years, of which 42.4% stated feelings of distress. Interestingly, neither frequency nor distress of psychotic experiences in our GHR sample differed from healthy controls. Moreover, the percentage of people that made a transition to psychosis over three years was relatively low in both groups (seven siblings (0.8%) and two controls (0.5%)). We found a substantial decrease in the frequency and distress of psychotic experiences between baseline and 3-year follow-up in both groups. This decrease may be due to the fact that baseline assessment of frequency psychotic experiences was lifetime frequency and follow-up assessment was over the three years before assessment. The high number of controls reporting at least one psychotic experience at some point in life, which is in line with previous findings in a large cohort of Dutch early adolescents in the general population, reporting a prevalence of 95% of psychotic experiences (Wigman et al., 2011). Participants in that study were younger than those in our sample (age 12-16), which may account for the fact that prevalence of psychotic experiences in this study is even somewhat higher than in our samples.

Siblings mean age was a little higher than controls (1.2 years), they had a lower mean IQ than controls and performed worse on tests of several other cognitive domains: verbal learning, visuospatial abilities, processing speed, verbal comprehension, recognition of facial affect, ToM and working memory. The widespread pattern of poorer cognitive functioning implicates that the cognitive profile of the current GHR sample is comparable to that of subjects at UHR who also show impairments in multiple cognitive domains (Fusar-Poli et al., 2012).

While baseline performance on tasks assessing verbal learning was not associated with baseline psychotic experiences frequency, poorer performance on this task predicted the occurrence psychotic experiences after three years and the distress associated with these psychotic experiences. Moreover, better baseline performance on a ToM task was associated with a decrease of psychotic symptoms after three years. Baseline distress was associated with poorer recognition of angry and neutral faces and, strikingly, with better recognition of faces in general.

Thus, in particular verbal learning and social cognitive measures were associated with frequency and distress of psychotic experiences in this GHR sample. In subjects at UHR, a broad range of cognitive functions was associated with conversion (Fusar-Poli et al., 2012; van Donkersgoed et al., 2015), among which also verbal memory and ToM. Verbal memory was among the most impaired cognitive domains in CHR and more impaired in converters than in non-converters (Seidman et al., 2016). Poorer verbal memory may make people more vulnerable for psychotic experiences because of misinterpretations of past situations and biases in the encoding of new information. Previous studies found verbal memory to be a robust predictor of social functioning as well (Green, 1996). It may be people with poorer verbal memory are less able to generate social support in case of psychotic experiences and therefore experience more distress.

ToM was the only social cognitive domain found to be associated with conversion in a previous meta-analysis (van Donkersgoed et al., 2015). In line with this, a study on the course of psychotic symptoms over time in children showed that poorer ToM predicted delusions after three year in children with auditory hallucinations (Bartels-Velthuis et al., 2011). Apparently the ability to infer mental state of others protects against psychotic experiences, probably since information on the mental state of others can be used to correct one's own thoughts and beliefs (Pijnenborg et al., 2013).

The present study has a number of limitations. First, the relatively long duration of GROUP (three years for the present study) might have the disadvantage (like other longitudinal studies on psychiatric disorders) that only more stable or better-functioning siblings will continue participating over time, while siblings who increase in psychotic experiences over time or even convert to psychosis, may have been more likely to drop out. Although there are many possible reasons for drop-out and the use of multiple imputation should have corrected substantially for its effect. It cannot be ruled out that these drop-outs may have developed more severe symptoms or may have converted to a psychotic disorder between baseline and 3-year follow-up, which could have been a reason for not being able/willing to participate. Therefore, the assessment of psychotic experiences at 3-year follow-up might have been biased, resulting in the observed decrease in psychotic experiences frequency and distress. Possibly, these drop-outs (non-responders) are the siblings of special interest, because they may have made the transition to psychosis. Indeed, it was shown that drop-outs at 3-year follow-up reported non-significantly more psychotic experiences at baseline compared with participants at 3-year follow-up. Furthermore, drop-outs at follow-up were already more neurocognitively affected at baseline compared with responders. That is, non-responders at follow-up showed decreased performance at baseline on verbal learning, IQ, problem solving and visuospatial skills, speed of processing, acquired knowledge and working memory. Second, it should be considered that about 11.6% of the siblings of the present study had mood disorders at baseline, which may have affected cognitive functioning (Baune et al., 2010). However, the fact that both mood disorders and cognitive impairments were more prevalent in siblings, also illustrates that GHR is associated with several additional risk factors that may be a cumulative risk for poor outcome in terms of symptoms. We decided not to exclude siblings suffering from mood disorders, since depression is frequently observed in schizophrenia (Buckley et al., 2009) and is found to be a predictor for psychosis (Yung et al., 2003). Moreover, a sample including siblings with mood disorders is more representative for this high risk population. Finally, psychotic experiences were assessed with a self-report questionnaire. This may have biased the results as not all psychotic experiences may be labeled as such by the participants, given that these are very personal experiences and thoughts. Reporting these experiences requires a certain level of self-reflection.

A strength of this study is the large sample size and the use of a neurocognitive test battery in which most of the cognitive domains suggested by the MATRICS consensus are incorporated (Nuechterlein et al., 2004), yielding a broad range of neurocognitive variables. Moreover, this study combines both neurocognition and social cognition, providing a comprehensive picture of the possible factors related to psychosis. Another strength is that we investigated the association between cognition and the development of psychotic experiences specifically over time, contrary to

most previous studies comparing performance of high risk subjects with healthy controls and/or individuals with psychotic disorders (Addington et al., 2008; Kim et al., 2010; Thompson et al., 2012; Laurent et al., 2001). In addition, the current study focused at baseline on non-help seeking, siblings of individuals with a psychotic disorder. This has the advantage, compared with studies on CHR groups, that cognitive performance was not confounded by the effects of antipsychotic medication or illness (duration) at the time of assessment.

In conclusion, the current study highlighted the importance of a further differentiation within a genetic high risk group based on neuro- and social-cognition. We found lower scores on tests of IQ verbal learning, visuospatial abilities, processing speed, verbal comprehension, recognition of facial affect, ToM and working memory may represent general vulnerability factors for psychotic experiences associated with their genetic liability, and may therefore not be specifically predictive of the development of psychosis. However, only a few cognitive domains were associated with frequency and distress of psychotic experiences at baseline in this study. In addition, cognitive domains that were associated with PE at baseline do not necessarily predict occurrence after three years, nor increase in psychotic experiences frequency and distress over time in people at genetic high risk for psychoses. In general, the fact that psychotic experiences were highly prevalent in both people at GHR and healthy controls may explain the lack of associations. Given that psychotic experiences are apparently widespread under healthy young adults, these may not be associated with impaired functioning in other domains, such as cognitive functioning. Only verbal learning and ToM were found to be predictive of respectively frequency and, distress and change in frequency of psychotic experiences after three years. Our findings suggest that even though cognitive functioning is poorer in people at GHR, this poorer functioning is not a robust predictor of the course of psychotic experiences.

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Supplementary Materials

Supplementary Methods

The general form of the mixture distribution model where the outcome has lots of zeros as defined as

$$f(y) = \begin{cases} P(Y=0) & \text{if } y = 0 \\ [1 - P(Y=0)]d(y) & \text{if } y > 0 \end{cases}$$

where *d(y)* is the probability density defined when *y* > 0 (Lachenbruch, 1976; Lachenbruch, 1992; Tooze et al., 2002).

Let Y_{hc} be score of the frequency of psychotic experiences or the amount of distress of those experiences for sibling *h* (=1, 2, …, *m*) at time *c* (=1, 2, …,n_h), and R_{hc} represent the occurrence of frequency/distress variable where $R_{hc} = \begin{cases} 0, & \text{if } Y_{hc} = 0 \\ 1, & \text{if } Y_{hc} > 0 \end{cases}$ and it has conditional probabilities

$$P(R_{hc} = r_{hc}|\theta_1) = \begin{cases} 1 - p_{hc}(\theta_1), & if\ r_{hc} = 0 \\ p_{hc}(\theta_1), & if\ r_{hc} = 1 \end{cases}$$

where $\boldsymbol{\theta}_1 = \left[\boldsymbol{\beta}_1^{/}, u_{1h}\right]^{/}$ is a vector of fixed occurrence effects $\boldsymbol{\beta}_1$, and random intercept unit (sibling) occurrence effect u_{1h}. We assume a logistic model for occurrence of the frequency of psychotic experiences or the amount of distress of those experiences so that $logit\left(p_{hc}(\theta_1)\right) = \boldsymbol{X}_{1hc}^{/}\boldsymbol{\beta}_1 + u_{1h}$ where X_{1hc} is a vector of independent variables for occurrence. Let $S_{hc} \equiv [Y_{hc}|R_{hc} = 1]$ be the intensity variable of frequency/distress psychotic experiences with pdf $f(s_{hc}|\boldsymbol{\theta}_2)$ for $s_{hc} > 0$, where $\boldsymbol{\theta}_2 = \left[\boldsymbol{\beta}_2^{/}, u_{2h}\right]^{/}$ is a vector of fixed effects of $\boldsymbol{\beta}_2$, and random intercept unit (sibling) of intensity effect u_{2h}. We assume a lognormal model for intensity so that $log(S_{hc}|\boldsymbol{\theta}_2) \sim N\left(\boldsymbol{X}_{2hc}^{/}\boldsymbol{\beta}_2 + u_{2h}, \sigma_e^2\right)$ where $\boldsymbol{X}_{2hc}$ is a vector of independent variables for intensity. We allow the random intercepts for both occurrence and intensity of the frequency of psychotic experiences or the amount of distress of those experiences with the assumption that they are bivariate normal and to be correlated as

$\begin{bmatrix} u_{1hc} \\ u_{2hc} \end{bmatrix} \sim BVN\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{bmatrix}\right)$, where ρ is the correlation coefficient.

Based on this assumption, the subject-specific average intensity of the frequency of psychotic experiences or the amount of distress of those experiences is $E(S_{hc}|\boldsymbol{\theta}_2) = exp\left(\boldsymbol{X}_{2hc}^{/}\boldsymbol{\beta}_2 + u_{2h} + \sigma_e^2/2\right)$ and the marginal average intensity is $E(S_{hc}|\boldsymbol{\theta}_2) = exp\left(\boldsymbol{X}_{2hc}^{/}\boldsymbol{\beta}_2 + \sigma_2^2/2 + \sigma_e^2/2\right)$.

The pdf of Y_{hc} is $f(y_{hc}|\boldsymbol{\theta}) = P(R_{hc} = 0|\boldsymbol{\theta}_1)\delta_0(y_{hc}) + P(R_{hc} = 1|\boldsymbol{\theta}_1)f(s_{hc}|\boldsymbol{\theta}_2)$

$$= [1 - p_{hc}(\boldsymbol{\theta}_1)]\delta_0(y_{hc}) + p_{hc}(\boldsymbol{\theta}_1)f(s_{hc}|\boldsymbol{\theta}_2)$$

Where $\boldsymbol{\theta} = \left[\boldsymbol{\theta}_1^{/}, \boldsymbol{\theta}_2^{/}\right]$ and $\delta_0(y_{hc})$ is Dirac delta function (Robertson et al., 1996) such that

$$\begin{cases} \int_{-\infty}^{\infty} \delta_0(y)dy_{hc} = 1 \\ \delta_0(y) = 0\ when\ y_{hc} \neq 0 \end{cases}$$

Therefore, the likelihood function for the correlated mixed distribution of Y_{hc} is

$$L(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \sigma_1, \sigma_2, \sigma_e, \rho)$$
$$= \prod_{h=1}^{m} \int_{u_{1h}} \int_{u_{2h}} \prod_{c=1}^{n_h} f(y_{hc}|\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, u_{1h}, u_{2h}) f(u_{1h}, u_{2h}|\sigma_1, \sigma_2, \sigma_e, \rho)\, du_{1h} du_{2h}$$
$$= \prod_{h=1}^{m} \int_{u_{1h}} \int_{u_{2h}} \prod_{c=1}^{n_h} [1 - p_{hc}(\boldsymbol{\beta}_1, u_{1h})]^{1-r_{hc}} [p_{hc}(\boldsymbol{\beta}_1, u_{1h})]^{r_{hc}}$$
$$\times f(s_{hc}|\boldsymbol{\beta}_2, u_{2h}) f(u_{1h}, u_{2h}|\sigma_1, \sigma_2, \sigma_e, \rho) du_{1h} du_{2h} \ldots\ldots\ldots\ldots (1)$$

If u_{1h} and u_{2h} are independent i.e. $\rho = 0$, the equation (1) will be decomposed into two parts that correspond to occurrence and intensity parts and termed as uncorrelated mixed distribution as

$$L(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \sigma_1, \sigma_2, \sigma_e)$$
$$= \prod_{h=}^{m} \int_{u_{1h}} \prod_{c=1}^{n_h} [1 - p_{hc}(\boldsymbol{\theta}_1)]^{1-r_{hc}} [p_{hc}(\boldsymbol{\theta}_1)]^{r_{hc}} f(u_{1h}|\sigma_1) du_{1h}$$
$$\times \prod_{h=1}^{m} \int_{u_{2h}} \prod_{c=1}^{n_h} f(s_{hc}|\boldsymbol{\theta}_2) f(u_{2h}|\sigma_2, \sigma_e) du_{2h} \ldots\ldots\ldots\ldots (2)$$

The correlated mixed-distribution model (1) is maximized by using quasi-Newton optimization of a likelihood approximated by adaptive Gaussian quadrature (Molenberghs and Verbeke, 2006; Zeger and Karim, 1991; Tooze et al., 2002). Two parts of the uncorrelated mixed distribution model (2) are maximized separately by adaptive Gaussian quadrature. A SAS macro MIXCORR developed by Tooze et al (Tooze et al., 2002) is used to fit the correlated and uncorrelated model. In short, within the MIXCORR macro, we fit the models with PROC GENMOD and PROC NLMIXED and the results of parameter estimates are used as starting values for the final estimation of the model parameters for both correlated and uncorrelated mixed effects models using PROC NLMIXED. The details of the estimation procedures have been found in elsewhere (Tooze et al., 2002).

Supplementary Table S1: Differences at baseline as a function of follow-up attrition of all characteristics for controls (N=386)

Variables	Type	CAPE[a] Positive symptoms, frequency				CAPE[a] Positive symptoms, distress			
		Mean or %	SD	N	P-value	Mean or %	SD	N	P-value
Age	No follow-up	22.70	4.77	108	**0.034**	22.79	4.77	110	0.054
	Follow-up	24.24	5.71	278		24.21	5.73	276	
Gender, Female	No follow-up	48.15	...	52	0.305	47.27	...	52	0.209
	Follow-up	53.96	...	150		54.35	...	150	
Education[b]	No follow-up	4.93	1.88	108	0.141	4.96	1.89	110	0.221
	Follow-up	5.26	1.74	277		5.24	1.74	275	
Ethnicity, Caucasian	No follow-up	88.35	...	91	0.875	87.62	...	92	0.829
	Follow-up	90.37	...	244		90.67	...	243	
Cannabis use last 12 months, Yes	No follow-up	23.36	...	25	0.419	22.94	...	25	0.492
	Follow-up	19.64	...	54		19.78	...	54	
Neurocognition:									
Immediate Recall[c]	No follow-up	29.16	4.66	104	0.767	29.07	4.68	106	0.971
	Follow-up	29.14	5.19	276		29.18	5.18	274	
Retention rate[d]	No follow-up	0.83	0.15	103	0.554	0.83	0.15	105	0.595
	Follow-up	0.84	0.15	271		0.84	0.15	269	
Sensitivity Index[e]	No follow-up	98.25	3.82	102	0.622	98.11	4.10	104	0.745
	Follow-up	97.62	7.76	249		97.67	7.73	247	
Accuracy Cost Score[f]	No follow-up	0.13	0.20	96	0.522	0.12	0.20	98	0.702
	Follow-up	0.12	0.19	253		0.12	0.19	251	
IQ[g]	No follow-up	106.02	14.21	105	**0.014**	105.81	14.25	107	**0.008**
	Follow-up	110.63	14.47	275		110.74	14.42	273	
Block Design[h]	No follow-up	46.10	13.43	105	**0.013**	45.66	13.75	107	**0.005**
	Follow-up	49.63	13.45	276		49.83	13.27	274	
Digit Symbol-coding[i]	No follow-up	85.01	13.22	105	0.751	84.76	13.22	107	0.568
	Follow-up	85.16	14.29	276		85.26	14.29	274	
Information[j]	No follow-up	17.57	5.21	105	**0.033**	17.63	5.18	107	**0.042**
	Follow-up	18.92	4.55	276		18.91	4.56	274	
Arithmetic[k]	No follow-up	14.16	4.29	105	**0.004**	14.17	4.32	107	**0.004**
	Follow-up	15.53	4.13	276		15.54	4.12	274	
Benton Facial[l]	No follow-up	23.06	2.03	104	0.162	22.99	2.08	106	0.083
	Follow-up	23.30	2.01	274		23.33	1.98	272	

Supplementary Table S1-Continued

Variables	Type	CAPE[a] Positive symptoms, frequency				CAPE[a] Positive symptoms, distress			
		Mean or %	SD	N	P-value	Mean or %	SD	N	P-value
Social Cognition:									
Hinting Task	No follow-up	19.04	1.20	103	0.480	19.03	1.21	105	0.433
	Follow-up	19.13	1.21	273		19.13	1.20	271	
Degraded Facial Affect Recognition									
Percent happy faces	No follow-up	90.13	10.40	100	0.131	90.01	10.34	102	0.181
	Follow-up	88.33	10.77	256		88.36	10.81	254	
Percent fearful faces	No follow-up	56.75	18.48	100	0.658	56.50	18.40	102	0.805
	Follow-up	55.74	17.13	256		55.83	17.15	254	
Percent angry faces	No follow-up	71.75	18.37	100	0.906	71.51	18.31	102	0.946
	Follow-up	71.44	19.01	256		71.53	19.03	254	
Percent neutral faces	No follow-up	82.63	13.95	100	0.607	82.60	13.92	102	0.625
	Follow-up	81.32	15.22	256		81.32	15.24	254	
Outcome variables:									
CAPE: Frequency of positive symptoms	No follow-up	0.24	0.19	99	**0.011**	...	...	...	...
	Follow-up	0.20	0.18	265		...	...	...	
CAPE: Distress of positive symptoms	No follow-up	...	...	...	...	0.46	0.47	99	0.105
	Follow-up	...	...	...		0.37	0.43	265	

[a]CAPE: Community Assessment of Psychic Experiences; [b]Education (Verhage): range 0 (no education), 3-5 (school diploma), 6-8 (professional education/university degree); [c]Immediate Recall: Word Learning Task (WLT) Immediate Recall; [d]Retention rate: WLT Retention Rate; [e]Sensitivity Index: Continuous Performance Test Sensitivity Index; [f]Accuracy Cost Score: Response Shifting Task Accuracy Cost Score; [g]IQ: WAIS-III Intelligence Quotient; [h]Block Design: WAIS-III Block Design; [i]Digit Symbol Coding: WAIS-III Digit Symbol Coding; [j]Information: WAIS-III Information; [k]Arithmetic: WAIS-III Arithmetic; [l]Benton Facial: Benton Facial Recognition Test.

Supplementary Table S2: Differences at baseline as a function of follow-up attrition of all characteristics for siblings (N=873)

Variables	Type	CAPE[a] Positive symptoms, frequency				CAPE[a] Positive symptoms, distress			
		Mean or %	SD	N	P-value	Mean or %	SD	N	P-value
Age	No follow-up	24.86	5.43	222	0.755	24.80	5.45	224	0.603
	Follow-up	24.94	5.30	651		24.96	5.29	649	
Gender, Female	No follow-up	48.20	...	107	**0.035**	47.77	...	107	**0.023**
	Follow-up	56.3	...	367		56.55	...	367	
Education[b]	No follow-up	4.50	2.15	215	**0.001**	4.47	2.15	217	**<0.001**
	Follow-up	5.10	2.04	642		5.12	2.04	640	
Ethnicity, Caucasian	No follow-up	69.37	...	154	**<0.001**	69.64	...	156	**<0.001**
	Follow-up	87.04	...	564		87.00	...	562	
Cannabis use last 12 months, Yes	No follow-up	29.36	...	64	**0.001**	29.09	...	64	**0.001**
	Follow-up	18.52	...	120		18.58		120	
Neurocognition:									
Immediate Recall[c]	No follow-up	26.11	5.83	210	**0.001**	26.17	5.84	212	**0.002**
	Follow-up	27.54	5.51	638		27.53	5.51	636	
Retention rate[d]	No follow-up	0.82	0.17	207	**0.020**	0.82	0.17	209	**0.010**
	Follow-up	0.85	0.17	630		0.85	0.17	628	
Sensitivity Index[e]	No follow-up	96.26	11.62	193	0.353	96.26	11.54	196	0.279
	Follow-up	96.87	9.96	595		96.88	9.99	592	
Accuracy Cost Score[f]	No follow-up	0.14	0.21	196	0.876	0.13	0.21	199	0.902
	Follow-up	0.14	0.22	591		0.14	0.22	588	
IQ[g]	No follow-up	97.75	13.83	204	**<0.001**	97.87	13.93	206	**<0.001**
	Follow-up	104.23	15.73	636		104.21	15.72	634	
Block Design[h]	No follow-up	41.78	15.74	211	**<0.001**	41.69	15.82	213	**<0.001**
	Follow-up	46.72	14.40	641		46.77	14.35	639	
Digit Symbol-coding[i]	No follow-up	76.92	15.00	213	**0.001**	76.98	14.98	215	**0.001**
	Follow-up	81.19	15.27	642		81.19	15.29	640	
Information[j]	No follow-up	15.43	4.97	212	**<0.001**	15.52	4.98	214	**<0.001**
	Follow-up	17.16	5.25	642		17.13	5.26	640	
Arithmetic[k]	No follow-up	12.64	4.56	213	**<0.001**	12.66	4.55	215	**<0.001**
	Follow-up	14.17	4.37	641		14.17	4.37	639	
Benton Facial[l]	No follow-up	23.40	2.02	209	0.223	23.38	2.01	211	0.271
	Follow-up	23.15	2.21	638		23.15	2.21	636	

Supplementary Table S2-continued

Variables	Type	CAPE[a] Positive symptoms, frequency				CAPE[a] Positive symptoms, distress			
		Mean or %	SD	N	P-value	Mean or %	SD	N	P-value
Social Cognition:									
Hinting Task	No follow-up	18.81	1.69	212	0.901	18.81	1.69	214	0.900
	Follow-up	18.80	1.70	637		18.80	1.71	635	
Degraded Facial Affect Recognition (DFAR)									
Percent happy faces	No follow-up	88.87	11.18	201	0.338	88.76	11.16	204	0.456
	Follow-up	88.24	10.47	606		88.28	10.48	603	
Percent fearful faces	No follow-up	54.91	19.83	201	0.701	54.84	19.72	204	0.749
	Follow-up	54.39	18.99	606		54.42	19.02	603	
Percent angry faces	No follow-up	69.34	17.99	201	0.860	69.27	17.97	204	0.807
	Follow-up	69.45	19.31	606		69.48	19.32	603	
Percent neutral faces	No follow-up	81.19	15.23	201	0.219	81.43	15.26	204	0.121
	Follow-up	79.91	15.13	606		79.82	15.11	603	
Outcome variables:									
CAPE: PE frequency	No follow-up	0.22	0.25	183	0.159	...	...	...	...
	Follow-up	0.22	0.19	574		...	...	...	
CAPE: PE Distress	No follow-up	...	...	...	...	0.37	0.47	182	0.126
	Follow-up	...	...	...		0.42	0.47	566	

[a]CAPE: Community Assessment of Psychic Experiences; [b]Education (Verhage): range 0 (no education), 3-5 (school diploma), 6-8 (professional education/university degree); [c]Immediate Recall: Word Learning Task (WLT) Immediate Recall; [d]Retention rate: WLT Retention Rate; [e]Sensitivity Index: Continuous Performance Test Sensitivity Index; [f]Accuracy Cost Score: Response Shifting Task Accuracy Cost Score; [g]IQ: WAIS-III Intelligence Quotient; [h]Block Design: WAIS-III Block Design; [i]Digit Symbol Coding: WAIS-III Digit Symbol Coding; [j]Information: WAIS-III Information; [k]Arithmetic: WAIS-III Arithmetic; [l]Benton Facial: Benton Facial Recognition Test.

Supplementary Table S3: Spearman correlation coefficients of all neuro and social cognition measurements for healthy controls (n = 318)[a]

	WLTTIR	WLTRR	CPT_SEN	RST_AC	IQ	WAIBD	WAIDS	WAIIN	WAICA	BENTFR	HINTS	DFR_PHF	DFR_PFF	DFR_PAF
WLTRR	0.36***													
CPT_SEN	0.12*	0.08												
RST_AC	-0.05	0.02	0.09											
IQ	0.27***	0.11*	0.09	-0.16**										
WAIBD	0.15**	0.03	0.05	-0.16**	0.65***									
WAIDS	0.28***	0.18***	0.11*	-0.06	0.59***	0.23***								
WAIIN	0.12*	-0.02	0.05	-0.12*	0.68***	0.30***	0.16**							
WAICA	0.20***	0.07	0.02	-0.1	0.75***	0.36***	0.22***	0.56***						
BENTFR	0.17**	0.13*	0.09	0.05	0.11	0.07	0.15**	0.14*	0					
HINTS	0.1	0.16**	0.13*	0.06	0.13*	0.05	0.09	0.07	0.1	0.15**				
DFR_PHF	0.14*	0.11	0.06	-0.07	0.01	0.02	0.04	0	-0.02	0.13*	0.1			
DFR_PFF	0.16**	0.05	0.09	-0.02	0.15**	0.14*	0.18**	0	0.04	0.01	0.02	0.18**		
DFR_PAF	0.09	-0.05	0.01	0	-0.01	0.03	0.03	-0.04	-0.05	0.11*	0.06	0.15**	0.28***	
DFR_PNF	0.03	-0.02	0.08	-0.07	0.04	0.08	0.02	0.07	0.05	0.16**	0.04	-0.05	-0.13*	-0.11*

[a]The table represents Spearman's correlation coefficients and their significance level; WLTTIR: Word Learning Task (WLT) Immediate Recall; WLTRR: WLT Retention Rate; CPT_SEN: Continuous Performance Test Sensitivity Index; RST_AC: Response Shifting Task Accuracy Cost Score; IQ: WAIS-III Intelligence Quotient; WAIBD: WAIS-III Block Design; WAIDS: WAIS-III Digit Symbol Coding; WAIIN: WAIS-III Information; WAICA: WAIS-III Arithmetic; BENTFR: Benton Facial Recognition Test; Hint: Hinting Task; DFR_PHF: Degraded Facial Affect Recognition (DFAR) Percent happy faces; DFR_PFF: DFAR Percent fearful faces; DFR_PAF: DFAR Percent angry faces; DFR_PNF: DFAR Percent neutral faces; Significance levels: ***P <0 .001, **P <0 .01 and *P < 0.05.

Supplementary Table S4: Spearman correlation coefficients of all neuro and social cognition measurements for siblings (n = 709)[a]

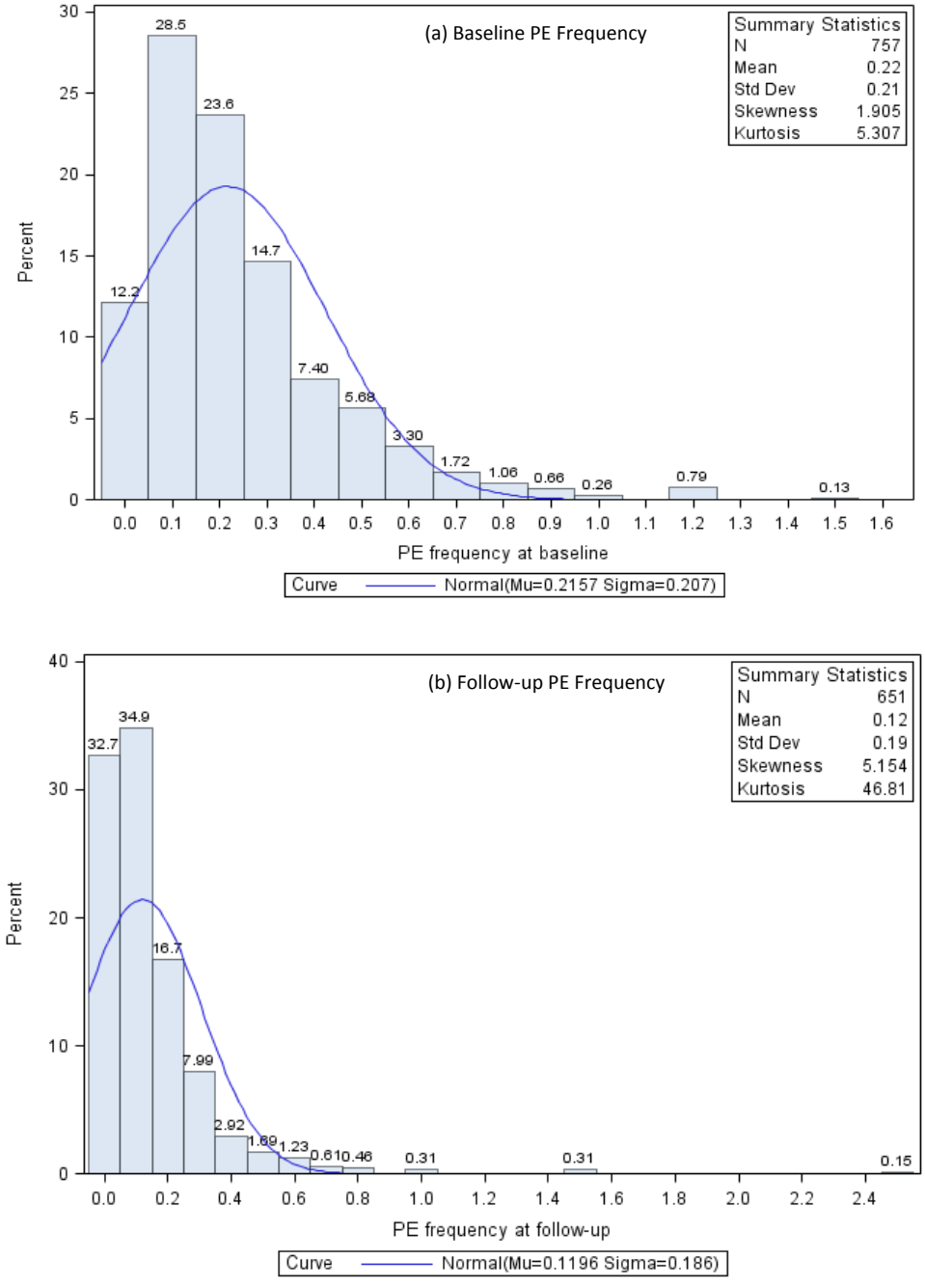
	WLTTIR	WLTRR	CPT_SEN	RST_AC	IQ	WAIBD	WAIDS	WAIIN	WAICA	BENTFR	HINTS	DFR_PHF	DFR_PFF	DFR_PAF
WLTRR	0.27***													
CPT_SEN	0.17***	0.04												
RST_AC	-0.08*	-0.07	-0.05											
IQ	0.32***	0.10**	0.30***	-0.13***										
WAIBD	0.19***	0.05	0.24***	-0.07	0.74***									
WAIDS	0.29***	0.14***	0.21***	-0.10**	0.64***	0.34***								
WAIIN	0.25***	0.07*	0.23***	-0.11**	0.77***	0.43***	0.30***							
WAICA	0.23***	0.04	0.25***	-0.10**	0.82***	0.50***	0.37***	0.63***						
BENTFR	0.10**	0.09*	0.05	-0.05	0.13***	0.11**	0.08*	0.13***	0.12**					
HINTS	0.17***	0.02	0.06	-0.05	0.20***	0.12***	0.15***	0.20***	0.19***	0.05				
DFR_PHF	0.06	0.06	0.15***	-0.06	0.14***	0.13***	0.14***	0.12**	0.07	0.19***	0.05			
DFR_PFF	0.10**	0.06	0.11**	-0.08*	0.06	0.08*	0.05	0	0.04	0.10*	0.01	0.15***		
DFR_PAF	0.12**	0.11**	0.06	-0.04	0.02	0.08*	0.08*	-0.04	-0.04	0.09*	0.04	0.14***	0.27***	
DFR_PNF	0.08*	-0.06	0.01	-0.07	0.11**	0.05	0.07*	0.11**	0.11**	0.11**	0.03	0	-0.04	-0.04

[a]The table represents Spearman's correlation coefficients and their significance level; WLTTIR: Word Learning Task (WLT) Immediate Recall; WLTRR: WLT Retention Rate; CPT_SEN: Continuous Performance Test Sensitivity Index; RST_AC: Response Shifting Task Accuracy Cost Score; IQ: WAIS-III Intelligence Quotient; WAIBD: WAIS-III Block Design; WAIDS: WAIS-III Digit Symbol Coding; WAIIN: WAIS-III Information; WAICA: WAIS-III Arithmetic; BENTFR: Benton Facial Recognition Test; Hint: Hinting Task; DFR_PHF: Degraded Facial Affect Recognition (DFAR) Percent happy faces; DFR_PFF: DFAR Percent fearful faces; DFR_PAF: DFAR Percent angry faces; DFR_PNF: DFAR Percent neutral faces; Significance levels: ***P <0 .001, **P <0 .01 and *P < 0.05.

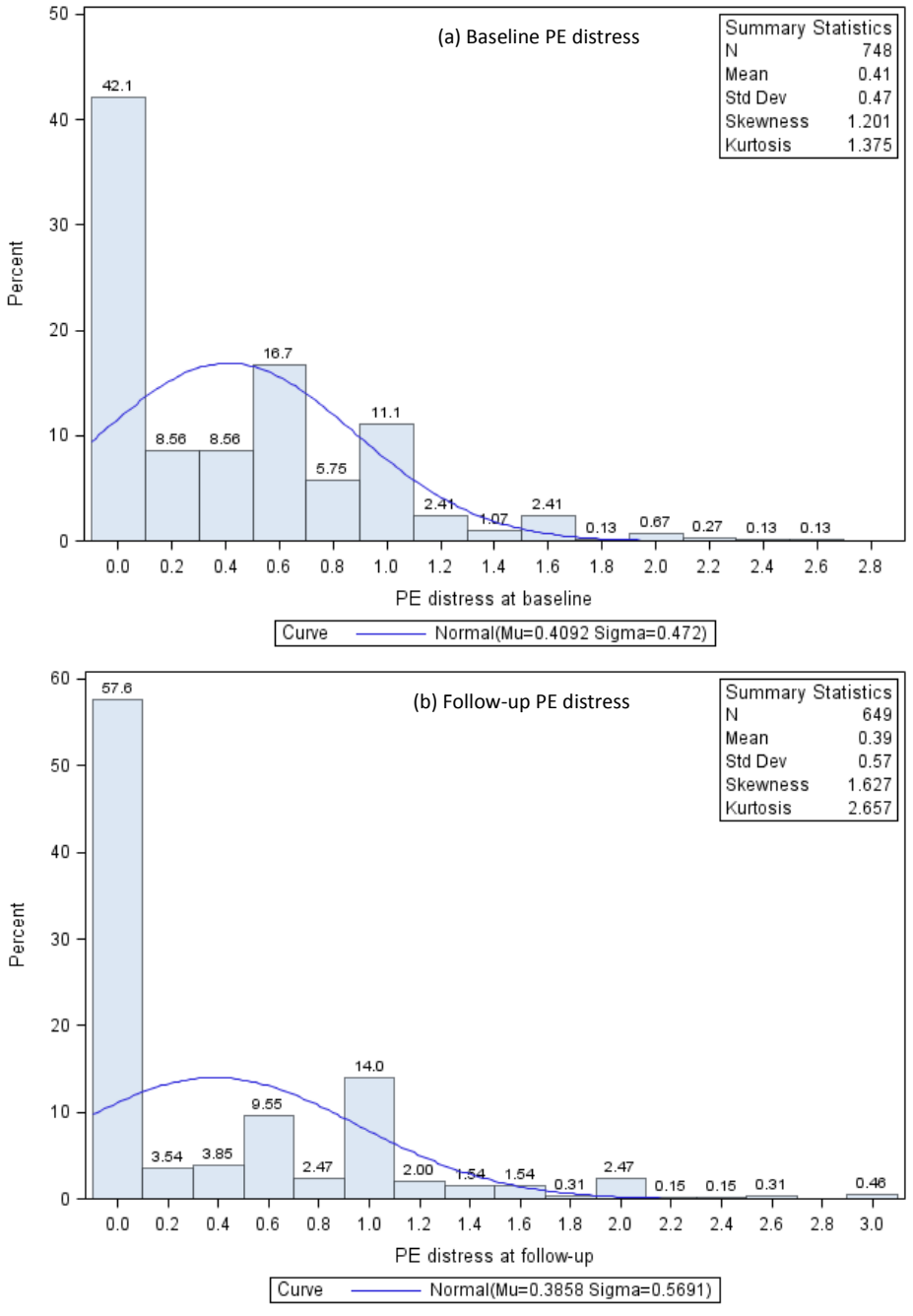
Supplementary Table S5: Pooled parameter estimates and model comparison for the frequency of positive psychotic experiences*

Parameter	Uncorrelated Model					Correlated Model**				
	Estimate	S.E.	95% C.I		P-value	Estimate	S.E.	95% C.I		P-value
			Lower	Upper				Lower	Upper	
Occurrence (Logistic)										
Intercept	0.946	1.377	-1.757	3.649	0.4923	0.877	1.245	-1.564	3.318	0.4813
Age	-0.013	0.023	-0.058	0.032	0.5711	-0.007	0.024	-0.055	0.041	0.7712
Sex	0.007	0.211	-0.407	0.420	0.9753	0.082	0.210	-0.333	0.497	0.6976
Education	-0.068	0.057	-0.180	0.045	0.2396	-0.083	0.056	-0.192	0.026	0.1339
Cannabis Use	-0.621	0.274	-1.158	-0.084	0.0234	-0.570	0.275	-1.114	-0.025	0.0404
Benton facial[a]	0.103	0.046	0.013	0.193	0.0245	0.091	0.041	0.011	0.170	0.0253
Time (3 years)	0.076	0.846	-1.590	1.741	0.9288	0.168	0.912	-1.713	2.048	0.8558
Immediate Recall[b]	0.047	0.027	-0.006	0.100	0.0809	0.054	0.025	0.004	0.103	0.0331
Immediate Recall*Time (3 years)	-0.068	0.030	-0.128	-0.009	0.0248	-0.077	0.032	-0.140	-0.013	0.0186
Var(random intercept): σ_1^2	2.791	0.685	1.447	4.135	<.0001	3.120	0.814	1.505	4.735	0.0002
Intensity (Lognormal)										
Intercept	-0.800	0.466	-1.718	0.117	0.0869	-0.741	0.430	-1.591	0.109	0.0871
Age	0.000	0.006	-0.012	0.012	0.9457	-0.002	0.006	-0.014	0.010	0.7648
Sex	0.028	0.053	-0.076	0.132	0.598	0.021	0.053	-0.083	0.126	0.6887
Education	-0.040	0.015	-0.071	-0.010	0.009	-0.043	0.018	-0.080	-0.006	0.0242
Cannabis Use	-0.108	0.065	-0.236	0.021	0.1007	-0.125	0.067	-0.257	0.007	0.0639
Sensitivity Index[c]	-0.006	0.003	-0.011	0.000	0.043	-0.006	0.003	-0.013	0.000	0.0444
Percent neutral faces[d]	-0.004	0.002	-0.007	-0.001	0.0238	-0.004	0.002	-0.007	-0.001	0.0177
Time (3 years)	0.543	0.427	-0.298	1.384	0.2051	0.582	0.438	-0.319	1.483	0.1957
Hinting Task	0.016	0.018	-0.020	0.051	0.3803	0.018	0.019	-0.020	0.056	0.3501
Hinting Task*Time (3 years)	-0.052	0.023	-0.096	-0.007	0.0233	-0.057	0.023	-0.104	-0.010	0.02
Var(res): σ_e^2	0.346	0.028	0.290	0.402	<.0001	0.325	0.022	0.280	0.369	<.0001
Var(random intercept): σ_2^2	0.256	0.031	0.195	0.317	<.0001	0.324	0.032	0.261	0.386	<.0001
Covariance	...	...	...	...	...	0.945	0.132	0.683	1.208	<.0001
Correlation (ρ)	...	...	...	...	...	0.941				
Model comparison (Fit Statistics)										
Criterion (Pooled)	Value					Value		Difference in -2LL		P-value
AIC	-275.30					-367.382				
-2LL	-319.30					-413.382		94.08		<.0001

*The model adjusted for age, gender, education, and cannabis used in past 12 months; [a]Benton Facial: Benton Facial Recognition Test; [b]Immediate Recall: WLT Immediate Recall; [c]Sensitivity Index: Continuous Performance Test Sensitivity Index; [d]Percent neutral faces: Degraded Facial Affect Recognition Task percent neutral faces; AIC: Akaike Information Criterion; -2LL: -2Log Likelihood. **Results of the correlated model are based on only four imputed datasets.



Supplementary Figure S1: Distribution of psychotic experiences (PE) positive frequency for siblings at (a) baseline and (b) 3-year follow-up



Supplementary Figure S2: Distribution of psychotic experiences (PE) distress for siblings at (a) baseline and (b) 3-year follow-up