Statistical approaches to explore clinical heterogeneity in psychosis

Islam, Atiqul

CHAPTER 3

Long-term cognitive trajectories in patients with schizophrenia and their unaffected siblings

Md. Atiqul Islam
Frank D. van Es
Tesfa D. Habtewold
Piotr J. Quee
Edwin R. van den Heuvel
Behrooz Z. Alizadeh[‡]
Richard Bruggeman[‡]
GROUP Investigators

[‡]Equal contribution

Submitted to Psychological Medicine

Abstract

Background: Heterogeneity of psychosis is reflected in the cognitive functioning of patients with psychosis and their unaffected siblings. This study assessed the heterogeneity and stability of cognition in patients with schizophrenia and their unaffected siblings, by forming separate longitudinal trajectories. Next, we aimed to predict cognitive subtypes of siblings by their probands.

Methods: Assessments were conducted at baseline, three and six years in 1,119 patients, 1,059 siblings and 586 controls from the Genetic Risk and Outcome of Psychosis (GROUP). Group-based trajectory modeling was applied to identify trajectories, and clustered multinomial logistic regression analysis was used for prediction modeling. Cognition was based on a composite measure of eight neurocognitive tests.

Results: Five cognitive trajectories were identified for patients, ranging from impaired to high performance. Four trajectories were found for siblings, ranging from moderately impaired to high performance. These distinct subtypes were stable and persisting over time. Siblings had higher risks to perform moderately impaired if patients perform mildly altered, moderately and severely impaired, compared to the combination of normal and high performance, with odds ratios 2.21 (95% CI 1.05-4.64), 5.70 (2.77–11.70) and 10.07 (4.15–24.44) respectively. The familial correlation coefficient between pairs of index patients and their siblings was 0.27 (P=0.003).

Conclusion: Cognitive performance of patients and of their unaffected siblings is heterogeneous and stable over time. Cognitive subtypes of patients significantly predicted subtypes of siblings. The profiling approach used in the current study is suitable for usage in future genetic studies, as well as in predicting functional and clinical outcomes.

Keywords: cognition; cognitive trajectory; heterogeneity, psychosis; siblings; subtypes

1. Introduction

Schizophrenia spectrum disorders consist of multiple symptom dimensions, caused by the interaction of genetic, environmental, and internal factors (van Os et al., 2010). One of these dimensions is cognitive impairment and it has been demonstrated that it is a predictor of symptomatic and functional outcome (*e.g.* working activity, daily living activity) (Heinrichs and Zakzanis, 1998; Green et al., 2000; Faber et al., 2011; Nuechterlein et al., 2014; Harvey, 2014).

Siblings of psychotic patients have been found to be a heterogeneous group with respect to cognition as well (Keri and Janka, 2004; Meijer et al., 2012). They exhibit subtle cognitive deficits in different domains, such as sustained attention, working memory, verbal memory and verbal fluency (Kremen et al., 1994; Chen and Faraone, 2000; Trandafir et al., 2006; Faraone et al., 1999; Krukow et al., 2017). From a clinical perspective, these subtle cognitive changes are thought of as markers for endophenotypic vulnerability to schizophrenia (Gur et al., 2007). The expression of psychotic vulnerability measured by neurocognition is higher in family members of patients, as compared to the normal population (Vollema and Postma, 2002). First-degree biological relatives of patients are approximately 10-fold risk of developing schizophrenia compared to the normal population (Kendler and Diehl, 1993). This indicates that cognitive impairment in schizophrenia cannot be solely attributed to the influence of disease-related factors, such as psychotic episodes, hospitalization, and unemployment or medication effects. Thus, studying relatives offers a unique possibility to unravel pathogenetic mechanisms, excluding confounding factors such as pharmacotherapy or life-style.

In First Episode Psychosis (FEP), patients' cognitive impairment seems stable during multiple years after onset (Barder et al., 2013; Townsend and Norman, 2004; Albus et al., 2006; Rodriguez-Sanchez et al., 2008; Leeson et al., 2011; Bozikas and Andreou, 2011). It has been suggested that their cognitive performance is stable over time regarding attention, verbal memory, and executive functioning (Faraone et al., 1995; Faraone et al., 1999). However, these studies of cognitive performance over time are based on mean values that do not take into account heterogeneity. In a previous study we demonstrated that subtype classification of unaffected siblings of patients with schizophrenia supports the evidence of heterogeneity in cognitive function (Quee et al., 2014).

In this study, we aimed to unravel the heterogeneity of neurocognition in patients and their siblings by classifying their neurocognitive performance time profile. Additionally, we aimed to predict cognitive subtypes of siblings by subtypes of patients.

2. Methods

2.1. Study design, setting and participants

The current study was performed within the framework of the Genetic Risk and Outcome of Psychosis (GROUP) project, a longitudinal multi-center cohort study in the Netherlands and Belgium. A group of outpatients and inpatients with psychotic disorder between 16 and 50 years were recruited. Siblings were asked to participate if they had at least one participating sibling with a non-affective psychotic disorder according to DSM-IV (American Psychiatric Association, 2000). Siblings were 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. For controls, the inclusion and exclusion criteria were the same as for siblings. The procedure of recruitment, informed consent, approval by the accredited

Medical Ethics Review Committee (METC) and population characteristics have been described in detail elsewhere (Korver et al., 2012). Between April 2004 and December 2013, participants were assessed at study entry, three and six years thereafter.

The full GROUP sample consisted of 1,119 patients, 1,059 unaffected siblings and 586 healthy controls at baseline. For standardization of the neurocognitive tests by age and gender, 586 subjects with seemingly no mental or somatic disease were included as a control group. We included all samples based on eight cognitive measures (see the details in section 2.3) from study entry, three and six years thereafter.

2.2. Sample size calculation

There was no formal sample size calculation for our intended analysis of trajectory modeling. However, Formann (1984) estimated the sample size for latent class analysis. According to Formann, the minimal sample size to include for latent class analysis was no less than 2^k cases with k the number of variables (Formann, 1984). In our case, we would need at least $2^k = 2^8 = 256$ subjects in our analysis, which we satisfy broadly.

2.3. Assessment of Neurocognition

Task selection was based on cognitive domains that have been shown to be impaired in schizophrenia (Nuechterlein et al., 2004). The cognitive battery has been described in details elsewhere (Meijer et al., 2012). This study focused on the neurocognitive measures which were related to outcome in an earlier study (Meijer et al., 2012). Supplementary Table S1 shows the list of cognitive domains, their corresponding tests, and outcome measures.

We calculated composite neurocognitive scores based on the following eight neurocognitive measures: the Continuous Performance Test (CPT), Word Learning Task immediate recall and delayed recall, WAIS-III Symbol Substitution, Information, Arithmetic, and Block Design (Supplementary Table S1). For the CPT, a measure was calculated for the performance index called 'CPT performance', and the reaction time variability called 'CPT variance' (See Supplementary Table S1). Subsequently, linear regression analyses (i.e. controls specific age and gender on each cognitive measure) were conducted for each time point. The scores of control subjects were used to obtain age and gender adjusted z-scores for both patients and siblings on all eight neurocognitive tests. Finally, composite scores for the overall cognitive functioning of patients and siblings respectively were computed by averaging z-scores of all eight tests.

2.4. Assessments of socio-demographics and clinical variables

Educational degree was evaluated as a continuous variable according to Verhage (Verhage, 1964). Level of premorbid functioning was assessed using Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). Positive and negative symptoms of schizotypy were measured using the Structured Inventory for Schizotypy-Revised (SIS-R) (Vollema and Ormel, 2000). Frequency and distress of psychotic experiences were measured by the Community Assessment of Psychic Experiences (CAPE) (Brenner et al., 2007). The symptom severity of patients was assessed with the 30-items five-factor Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987; Lancon et al., 2000). Age of onset of

psychosis was also measured for patients. Other socio-demographics variables were age of participants, gender and ethnicity.

2.5. Data analysis and Statistical Modeling

2.5.1. Descriptive Statistics

The socio-demographics characteristics at baseline for the controls, siblings, and patients were compared using univariate analyses. For gender and ethnicity, Pearson's Chi-square test was used to test the difference between groups (controls, siblings, and patients). Due to the family structure data, linear mixed effects models were applied on all continuous variables (e.g. socio-demographics, clinical and individual cognitive tests) to test for differences between the groups (controls, siblings, and patients). Family was taken as a random effect variable. The method of Maximum Likelihood (ML) was used to estimate the model parameters and Type-III (overall) tests of fixed effects were used to test for differences between groups. Significant differences were followed by pair-wise post-hoc comparisons between groups. Additionally, Pearson's correlation coefficients between cognitive performances of both patients and siblings were computed to explore the possible predictive relationship.

2.5.2. Trajectory modeling

Group-based trajectory modeling (Nagin, 1999; Jones et al., 2001; Nagin and Odgers, 2010; Niyonkuru et al., 2013) was conducted in order to identify clusters of patients and siblings, separately with similar patterns of composite neurocognitive scores over time. Longitudinal measurements of composite scores were treated as dependent variables and follow-up time (baseline, three and six years) as independent variables. The first order linear and second order quadratic polynomial model was fitted assuming that individual differences in trajectories could be summarized by a finite set of polynomial functions of time. To determine the number of clusters, a sequential approach was applied where the number of clusters is increased by one. The less complex model (i.e. less trajectory groups) was compared with the complex model (i.e. more groups) using the Bayesian Information Criterion (BIC) (Schwarz, 1978) and logged Bayes factor (2*ΔBIC), where ΔBIC = BIC (complex) – BIC (less complex) (Wit et al., 2012; Kass and Raftery, 1995) and where the logged Bayes factor (2*ΔBIC) would indicate trivial (0-2), positive (2-6), strong (6-10) or very strong (>10) evidence for the null hypothesis that the less complex model is the best fit. At first, a single quadratic polynomial trajectory model was examined. If the quadratic term was not significant, the model was re-run with linear trajectory to determine the BIC value. If the quadratic component in one trajectory model was significant, the quadratic two-trajectory model was performed. Next, the BIC value of the appropriate two-trajectory model compared to the BIC value of the appropriate one-trajectory model. The process was repeated with an increasing number of trajectories until the best fit model was found, as determined by comparing the BIC values and logged Bayes factor (Andruff et al., 2009). The trajectory modeling will be stopped at the moment when the ΔBIC becomes negative value. The ML estimation can handle missing data in the cognition score when it would satisfy the missing at random mechanism (Little and Rubin, 2002). We also checked the dropout model which includes a logistic model of dropout probability of cognitive functioning per period to see the dependency of

the cognitive functioning of patients and their siblings with the function of three time points. For each group, 0 = constant rate, 1 = depends on the previous response (baseline), 2 = depends on the two previous responses (baseline and three years).

2.5.3. Comparison among cognitive subtypes on all baseline characteristics

Differences in all continuous variables between the subtypes of patients and siblings respectively were investigated using linear mixed effect models taking into account familial relationship. Type-III (overall) tests of fixed effects were used to test for differences between cognitive subtypes. If these were significant, pair-wise comparisons between subtypes were investigated with Dunnet's method (taking the most normal cognitive profile as reference group). For gender and ethnicity, Pearson's Chi-square test was used to test the difference between trajectory groups of patients and siblings respectively.

2.5.4. Cognitive subtypes of Patients predict subtypes of siblings

Our hypothesis of the sibling-patient analysis was that subtype of patient predicted the subtype of sibling. We considered sibling subtype (multi-category) as dependent and patient subtype (multi-category) as independent variables. Concordant, discordant and Somers' D statistic (Somers, 1962) were computed on the pairs of subtypes of patients and siblings. A pair of subtypes of patients, subtypes of siblings-pairs was said to be concordant if the larger value of subtypes of patients was paired with the larger value of subtypes of siblings, and was said to be discordant if the larger value of subtypes of patients was paired with the smaller value of subtypes of siblings. Somers' D of subtypes of siblings with respect to subtypes of patients was defined as the difference between the two conditional probabilities of concordance and discordance. In the modeling, given the family structure of the data (as siblings-patients belong within the same family) clustered multinomial logistic regression was conducted taking into account family as a random effect. PROC NLMIXED in SAS (Statistical Analysis System) was applied to determine the predictive relationship between subtypes of patients and siblings. An adaptive Gaussian quadrature with 10 quadrature points was specified to integrate out the random effect of the likelihood function (Kuss and McLerran, 2007; de Rooij and Worku, 2012) and to estimate the parameters (i.e. subtypes of patients) and their standard errors. The intra-cluster correlation coefficient (ICC) was calculated to estimate the familial correlation between pairs of unaffected siblings and schizophrenic index patients in the same family. The ICC was calculated as

$ICC_{Family} = var(family)/(var(family) + \pi^2/3)$, where, *var(family)* is the variance of random effect and π is 3.14159.

A two-tailed test at P<0.05 is considered as statistical significant throughout the analyses. All analyses were performed using Statistical Analysis System (SAS), version 9.4.

3. Results

3.1. Descriptive of study population

Differences between patients, siblings, and controls were significant (P<0.001) on socio-demographic, cognitive and clinical variables at baseline (Table 1). Pair-wise comparisons revealed that differences were significant between patients and controls as well as between siblings and controls. On all measures, patients and siblings displayed poorer performances than controls. Additionally, performances on cognitive outcomes of patients with schizophrenia were found to be significantly lower than the performances of their unaffected siblings (Table 1).

Pearson's correlation coefficients between cognitive performances were significant for all cognitive tests in patients and in siblings; except for Block Design, Arithmetic and Information with CPT performance of siblings (Supplementary Table S2-S3).

Table 1: Comparison of baseline characteristics for controls, siblings, and patients*.

Variable/Group	Group			Overall group difference	Pair-wise group comparison
	1. Controls (n=586)	2. Siblings (n=1,059)	3. Patients (n=1,119)		
Age	30.42 (10.58)	27.84 (8.28)	27.58 (7.94)	F=22.8, P<0.001	2<1, 3<1
Gender, % male	45.90	45.51	76.14	χ^2=254.1, P<0.001	2<1<3
Education (Verhage)[a]	5.41 (1.78)	5.07 (2.11)	4.04 (2.05)	F=128.5, P<0.001	3<2<1
Ethnicity, % Dutch	92.12	83.24	79.22	χ^2=45.2, P<0.001	3<2<1
IQ, Estimated[b]	109.75 (15.08)	102.76 (15.60)	94.99 (16.12)	F=185.6, P<0.001	3<2<1
PAS, overall score[c]	1.13 (0.59)	1.13 (0.66)	1.98 (0.88)	F=439.0, P<0.001	2<3, 3<1
SIS-R[d]					
Positive	0.31 (0.35)	0.38 (0.42)	…	F=15.4, P<0.001	1<2
Negative	0.24 (0.22)	0.27 (0.26)	…	F=9.0, P=0.002	1<2
Age of onset	…	…	23.69 (7.59)	…	…
PANSS 5-factor					
Positive	…	…	13.90 (6.55)	…	…
Negative	…	…	15.00 (6.64)	…	…
Disorganization	…	…	16.77 (6.27)	…	…
Excitement	…	…	12.05 (4.05)	…	…
Emotional distress	…	…	15.82 (5.73)	…	…
CAPE (Positive dimension)[e]					
PE Frequency	0.19 (0.17)	0.21 (0.20)	0.67 (0.49)	F=566.5, P<0.001	2<3, 3<1
PE Distress	0.43 (0.45)	0.46 (0.48)	1.26 (0.69)	F=531.0, P<0.001	2<3, 3<1
Cognitive Performance					
CPT performance[f]	246.36 (54.78)	243.70 (57.86)	220.82 (62.14)	F=52.0, P<0.001	3<2, 1<3
CPT variance (ms)[g]	72.76 (28.28)	75.80 (28.44)	92.99 (36.51)	F=108.4, P<0.001	2<3, 3<1
Block Design[h]	46.55 (14.16)	44.87 (15.07)	40.42 (16.99)	F=39.2, P<0.001	3<2<1
Digit Symbol[i]	84.01 (14.58)	79.21 (15.39)	65.41(16.27)	F=379.9, P<0.001	3<2<1
Arithmetic[j]	15.32 (4.16)	13.86 (4.43)	12.27 (4.79)	F=93.1, P<0.001	3<2<1
Information[k]	18.84 (4.67)	16.83 (5.22)	16.77 (5.47)	F=31.5, P<0.001	2<1, 3<1
Immediate Recall[l]	28.47 (5.37)	26.89 (5.77)	22.94 (6.09)	F=224.5, P<0.001	3<2<1
Delayed Recall[m]	9.74 (2.70)	9.33 (2.64)	7.53 (2.87)	F=181.6, P<0.001	3<2<1

*Table presents means (SD) or %; Empty space (…) means no measurments in the respective group (row/column wise); [a]Education (Verhage): range 0 (no education), 3-5 (school diploma) to 8 (university degree); [b]IQ: Wechsler Adult Intelligence Scale-III (WAIS-III), short form; [c]PAS: Premorbid Adjustment Scale; [d]SIS-R: Structured Inventory for Schizotypy – Revised; [e]CAPE: Community Assessment for Psychic Experiences; PE frequency and distress: Frequency of positive psychotic experiences and amount of distress of these PE; [f]CPT performance: Continuous Performance Test HQ, performance index, [g]CPT variance (ms): CPT-HQ variance in reaction time (ms); [h]Block Design: WAIS-III Block Design; [i]Digit Symbol: WAIS-III Digit Symbol Substitution Test; [j]Arithmetic: WAIS-III Arithmetic; [k]Information: WAIS-III Information; [l]Immediate recall: Word Learning Task (WLT) immediate recall; [m]Delayed recall: WLT Delayed recall. For the PAS, higher scores reflect poorer premorbid adjustment. [1]Control, [2]Sibling and [3]Patient; Pair-wise group comparison explains which group better or worse in terms of measurements.

3.2. Trajectory modeling and longitudinal course

To identify cognitive trajectories of patients and their unaffected siblings over time, group-based trajectory modeling was applied. A five-group cognitive trajectory model for patients and a four-group trajectory model for siblings were very strongly favoured for overall cognitive scores (z-scores) according to the smallest BIC and the logged Bayes factor (Supplementary Table S4). In patients, the value of logged Bayes factor 17.34 (>10) favouring the five-cluster model over a six-cluster model. In siblings, the value of logged Bayes factor 94.62 (>10) considering the four-trajectory model over a five-cluster model (Supplementary Table S4). Parameter estimates of linear and quadratic polynomial time functions of trajectory modeling including dropout models are presented in the Supplementary Table S5 and S6.

The figure 1a and 1b displayed the changes of cognitive trajectories of patients and their siblings on z-scores of composite cognitive measure over six years. The cognitive trajectories in patients were labeled as ‘severely impaired’, ‘moderately impaired’, ‘mildly altered’, ‘normal’ and ‘high performer’. Similarly, the trajectories in siblings were labeled as ‘moderately impaired’, ‘mildly altered’, ‘normal’ and ‘high performer’. All initial profiles of composite neuro-cognition for patients and siblings were stable over time (Figure 1a-1b). Severe and moderate groups were identified based on a broad-based cognitive impairment of, on average, about 1 SD below the normal across a range of composite cognition score. A large group of patients (26.7%) and the largest group of sibling (37.6%) displayed normal cognitive functioning. The majority of patients (30.4%) and a large group of siblings (25.1%) showed mild cognitive alterations across all time points. Then, a group of patients (28.4%) and a smaller group of siblings (13.0%) manifested moderate cognitive impairment. The latter group of siblings showed steady and slight improvement of performance over time. Severe impairment was only seen in a small group of patients (10.7%).

The smallest patient group (3.8%) and a substantial group of siblings (24.2%) performed higher cognitive functioning, compared to the mean level of the normal cognitive subtype. Patients in this cluster showed a slight decline over time (Figure 1a), whereas the pattern was stable for siblings (Figure 1b).

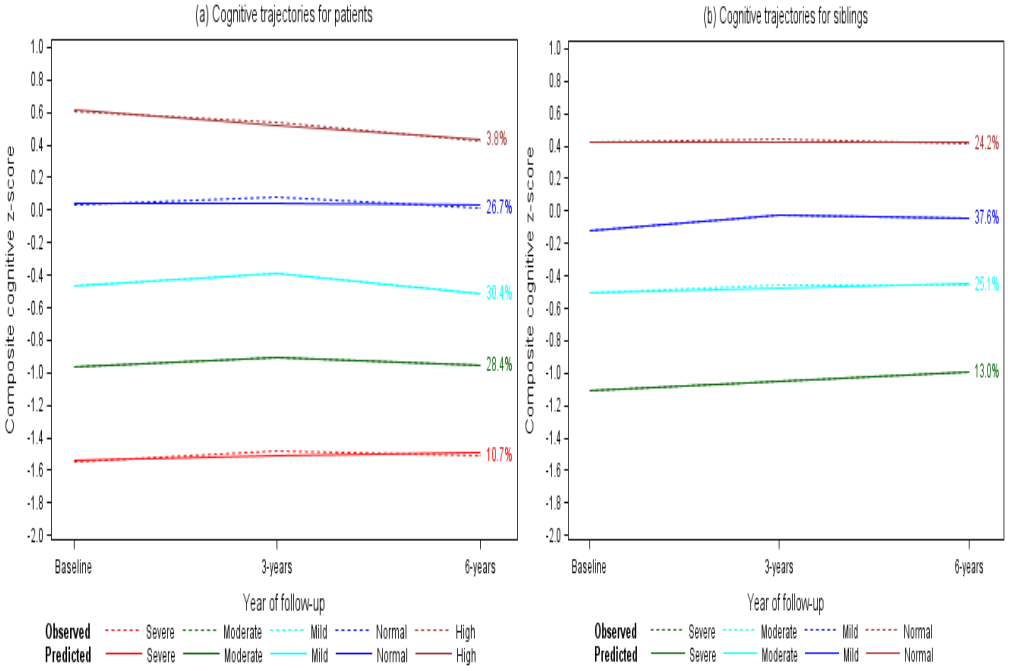

Figure 1: (a) Cognitive trajectories for patients (n=1,119), (b) Cognitive trajectories for siblings (n=1,059)

3.3. Comparison of cognitive subtypes on all baseline characteristics

Differences between cognitive subtypes of siblings were significant with regard to age, gender, education, ethnicity, IQ, PAS overall score and SIS-R positive symptoms, CAPE frequency of psychotic experiences (PE) and all cognitive performances except CPT variance (Table 2). Siblings with a moderate impaired profile were lower educated and poorer cognitive performance than those with a normal profile. Similarly, mild altered group of siblings had lower education, lower IQ and poorer cognitive performance compared to the performance of normal profile (Table 2).

Cognitive subtypes of patients were compared on all cognitive measures and on demographic and clinical variables (Table 3). Pair-wise comparisons of subtypes revealed that patients with a severely impaired profile performed poorer on all cognitive measures. Besides, significant differences were found between profiles of severe impairment and normal performance, on measures of education, age of onset of psychosis, IQ, the PAS overall score, and PANSS negative, disorganization and excitement score. Patients with a moderate impaired profile were lower educated, lower IQ, poorer premorbid functioning, poorer symptoms of PANSS on all five factors, and poorer cognitive performance than those with a normal profile. Difference between the mildly altered and normal group of patients were found on measures of education, IQ and all cognitive measures except CPT variance.

Table 2: Characteristics, main effects and pair-wise comparisons for the four subtypes of non-affected siblings (n=1,059)*

Variable/Trajectory	Cognitive trajectory group				Overall trajectory group difference	Pair-wise comparison**
	1. High (n=254)	2. Normal (n=413)	3. Mild (n=260)	4. Moderate (n=132)		
Age	28.6 (7.7)	27.9 (8.0)	27.8 (8.9)	26.3 (8.9)	F=5.6, P=0.001	2<1
Gender, % male	55.5	43.6	41.5	40.2	χ^2=14.1, P=0.003	2<1; 2>4
Education (Verhage)[a]	6.1 (1.8)	5.3 (2.0)	4.5 (2.0)	3.5 (2.1)	F=62.2, P<0.001	2<1,3,4
Ethnicity, % Dutch	87.4	85.7	79.5	74.8	χ^2=14.1, P=0.003	2<1; 2>3,4
IQ, Estimated[b]	120.7 (9.9)	104.9 (9.5)	92.1 (7.9)	81.9 (6.7)	F=684.7, P<0.001	2<1,3,4
PAS, overall score[c]	0.9 (0.6)	1.1 (0.7)	1.2 (0.6)	1.3 (0.7)	F=13.6, P<0.001	2<4, 2<1
SIS-R[d]						
Positive	0.3 (0.4)	0.4 (0.4)	0.4 (0.4)	0.5 (0.5)	F=4.2, P=0.006	2<4
Negative	0.3 (0.3)	0.3 (0.2)	0.3 (0.3)	0.3 (0.3)	F=2.5, P=0.108	
CAPE (Positive dimension)[e]						
PE Frequency	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.3 (0.3)	F=4.3, P=0.006	2<4
PE Distress	0.4 (0.4)	0.5 (0.5)	0.5 (0.5)	0.6 (0.5)	F=2.4, P=0.074	
Cognitive Performance						
CPT performance[f]	254.9 (58.9)	245.3 (49.8)	242.4 (59.7)	220.9 (68.3)	F=9.3, P<0.001	4<2
CPT variance (ms)[g]	70.9 (26.0)	74.6 (26.7)	80.0 (30.3)	80.2 (32.3)	F=4.8, P=0.003	
Block Design[h]	56.3 (8.4)	48.2 (12.4)	37.1 (13.8)	28.1 (11.9)	F=208.3, P<0.001	2<1,3,4
Digit Symbol[i]	89.7 (11.9)	81.4 (13.0)	72.7 (14.4)	65.5 (13.8)	F=121.7, P<0.001	2<1,3,4
Arithmetic[j]	17.7 (2.6)	14.9 (3.2)	11.5 (3.6)	8.2 (3.1)	F=318.5, P<0.001	2<1,3,4
Information[k]	21.8 (3.5)	17.5 (4.0)	14.1 (3.8)	10.6 (3.6)	F=299.9, P<0.001	2<1,3,4
Immediate Recall[l]	31.4 (4.4)	27.3 (4.9)	25.0 (5.0)	20.7 (4.8)	F=159.0, P<0.001	2<1,3,4
Delayed Recall[m]	11.3 (2.1)	9.5 (2.4)	8.5 (2.3)	6.6 (1.8)	F=113.2, P<0.001	2<1,3,4

*Table presents mean (standard deviation) or %; **Pair-wise trajectory comparison: always compared with normal group using Dunnett's adjustment; (1, 3, 4) ordering is lower to higher difference (with respect to mean or proportion) than normal. [a]Education (Verhage): range 0 (no education), 3-5 (school diploma) to 8 (university degree); [b]IQ: Wechsler Adult Intelligence Scale-III (WAIS-III), short form; [c]PAS: Premorbid Adjustment Scale; [d]SIS-R: Structured Inventory for Schizotypy – Revised (higher scores in PAS and SIS-R reflect poorer outcomes); [e]CAPE: Community Assessment for Psychic Experiences; PE frequency and distress: Frequency of positive psychotic experiences and amount of distress of these PE; [f]CPT performance: Continuous Performance Test HQ, performance index, [g]CPT variance (ms): CPT-HQ variance in reaction time (ms); [h]Block Design: WAIS-III Block Design; [i]Digit Symbol: WAIS-III Digit Symbol Substitution Test; [j]Arithmetic: WAIS-III Arithmetic; [k]Information: WAIS-III Information; [l]Immediate recall: Word Learning Task (WLT) immediate recall; [m]Delayed recall: WLT Delayed recall; Cognitive trajectory: high (1) to worst (4).

Table 3: Characteristics, main effects and pair-wise comparisons for the five subtypes of patients (n=1,119)*

Variable/Trajectory	Cognitive trajectory group					Overall trajectory group difference	Pair-wise comparison**
	1. High (n=31)	2. Normal (n=290)	3. Mild (n=377)	4. Moderate (n=312)	5.Severe (n=109)		
Age	31.4 (8.3)	27.3 (7.2)	28.0 (8.0)	27.3 (8.4)	26.8 (8.0)	F=2.5, P=0.051	2<1
Gender, % male	74.2	77.9	74.3	77.2	75.2	χ^2=1.6, P=0.816	
Education (Verhage)[a]	5.8 (1.9)	4.9 (1.8)	4.3 (2.0)	3.3 (1.9)	2.6 (1.8)	F=49.0, P<0.001	2<1,3,4,5
Ethnicity, % Dutch	90.3	87.2	79.9	75.1	64.5	χ^2=30.6, P<0.001	2<1; 2>3,4,5
Age of Onset	26.2 (8.1)	23.0 (6.5)	23.2 (7.9)	22.9 (7.9)	23.0 (7.3)	F=1.4, P=0.253	
IQ, Estimated[b]	127.8 (10.7)	110.5 (10.4)	95.7 (8.6)	83.3 (7.7)	72.9 (6.7)	F=615.6, P<0.001	2<1,3,4,5
PAS, overall score[c]	1.8 (1.0)	1.8 (0.8)	1.9 (0.8)	2.1 (1.0)	2.3 (0.8)	F=9.7, P<0.001	2<5; 2<4
PANSS 5-factor[d]							
Positive	14.0 (8.2)	13.4 (5.9)	13.1 (5.9)	15.0 (7.1)	14.8 (7.7)	F=4.0, P=0.003	2<4
Negative	15.1 (6.4)	13.6 (5.9)	14.3 (6.4)	16.1 (7.0)	18.0 (7.1)	F=11.1, P<0.001	2<5; 2<4
Disorganization	16.0 (6.8)	14.8 (4.9)	15.7 (5.6)	18.3 (6.6)	21.3 (7.1)	F=30.5, P<0.001	2<5; 2<4
Excitement	12.8 (5.2)	11.5 (3.5)	11.5 (3.7)	12.7 (4.4)	13.2 (4.5)	F=7.0, P=0.001	2<5; 2<4
Emotional distress	16.0 (5.7)	15.4 (5.4)	15.2 (5.5)	16.7 (5.8)	16.4 (6.8)	F=3.3, P=0.024	2<4
Cognitive Performance							
CPT performance[e]	256.1 (45.7)	240.9 (52.2)	225.8 (59.6)	210.7 (56.5)	170.0 (78.8)	F=30.1, P<0.001	2<3,4,5
CPT variance (ms)[f]	84.2 (35.3)	83.1 (31.9)	90.1 (36.0)	101.8 (37.2)	106.3 (38.9)	F=13.4, P<0.001	2<4,5
Block Design[g]	60.4 (8.8)	53.5 (10.9)	42.2 (14.3)	30.7 (13.8)	20.6 (11.0)	F=197.6, P<0.001	2<1,3,4,5
Digit Symbol[h]	85.2 (14.6)	76.2 (14.6)	66.5 (12.5)	57.8 (12.9)	47.5 (11.7)	F=138.7, P<0.001	2<1,3,4,5
Arithmetic[i]	18.8 (2.5)	16.2 (3.2)	13.0 (3.8)	9.1 (3.3)	6.7 (2.7)	F=264.22, P<0.001	2<1,3,4,5
Information[j]	24.6 (2.3)	21.1 (3.4)	17.4 (4.3)	13.6 (4.3)	9.9 (3.5)	F=243.9, P<0.001	2<1,3,4,5
Immediate Recall[k]	32.4 (3.8)	27.1 (4.7)	23.4 (4.7)	19.9 (4.8)	15.9 (5.0)	F=173.2, P<0.001	2<1,3,4,5
Delayed Recall[l]	12.1 (1.8)	9.4 (2.4)	7.6 (2.4)	6.2 (2.2)	4.6 (2.0)	F=142.7, P<0.001	2<1,3,4,5

*Table presents mean (standard deviation) or %; **Pair-wise trajectory comparison: always compared with normal group using Dunnett's adjustment; (1, 3, 4, 5) ordering is lower to higher difference (with respect to mean or proportion) than normal. [a]Education (Verhage): range 0 (no education), 3-5 (school diploma) to 8 (university degree); [b]IQ: Wechsler Adult Intelligence Scale-III (WAIS-III), short form; [c]PAS: Premorbid Adjustment Scale; [d]PANSS: Positive and Negative Syndrome Scale (higher scores in PAS and PANSS reflect poorer outcomes); [e]CPT performance: Continuous Performance Test HQ, performance index, [f]CPT variance (ms): CPT-HQ variance in reaction time (ms); [g]Block Design: WAIS-III Block Design; [h]Digit Symbol: WAIS-III Digit Symbol Substitution Test; [i]Arithmetic: WAIS-III Arithmetic; [j]Information: WAIS-III Information; [k]Immediate recall: Word Learning Task (WLT) immediate recall; [l]Delayed recall: WLT Delayed recall; Cognitive trajectory: high (1) to worst (5).

3.4. Cognitive subtypes of patients in relation to subtypes of siblings

In sibling-patient pair analysis, we generated 1,070 pairs of affected and unaffected siblings. The number of pairs was more than 1,059 because we paired multiple unaffected siblings with their single affected sibling or multiple affected siblings with their single unaffected sibling within a family. The contigency table of the subtypes of patients and siblings is presented in the Supplementary Table S7. Somers' *D* determined the association between cognitive subtypes of patients and subtypes of siblings amongst 1070 sib-pairs. A positive value of Somers' *D* (0.29) indicates that the siblings have better cognitive scores than their probands. Thus, being ill means a deterioration of cognitive performances or a lower cognitive performance means a higher risk of becoming ill.

Since the cell frequency of a moderate group of siblings and high cognitive performance group of patients was empty (Supplementary Table S7), i.e. moderate group of siblings did not have probands who were in high performer groups, we combined high cognitive performer group of patients to the normal cognitive group. The combined normal and high performer group of patients was considered as the reference group.

Table 4 presents the predictive relationship between cognitive sybtypes of patients and siblings. Overall, cognitive subtypes of patients significantly predicted the sibling subtype. Here, we present a risk of an unaffected sibling to be grouped in any of mildly altered, moderately impaired and severely impaired groups given the cognitive trajectory of their corresponding affected sibling. The familial correlation i.e. the intra-class correlation coefficient between pairs of unaffected siblings and index patients in the same family accounted 27% (P=0.003) of total variation.

We observed that a sibling in the group of severely impaired patients was at risk (odds ratio (OR) 2.56, 95% CI 1.26–5.18) of having mild alterations of unaffected siblings. This estimate was 1.83 (95% CI 1.12 – 2.98) for affected siblings of moderately impaired patients. However, mild cognitive alterations of patients did not predict mild alterations of his/her unaffected sibling (OR 0.86, P=0.545; Table 4a).

Siblings showed to be at risk to perform moderately impaired if their probandsperformed mildly altered, moderately or severely impaired, compared to the combined normal and high performer group of affected siblings, with OR's of 2.21 (95% CI 1.05-4.64), 5.70 (95% CI 2.77–11.70) and 10.07 (95% CI 4.15–24.44) respectively (Table 4b).

Subsequently, unaffected siblings had low risks to have high cognitive performance if patients were severely (OR 0.26, 95% CI 0.09-0.63) or moderately (OR 0.39, 95% CI 0.24-0.64) impaired; and to have mildly altered (OR 0.37, 95% CI 0.24-0.59) cognitive functioning, when the probands performed in the combined normal and high performance group (Table 4c). In general, of patients who performed severely impaired, unaffected siblings were likely to show moderate to mild alterations of cognitive functioning.

Table 4: Parameter estimates of subtypes of patients on the subtype of sibling (n=1,070 pairs)*.

Cognitive performance of patient subtype	Prediction of cognitive subtypes in siblings	
	OR (95% C.I)	P-value
a. Siblings with mild alterations		
Intercept	0.56 (0.38 - 0.81)	0.002
Severe impairment of affected sib	2.56 (1.26 – 5.18)	0.009
Moderate impairment of affected sib	1.83 (1.12 – 2.98)	0.015
Mild alterations of affected sib	0.86 (0.53 – 1.41)	0.545
b. Siblings with moderate impairment		
Intercept	0.11 (0.06 - 0.21)	<0.001
Severe impairment of affected sib	10.07 (4.15 – 24.44)	<0.001
Moderate impairment of affected sib	5.70 (2.77 – 11.70)	<0.001
Mild alterations of affected sib	2.21 (1.05 - 4.64)	0.036
c. Siblings with high performance		
Intercept	1.24 (0.90 - 1.71)	0.186
Severe impairment of affected sib	0.24 (0.09 - 0.63)	0.003
Moderate impairment of affected sib	0.39 (0.24 - 0.64)	<0.001
Mild alterations of affected sib	0.37 (0.24 - 0.59)	<0.001
Random effect variance and ICC	Estimate (95% C.I)	P-value
Variance (Family)	1.19 (0.12 – 2.26)	0.029
ICC	0.27 (0.09 – 0.44)	0.003

*Reference category for patients is the combination of normal and high cognitive performance, and for siblings normal performance. OR = Odds Ratio; C.I = Confidence Interval; ICC = Intra-class correlation coefficient.

4. Discussion

The aim of this study was two-fold. Firstly, we examined ways to unravel the heterogeneity of neurocognition, by classifying patients and siblings respectively into different subgroups based on the course of composite overall cognition scores over time, separately from each other, based on eight neurocognitive tests. After determining the meaningful subgroups of patients and siblings, we aimed to predict the cognitive subtypes of siblings by subtypes of patients within a family using sibling-patient analysis. Most of the longitudinal studies published in literature investigated the cognitive trajectories over time in patients only. Therefore, to the best of our knowledge, this is the first large-scale study which included cognitive trajectory modeling for both patients and their unaffected siblings.

At baseline, cognitive performance in first-degree relatives of patients with schizophrenia was worse, compared to controls. In line with previous studies (Braff et al., 2007; Krabbendam et al., 2001; Quee et al., 2014), we demonstrated that the performance of siblings were between those of patients and controls. This indicates a parallel between cognitive performance and familial liability.

Trajectory modeling demonstrated a five-trajectory model for patients and a four-trajectory model for siblings that were stable over time. Approximately 70% of patients demonstrated poor cognitive performance (Severe + moderate + mild) (Figure 1a), which was similar to other schizophrenia studies (Thompson et al., 2012; Irani et al., 2011; Szoke et al., 2008). Two of these studies (Barder et al., 2013; Barder et al., 2013), used continuous scale of cognitive measures, demonstrated that cognitive domains remained stable over five to ten years after first episode psychosis. However, they did not classify sub-groups of cognitive performance. In our study, a sub-group of 10.7% patients showed severe cognitive impairment and it was stable over a six-year period.

On the other hand, in the sibling model, a total of 38% (Moderate + mild) exhibited lower cognitive performance than the normal performing subtype over the full period of six years. Both moderate and mild alterations groups of siblings were stable over time (Figure 1b). This result is similar to an earlier analysis of a cross-sectional study done by our research group (Quee et al., 2014). In this study, mild to severely impaired groups of patients- and siblings performed at least -1SD below normal cognition and their trajectories were stable over time.

Studying cognitive trajectories in siblings may provide insight into individuals who are at risk for psychosis. Siblings in the moderate impaired group were more often an ethnic minority, younger, of low IQ, and with a higher level of psychotic experiences (Table 1). This study rated 13% of siblings and 10.7% of patients as moderate to severely impaired. As was found during earlier analysis (Quee et al., 2014) and other studies (Palmer et al., 1997; Kremen et al., 2000), clinical outcomes (e.g. PANSS) and premorbid functioning was poorer in these subgroups (Table 2). Identifying meaningful trajectories lends support to the clinical notion that cognitive deficits are moderate to severely impaired across several domains of cognitive battery, and these impairments are the reasons of disabilities in functioning (Bowie and Harvey, 2006; Keefe and Harvey, 2012).

The positive value for the measure of Somers' *D* (0.29) from the sib-pair analysis showed that the proband is more likely to show low cognitive performance than the sibling, indicating that the disease has a direct impact on cognitive performance. On the other hand, the cognitive subtype of the patient significantly predicted the cognitive subtype of the sibling within the family. The poorer the cognitive profile of the patient, the better it predicted (OR 10.07) the profile of a more cognitively impaired sibling. Moreover, siblings in high performer group are less predicted when their probands were severely impaired (OR 0.24).

We found a familial correlation of 27%, which is high compared to other complex diseases such as depression or bipolar disorder. Of note, this correlation did not take into account the genetic and other environmental factors as it takes only the familial effect. Literature found that neurocognitive impairment is a known inherited form of familial schizophrenia (Brzustowicz et al., 2000; Brzustowicz et al., 2004; Husted et al., 2009). Some family-based studies have already found high rates of cognitive impairment in unaffected relatives of individuals with schizophrenia than in the general population (Snitz et al., 2006). Husted et al. (2009) investigated the heritability of seven distinct neurocognitive measures for schizophrenia, and found significant heritability between 31 to 62% (Husted et al., 2009). Therefore, we would have expected stronger familial effect if we should have taken genetic and other environmental factors into account, since cognitive impairment is not the only factor related to the symptoms of schizophrenia, it is one of the proxies of schizophrenia.

Neurocognitive measures have been proposed as reliable endophenotypic markers of liability for schizophrenia, as cognitive deficits are transmitted within families of patient with schizophrenia (Gur et al., 2007; Krabbendam et al., 2001). The presented subtypes of neurocognition can also be regarded as candidate endophenotypic markers, as they are associated with socio-demographic and clinical variables. Additionally, cognitive subtypes are stable over time and are an inherited form of psychotic disorder. Several studies have shown that cognitive function as a composite measure is a better predictor of functional outcome than any single cognitive test (Bilder et al., 2000; Mohamed et

al., 1999). Further studies are needed to evaluate the additive value of cognitive subtypes of siblings and patients in predicting functional, clinical outcomes and quality of life.

The strength of the study is that we included a large number of patients with schizophrenia, their unaffected siblings, and healthy controls. We included multiple patients and siblings within the same family and their measurements over time yielded an effective study which jointly investigated on the cognitive trajectory of patients and siblings. Moreover, we provided a hint of prediction of sibling's cognitive impairment by the different cognitive profiles of schizophrenia patients. In the methodological perspective, we used group-based trajectory modeling (Nagin, 2014) to identify the significant long-term cognitive trajectory considering drop-out modeling within the same model. Other studies did not take into account the drop-out modeling of the dependency of cognitive functioning with the function of several time points separately when they identified groups (Barder et al., 2013; Barder et al., 2013; Thompson et al., 2012). Some limitations should also be mentioned in this study. There was selection bias in data collection with respect to patients or siblings compared to controls, as controls were selected by random mailing. We found that the prediction of the high cognitive performer group of patients on a moderate group of siblings was ambiguous and unstable due to low frequency. Generating composite cognition scores might have an impact on finding meaningful trajectory instead of using multivariate cognitive tests. This is one of the major limitations of trajectory modeling (Jones et al., 2001) which dealt with one variable at a time. This study used eight neurocognitive tests but including other tests might lead to different trajectories with different predictions, as the cognitive battery was comprehensive but not complete.

In conclusion, our findings confirmed that cognitive functioning in patients with schizophrenia and their unaffected siblings is heterogeneous. We demonstrated that the cognitive performance of siblings of schizophrenia stayed between that of the patients and the healthy controls. We also identified five distinct cognitive trajectories in patients and four trajectories in siblings, which remained stable during six years follow-up. These trajectories are validated by observing the association with external factors e.g. socio-demographic, clinical and cognitive measures confirming the meaningful cognitive subtypes in patients and siblings. Moreover, cognitive subtypes in patients significantly predicted the sibling subtypes, highlighting the familial contribution to cognition. The study supports neurocognitive profiling as a valuable endophenotype. This profiling approach warrants further evaluation in future molecular studies as well as in studies predicting functional and clinical outcomes.

References

Albus, M., Hubmann, W., Mohr, F., Hecht, S., Hinterberger-Weber, P., Seitz, N.N., Kuchenhoff, H. (2006). Neurocognitive functioning in patients with first-episode schizophrenia : results of a prospective 5-year follow-up study. *European archives of psychiatry and clinical neuroscience* 256:442-451.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders*. Washington DC.

Andruff, H., Carraro, N., Thompson, A., Gaudreau, P., Louvet, B. (2009). Latent Class Growth Modelling: A Tutorial. *Tutorials in Quantitative Methods for Psychology* 5:11-24.

Barder, H.E., Sundet, K., Rund, B.R., Evensen, J., Haahr, U., Ten Velden Hegelstad, W., Joa, I., Johannessen, J.O., Langeveld, H., Larsen, T.K., Melle, I., Opjordsmoen, S., Rossberg, J.I., Simonsen, E., Vaglum, P., McGlashan, T., Friis, S. (2013). Neurocognitive development in first episode psychosis 5 years follow-up: associations between illness severity and cognitive course. *Schizophrenia research* 149:63-69.

Barder, H.E., Sundet, K., Rund, B.R., Evensen, J., Haahr, U., Ten Velden Hegelstad, W., Joa, I., Johannessen, J.O., Langeveld, J., Larsen, T.K., Melle, I., Opjordsmoen, S., Rossberg, J.I., Simonsen, E., Vaglum, P., McGlashan, T., Friis, S. (2013). Ten year neurocognitive trajectories in first-episode psychosis. *Frontiers in human neuroscience* 7:643.

Bilder, R.M., Goldman, R.S., Robinson, D., Reiter, G., Bell, L., Bates, J.A., Pappadopulos, E., Willson, D.F., Alvir, J.M.J., Woerner, M.G., Geisler, S., Kane, J.M., Lieberman, J.A. (2000). Neuropsychology of First-Episode Schizophrenia: Initial Characterization and Clinical Correlates. *AJP* 157:549-559.

Bowie, C.R., Harvey, P.D. (2006). Cognitive deficits and functional outcome in schizophrenia. *Neuropsychiatric Disease and Treatment* 2:531-536.

Bozikas, V.P., Andreou, C. (2011). Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. *The Australian and New Zealand Journal of Psychiatry* 45:93-108.

Braff, D.L., Freedman, R., Schork, N.J., Gottesman, I.I. (2007). Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophrenia bulletin* 33:21-32.

Brenner, K., Schmitz, N., Pawliuk, N., Fathalli, F., Joober, R., Ciampi, A., King, S. (2007). Validation of the English and French versions of the Community Assessment of Psychic Experiences (CAPE) with a Montreal community sample. *Schizophrenia research* 95:86-95.

Brzustowicz, L.M., Hodgkinson, K.A., Chow, E.W., Honer, W.G., Bassett, A.S. (2000). Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21-q22. *Science (New York, N.Y.)* 288:678-682.

Brzustowicz, L.M., Simone, J., Mohseni, P., Hayter, J.E., Hodgkinson, K.A., Chow, E.W., Bassett, A.S. (2004). Linkage disequilibrium mapping of schizophrenia susceptibility to the CAPON region of chromosome 1q22. *American Journal of Human Genetics* 74:1057-1063.

Cannon-Spoor, H.E., Potkin, S.G., Wyatt, R.J. (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia bulletin* 8:470-484.

Chen, W.J., Faraone, S.V. (2000). Sustained attention deficits as markers of genetic susceptibility to schizophrenia. *American Journal of Medical Genetics* 97:52-57.

de Rooij, M., Worku, H.M. (2012). A warning concerning the estimation of multinomial logistic models with correlated responses in SAS. *Computer methods and programs in biomedicine* 107:341-346.

Faber, G., Smid, H.G., Van Gool, A.R., Wunderink, L., Wiersma, D., van den Bosch, R.J. (2011). Neurocognition and recovery in first episode psychosis. *Psychiatry research* 188:1-6.

Faraone, S.V., Tsuang, D., Tsuang, M.T. (1999). *Genetics and Mental Disorders: A Guide for Students, Clinicians, and Researchers*. New York: Guilford Press.

Faraone, S.V., Kremen, W.S., Lyons, M.J., Pepple, J.R., Seidman, L.J., Tsuang, M.T. (1995). Diagnostic accuracy and linkage analysis: how useful are schizophrenia spectrum phenotypes?. *The American Journal of Psychiatry* 152:1286-1290.

Formann, A.K. (1984). *Die Latent-Class-Analyse: Einführung in Theorie und Anwendung [Latent class analysis: Introduction to theory and application]*. Germany: Weinheim: Beltz.

Green, M.F., Kern, R.S., Braff, D.L., Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"?. *Schizophrenia bulletin* 26:119-136.

Gur, R.E., Nimgaonkar, V.L., Almasy, L., Calkins, M.E., Ragland, J.D., Pogue-Geile, M.F., Kanes, S., Blangero, J., Gur, R.C. (2007). Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. *The American Journal of Psychiatry* 164:813-819.

Harvey, P.D. (2014). What is the evidence for changes in cognition and functioning over the lifespan in patients with schizophrenia?. *The Journal of clinical psychiatry* 75 Suppl 2:34-38.

Heinrichs, R.W., Zakzanis, K.K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* 12:426-445.

Hilti, C.C., Hilti, L.M., Heinemann, D., Robbins, T., Seifritz, E., Cattapan-Ludewig, K. (2010). Impaired performance on the Rapid Visual Information Processing task (RVIP) could be an endophenotype of schizophrenia. *Psychiatry research* 177:60-64.

Husted, J.A., Lim, S., Chow, E.W.C., Greenwood, C., Bassett, A.S. (2009). Heritability of Neurocognitive Traits in Familial Schizophrenia. *American journal of medical genetics.Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 150B:845-853.

Irani, F., Kalkstein, S., Moberg, E.A., Moberg, P.J. (2011). Neuropsychological performance in older patients with schizophrenia: a meta-analysis of cross-sectional and longitudinal studies. *Schizophrenia bulletin* 37:1318-1326.

Jones, B.L., Nagin, D.S., Roeder, K. (2001). A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. *Sociological Methods & Research* 29:374-393.

Kass, R.E., Raftery, A.E. (1995). Bayes Factors. *Journal of the American Statistical Association* 90:773-795.

Kay, S.R., Fiszbein, A., Opler, L.a. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin* 13:261-76.

Keefe, R.S., Harvey, P.D. (2012). Cognitive impairment in schizophrenia. *Handbook of Experimental Pharmacology* (213):11-37. doi:11-37.

Kendler, K.S., Diehl, S.R. (1993). The genetics of schizophrenia: a current, genetic-epidemiologic perspective. *Schizophrenia bulletin* 19:261-285.

Keri, S., Janka, Z. (2004). Critical evaluation of cognitive dysfunctions as endophenotypes of schizophrenia. *Acta Psychiatrica Scandinavica* 110:83-91.

Korver, N., Quee, P.J., Boos, H.B.M., Simons, C.J.P., de Haan, L., Investigators, G. (2012). Genetic Risk and Outcome of Psychosis (GROUP), a multi-site longitudinal cohort study focused on gene-environment interaction: objectives, sample characteristics, recruitment and assessment methods. *International Journal of Methods in Psychiatric Research* 21:205-221.

Krabbendam, L., Marcelis, M., Delespaul, P., Jolles, J., van Os, J. (2001). Single or multiple familial cognitive risk factors in schizophrenia?. *American Journal of Medical Genetics* 105:183-188.

Kremen, W.S., Seidman, L.J., Faraone, S.V., Toomey, R., Tsuang, M.T. (2000). The paradox of normal neuropsychological function in schizophrenia. *Journal of abnormal psychology* 109:743-752.

Kremen, W.S., Seidman, L.J., Pepple, J.R., Lyons, M.J., Tsuang, M.T., Faraone, S.V. (1994). Neuropsychological risk indicators for schizophrenia: a review of family studies. *Schizophrenia bulletin* 20:103-119.

Krukow, P., Karakuła-Juchnowicz, H., Juchnowicz, D., Morylowska-Topolska, J., Flis, M., Jonak, K. (2017). Processing speed is associated with differences in IQ and cognitive profiles between patients with schizophrenia and their healthy siblings. *Nordic Journal of Psychiatry* 71:33-41.

Kuss, O., McLerran, D. (2007). A note on the estimation of the multinomial logistic model with correlated responses in SAS. *Computer methods and programs in biomedicine* 87:262-269.

Lancon, C., Auquier, P., Nayt, G., Reine, G. (2000). Stability of the five-factor structure of the Positive and Negative Syndrome Scale (PANSS). *Schizophrenia research* 42:231-239.

Leeson, V.C., Sharma, P., Harrison, M., Ron, M.A., Barnes, T.R., Joyce, E.M. (2011). IQ trajectory, cognitive reserve, and clinical outcome following a first episode of psychosis: a 3-year longitudinal study. *Schizophrenia bulletin* 37:768-777.

Little, R.J.A., Rubin, D.B. (2002). *Statistical Analysis with Missing Data*. New York: John Wiley & Sons.

Meijer, J., Simons, C.J., Quee, P.J., Verweij, K., GROUP Investigators. (2012). Cognitive alterations in patients with non-affective psychotic disorder and their unaffected siblings and parents. *Acta Psychiatrica Scandinavica* 125:66-76.

Mohamed, S., Paulsen, J.S., O'Leary, D., Arndt, S., Andreasen, N. (1999). Generalized cognitive deficits in schizophrenia: a study of first-episode patients. *Archives of General Psychiatry* 56:749-754.

Nagin, D.S. (1999). Analyzing Developmental Trajectories: A Semiparametric, Group-Based Approach. *Psychological Methods* 4:139-157.

Nagin, D.S. (2014). Group-based trajectory modeling: an overview. *Annals of Nutrition & Metabolism* 65:205-210.

Nagin, D.S., Odgers, C.L. (2010). Group-based trajectory modeling in clinical research. *Annual review of clinical psychology* 6:109-138.

Niyonkuru, C., Wagner, A.K., Ozawa, H., Amin, K., Goyal, A., Fabio, A. (2013). Group-based trajectory analysis applications for prognostic biomarker model development in severe TBI: a practical example. *Journal of neurotrauma* 30:938-945.

Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., Heaton, R.K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia research* 72:29-39.

Nuechterlein, K.H., Ventura, J., Subotnik, K.L., Hayata, J.N., Medalia, A., Bell, M.D. (2014). Developing a Cognitive Training Strategy for First-Episode Schizophrenia: Integrating Bottom-Up and Top-Down Approaches. *American journal of psychiatric rehabilitation* 17:225-253.

Palmer, B.W., Heaton, R.K., Paulsen, J.S., Kuck, J., Braff, D., Harris, M.J., Zisook, S., Jeste, D.V. (1997). Is it possible to be schizophrenic yet neuropsychologically normal?. *Neuropsychology* 11:437-446.

Quee, P.J., Alizadeh, B.Z., Aleman, A., van den Heuvel, E.R., GROUP Investigators. (2014). Cognitive subtypes in non-affected siblings of schizophrenia patients: characteristics and profile congruency with affected family members. *Psychological medicine* 44:395-405.

Rodriguez-Sanchez, J.M., Crespo-Facorro, B., Gonzalez-Blanch, C., Perez-Iglesias, R., Alvarez-Jimenez, M., Martinez, O., Vazquez-Barquero, J.L. (2008). Cognitive functioning and negative symptoms in first episode schizophrenia: different patterns of correlates. *Neurotoxicity research* 14:227-235.

Schwarz, G. (1978). Estimating the dimension of a model. *Annals of Statistics* 6:461-464.

Snitz, B.E., Macdonald, A.W.,3rd, Carter, C.S. (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophrenia bulletin* 32:179-194.

Somers, R.H. (1962). A New Asymmetric Measure of Association for Ordinal Variables. *American Sociological Review* 27:799-811.

Szoke, A., Trandafir, A., Dupont, M.E., Meary, A., Schurhoff, F., Leboyer, M. (2008). Longitudinal studies of cognition in schizophrenia: meta-analysis. *The British journal of psychiatry : the journal of mental science* 192:248-257.

Thompson, W.K., Savla, G.N., Vahia, I.V., Depp, C.A., Oâ€™Hara, R., Jeste, D.V., Palmer, B.W. (2012). Characterizing Trajectories of Cognitive Functioning in Older Adults with Schizophrenia: Does Method Matter?. *Schizophrenia research* 143:90-96.

Townsend, L.A., Norman, R.M. (2004). Course of cognitive functioning in first episode schizophrenia spectrum disorders. *Expert review of neurotherapeutics* 4:61-68.

Trandafir, A., Meary, A., Schurhoff, F., Leboyer, M., Szoke, A. (2006). Memory tests in first-degree adult relatives of schizophrenic patients: a meta-analysis. *Schizophrenia research* 81:217-226.

van Os, J., Kenis, G., Rutten, B.P. (2010). The environment and schizophrenia. *Nature* 468:203-212.

Verhage, F. (1964). *Intelligentie en leeftijd: Onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar*. Assen: Van Gorcum.

Vollema, M.G., Ormel, J. (2000). The reliability of the structured interview for schizotypy-revised. *Schizophrenia bulletin* 26:619-629.

Vollema, M.G., Postma, B. (2002). Neurocognitive correlates of schizotypy in first degree relatives of schizophrenia patients. *Schizophrenia bulletin* 28:367-377.

Wit, E., Heuvel, E.v.d., Romeijn, J. (2012). 'All models are wrong...': an introduction to model uncertainty. *Statistica Neerlandica* 66:217-236.

Supplementary Materials

Supplementary Table S1: Measures of neurocognition

Cognitive domains	Group Tests	Outcome measure
Sustained attention and vigilance	Continuous Performance Test (CPT-HQ) (CPT performance and CPT variance)	An efficiency score [(accuracy/reaction time) ×1000] was created, in which accuracy was measured as the total number of hits (range 0–28) minus the total number of errors (range 0–28), divided by 28. If this calculation of accuracy was non-positive (i.e. the number of errors equaled or exceeded the number of hits), then the accuracy was set equal to 0.005. This score was referred to as 'CPT performance'. Intra-individual variability in reaction time on the CPT was also evaluated (CPT variance), using the standard deviation score of the subject's mean response time on the hit trials (Hilti et al., 2010; Quee et al., 2014).
Verbal learning and memory	Word Learning Task (WLT) (Immediate and Delayed Recall)	Immediate recall (total score of three consecutive trials of 15 words learning) and 'Delayed recall' was assessed after 20 minutes delay.
Global cognitive functioning		
Processing speed	Digit Symbol Substitution	Total raw score (0-133)
Verbal comprehension	Information	Total raw score (0-28)
Working memory	Arithmetic	Total raw score (0-22)
Problem solving and visuospatial abilities	Block Design	Total raw score (0-68)

Supplementary Table S2: Pearson's correlation coefficients of cognitive tests at baseline for patients (n=1,119)

Cognitive measures	CPT performance	CPT variance	Block Design	Digit Symbol	Arith-metic	Information	Immediate Recall	Delayed Recall
CPT variance	-0.54***							
Block Design	0.21***	-0.24***						
Digit Symbol	0.35***	-0.37***	0.43***					
Arithmetic	0.22***	-0.28***	0.52***	0.47***				
Information	0.16***	-0.20***	0.54***	0.43***	0.62***			
Immediate Recall	0.25***	-0.24***	0.32***	0.38***	0.40***	0.39***		
Delayed Recall	0.20***	-0.20***	0.32***	0.34***	0.35***	0.37***	0.77***	
Composite	0.39***	-0.20***	0.70***	0.67***	0.74***	0.75***	0.72***	0 .69***

*** P<0.001

3

Supplementary Table S3: Pearson's correlation coefficients of cognitive tests at baseline for siblings (n=1,059)

Cognitive measures	CPT performance	CPT variance	Block Design	Digit Symbol	Arithme tic	Informat ion	Immediate Recall	Delayed Recall
CPT variance	-0.44***							
Block Design	0.06	-0.15***						
Digit Symbol	0.12***	-0.26***	0.37***					
Arithmetic	0.06	-0.13***	0.50***	0.40***				
Information	0.06	-0.10**	0.44***	0.35***	0.60***			
Immediate Recall	0.11***	-0.15***	0.22***	0.32***	0.30***	0.34***		
Delayed Recall	0.09**	-0.12***	0.20***	0.28***	0.24***	0.29***	0.78***	
Composite	0.25***	-0.08*	0.64***	0.62***	0.72***	0.72***	0.69***	0.65***

*** P<0.001

Supplementary Table S4: Bayesian Information Criterion (BIC) and logged Bayes factor (2*ΔBIC) in patients' and siblings' model

Number of groups	BIC	*ΔBIC*	2**ΔBIC*	Evidence against H_0
Composite cognition (all tests) score of patients (n=1075)				
1	-2400.00			
2	-2042.31	357.69	715.38	
3	-1930.63	111.68	223.36	
4	-1899.23	31.40	62.8	
5	**-1890.56**	**8.67**	**17.34**	**Very strong**
6	-1897.51	-6.95	-13.90	
Composite cognition (all tests) score of siblings (n=1042)				
Number of groups	BIC	*ΔBIC*	2**ΔBIC*	Evidence against H_0
1	-2066.53			
2	-1718.39	348.14	696.28	
3	-1506.76	211.63	423.26	
4	**-1459.45**	**47.31**	**94.62**	**Very strong**
5	-1464.95	-5.50	-11.00	

Table S5: Parameter estimates of trajectory model for patients

Trajectory	Parameter	Estimate	SE	t-value	P-value
Severe	Intercept	-1.57	0.06	-25.78	<0.001
	Linear	0.03	0.03	0.93	0.353
Moderate	Intercept	-1.11	0.11	-10.19	<0.001
	Linear	0.20	0.12	1.61	0.107
	Quadratic	-0.05	0.03	-1.56	0.118
Mild	Intercept	-0.75	0.11	-7.07	<0.001
	Linear	0.39	0.13	3.07	0.002
	Quadratic	-0.10	0.03	-3.18	0.002
Normal	Intercept	0.05	0.05	1.04	0.297
	Linear	-0.01	0.02	-0.32	0.750
High	Intercept	0.71	0.12	6.12	<0.001
	Linear	-0.09	0.04	-2.08	0.038
Drop-out model					
Severe	Drop0	-1.33	2.41	-0.55	0.580
	Drop1	-0.25	0.93	-0.27	0.789
	Drop2	-0.35	1.01	-0.35	0.730
Moderate	Drop0	0.19	1.38	0.14	0.891
	Drop1	0.46	0.88	0.52	0.604
	Drop2	0.65	0.83	0.78	0.436
Mild	Drop0	-0.77	1.19	-0.65	0.518
	Drop1	0.83	2.04	0.40	0.686
	Drop2	0.80	1.35	0.60	0.552
Normal	Drop0	-1.55	0.44	-3.52	0.001
	Drop1	-2.63	1.21	-2.17	0.030
	Drop2	0.90	1.52	0.59	0.555
High	Drop0	1.65	2.56	0.65	0.518
	Drop1	-7.63	5.25	-1.45	0.146
	Drop2	2.40	2.27	1.06	0.291
	Sigma	0.29	0.01	51.79	<0.001
Group	Membership				
Severe	(%)	10.73	1.64	6.56	<0.001
Moderate	(%)	28.44	2.57	11.07	<0.001
Mild	(%)	30.37	2.65	11.46	<0.001
Normal	(%)	26.68	2.38	11.22	<0.001
High	(%)	3.78	1.27	2.98	0.003

BIC= -1902.45 (N=2260), **BIC= -1890.56 (N=1075),** AIC= -1810.88, L= -1778.88; Sigma: The amount of variance in the data accounted for by the model and its significance. Note: Drop0 = constant rate, Drop1 = depends on the previous response (baseline), Drop2 = depends on the two previous responses (baseline and three years).

Table S6: Parameter estimates of trajectory model for siblings

Trajectory	Parameter	Estimate	SE	t-value	P-value
Moderate	Intercept	-1.17	0.04	-26.79	<0.001
	Linear	0.06	0.02	2.82	0.005
Mild	Intercept	-0.53	0.05	-11.61	<0.001
	Linear	0.03	0.02	1.51	0.131
Normal	Intercept	-0.33	0.08	-4.17	<0.001
	Linear	0.26	0.09	2.91	0.004
	Quadratic	-0.06	0.02	-2.49	0.013
High	Intercept	0.43	0.02	14.11	<0.001
	Linear	-0.003	0.01	-0.23	0.818
Drop-out model					
Moderate	Drop0	-1.10	1.29	-0.86	0.390
	Drop1	-0.08	0.86	-0.09	0.928
	Drop2	-0.28	1.08	-0.26	0.793
Mild	Drop0	-0.22	1.55	-0.14	0.886
	Drop1	2.33	2.01	1.16	0.248
	Drop2	0.52	1.61	0.32	0.746
Normal	Drop0	-2.41	0.50	-4.85	<0.001
	Drop1	-4.42	1.97	-2.24	0.025
	Drop2	-0.23	1.38	-0.17	0.869
High	Drop0	-0.45	0.74	-0.61	0.544
	Drop1	-1.14	1.25	-0.92	0.359
	Drop2	-2.11	1.12	-1.89	0.059
	Sigma	0.26	0.01	55.67	<0.001
Group	Membership				
Moderate	(%)	13.03	1.35	9.64	<0.001
Mild	(%)	25.13	2.84	8.86	<0.001
Normal	(%)	37.61	2.83	13.30	<0.001
High	(%)	24.23	1.81	13.35	<0.001

BIC= -1469.44 (N=2316), **BIC= -1459.45 (N=1042),** AIC= -1397.59, L= -1372.59; Sigma: The amount of variance in the data accounted for by the model and its significance. Note: Drop0 = constant rate, Drop1 = depends on the previous response (baseline), Drop2 = depends on the two previous responses (baseline and three years).

Table S7: Contingency table of subtypes for the pair of siblings and patients*

Patient Subtypes	Sibling Subtypes				Total	Somers' *D*±ASE
	High	Normal	Mild	Moderate		
High	15 (6.7)	9 (10.9)	4 (6.8)	0 (3.5)	28	
Normal	119 (72.0)	114 (117.6)	56 (73.4)	12 (38.0)	301	
Mild	68 (78.7)	155 (128.5)	70 (80.3)	36 (41.5)	329	0.29±0.02
Moderate	47 (76.1)	112 (124.2)	98 (77.6)	61 (40.1)	318	
Severe	7 (22.5)	28 (36.7)	33 (22.9)	26 (11.9)	94	
Total	256	418	261	135	1070	

*Table represents Observed (Expected) frequencies and Somers' *D* statistic with asymptotic standard error (ASE)