European Archives of Psychiatry and Clinical Neuroscience (2020) 270:739–748
https://doi.org/10.1007/s00406-019-01044-7

ORIGINAL PAPER

Neuropsychological, clinical and environmental predictors of severe mental disorders in offspring of patients with schizophrenia

Teresa Sánchez-Gutiérrez[1,2] · Elisa Rodríguez-Toscano[2,6] · Cloe Llorente[2] · Elena de la Serna[3,4] · Carmen Moreno[2] · Gisela Sugranyes[3,4] · Soledad Romero[3,4,5] · Ana Calvo[1,2] · Immaculada Baeza[3,4,5] · Vanessa Sánchez-Gistau[3,4] · Ana Espliego[2] · Josefina Castro-Fornieles[3,4,5] · Dolores Moreno[2]

Received: 27 November 2018 / Accepted: 3 July 2019 / Published online: 16 July 2019

Abstract

Offspring of individuals with schizophrenia (SZCOff) are at an increased risk for this disorder. Neuropsychological decline is a core feature of the disorder and researchers have reported increasing impairments in cognition during the prodromal phase in high-risk adolescents. Additionally, factors like the presence of prodromal symptoms or specific behavioral patterns could predict, together with neurocognitive functioning, the risk of conversion to severe mental disorders in SCZOff. This study aims to compare the neuropsychological functioning of a sample of 41 SCZOff children and adolescents and 105 community control offspring (CCOff) and to develop a prediction model to examine whether neuropsychological functioning, clinical and behavioral factors predict subsequent risk of severe mental disorders. We collected demographic, clinical and neuropsychological data. We found significant differences between groups in working memory, speed of processing, verbal memory and learning, visual memory and intelligence quotient (IQ). The socioeconomic status, verbal memory, working memory and positive prodromal symptoms predicted a significant proportion of the dependent variable variance. In conclusion, SCZOff showed neurocognitive impairments in several neuropsychological domains compared to CCOff. Neuropsychological functioning, environmental factors and positive prodromal symptoms could predict the risk of onset of severe mental disorders in SCZOff.

Keywords Neurocognition · Schizophrenia · Offspring · Psychosis · High risk

Introduction

Schizophrenia (SCZ) is a neurodevelopmental disorder with a multifactorial etiology that includes both genetic and environmental influences [1, 2]. Its heritability has been estimated to be between 60 and 90% [3]. Offspring of individuals with schizophrenia are at an increased risk of developing the disorder themselves [4]. The overall risk for SCZ among both biological siblings and offspring ranges between 9 and 13% [5, 6]. Therefore, assessing child and adolescent offspring of patients diagnosed with SCZ (SCZOff) provides an opportunity to investigate the vulnerability factors for the illness in a sample with an elevated risk [7] and to adjust clinical interventions considering the neurocognitive function of SCZOff [8, 9].

Several studies explored the factors that could predict the risk of conversion to severe mental disorders like psychosis, bipolar disorder, depression or behavioral disorders. Structural changes in the brain, like the decrease in

✉ Teresa Sánchez-Gutiérrez
teresa.sanchez@unir.net

1 Faculty of Health Science, Universidad Internacional de la Rioja (UNIR), Madrid, Spain

2 Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, CIBERSAM, Madrid, Spain

3 Department of Child and Adolescent Psychiatry and Psychology, 2017SGR88, Institute of Neuroscience, Hospital Clínic of Barcelona, Barcelona, Spain

4 Biomedical Research Networking Centre Consortium (CIBERSAM), August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain

5 Department of Medicine, University of Barcelona, Barcelona, Spain

6 Experimental Psychology, Cognitive Processes and Speech Therapy Department, Faculty of Psychology, Universidad Complutense, Madrid, Spain

the gray matter volume [10], greater neurological soft sings (NSS), a higher frequency of obstetric complications and a low intelligence quotient (IQ) [11–13] and the presence of attenuated positive symptoms [14] are potential markers that could work as predictors of vulnerability to psychosis. A recent systematic review showed that SCZOff presented distinct developmental patterns characterized by higher rates of obstetric complications, neurodevelopmental features such as motor and cognitive deficits, and distinctive social behavior than CCOff, suggesting that SCZOff are at high risk not just for schizophrenia but for poor developmental and general mental health outcomes [15]. Additionally, environmental factors like socioeconomic status [16], migration and use of cannabis [2, 17] are associated with an increased risk for severe mental disorders' onset.

Evidence for declining neurocognitive performance during the development of SCZ has been widely documented [18, 19] and has come to be regarded as a core component of the disorder [20–23]. It has been proposed that SCZ involves both neurodevelopmental and neurodegenerative processes and this hypothesis is in line with the existence of a prodromal phase with increasing impairments in cognition and adaptive functioning in high-risk adolescents [24, 25]. Therefore, it is suggested that some neurocognitive deficits, such as low IQ at age 7, may be associated with genetic vulnerability to psychoses in SCZOff [26]. The most consistent findings in children and adult samples of patients at genetic risk for SCZ are difficulties in verbal memory, attention and executive functions [27, 28].

Some studies conclude that adolescents with familial risk for SCZ present declining performance in executive functioning tasks [29, 30]. This suggests an altered maturational trajectory during adolescence and early adulthood. A cross-sectional study with adolescent SCZOff detected attention deficits in asymptomatic SCZOff compared to offspring of healthy controls [31]. Another study with 96 adolescent and siblings SCZOff and 193 adolescent CCOff showed significant impairments in the executive function and working memory of the SCZOff group [32]. Other impairments were related to the verbal memory, attention and gross motor skills in the SCZOff group [33]. Further studies also found significant differences in aspects of emotional perception, verbal abilities, inhibition, visuospatial skills, working memory [34], lower performance in IQ [4], attention, verbal fluency [35] and visuospatial abilities [3]. However, most of these studies have not used comprehensive neuropsychological batteries in homogenous samples of children and adolescents offspring of patients with schizophrenia and some of them included differential analyses not only with offspring but also with unaffected siblings [36–40].

This study has two aims: (1) to compare the neuropsychological functioning of a sample of SCZOff children and adolescents with community control offspring (CCOff) and (2) to develop an optimized prediction model to examine whether neuropsychological functioning, clinical and behavioral factors predict subsequent risk of severe mental disorders. We hypothesized that SCZOff would present greater neuropsychological functioning deficits than offspring of controls, specifically in the attention, verbal memory and learning, executive functioning and working memory domains. Additionally, SCZOff who were impaired at baseline in the neuropsychological, clinical and behavioral areas would have a higher risk to convert to severe mental disorders than CCOff.

Methods

Participants

This study is part of the bipolar and schizophrenia young offspring study (BASYS), a multi-center, longitudinal and naturalistic study which aims to evaluate clinical, neuropsychological, neurobiological and neuroimaging variables of the child and adolescent offspring of patients with bipolar disorder or SCZ. A sample of 41 offspring of patients with SCZ (65.9% males, 92.7% Caucasian, age = 10.4 ± 3.5) was recruited from the hospitalization and outpatient settings of the Adult Psychiatry Departments at two Spanish hospitals: Hospital Clínic in Barcelona and Gregorio Marañón University Hospital in Madrid. Inclusion criteria for SCZ offspring comprised: (1) parental diagnosis of SCZ or schizoaffective disorder according to DSM-IV-TR criteria, ascertained by a psychiatrist from either of the two study sites and (2) age inclusion criteria for offspring from both groups ranged from 6 to 17 years old. Exclusion criteria for the offspring included (1) intellectual disability (IQ below 70) with impaired functioning and (2) presence of current neurological disorders or history of head trauma with loss of consciousness. Moreover, a community control group of 105 offspring of parents without schizophrenia or bipolar disorder diagnoses according to DSM-IV criteria (44.8% males, 96.2% Caucasian, age = 11.6 ± 3.2) was also recruited through advertisements in general practitioner's centers and other locations in the same geographical area. In the community control group, inclusion criteria (except for criterion one) were the same as in the SCZ offspring group and diagnosis of psychotic spectrum disorders in parents or second-degree relatives constituted an additional exclusion criterion.

Parents from the adult units of both the hospitals were recruited via their psychiatrists, who checked if patients met the inclusion criteria, had children aged between 6 and 17 years and agreed to participate in the study. Control parents were recruited through advertisements posted in primary health care centers and other community locations within the same geographical area.

More details about the sample and the recruitment methodology can be found in previous BASYS manuscripts [37, 38].

The study was approved by the participating institutions' Ethics Committees and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Offspring older than 12 years old and parents or legal guardians signed the written informed consent statement prior to participation.

Assessment instruments

Demographical and clinical assessment

Data about age, sex, ethnicity and parental socioeconomic status (SES), measured with the Hollingshead–Redlich Index of social position [41] were obtained from both SCZOff and CCOff groups.

The clinical assessment consisted of the following instruments:

- Kiddie schedule for affective disorders and schizophrenia, present and lifetime version (K-SADS-PL) [42]. This interview has been considered a reliable and valid instrument to assess present and lifetime mental disorders in children and adolescents up to 18 years old. The Spanish adaptation was used in this study [43, 44]. Children from both the SCZOff and the control group and their parents were interviewed individually by clinical psychiatrists trained in the use of this interview. If applicable, lifetime diagnoses were established and used in the data analysis.
- Structured clinical interview for DSM-IV axis I disorders (SCID-I) [45]. This interview was used to confirm the presence of SCZ or schizoaffective disorder in patients with offspring meeting inclusion criteria and to verify the absence of current mental disorders in the control parent group. It was administered by a trained clinical psychiatrist.
- Family history score sheet (first- and second-degree relatives). This instrument was individually administered to both of the parents in each group (SCZ and CC) to assess the presence of any psychiatric diagnoses in family members of first- and second-degree relatives. In the case of the CC parents, the presence of personal psychiatric antecedents in any kinship was a reason for exclusion from the study.
- The scale of prodromal symptoms (SOPS) [46, 47] is a 19-item scale designed to measure the severity of prodromal symptoms and changes over time. The SOPS contains four subscales for positive, negative, disorganization, and general symptoms constructs. There are five positive, six negative, four disorganization, and four general symptom's items.
- The strengths and difficulties questionnaire (SDQ) [48] is a brief behavioral screening questionnaire for children and adolescents from 3 to 16 year old. The test has 25 items divided into 5 scales of 5 items each: (1) emotional symptoms, (2) conduct problems, (3) hyperactivity/inattention, (4) peer relationship problems and (5) prosocial behavior. We used the version for parent's completion.

Neuropsychological assessment

Neurocognitive functioning was assessed with the following tests and subtests:

- *Intelligence quotient (IQ)* the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) [49] was used to assess global IQ and different intellectual abilities grouped in four indices: (1) Verbal Comprehension Index (VCI), which measures verbal skills; (2) Perceptual Reasoning Index (PRI), which assesses non-verbal and fluid reasoning; (3) Working Memory Index (WMI), which estimates short-term ability to attend, process and recall new information and already-stored information; and (4) Processing Speed Index (PSI), which measures the speed of information processing. WMI and PSI were selected as independent indices in this study. WISC-IV was administered in children under 16 years of age.
- *Verbal memory and learning* two subtests of the TOMAL test [50] were used: (1) Story recall, which consists of the immediate and long-term recall of three short stories and which allows the assessment of logical memory and (2) Selective recall of words, which assessed verbal learning by the immediate and long-term recall of 16 words. These subtests provide immediate and delayed recall scores and a learning curve.
- *Visual memory* this domain was assessed with the subtest Visual Reproduction from the Wechsler Memory Scale III (WMS-III) [51] which consists of the reproduction of five progressively more difficult figures. Due to the fact that this test is validated in an over-16 population, direct scores were used for statistical analysis. Furthermore, this domain included a measure of perceptual organization assessed with the Rey complex figure (RCF), where participants were asked to copy and recall a complex figure presented once [52].
- *Attention* sustained attention was assessed with the Conner's Continuous Performance Test (CPT) [53]. Participants were asked to press the space bar each time any letter appeared in the screen except for the *X*, when participants were required to inhibit their response. This test included different sub-scores: omissions, commissions, reaction time, variability of standard error, d´ prime (attentiveness) and perseverations.

– *Executive functions* this domain included two tests. First, the Stroop test [54] an inhibition-of-response test where participants were asked to read a list of names of colors, followed by the reading of the color of several cues and, finally to say the ink color in which words were written while ignoring what the words said (which was always different from the color in which they were printed). Interference score was included in the analyses. Second, we administered the Wisconsin Card Sorting Test (WCST) [55] which is a measure of planning, alternation and inhibition strategies.

All neuropsychological raw scores were transformed into standard equivalents and corrected by age despite from the WMS-III scores, in which we used raw scores because of the absence of a Spanish comparison scale for participants younger than 16 years old. The scores for cognitive domains were converted into scalar scores in TOMAL, and into *T* scores in RCF, CPT, WCST according to the manuals of each test. Every test provided a standardization based on age. All cognitive scores were calculated such that higher values indicated better performance. All of the neuropsychological assessments were conducted by trained neuropsychologists.

Data analysis

The demographic characteristics of the samples were compared between groups using the χ^2 test for categorical variables such as sex, ethnicity and personal psychiatric antecedents. Normality was checked with the Kolmogorov–Smirnoff test and this condition was achieved in all neuropsychological variables. Inter-group mean comparisons including quantitative variables were analyzed using parametric tests (*t* student). Analyses of covariance were performed when comparing the influence of the diagnostic groups on neuropsychological test scores including age, sex, SES and lifetime history of axis I disorders as covariates. Intelligence quotient was analyzed as a neurocognitive global index, but it was afterwards included as a covariable in the neuropsychological test comparisons except for those tests related to the Weschler intelligence scale. Moreover, we ran mixed models to test whether the results were independent of the familial relationships between some participants. Each of the cognitive domains was included as a dependent variable, group and family as fixed factors and sex, SES and lifetime history of axis I disorders as covariables. Backwards-stepwise logistic regression was performed to determine the best set of clinical and cognitive variables that would better predict the subjects that belong to the high risk of psychopathology group in this specific sample. The variable 'group' (being the offspring of parents with at least one member with schizophrenia vs. offspring of parents controls without psychopathology) was used as a dependent variable and, as independent factors, we included the cognitive variables (verbal comprehension, perceptual reasoning, working memory, processing speed, verbal memory, visual memory, attention, executive function), the four subscales of SOPS (positive, negative, disorganization and general), the five scales of the SDQ (emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, prosocial behavior) and the socioeconomic status. The regression model was repeated adding the variables current diagnosis (yes/no), and the type of diagnosis as independent variable to confirm that the clinical diagnosis did not influence the results. All statistical analyses were conducted using SPSS version 20.0 for Windows [56].

Results and statistical analyses

Demographics

Comparison of demographic characteristics between the SCZOff and control (CCOff) groups showed significant differences in sex ($\chi^2 = 5.25$; $p = 0.022$), personal psychiatric antecedents ($\chi^2 = 10.10$; $p = 0.001$) and SES ($t = -7.34$; $p \leq 0.001$), with the SCZOff group presenting a higher percentage of males, personal psychiatric antecedents and less SES than the CCOff group.

The most prevalent diagnoses in the SZOff group were attention deficit hyperactivity disorder (ADHD) (46.3%), anxiety disorders (17.1%), disruptive disorders (14.6%), mood disorders (4.9%) and other psychiatric disorders (4.9%). In the CCOff group, the most prevalent diagnoses were ADHD (7.5%), anxiety disorders (5.6%), mood disorders (4.7%), other psychiatric disorders (3.7%) and disruptive disorders (1.9%).

Ten SZOff and one CCOff were receiving psychiatric–pharmacological treatment, whereas nine SZOff and 19 CCOff were receiving psychological or psychopedagogical treatment. However, as the number of subjects was so small, it was not possible to run subanalyses by the type of treatment (Table 1).

Neurocognitive function comparisons

Comparison of the two groups in neurocognitive function revealed significant differences in the following domains: working memory ($t = -5.48$; $p \leq 0.001$), speed of processing ($t = -4.69$; $p \leq 0.001$), verbal memory and learning ($t = -5.17$; $p \leq 0.001$), visual memory ($t = -4.83$; $p \leq 0.001$) and global cognitive index (IQ) ($t = -5.21$; $p \leq 0.001$). The SCZOff group scored lower in all the domains compared to the CCOff group. When controlling for personal psychiatric antecedents in offspring of both groups, all of the indicated domains remained significantly

Table 1 Sociodemographic characteristics in patients with schizophrenia offspring (SCZOff) and control offspring (CCOff)

Mean[a]	SCZOff $N=41$	CCOff $N=105$	χ^2/Student's t test[b]	p value
Sex, male N (%)	27 (65.9)	47 (44.8)	5.25	**0.022***
Race, Caucasian N (%)	38 (92.7)	101 (96.2)	0.79	0.373
Personal psychiatric antecedents, presence N (%)	20 (48.8)	24 (22.9)	10.10	**0.001***
Age, mean ± SD	10.4 ± 3.5	11.6 ± 3.2	− 1.97	0.051
SES, mean ± SD[c]	31.8 ± 14.7	50.8 ± 12.4	− 7.34	< **0.001***
Treatment, psychiatric–pharmacological/psychological or psycho-pedagogical, N (%)	10 (25.64)/9 (23.08)	1 (0.93)/19 (17.75)	10.80	**0.005***
Diagnose: attention deficit hyperactivity disorder (ADHD)/anxiety disorders/disruptive disorders/mood disorders/other psychiatric disorders (%)	46.3/17.1/14.6/4.9/4.9	7.5/5.6/1.9/4.7/3.7	48.90	**0.001***

SES socioeconomic status

[a]N (%) was calculated for categorical variables and mean (standard deviation) for continuous variables

[b]χ^2 was used for categorical variables and Student's t test for continuous variables

different: working memory ($F=21.24$; $p \leq 0.001$), speed of processing ($F=12.33$; $p=0.001$), verbal memory and learning ($F=22.52$; $p \leq 0.001$), visual memory ($F=28.06$; $p \leq 0.001$) and IQ ($F=17.39$; $p \leq 0.001$). However, when age, sex, SES and IQ were added to the personal psychiatric antecedent covariable, just the verbal memory and learning domain remained significant (see Table 2).

Information about the differences in the subtests, after controlling for the above-mentioned covariables (including IQ as a covariable in the subtests not related to Weschler intelligence scale) is shown in Table 3. Within all significant differences in the neurocognitive subtests, SCZOff group scored lower than the CCOff group.

Table 2 shows the results obtained in the mixed model analysis of familial independence. Two domains were significant (verbal memory and learning ($F=8.75$; $p=0.004$) and visual memory ($F=5.003$; $p=0.029$).

Cognitive and clinical prediction of the risk for psychopathology

The logistic regression displayed the set of the following variables (using the group variable as a dependent variable, and the cognitive domains, clinical prodromes according to SOPS and the SDQ subtests as independent variables): socioeconomic status ($B=0.09$, $p=0.006$), verbal memory ($B=0.74$, $p=0.028$), working memory ($B=0.06$, $p=0.051$) and positive prodromal symptoms according to SOPS scale ($B=-0.64$, $p=0.007$). These variables explained a significant proportion of the dependent variable variance (65.7%). The same model was maintained when including current

Table 2 Comparison of the neuropsychological domain assessment between SCZOff and CCOff controlled by age, sex, socioeconomic status, IQ and personal psychiatric antecedents

Domain	SCZOff $N=28$ (mean ± SD)	CCOff $N=93$ (mean ± SD)	F	p value	Ancova controlling for IQ	Mixed model
Intelligence quotient (GCI-WISC-IV)	94.8 ± 15.8	107.2 ± 12.5	3.05	0.084	–	–
Working memory	86.3 ± 15.2	100.8 ± 14.2	8.45	**0.004**	–	–
Speed of processing	92.7 ± 15.2	106.7 ± 12.6	8.77	**0.004**	–	–
Verbal memory and learning	9.8 ± 1.5	11.6 ± 1.9	11.64	**0.001**	$F=9.71$, $\boldsymbol{p=0.002}$	$F=8.75$, $\boldsymbol{p=0.004}$
Visual memory	38.8 ± 13.7	49.5 ± 9.5	9.49	**0.003**	$F=3.32$, $p=0.071$	$F=5.003$, $\boldsymbol{p=0.029}$
Attention	52.9 ± 8.6	50.4 ± 10.0	0.20	0.655	$F=0.11$, $p=0.735$	$F=0.37$, $p=0.543$
Executive function	52.8 ± 10.4	54.3 ± 8.1	0.09	0.759	$F=0.31$, $p=0.578$	$F=0.00$, $p=0.987$

IQ was not included as a covariable when the neuropsychological domains comprised Weschler intelligence scale

Mixed model including the family codes as a random variable and age, sex, socioeconomic status, intelligence quotient and personal psychiatric antecedents as covariables

GCI global cognitive index, *SCZOff* offspring of patients with schizophrenia, *CCOff* offspring of community controls, *WISC*-IV Weschler intelligence scale for children

Table 3 Comparison of the neuropsychological subtest assessment between SCZOff and CCOff controlled by age, sex, socioeconomic status, IQ and personal psychiatric antecedents

Domain	Subtests (test)	SCZOff $N=41$ (mean ± SD)	CCOff $N=105$ (mean ± SD)	F	p value
Intelligence quotient (GCI-WISC-IV)	VCI (WISC-IV)	98.4 ± 17.4	107.3 ± 12.7	3.22	0.075
	PRI (WISC-IV)	97.8 ± 17.9	107.9 ± 13.7	1.31	0.255
Working memory	WMI (WISC-IV)	86.3 ± 15.2	100.8 ± 14.2	6.89	**0.010**
Processing speed	PSI (WISC-IV)	92.7 ± 15.2	106.7 ± 12.6	8.90	**0.003**
Verbal memory and learning	Logical memory immediate recall (TOMAL)	10.4 ± 2.2	12.2 ± 2.6	2.66	0.105
	Logical memory delayed recall (TOMAL)	9.9 ± 2.5	11.8 ± 2.8	3.75	0.055
	Verbal learning immediate recall (TOMAL)	7.9 ± 2.7	10.6 ± 3.1	5.73	**0.018**
	Verbal learning delayed recall (TOMAL)	10.5 ± 1.8	12.0 ± 1.7	7.22	**0.008**
Visual memory	Visual memory immediate recall (WMS-III)	73.5 ± 19.4	89.3 ± 12.7	6.73	**0.011**
	Visual memory delayed recall (WMS-III)	42.8 ± 22.3	59.9 ± 20.9	2.91	0.091
	Copy (Rey)	23.9 ± 8.6	29.8 ± 5.7	5.05	**0.027**
	Memory (Rey)	13.2 ± 7.5	18.2 ± 6.5	2.03	0.157
Attention	Omissions (CPT)	55.1 ± 13.0	51.6 ± 13.0	0.90	0.344
	Commissions (CPT)	49.8 ± 9.2	48.8 ± 10.0	0.14	0.708
	Reaction time (CPT)	54.0 ± 11.7	51.2 ± 10.4	0.09	0.766
	Variability (CPT)	55.1 ± 10.7	50.0 ± 12.3	0.08	0.778
	D′ prime (CPT)	51.2 ± 7.3	50.0 ± 8.9	0.40	0.529
	Perseverations (CPT)	56.0 ± 17.9	52.4 ± 12.3	0.25	0.617
Executive function	Correct answers (WCST)	70.4 ± 12.0	72.4 ± 11.1	1.01	0.317
	Errors (WCST)	53.7 ± 13.0	53.6 ± 10.9	0.41	0.523
	Perseverations (WCST)	54.5 ± 16.7	55.6 ± 10.5	0.21	0.650
	Perseverative errors (WCST)	55.2 ± 16.6	55.8 ± 10.8	0.27	0.606
	Categories (WCST)	4.9 ± 1.6	5.2 ± 1.5	0.40	0.529
	Interference (Stroop)	51.9 ± 7.9	52.3 ± 6.9	0.01	0.906

IQ was not included as a covariable when the neuropsychological domains comprised Weschler intelligence scale

WMI Working Memory Index, *PSI* Processing Speed Index, *GCI* global cognitive index, *SCZOff* offspring of patients with schizophrenia, *CCoff* offspring of community controls, *WISC*-IV Weschler intelligence scale for children, *TOMAL* test of memory and learning, *WMS* Weschler memory scale, *Rey* Rey–Osterrieth complex figure, *CPT* continuous performance test, *WCST* Wisconsin card sorting test

diagnosis (yes/no), or the type of diagnosis in the model as independent variables.

Discussion

The findings of this study indicate that offspring of patients with schizophrenia are neurocognitively impaired when compared to offspring of individuals without a diagnosis of SCZ or genetic antecedents of psychosis. Specifically, we found that SCZOff obtained lower scores in verbal memory and learning, working memory, speed of processing and visual memory than controls. These results are consistent with previous literature showing significant differences between SCZOff and schizoaffective disorder offspring in verbal memory [4, 35], working memory [34, 57] and visuospatial ability domains [3].

The results regarding group differences in verbal memory were consistent with previous literature which suggest that an average effect size of 0.4–0.6 for verbal declarative memory tests on the Wechsler Memory Scale [3] or the Rey Auditory Verbal Learning Test [35]. In a previous study, the use of different neuropsychological tests highlighted the importance of optimally stressing a vulnerable declarative memory system [3]. Moreover, the differences obtained in the information test and in the verbal IQ scores suggested some alteration in data and language acquisition by age 11 [4].

The impairments in verbal memory and working memory showed in the SCZOff group, together with the presence of low socioeconomic status and positive prodromal symptoms could be related to the risk of psychopathology onset. These results are in line with previous studies that observed impairments in working memory [32] and verbal memory. Concretely, verbal memory deficits in childhood identified

83% of the subjects with schizophrenia-related psychoses [33]. Low economic status and positive prodromal symptoms have previously been specified as risk factors for the development of severe mental disorders [2, 14, 16, 17], however, regarding schizophrenia, a modest increase was seen in the incidence of schizophrenia only in offspring from the lowest social class [58].

Our results are similar to those found in several studies that used a wide range of working memory tests. Auditory working memory was measured by the number of trials of visual stimuli completed during the Counting Span task and by the number of correctly completed statements in the sentence span task [34]. Moreover, the auditory consonant trigram test [35], the digit span test [3] and the compound of the Wechsler memory scale spatial span task, the auditory consonant trigram test, WCST and the Stroop were used to measure working memory in a sample of 212 adolescents with prodromal symptoms of psychosis [59]. However, this latter study did not find significant differences in the digit span backwards test section. The present study describes significant results in the working memory index composed by the digits and letters and numbers tests. This result could be due to a higher effect for letters and numbers (which do not require arithmetic skills) than the digits-only test. Given that we found a group effect on the digit test in a SCZOff sample but not in a prodromal sample, working memory may be more affected in the genetically at-risk sample.

We also found significant differences in the processing speed domain between SCZ patients and control offspring. To our knowledge, there is no previous literature addressing this finding, which was beyond the scope of our hypotheses. However, a study that enrolled a sample of 212 adolescents with prodromal symptoms of psychosis and used the trail-making test part A and the brief assessment of cognition in schizophrenia symbol coding task concluded that processing speed was a central deficit associated with psychosis risk [59]. Concretely, this difference was found in the brief assessment of cognition in schizophrenia symbol coding task, which was described as the most pronounced difference between ultra-high-risk patients and healthy controls [60, 61] and in first-episode psychosis [62]. Knowles et al. [63] reported in a meta-analysis that a number of variables moderated the effect size of processing speed deficits, namely the year of publication, IQ differences between cases and controls, and chlorpromazine equivalent daily dose. In the current study, however, cases and controls did not differ in IQ [63]. Nonetheless, we have identified processing speed as a core neurocognitive deficit associated with psychosis in a high-risk population and a good predictor of functionality in a high-risk population [60].

Paradoxically, no differences were found in the attention and executive function domains, both of which the previous groups have reported as essential deficits in SCZOff [64, 65] and a vulnerable marker in ultra-high-risk population [66]. Nevertheless, other studies found a lack of significant differences in tasks related to executive function measures, such as the Stroop interference index [4], CPT measures [3] or TOVA test [35] suggesting that executive control of behavior was not impaired. One possible explanation could be the relationship between the age of offspring assessment and their attention and executive function development [67]. In this study, the mean age was 10.4 years old, whilst executive functions continue developing through the 3rd decade of life [68]. Thus, executive and attentional functions may not show significant low values, because more complex tasks will be required in the short-term future, when substantial deficits would be observed. Future studies would need to include a wide age range comparing the performance of children, adolescents and adult offspring of patients with SCZ.

This study has several strengths: it includes representative samples of SCZOff and community control children and adolescents from multiple sites, making its results more generalizable. Also, we used a comprehensive neuropsychological battery to assess a wide range of neurocognitive function domains, including global IQ, which helps characterize the complete picture of the neuropsychological difficulties of offspring of patients with schizophrenia.

The results of the present study need to be interpreted with caution in the light of a number of limitations. First, the patient sample size was small. Nonetheless, the cognitive differences appeared significant, which highlights their magnitude. Furthermore, the groups significantly differed in the distribution of sex and personal psychiatric history. Although these variables were included in the neuropsychological between-group comparisons and in the mixed model as covariables, the logistic regression did not control for this issue. Therefore, the percentage of prediction of the model should be interpreted with caution.

Moreover, the absence of follow-up data limits our ability to understand the heterogeneity of neurocognitive functioning and its evolution. The regression model highlighted a set of cognitive and clinical variables that were related in this sample to the high-risk group. However, the validity and generalizability of the model could be improved with its replication in multiple independent samples. Finally, subtle differences in test administration between the collaborating sites may have attenuated our results.

We identify several paths for follow-up work: one is to conduct complex reviews and meta-analyses of different cognitive tests in related literature. Larger longitudinal studies of neurocognitive function and genetic analysis could also help characterize the cognitive endophenotype of schizophrenia and conducting cognitive tests with functional neuroimaging could help determine the physiology of the disorder.

The results of the present study may also have some clinical implications. Since it seems that the offspring of patients with schizophrenia are a high-risk population with a well-defined cognitive and clinical endophenotype, this subgroup merits more extensive treatment and support for its cognitive problems, focusing on verbal memory and learning, working memory, speed of processing and visual memory. Moreover, the increasing evidence on neuropsychological deficits in individuals at risk for schizophrenia spectrum disorders might imply that early intervention programs in SCZ offspring target cognitive function to improve their efficacy [9] and that personalized interventions in vulnerable individuals become decisive [8, 69]. According to the present findings, the formulation of individualized intervention plans is essential for offspring who have positive prodromal symptoms and low socioeconomic status. The concurrence of these factors seems to have different effects on the neurocognitive function of SCZOff.

In conclusion, by comprehensively assessing cognitive deficits through multiple measures and replication of studies, clinical features and environmental factors, more useful profiles of schizophrenia-vulnerable children may be developed and used for early identification and preventative therapy.

Acknowledgements We express all our thanks to the families who participated in the study. Dr. D. Moreno has been a consultant to or has received honoraria from Janssen Cilag, Shire and Rovi. Dr. Sanchez-Gutierrez has received a research grant from the Carlos III Health Institute. Dr. Sugranyes has received research grants from the Alicia Koplowitz Foundation and the Carlos III Health Institute. She has received research support from Janssen and Otsuka, educational support from Otsuka, and travel support from Adamed Pharma. Dr. Baeza has received honoraria and travel support from Otsuka and Janssen. Dr. Calvo has received a predoctoral fellowship award from Gobierno de La Rioja, a Fellowship Award for short-term placements from the Health Research Institute of Hospital Gregorio Marañon (IiSGM) and a grant for short-term placements from the Alicia Koplowitz Foundation. Dr. C. Moreno has served as a consultant to Janssen, Servier, and Lundbeck. Dr. Rodríguez-Toscano has received a research grant from the Carlos III Health Institute. Drs. Llorente, Romero, Espliego, de la Serna, Sánchez-Gistau and Castro-Fornieles have declared that they do not have conflicts of interest in relation to the subject of this study.

Funding This work was supported by the Spanish Ministry of Economy, Industry and Competitiveness; Carlos III Health Institute [PI070066, PI1100683, PI15/00810]; and Catalonia Government [DIUE 2014SGR489]; co-financed by ERDF Funds from the European Commission, "A way of making Europe"; CIBERSAM; Madrid Regional Government [S2010/BMD-2422 AGES]; European Union Structural Funds and European Union Seventh Framework Program and H2020 Program; the Alicia Koplowitz Foundation and the Mutua Madrileña Foundation.

Compliance with ethical standards

Conflict of interest None.

References

1. Tsuang MT, Stone WS, Faraone SV (1999) The genetics of schizophrenia. Curr Psychiatry Rep 1(1):20–24
2. van Os J, Kenis G, Rutten BP (2010) The environment and schizophrenia. Nature 468(7321):203–212. https://doi.org/10.1038/nature09563
3. Seidman LJ, Giuliano AJ, Smith CW, Stone WS, Glatt SJ, Meyer E, Faraone SV, Tsuang MT, Cornblatt B (2006) Neuropsychological functioning in adolescents and young adults at genetic risk for schizophrenia and affective psychoses: results from the Harvard and Hillside adolescent high risk studies. Schizophr Bull 32(3):507–524. https://doi.org/10.1093/schbul/sbj078
4. Oner O, Munir K (2005) Attentional and neurocognitive characteristics of high-risk offspring of parents with schizophrenia compared with DSM-IV attention deficit hyperactivity disorder children. Schizophr Res 76(2–3):293–299. https://doi.org/10.1016/j.schres.2005.01.005
5. Andreasen NC (2000) Schizophrenia: the fundamental questions. Brain Res Brain Res Rev 31(2–3):106–112
6. Fuller Torrey E, Yolken RH (2000) Familial and genetic mechanisms in schizophrenia. Brain Res Brain Res Rev 31(2–3):113–117
7. Thorup AA, Jepsen JR, Ellersgaard DV, Burton BK, Christiani CJ, Hemager N, Skjaerbaek M, Ranning A, Spang KS, Gantriis DL, Greve AN, Zahle KK, Mors O, Plessen KJ, Nordentoft M (2015) The danish high risk and resilience study–VIA 7—a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders. BMC Psychiatry 15:233. https://doi.org/10.1186/s12888-015-0616-5
8. Zouraraki C, Karagiannopoulou L, Karamaouna P, Pallis EG, Giakoumaki SG (2019) Schizotypal traits, neurocognition, and paternal age in unaffected first degree relatives of patients with familial or sporadic schizophrenia. Psychiatry Res 273:422–429. https://doi.org/10.1016/j.psychres.2018.12.142
9. Kar SK, Jain M (2016) Current understandings about cognition and the neurobiological correlates in schizophrenia. J Neurosci Rural Pract 7(3):412–418. https://doi.org/10.4103/0976-3147.176185
10. Sugranyes G, de la Serna E, Romero S, Sanchez-Gistau V, Calvo A, Moreno D, Baeza I, Diaz-Caneja CM, Sanchez-Gutierrez T, Janssen J, Bargallo N, Castro-Fornieles J (2015) Gray matter volume decrease distinguishes schizophrenia from bipolar offspring during childhood and adolescence. J Am Acad Child Adolesc Psychiatry 54(8):677–684.e672. https://doi.org/10.1016/j.jaac.2015.05.003
11. Sugranyes G, de la Serna E, Borras R, Sanchez-Gistau V, Pariente JC, Romero S, Baeza I, Díaz-Caneja CM, Rodriguez-Toscano E, Moreno C, Bernardo M, Moreno D, Vieta E, Castro-Fornieles J (2017) Clinical, cognitive, and neuroimaging evidence of a neurodevelopmental continuum in offspring of probands with schizophrenia and bipolar disorder. Schizophr Bull 43(6):1208–1219. https://doi.org/10.1093/schbul/sbx002
12. Suvisaari JM, Taxell-Lassas V, Pankakoski M, Haukka JK, Lönnqvist JK, Häkkinen LT (2013) Obstetric complications as risk factors for schizophrenia spectrum psychoses in offspring of mothers with psychotic disorder. Schizophr Bull 39(5):1056–1066. https://doi.org/10.1093/schbul/sbs109
13. Buka SL, Seidman LJ, Tsuang MT, Goldstein JM (2013) The New England family study high-risk project: neurological impairments among offspring of parents with schizophrenia and other psychoses. Am J Med Genet B Neuropsychiatr Genet 162B(7):653–660. https://doi.org/10.1002/ajmg.b.32181
14. Ziermans T, de Wit S, Schothorst P, Sprong M, van Engeland H, Kahn R, Durston S (2014) Neurocognitive and clinical

predictors of long-term outcome in adolescents at ultra-high risk for psychosis: a 6-year follow-up. PLoS One 9(4):e93994. https://doi.org/10.1371/journal.pone.0093994
15. Hameed MA, Lewis AJ (2016) Offspring of parents with schizophrenia: a systematic review of developmental features across childhood. Harv Rev Psychiatry 24(2):104–117. https://doi.org/10.1097/HRP.0000000000000076
16. Agerbo E, Sullivan PF, Vilhjálmsson BJ, Pedersen CB, Mors O, Børglum AD, Hougaard DM, Hollegaard MV, Meier S, Mattheisen M, Ripke S, Wray NR, Mortensen PB (2015) Polygenic risk score, parental socioeconomic status, family history of psychiatric disorders, and the risk for schizophrenia: a danish population-based study and meta-analysis. JAMA Psychiatry 72(7):635–641. https://doi.org/10.1001/jamapsychiatry.2015.0346
17. van Os J, Hanssen M, de Graaf R, Vollebergh W (2002) Does the urban environment independently increase the risk for both negative and positive features of psychosis? Soc Psychiatry Psychiatr Epidemiol 37(10):460–464. https://doi.org/10.1007/s00127-002-0588-x
18. Seidman LJ, Buka SL, Goldstein JM, Tsuang MT (2006) Intellectual decline in schizophrenia: evidence from a prospective birth cohort 28 year follow-up study. J Clin Exp Neuropsychol 28(2):225–242. https://doi.org/10.1080/13803390500360471
19. Arango C, Fraguas D, Parellada M (2014) Differential neurodevelopmental trajectories in patients with early-onset bipolar and schizophrenia disorders. Schizophr Bull 40(Suppl 2):S138–146. https://doi.org/10.1093/schbul/sbt198
20. Green MF (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153(3):321–330. https://doi.org/10.1176/ajp.153.3.321
21. Nuechterlein KH, Dawson ME (1984) Information processing and attentional functioning in the developmental course of schizophrenic disorders. Schizophr Bull 10(2):160–203
22. Heinrichs RW, Zakzanis KK (1998) Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12(3):426–445
23. Bora E, Lin A, Wood SJ, Yung AR, McGorry PD, Pantelis C (2014) Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. Acta Psychiatrica Scand 130(1):1–15. https://doi.org/10.1111/acps.12261
24. Cornblatt BA, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E (2003) The schizophrenia prodrome revisited: a neurodevelopmental perspective. Schizophr Bull 29(4):633–651
25. McGorry PD, Yung AR, Phillips LJ (2003) The "close-in" or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. Schizophr Bull 29(4):771–790
26. Goldstein JM, Seidman LJ, Buka SL, Horton NJ, Donatelli JL, Rieder RO, Tsuang MT (2000) Impact of genetic vulnerability and hypoxia on overall intelligence by age 7 in offspring at high risk for schizophrenia compared with affective psychoses. Schizophr Bull 26(2):323–334
27. Giuliano AJ, Li H, Mesholam-Gately RI, Sorenson SM, Woodberry KA, Seidman LJ (2012) Neurocognition in the psychosis risk syndrome: a quantitative and qualitative review. Curr Pharm Des 18(4):399–415
28. Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rossler A, Schultze-Lutter F, Keshavan M, Wood S, Ruhrmann S, Seidman LJ, Valmaggia L, Cannon T, Velthorst E, De Haan L, Cornblatt B, Bonoldi I, Birchwood M, McGlashan T, Carpenter W, McGorry P, Klosterkotter J, McGuire P, Yung A (2013) The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 70(1):107–120. https://doi.org/10.1001/jamapsychiatry.2013.269
29. Diwadkar VA, Montrose DM, Dworakowski D, Sweeney JA, Keshavan MS (2006) Genetically predisposed offspring with schizotypal features: an ultra high-risk group for schizophrenia? Prog Neuro-psychopharmacol Biol Psychiatry 30(2):230–238. https://doi.org/10.1016/j.pnpbp.2005.10.019
30. Shad MU, Tamminga CA, Cullum M, Haas GL, Keshavan MS (2006) Insight and frontal cortical function in schizophrenia: a review. Schizophr Res 86(1–3):54–70. https://doi.org/10.1016/j.schres.2006.06.006
31. Schreiber H, Stolz-Born G, Heinrich H, Kornhuber HH, Born J (1992) Attention, cognition, and motor perseveration in adolescents at genetic risk for schizophrenia and control subjects. Psychiatry Res 44(2):125–140
32. Li P, Zhang Q, Robichaud AJ, Lee T, Tomesch J, Yao W, Beard JD, Snyder GL, Zhu H, Peng Y, Hendrick JP, Vanover KE, Davis RE, Mates S, Wennogle LP (2014) Discovery of a tetracyclic quinoxaline derivative as a potent and orally active multifunctional drug candidate for the treatment of neuropsychiatric and neurological disorders. J Med Chem 57(6):2670–2682. https://doi.org/10.1021/jm401958n
33. Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, Adamo UH, Gottesman II (2000) Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York high-risk project. Am J Psychiatry 157(9):1416–1422. https://doi.org/10.1176/appi.ajp.157.9.1416
34. Davalos DB, Compagnon N, Heinlein S, Ross RG (2004) Neuropsychological deficits in children associated with increased familial risk for schizophrenia. Schizophr Res 67(2–3):123–130. https://doi.org/10.1016/S0920-9964(03)00187-7
35. Ozan E, Deveci E, Oral M, Karahan U, Oral E, Aydin N, Kirpinar I (2010) Neurocognitive functioning in a group of offspring genetically at high-risk for schizophrenia in Eastern Turkey. Brain Res Bull 82(3–4):218–223. https://doi.org/10.1016/j.brainresbull.2010.04.013
36. Sugranyes G, de la Serna E, Borras R, Sanchez-Gistau V, Pariente JC, Romero S, Baeza I, Diaz-Caneja CM, Rodriguez-Toscano E, Moreno C, Bernardo M, Moreno D, Vieta E, Castro-Fornieles J (2017) Clinical, cognitive, and neuroimaging evidence of a neurodevelopmental continuum in offspring of probands with schizophrenia and bipolar disorder. Schizophr Bull. https://doi.org/10.1093/schbul/sbx002
37. de la Serna E, Sugranyes G, Sanchez-Gistau V, Rodriguez-Toscano E, Baeza I, Vila M, Romero S, Sanchez-Gutierrez T, Penzol MJ, Moreno D, Castro-Fornieles J (2017) Neuropsychological characteristics of child and adolescent offspring of patients with schizophrenia or bipolar disorder. Schizophr Res 183:110–115. https://doi.org/10.1016/j.schres.2016.11.007
38. de la Serna E, Vila M, Sanchez-Gistau V, Moreno D, Romero S, Sugranyes G, Baeza I, Llorente C, Rodriguez-Toscano E, Sanchez-Gutierrez T, Castro-Fornieles J (2016) Neuropsychological characteristics of child and adolescent offspring of patients with bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 65:54–59. https://doi.org/10.1016/j.pnpbp.2015.08.014
39. Sugranyes G, de la Serna E, Romero S, Sanchez-Gistau V, Calvo A, Moreno D, Baeza I, Diaz-Caneja CM, Sanchez-Gutierrez T, Janssen J, Bargallo N, Castro-Fornieles J (2015) Gray matter volume decrease distinguishes schizophrenia from bipolar offspring during childhood and adolescence. J Am Acad Child Adolesc Psychiatry 54(8):677–684. https://doi.org/10.1016/j.jaac.2015.05.003
40. Sanchez-Gistau V, Romero S, Moreno D, de la Serna E, Baeza I, Sugranyes G, Moreno C, Sanchez-Gutierrez T, Rodriguez-Toscano E, Castro-Fornieles J (2015) Psychiatric disorders in child and adolescent offspring of patients with schizophrenia and bipolar disorder: a controlled study. Schizophr Res 168(1–2):197–203. https://doi.org/10.1016/j.schres.2015.08.034

41. Hollingshead AB, Redlich FC (1958) Social class and mental illness. Wiley, New York
42. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N (1997) Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36(7):980–988. https://doi.org/10.1097/00004583-199707000-00021
43. Ulloa RE, Ortiz S, Higuera F, Nogales I, Fresan A, Apiquian R, Cortes J, Arechavaleta B, Foulliux C, Martinez P, Hernandez L, Dominguez E, de la Pena F (2006) Interrater reliability of the Spanish version of schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL). Actas Esp Psiquiatr 34(1):36–40
44. Soutullo C (1999) Traducción al español de la entrevista diagnóstica: kiddie-schedule for affective disorders and schizophrenia, present and lifetime version (K-SADS-PL, 1996). http://www.cun.es/la-clinica/departamentos-yservicios-medicos/psiquiatria-y-psicologia-medica/mas-sobreel-departamento/unidades/psiquiatria-infantil-y-adolescente. Accessed May 2003
45. First MB, Spitzer RL, Gibbon M, Williams JB (1996) Structured clinical interview for DSM-IV axis I disorders, clinician version (SCID-CV). American Psychiatric Press Inc, Washington
46. Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, McFarlane W, Perkins DO, Pearlson GD, Woods SW (2003) Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull 29(4):703–715
47. McGlashan TH, Miller TJ, Woods SW, Hoffman RE, Davidson L (2001) A scale for the assessment of prodromal symptoms and states. In: Miller TJ, Mednick SA, McGlashan TH, Liberger J, Johannessen JO (eds) Early intervention in psychotic disorders. Kluwer Academic Publishers, Dordrecht, pp 135–149
48. Goodman R (1997) The strengths and difficulties questionnaire: a research note. J Child Psychol Psychiatry 38(5):581–586
49. Wechsler D (2001) Escala de inteligencia de wechsler para niños—revisada. TEA Ediciones S.A., Madrid
50. Reynolds CR y Bigler ED (2001) TOMAL: Test de Memoria y Aprendizaje, Madrid: TEA Ediciones
51. Wechsler D (1997) Wechsler Memory Scale-(WMS-III) Administration and scoring manual third, San Antonio: Psychological Corporation
52. Rey A (1964) L'examen clinique en psychologie (The Clinical Psychological Examination). Paris: Presse Universitaires de France
53. Conners CK (2000) Conners' continuous performance test II: computer program for windows technical guide and software manual. North Tonwanda: Multi-Health Systems
54. Golden CJ (1978) Stroop color and word test. A manual for clinical and experimental uses. Stoelting Co, Illinois
55. Heaton RK, Chelune GJ, Talley JL, Kay GG, Custiss GC (2001) Test de clasificación de tarjetas de Wisconsin. TEA Ediciones S.A., Madrid
56. IBM Corp (2010) IBM SPSS statistics for windows, vol 19.0, 19.0th edn. IBM Corp, Armonk
57. Cornblatt B, Obuchowski M, Schnur DB, O'Brien JD (1997) Attention and clinical symptoms in schizophrenia. Psychiatric Q 68(4):343–359
58. Corcoran C, Perrin M, Harlap S, Deutsch L, Fennig S, Manor O, Nahon D, Kimhy D, Malaspina D, Susser E (2009) Effect of socioeconomic status and parents' education at birth on risk of schizophrenia in offspring. Soc Psychiatry Psychiatr Epidemiol 44(4):265–271. https://doi.org/10.1007/s00127-008-0439-5
59. Kelleher I, Murtagh A, Clarke MC, Murphy J, Rawdon C, Cannon M (2013) Neurocognitive performance of a community-based sample of young people at putative ultra high risk for psychosis: support for the processing speed hypothesis. Cogn Neuropsychiatr 18(1–2):9–25. https://doi.org/10.1080/13546805.2012.682363
60. Carrion RE, Goldberg TE, McLaughlin D, Auther AM, Correll CU, Cornblatt BA (2011) Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. Am Jo Psychiatry 168(8):806–813. https://doi.org/10.1176/appi.ajp.2011.10081209
61. Frommann I, Pukrop R, Brinkmeyer J, Bechdolf A, Ruhrmann S, Berning J, Decker P, Riedel M, Moller HJ, Wolwer W, Gaebel W, Klosterkotter J, Maier W, Wagner M (2011) Neuropsychological profiles in different at-risk states of psychosis: executive control impairment in the early—and additional memory dysfunction in the late—prodromal state. Schizophr Bull 37(4):861–873. https://doi.org/10.1093/schbul/sbp155
62. Rodriguez-Sanchez JM, Crespo-Facorro B, Gonzalez-Blanch C, Perez-Iglesias R, Vazquez-Barquero JL, Study PG (2007) Cognitive dysfunction in first-episode psychosis: the processing speed hypothesis. B J Psychiatry Suppl 51:s107–110. https://doi.org/10.1192/bjp.191.51.s107
63. Knowles EE, David AS, Reichenberg A (2010) Processing speed deficits in schizophrenia: reexamining the evidence. Am J Psychiatry 167(7):828–835. https://doi.org/10.1176/appi.ajp.2010.09070937
64. Erlenmeyer-Kimling L (2000) Neurobehavioral deficits in offspring of schizophrenic parents: liability indicators and predictors of illness. Am J Med Genet 97(1):65–71
65. Byrne M, Hodges A, Grant E, Owens DC, Johnstone EC (1999) Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared with controls: preliminary findings of the edinburgh high risk study (EHRS). Psychol Med 29(5):1161–1173
66. Cornblatt B, Obuchowski M, Schnur D, O'Brien JD (1998) Hillside study of risk and early detection in schizophrenia. Br J Psychiatry Suppl 172(33):26–32
67. Reetzke R, Maddox WT, Chandrasekaran B (2016) The role of age and executive function in auditory category learning. J Exp Child Psychol 142:48–65. https://doi.org/10.1016/j.jecp.2015.09.018
68. Luna B, Garver KE, Urban TA, Lazar NA, Sweeney JA (2004) Maturation of cognitive processes from late childhood to adulthood. Child Dev 75(5):1357–1372. https://doi.org/10.1111/j.1467-8624.2004.00745.x
69. Medalia A, Saperstein AM, Hansen MC, Lee S (2018) Personalised treatment for cognitive dysfunction in individuals with schizophrenia spectrum disorders. Neuropsychol Rehabil 28(4):602–613. https://doi.org/10.1080/09602011.2016.1189341